Medicina perioperatoria individualizada en cirugía oncológica

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" Medicina Perioperatoria individualizada en cirugía oncológica "

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Dedicado a mi familia

Índice

GLOSARIO DE ABREVIATURAS:

ACS: Abdominal compartment syndrome
ADP: Asymptotic deceleration point
AE: Adverse event serious
AEMPS: Agencia Española del Medicamento y Productos sanitarios
ARDS: Acute respiratory distress syndrome
ASA: American Society of Anesthesiologists
ATT: abdomino–thoracic transmission
BMI: Body mass index
BIS: Bispectral index
C_{abd}: Abdominal compliance
C_{CW}: Chest wall compliance
CEA: Carcinoembryonic antigen
CNS: Central nervous system
CRC: Colorectal cancer
CRF: Case Report Form
CRP: C–reactive protein
DFS: Disease free survival
DOB: Date of birth
EPCO: European Perioperative Clinical Outcome
ERAS: Enhanced Recovery after surgery
ERP: Enhanced Recovery Pathways
GCP: Good Clinical Practice
IAP: Intra–abdominal pressure
IAV: Intra–abdominal volume
ICG: Indocyanine green
ICU: Intensive Care Unit
ICMJE: International committee of medical journal editors
ICH: International Conference on Harmonization
IHC: Immunohistochemistry
IPP: Individualised pneumoperitoneum pressure
IRB: Institutional Review Board
LOS: Length of stay

MDP: Maximum deceleration point

MOR: Mu opioid receptor

NLR: neutrophil–lymphocyte ratio

NMB: Neuromuscular Blockade

NMBAs: Neuromuscular blockade agents

NSAIs: Non steroideal anti-inflammatory drugs

nSAE: Non-serious adverse event

OR: odds ratio

OS: Overall survival

PACU: Post Anaesthesia Care Unit

P_{aw}: airway pressures

PBW: Predicted ideal body weight

PCA: Patient controlled analgesia

PDRICG: Plasma disappearance rate of indocyanine green

PEEP: Positive end-expiratory pressure

POD1: Postoperative day 1

POD 3: Postoperative day 3

PONV: Postoperative nausea and vomiting

PPC: Postoperative pulmonary complications

PQRS: Postoperative Quality of Recovery Scale

$\Delta P_{RS:}$ Driving *pressure respiratory system*

PROs: Patient reported outcomes

PTC: Post–tetanic count

PV: pressure–volume

PV0: Intra–abdominal pressure at volume zero

QoR: quality of recovery

RCT: Randomized clinical trial

RR: respiratory rate

SAE: Serious adverse event.

SAP: statistical analysis plan

SCREN: Spanish Clinical Research Network

SOP: Standard Operating Procedure

SPP: Standard pneumoperitoneum

TIA: transient ischemic attacks

TOF: Train of four

UPLC: Ultra performance liquid chromatography

VT: volume tidal

Capítulo 1

Introducción y objetivos

La especialidad de Anestesiología, Reanimación y Terapéutica del dolor ha evolucionado en la última década hacia un concepto asistencial global adquiriendo responsabilidades sobre el paciente, no solo en el quirófano y las Unidades de Cuidados críticos, sino desde el momento de la indicación quirúrgica hasta su recuperación completa. Se ha integrado con el concepto desarrollado en el ámbito quirúrgico de "fast track" o recuperación intensificada para dar lugar a la Medicina perioperatoria.

Se define la Medicina perioperatoria como la asistencia integral, multidisciplinar y centrada en el paciente desde la indicación de un proceso quirúrgico hasta su recuperación completa. Estos tres conceptos permiten sinérgicamente obtener una asistencia de calidad y mejores resultados.

El objetivo de esta tesis ha sido plasmar este nuevo modo de entender la atención médica perioperatoria a través varios proyectos de investigación. Se han agrupado en cuatro bloques principales: estrategia individualizada de neumoperitoneo, ventilación mecánica y bloqueo neuromuscular en cirugía laparoscópica, y la estrategia analgésica en cirugía oncológica.

Bloque 1: Estrategia individualizada de neumoperitoneo en cirugía laparoscópica.

La cirugía laparoscópica exige la introducción de CO2 a una determinada presión en la cavidad abdominal para crear un adecuado espacio de trabajo. Esta presión intraabdominal generada se denomina presión de neumoperitoneo. Las guías de cirugía abdominal laparoscópica recomiendan trabajar a la menor presión de neumoperitoneo posible a la que el cirujano disponga de un adecuado espacio de trabajo y no utilizar niveles fijos. Sin embargo, en la práctica clínica la presión del neumoperitoneo se establece habitualmente entre 12-15 mmHg desde el inicio y habitualmente permanece fija durante todo el procedimiento quirúrgico, solo se incrementa si las condiciones quirúrgicas no son buenas, para intentar mejorar el espacio de trabajo. Por el contrario, nunca se mide el volumen que hay en la cavidad ni si este aumento de presión se relaciona con una ganancia de volumen.

Una elevada presión del neumoperitoneo lesiona el peritoneo, compromete de manera global la perfusión esplácnica y dificulta la ventilación mecánica. De

este modo individualizar la presión de neumoperitoneo para cada paciente a la mínima posible puede ser beneficioso para el paciente siempre que se aseguren unas adecuadas condiciones quirúrgicas que no comprometan su seguridad ni alarguen la duración del procedimiento quirúrgico. La colaboración multidisciplinar con los cirujanos generales expertos en cirugía colorrectal laparoscópica nos ha permitido evaluar de manera individualizada la posibilidad de disminuir la presión del neumoperitoneo y valorar el impacto en la ventilación mecánica y en la recuperación del paciente. A lo anterior se añade considerar al paciente en el centro de la asistencia ya que evaluamos el impacto a través del análisis de los resultados reportados por el propio paciente (patient reported outcomes - PROs).

En el capítulo 2 se detalla el estudio observacional multicéntrico '*Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery' (IPPColLapSe I)*. Participaron investigadores del Hospital General Universitari de Castellón (Castellón) y del Hospital General Universitario Gregorio Marañon (Madrid). El objetivo principal era evaluar la posibilidad de individualizar para cada paciente la presión del neumoperitoneo utilizada en cirugía laparoscópica a la menor posible mediante la introducción de un paquete de medidas orientadas a mejorar la compliance y el volumen abdominal. Estas medidas incluían posicionamiento elevado de las piernas del paciente, pre-estiramiento de la pared abdominal durante la generación del neumoperitoneo, estrategia de ventilación de protección pulmonar y bloqueo neuromuscular profundo. La hipótesis fue que la aplicación de este paquete de medidas permitiría disminuir la presión del neumoperitoneo utilizada manteniendo unas adecuadas condiciones quirúrgicas en cirugía laparoscópica colorrectal. El estudio está registrado en www.clinicaltrials.gov (study identifier: NCT03000465).

El capítulo 3 se detalla el protocolo del ensayo clínico con medicamentos de bajo nivel de intervención, randomizado, multicéntrico, *"Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery versus standard theraphy" (IPPColLapSe II).* Participaron investigadores del Hospital General Universitari de Castellón (Castellón), Hospital Universitario Virgen del Rocio (Sevilla) y del Hospital General Universitario Gregorio Marañon (Madrid).

El estudio está registrado en www.clinicaltrials.gov (study identifier: NCT02773173) y EudraCT 2016-001693-15. Este estudio obtuvo la integración en la plataforma de apoyo a la investigación clínica independiente de excelencia, Spanish Clinical Research Network, SCREN (https://www.scren.es). Además sigue las recomendaciones internacionales para estudios de intervención que analizan resultados reportados por el paciente, (PROs),"Standard Protocol Items: Recommendations for Interventional Trials and Patient–Reported Outcomes' (SPIRIT–PRO) guidelines". El objetivo principal era evaluar los resultados comunicados por el paciente mediante una escala de calidad de recuperación postoperatoria, PQRS, (www.postopqrs.com) cuando se realiza cirugía laparoscópica colorrectal programada con una estrategia de presión de neumoperitoneo individualizada frente a una estrategia convencional de presión de neumoperitoneo fija. La escala de calidad de recuperación postoperatoria, PQRS evalúa cinco dominios: fisiológico, nociceptivo, emocional, cognitivo y funcional, en cinco puntos temporales. Basal previo a la cirugía, a los 15 y 40 minutos tras la cirugía y en los días uno y tres del postoperatorio. La hipótesis es que una estrategia de presión de neumoperitoneo individualizada mejoraría la calidad de recuperación postoperatoria comunicada por el paciente, PQRS, en el día 1 del postoperatorio.

Se publicó con posterioridad una corrección al plan de análisis estadístico para detallar que el objetivo principal era evaluar el dominio fisiológico, siendo el resto de los dominios objetivos secundarios, así como que se analizarían como datos longitudinales o medidas repetidas, no como medidas independientes.

En el capítulo 4 se detallan los resultados del ensayo clínico con medicamentos de bajo nivel de intervención, randomizado, multicéntrico, "*Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery versus standard theraphy" (IPPColLapSe II).*

Bloque 2: Estrategia de ventilación mecánica en cirugía laparoscópica

La cirugía abdominal mayor oncológica presenta una elevada incidencia de complicaciones pulmonares postoperatorias, que prolongan la estancia hospitalaria y afectan negativamente al pronóstico de los pacientes. Se han

investigado diferentes estrategias de ventilación mecánica y soporte respiratorio postoperatorio para disminuir esta complicación. Realizar una estrategia de ventilación mecánica orientada a obtener la menor "driving pressure" se ha postulado como una estrategia efectiva para disminuir la incidencia de complicaciones pulmonares postoperatorias. La posibilidad de individualizar la presión del neumoperitoneo en cirugía laparoscópica a la menor posible podría contribuir a disminuir la "driving pressure" y reducir la incidencia de complicaciones pulmonares postoperatorias.

En el capítulo 5 se detallan los resultados del estudio clínico cruzado prospectivo, no randomizado "*Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery. An open-label, nonrandomized, crossover, clinical trial" (IPPColLapSe III).* El objetivo era evaluar la capacidad de disminuir la "driving pressure" transpulmonar aplicando niveles de presión positiva al final de la espiración, (positive end-expiratory pressure-PEEP) titulados según la presión del neumoperitoneo en cirugía laparoscópica comparada con una estrategia de PEEP fija de 5 cmH2O. La hipótesis fue que una estrategia orientada a igualar los niveles de PEEP a los niveles de presión del neumoperitoneo prevendría el aumento en la "driving pressure" transpulmonar en cirugía laparoscópica. El estudio está registrado en www.clinicaltrials.gov (study identifier: NCT03435913).

En el capítulo 6 se presenta un metaanálisis de los estudios *IPPColLapSe I, II y III (*capítulos 2, 3, 4 y 5) con el objetivo de evaluar la relación entre la presión intraabdominal del neumoperitoneo y el volumen en cirugía laparoscópica y entre presión intraabdominal del neumoperitoneo y la "driving pressure" respiratoria. El estudio está registrado en www.clinicaltrials.gov (study identifier: NCT04468698).

Bloque 3: Estrategia de bloqueo neuromuscular en cirugía laparoscópica

El bloqueo neuromuscular es un componente fundamental de la anestesia moderna en cirugía abdominal. Aunque su uso se ha relacionado con un aumento de la morbilidad perioperatoria, pensamos que un manejo óptimo con monitorización cuantitativa del bloqueo neuromuscular y reversión farmacológica podría contribuir a disminuir las complicaciones postoperatorias,

fundamentalmente de origen pulmonar. No obstante, su manejo óptimo no está incluido dentro de las medidas habituales en los programas de recuperación y era importante conocer el impacto de un uso seguro del bloqueo neuromuscular en los resultados de estos programas.

En el capítulo 7 se detalla un subestudio preprogramado del estudio *"Postoperative Outcomes Within an Enhanced Recovery After Surgery Protocol (POWER)",* estudio observacional, multicéntrico, nacional que evaluaba el impacto en las complicaciones postoperatorias de un paquete de medidas de un programa de recuperación intensificada en cirugía colorrectal. El estudio está registrado en www.clinicaltrials.gov (study identifier: NCT03012802) y sigue las recomendaciones internacionales para estudios observacionales "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE). El objetivo del subestudio era evaluar la relación entre la monitorización cuantitativa del bloqueo neuromuscular y la reversión farmacológica con las complicaciones postoperatorias y la estancia hospitalaria. La hipótesis fue que un manejo óptimo del bloqueo neuromuscular (monitorización cuantitativa y reversión farmacológica en el contexto de un programa de recuperación intensificada se asociaría a menos complicaciones postoperatorias.

Bloque 4: Estrategia analgésica en cirugía oncológica

Un adecuado manejo del periodo perioperatorio en cirugía oncológica es fundamental, ya que la respuesta inflamatoria sistémica relacionada con el trauma quirúrgico puede condicionar inmunosupresión y aumentar el riesgo de recidiva oncológica por la incapacidad para eliminar la enfermedad residual-células tumorales que se liberan habitualmente durante la manipulación quirúrgica del cáncer. Los fármacos que utilizamos durante el perioperatorio pueden modular esta respuesta y es importante evaluar su impacto en los resultados a largo plazo. Aunque un adecuado control del dolor contribuye a disminuir esta respuesta inflamatoria, el uso de analgésicos opioides se ha relacionado en diversos tipos de tumor con una mayor incidencia de recidiva tumoral y peores resultados a largo plazo.

En el capítulo 8 se detalla una revisión sistemática de la literatura sobre el efecto a largo plazo de los opioides perioperatorios en la recurrencia del cáncer colorrectal. La hipótesis era que los opioides perioperatorios se asocian a peores resultados oncológicos a largo plazo. Seguía las recomendaciones internacionales para revisiones sistemáticas y metaanálisis “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement”.

En el capítulo 9 se detalla un estudio observacional *“Mu opioid receptor 1 (MOR-1) expression in colorectal cancer and disease-free survival relationship (Morocco). Five-year follow-up”.* El objetivo era evaluar la asociación entre la expresión del receptor opioide mu tipo 1 (MOR1) y los resultados oncológicos a largo plazo en cirugía oncológica colorrectal. La hipótesis era que había un aumento de la expresión de receptor opioide mu tipo 1 (MOR1) en el tejido tumoral al compararlo con el tejido no tumoral adyacente y esto se asociaría a una menor supervivencia libre de enfermedad. El estudio esta registrado en www.clinicaltrials.gov (study identifier: NCT03601351). Sigue las recomendaciones internacionales “REporting recommendations for tumour MARKer prognostic studies (REMARK)".

Estrategia individualizada de pneumoperitoneo en cirugía laparoscópica

Capítulo 2

A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study.

Díaz-Cambronero O, *Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, Olmedilla Arnal LE, Argente Navarro MP, Schultz MJ, Errando CL; IPPColLapSe study group et al.*

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INTRODUCTION

Guidelines for laparoscopic abdominal surgery recommend using the lowest possible intra–abdominal pressure (IAP) at which the surgeon has adequate workspace rather than using a standard level of IAP [1,2]. In clinical practice, though, IAP is typically set between 12 and 15 mmHg throughout the entire surgical procedure [3]. Using the lowest possible IAP could be beneficial, as high IAP is associated with peritoneal damage, impaired splanchnic, hepatic and abdominal wall perfusion, decreased gastric mucosal oxygen saturation, and postoperative pain [4-8]. However, a low IAP could result in unacceptable surgical conditions, which could not only lengthen duration of surgery but also increase the risk of complications, eventually worsening outcomes [9,10].

Surgical workspace is linked to the intraabdominal volume (IAV), the amount of insufflated CO_2 gas to create the pneumoperitoneum. The IAV needed has been related to multiple but foremost modifiable factors [11]. Indeed, factors like neuromuscular blockade, pre–stretching of the abdominal wall, and patient positioning has been shown to affect the relationship between IAP and workspace[12-24]. Besides, ventilation–induced changes in intra–thoracic pressures and probably individual patient factors might impact IAP. All these factors have been studied before, but were never addressed neither investigated together.

Thus, we performed the 'Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery' (IPPColLapSe) study to investigate whether a multifaceted individualized strategy, focusing on optimizing the combination of factors mentioned above during laparoscopic abdominal surgery. We were interested in its feasibility, but also the lowest IAP at which surgery could be performed using this strategy. Specifically, we assessed the proportion of patients in whom surgery was performed and completed at each individualized IAP level. We also determined the association between changes in IAP and intrathoracic pressures, and estimated the IAV at which the laparoscopic procedure was performed. We hypothesized that a multifaceted individualized pneumoperitoneum strategy would result in lower IAP with adequate workspace for surgeons during laparoscopic colorectal surgery.

MATERIALS AND METHODS

Design

The IPPColLapSe study was an investigator–initiated multicenter prospective cohort investigation performed between May 2015 and October 2016 in three Spanish hospitals: The Hospital Universitario y Politécnico La Fe, Valencia, the Hospital General de Castellón, Castellon, and the Hospital Universitario Gregorio Marañon, Madrid. The study protocol was approved by the Institutional Review Boards (IRB) of all three hospitals (protocol number: 2015/0094). The trial was registered with ClinicalTrials.gov (Trial Identifier: NCT03000465). Written informed consent was obtained from all participants before surgery.

Population

Patients were eligible for participation if (a) scheduled for laparoscopic colorectal surgery; (b) age > 18 year-old; and (c) American Society of Anesthesiologists (ASA) physical status I to III, with no cognitive deficits. Exclusion criteria included: (a) emergency or unplanned surgery; (b) impossibility to obtain written informed consent; and (c) allergy to, or contraindication for rocuronium or sugammadex. Women who were pregnant or breastfeeding, patients with known immunologic or neuromuscular diseases, and patients with an advanced stage of cardiopulmonary, renal or hepatic diseases were excluded from participation.

Standard procedures

After initiation of standard monitoring (electrocardiography, noninvasive intermittent arterial blood pressure measurement, continuous pulse oximetry) and continuous neuromuscular monitoring (TOF–Watch–SX™, Organon–Teknika, Oss, The Netherlands). Anesthesia was induced using propofol (1.5 to 2 $mg \cdot kg^{-1}$) plus fentanyl (1 $\mu g \cdot kg^{-1}$). Tracheal intubation was facilitated with rocuronium 0.6 $mg \cdot kg^{-1}$. Anesthesia was maintained using propofol infusion titrated to a bispectral index (BIS, BIS™, Covidien, Mansfield, MA, USA) between 40–60. Additional fentanyl boluses (1 $\mu g \cdot kg^{-1}$) were used for intraoperative analgesia. An electronic CO_2 gas insufflator (Endoflator™, Karl Storz, Tuttlingen, Germany) was used for CO_2 insufflation into the abdominal cavity through a paraumbilical–placed laparoscopic trocar.

Intervention

The following predefined interventions, as part of the multifaceted individualized pneumoperitoneum strategy, were performed in all patients, in the same order:

1. Tidal volume reduction with volume controlled ventilation mode to 8 $ml \cdot kg^{-1}$ of predicted ideal body weight (PBW), 20% inspiratory pause, positive end–expiratory pressure (PEEP) set at 5 or 10 mm Hg, in patients with a body mass index (BMI) < 30 or > 30 $kg \cdot m^{-2}$ respectively, oxygen inspiratory fraction 0.8 and respiratory rate 12 to 15 respirations per minute to maintain standard end–tidal CO_2 values[25].
2. A 'modified lithotomy position' with slightly flexed hips (45-90º) respect to patients' legs raised in padded supports. This increase the anteroposterior intra–abdominal space by correcting lumbar lordosis;
3. Continuous deep neuromuscular blockade throughout surgery to maintain a train–of–four (TOF) of 0 and post–tetanic count (PTC) between 1 and 5;
4. Prestretching of the abdominal wall muscles, setting pneumoperitoneum at 15 mmHg for a maximum of 5 minutes during initial CO_2 gas insufflation and trocars insertion; (insufflator initially set at 15 mmHg with an initial flow rate of 3 $L \cdot min^{-1}$);
5. Individualized IAP titration. After pre–stretching, the patient was placed in the 20º Trendelemburg position. Flow rate was set at 30 $L \cdot min^{-1}$ and the surgery began. The IAP was initially decreased from 15 to 12 mmHg, and then stepwise to 11, 10, 9 and finally 8 mmHg. IAP was allowed to stabilization after each step, lasting usually 3 to 5 minutes. Surgeons were blinded to the actual IAP used, and could request at any time to increase IAP, if workspace became 'non–adequate'. If deemed necessary this increment was done in 1 mmHg steps lasting at least 1 minute, up to the level at which the surgical workspace became adequate with an upper limit of 15 mm Hg. While it is common that the surgeon decides on the level of IAP to be used, here an anesthesiologist managed the pneumoperitoneum insufflator and surgeons remained blinded to the level of IAP used.

Data collected

Data on weight, sex, height, age, gender, body mass index (BMI), number of pregnancies, number of previous laparoscopic surgeries, and type and duration of surgery were collected. IAP was measured at every liter during pneumoperitoneum insufflation until 15 mmHg level was reached. We also measured the IAV of CO_2 gas insufflated at 15 mmHg. Ventilation parameters were collected at each down titration step of IAP. Parameters recorded included

PEEP, peak pressure (Ppeak) and plateau pressure (Pplat), and respiratory system compliance (C_{RS}).

Definitions

The 'individualized IAP' was defined as the highest IAP needed to obtain *and* maintain an adequate workspace until completion of surgery. 'Adequate workspace' was defined as the workspace sufficient to perform the surgical procedure with no need for corrective measures (IAP increment) as judged by the operating surgeon. Consequently, 'non–adequate workspace' was defined as workspace insufficient to perform the surgical procedure with the need for corrective measures. Surgeons were kept blinded to the actual level of IAP used at any time during the surgical procedure, but were advised if the level was over the predefined upper limit.

The 'respiratory system driving pressure' (ΔP_{RS}) was calculated by subtracting PEEP from Pplat. The optimized IAV was defined as the 'volume of insufflated CO_2 at the individualized IAP' and was estimated from the IAP/IAV curve for each patient during insufflation.

Endpoints

The primary endpoint was the proportion of patients at each level of individualized IAP. Secondary endpoints were ventilation parameters evaluation during the stepwise IAP deflation, including Ppeak, Pplat and PEEP, and the ΔP_{RS}, and IAV estimation at the individualized IAP.

Sample size calculation

Assuming that surgery can be performed with a mean IAP of 9 mmHg with standard deviation (SD) of 1.9, (pilot unpublished study, laparoscopic colorectal surgery), 78 patients would be included to assess the individualized IAP with 95% confidence and achieving an accuracy of ± 0.5 in the determination of the 50^{th} percentile, ± 0.55 in the 25^{th} and 75^{th} percentiles and of ± 0.65 in the 10^{th} and 90^{th} percentiles.

If conversion to open surgery was decided the patient were excluded from the analysis of the primary outcome, and replaced with a new patient until 78 patients were enrolled and completed the study concerning the primary endpoint. Patients in whom surgeons decided to convert to open surgery remained analyzable for the other endpoints.

Analysis plan and statistical analyses

Data were expressed as mean (SD) or median [IQR] for continuous variables and by counts and proportions for categorical variables with. The 95% confidence intervals were calculated for each of the estimated percentiles.

The proportion of patients in whom surgery was finished at each IAP level was first analyzed. Next, the relationship between IAP and ventilation parameters, in particular, ΔP_{RS}. was calculated. For this calculation a quantile regression model with splines for the median and 10^{th} and 90^{th} percentiles, adding BMI and age as covariates was adjusted.

The relationship between IAP and the insufflated volume of CO_2 was determined for each patient during initial pneumoperitoneum insufflation until an IAP of 15 mmHg was reached. The optimized IAV was estimated from data in patients in whom surgery was finished by laparoscopy. The relationship between IAP and IAV was analyzed by linear interpolation from the individual IAP/IAV curves. The IAP before CO_2 gas insufflation was considered the basal IAP or intra–abdominal pressure at volume zero, and was estimated by fitting multiadaptive linear regression splines to intraabdominal volume and pressure relationship.

We performed a *posthoc* analysis fitting a linear mixed model with surgeon as random effect to determine factors that influenced the optimized IAV. The factors tested in the model included: Age, gender, BMI, pregnancies, previous laparoscopic or open surgeries, type of surgery (right or left hemicolectomy, rectum or other surgeries), IAV at 15 mmHg of IAP, and intra–abdominal pressure at volume zero (Pv0) were included.

Statistical analyses were performed with R statistical software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Ninety-two patients were finally enrolled. Fourteen procedures were converted to open surgery (Figure 1). In all cases the surgeons confirmed that the decision to conversion was not related to the IPP. All other 78 patients could be followed to the primary endpoint of the study. Baseline characteristics are presented in Table 1. Surgeons experience is detailed in eTable1.

Feasibility

The multifaceted and individualized strategy was feasible in all 92 enrolled patients, resulting in adequate workspace for the surgeon in all cases. Seventy-eight patients fulfill criteria to be analyzed for the primary endpoint. In 61 patients (78% [CI95%: 70–89%]) the lowest IAP was 8 mmHg until the end of surgery. In the remainder 17 patients, up titration was necessary during surgery, up to IAPs between 9 and 12 mmHg (Figure 2).

The median optimized IAV of insufflated CO_2 was 3.2 [2.7–4.2] liters, or 58 [49–67] ml·kg^{-1} body weight (eFigure 1 and eFigure 2).

Relationship between IAP and ΔP_{RS}

The relationship between IAP and ΔP_{RS} was almost linear (Figure 3 and eTable 2)., every reduction in IAP of 1 mmHg resulted in a reduction in ΔP_{RS} of 0.74 cmH_2O (or 0.56 mm Hg) between 8 and 15 mmHg.

Relationship between IAP and volume of insufflated CO_2 gas

A nonlinear relationship between IAP and volume of insufflated gas was found (Figure 4). A breakpoint in the IAP/IAV at 10 mmHg (mean) was observed between 8 and 15 mm Hg IAP.

Posthoc analysis

Mainly the volume of CO_2 insufflated at 15 mm Hg of IAP during pneumoperitoneum generation and Pv0 were associated with the optimized IAV (eTable 3).

DISCUSSION

The findings of this study in patients undergoing laparoscopic colorectal surgery can be summarized as follows: (a) the tested multifaceted individualized strategy was feasible; (b) resulted in an adequate workspace throughout surgery, and (c) allows to use lower IAP than frequently selected for pneumoperitoneum in most patients. Moreover, lowering IAP resulted in (d) a substantial decrease of ΔP_{RS}; and (e) an optimized IAV close to 3 liters. Finally, (f) a decrease in abdominal compliance was identified at a mean IAP of 10 mm Hg.

This study tested the feasibility of a multifaceted and individualized intervention focusing on IAP in colorectal laparoscopic surgery. The multidisciplinary teamwork with close collaboration between surgeons and anesthesiologist allowed us to develop and perform this study. Over ten surgeons participated in this study, external validity of results was warranted provided the range of surgeons' experience in colorectal laparoscopic surgery. There have been no prior studies in which the relation between IAP and IAV was determined for each individual patient.

Since we tested a multifaceted strategy, with five different elements, it remains uncertain what exactly allowed us to reduce IAP, i.e. which one factor had the biggest impact. Previous studies tested the individual elements, but there were no investigations that combined all five items into one bundle.

The impact of ventilator settings on IAP, and vice versa has been extensively studied in the critical care setting, but not in laparoscopic abdominal surgery, in the tested strategy we deliberately choose using low tidal volume to decrease the impact on IAV [25]. One study in 20 patients under bariatric laparoscopic surgery showed that, in supine position, raising the legs to a modified lithotomy position increased the IAV generated during pneumoperitoneum, the effect being more important in Trendelenburg position [26]. Deep neuromuscular blockade throughout the surgical procedure has been compared with moderate or no blockade, studies offering inconclusive results, or marginal gains [12-16]. Seven randomized clinical trials comparing deep versus moderate neuromuscular blockade showed positive effects on surgical conditions during retroperitoneal laparoscopic procedures [17], laparoscopic donor nephrectomy [18], and laparoscopic hysterectomy [19], and a marginally positive

effect in laparoscopic cholecystectomy [20-24]. In laparoscopic cholecystectomies, the percentage of procedures finished at low IAP was 60% with deep neuromuscular blockade versus 35% with moderate neuromuscular blockade [20]. On the other hand, pre–stretching of the abdominal wall muscles has only been evaluated in animal studies, showing an increase in IAV, when insufflated at 15 mmHg, with a more important effect at lower IAP [27]. Finally, individually IAP titration has been studied in two investigations at different levels of neuromuscular blockade. In a prospective observational study in 20 patients undergoing laparoscopic cholecystectomy, deep versus no neuromuscular blockade allowed a decrease in mean IAP of 6 mm Hg (starting with 13 mmHg), but a further increase in 3 mm Hg after 15 min was necessary [28]. In a clinical trial including 61 patients undergoing colorectal laparoscopic surgery, moderate neuromuscular blockade was compared with deep neuromuscular blockade. Deep neuromuscular blockade resulted in a lower mean IAP (9 mm Hg) [29]. In our study we combined all measures into a multifaceted individualized IAP strategy, resulting in lower levels of IAP.

In recent studies, ΔP_{RS} has been shown to be independently associated with the development of postoperative pulmonary complications (PPC) in surgical patients [30]. It is known that pneumoperitoneum insufflation decreases chest wall compliance, impairing respiratory function [31,32]. Studies in animal models have further shown a 40 to 50% transmission of IAP to the intrathoracic one, and thus on ventilation pressures [33,34]. Of note, there have been no studies in humans yet, and the impact of IAP on ΔP_{RS} in the laparoscopic surgery setting remains to be explored, we tested the impact of our strategy on the resulting relationship between IAP and ΔP_{RS}. The results suggest a transmission rate of 56% at clinically relevant pressure ranges for laparoscopy (i.e., 8–15 mmHg). Although the design of a comprehensive protective ventilation strategy is beyond the scope of the present investigation, its results suggest that an individualized multifaceted strategy aimed at lowering IAP during laparoscopy could benefit patients through a lower ΔP_{RS}.

The relationship between IAP and IAV is often considered to be linear during laparoscopic surgery in the 12 to 15 mmHg range [35,36]. However, we observed a ‘breakpoint’ at IAP of 10 mm Hg. It would be interesting to identify it

to avoid IAP increases that correlate with minor or no IAV increases at all, i.e., no clinical benefit.

The present study reported the precise IAV needed to perform lower abdominal laparoscopic surgery. Our results are in line with results reported for upper abdominal bariatric laparoscopic surgery. Indeed, an IAV of 3 litres seems to be the threshold for optimal surgical conditions [26]. Being aware of the optimized IAV allows a goal directed initial insufflation of CO_2. Future CO_2 insufflators may include automatic and real-time determination of the relationship between IAP and IAV to allow better individualization of IAP throughout the entire surgical procedure.

This study has several limitations. Although the surgeons confirmed that the reasons for conversion to open surgery were independent from the tested intervention, we cannot be certain this was really the case. Of note, in none of these patient was there a request to increase the IAP. A conversion rate of ~15% is commonplace for this type of surgery [37]. We tested a bundle of measures, some of them could be standard of care, and, as mentioned above, it remains uncertain which of those factors had the biggest impact on IAP. Surgeons were blinded for the IAP but not for the patient's inclusion in the study. As dictated by the study protocol, IAP down titration stopped at 8 mmHg while in some patients a lower IAP could still have resulted in acceptable workspace for the surgeon. Again, in the patients with highest intra–abdominal volumen during pneumoperitoneum insufflation the optimized calculated Intraabdominal volumen at individualized IAP was probably higher than needed. In this real-life study with several study centers and several surgeons involved, there is a possibility of significant variability in the surgeon's comfort level with respect to available workspace, (efigure1 and efigure2). Blinded surgeons evaluate surgical conditions in a practical dichotomous manner as adequate or not depending on whether they needed any corrective action. This makes comparison with other studies as those using the Leiden–Surgical Rating Scale, difficult [17,18]. We did not use oesophageal catheters to estimate intrapleural pressures. The transpulmonary pressure ΔP, calculated from intrapleural pressures, could be more informative than the ΔP_{RS}. Besides, clinical outcomes after surgery were not evaluated.

As conclusion a multifaceted individualized pneumoperitoneum strategy was feasible and resulted in an adequate workspace for surgeons at lower IAP than usually applied during laparoscopic colorectal surgery. Furthermore, through intra-abdominal pressure optimization lower respiratory driving pressure was achieved. Benefits of the tested intervention on patient recovery and perioperative morbidity must be tested in randomized controlled trials.

References

1. Neudecker J, Sauerland S, Neugebauer E, Bergamaschi R, Bonjer HJ, Cuschieri A, Fuchs KH, Jacobi Ch, Jansen FW, Koivusalo AM, Lacy A, McMahon MJ, Millat B, Schwenk W. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc 2002; 16: 1121-43.

2. Hatipoglu S, Akbulut S, Hatipoglu F, Abdullayev R. Effect of laparoscopic abdominal surgery on splanchnic circulation: Historical developments. World J Gastroenterol 2014; 20 :18165-76.

3. Gurusamy KS, Vaughan J, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database of Systematic Reviews 2014, 3. CD006930.

4. Brokelman WJ, Lensvelt M, Borel Rinkes IH, Klinkenbijl JH, Reijnen MM. Peritoneal changes due to laparoscopic surgery. Surg Endosc 2011; 25: 1-9.

5. Maddison L, Karjagin J, Tenhunen J, Starkopf J. Moderate intra-abdominal hypertension is associated with an increased lactate-pyruvate ratio in the rectus abdominis muscle tissue: A pilot study during laparoscopic surgery. Ann Intensive Care 2012; 2 Suppl 1: S14.

6. Malbrain ML, Viaene D, Kortgen A, De Laet I, Dits H, Van Regenmortel N, Schoonheydt K, Bauer M. Relationship between intra-abdominal pressure and indocyanine green plasma disappearance rate: Hepatic perfusion may be impaired in critically ill patients with intra-abdominal hypertension. Ann Intensive Care 2012; 2 Suppl 1: S19.

7. Papparella A, Nino F, Coppola S, Noviello C, Paciello O, Papparella S. Peritoneal morphological changes due to pneumoperitoneum: The effect of intra-abdominal pressure. Eur J Pediatr Surg 2013; 24: 322-7.

8. Schwarte LA, Scheeren TW, Lorenz C, De Bruyne F, Fournell A. Moderate increase in intraabdominal pressure attenuates gastric mucosal oxygen saturation in patients undergoing laparoscopy. Anesthesiology 2004; 100: 1081-7.

9. Procter LD, Davenport DL, Bernard AC, Zwischenberger JB. General surgical operative duration is associated with increased risk-adjusted infectious complication rates and length of hospital stay. J Am Coll Surg 2010; 210: 60-5. e1-2.

10. Cheng H, Chen BP, Soleas IM, Ferko NC, Cameron CG, Hinoul P. Prolonged operative duration increases risk of surgical site infections: A systematic review. Surg Infect (Larchmt) 2017;18: 722-35.

11. Vlot J, Wijnen R, Stolker RJ, Bax K. Optimizing working space in porcine laparoscopy: CT measurement of the effects of intra-abdominal pressure. Surg Endosc 2013; 27: 1668-73.

12. Madsen MV, Staehr-Rye AK, Gätke MR, Claudius C. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: A systematic review. Acta Anaesthesiol Scand 2015; 59: 1-16.

13. Madsen MV, Staehr-Rye AK, Claudius C, Gätke MR. Is deep neuromuscular blockade beneficial in laparoscopic surgery? Yes, probably. Acta Anaesthesiol Scand 2016; 60: 710-6.

14. Kopman AF, Naguib M. Laparoscopic surgery and muscle relaxants. Anesth Analg 2015; 120: 51-8.

15. Kopman AF, Naguib M. Is deep neuromuscular block beneficial in laparoscopic surgery? No, probably not. Acta Anaesthesiol Scand 2016; 60:717-22.

16. Bruintjes MH, van Helden EV, Braat AE, Dahan A, Scheffer GJ, van Laarhoven CJ, Warlé MC. Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: A systematic review and meta-analysis. Br J Anaesth 2017; 118: 834-42.

17. Martini CH, Boon M, Bevers RF, Aarts LP, Dahan A. Evaluation of surgical conditions during laparoscopic surgery in patients with moderate vs deep neuromuscular block. Br J Anaesth 2014; 112: 498-505.

18. Özdemir-van Brunschot, A. E. Braat, M. F. P. van der Jagt, G. J. Scheffer, C. H. Martini, J. F. Langenhuijsen, R. E. Dam, V. A. Huurman, D. Lam, F. C. d'Ancona, A. Dahan, M. C. Warle.Deep neuromuscular blockade improves surgical conditions during low-pressure pneumoperitoneum laparoscopic donor nephrectomy. Surg Endosc 2018; 32: 245–51.

19. Dubois PE, Putz L, Jamart J, Marotta ML, Gourdin M, Donnez O. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: A randomised controlled trial. Eur J Anaesthesiol 2014; 31: 430-6.

20. Staehr-Rye AK, Rasmussen LS, Rosenberg J, Juul P, Lindekaer AL, Riber C, Gätke MR. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade: A randomized clinical study. Anesth Analg 2014; 119: 1084-92.

21. Madsen MV, Gätke MR, Springborg HH, Rosenberg J, Lund J, Istre O. Optimising abdominal space with deep neuromuscular blockade in gynaecologic laparoscopy--a randomised, blinded crossover study. Acta Anaesthesiol Scand 2015; 59: 441-7.

22. Barrio J, Errando CL, San Miguel G, Salas BI, Raga J, Carrión JL, García-Ramón J, Gallego J. Effect of depth of neuromuscular blockade on the abdominal space during

pneumoperitoneum establishment in laparoscopic surgery. J Clin Anesth 2016; 34: 197-203.

23. Rosenberg J, Herring WJ, Blobner M, Mulier JP, Rahe-Meyer N, Woo T, Li MK, Grobara P, Assaid CA, Fennema H, Szegedi A Deep neuromuscular blockade improves laparoscopic surgical conditions: A randomized, controlled study. Adv Ther 2017; 34: 925-36.

24. Barrio J, Errando CL, García-Ramón J, Sellés R, San Miguel G, Gallego J. Influence of depth of neuromuscular blockade on surgical conditions during low-pressure pneumoperitoneum laparoscopic cholecystectomy: A randomized blinded study. J Clin Anesth 2017; 42: 26-30.

25. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, Canet J, Fernandez-Bustamante A, Futier E, Gajic O, Hedenstierna G, Hollmann MW, Jaber S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Putensen C, Ranieri M, Scavonetto F, Schilling T, Schmid W, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators. Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis. Anesthesiology. 2015 Jul;123(1):66-78.

26. Mulier JP, Dillemans B, Van Cauwenberge S. Impact of the patient's body position on the intraabdominal workspace during laparoscopic surgery. Surg Endosc 2010; 24: 1398-402.

27. Vlot J, Wijnen R, Stolker RJ, Bax KN. Optimizing working space in laparoscopy: CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model. Surg Endosc 2014; 28: 841-6.

28. Van Wijk RM, Watts RW, Ledowski T, Trochsler M, Moran JL, Arenas GW. Deep neuromuscular block reduces intra-abdominal pressure requirements during laparoscopic cholecystectomy: A prospective observational study. Acta Anaesthesiol Scand 2015; 59: 434-40.

29. Kim MH, Lee KY, Lee KY, Min BS, Yoo YC. Maintaining optimal surgical conditions with low insufflation pressures is possible with deep neuromuscular blockade during laparoscopic colorectal surgery: A prospective, randomized, double-blind, parallel-group clinical trial. Medicine (Baltimore) 2016; 95: e2920.

30. Serpa Neto A, Hemmes SN, Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E, Hollmann MW, Jaber S, Kozian A, Licker M, Lin WQ, Moine P, Scavonetto F, Schilling T, Selmo G, Severgnini P, Sprung J, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network

investigators. Incidence of mortality and morbidity related to postoperative lung injury in patients who have undergone abdominal or thoracic surgery: a systematic review and meta-analysis. Lancet Respir Med. 2014 Dec;2(12):1007-15.

31. Cinnella G, Grasso S, Spadaro S, Rauseo M, Mirabella L, Salatto P, De Capraris A, Nappi L, Greco P, Dambrosio M. Effects of recruitment maneuver and positive end-expiratory pressure on respiratory mechanics and transpulmonary pressure during laparoscopic surgery. Anesthesiology 2013, Jan;118(1):114-22.

32. D'Antini D, Rauseo M, Grasso S, Mirabella L, Camporota L, Cotoia A, Spadaro S, Fersini A, Petta R, Menga R, Sciusco A, Dambrosio M, Cinnella G. Physiological effects of the open lung approach during laparoscopic cholecystectomy: Focus on driving pressure. Minerva Anestesiol 2018 Feb;84(2):159-167.

33. Regli A, De Keulenaer BL, Singh B, Hockings LE, Noffsinger B, van Heerden PV. The respiratory pressure-abdominal volume curve in a porcine model. Intensive Care Med Exp 2017; 5 :11.

34. Cortes-Puentes GA, Gard KE, Adams AB, Faltesek KA, Anderson CP, Dries DJ, Marini JJ. Value and limitations of transpulmonary pressure calculations during intra-abdominal hypertension. Crit Care Med 2013;41(8):1870-7.

35. Mulier, J.P., Dillemans, B.R.S., Crombach, M., Missant, C., Sels, A. On the abdominal pressure volume relationship. Internet J Anesthesiol.2009; 21: 1.

36. Malbrain ML, Peeters Y, Wise R. The neglected role of abdominal compliance in organ-organ interactions. Crit Care 2016;20(1):67.

37. Allaix ME, Furnée EJ, Mistrangelo M, Arezzo A, Morino M. Conversion of laparoscopic colorectal resection for cancer: What is the impact on short-term outcomes and survival? World J Gastroenterol. 2016 Oct 7;22(37):8304-8313.

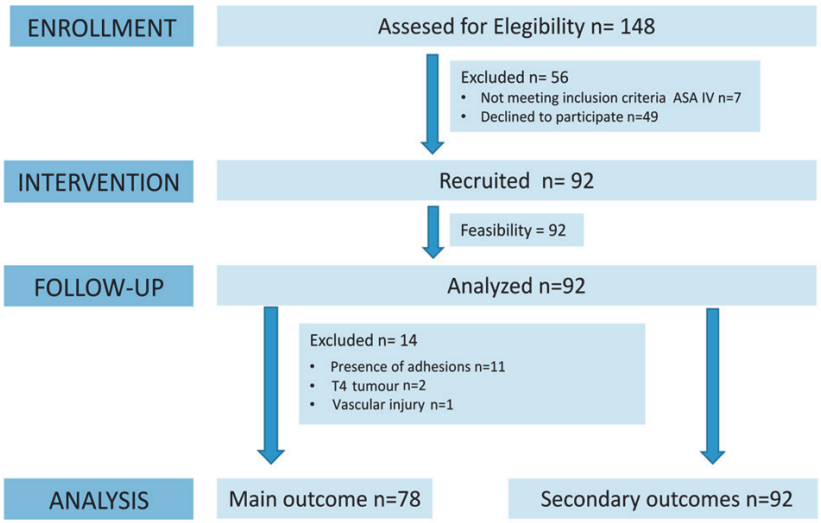


Figure 1. IPPColLapSe Flowchart.

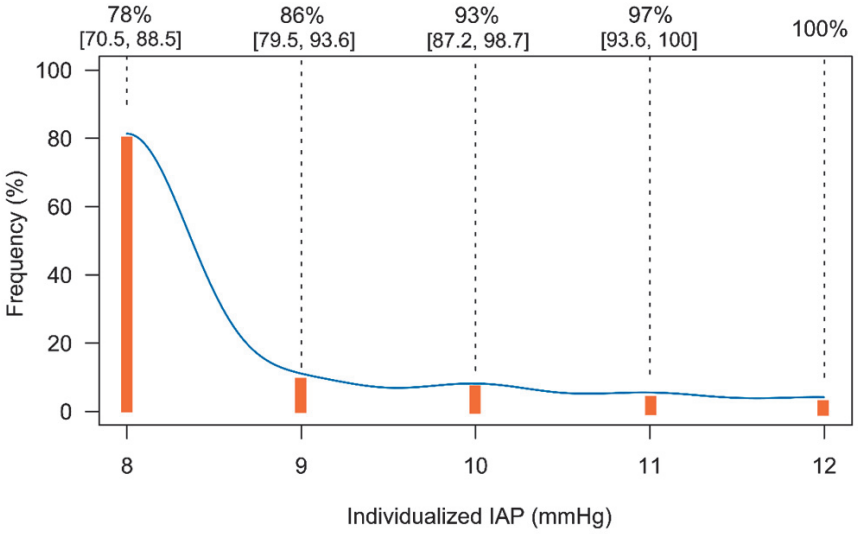


Figure 2. Proportion of surgical procedures finished at each IAP level; IAP in mmHg. Solid blue line: estimated probability density function distribution in the population for IAP. Orange columns: patients' relative frequency. Upper row: cumulative frequency and 95% CI. Data are reported for the 78 patients analyzed for primary outcome.

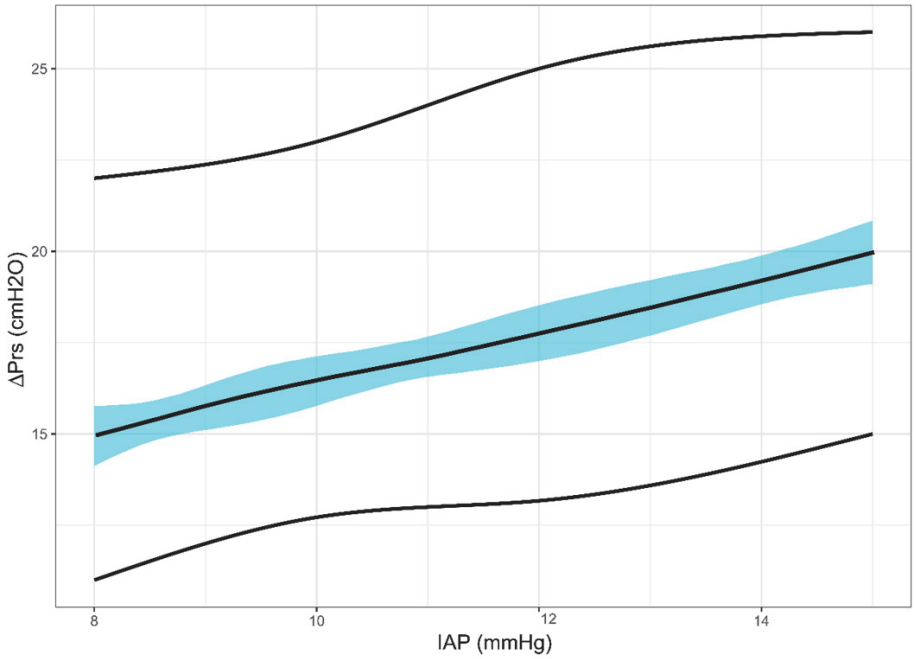


Figure 3. The relationship between (IAP) and respiratory driving pressure (ΔP_{RS}). IAP in mmHg and ΔP_{RS} in cmH_2O. Upper line 90^{th} percentile; Lower line, 10^{th} percentile; Middle line 50^{th} percentile. Blue is 95% confidence bandwidth for 50^{th} percentile. Data are reported for the 92 patients analyzed for all outcomes.

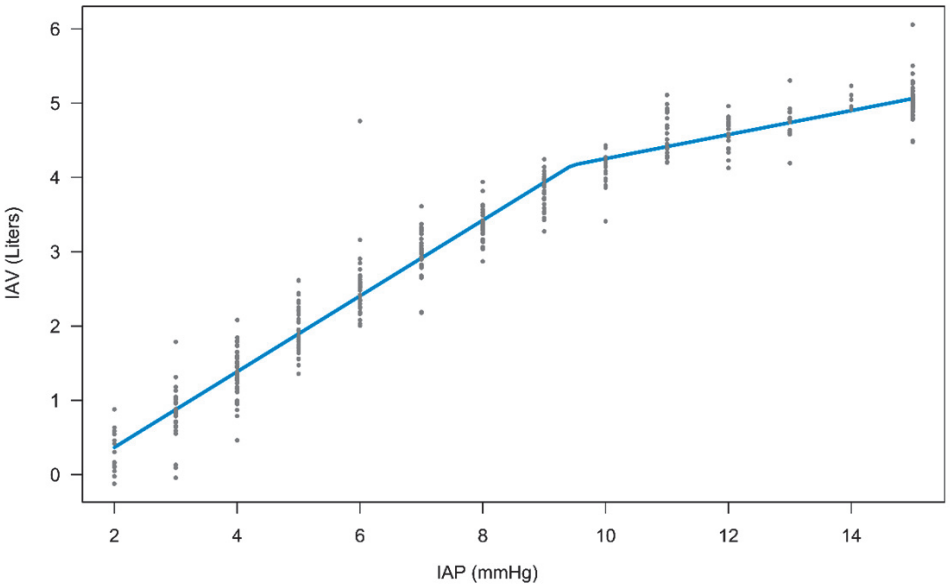
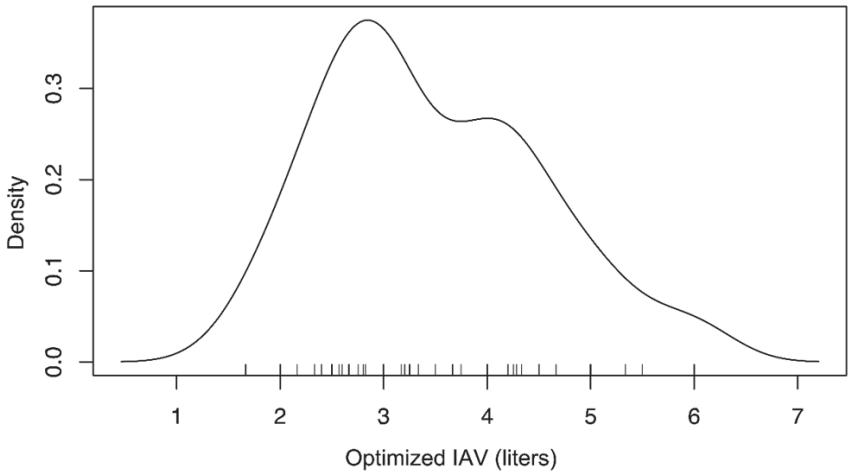


Figure 4. The relationship between IAV and IAP; IAP in mmHg, IAV in liters; Grey points: individual patient data. Data are reported for the 92 patients analyzed for all outcomes.

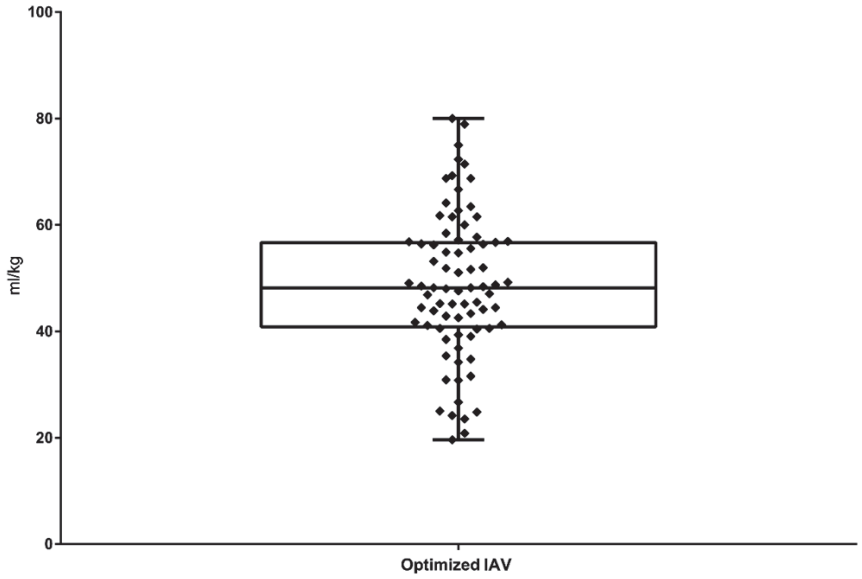
Table 1. Patients' characteristics.

	All outcomes analyzed (n = 78)	Only Secondary outcome Analyzed (n = 14)	All patients (n = 92)
Age year-old	64.1 (13.2)	68.7 (11.5)	64.8 (13.0)
Gender male/female	45/33 (58/42)	9/5 (64/36)	54/38 (59/41)
BMI Kg m $^{-2}$	26.4 (4.0)	28.6 (4.5)	26.7 (4.2)
Surgery time minutes	232 (89)	284 (79)	240 (89)
Hospital Marañón/La Fe/Castellón	5/49/24 (6/63/31)	0/11/3 (0/79/21)	5/60/27 (5/65/30)
ASA I/II/III	10/54/14 (13/69/18)	1/10/3 (7/71/21)	11/64/17 (12/70/18)
Previous laparoscopic surgery 0/1/2/3/4	64/12/1/1 (82/16/1/1)	10/3/0/1 (72/21/7)	73/14/1/1/1 (81/16/1/1)
Previous pregnancies 0/1/2/3/4/5/6	58/7/5/5/1/1/1 (74/9/7/7/1/1/1)	9/1/3/1/0/0/0 (64/7/21/8/0/0)	67/8/8/6/1/1/1 (73/9/9/6/1/1/1)
Scheduled surgery (n = 77)			
Right hemicolectomy	40 (52)	8 (57)	48 (53)
Left hemicolectomy	9 (12)	2 (14)	11 (12)
Sigmoidectomy	15 (18)	3 (21)	17 (19)
Rectum anterior resection	9 (12)	0 (0)	9 (10)
Total colectomy	2 (3)	1 (7)	3 (3)
Ileocecal resection	2 (3)	0 (0)	2 (2)
Terminal colostomy	1 (1)	0 (0)	1 (1)
Oncologic surgery (Yes/No)	68/10 (87/13)	14/0 (100/0)	82/10 (89/11)
Hospital Length of Stay Days	6 [5 – 8]	6 [6 – 8]	6 [5 – 8]

Data as mean (SD), number (%) or median [25th–75th percentile]. BMI, Body mass index; ASA, American Society of Anesthesiologists physical status.



eFigure 1 Optimized IAV distribution. Intra-abdominal volume (IAV) reported in liters. Vertical lines: individual patient data Data are reported for the 78 patients analyzed for primary outcome.



eFigure 2. Optimized intraabdominal volume (IAV) distribution in ml kg-1. Optimized IAV is the estimated volume at individualized intraabdominal pressure. Data are reported for the 78 patients analyzed for primary outcome.

eTable1. Surgeons' experience

	All outcomes analyzed (n = 78)	**Only Secondary outcome Analyzed (n = 14)**	**All patients (n = 92)**
Number of cases performed per month	9 (1.5)	9 (1.6)	9 (1.6)
Years of experience in laparoscopic surgery	12 [2 – 15]	11 [2 – 15]	12 [2 – 15]
Experience with low intra–abdominal pressure Yes/no	47/31 (60/40)	8/6 (57/43)	55/37 (60/40)

Data are reported as mean (SD), number (%) or median [minimum–maximum]. Data are reported for the 92 patients analyzed for all outcomes.

eTable2. Multivariate analysis ΔP_{RS} / IAP relationship

	Estimate	**Std. Error**	**Lower 95%**	**Upper 95%**	**P-value**
(Intercept)	1.643	1.795	-2.334	5.452	0.36
IAP	0.741	0.109	0.554	0.92	<0.001
Age	0.067	0.018	0.034	0.121	<0.001
BMI	0.349	0.061	0.22	0.445	<0.001
AIC	2772.442				

IAP (intraabdominal pressure) in mmHg, ΔP_{RS} in cmH2O, Age in years, BMI (Body mass index) in Kg/m^{-2}. Data are reported for the 92 patients analysed for all outcomes.

eTable 3. Model multivariate analysis for optimized IAV

	Estimate	Std. Error	Lower 95%	Upper 95%	P-value
(Intercept)	1.243	0.659	0.015	2.471	0.064
Gender	-0.38	0.215	-0.78	0.02	0.081
Age	0.006	0.006	-0.006	0.017	0.361
BMI	-0.034	0.023	-0.076	0.008	0.133
Pregnancies	0.076	0.078	-0.068	0.221	0.329
PrevAbdSurg	-0.123	0.129	-0.363	0.116	0.342
Type of surgery	0.045	0.058	-0.063	0.153	0.442
IAV15	0.623	0.074	0.485	0.761	<0.001
pv0	-0.13	0.06	-0.242	-0.018	0.034
AIC	198.69				
Surgeon (Intercept)	0				
Residual	0.654				

Optimized IAV (volume values at optimized intra-abdominal pressure). Gender (male/female), Body mass index (BMI), Age in years, pregnancies (number of pregnancies), PrevAbdSurg (Previous abdominal laparoscopic or open surgeries), type of surgery, IAV15 (intraabdominal volume reached at an intra-abdominal pressure of 15 mmHg during initial insufflation) and Pv0 (estimated intra-abdominal pressure at zero volume). Data are reported for the 78 patients analyzed for primary outcome.

Capítulo 3

An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study.

Díaz-Cambronero O, *Mazzinari G, Errando CL, Schultz MJ, Flor Lorente B, García-Gregorio N, Vila Montañés M, Robles-Hernández D, Olmedilla Arnal LE, Martín-DePablos A, Marqués Marí A, Argente Navarro MP, for the IPPCollapse-II study group.*

Trials. 2019 *Apr 3;20(1):190.*
doi: 10.1186/s13063-019-3255-1. PMID: 30944044
Q1 IF 2.00

Correction to: An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study.

Díaz-Cambronero O, *Mazzinari G, Errando CL, Schultz MJ, Lorente BF, García-Gregorio N, Montañés MV, Robles-Hernández D, Arnal LEO, Martín-De-Pablos A, Marí AM, Navarro MPA*

Trials. 2020 *Jan 13;21(1):70.*
doi: 10.1186/s13063-020-4055-3. PMID: 31931888
Q1 IF 2.00

Background

Compared to open surgery, laparoscopic surgery generally results in better outcomes. (1,2) Compared to open abdominal surgery, a laparoscopic approach during abdominal surgery is associated with less blood loss and fewer needs for blood transfusions,(3,4) faster recovery of bowel function and oral intake resumption,(5,6) less analgesics requirements,(6,7) and shorter length of hospital stay (LOS).(3–8) Patient reported outcomes (PROs) are new tools for testing quality of recovery in the postoperative seeting and Post operative quality of recovery scale (PQRS) has been successfully tested in previous studies.

A high intraoperative intra–abdominal pressures (IAPs) is clearly associated with perioperative morbidity.(9–14) While guidelines for laparoscopic abdominal surgery recommend the lowest possible IAP at which the surgeon has adequate workspace rather than using a predetermined level,(15,16) it remains common practice to use a standard IAP level throughout the surgical procedure, usually between 12 and 15 mm Hg and sometimes even higher depending on surgical indication.(17) Interestingly, while the surgical condition depends mainly on the intra–abdominal volume (IAV) and the workspace obtained at a given IAP, the focus during pneumoperitoneum insufflation remains with the applied IAP.(18)

Several factors improve the relation between IAP and the obtained surgical workspace, including patient positioning,(19) use of neuromuscular blockade,(20,21) and pre–stretching of the abdominal wall.(22) The preceding ‘Individualized Pneumoperitoneum Pressure in Colorectal Laparoscopic Surgery’ (IPPColLapSe) I study shows that combining all these factors with individualized IAP titration resulted in an acceptable working space at 8 mmHg IAP in 61 out of 78 patients (78%).(23) The here presented ‘IPPCollapse II’ study tests the hypothesis that this individualized pneumoperitoneum pressure strategy improves PQRS when compared to a conventional strategy that uses a fixed pneumoperitoneum pressure approach in patients undergoing scheduled colorectal laparoscopic surgical intervention.

Methods/Design

Study reporting

This report follows the 'Standard Protocol Items: Recommendations for Interventional Trials and Patient–Reported Outcomes' (SPIRIT–PRO) guidelines. (24,25) Online IPPCollapse II SPIRIT checklist.

Study design

The IPPCollapse II study is a multicentre two–arm parallel–group single–blinded randomized clinical study (Figure 1).

Study setting

The IPPCollapse II study runs in the operating room and surgical wards of four academic hospitals in Spain (OnlineTable 1).

Study population

Patients are eligible for participation if (a) scheduled for laparoscopic colorectal surgery; (b) aged > 18 years; (c) have an American Society of Anaesthesiologists (ASA) physical status I to III; and (d) have no cognitive deficits. Exclusion criteria are: (a) no written informed consent; (b) emergency or unplanned surgery; (c) pregnancy or breastfeeding; (d) immunologic or neuromuscular diseases; (e) advanced stage of cardiopulmonary, renal or hepatic disease; and (f) allergy to or contraindications for rocuronium or sugammadex.

Randomization and blinding

Patients are randomized in a 1:1 ratio to an individualized pneumoperitoneum pressure strategy (the intervention group) or a standard pneumoperitoneum pressure strategy (the control group). Local investigators perform randomisation using a web–based automated randomization system (Biostatistics Unit of the Health Research Institute la Fe, Valencia, Spain).

Randomisation is performed with random block sizes and is stratified per centre. While attending anaesthesiologists are aware of the assigned pneumoperitoneum pressure strategy, patients and attending surgeons remain unaware of the assigned pneumoperitoneum pressure strategy at all times. PQRS is a patient reported outcome where the care provider has little room for causing bias even unwillingly. Patient is actually blinded to the treatment arm. Pneumoperitoneum insufflator screen is covered by a surgical drap. Study team member, who are not blinded to randomization, perform postoperative PQRS measurements.

Standard pneumoperitoneum pressure strategy

The standard strategy consists of the following elements, to be performed in the same order in all patients in the control group: (a) patients are placed in a position according to the surgeon's preference within a predefined range of Trendelemburg (0–30°); (b) patients receive moderate neuromuscular blockade with rocuronium, cisatracurium or atracurium throughout surgery to maintain a train–of–four (TOF) between 2 and 4; and (c) IAP is set at 12 mm Hg throughout surgery. At any time, surgeons can request for an IAP increase if workspace becomes 'inadequate'; in that case IAP is increased in steps of 1 mm Hg during 1–minute intervals to a maximum of 15 mm Hg, but not higher than the level at which the surgical workspace returns to become 'adequate'. Surgeons will be warned if the IAP reaches the predefined upper limit. Neuromuscular blockade pharmacological reversion is achieved with neostigmine (2.5 mg or 30–50 μg·kg-1), according to usual care.

Individualized pneumoperitoneum pressure strategy

The multifaceted individualized pneumoperitoneum strategy consists of the following elements, that will be performed in the same order in all patients in the intervention group: (1) patient position is modified to increase the anteroposterior intra–abdominal space by correcting lumbar lordosis (2) patients receive deep neuromuscular blockade throughout surgery to maintain a (TOF) of 0 and a Post–Tetanic Count (PTC) between 1 and 5; (3) the abdominal wall and muscles are pre–stretched by maintaining an IAP of 15 mm Hg for 5 minutes during the first CO2 gas insufflation and insertion of trocars (to achieve this the CO2 gas insufflator will be initially set at 15 mm Hg with a flow rate of 3 L·min-1); and (4) individualized IAP titration when the patient is placed in the surgical position (0–30º Trendelenburg); for this, the flow rate is increased to 30 L·min-1 and IAP is decreased from 15 to 12 mmHg, and thereafter stepwise to 11, 10, 9 and finally 8 mm Hg as long as the attending surgeon keeps 'adequate' workspace. As in the standard pneumoperitoneum pressure group surgeons can request an IAP increase up to 15 mm Hg which will be performed likewise. Of note, the pressure increment is available in both groups with the same methodology, a previous feasibility study showed that pressure increase is seldom needed (17 out of 78 need limited increase during pelvic dissection). (23)

Neuromuscular blockade pharmacological reversion at the end of surgery, before tracheal extubation, is achieved with sugammadex 4 mg·kg-1.

For clarity, the elements of the two groups strategies compared are summarized in Table 1.

Standard care

Perioperative management other than the pneumoperitoneum strategy is suggested to follow the Spanish Enhanced Recovery Pathway recommendations (detailed in onlineTable 2) (26). Continuous intraoperative neuromuscular monitoring with acceleromyography (TOF–Watch–SX™, Organon–Teknika, Oss, The Netherlands) is used. At the end of surgery neuromuscular blockade will be fully reversed to a TOF ratio (TOFr) of at least 0.9 before tracheal extubation. An electronic CO2 insufflator (Endoflator™, Karl Storz, Tuttlingen, Germany) will be used for gas insufflation into the abdominal cavity through a paraumbilical–placed laparoscopic trocar/Veress needle.

Patients in both groups will be ventilated in a volume controlled ventilation mode, using a tidal volume of 8 ml/kg predicted ideal body weight, with a 20% inspiratory pause time, and positive end–expiratory pressure set at 5 or 10 mm Hg, in patients with a body mass index (BMI) < 30 or ≥ 30 kg·m-2, respectively. Oxygen inspiratory fraction is 0.8 throughout surgery. Respiratory rate is set at 12 to 15 per minute to maintain normal end–tidal CO2 values (27).

Primary outcome

The primary outcome is the Post–operative Quality of Recovery Scale (PQRS) at postoperative day 1 (POD1) (see below for details).

Secondary outcomes

Secondary outcomes include PQRS at 15 minutes (T15) and at 40 minutes (T40) after arrival in the Post Anaesthesia Care Unit (PACU), and in the surgical wards during the morning at postoperative day 3 (POD3). Other secondary clinical outcomes include daily postoperative complications until hospital discharge, and at postoperative day 28, hospital length of stay and secondary process–related outcomes that include the highest IAP level and intra–abdominal volume (IAV) at which surgery could be performed, hepatic perfusion during pneumoperitoneum, and the ventilatory parameters plateau pressure and driving pressure.

Occurrences of diaphragm and abdominal wall contractions or spontaneous breathing efforts and coughing during surgery are collected and compared between the two study groups.

Substudies

The IPPCollapse II study has three substudies (please see Protocol supplementary content for additional details):

1. Levels of biomarkers (neutrophil–lymphocyte ratio, C–reactive protein, Interleukin 6, and procalcitonin) are measured in peripheral venous blood samples obtained before surgery and at POD1 and POD 3 and compared between the two study groups. For this substudy, blood samples are obtained in all participating centres.
2. Untargeted metabolomics analysis is performed of peripheral venous blood samples and peritoneal tissue, both obtained after initial insufflation of pneumoperitoneum and at the end of the procedure. This substudy includes the first 10 patients in the Hospital Universitari i Politecnic La Fe, Valencia, Spain.
3. Plasma disappearance rate of indocyanine green (PDRICG) after intravenous ICG injection, to evaluate hepatic perfusion during pneumoperitoneum as a marker of liver function. (28) This substudy runs only at the University Hospital Gregorio Marañon, Madrid, Spain.

Post–operative Quality of Recovery Scale

PQRS is a validated multi–dimensional Patient–Reported Outcomes (PROs)–tool,(29–31) designed to assess patients' recovery to baseline status in the postoperative period (www.postopqrs.com). In every patient a baseline measurement of PQRS is performed prior to surgery. After surgery, the measurement of PQRS is repeated at 15 minutes (T15) and at 40 minutes (T40) after arrival in the Post Anaesthesia Care Unit (PACU), as well as in the ward in the morning of postoperative day 1 (POD1) and 3 (POD3). PQRS is a verbal survey tool that depicts recovery in the following 5 domains: physiologic, nociceptive, emotive, functional, cognitive, and also collects overall patient perspective. Each of these domains is assessed with multiple items on an ordinal scale and compared with baseline to evaluate recovery (see Table 2 for details). Recovery is a dichotomized outcome defined by a return to at least baseline values or better at each of the postoperative measurement time points.

Overall recovery requires recovery in all domains being assessed, and failure in any domain results in failure of overall recovery.

Definitions

IAP will be recorded as read from the gas insufflator device. In the intervention group the 'individualized IAP' is defined as the highest IAP needed to obtain and maintain an adequate workspace until completion of surgery. IAV is calculated by linear interpolation from patient's IAP–IAV curve obtained during initial pneumoperitoneum insufflation matching to IAP at which surgery is performed.

'Adequate' workspace is defined as the intra–abdominal workspace sufficient to perform the surgical procedure with no need for corrective manoeuvres (i.e., IAP increase) as judged by the attending surgeon who remains blinded for the actual IAP. Consequently, 'inadequate' workspace is defined as the intra–abdominal workspace insufficient to perform the surgical procedure with the need for corrective manoeuvres (i.e., IAP increase).

Definitions of the various postoperative complications recorded are according to the current European standards for perioperative outcomes (Table 3). (32) Severity of postoperative complications is evaluated using Clavien–Dindo grading (Table 4).(33)

Respiratory system driving pressure (ΔPrs) is calculated by subtracting PEEP from Pplat. (34)

Perioperative safety issues are recorded during the surgery and are related to involuntary patient movements, and defined as diaphragm or abdominal wall contractions, or spontaneous breathing efforts or coughing during anaesthesia.

Hospital length of stay is defined as hospital discharge date minus hospital admission date.

Data to be collected

Before anaesthesia: demographic data including age (years), gender, body height (cm) and body weight (kg), BMI (kg.m-2), ASA physical status score; comorbidities; number of previous abdominal surgeries and number of previous laparoscopic surgeries; PQRS.

During anaesthesia: levels of IAPs at which surgery is performed (mmHg) in both groups; proportion of patients that needed a pressure increment

to achieve acceptable surgical workspace; IAV at start of pneumoperitoneum (litres); coughing and spontaneous movements (yes/no); type of surgery and oncologic status; duration of surgery (minutes), duration of anaesthesia (minutes); proportion of patient that needed conversion from laparoscopic to open surgery and the reason for it (only if applicable); ventilation data including PEEP (cm H2O), plateau pressure (cm H2O), respiratory driving pressure (ΔPrs,) (cm H2O) before pneumoperitoneum generation and during initial IAP titration until a stable level of IAP is reached in both groups; type and dose of neuromuscular blocking agent (mg); type and dose of neuromuscular blocking reversal agent (mg); total opioid requirement during the first 24 hours if used (mg); and plasma disappearance rate of indocyanine green (PDRICG) in the stable pneumoperitoneum phase.

Directly after anaesthesia, in the PACU: PQRS at 15 and 40 minutes after PACU admission and on Postoperative day 1 and 3: PQRS in the morning and peripheral venous blood samples are obtained for determination levels of biomarkers.

All postoperative days till hospital discharge and at day 28: occurrence of postoperative complications and location.

Analysis plan

The statistical analysis plan (SAP) is specified before enrolment of the first patient. In the absence of studies assessing differences in recovery, based on intraoperative IAP management during laparoscopic colorectal surgery, we performedthe sample size calculation assuming an odds ratio of 2.65 (equivalent to a difference of 0.5 units in the logit scale) between groups in the physiologic PQRS recovery scale, it was estimated that a sample size of 170 patients is required to achieve 80% power at a significance level of alpha = 0.05. All reasons for dropouts, expected to be as low as 10%, will be collected and reported. Conversion to open surgery was the main reason for drop out in previous study. We will recruit a total of 190 patients to compensate for potential losses.

All analysis will be performed with R software (R Foundation for Statistical Computing, Vienna, Austria). Data will be expressed as the mean (SD) or median [IQR] for continuous variables depending on their distribution (normality will be checked with Shapiro–Wilks test), and by counts and

proportions for categorical variables. The 95% confidence intervals will be calculated for each of the estimated percentiles. Statistical significance level will be set at $P < 0.05$.

The analysis of the primary endpoint follows the intention–to–treat principle. The difference between the PQRS score between groups, primary outcome on POD1, will be assessed by mixed ordinal logistic regression introducing the patient as random factor, and age, weight, BMI and sex as covariables.

The differences in Clavien–Dindo grading of postoperative complications will be assessed by ordinal regression.

For IAV calculation the relationship between IAP and the insufflated volume of CO2 will be determined for each patient during initial pneumoperitoneum insufflation. The relationship between IAP and IAV was analysed by linear interpolation from the individual IAP/IAV curves to determine the actual IAV at which surgery is performed. The IAP before CO2 gas insufflation was considered the basal IAP or intra–abdominal pressure at volume zero, and was estimated by fitting multiadaptive linear regression splines to intraabdominal volume and pressure relationship.

Differences in continuous variables between groups (IAP, IAV, LOS, inflammatory biomarkers) will be assessed by linear regression or with Mann–Whitney U test (if normal distribution assumption rejected by Shapiro-Wilks test).

Differences in ΔPrs between groups will be assessed by linear regression. A multivariable model introducing BMI, previous laparoscopic surgery and age, will be fitted for predictive purposes.

Differences in the plasma disappearance rate of ICG are assessed by beta regression.

The occurrence of cough or spontaneous movements during anaesthesia are assessed by logistic regression.

The relationship between IAP and IAV will analysed by linear interpolation from the individual IAP/IAV curves. The IAP before CO2 gas insufflation (IAP at volume zero) will be estimated by fitting multi–adaptive linear regression splines to intra-abdominal volume and pressure relationship. If a

variable has a frequency of missing data > 5% data will be imputed by the multiple imputation method.

As there is no ethically unacceptable risk related to the primary outcome analyzed there will be no planned interim analysis.

Adverse events

The investigator record in the CRF any adverse event (AE, serious, SAE or non-serious, nSAE) that occurs in a patient in the clinical trial, related to the study medication or not, (including the observational period, and before and after treatment). The AE will be followed up by the investigator and documented in the CRF up to 28 days after the end of the treatment period. All AEs (except those identified as not requiring immediate notification by the study protocol) will be notified within 24 hours to the Steering committee of the investigator becoming aware of the SAE.

Auditing

Site may be subject to audits, IEC/IRB review, and regulatory inspection(s). Local investigators will provide direct access to the source data documents (See Additional file 4 content for full detail).

Ethics and dissemination

The study will be carried out according to a protocol reviewed and approved at a national level by the Institutional Review Board (IRB) of Hospital Universitari I Politécnic la Fe, Valencia, Spain, and Agencia Española del Medicamento y Productos sanitarios (AEMPS). The study has been registered at clinicaltrials.gov (identifier: NCT02773173, May 16, 2016) and EudraCT (2016–001693–15), and is conducted in accordance with the Declaration of Helsinki on ethical principles for medical research in human subjects, adopted by the General Assembly of the World Medical Association (1996). Data management, monitoring and reporting of the study is performed in accordance with the International Conference on Harmonization – Good Clinical Practice guidelines (ICH) (CPMP/ICH/135/95) and the regulatory requirements for participating institutions by Spanish Clinical Research Network (SCReN). Investigators collect a written informed consent form in compliance with the GCP recommendations to the patient or his/her legal representative if his/her clinical conditions do not allow him to review and approve it. Investigators provide a copy of the signed informed consent form to each subject and keep a copy in

the subject's study file. This study protocol is reported following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Patient–Reported Outcomes (SPIRIT–PRO) guidelines (24)(25).

The results of the study will be communicated through the portal of European Medicine Agency and will be sent for publication in a peer–reviewed medical journal. Authorship will be based on International committee of medical journal editors (ICMJE) criteria. No professional writer will be involved. After publication of the primary results, upon request, the pooled dataset will be available for all members of the IPPColLapSe II study group for secondary analysis, after judgment and approval of scientific quality and validity of the proposed analysis by the Steering Committee. Access to source data will be made available through national or international anonymized datasets upon request and after agreement of the IPPColLapSe II steering committee.

Discussion

This study is the first randomized clinical study that tests the hypothesis that an individualized pneumoperitoneum pressure strategy focusing on using the lowest possible IAP, compared to a conventional pneumoperitoneum pressure strategy, improves recovery after laparoscopic colorectal surgery. This study uses PQRS as well as the occurrence of postoperative complications until postoperative day 28, and hospital length of stay. Furthermore, we assess process–related outcomes like IAP and IAV during pneumoperitoneum, and associated ventilator parameters. A strong multidisciplinary commitment between members of the perioperative team, consisting of surgeons and anesthesiologists, makes this complex study feasible.

The IPPColLapSe II study has several strengths. Its prospective design will allow high accuracy of data to be collected, and its sample size allows us to draw valid conclusions. Selection of patient–reported outcomes as the primary outcome of this study facilitate the translation into clinical practice. To the best of our knowledge this is the first multicentre randomized clinical study evaluating the clinical effect of a tailored IAP management. Surgeon will remain blinded for the IAP allowing us to titrate the IAP to the lowest possible level, i.e., the level at which surgeons have adequate working space. Furthermore, we aim

to describe the relationship between IAP and actual IAV at which surgery is performed. This could lead, on one hand, to gather evidence towards establishing a volume threshold (e.g. actual workspace) for colorectal laparoscopic to replace the standard pressure threshold, and on the other, to describe the abdominal pressure–volume relationship in a first attempt to achieve something similar to our understanding of lung dynamics during ventilation. Additionally, we link directly the respiratory system and abdomen by assessing IAP and respiratory driving pressure relationship. This could lead to make a step further as far as protective ventilation in the operating room in concerned.

The here proposed study differs from previous studies on this topic. Most studies so far evaluated the individual components of the multifaceted strategy and are largely focused on surgical conditions and not patient–centred outcomes. Besides they just find minor gains from abdominal pre-stretching, or patient positioning optimization and offer inconclusive results or marginally positive effect for the level of neuromuscular blockade. (35–45) Two studies find useful IAP titration in decreasing conventional IAP management, but do not focus on clinical outcomes (46,47).

From our knowledge, only one study so far focused on quality of recovery, using the QoR–40, a 40–item questionnaire on quality of recovery from anaesthesia (36). This study, comparing surgery at low IAP (6 mm Hg) versus standard IAP (12 mm Hg) during laparoscopic donor nephrectomy under deep neuromuscular blockade, found no differences in QoR–40. Of note, in this study surgeons were not blinded for the IAP and in 25% of patients surgery had to be converted to the standard pressure, probably due to surgeon's learning curve. We recently performed the IPPColLapSe I study in which we evaluated feasibility of the intervention that is to be tested in the present study (23). The intervention was found to be safe, highly feasible and resulted in an acceptable working space at low IAP in most patients. We did not look at patient outcomes in the preceding study.

PQRS has been successfully tested in previous studies to evaluate differences in recovery.(48-51) We acknowledge that finding differences in patient reported outcomes by PQRS modifying a single strategy in a high quality environment could be difficult (52–54). In order to evaluate minor differences in

recovery mainly in laboratory data we perform three substudies. Levels of biomarkers (neutrophil–lymphocyte ratio, C–reactive protein, Interleukin 6, and procalcitonin) in the postoperative recovery period are linked to immunosuppression and postoperative complications.(55,56) Metabolomics untargeted intraoperative analysis of blood samples and peritoneum biopsies allow us to depicted differences between groups in the intraoperative and generate hypothesis for new studies. Plasma disappearance rate of indocyanine green (PDRICG) has been used successfully to evaluate hepatic perfusion in critically ill patients with intra-abdominal hypertension (28) and could draw differences in hepatic perfusion during pneumoperitoneum in this study.

This study has limitations. We exclude ASA IV patients that could benefit more from working with low IAP: Since we test a multifaceted strategy it will remain uncertain which part of the strategy will have the largest impact. In fact, it could be that not all parts have the same magnitude of effect, and it could even be that some parts have no effect at all. Of note, reversal of neuromuscular blockade with sugammadex instead of neostigmine could improve PQRS recovery at T40 although not at POD1 or POD3. Surgeons, blinded for the actual IAP, will evaluate surgical conditions in a practical dichotomous manner as adequate or not, depending on whether any corrective action is needed. This way of measurement might difficult comparisons with other studies, as those using the Leiden–Surgical Rating Scale. The investigators performing PQRS evaluation are not blinded for the intervention, creating a risk of detection bias. Nevertheless, this risk is somewhat attenuated by the fact that as with PRO by design, the ultimate outcome assessor is the patient which is kept blind to the intervention. We calculated the sample size of our study on PQRS differences thus our sample could be underpowered for some secondary outcome that can potentially require a larger sample. In conclusion IPPColLapSe II study is designed to test if an individualized pneumoperitoneum pressure and optimized management versus conventional care affects outcome of patients undergoing colorectal laparoscopic surgery using relevant patient-centred outcomes.

References

1.Trastulli S, Cirocchi R, Listorti C, et al. Laparoscopic vs open resection for rectal cancer: A meta-analysis of randomized clinical trials. Colorectal Dis. 2012;14:277–96.

2.Van Vugt JLA, Reisinger KW, Derikx JPM, et al. Improving the outcomes in oncological colorectal surgery. World J Gastroenterol. 2014;20:12445–57.

3.Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: A randomised trial. Lancet. 2002;359:2224–9.

4.Clinical Outcomes of Surgical Therapy Study Group, Nelson H, Sargent D, Wieand H, et al. A Comparison of Laparoscopically Assisted and Open Colectomy for Colon Cancer. N Engl J Med. 2004;350:2050–9.

5.Guillou P, Quirke P, Thorpe H, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial):multicentre, randomised controlled trial. Lancet. 2005; May 14-20;365:1718-26.

6.Veldkamp R, Kuhry E, Hop W, et al. Laparoscopic surgery versus open surgery for colon cancer: Short-term outcomes of a randomised trial. Lancet Oncol. 2005;6:477–84.

7.Kang SB, Park JW, Jeong SY, et al. Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): Short-term outcomes of an open-label randomised controlled trial. Lancet Oncol. 2010;11:637–45.

8.Braga M, Frasson M, Vignali A, et al. Laparoscopic resection in rectal cancer patients: Outcome and cost-benefit analysis. Dis Colon Rectum. 2007;50:464–71.

9.Maddison L, Karjagin J, Tenhunen J, et al. Moderate intra-abdominal hypertension is associated with an increased lactate-pyruvate ratio in the rectus abdominis muscle tissue: A pilot study during laparoscopic surgery. Ann Intensive Care 2012; 2 (Suppl 1): S14.

10.Matsuzaki S, Jardon K, Maleysson E, et al. Impact of intraperitoneal pressure of a CO2 pneumoperitoneum on the surgical peritoneal environment. Hum Reprod. 2012;27(6):1613–23.

11.Sammour T, Mittal a., Loveday BPT, et al. Systematic review of oxidative stress associated with pneumoperitoneum. Br J Surg. 2009;96:836–50.

12.Brokelman WJA, Lensvelt M, Rinkes IHMB, et al. Peritoneal changes due to laparoscopic surgery. Surg Endosc. 2011;25:1–9.

13.Schwarte LA, Scheeren TWL, Lorenz C, et al. Moderate Increase in Intraabdominal Pressure Attenuates Gastric Mucosal Oxygen Saturation in Patients Undergoing Laparoscopy. Anesthesiology. 2004;100:1081–7.

14.Barczyński M, Herman RM. A prospective randomized trial on comparison of low-pressure (LP) and standard-pressure (SP) pneumoperitoneum for laparoscopic cholecystectomy. Surg Endosc. 2003;17:533–8.

15.Neudecker J, Sauerland S, Neugebauer E, et al. The European Association for Endoscopic Surgery clinical practice guideline on the pneumoperitoneum for laparoscopic surgery. Surg Endosc. 2002;16:1121–43.

16.Hatipoglu S, Akbulut S, Hatipoglu F, et al. Effect of laparoscopic abdominal surgery on splanchnic circulation: Historical developments. World J Gastroenterol. 2014;20:18165–76.

17.Jones O, Lindsey I, Cunningham C. Laparoscopic colorectal surgery. Br Med J. 2014;32:197–203.

18.Vlot J, Wijnen R, Stolker RJ, et al. Optimizing working space in porcine laparoscopy: CT measurement of the effects of intra-abdominal pressure. Surg Endosc. 2013;27:1668–73.

19.Mulier JPJ, Dillemans B, Van Cauwenberge S. Impact of the patient's body position on the intraabdominal workspace during laparoscopic surgery. Surg Endosc . 2010;24:1398–402.

20.Madsen M V., Staehr-Rye AK, Gätke MR, et al. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: A systematic review. Acta Anaesthesiol Scand. 2015;59:1–16.

21.Bruintjes MH, Van Helden E V., Braat AE, et al. Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: A systematic review and meta-analysis. Br J Anaesth. 2017;118:834–42.

22.Vlot J, Wijnen R, Stolker RJ, et al. Optimizing working space in laparoscopy: CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model. Surg Endosc. 2014;28:841–6.

23.Diaz-Cambronero, O., Flor Lorente, B., Mazzinari, G. et al. A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study. Surg Endosc (2018). https://doi.org/10.1007/s00464-018-6305-y (Online first)

24.Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:1–42.

25.Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols the spirit-pro extension. J Am Med Assoc. 2018;319:483–94.

26.Ministerio de Sanidad SS e IA de C de la S. ViaClinica-RICA. 2018. Report No.: NIPO: 680-15-085-5. Date accessed March 2018.

Online:http://portal.guiasalud.es/contenidos/iframes/documentos/opbe/2015-07/ViaClinica-RICA.pdf

27.Serpa Neto A, Hemmes SNT, Barbars CS V, et al. Protective versus Conventional Ventilation for Surgery: A systematic review and Patient Data Meta-Analysis. Anesthesiology. 2015;123:66–78.

28.Malbrain MLNG, Viaene D, Kortgen A, et al. Relationship between intra-abdominal pressure and indocyanine green plasma disappearance rate: Hepatic perfusion may be impaired in critically ill patients with intra-abdominal hypertension. Ann Intensive Care. 2012;2012(Suppl 1):S19.

29.Royse F C, Newman S, Chung F, et al. Development and Feasibility of a Scale to Assess Postoperative Recovery. Anesthesiology. 2010;113:892–905.

30.Bowyer A, Jakobsson J, Ljungqvist O, et al. A review of the scope and measurement of postoperative quality of recovery. Anaesthesia. 2014;69:1266–78.

31.Royse CF, Saager L, Whitlock R, et al. Impact of Methylprednisolone on Postoperative Quality of Recovery and Delirium in the Steroids in Cardiac Surgery Trial: A Randomized, Double-blind, Placebo-controlled Substudy. Anesthesiology. 2017;126:223–33.

32.Jammer I, Wickboldt N, Sander M, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. Eur J Anaesthesiol. 2015;32:88–105.

33.Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13.

34.Neto AS, Hemmes SNT, Barbas CSV, et al. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: A meta-analysis of individual patient data. Lancet Respir Med. 2016;4:272–80.

35.Madsen M V., Gätke MR, Springborg HH, et al. Optimising abdominal space with deep neuromuscular blockade in gynaecologic laparoscopy-A randomised, blinded crossover study. Acta Anaesthesiol Scand. 2015;59:441–7.

36.Özdemir-van Brunschot DMD, Scheffer GJ, van der Jagt M, et al. Quality of Recovery After Low-Pressure Laparoscopic Donor Nephrectomy Facilitated by Deep Neuromuscular Blockade: A Randomized Controlled Study. World J Surg. 2017;41:2950–8.

37.Özdemir-van Brunschot DM, E Braat BA, et al. Deep neuromuscular blockade improves surgical conditions during low-pressure pneumoperitoneum laparoscopic donor nephrectomy. Surg Endosc. 2018;32:245–51.

38.Staehr-Rye AK, Rasmussen LS, Rosenberg J, et al. Surgical space conditions during low-pressure laparoscopic cholecystectomy with deep versus moderate neuromuscular blockade: A randomized clinical study. Anesth Analg. 2014;119:1084–92.

39.Barrio J, Errando CL, García-Ramón J, et al. Influence of depth of neuromuscular blockade on surgical conditions during low-pressure pneumoperitoneum laparoscopic cholecystectomy: A randomized blinded study. J Clin Anesth. 2017;42:26–30.

40.Barrio J, Errando CL, San Miguel G, et al. Effect of depth of neuromuscular blockade on the abdominal space during pneumoperitoneum establishment in laparoscopic surgery. J Clin Anesth. 2016;34:197–203.

41.Dubois PE, Putz L, Jamart J, et al. Deep neuromuscular block improves surgical conditions during laparoscopic hysterectomy: A randomised controlled trial. Eur J Anaesthesiol. 2014;31:430–6.

42.Rosenberg J, Herring WJ, Blobner M, et al. Deep Neuromuscular Blockade Improves Laparoscopic Surgical Conditions: A Randomized, Controlled Study. Adv Ther. 2017;34:925–36.

43.Madsen M V., Staehr-Rye AK, Claudius C, et al. Is deep neuromuscular blockade beneficial in laparoscopic surgery? Yes, probably. Acta Anaesthesiol Scand. 2016;60:710–6.

44.Kopman AF, Naguib M. Is deep neuromuscular block beneficial in laparoscopic surgery? No, probably not. Acta Anaesthesiol Scand. 2016;60:717–22.

45.Kopman AF, Naguib M. Laparoscopic surgery and muscle relaxants: Is deep block helpful? Anesth Analg. 2015;120:51–8.

46.Van Wijk RM, Watts RW, Ledowski T, et al. Deep neuromuscular block reduces intra-abdominal pressure requirements during laparoscopic cholecystectomy: A prospective observational study. Acta Anaesthesiol Scand. 2015;59:434–40.

47.Kim MH, Lee KY, Lee KY, et al. Maintaining optimal surgical conditions with low insufflation pressures is possible with deep neuromuscular blockade during laparoscopic colorectal surgery: A prospective, randomized, double-blind, parallel-group clinical trial. Med . 2016;95:1–7.

48.Abola RE, Bennett-Guerrero E, Kent ML, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Patient-Reported Outcomes in an Enhanced Recovery Pathway. Anesth Analg .2017 Dec 29. doi: 10.1213/ANE.0000000000002758. [Epub ahead of print]

49.Myles PS, Boney O, Botti M, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. Br J Anaesth. 2018;12:705–11.

50.Bowyer A, Royse CF. The future of postoperative quality of recovery assessment: Multidimensional, dichotomous, and directed to individualize care to patients after surgery. Curr Opin Anaesthesiol. 2016;29:683–90.

51.Royse CF, Williams Z, Ye G, et al. Knee surgery recovery: Post-operative Quality of Recovery Scale comparison of age and complexity of surgery. Acta Anaesthesiol Scand. 2014;58:660–7.

52.Ansari BM, Hogan MP, Collier TJ, et al. A Randomized Controlled Trial of High-Flow Nasal Oxygen (Optiflow) as Part of an Enhanced Recovery Program After Lung Resection Surgery. Ann Thorac Surg . 2016;10:459–64.

53.Poitras S, Wood KS, Savard J, et al. Assessing functional recovery shortly after knee or hip arthroplasty: A comparison of the clinimetric properties of four tools. BMC Musculoskelet Disord . 2016;17:1–9.

54.Pérez Herrero MA, López Álvarez S, Fadrique Fuentes A, et al. Calidad de la recuperación posquirúrgica tras cirugía de mama. Anestesia general combinada con bloqueo paravertebral versus bloqueo del espacio serrato-intercostal. Rev Esp Anestesiol Reanim. 2016;63:564–71.

55.Ni Eochagain A, Burns D, Buggy DJ. Effect of anaesthetic technique during primary breast cancer surgery on neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, and time of commencement of intended oncologic therapy: a follow-up analysis of a prospective randomised trial. Anaesthesia 2018 Feb 19. doi: 10.1111/anae.14207. [Epub ahead of print]

56.Garcia-Granero A, Frasson M, Flor-Lorente B, et al. Procalcitonin and C-reactive protein as early predictors of anastomotic leak in colorectal surgery: A prospective observational study. Dis Colon Rectum. 2013;56:475–83.

	STUDY PERIOD							
	ENROLMENT	ALLOCATION	POST ALLOCATION					CLOSE OUT
Timepoints	Preanaesthetic visit	Prior to surgery	Intraoperative evaluation	Postoperative evaluation	POD1 evaluation	POD 3 evaluation	Hospital Discharge evaluation	POD28
ENROLMENT:								
Informed consent	+							
Eligibility screen	+							
Inclusion /exclusion criteria	+							
Demographic data	+							
Comorbidities	+							
Allocation		+						
ASSESSMENTS:								
PQRS baseline		+						
PQRS T15/T40				+				
PQRS POD 1					+			
PQRS POD 3						+		
Blood sample					+	+		
Abdominal compliance data			+					
Airway pressures			+					
PDRicg (HUGMarañon)			+					
Metabolomics sampling (HUiPlaFe)			+					
Pain evaluation VAS					+			
Complications Clavier-Dindo							+	+
Adverse events							+	+

PQRS: Postoperative Quality Recovery Scale. POD: Postoperative Day. VAS: Visual Analogic Scale. PDRicg: Plasma disappearance rate indocyanin green. PACU Post Anaesthesia Care Unit T15. 15 minutes in PACU. T40. 40 minutes in PACU. HUGMarañon. University Hospital Gregorio Marañon. HUiPlaFe. University and Polytechnic Hospital la Fe.

Figure 1. Study time-points.

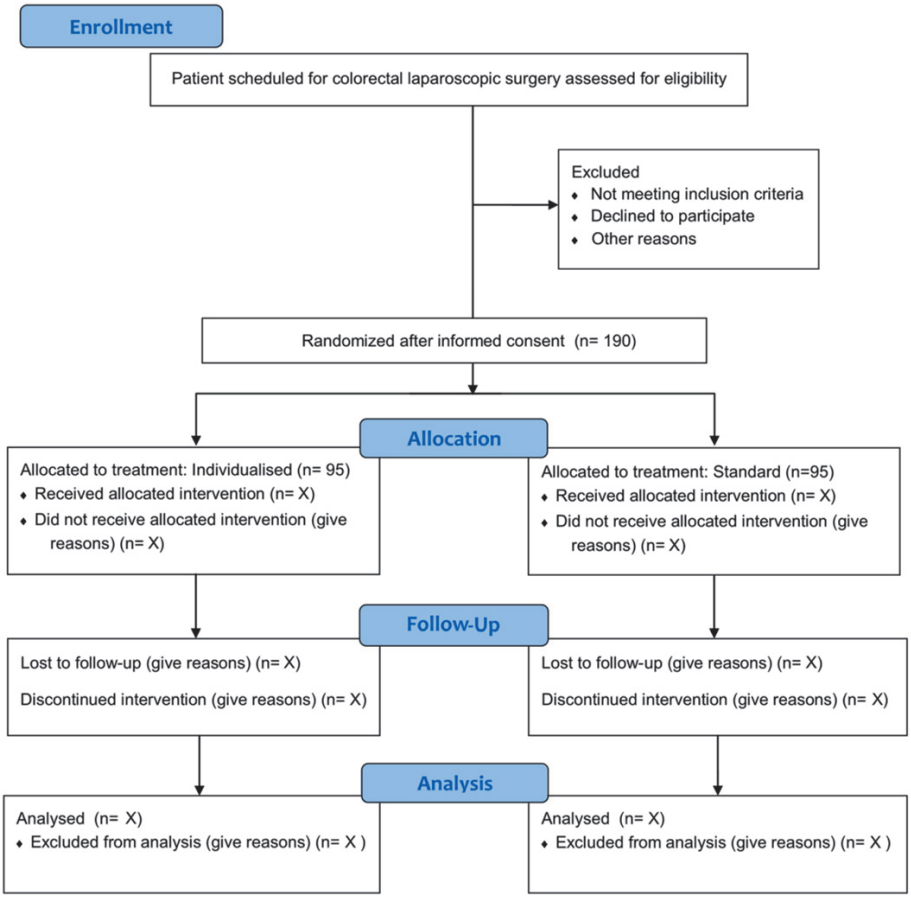


Figure 2. IPPCollapse II flowchart.

Table 1. Collaborating centres in the IPPCOLLAPSE II study, and expected number of patients recruited	
Hospital	**Number of patients expected to be recruited (n)**
Hospital Universitari I Politecnic la Fe, *Valencia*, Spain	100
Hospital General Universitario, *Castellon*, Spain	30
Hospital General Universitario Gregorio Marañon, *Madrid*, Spain	30
Hospital Universitario Virgen Macarena, *Sevilla*, Spain	30

Table 2. Postoperative Quality of Recovery Scale (PQRS).

Domain	Variable	Score	Baseline	T15	T40	POD1	POD3
Physiologic	Blood pressure	1-3	+	+	+	+	+
Physiologic	Heart rate	1-3	+	+	+	+	+
Physiologic	Temperature	1-3	+	+	+	+	+
Physiologic	Respiration	1-3	+	+	+	+	+
Physiologic	SpO2	1-3	+	+	+	+	+
Physiologic	Airway	1-3	+	+	+	+	+
Physiologic	Agitation	1-3	+	+	+	+	+
Physiologic	Consciousness	1-3	+	+	+	+	+
Physiologic	Activity on command	1-3	+	+	+	+	+
Nociceptive	Pain	1-5 Likert	+	+	+	+	+
Nociceptive	PONV	1-5 Likert	+	+	+	+	+
Emotional	Sadness/Depression	1-5 Likert	+	+	+	+	+
Emotional	Anxiety/Nervousness	1-5 Likert	+	+	+	+	+
Functional	Stand	1-3	+	-	-	+	+
Functional	Walk	1-3	+	-	-	+	+
Functional	Eat/drink	1-3	+	-	-	+	+
Functional	Get dressed	1-3	+	-	-	+	+
Cognitive	Name, city and DOB	TF 0	+	-	-	+	+
Cognitive	Numbers forward	TF 2	+	-	-	+	+
Cognitive	Numbers backwards	TF 1	+	-	-	+	+
Cognitive	Word task: list	TF 3	+	-	-	+	+
Cognitive	Executive memory	TF 3	+	-	-	+	+

Online scale to assess multiple domains of post-operative recovery over time. Timeline: **T15** - 15 minutes in PACU; **T 40**- 40 minutes in PACU; **POD1**- Postoperative day 1; **POD3** - postoperative day 3. **PONV**: Postoperative Nausea and Vomiting. **DOB**: Date of birth. **Scoring**: Physiologic 1-3; Nociceptive/emotional: 1–5 Likert rating scale using a faces pictorial display; Functional: Scored as 3: easily, 2: difficulty, and 1: not at all; Cognitive: Performance variability tolerance factor (TF) is applied. Participants not included in subsequent analysis if baseline scores are equal to or less than the tolerance factor.

Table 3. Classification of post-operative complications
1. Acute kidney damage.
2. Acute respiratory distress syndrome (ARDS)
3. Suture dehiscence
4. Arrhythmia
5. Cardiac arrest
6. Cardiogenic pulmonary edema
7. Deep vein thrombosis
8. Postoperative delirium
9. Gastrointestinal bleeding
10. Infection
11. Bacteremia
12. Myocardial infarction.
13. Myocardial injury after non-cardiac surgery
14. Pneumonia
15. Paralytic ileus
16. Post-operative hemorrhage
17. Pulmonary embolism
18. Cerebrovascular accident
19. Infection of surgical wound (superficial)
20. Infection of surgical wound (deep)
21. Infection of surgical (organ) wound
22. Urinary tract infection
Postoperative pulmonary complications:
1. Respiratory infection
2. Respiratory failure
3. Pleural effusion
4. Atelectasis
5. Pneumothorax
6. Bronchospasm
7. Pneumonia due to aspiration
Postoperative complications recorded according to the current European standards for perioperative outcomes

Table 4. Severity grade by Clavien-Dindo definition.	
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetic, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.
Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit CNS: Central Nervous system	

Suplemento Capítulo 3

Published as online supplement and as a correction to the original protocol

SPIRIT checklist for IPPCollapse II study

		Reporting Item	Page
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	#3	Date and version identifier	2
Funding	#4	Sources and types of financial, material, and other support	2
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1,35
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	2
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18-21
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	11-12
Objectives	#7	Specific objectives or hypotheses	6-8
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, table 1
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening	8-14

		disease)	
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8-14
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9-10
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 5
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16-19
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	16-19
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8-9
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8-9
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8-9
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8-9
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18-21
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18-21
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18-21
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18-21
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-19

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-19
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-19
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	19-20
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	18-21
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-21
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20-21
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	18-21
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18-21
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	18-21
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18-21
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18-21
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18-21
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	21
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a just in spanish
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if	14-16

		applicable	

Enhanced Recovery Pathways Spanish guidelines summary RICA (Intensive recovery in abdominal surgery)		
TIME	**PROTOCOL**	**PROFESSIONAL**
Before hospitalization	Preoperatory evaluation, nutritional optimization, cardiologic test if it is indicated.	Surgeon + Anaesthesiologist
Immediate preoperative (without previous hospitalization)	Thromboembolic prophylaxis (12 h before surgery). Preoperative solid fast 6 hours and clear liquid fast 2 hours. In colon surgery is not indicated bowel mechanical preparation (reserve to rectum surgery)	Surgeon + Anaesthesiologist + Nurse
Perioperative	**Previous surgery** Cleaning enema at 7 am (colorectal surgery) Compression tights or intermittent pneumatics socks for thromboembolic prophylaxis. Carbohydrate 12,5% maltodextrins drinks 250cc 2 hours before surgery. Antibiotic prophylaxis 1 hour before incision. **Intraoperative** Insertion epidural catheter in laparotomy surgery Anaesthesia induction Oxygenation FiO2 60-80% Active warming with air convection blanket Goal directed fluid therapy Balanced solution (laparoscopy 3,5ml/Kg/h) Minimal invasive surgery (when it is possible) Avoid nasogastric tube Nauseas and vomits prophylaxis using Apfel scale. Local anaesthesia in laparoscopic access vs Abdominal Transverse Block. Bladder catheter **Immediate postoperative** Maintenance active warming. FiO2 50% at least 2 hours. Restrictive fluid therapy Oral tolerance 6 hours after surgery Early mobilization Thromboembolic prophylaxis with Enoxaparin 40mg at 10pm. Reduce as minimal opioid administration	Surgeon + Anaesthesiologist + Nurse
POD1	Diet depends on tolerance Active mobilisation (sitting) Intravenous analgesia Consider withdraw bladder catheter Consider withdraw abdominal drains. Nutritional supplements	Nurse + Surgeon + Anaesthesiologist
POD2	Normal diet Active mobilisation (start ambulation) Thromboembolic prophylaxis	Nurse + Surgeon + Anaesthesiologist
Postoperative until hospital discharge	Normal diet Oral analgesia Active mobilisation Thromboembolic prophylaxis	Nurse + Surgeon + Anaesthesiologist
Home	Thromboembolic prophylaxis until POD28 Phone contact Ambulatory support	

Additional protocol details

1. Sample processing, preparation and analysis. Protocol for substudies of IPPCollapse–II.

Sample processing

Blood samples for the level of biomarkers are collected according to usual clinical practice in each collaborating centre and analysed by its respective reference laboratory.

Blood samples for metabolomics analysis are collected prior to anesthesia induction, immediately after pneumoperitoneum generation and at the end of the laparoscopic procedure. Samples consisting of 5 ml of blood are extracted from a peripheral venous access in a heparin anticoagulant tube, and identified with the patient's identification number and sample number. Samples are kept at 4ºC before being transferred to the metabolomics unit within the hospital within 2 hours. The samples are centrifuged for 10 minutes at 1300 rpm and 4ºC. After centrifugation, 400uL plasma is aliquoted and stored at –80º C.

Peritoneal tissue samples for metabolomics analysis are collected following the same methodology at baseline after pneumoperitoneum generation and at the end of the laparoscopic procedure. Samples are identified with the patient's identification number and sample number and kept in liquid nitrogen tank located in the surgical unit until analysis.

Sample preparation

For the procedure of the plasma samples, once thawed, the proteins will be precipitated by using three volumes of organic solvent, centrifugation (3500 rpm), collecting the supernatant and transferring it to a chromatographic vial for analysis.

The treatment of the tissue samples will be carried out by homogenization with methanol in Precellys homogenizer at 4 ° C using two cycles of 25s at a speed of 6500rpm with intervals of 10 s. After centrifugation of the extract, the supernatant will be concentrated and redissolved in the ideal solution for subsequent chromatographic analysis.

LC-QToF Analysis

The metabolomics analysis will be carried out by means of a chromatographic separation using the UPLC (ultra performance liquid chromatography)

chromatographic system available in the Analytical Unit and a Acquity UPLC HSS T3 type chromatographic column (100 x 2.1 mm, 1.8 µm) from Waters (Wexford, Ireland) or similar. The detection will be carried out by means of a mass spectrometer with time of flight analyser, 6550 QTOF Agilent, available in the Analytical Unit and ideal for "untargeted" approaches. The data in TOF MS full scan mode will be recorded from 50 to 1000 m / z (mass / load ratio) with a scan time of 0.1 s. A LockSpray interface will be used to maintain mass accuracy during the analysis.

The treatment of the samples, as well as the acquisition of data will be carried out under BPL regulations (good laboratory practices), which guarantees the quality and traceability of the results obtained.

Data analysis

The metabolomics comparative analysis between the different samples (data matrices) will require a processing of the data before its analysis, normally an alignment and a normalization. A chemometric approach will be applied, based on PACA and PLSDA models, for the selection of informative and discriminant variables (metabolites) that facilitate the marker selection process. Once the list of possible markers is configured, an unsupervised hierarchical analysis will be carried out in order to check their discriminatory capacity and subsequently they will be identified by consulting databases (HMDB, KEGG), MS / MS spectra and / or injection. of standards.

2. Details on study logistics and data management

Study organization

The principle investigator (Diaz-Cambronero) and the two investigators involved in the initial design of IPPColLapSe II study (Mazzinari and Errando) form the Steering Committee. Local main investigators are responsible for identifying and recruiting participating patients in each centre. They will assist and train local investigators and oversee conduct of the study, including administrative management, record keeping and data management. Local investigators at individual participating centres will provide scientific and structural leadership, ensuring local ethical and regulatory approvals are obtained before patient inclusion starts. The sponsor guarantees the quality and security of the data collected.

Prior to the start of the study, the teams in each centre will receive a training session on how to capture data in the electronic Case Report Form (eCRF). All team members will be provided with a manual of operations with instructions on how to accurately fill the forms and the screening log.

Data management

Data will be collected from the patient paper/electronic medical chart and recorded on paper CRF and successively transcribed into an electronic CRF (eCRF) at a later time point. Local investigators transcribe the collected data directly onto an anonymized internet–based eCRF (http://remote.iislafe.san.gva.es/ippcollapse/). Access to the data–entry system is protected by a personalized username and password. To optimize the quality of the data, the implemented eCRF automatically cross–check the entries and check for abnormal or erroneous values in data.

The data will be kept on a central secured server located at the Hospital Universitari i Politecnic la Fe, Valencia, Spain. Personal information will be protected as dictated by the Spanish Personal Data Protection Law (Ley Orgánica 15/1999 de Protección de Datos de Carácter Personal).

Data monitoring

Data managing, monitoring, and study reports will be done by independent monitors from the Spanish Clinical Research Network (SCReN; https://www.scren.es) as per the ICH-GCP Guidelines (CPMP/ICH/135/95). Monitoring activities will be conducted to ensure the protection of the rights and well–being of the participants in the clinical trial, to ensure that the data recorded are precise, complete and verifiable from the source documentation and that the conduct of the trial is done in accordance with the current approved version of the protocol and modifications in effect, with the GCPs, SOPs and any other applicable regulations. Sponsor's monitors will guarantee that all parts involved in the trial receive training in the specific protocol procedures, that adverse events and follow–up are adequately reported, that the CRFs are completed on time, and that any major deviations from the protocol are identified and reported without delay. The frequency and proportion of parameter verifications will be performed at each centre in accordance with what is established in the Monitoring Plan. All monitoring activities, including

initiation, follow–up and close out visits will be documented in accordance with the Sponsor's procedures.

Correction to the original protocol.

Published in Trials 2020; 21:70

After the publication of the original article [1], the authors have notified us that there are changes in the primary outcome and the statistical analysis plan of the study. These changes were made after the recruitment of participants and after approval by the Institutional Review Board, and registration at clinicaltrials.gov (study identifier), but before cleaning and closing of the database.

The Postoperative Quality of Recovery Scale (PQRS), an outcome used in the IPPCollapse II study, is a five–dimensional ordinal scale designed to estimate patients' recovery in the postoperative period [2]. Each patient is scored at predefined time points and is classified as either 'recovered' if the score reaches at least the predetermined baseline score or 'not recovered' if otherwise. The five dimensions are then combined in an 'overall score' – a patient is classified as 'overall recovered' if 'recovered' in *every* domain and as 'overall not recovered' if 'not recovered' in *any* of the five domains.

Outcome variables that are repeatedly assessed over time in the same study patients are to be treated as 'repeated measures' or 'longitudinal data' [3]. Common statistical techniques applied on cross-sectional data assume independence between observations [4]. This crucial assumption is not fulfilled by 'repeated measures' or 'longitudinal data'. Ignoring this correlation can lead to biased estimates, invalid P values and confidence intervals, as well as loss of statistical power [5,6].

We incorrectly detailed how the PQRS score was to be analysed. We suggested to treat the scores at the four different time points as individual outcomes. From hindsight we feel that this approach does not consider the conceptual underlying model (i.e., between patients' variability) and the temporal design. Furthermore we also imperfectly reported our primary outcome since we did not specified which domain of the scale was analyzed as primary endpoint although we did report which one we used (i.e. physiologic score) in the sample size calculation. We therefore changed the primary and secondary outcomes as follows:

1. The primary outcome of the IPPCollapse II study is the recovery of the 'physiologic' component of the PQRS score over the assessed time points;
2. The other domains, i.e., the 'nociceptive', 'emotional', 'cognitive', and 'functional' components, as well as the 'overall score' are used as secondary outcomes;
3. Association between group assignment and recovery of PQRS score in each domain is assessed by a mixed logistic regression, introducing patients as random factors, and age, weight, BMI and sex as covariables;
4. The originally reported analysis (i.e. ordinal regression) is still carried out, however only as a sensitivity analysis.

References

1.Diaz-Cambronero O, Mazzinari G, Errando CL, Schultz MJ, Flor Lorente B, García-Gregorio N, et al. An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: Rationale and study protocol for a multicentre randomised clinical study. Trials. 2019;20(1):1–13.

2.Royse CF, Newman S, Chung F, Stygall J, McKay RE, Boldt J, et al. Development and feasibility of a scale to assess postoperative recovery : The post-operative quality recovery scale. Anesthesiology. 2010;113(4):892–905.

3.Schober P, Vetter TR. Repeated Measures Designs and Analysis of Longitudinal Data: If at First You Do Not Succeed—Try, Try Again. Anesth Analg. 2018 Aug;127:569-575.

4.Verbeke G, Fieuw S, and Molenberghs G, Davidian M. The analysis of multivariate longitudinal data: A review. Stat Methods Med Res. 2014; 23: 42–59.

5.Ma Y, Mazumdar M, Memtsoudis SG. Beyond Repeated-Measures Analysis of Variance Data in Anesthesia Research. Reg Anesth Pain Med. 2012;37:99–105.

6.Windt J, Ardern CL, Gabbett TJ, Khan KM, Cook CE, Sporer BC, et al. Getting the most out of intensive longitudinal data: A methodological review of workload-injury studies. BMJ Open. 2018;8:1–17.

Capítulo 4

Effect of an Individualized vs Standard Pneumoperitoneum Pressure Strategy on Postoperative Recovery – a randomized clinical trial in laparoscopic colorectal surgery.

***Diaz-Cambronero,O**, Mazzinari G, Flor Lorente B, Robles-Hernández D, Olmedilla Arnal LE, Martín-DePablos A, Schultz MJ, Errando CL, Argente Navarro MP, for the IPPCollapse-II study group.*

***Br J Surg. 2020** Nov;107(12):1605-1614.*
doi: 10.1002/bjs.11736. Epub 2020 Jun 7. PMID: 32506481
Q1 IF 5.02

Author response to: Comment on: Effect of an individualized versus standard pneumoperitoneum pressure strategy on postoperative recovery: a randomized clinical trial in laparoscopic colorectal surgery.

Díaz-Cambronero O.

***Br J Surg. 2020** Nov;107(12): e630-e631.*
doi: 10.1002/bjs.11932. Epub 2020 Sep 21. PMID: 32964433
Q1 IF 5.02

Introduction

While it is recommended to use the lowest possible intra–abdominal pressure (IAP) during laparoscopic surgery at which an acceptable surgical workspace is maintained[1], it is common practice to use a 'fixed' and usually high IAP level[2]. Indeed, IAP is frequently set between 12 and 15 mmHg, and even higher depending on the surgeon's preference[3]. An increase in IAP during pneumoperitoneum for laparoscopic surgery may cause inflammation and injury of the peritoneal mesothelium[4,5]. A low IAP leads to less postoperative pain[6], but definitive evidence for the benefit of a low IAP during pneumoperitoneum concerning other patient–centred outcomes remains lacking.

Patient positioning[7], use of deep neuromuscular blockade[8,9], intraoperative ventilation with a low tidal volume[10], and pre–stretching of the abdominal wall[11] all help to improve the relationship between IAP and intra–abdominal volume (IAV). Combining these measures results in an adequate working space at lower IAP in most patients[12]. The current study aimed to assess if a recently developed individualised pneumoperitoneum pressure (IPP) strategy, that uses all above–mentioned measures, improves patient–centred outcomes. It was hypothesized that use of an IPP strategy, compared with the use of a standard pneumoperitoneum (SPP) strategy, leads to faster patient recovery.

Methods

Study design

The 'Individualized Pneumoperitoneum Pressure in Colorectal Laparoscopic Surgery versus Standard Therapy II study' (IPPCollapse II) is a double–blind two–arm parallel–group multicentre randomised clinical trial performed at four university–affiliated hospitals in Spain. The Institutional Review Board of the Hospital Universitario y Politécnico la Fe in Valencia, Spain, approved the study protocol as well as a subsequent modification of the protocol concerning extension of recruitment. The study protocol, and study conduct was in compliance with the Helsinki Declaration and Spanish legislation for biomedical research. Written informed consent was obtained from all subjects before entering the trial. The study was registered before patient enrolment at EudraCT

(study identifier: 2016–001693–15) and clinicaltrials.gov (study identifier NCT03435913), and the study protocol was prepublished[13] and updated[14].

Inclusion and exclusion criteria

Patients were eligible if: (1) scheduled for laparoscopic colorectal surgery, (2) aged > 18 years, (3) with an American Society of Anesthesiologists (ASA) physical status < IV, and (d) without cognitive deficits. Exclusion criteria included: (1) absence of written informed consent; (2) emergency or unplanned surgery; (3) pregnancy or breastfeeding; (4) immunologic or neuromuscular diseases; (5) advanced stage of cardiopulmonary, renal or hepatic disease; and (6) allergy to or contraindications for rocuronium or sugammadex.

Randomisation and blinding

Patients were randomised in a 1:1 fashion to the IPP strategy or the SPP strategy. Local investigators performed randomisation using a web–based automated randomisation system. Randomisation was performed with random block sizes and stratified per centre. While attending anaesthesiologists were aware of group assignment, the attending surgeons as well as the patients remained unaware of assignment at all times, i.e., before, during and after surgery.

Details of the two IAP strategies

The IPP strategy has been described before in detail[12]. In short, this strategy consists of (i.) 'modified lithotomy position', with flexed hips (between 45 and 90°) and raised legs in padded supports to increase the anteroposterior intra–abdominal space by correcting lumbar lordosis; (ii.) deep neuromuscular blockade throughout surgery to maintain a train–of–four (TOF) count of 0 and a post–tetanic count (PTC) between 1 and 5 both assessed with acceleromyography at the thumb; (iii.) pre–stretching of the abdominal wall muscles by maintaining an IAP of 15 mmHg for five minutes at the beginning of CO_2 insufflation and insertion of abdominal trocars; (iv.) IAP titration from 15 to 12 mmHg, and stepwise to 11, 10, 9 and finally 8 mmHg as long as the attending surgeon keeps an 'adequate' workspace after the patient was placed in a 0–30° Trendelenburg position; and (v.) neuromuscular blockade reversal at the end of surgery, before tracheal extubation, with sugammadex 4 $mg \cdot kg^{-1}$.

The SPP strategy consists of (i.) patient positioning according to the surgeon's preference in the Trendelenburg position (0–30°); (ii.) moderate

neuromuscular blockade with rocuronium, cisatracurium or atracurium throughout surgery to maintain a TOF count between 2 and 4; (iii.) IAP set at 12 mmHg throughout surgery; and (iv.) neuromuscular blockade reversal, according to usual care with neostigmine (2.5 mg or 30–50 $\mu g \cdot kg^{-1}$).

The two IAP strategies are further detailed in the Supplementary Digital Content eTable 1. With both IAP strategies, the surgeon could request for an increase in IAP if the workspace became 'inadequate'. This was done in steps of 1 mmHg during 1–minute intervals until the workspace became 'adequate', but never higher than 15 mmHg at which surgeons were warned that the upper IAP limit was reached.

Standard care

In both groups, intraoperative ventilation consisted of volume–controlled ventilation, using a tidal volume of 8 $ml \cdot kg^{-1}$ of predicted ideal body weight, with a 20% inspiratory pause time, and a positive end–expiratory pressure (PEEP) set at 5 or 10 cm H_2O in patients with a body mass index (BMI) of < 30 or ≥ 30 $kg \cdot m^{-2}$, respectively. Respiratory rate was set between 12 and 15 breaths per minute to maintain normal end–tidal CO_2 values. Perioperative analgesia management included the use of intravenous opioids and non–steroidal anti–inflammatory drugs, and CO_2 insufflation was performed with a standard commercial gas that was neither heated nor humidified. Other aspects of perioperative management were to follow where possible the recommendations of the Spanish 'Enhanced Recovery After Surgery' guidelines (the full guidelines are in Supplementary Digital Content).

Measurements and definitions

The 'Post–operative Quality of Recovery Scale' (PQRS), used for the primary endpoint, is a verbal survey tool that assesses recovery in the following five domains: physiologic, nociceptive, emotive, functional, cognitive, and also collects overall patient perspective[15]. Each of these domains is assessed with multiple items on an ordinal scale and compared with baseline to evaluate recovery (detailed in Supplementary Digital Content eTable 2). A baseline PQRS was obtained before surgery. After surgery, the PQRS was obtained at 15 min (T15) and 40 min (T40) after arrival in the PACU, and in the ward in the morning of the first and third postoperative day (POD1 and POD3). We anticipated patients to stay within the hospital of surgery for at least 3 days,

based on local experiences. If hospital discharge would happen before day 3, it was planned to censor data from the moment of the last follow–up within the hospital of surgery. 'Recovery' is a dichotomised outcome defined by a return to at least baseline value or better. 'Overall recovery' requires recovery in all domains, i.e., failure in any domain means a lack of 'overall recovery'.

Intraoperative adverse events (AEs) were involuntary patient movements, like diaphragm or abdominal wall contractions, and spontaneous breathing efforts or coughing. Postoperative complications definitions were in accordance with the current European standards for perioperative outcomes (for details see Supplementary Digital Content eTable 3). To evaluate the severity of postoperative complications we used the Clavien–Dindo grading (for details see Supplementary Digital Content eTable 4).

Blood samples were obtained on the POD1 and POD3 follow up visits for PQRS assessment. Plasma samples were analysed for the neutrophil–lymphocyte ratio (NLR) and C–reactive protein (CRP) level at the central laboratory in participating hospitals with particle-enhanced immunoturbidimetry.
In the IPP group, the 'individualised IAP' was the highest IAP needed to obtain and maintain an adequate workspace until completion of surgery. 'Adequate' workspace was defined as an intra–abdominal workspace sufficient to perform the surgical procedure with no need for an increase in IAP, as judged by the attending surgeon. 'Inadequate' workspace was defined as an intra–abdominal workspace insufficient to perform the surgical procedure.

Endpoints

The primary endpoint was the PQRS for the physiologic domain[15,16]. Secondary outcomes included the PQRS for nociceptive, emotive, cognitive recovery and activity of daily life, and the overall PQRS, and occurrence of intraoperative and postoperative complications, hospital length of stay, and course of plasma markers of inflammation up to postoperative day three.

Power calculation and modification

In the absence of studies that used PQRS in the setting of intraoperative IAP management during laparoscopic surgery, we performed a sample size calculation assuming an odds ratio (OR) of 2.65 between groups in the recovery of physiologic PQRS score, which is equivalent to a difference of 0.5 unit in the

logit scale. A sample size of 170 patients was required to achieve 80% power at an alpha of 5%, with a dropout rate of 20%.

During the conduct of the study it was decided to proceed with an open surgical approach in a larger than expected number of patients. Therefore, an extension to recruit 205 patients was requested, which was approved by the Institutional Review Board of the Hospital Universitario y Politécnico la Fe, Valencia, Spain.

Statistical analysis

The primary analysis concerned a modified intention–to–treat analysis based on the target condition, i.e., patients that actually underwent laparoscopic colorectal surgery, and in whom the surgical procedure was not converted to open abdominal surgery[17].

Continuous variables are reported as median [25^{th}–75^{th} percentile]. Normality was checked by examination of quantile–quantile plot. Categorical variables are reported as percentages and proportions. In case of >5% of missing data, imputation was performed using the *mice* package for R software. Values were imputed by chained equation with predictive mean matching creating 5 datasets that were jointly used to fit regression models[18].

To assess the association between the pneumoperitoneum strategy (IPP or SPP) and PQRS scores, a mixed logistic regression model was fitted with age, IMC, duration of surgery and gender as covariables and patient as a random factor to count for interindividual variability. The association between the two strategies and the incidence of intraoperative adverse events was assessed by Fisher's exact test. To assess the association between the pneumoperitoneum strategy (IPP or SPP) and postoperative complications, an ordinal model was fitted with postoperative complications introduced as an ordinal scale according to Clavien–Dindo severity score and age, IMC, ASA, duration of surgery and gender as covariables. To assess the association between the pneumoperitoneum strategy (IPP or SPP) and hospital length of stay a Cox regression model was fitted introducing an interaction term between incidence of complications and severity of complications.

Also, we analysed the PQRS scores as ordinal variables[13]. This approach implies no dichotomisation of PQRS outcomes and treating them as ordered categories variables.

A mixed linear regression with age, IMC, duration of surgery as covariables was fitted to assess the association between the two pneumoperitoneum strategies and course of NFL and CRP plasma levels. Study protocol prespecified a missing data threshold of 5% to perform imputation. NLR and CRP had a missing rate of 6.4% and 13.2% respectively, thus analysis for these outcomes were performed after missing values imputation. In a posthoc analysis, a mixed logistic regression was used to assess if postoperative plasma NFL or plasma CRP levels were associated with the primary endpoint

All analyses were performed with R software version 3.5.2 (R Foundation for Statistical Computing, www.r-project.org). Statistical significance was set for two–tailed at $P < 0.05$ and no correction for multiple comparison was preplanned.

Results

Patients

Patient flow and patient demographics are presented in Figure 1 and Table 1. In total, 204 patients were included and randomised between February 2017 and November 2018. Of them, 38 patients did not receive the allocated intervention, mainly because it was decided to perform open surgery instead of the planned laparoscopic intervention. Thus, 166 were included in the modified intention–to–treat analysis. Baseline characteristics were well balanced and intraoperative characteristics were not different between the two groups. Follow–up for the primary endpoint was complete up to POD3, since all patients stayed in the hospital till at least postoperative day 3.

Intervention

Empirical cumulative distribution function and relative percentages of the IAP used during pneumoperitoneum in the two groups are presented in Figure 2. In 80 (94%) patients in the IPP group, IAP during pneumoperitoneum remained below 12 mmHg. A rise in IAP was requested in 20 (24%) patients and in 7 (7%) patients in the IPP group and the SPP group, respectively ($P<0.001$). This need for a higher IAP resulted in an increase to 10 [95%–CI 10–10] and to 15 [95%–CI 14–15] mmHg, in the IPP and the SPP group, respectively. The

request for an increase in IAP was mainly during the pelvic phase of the surgical procedure.

Primary outcome

PQRS score results are presented in Figure 3. Patients in the IPP group had a higher probability of physiologic recovery (OR, 2.8 [95%CI 1.2–6.4]; P=0.017; RR 1.8 [95%CI 1.7–1.9], P=0.05). Of note, the interaction between time and group assignment was significant, with the probability of recovery equalising at POD3 (Supplementary Digital Content eTable 5).

Secondary outcomes

The probability of emotive recovery was higher in IPP group (OR 4.6 [95%CI 1.4–15.3]; P=0.013, RR 1.2 [95%CI 1.1–1.3, P<0.001), with no significant time interaction (Supplementary Digital Content eTable 6). Patients in the IPP group had a higher probability of overall recovery (OR, 3.7 [95%CI 1.4–10.0]; P=0.011; RR 2.7 [95%CI 13–5.6], P=0.016), with a significant interaction between time and group assignment (Supplementary Digital Content eTable 7). The quality of recovery in the other domains was not affected by the IPP strategy (Figure 3, Supplementary Digital Content, eTable 8–10).

The PQRS ordinal regression analysis yielded similar results for every PQRS domain except for the nociceptive PQRS, which was significantly lower in the IPP group (OR 0.5 [95%–CI 0.2–1.0], P=0.047, RR 0.3 [95%CI 0.1–0.8, P=0.023).

The incidence of intraoperative cough or movement was lower in the IPP group compared to SPP group (1 versus 54%, P<0.001). No differences were observed in the incidence of postoperative complications nor in length of stay between the two randomisation groups.

The plasma NRL was lower in the IPP compared to SPP group (Supplementary eFigure 1 and eTable 11). Plasma CRP levels were not affected by the IPP strategy (Figure 4b, Supplementary eTable 12). Inflammation markers were not associated with recovery (Supplementary eTable 13 and 14).

Discussion

The main findings of this study in patients undergoing laparoscopic colorectal surgery can be summarised as follows. Compared to a standard insufflation strategy, an individualised strategy is associated with (i.) faster physiologic recovery, (ii.) faster emotional recovery and (iii.) faster overall recovery in the early postoperative period. Besides, (iv.), the IPP strategy was associated with less intraoperative coughing and movements, and (v.) a lower NLR in blood plasma.

This study has several strengths. The study tested a previously designed and evaluated IPP strategy that was easy to perform and maintain during surgery, with no deviations from the protocol. There was a clear separation between the two strategies with respect to the pneumoperitoneum pressure, while keeping sufficient surgical working space with the individualised approach. The primary outcome used a previously validated comprehensive scoring system that evaluates early postoperative recovery focusing on clinical rather than surrogate measures or pre–clinical endpoints[21]. Patients and surgeons were kept blinded for group assignment, thereby reducing bias towards recovery scores and surgical conditions and conversion rate. The statistical analysis accounted for the longitudinal nature of the primary outcome using a mixed effect model including individual variability and the effect of time and adjusting for pre– and post–randomisation covariables to control for attrition bias[22].

Findings of previous systematic reviews assessing the effect of a low IAP on perioperative outcomes in patients undergoing laparoscopic surgery are conflicting, either showing a significant reduction in pain scores[23] or no effects[6,24]. Significant decreases in perioperative complications were found in prospective studies[25–27]. Only one single study that reported on the quality of recovery found no difference between a low and standard IAP strategy[28]. In this study in laparoscopic nephrectomies, quality of recovery was evaluated with another assessment tool, the 'QoR–40 questionnaire', and different from the current study, moreover, no longitudinal analysis was performed[29].

Several studies showed low pneumoperitoneum pressure during laparoscopic surgery to be feasible[12,30,31]. None of these studies though assessed the effects on quality of recovery. The current trial shows an IPP strategy to be associated with faster recovery in the early postoperative period.

Of note, while parts of the applied bundle of measures in the intervention arm was prespecified and, in fact 'standard', the IPP strategy protocol aimed at an individualized pneumoperitoneum pressure at which surgeons could perform the intervention. The lithotomy position, deep NMB, and pre–stretch of the abdominal wall are crucial elements allowing a better individualisation of the intra–operative pneumoperitoneum pressure[12]. Surgical experience was comparable between the two study groups, as in each participating centre, the surgical procedure was performed by a staff surgeon who is experienced in colorectal and laparoscopic surgery.

Patients in the IPP group had a much lower incidence of intraoperative adverse events, mainly intraoperative cough or patient movement, at least in part because of the deeper neuromuscular blockade, but definitive association could not be established since the IPP intervention consisted of several procedures. Deep neuromuscular blockade has been associated with better surgical conditions in previous studies[8,32], but robust evidence on its benefit is still lacking[33]. Intraoperative complications have been linked to increased postoperative morbidity and mortality[34,35], thus reducing them can improve surgical outcomes.

Plasma NLR, but not plasma CRP levels were lower with the IPP strategy, although statistical significance was borderline. The physiologic effect of CO_2 insufflation on diaphragm and other tissues surrounding the abdominal cavity is well known[5,36,37]. The findings of this study suggest that insufflation at individualized IAP could reduce these injurious effects, although the differences found in the current study are at best hypothesis generating. Future studies should focus on the clinical meanings of these differences.

This study has some limitations. The long–term effects of an IPP strategy remain uncertain, as follow–up was limited to the early postoperative period. This study used a restrictive number of intraoperative adverse events. Future studies could use more or other adverse events as endpoints, like those reported elsewhere[38,39]. Although reported adverse events like major intraoperative bleedings, and injury to bowel and intraabdominal organs were not different between the two groups, these outcomes were not recorded as part of this study. The number of recruited patients was lower than planned, which especially reduces the statistical power to show differences in the

secondary outcomes. The analysis concerned a modified intention–to–treat analysis based on the target condition, i.e., patients that actually underwent laparoscopic colorectal surgery, and in whom the surgical procedure was not converted to open abdominal surgery. This approach is appropriate for pragmatic randomized controlled trials[40,41]. The validity of the results in samples of surgical teams with a different level of experience has to be further investigated, as not only technical but also teamwork skills may be involved. The study protocol advised postoperative nausea and vomiting (PONV) prophylaxis according to ERAS guidelines, but data regarding administration of certain drugs like dexamethasone was not collected. Finally, multiple comparison corrections were not performed, meaning that the findings regarding the secondary outcomes should be viewed as exploratory.

In conclusion, an IPP strategy aiming at the lowest possible IAP that preserves optimal surgical condition is associated with faster recovery in the early postoperative period. Future studies should focus on the effect of this approach on long–term clinical endpoints.

References

1.Neudecker J, Sauerland S, Neugebauer EAM, Bergamaschi R, Bonjer HJ, Cuschieri A, et al. The European Association for Endoscopic Surgery clinical practice guidelines on the pneumoperitoneum for laparoscopic surgery. Surg Endosc 2002; 16: 1121–43.

2.Vlot J, Wijnen R, Stolker RJ, Bax K. Optimizing working space in porcine laparoscopy: CT measurement of the effects of intra-abdominal pressure. Surg Endosc 2013; 27:1668–73.

3.Jones O, Lindsey I, Cunningham C. Laparoscopic colorectal surgery. BMJ 2011; 343: d8029.

4.Maddison L, Karjagin J, Tenhunen J, Starkopf J. Moderate intra-abdominal hypertension is associated with an increased lactate-pyruvate ratio in the rectus abdominis muscle tissue : a pilot study during laparoscopic surgery. Ann Intensive Care 2012; 2 Suppl 1:S14.

5.Brokelman WJA, Lensvelt M, Rinkes IHMB, Klinkenbijl JHG, Reijnen MMPJ. Peritoneal changes due to laparoscopic surgery. Surg Endosc 2011; 25:1–9.

6.Özdemir-van Brunschot DMD, van Laarhoven KCJHM, Scheffer GJ, Pouwels S, Wever KE et al. What is the evidence for the use of low-pressure pneumoperitoneum? A systematic review. Surg Endosc 2016; 30:2049–65.

7.Mulier JPJ, Dillemans B, Van Cauwenberge S. Impact of the patient's body position on the intraabdominal workspace during laparoscopic surgery. Surg Endosc 2010; 24:1398–402.

8.Madsen M V., Staehr-Rye AK, Gätke MR, Claudius C. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: A systematic review. Acta Anaesthesiol Scand 2015; 59:1–16.

9.Bruintjes MH, Van Helden E V., Braat AE, Dahan A, Scheffer GJ, Van Laarhoven CJ, et al. Deep neuromuscular block to optimize surgical space conditions during laparoscopic surgery: A systematic review and meta-analysis. Br J Anaesth. 2017; 118:834–42.

10.Serpa Neto A, Hemmes SNT, Barbas CS V., Beiderlinden M, Biehl M, Binnekade JM, et al. Protective versus Conventional Ventilation for Surgery. Anesthesiology 2015; 123:66–78.

11.Vlot J, Wijnen R, Stolker RJ, Bax K. Optimizing working space in laparoscopy: CT measurement of the effect of pre-stretching of the abdominal wall in a porcine model. Surg Endosc 2014; 28:841–6.

12.Diaz-Cambronero O, Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, et al. A multifaceted individualized

pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study. Surg Endosc 2019; 33:252–60.

13.Diaz-Cambronero O, Mazzinari G, Errando CL, Schultz MJ, Flor Lorente B, García-Gregorio N, et al. An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: Rationale and study protocol for a multicentre randomised clinical study. Trials 2019; 20:1–13.

14.Diaz-Cambronero O, Mazzinari G, Errando CL, Schultz MJ, Flor Lorente B, García-Gregorio N, et al. Correction to: An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study. Trials 2020; 21:70.

15.Royse CF, Newman S, Chung F, Stygall J, McKay RE, Boldt J, et al. Development and feasibility of a scale to assess postoperative recovery : The post-operative quality recovery scale. Anesthesiology 2010; 113:892–905.

16.Bowyer A, Jakobsson J, Ljungqvist O, Royse C. A review of the scope and measurement of postoperative quality of recovery. Anaesthesia 2014; 69:1266–78.

17.European Medicines Agency (EMA). International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. (ICH). E9 Statistical principles for Clinical Trials. CPMP/ICH/363/96. 1998; [cited 15 April 2020]. Section 5.2.1:24–5. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

18.van Buuren S, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. J Stat Softw 2011; 45:1–67.

19.van Buuren S, Groothuis-Oudshoorn K. mice: Estimating the relative risk in cohort studies and clinical trials of common outcomes. Am J Epidemiol 2003; 157:940–3.

20.Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol. 2004; 159:702-6.

21.Bowyer AJ, Royse CF. Postoperative recovery and outcomes - What are we measuring and for whom? Anaesthesia 2016; 71:72–7.

22.Murray EJ, Hernán MA. Adherence adjustment in the Coronary Drug Project: A call for better per-protocol effect estimates in randomized trials. Clin Trials 2017; 13:372–8.

23.Hua J, Gong J, Yao L, Zhou B, Song Z. Low-pressure versus standard-pressure pneumoperitoneum for laparoscopic cholecystectomy: A systematic review and meta-analysis. Am J Surg 2014; 208:143–50.

24.Gurusamy KS, Samraj K, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014;3:CD006930.

25.Ferroni MC, Abaza R. Feasibility of robot-assisted prostatectomy performed at ultra-low pneumoperitoneum pressure of 6 mmHg and comparison of clinical outcomes vs standard pressure of 15 mmHg. BJU Int 2019; 124:308–13.

26.Rohloff M, Cicic A, Christensen C, Maatman TK, Lindberg J, Maatman TJ. Reduction in postoperative ileus rates utilizing lower pressure pneumoperitoneum in robotic-assisted radical prostatectomy. J Robot Surg 2019; 13:671–674.

27.Madsen M V., Istre O, Staehr-Rye AK, Springborg HH, Rosenberg J, Lund J, et al. Postoperative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low-pressure pneumoperitoneum. Eur J Anaesthesiol 2016; 33:341–7.

28.Özdemir-van Brunschot DMD, Scheffer GJ, van der Jagt M, Langenhuijsen H, Dahan A, Mulder JEEA, et al. Quality of recovery after low-pressure laparoscopic donor nephrectomy facilitated by deep neuromuscular blockade: A randomized controlled study. World J Surg 2017; 41:2950–8.

29.Myles PS, Weitkamp B, Jones K, Melick J, Hensen S. Validity and reliability of a postoperative quality of recovery score: The QoR-40. Br J Anaesth 2000; 84:11–5.

30.Xia PT, Yusofu M, Han HF, Hu CX, Hu SY, Yu W Bin, et al. Low-pressure pneumoperitoneum with abdominal wall lift in laparoscopic total mesorectal excision for rectal cancer: Initial experience. World J Gastroenterol 2018; 24:1278–84.

31.Park JS, Ahn EJ, Ko DD, Kang H, Shin HY, Baek CH, et al. Effects of pneumoperitoneal pressure and position changes on respiratory mechanics during laparoscopic colectomy. Korean J Anesthesiol 2012; 63:419–24.

32.Özdemir-van Brunschot DMD, Braat AE, van der Jagt MFP, Scheffer GJ, Martini CH, Langenhuijsen JF, et al. Deep neuromuscular blockade improves surgical conditions during low-pressure pneumoperitoneum laparoscopic donor nephrectomy. Surg Endosc. 2018;32(1):245–51.

33.Kopman AF, Naguib M. Is deep neuromuscular block beneficial in laparoscopic surgery? No, probably not. Acta Anaesthesiol Scand. 2016;60(6):717–22.

34.Bohnen JD, Mavros MN, Ramly EP, Chang Y, Yeh DD, Lee J, et al. Intraoperative adverse events in abdominal surgery: What happens in the operating room does not stay in the operating room. Ann Surg. 2017;265(6):1119–25.

35.Garbens A, Goldenberg M, Wallis CJD, Tricco A, Grantcharov TP. The cost of intraoperative adverse events in abdominal and pelvic surgery: A systematic review. Am J Surg [Internet]. 2018;215(1):163–70. Available from: https://doi.org/10.1016/j.amjsurg.2017.06.025

36.Neudecker J, Sauerland S, Neugebauer EAM, Bergamaschi R, Bonjer HJ, Cuschieri A, et al. The European Association for Endoscopic Surgery clinical practice guidelines on the pneumoperitoneum for laparoscopic surgery. In: EAES Guidelines for

Endoscopic Surgery Twelve Years Evidence-Based Surgery in Europe. New York:Springer, 2006;39–85.

37.Sharma KC, Brandstetter RD, Brensilver JM, Lung LD. Cardiopulmonary physiology and pathophysiology as a consequence of laparoscopic surgery. Chest 1996; 110:810–5.

38.Fahy BG. Cardiopulmonary effects of laparoscopic surgery, revisited. Chest 1997; 111:1787–8.

39.Rosenthal R, Hoffmann H, Clavien PA, Bucher HC, Dell-Kuster S. Definition and classification of intraoperative complications (classic): Delphi study and pilot evaluation. World J Surg 2015; 39:1663–71.

40.Kaafarani HMA, Mavros MN, Hwabejire J, Fagenholz P, Yeh DD, Demoya M, et al. Derivation and validation of a novel severity classification for intraoperative adverse events. J Am Coll Surg 2014; 218:1120–8.

41.Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017; 377:1391–8.

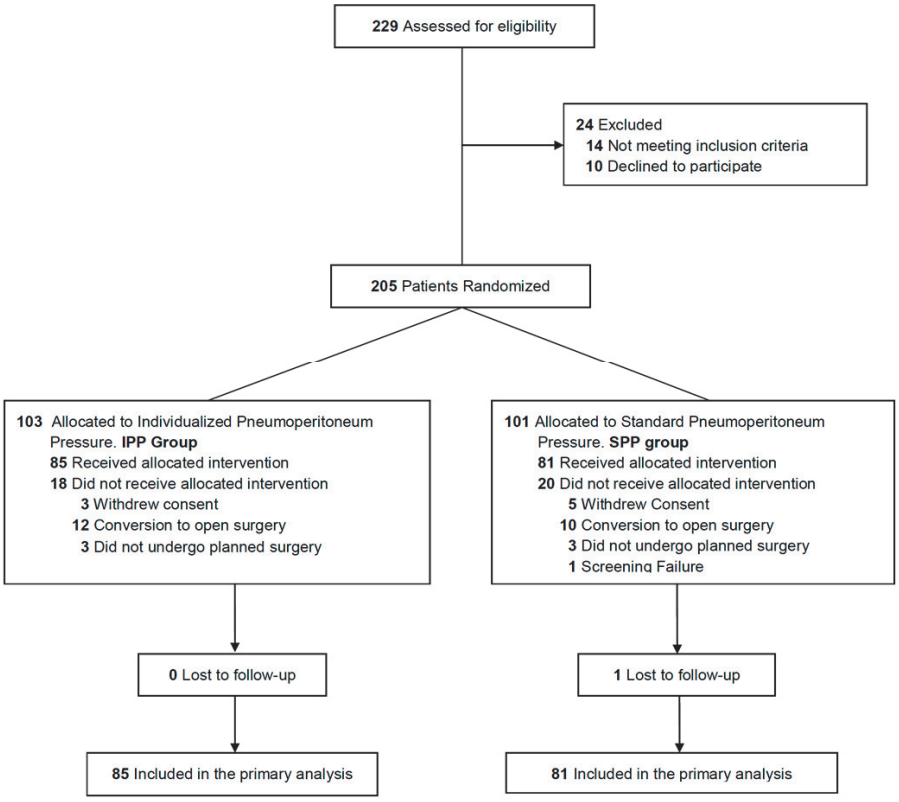


Figure 1. CONSORT diagram.

Figure 2

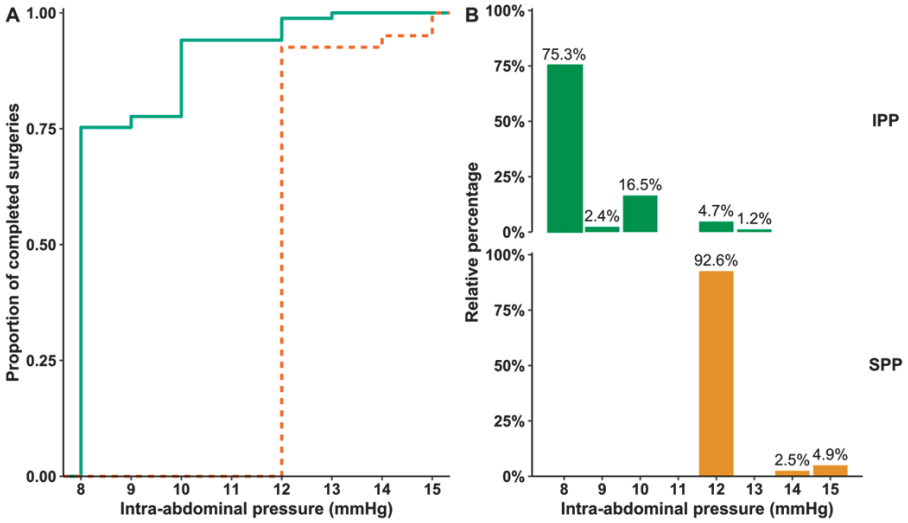


Figure 2. Intra–abdominal pressure at which surgery could be performed. (A) empirical cumulative distribution function for the individualized pneumoperitoneum group (green lines), and the standard pneumoperitoneum group (orange lines); (B) bar chart by group. Abbreviations: IPP, individualized pneumoperitoneum; SPP, standard pneumoperitoneum.

Figure 3

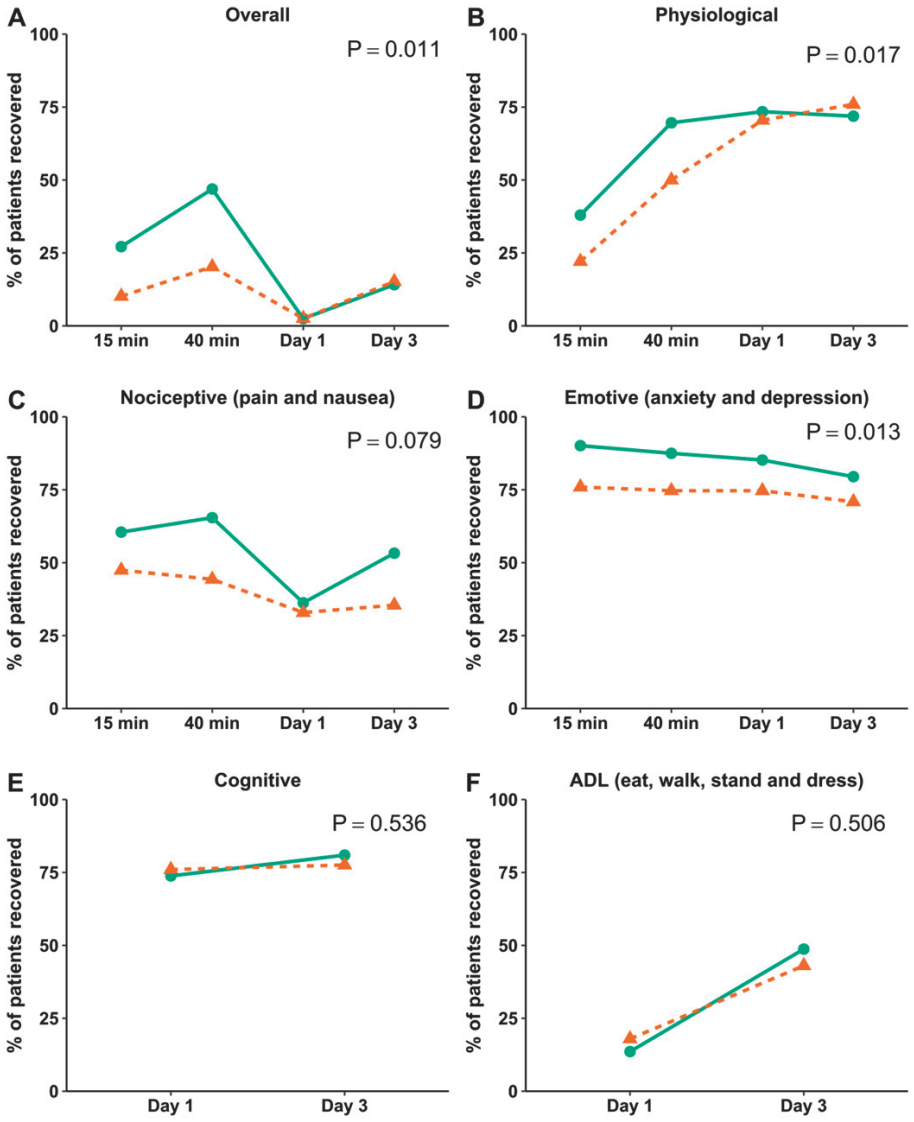


Figure 3. Postoperative quality of recovery for all participants in the individualized pneumoperitoneum strategy groups (green line) and the standard pneumoperitoneum group (orange line). Abbreviations: IPP, individualized pneumoperitoneum; SPP, standard pneumoperitoneum.

Table 1 Baseline characteristics			
	All patients (N = 166)	**IPP Group (N = 85)**	**SPP Group (N = 81)**
Age (Years)	68 [59 – 74]	68 [58 – 74]	67 [59 – 77]
Gender (Female)	38.0% (63/166)	31.8% (27/85)	44.4% (36/81)
BMI ($Kg \cdot m^{-2}$)	27.0 [24.0 – 30.0]	27 [24.2 – 29.9]	26.6 [23.8 – 29.0]
ASA			
1	14.5% (24/166)	14.5% (13/85)	14.8% (12/81)
2	58.5% (97/166)	56.0% (47/85)	60.5% (49/81)
3	27.0% (45/166)	29.5% (25/85)	24.7% (20/81)
Respiratory Disease (Yes)	9.1% (15/166)	10.5% (9/85)	7.2% (6/81)
Diabetes (Yes)	23.0% (38/166)	20.0% (17/85)	25.9% (21/81)
Hypertension (Yes)	51.2% (85/166)	48.2% (41/85)	54.3% (44/81)
Ischemic Disease (Yes)	11.6% (19/166)	9.0% (8/85)	13.6% (11/81)
Previous pregnancies			
0	76.6% (105/137)	78.7% (59/75)	74.2% (46/62)
1	4.4% (6/137)	4.0% (3/75)	4.8% (3/62)
2	11.7% (16/137)	10.7% (8/75)	12.9% (8/62)
3	4.4% (6/137)	5.3% (4/75)	3.2% (2/62)
4	2.2% (3/137)	1.3% (1/75)	3.2% (2/62)
5	0.7% (1/137)	0% (0/75)	1.6% (1/62)
Type of Surgery			
Lower anterior rectum resection	27.0% (45/166)	27.7% (24/85)	26.2% (21/81)
Right hemicolectomy	36.0% (59/166)	34.9% (30/85)	37.5% (31/81)
Left hemicolectomy	3.0% (5/166)	4.8% (4/85)	1.2% (1/81)
Sigmoidectomy	20.2% (34/166)	20.5% (17/85)	20.0% (16/81)
Total colectomy	1.2% (2/166)	1.2% (1/85)	1.2% (1/81)
Other (ileocecal resection, perineal amputation, segmental resection)	12.3% (21/166)	10.8% (9/85)	13.8% (11/81)
Previous laparoscopic surgeries			
0	70.3% (90/128)	72.5% (50/69)	67.8% (40/59)
1	24.2% (31/128)	23.2% (16/69)	25.4% (15/59)
2	3.1% (4/128)	1.4% (1/69)	5.1% (3/59)
3	2.3% (3/128)	2.9% (2/69)	1.7% (1/59)
Oncological surgery (Yes)	91.4% (149/166)	92.9% (79/85)	86.4% (70/81)
Hospital of recruitment			
La Fe, Valencia	51.8% (86/166)	51.8% (44/85)	51.9% (42/81)
Gregorio Marañon, Madrid	15.7% (26/166)	15.3% (13/85)	16.0% (13/81)
General, Castellon	17.5% (29/166)	17.6% (15/85)	17.3% (14/81)
Virgen Macarena, Sevilla	15.1 % (25/166)	15.3% (13/85)	14.8% (12/81)
Surgeons' previous laparoscopic colorectal surgery experience (years)	10 [8 – 15]	10 [8 – 15]	1- [8 – 15]

Data are reported as number (%) or median [25th–75th percentile]. *IPP*, Individualized pneumoperitoneum pressure; *SPP*, Standard pneumoperitoneum pressure; *BMI*, Body mass index; *ASA*, American Society of Anesthesiologists physical status.

Suplemento capítulo 4

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eTable 1. Intervention sequence	
Standard pneumoperitoneum pressure strategy (SPP group)	**Individualized pneumoperitoneum pressure strategy (IPP group)**
1. Trendelenburg (0–30°) placement	**1.** Trendelenburg (0–30°) + 'modified lithotomy position', with flexed hips (between 45 and 90°) and legs raised in padded supports to increase anteroposterior intra–abdominal space
2. Moderate neuromuscular blockade throughout surgery (TOF between 2 and 4)	**2.** Deep neuromuscular blockade throughout surgery (TOF of 0 and a PTC between 1 and 5)
3. No pre–stretching of abdominal wall and muscles	**3.** Pre–stretching of abdominal wall and muscles by maintaining an IAP of 15 mmHg for 5 minutes at the beginning of CO_2 gas insufflation and insertion of trocars (flow rate at 3 $L \cdot min^{-1}$)
4. IAP is set at 12 mmHg throughout surgery	**4.** IAP down–titration (flow rate at 30 $L \cdot min^{-1}$) from 15 to 12 mmHg, and thereafter stepwise to 11, 10, 9 and finally 8 mmHg as long as 'adequate' workspace is preserved (by surgeons judgement)
5. Surgeons can request an IAP increase if workspace becomes 'inadequate. IAP is increased in steps of 1 mm Hg during one minute intervals to a maximum of 15 mmHg. Surgeons are warned when upper limit is reached	**5.** Surgeons can request an IAP increase if workspace becomes 'inadequate'; IAP is increased in steps of 1 mm Hg during one minute intervals to a maximum of 15 mmHg, Surgeons are warned when upper limit is reached
TOF, train–of–four; IAP, intra–abdominal pressure; PTC, post–tetanic–count. Standard perioperative management was carried out following the Spanish Enhancement Recovery after Surgery guidelines.[1]	

eTable 2. Postoperative Quality of Recovery Scale (PQRS).							
Domain	**Variable**	**Score**	**Baseline**	**T15**	**T40**	**POD1**	**POD3**
Physiologic	Blood pressure	1-3	+	+	+	+	+
Physiologic	Heart rate	1-3	+	+	+	+	+
Physiologic	Temperature	1-3	+	+	+	+	+
Physiologic	Respiration	1-3	+	+	+	+	+
Physiologic	SpO2	1-3	+	+	+	+	+
Physiologic	Airway	1-3	+	+	+	+	+
Physiologic	Agitation	1-3	+	+	+	+	+
Physiologic	Consciousness	1-3	+	+	+	+	+
Physiologic	Activity on command	1-3	+	+	+	+	+
Nociceptive	Pain	1-5 Likert	+	+	+	+	+
Nociceptive	PONV	1-5 Likert	+	+	+	+	+
Emotional	Sadness/Depression	1-5 Likert	+	+	+	+	+
Emotional	Anxiety/Nervousness	1-5 Likert	+	+	+	+	+
Activity of daily life	Stand	1-3	+	-	-	+	+
Activity of daily life	Walk	1-3	+	-	-	+	+
Activity of daily life	Eat/drink	1-3	+	-	-	+	+
Activity of daily life	Get dressed	1-3	+	-	-	+	+
Cognitive	Name, city and DOB	TF 0	+	-	-	+	+
Cognitive	Numbers forward	TF 2	+	-	-	+	+
Cognitive	Numbers backwards	TF 1	+	-	-	+	+
Cognitive	Word task: list	TF 3	+	-	-	+	+
Cognitive	Executive memory	TF 3	+	-	-	+	+

Online scale to assess multiple domains of post-operative recovery over time. Timeline: **T15** - 15 minutes in PACU; **T 40**- 40 minutes in PACU; **POD1**- Postoperative day 1; **POD3** - postoperative day 3. **PONV**: Postoperative Nausea and Vomiting. **DOB**: Date of birth. **Scoring**: Physiologic 1-3; Nociceptive/emotional: 1–5 Likert rating scale using a faces pictorial display; Functional: Scored as 3: easily, 2: difficulty, and 1: not at all; Cognitive: Performance variability tolerance factor (TF) is applied. Participants not included in subsequent analysis if baseline scores are equal to or less than the tolerance factor

Table 3. Classification of post-operative complications[2]

Type	Definition		
	Stage	**Serum Creatinine**	**Urine Output**
1. Acute kidney damage.[3]	1	1.5–1.9 times baseline value within 7 days or ≥27 μmol·L^{-1} (0.3 mg·dl^{-1}) increase within 48h	≤0.5 ml·kg^{-1}·h^{-1} for 6–12h
	2	2.0–2.9 times baseline value within 7 days	≤0.5 ml·kg^{-1}·h^{-1} for 12h
	3	3.0 times baseline within 7 days or Increase in serum creatinine to ≥354 μmol·L^{-1} or Initiation of renal replacement therapy	≤0.3 ml·kg^{-1}·h^{-1} for 24h or Anuria for 12h
2. Acute respiratory distress syndrome (ARDS)[4]	Timing. Within one week of a known clinical insult or new or worsening respiratory symptoms and Chest imaging Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules and Origin of oedema. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema if no risk factor present and Oxygenation. – *Mild*. PaO_2:FIO_2 between 26.7 and 40.0 kPa (200–300mmHg) with PEEP or CPAP ≥5 cmH_2O – *Moderate*. PaO_2:FIO_2 between 13.3 and 26.6 kPa (100–200mmHg) with PEEP ≥5 cmH_2O – *Severe*. PaO_2:FIO_2 ≤13.3 kPa (100mmHg) with PEEP ≥5 cmH_2O		
3. Anastomotic leak[5]	Leak of luminal contents from a surgical connection between two hollow viscera. The luminal contents may emerge either through the wound or at the drain site, or they may collect near the anastomosis, causing fever, abscess, septicaemia, metabolic disturbance and/or multiple organ failure. The escape of luminal contents from the site of the anastomosis into an adjacent localised area, detected by imaging, in the absence of clinical symptoms and signs should be recorded as a subclinical leak There is a lack of consensus regarding the definition of anastomotic leakage. It is important to use this definition together with a grading system to measure the impact of the anastomotic breakdown on patient outcome: – *Mild*. Results in only temporary harm and would not usually require specific clinical treatment – *Moderate*. More serious complication but one which does not usually result in permanent harm or functional limitation. Usually requires clinical treatment – *Severe*. Results in significant prolongation of hospital stay and/or permanent functional limitation or death. Almost always requires clinical treatment		
4. Arrhythmia	Arrhythmia is defined as electrocardiograph (ECG) evidence of cardiac rhythm disturbance.		

5. Cardiac arrest	The International Liaison Committee on Resuscitation defines cardiac arrest as the cessation of cardiac mechanical activity, as confirmed by the absence of signs of circulation
6. Cardiogenic pulmonary oedema	Cardiogenic pulmonary oedema is defined as evidence of fluid accumulation in the alveoli due to poor cardiac function
7. Deep vein thrombosis	A new blood clot or thrombus within the venous system
8. Postoperative delirium[6]	Delirium may be identified using the Intensive Care Delirium Screening Checklist. Patients are first evaluated for an altered level of consciousness. Those with a response to mild or moderate stimulation, an exaggerated response to stimulation or normal wakefulness are evaluated fully. Patients receive one point for each of the following criteria: inattention, disorientation, hallucination-delusion-psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance or symptom fluctuation. Delirium is diagnosed with a score ≥4
9. Gastrointestinal bleeding	Gastrointestinal bleed is defined as unambiguous clinical or endoscopic evidence of blood in the gastrointestinal tract. Upper gastrointestinal bleeding (or haemorrhage) is that originating proximal to the ligament of Treitz, in practice from the oesophagus, stomach and duodenum. Lower gastrointestinal bleeding is that originating from the small bowel or colon
10. Infection, source uncertain[7]	The Center for Disease Control and prevention (CDC) defines infection, source uncertain as one where there is strong clinical suspicion of infection but the source has not been confirmed because clinical information suggests more than one possible site, meeting two or more of the following criteria:27 core temperature <36°C or >38°C; white cell count $>12{\cdot}10^{9}{\cdot}L^{-1}$ or $< 4{\cdot}10^{9}{\cdot}L^{-1}$, respiratory rate >20 breaths per minute or $PaCO_2$ < 4.7 kPa (35mmHg); pulse rate >90 beats per minute
11. Laboratory confirmed bloodstream infection[7]	The CDC defines laboratory confirmed bloodstream infection as one which meets at least one of the following criteria which should not be related to infection at another site: 1. Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site 2. Patient has at least one of the following signs or symptoms: fever >388C, chills or hypotension, and at least one of the following: – Common skin contaminant cultured from two or more blood cultures drawn on separate occasions – Common skin contaminant cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy – Positive blood antigen test
12. Myocardial infarction[8]	Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria: – symptoms of ischaemia – new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block – development of pathological Q waves on ECG; radiological or echocardiographic evidence of

	new loss of viable myocardium or new regional wall motion abnormality – identification of an intracoronary thrombus at angiography or autopsy
13. Myocardial injury after non-cardiac surgery (MINS)	Peak troponin T (TnT) ≥0.03 $ng \cdot ml^{-1}$ judged due to myocardial ischaemia (i.e. no evidence of a non–ischaemic aetiology causing the TnT elevation). This criterion excludes troponin abnormalities related to other causes e.g. sepsis
14. Pneumonia[7]	Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): – new or progressive and persistent infiltrates – consolidation – cavitation at least one of the following – fever (>38°C) with no other recognised cause – leukopoenia (white cell count < $4 \cdot 10^9 \cdot L^{-1}$) or leucocytosis (white cell count > $12 \cdot 10^9 \cdot L^{-1}$) – for adults >70 years old, altered mental status with no other recognised cause; and at least two of the following – new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements – new onset or worsening cough, or dyspnoea, or tachypnoea – bronchial breath sounds – worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)
15. Paralytic ileus[9]	Failure to tolerate solid food or defecate for three or more days after surgery
16. Post-operative haemorrhage	The American College of Surgeons. National Surgical Quality Improvement Program defines postoperative haemorrhage as blood loss within 72 h after the start of surgery which would normally result in transfusion of blood
17. Pulmonary embolism (PE)	A new blood clot or thrombus within the pulmonary arterial system. We did not identify a suitable definition for postoperative PE in the literature. Treatment is often determined by clinical risk of PE rather than a definitive diagnosis. Systematic screening is required in trials where PE is an important outcome measure. Appropriate diagnostic tests include scintigraphy and CT angiography. Plasma D-dimer measurement is not recommended as a diagnostic test in the first three weeks following surgery
18. Cerebrovascular accident	The American College of Surgeons. National Surgical Quality Improvement Program defines stroke as an embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (e.g. hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory)
19. Infection of surgical wound (superficial)[7]	1. Infection occurs within 30 days after surgery and 2. Involves only skin and subcutaneous tissue of the incision and 3. The patient has at least one of the following: – purulent drainage from the superficial incision

	– organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision – at least one of the following symptoms or signs of infection: pain or tenderness, localised swelling, redness or heat, and superficial incision is deliberately opened by surgeon and is culture–positive or not cultured. A culture–negative finding does not meet this criterion. – diagnosis of an incisional surgical site infection by a surgeon or attending physician
20. Infection of surgical wound (deep)[7]	1. Infection occurs within 30 days after surgery if no implant is left in place or 1 year if implant is in place 2. Involves deep soft tissues (e.g. fascial and muscle layers) of the incision. 3. The patient has at least one of the following: – purulent drainage from the deep incision but not from the organ/space component of the surgical site – a deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture-positive or not – cultured when the patient has at least one of the following symptoms or signs: fever (>388C), or localised pain or tenderness. A culture-negative finding does not meet this criterion – an abscess or other evidence of infection involving the deep incision is found on direct examination, during surgery, or by histopathological or radiological examination – (d) diagnosis of an incisional surgical site infection by a surgeon or attending physician
21. Infection of surgical (organ) wound[7]	1. Infection occurs within 30 days after surgery 2. The infection appears to be related to the surgical procedure and involves any part of the body, excluding the skin incision, fascia or muscle layers opened or manipulated during the operative procedure 3. The patient has at least one of the following: – purulent drainage from a drain that is placed through a stab wound into the organ/space – organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space – an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation or by histopathological or radiological examination – (d) diagnosis of an organ/space surgical site infection by a surgeon or attending physician
22. Urinary tract infection[7]	A simplified version of the CDC recommendations defines a urinary tract infection as follows: a positive urine culture of $>10^5$ colony forming units per ml^{-1} with no more than two species of micro-organisms, and with at least one of the following symptoms or signs: fever (>38°C), urgency, frequency, dysuria, suprapubic tenderness, costovertebral angle pain or tenderness with no other recognised cause
Postoperative pulmonary complications:	

1. Respiratory infection	See Pneumonia
2. Respiratory failure	Postoperative PaO_2 < 8 kPa (60 mmHg) on room air, a PaO_2:FIO_2 ratio <40 kPa (300 mmHg) or arterial oxyhaemoglobin saturation measured with pulse oximetry < 90% and requiring oxygen therapy
3. Pleural effusion	Chest radiograph demonstrating blunting of the costophrenic angle, loss of sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
4. Atelectasis	Lung opacification with a shift of the mediastinum, hilum or hemidiaphragm toward the affected area, and compensatory over-inflation in the adjacent non-atelectatic lung
5. Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
6. Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
7. Pneumonia due to aspiration	Acute lung injury after the inhalation of regurgitated gastric contents

Table 4. Severity grade by Clavien-Dindo definition.[10]	
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions Allowed therapeutic regimens are: drugs as antiemetic, antipyretics, analgesics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
- IIIa	Intervention not under general anaesthesia
- IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU-management
- IVa	Single organ dysfunction (including dialysis)
- IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patients suffers from a complication at the time of discharge, the suffix "d" (for 'disability') is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication
Brain hemorrhage, ischemic stroke, subarachnoid bleeding but excluding transient ischemic attacks (TIA);IC: Intermediate care; ICU: Intensive care unit CNS: Central Nervous system	

eTable 5. Logistic mixed model with a random factor for individual patient with physiologic PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	0.670	1.128	0.073	6.114	0.723
IPP Group	2.771	0.427	1.198	6.407	0.017
Age	0.990	0.010	0.971	1.010	0.322
BMI	0.992	0.029	0.937	1.051	0.789
Time of Surgery	0.998	0.001	0.995	1.001	0.243
Gender (Female)	1.245	0.260	0.748	2.074	0.399
Time point (Reference category 15 minutes)					
40 minutes	4.723	0.403	2.142	10.415	<0.001
POD 1	12.908	0.430	5.547	30.036	<0.001
POD 3	19.402	0.449	8.046	46.783	<0.001
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	1.054	0.542	0.364	3.054	0.923
POD1* IPP group	0.447	0.558	0.150	1.335	0.149
POD3* IPP group	0.129	0.566	0.043	0.392	<0.001

Akaike Information Criterion 758.8; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 6. Logistic mixed model with a random factor for individual patient with emotive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	78.154	1.712	2.723	2243.291	0.011
IPP Group	4.591	0.613	1.379	15.290	0.013
Age	0.973	0.015	0.944	1.002	0.071
BMI	0.966	0.043	0.886	1.053	0.431
Time of Surgery	1.001	0.002	0.996	1.005	0.783
Gender (Female)	1.001	0.381	0.474	2.114	0.997
Time point (Reference category 15 minutes)					
40 minutes	0.901	0.444	0.378	2.152	0.815
POD 1	0.899	0.443	0.377	2.147	0.811
POD 3	0.677	0.436	0.288	1.594	0.372
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	0.738	0.736	0.174	3.128	0.680
POD1* IPP group	0.565	0.723	0.137	2.331	0.429
POD3* IPP group	0.403	0.701	0.102	1.593	0.194

Akaike Information Criterion 575.2; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 7. Logistic mixed model with a random factor for individual patient with overall PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	0.057	1.405	0.004	0.901	0.042
IPP Group	3.684	0.511	1.353	10.036	0.011
Age	1.013	0.012	0.987	1.039	0.326
BMI	0.965	0.037	0.897	1.039	0.342
Time of Surgery	1.002	0.001	0.998	1.005	0.343
Gender (Female)	1.222	0.322	0.649	2.300	0.535
Time point (Reference category 15 minutes)					
40 minutes	2.129	0.493	0.810	5.601	0.126
POD 1	0.088	1.131	0.010	0.807	0.032
POD 3	1.540	0.509	0.568	4.176	0.397
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	1.385	0.620	0.410	4.678	0.600
POD1* IPP group	0.576	1.378	0.039	8.586	0.689
POD3* IPP group	0.216	0.687	0.056	0.832	0.026

Akaike Information Criterion 499.5; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index;POD, Postoperative Day; *CI*, confidence interval.

eTable 8. Logistic mixed model with a random factor for individual patient with nociceptive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	0.354	1.322	0.027	4.727	0.432
IPP Group	2.182	0.444	0.913	5.216	0.079
Age	1.029	0.012	1.004	1.054	0.023
BMI	0.954	0.036	0.889	1.023	0.187
Time of Surgery	1.001	0.002	0.996	1.005	0.543
Gender (Female)	1.231	0.310	0.670	2.260	0.503
Time point (Reference category 15 minutes)					
40 minutes	0.771	0.380	0.366	1.624	0.493
POD 1	0.396	0.392	0.184	0.854	0.183
POD 3	0.463	0.388	0.216	0.990	0.047
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	1.630	0.544	0.561	4.737	0.369
POD1* IPP group	0.558	0.554	0.188	1.656	0.293
POD3* IPP group	1.259	0.546	0.431	3.676	0.673

Akaike Information Criterion 797.3; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 9. Logistic mixed model with a random factor for individual patient with ADL (eat, walk, stand and dress) PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	31.418	1.669	1.193	827.655	0.039
IPP Group	0.697	0.541	0.241	2.016	0.506
Age	0.981	0.014	0.953	1.009	0.188
BMI	0.948	0.043	0.870	1.034	0.227
Time of Surgery	0.988	0.002	0.983	0.994	<0.001
Gender (Female)	0.398	0.407	0.179	0.885	0.024
Time point (Reference category POD1)					
POD 3	5.265	0.488	2.019	13.727	<0.001
Interaction Time point *Study group (Reference category POD1*Study group)					
POD3* IPP group	2.290	0.652	0.638	8.228	0.204

Akaike Information Criterion 325.9; ADL, activities of daily life; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 10. Logistic mixed model with a random factor for individual patient with cognitive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	376.1	5.754	0.005	5750.583	0.303
IPP Group	0.422	1.394	0.027	6.485	0.536
Age	0.984	0.054	0.884	1.095	0.766
BMI	0.975	0.152	0.723	1.313	0.865
Time of Surgery	1.009	0.008	0.992	1.027	0.288
Gender (Female)	1.118	1.354	0.079	15.902	0.934
Time point (Reference category POD1)					
POD 3	0.926	0.844	0.177	4.847	0.928
Interaction Time point *Study group (Reference category POD1*Study group)					
POD3* IPP group	7.095	1.607	0.304	165.5	0.223

Akaike Information Criterion 190.2; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 11. Linear mixed model with a random factor for individual patient with Neutrophyl-Lymphocyte ratio as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	8.898	2.501	4.057	13.740	<0.001
IPP Group	-1.952	0.891	-3.680	-0.226	0.029
Age	-0.010	0.028	-0.065	0.044	0.712
BMI	0.014	0.019	-0.023	0.051	0.469
Time of Surgery	0.006	0.005	-0.003	0.014	0.227
Gender (Female)	-1.447	0.773	-2.943	0.049	0.063
Time point (Reference category POD1)					
POD 3	-3.495	0.700	-4.866	-2.123	<0.001
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
POD3* IPP group	1.924	0.973	0.018	3.83	0.050

Akaike Information Criterion 2151.86; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 12. Linear mixed model with a random factor for individual patient with C–reactive protein as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	-11.721	25.791	-61.990	38.537	0.652
IPP Group	-1.510	9.825	-20.572	17.538	0.878
Age	0.823	0.292	0.259	1.388	0.005
BMI	-0.207	0.198	-0.590	0.177	0.299
Time of Surgery	0.111	0.047	0.025	0.202	0.020
Gender (Female)	-12.250	7.988	-27.708	3.209	0.127
Time point (Reference category POD1)					
POD 3	13.731	8.754	-3.425	30.887	0.119
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
POD3*Study group	12.929	12.167	-10.917	36.774	0.289

Akaike Information Criterion 3771.84; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 13. Linear mixed model with a random factor for individual patient with postoperative complications as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	-9.711	5.308	-20.116	0.694	0.067
IPP Group	-0.509	1.242	-2.945	1.927	0.682
Age	0.006	0.055	-0.103	0.114	0.920
BMI	-0.004	0.147	-0.294	0.286	0.978
Time of Surgery	0.007	0.006	-0.007	0.020	0.316
Gender (Female)	-0.308	1.360	-2.975	2.359	0.821
ASA risk score (Reference cateory: ASA 1)					
2	-1.020	1.702	-4.357	2.318	0.549
3	-1.627	2.345	-6.224	2.970	0.488

Akaike Information Criterion 140.19; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval; ASA, American Society of Anesthesiology.

eTable 14. Linear mixed model with a random factor for individual patient with hospital length of stay as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
(Intercept)	1.807	0.024	1.760	1.855	<0.001
IPP Group	0.051	0.032	-0.012	0.115	0.114
complications	-0.157	0.064	-0.282	-0.032	0014
Interaction Complications*Severity	0.09	0.021	0.049	0.131	<0.001

IPP, Individualized pneumoperiteneum pressure;

eTable 15. Ordinal mixed model with a random factor for individual patient with physiologic PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
IPP Group	2.391	0.347	1.212	4.716	0.012
Age	0.983	0.01	0.963	1.003	0.104
BMI	0.996	0.03	0.939	1.057	0.893
Time of Surgery	0.998	0.002	0.995	1.001	0.132
Gender (Female)	1.304	0.265	0.776	2.191	0.315
Time point (Reference category 15 minutes)					
40 minutes	3.496	0.303	1.929	6.336	<0.001
POD 1	13.942	0.348	7.049	27.577	<0.001
POD 3	13.627	0.351	6.855	27.091	<0.001
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	1.167	0.44	0.493	2.764	0.726
POD1* IPP group	0.443	0.465	0.178	1.102	0.08
POD3* IPP group	0.134	0.457	0.055	0.328	<0.001

Akaike Information Criterion 1585.50; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 16. Logistic mixed model with a random factor for individual patient with emotive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
IPP Group	0.36	0.469	0.144	0.904	0.030
Age	0.997	0.013	0.973	1.022	0.821
BMI	1.043	0.038	0.969	1.123	0.259
Time of Surgery	1	0.002	0.997	1.004	0.813
Gender (Female)	1.433	0.333	0.746	2.754	0.281
Time point (Reference category 15 minutes)					
40 minutes	1.164	0.343	0.594	2.282	0.658
POD 1	1.478	0.356	0.735	2.972	0.273
POD 3	1.878	0.344	0.957	3.683	0.067
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes* IPP group	0.814	0.539	0.283	2.34	0.703
POD1* IPP group	1.989	0.527	0.709	5.584	0.192
POD3* IPP group	1.529	0.521	0.55	4.249	0.415

Akaike Information Criterion 1397.78; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 17. Ordinal mixed model with a random factor for individual patient with nociceptive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
IPP Group	0.472	0.378	0.225	0.990	0.047
Age	0.967	0.01	0.948	0.986	0.001
BMI	1.049	0.029	0.99	1.112	0.102
Time of Surgery	1	0.002	0.997	1.003	0.938
Gender (Female)	1.375	0.261	0.825	2.292	0.222
Time point (Reference category 15 minutes)					
40 minutes	1.045	0.307	0.573	1.907	0.886
POD 1	2.628	0.311	1.429	4.833	0.002
POD 3	2.177	0.311	1.183	4.007	0.012
Interaction Time point *Study group (Reference category 15 minutes*Study group)					
40 minutes*IPP group	0.666	0.456	0.273	1.627	0.372
POD1* IPP group	0.975	0.442	0.41	2.317	0.955
POD3* IPP group	0.61	0.456	0.25	1.49	0.278

Akaike Information Criterion 1691.06; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 18. Ordinal mixed model with a random factor for individual patient with ADL (eat, walk, stand and dress) PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
IPP Group	1.207	0.323	0.64	2.275	0.561
Age	0.98	0.01	0.96	1	0.045
BMI	1.022	0.031	0.963	1.085	0.469
Time of Surgery	0.989	0.002	0.986	0.993	<0.001
Gender (Female)	0.458	0.273	0.268	0.781	0.004
Time point (Reference category POD1)					
POD 3	7.54	0.346	3.824	14.866	<0.001
Interaction Time point *Study group (Reference category POD1*Study group)					
POD3*Study group	1.232	0.432	0.528	2.875	0.63

Akaike Information Criterion 1147.06; ADL, activities of daily life; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

eTable 19. Logistic mixed model with a random factor for individual patient with cognitive PQRS recovery as dependent variable and study group as main independent variable.

Variable	Estimate	Standard Error	Lower 95% CI	Upper 95% CI	P–value
IPP Group	1.301	0.543	0.449	3.773	0.628
Age	0.834	0.024	0.796	0.875	<0.001
BMI	0.894	0.061	0.793	1.008	0.066
Time of Surgery	0.998	0.003	0.992	1.004	0.576
Gender (Female)	0.458	0.534	0.161	1.305	0.144
Time point (Reference category POD1)					
POD 3	3.918	0.316	2.108	7.283	<0.001
Interaction Time point *Study group (Reference category POD1*Study group)					
POD3* IPP group	0.541	0.425	0.235	1.245	0.149

Akaike Information Criterion 1936.01; PQRS, Postoperative Quality of Recovery Score; IPP, Individualized pneumoperitoneum pressure; BMI, Body Mass Index; POD, Postoperative Day; *CI*, confidence interval.

References

1.Spanish Ministry of Health, Social Services and Equality. Enhanced recovery for abdominal surgery Clinical pathway. Last updated March 2018. https://portal.guiasalud.es/wp-content/uploads/2019/10/viaclinica-rica_english.pdf. Last access on 22 February 2019.

2.Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. Eur J Anaesthesiol. 2015; 32:88–105.

3.Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012; 120:179–84.

4.Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA 2012; 307:2526–33.

5.Bruce J, Krukowski ZH, Al-Khairy G, Russell EM, Park KGM. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 2001; 88:1157–68.

6.Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive care delirium screening checklist: Evaluation of a new screening tool. Intensive Care Med 2001;27:859–64.

7.Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008; 36:309–32.

8.Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J 2012; 33:2551–67.

9.Van Bree SHW, Bemelman WA, Hollmann MW, Zwinderman AH, Matteoli G, El Temna S, et al. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. Ann Surg 2014; 259:708–14.

10.Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240:205–13.

Estrategia de ventilación mecánica en cirugía laparoscópica

Capítulo 5

Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery: An Open-label, Nonrandomized, Crossover, Clinical Trial.

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Introduction

The intraoperative driving pressure, the ratio of tidal volume (V_T) to respiratory system compliance, reflects the strain applied on lung tissue in patients receiving ventilation during general anesthesia for surgery.[1] Driving pressure depends on the amounts of atelectatic and overdistended lung tissue during intraoperative ventilation.[2] Since a rise in intraoperative driving pressure, irrespective of its cause, increases the risk of postoperative pulmonary complications (PPCs),[3] strategies aiming at preventing a rise in driving pressure may benefit surgery patients.[4]

In patients undergoing laparoscopic abdominal surgery, the intraoperative driving pressure rises because of several reasons other than those described above and to a greater extent than with non–laparoscopic surgery: 1) the chest wall becomes stiffer during peritoneum insufflation, causing a rise of ΔP of the respiratory system driving pressure, this may not necessarily mean that the transpulmonary driving pressure rises equally,[5–12] 2) the cranial shift of the diaphragm with pneumoperitoneum strongly favors the formation of atelectases,[13,14] 3) intraoperative ventilation with low V_T, by now a standard preventive measure against the development of PPCs,[11,12,15] could further favor the formation atelectases during peritoneum insufflation.[16]

Individualized positive end–expiratory pressure (PEEP) titration has been shown to prevent a rise in transpulmonary and respiratory system driving pressure during pneumoperitoneum,[5–8] as it may counterbalance the atelectasis–inducing effects of the cranial shift of the diaphragm, mainly with use of low V_T.[7,11] However, PEEP could also cause a rise in driving pressure when it results in overdistension of the nondependent lung parts.[17] The current clinical trial in patients undergoing laparoscopic cholecystectomy was conducted to determine the feasibility of PEEP titrated to the intraoperative abdominal pressure levels to lower transpulmonary driving pressure. It was hypothesized that higher PEEP targeting the intra–abdominal pressure prevents a rise in transpulmonary driving pressure during intraoperative ventilation with pneumoperitoneum.

Methods

Study design

This was an open–label, prospective, non–randomized, crossover, single center clinical trial performed at the Hospital Universitario y Politécnico la Fe in Valencia, Spain. The Institutional Review Board of the hospital approved the investigational protocol (protocol number 2016/0602), and the trial was compliant with the Helsinki Declaration. Written informed consent was obtained from all subjects before entering the trial. The trial was registered at www.clinicaltrials.gov (study identifier NCT03435913). Full access to the protocol is available by request.

Inclusion and exclusion criteria

Patients were approached by study staff and were eligible if: (a) aged ≥ 18 years; (b) had an American Society of Anesthesiology (ASA) score < IV; and (c) planned for laparoscopic cholecystectomy. Exclusion criteria included: (a) pregnancy or breastfeeding; (b) or advanced renal, hepatic or cardiopulmonary disease.

Anesthesia and pneumoperitoneum induction and maintenance

All patients were monitored continuously using electrocardiography, noninvasive blood pressure registration, pulse oximetry and capnography, respiratory gas analysis (Carescape^{TM},GE Healthcare, Chicago, Illinois) and Bispectral (BIS^{TM}) index monitoring (Covidien, Dublin, Ireland). General anesthesia was induced with propofol and maintained with either desflurane or sevoflurane, targeting a BIS^{TM} value between 40 and 60, and remifentanil through continuous intravenous infusion with fentanyl boluses as required. An upper body forced–air warming blanket (Bair Hugger^{TM}, 3M, Maplewood, Minnesota) was used to maintain normothermia.

Kinesimyography was performed by placing sensors on the thenar eminence of the hand to assess neuromuscular block (NMT Mechanosensor^{TM}, GE Healthcare, Chicago, Illinois). Patients received deep neuromuscular blockade throughout ventilation to maintain a train–of–four (TOF) of 0 and a Post–Tetanic Count (PTC) between 1 and 5.

Ventilator settings were set as follows: V_T of 7 ml·kg^{-1} of predicted body weight, respiratory rate (RR) of 12 breaths/min, inspiration to expiration ratio of

1:2, and inspiratory pause of 20% of the total inspiratory time.

Pneumoperitoneum was created by initially setting the CO_2 gas insufflator (Endoflator^{TM}, Karl Storz, Tuttlingen, Germany) to achieve a pressure of 15 mmHg with a flow rate of 1.5 L·min^{-1} and perform insertion of trocars. Subsequently, the patient was placed in the surgical position (20º anti–Trendelenburg).

Esophageal probe placement and pressure monitoring

A balloon–tipped latex esophageal probe (Esophageal probe^{TM}, MBMED, Buenos Aires, Argentina) was inserted through the mouth and advanced ~ 55 to 60 cm. According to manufacturer's recommendations, the balloon was filled with 1.5 ml of air, the top value of the manufacturer's recommended range, after which the intragastric position was checked by observing a pressure deflection with gentle external manual epigastric pressure. The catheter was then withdrawn into the esophagus. Subsequently, the positioning in the lower third was checked by assessing heart artifacts and by performing the expiratory occlusion test as described before.[18] The catheter was considered properly placed if during the test esophageal pressure changes were related to changes in airway pressure within a ratio range of 0.9–1.1. The catheter was then connected to a pressure monitor (FluxMed GrE^{TM}, MBMED, Buenos Aires, Argentina) to measure the esophagus pressure.

Study interventions and measurements

Study interventions and measurements were performed in the time–window between stable pneumoperitoneum and start of the surgical procedure, typically lasting 20 to 30 minutes. During this period, the patient was left untouched by the anesthesiologists and surgeons. Due to this pragmatic setting, blinding of healthcare providers was unfeasible.

At three different predetermined intra–abdominal pressure levels, PEEP was set at 5 cm H_2O ('standard PEEP') for 2 minutes, and after that at 2 cm H_2O above intra–abdominal pressure ('targeted PEEP', where 1 mmHg intra–abdominal pressure equals 1.36 cmH_2O) for 2 minutes. Every protocol–dictated change in PEEP and intra–abdominal pressure was preceded by a standard recruitment maneuver as described before,[19] and detailed in the eMethods and eFigure 1 in the Supplemental Digital Content. With each new step in the study protocol, PEEP was reduced to 5 cm H_2O and a recruitment maneuver was

repeated so that we returned for as much as possible to baseline pulmonary conditions. To achieve the three predefined intra–abdominal pressure levels, the flow rate at the CO_2 gas insufflator was increased to 30 $L \cdot min^{-1}$, and intra–abdominal pressure lowered first to 8 mmHg, and later increased to 12 and finally at 15 mmHg. Each patient was subjected to every intra–abdominal pressure step in a strict sequence always before the start of the surgical intervention.

At baseline before pneumoperitoneum, and two minutes after each PEEP adjustment, airway and esophagus pressure measurements were performed, to obtain the plateau pressure and peak inspiratory pressure, the end–inspiratory and the end–expiratory esophageal pressure. After the last measurement, PEEP and intra–abdominal pressure were set following surgical team clinical criteria and surgery started. For details, see the eMethods and eFigure 1 in the Supplemental Digital Content.

Data collection

Patient height, weight, body mass index and gender, ASA physical status, number of previous abdominal surgeries, number of previous pregnancies, and respiratory comorbidities were recorded before surgery. In addition the following parameters were calculated as follows: respiratory system driving pressure = plateau pressure minus PEEP; end–inspiratory pulmonary pressure = plateau pressure minus end–inspiratory esophageal pressure; end–expiratory pulmonary pressure = end–expiratory airway pressure (defined as PEEP during expiratory hold) minus EEP_{es}; transpulmonary driving pressure = end–inspiratory pulmonary pressure minus end–expiratory pulmonary pressure; respiratory system compliance = $V_T/(P_{plat}$ minus PEEP); chest wall compliance = V_T/(end–inspiratory esophageal pressure minus end–expiratory esophageal pressure); and pulmonary compliance = V_T/ transpulmonary driving pressure. We measured plateau pressure by using an end–inspiratory occlusion of 0.5s. Hemodynamic instability was defined as any episodes of hypotension, with the systolic arterial pressure < 90 mmHg for 3 minutes or longer. Blood pressure was monitored during all study-related interventions, including recruitment maneuvers.

Study endpoints

The primary endpoint was the difference in transpulmonary driving pressure between 'targeted PEEP' and 'standard PEEP' at the three predefined intra–abdomnial pressure levels. Secondary endpoints included the relationship between respiratory system driving pressure and transpulmonary driving pressure and the difference in respiratory system driving pressure between 'targeted PEEP' and 'standard PEEP' at the three predefined intra–abdomnial pressure levels. No interim analyses or rules for early stopping of the trial were included in the study protocol.

Sample size calculation

Comparable studies have been carried out in animal models of abdominal hypertension, but in those studies neuromuscular blockage agents were not used. Therefore, the assumptions for the sample size calculation were built upon findings in clinical investigations.[21,22] Based on respiratory system driving pressure measurements in those studies and the assumption that transpulmonary driving pressure would drop from 18 ± 6 cmH_2O to below a safer level of 13 cmH_2O with PEEP matching, we calculated that 25 patients would be needed to have a power of 90% and an alpha error of 0.05 for a two–tailed hypothesis test. To compensate for dropouts due to potential problems while placing, or using the esophagus pressure catheter, 30 patients were included (see eFigure 2 in the Supplemental Digital Content).

Statistical analysis

Data are presented as proportions and percentages or medians (with 25th–75th percentiles) where appropriate. Normality of distributions was assessed by inspection of quantile–quantile plots. Logarithmic transformation of variables for regression models fitting were performed for non–normally distributed variables. Differences in medians were assessed with a Wilcoxon rank sum test.

First, transpulmonary driving pressure was compared at the three intra–abdominal pressure levels between 'targeted PEEP' and 'standard PEEP'. For this, a mixed–effect linear regression model was used with the following prespecified features: transpulmonary driving pressure as the dependent variable and PEEP level (targeted and standard) as fixed effect; individuals were introduced as a random factor with a random intercept. Intra–abdominal pressure level, as an ordinal categorical variable with three levels, body mass

index and baseline transpulmonary driving pressure before peritoneum were introduced as covariables. Moreover, an interaction term between intra–abdominal pressure level and PEEP level were also included in the model. Also, a similar mixed–effect linear regression model was used with respiratory system driving pressure as the dependent variable. Covariables' adjustment were pre–specified in the analysis plan. No stratification analysis was performed.

Second, the relationship between transpulmonary driving pressure and respiratory system driving pressure was determined by Pearson's correlation coefficient and local polynomial regressionΔ.

In a posthoc analysis, Bayesian mixed–effect modeling was performed with intra–abdominal pressure as a monotonic effect. These models were built to evaluate the effect of simulating a stepwise behavior in the variable at every 1 mmHg of intra–abdominal pressure on the relationship between PEEP regime and transpulmonary driving pressure and respiratory system driving pressure with the same covariable structure of the mixed–effect models reported above. We used for this analysis the R package *brms* which implements mixed–effects models estimated with Hamiltonian Markov No U–turn sampler setting prior distribution with the default from the package to have a weak prior with small influence (half Student-t prior with 3 degrees of freedom, location of 0 and scale of 10).

All analyses were repeated for lung compliance and respiratory system compliance and reported in the Supplemental Digital Content.

All statistical analyses were performed with Stata (Statacorp^{TM}, College Station, TX, USA) and R 3.5.1 (The R Foundation for Statistical Computing, www.r-project.org). Statistical significance was set for two–tailed at $P < 0.05$.

Results

Patients

In total, 30 patients were included in this study between April 2018 and November 2018. Patients' demographics and ventilation characteristics are presented in Table 1. The study protocol was strictly followed and completed in all patients, without episodes of hemodynamic instability in the time–window of intra–abdominal pressure and PEEP titrations for this study. There were no

missing data. The trial was conducted and finished in accordance to the study protocol.

Effect of 'targeted PEEP' on transpulmonary and respiratory system driving pressure at three intra–abdominal pressure levels

Transpulmonary and respiratory system driving pressure at 'standard PEEP' and 'targeted PEEP' at the three predefined intra–abdominal pressure levels are presented in Figure 1 and Table 2. At 'standard PEEP', median transpulmonary driving pressure at intra–abdominal pressure of 15 mmHg was higher compared to median transpulmonary driving pressure at intra–abdominal pressure of 12 mmHg or 8 mmHg. 'Targeted PEEP' resulted in a lower median transpulmonary driving pressure at all three intra–abdominal pressure levels compared to 'standard PEEP'. As shown in eTables 1 and 2 in the Supplemental Digital Content, Transpulmonary and respiratory system driving pressure were lower at 'targeted PEEP' when compared to 'standard PEEP', after controlling for several confounders and individual variability.

Relationship between transpulmonary and respiratory system driving pressure

Transpulmonary and respiratory system driving pressure showed a moderate–to–strong linear relationship (Figure 2) and a strong correlation. Table 3 presents Transpulmonary and respiratory system driving pressure correlation by intra–abdominal pressure level. Correlation between transpulmonary and respiratory system driving pressure decreased at intra–abdominal pressure of 12 and intra–abdominal pressure of 15 mmHg, compared to the decrease at intra–abdominal pressure of 8 mm Hg, but remained moderate–to–strong. The full correlation matrix is showed in eFigures 3–5 in Supplemental Digital Content.

Effect of 'targeted PEEP' on respiratory system, lung, and chest wall compliance

At 'standard PEEP', median lung compliance at intra–abdominal pressure of 15 mmHg was lower compared to median lung compliance at intra–abdominal pressure of 8 mm Hg or 12 mm Hg. Likewise, 'targeted PEEP' increased median lung compliance compared to 'standard PEEP' at all three intra–abdominal pressure levels. While 'targeted PEEP' significantly increased respiratory system compliance at all three intra–abdominal pressure levels, chest wall compliance had no relationship in the univariate analysis. Multivariable regression showed that lung compliance decreased at 'standard

PEEP' when compared to 'targeted PEEP'. (eTable 3, eTable 4 and eFigures 6 and 7 in the Supplemental Digital Content).

Effect of 'targeted PEEP' on pulmonary and esophageal pressure

With 'targeted PEEP' end–inspiratory pulmonary pressure was higher at all three intra–abdominal pressure level with an increasing difference with increasing intra–abdominal pressure levels. Similarly, end–expiratory pulmonary pressure was higher with 'targeted PEEP', and at 'standard PEEP' the median end–expiratory pulmonary pressure was negative (Table 2).

Posthoc analysis

The results of the posthoc analysis are presented in Figure 3, eFigure 7, and eTables 5, 6, and 7 in the Supplemental Digital Content. Intra–abdominal pressure had a significant monotonic effect with higher intra–abdominal pressures being associated with higher transpulmonary and respiratory system driving pressure, with a larger effect at intra–abdominal pressure > 12 mm Hg with a posterior probability > 0.999. Moreover, 'targeted PEEP' reduced transpulmonary driving pressure by 2.41 [95% Credibility Interval, CI: 1.45 – 3.34] cmH_2O compared to 'Standard PEEP' with a posterior probability > 0.999. The model estimated that the difference in transpulmonary driving pressure between 8 and 15 mmHg intra–abdominal pressure was 1.83 [95% CI: 0.82 – 2.86] cmH_2O (eTable 5a) and that the difference between adjacent level of intra–abdominal pressure increased from 12 mmHg (simplex parameter 0.11 from 8 to 12 and 0.18 from 12 to 15 mmHg, eTable 5b). Accordingly, intra–abdominal pressure had a significant negative monotonic on lung compliance with higher intra–abdominal pressures being associated with lower lung compliance (eTable 7a and b).

Discussion

In this single–center study comparing intraoperative ventilation with 'targeted PEEP' versus 'standard PEEP' at three predefined and clinically relevant intra–abdominal pressure levels in patients planned for laparoscopic cholecystectomy, it was found that (a) pneumoperitoneum increases transpulmonary and respiratory system driving pressure in a non–linear fashion with an increasing rate when intra–abdominal pressure is equal or higher than

12 mmHg; (b) transpulmonary and respiratory system driving pressure have an almost linear relationship and a moderate correlation that decreases as intra–abdominal pressure increase; and (c) 'targeted PEEP' decreases transpulmonary driving pressure.

This study has several strengths. First, an esophagus balloon was used to capture pressures that allowed accurate calculations of transpulmonary driving pressure. During intraoperative ventilation under pneumoperitoneum, transpulmonary driving pressure is more informative than respiratory system driving pressure. Second, all titration steps of the study protocol were feasible, and in all patients the protocol was followed step–by–step and completed. Third, the study had little exclusion criteria, increasing its generalizability and a clear and predefined analysis plan as a measure against reporting bias. Fourth, meticulous multivariable and mixed effect statistical methods were used to control for potentially confounding variables, and to include interindividual variability in the various estimates, and also an analysis of intra–abdominal pressure as a quantitative variable and not solely as a dichotomic feature.

Although previous trials reported a small reduction in transpulmonary driving pressure by applying PEEP in an animal model of abdominal hypertension without neuromuscular block,[20] to our best knowledge there is no previous human study that investigates the effects of PEEP titrations linked to *variable* intra–abdominal pressure levels in the laparoscopic surgical setting. The results of the current study, are in line with findings in recent investigations on titration of PEEP according to certain ventilator parameters, like respiratory system compliance,[7] and chest wall and lung compliance.[21] The results of the current study add to our understanding of the effects of PEEP by showing that 'targeted PEEP' reduces transpulmonary and respiratory system driving pressure at all three intra–abdominal pressure levels. In addition, the current study found that the intra–abdominal pressure level 'per se' influences transpulmonary and respiratory system driving pressure and that the effects of 'targeted PEEP' increase at higher intra–abdominal pressure levels, building up from findings from previous studies using a conventional intra–abdominal pressure level,[8] and preclinical study using an animal model of abdominal hypertension.[20] These findings, possibly due to increased alveolar collapse at higher intra–abdominal pressure level, suggest a non–linear thoraco–abdominal

relationship especially at 'standard PEEP' level, as also shown in the posthoc mixed regression analysis. The Bayesian model simplex parameters, which estimate the amount of change at each step of pressure, increase for intra–abdominal pressure > 12 mmHg, therefore it can be speculated that thoraco–abdominal transmission varies with different intra–abdominal pressure levels. The anti–Trendelenburg position may have played a role in mitigating the rate of transmission of intra–abdominal pressure to the lungs. Therefore, the potential effects of other surgical positions remain to be tested in future studies.

Interestingly, we observed stable median transpulmonary driving pressure values while rising intra–abdominal pressure at 'targeted PEEP' while median respiratory system driving pressure keeps increasing. One possible explanation for this finding is that the applied PEEP counterbalances the rising intra–abdominal pressure avoiding, or minimizing alveolar collapse. The resulting increasing difference between the two pressures suggests that at higher intra–abdominal pressure, respiratory system driving pressure could not be a good reflection of transpulmonary driving pressure. We observed a similar effect of PEEP on end–expiratory pulmonary pressure across all intra–abdominal pressure levels, which suggests an improved alveolar recruitment. An increase in alveolar recruitment not only improves oxygenation[5] but also leads to a more homogeneous ventilation.[6,23] The clinical implications of these improvements, however, remain uncertain. For instance, in critically ill patients with acute respiratory distress syndrome, these improvements did not translate in better clinical outcomes.[24,25]

Postoperative pulmonary complications are a significant source of perioperative morbidity and mortality,[8] and while the protective role of low V_T during intraoperative ventilation is well accepted,[15,26] the role of high PEEP remains highly uncertain.[8,16] Intraoperative respiratory system driving pressure has been suggested to be a risk factor for the development of pulmonary complications after surgery.[3] Whether an intraoperative ventilation strategy directly or indirectly targeting a low respiratory system driving pressure successfully prevents such complications is still debatable. A recently published large trial in general surgery patients found that an open lung approach resulted in a lower incidence of PPCs. PPCs, however, were a secondary outcome of that study.[4] Therefore, present evidence does not allow a definitive conclusion

to be drawn.

In the laparoscopic surgery setting, at least in theory, transpulmonary driving pressure could provide better information than respiratory system driving pressure on dynamic lung strain.[24,25] In this regard, data from previous investigations consistently showed how respiratory system compliance decreases with peritoneal insufflation but which part of the respiratory system (chest wall or lung) contributes the most is still debated. While chest wall stiffening is undisputed,[27–32] there is some difference as far as lung compliance is concerned, with some studies showing a reduction in lung compliance,[27–29] and other showing no pneumoperitoneum related effect.[30–32] Preclinical and clinical studies have shown reductions in transpulmonary driving pressure by applying PEEP.[7,20,21] It must be mentioned, though, that these studies differed from our clinical scenario in many ways. For instance, preclinical evidence was obtained at different intra–abdominal pressure levels of PEEP without using neuromuscular blocking agents.[20] Also, to our best knowledge no human study has been performed that investigated the effects of PEEP titrations linked to variable intra–abdominal pressure levels in a human setting during surgery. Important to notice is that the results of the current clinical study are in line with findings in recently published studies on PEEP titration to respiratory system compliance during laparoscopic surgery,[7] and on PEEP plus recruitment maneuver at a fixed intra–abdominal pressure level.[21]

The current study suggests a moderate–to–strong correlation between transpulmonary and respiratory system driving pressure across all three intra–abdominal pressure levels, independent from the two levels of PEEP tested. It cannot be excluded that this was caused by the use of repeated recruitment maneuvers before each PEEP titration. While ‘targeted PEEP’ at high intra–abdominal pressure resulted in comparable driving pressure as ‘standard PEEP’ at low intra–abdominal pressure, the intra–abdominal pressure level 'per se' can have an effect on respiratory pressures and mechanics. These findings, at least in part suggest that performing surgery at a lower intra–abdominal pressure 'per se' results in a low transpulmonary driving pressure. Surgery at a lower intra–abdominal pressure, instead of surgery with high PEEP, could have several advantages. For instance, high PEEP may increase lung static strain, potentially leading to more inflammation.[33] High PEEP may also negatively affect right

ventricular function.[34,35] In addition, high PEEP could favor the development of pleural effusions through compression of lymphatic vessels as shown in previous trials.[4,19,36] Future studies of strategies that may affect transpulmonary driving pressure, and their effects on clinical outcomes. should therefore not only focus on the best level of PEEP, but probably also the best intra–abdominal pressure. As shown before, the best intra–abdominal pressure is not necessarily a high intra–abdominal pressure.[22]

This study has several limitations. As mentioned above, in this study PEEP was titrated only at one single time point, and before the start of the surgical procedure itself. To prevent a possible carryover effect between the successive intra–abdominal pressure steps, each new step in the study protocol started with a reduction of PEEP to 5 cm H_2O, plus a recruitment maneuver. Nevertheless, a carryover effect from the preceding PEEP titrations cannot be ruled out entirely. It must be acknowledged that the effect of high PEEP on transpulmonary pressure and lung compliance was studied in a particular surgical positioning, and it could be that effects are different when another surgical position is used. In addition, this study compared only two PEEP levels, i.e., without individualization. We did not record cardiac output and monitor for hemodynamic instability during the protocol time–frame period. Moreover, the study protocol did neither allow us to determine end–expiratory volumes nor extent of atelectasis or overdistension.[37–39] Also, we measured plateau pressure by using an end inspiratory occlusion of 0.5s. Thus, it is possible that we did not reach a static plateau pressure at end-inspiration, likely yielding a minimal overestimation of the driving pressure. However, this method and short duration of occlusion has been previously used in patients undergoing general anesthesia to estimate plateau pressure.[40] Further, most of ventilators actually used in anesthesia do not allow longer period of inspiratory occlusion. Also, due to the specific esophagus probe filling procedure, comparison with other probes with different inflating volume have to be interpreted with some caution. Moreover, since our main objective was the transpulmonary driving pressure we did not perform a calibration of absolute values thus interpretation on individual values such as end–expiratory pulmonary pressure must be done with caution. Finally, we conceived our study as a physiological proof of concept with a power estimation for a limited number of patients and without prespecified correction

for multiple comparisons. Therefore, our result should be seen as exploratory. Esophageal monitoring can be cumbersome in operating room conditions and may represent only an estimation of regional pressure. Due to this technique related pitfalls relying on respiratory system driving pressure is appealing, provided that its value can be reliably related to the real lung strain.

In conclusion, in this cohort of patients planned for laparoscopic cholecystectomy, using three different but relevant intra–abdominal pressure levels, transpulmonary driving pressure increased at higher intra–abdominal pressure levels. These effects could be counterbalanced with 'targeted PEEP', with the strongest effect at the highest intra–abdominal pressure level. However, lowering intra–abdominal pressure could be a more attractive approach to lower the transpulmonary driving pressure than using 'targeted PEEP'.

Referencias

1.Silva PL, Rocco PRM. The basics of respiratory mechanics: ventilator-derived parameters: Ann Transl Med 2018; 6: 376–376.

2.Güldner A, Kiss T, Serpa Neto A, Hemmes SN, Canet J, Spieth PM, Rocco PR, Schultz MJ, Pelosi P, Gama de Abreu M: Intraoperative Protective Mechanical Ventilation for Prevention of Postoperative Pulmonary Complications. Anesthesiology 2015; 123: 692–713.

3.Neto AS, Hemmes SNT, B Barbas CS, Beiderlinden M, Fernandez-Bustamante A, Futier E, Gajic O, El-Tahan MR, Ghamdi AA, Günay E, Jaber S, Kokulu S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Ranieri VM, Scavonetto F, Schilling T, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Amato MB, Costa EL, de Abreu MG, Pelosi P, Schultz MJ; PROVE Network Investigators: Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: A meta-analysis of individual patient data. Lancet Respir Med 2016; 4: 272–80.

4.Ferrando C, Soro M, Unzueta C, Suarez-Sipmann F, Canet J, Librero J Pozo N, Peiró S, Llombart A, León I, India I, Aldecoa C, Díaz-Cambronero O, Pestaña D, Redondo FJ, Garutti I, Balust J, García JI, Ibáñez M, Granell M, Rodríguez A, Gallego L, de la Matta M, Gonzalez R, Brunelli A, García J, Rovira L, Barrios F, Torres V, Hernández S, Gracia E, Giné M, García M, García N, Miguel L, Sánchez S, Piñeiro P, Pujol R, García-Del-Valle S, Valdivia J, Hernández MJ, Padrón O, Colás A, Puig J, Azparren G, Tusman G, Villar J, Belda J; Individualized PeRioperative Open-lung VEntilation (iPROVE) Network: Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. Lancet Respir Med. 2018; 6: 193–203.

5.Ferrando C, Tusman G, Suarez-Sipmann F, León I, Pozo N, Carbonell J, Puig J, Pastor E, Gracia E, Gutiérrez A, Aguilar G, Belda FJ, Soro M: Individualized lung recruitment maneuver guided by pulse-oximetry in anesthetized patients undergoing laparoscopy: a feasibility study. Acta Anaesthesiol Scand 2018; 62: 608–19.

6.Eichler L, Truskowska K, Dupree A, Busch P, Goetz AE, Zöllner C: Intraoperative Ventilation of Morbidly Obese Patients Guided by Transpulmonary Pressure. Obes Surg 2018; 28: 122–129.

7.D'Antini D, Rauseo M, Grasso S, Mirabella L, Camporota L, Cotoia A, Spadaro S, Fersini A, Petta R, Menga R, Sciusco A, Dambrosio M, Cinnella G: Physiological effects of the open lung approach during laparoscopic cholecystectomy: Focus on

driving pressure. Minerva Anestesiol 2018; 84: 159–67.

8.Cinnella G, Grasso S, Spadaro S, Rauseo M, Mirabella L, Salatto P, De Capraris A, Nappi L, Greco P, Dambrosio M: Effects of recruitment maneuver and positive end-expiratory pressure on respiratory Mechanics and transpulmonary pressure during laparoscopic surgery. Anesthesiology 2013; 118: 114–22.

9.Chiumello D, Carlesso E, Cadringher P, Caironi P, Valenza F, Polli F, Tallarini F, Cozzi P, Cressoni M, Colombo A, Marini JJ, Gattinoni L: Lung stress and strain during mechanical ventilation for acute respiratory distress syndrome. Am J Respir Crit Care Med 2008; 178: 346–55.

10.Valenza F, Chevallard G, Fossali T, Salice V, Pizzocri M, Gattinoni L: Management of mechanical ventilation during laparoscopic surgery. Best Pract Res Clin Anaesthesiol 2010; 24: 227–41.

11.Futier E, Constantin J-M, Paugam-Burtz C, Pascal J, Eurin M, Neuschwander A, Marret E, Beaussier M, Gutton C, Lefrant JY, Allaouchiche B, Verzilli D, Leone M, De Jong A, Bazin JE, Pereira B, Jaber S; IMPROVE Study Group: A Trial of Intraoperative Low-Tidal-Volume Ventilation in Abdominal Surgery. N Engl J Med 2013; 369: 428–37.

12.Severgnini P, Selmo G, Lanza C, Chiesa A, Frigerio A, Bacuzzi A, Dionigi G, Novario R, Gregoretti C, de Abreu MG, Schultz MJ, Jaber S, Futier E, Chiaranda M, Pelosi P: Protective Mechanical Ventilation during General Anesthesia for Open Abdominal Surgery Improves Postoperative Pulmonary Function. Anesthesiology 2013; 118: 1307–21.

13.Andersson LE, Bååth M, Thörne A, Aspelin P, Odeberg-Wernerman S: Effect of carbon dioxide pneumoperitoneum on development of atelectasis during anesthesia, examined by spiral computed tomography. Anesthesiology 2005; 102: 293–9.

14.Gurusamy KS, Samraj K, Davidson BR: Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. Cochrane Database Syst Rev 2014; 18: CD006930.

15.Serpa Neto A Hemmes SN, Barbas CS, Beiderlinden M, Biehl M, Binnekade JM, Canet J, Fernandez-Bustamante A, Futier E, Gajic O, Hedenstierna G, Hollmann MW, Jaber S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Putensen C, Ranieri M, Scavonetto F, Schilling T, Schmid W, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Gama de Abreu M, Pelosi P, Schultz MJ; PROVE Network Investigators: Protective versus Conventional Ventilation for Surgery: A Systematic Review and Individual Patient Data Meta-analysis. Anesthesiology 2015; 123: 66–78.

16.Henny CP, Hofland J. Laparoscopic surgery: Pitfalls due to anesthesia, positioning,

and pneumoperitoneum. Surg Endosc 2005; 19: 1163–71.

17.Pelosi P, Ball L. Should we titrate ventilation based on driving pressure? Maybe not in the way we would expect. Ann Transl Med 2018; 6: 389.

18.Yoshida T, Bellani G, Goligher EC, Carteaux G, Rittayamai N, Mojoli F, Chiumello D, Piquilloud L, Grasso S, Jubran A, Laghi F, Magder S19, Pesenti A, Loring S, Gattinoni L, Talmor D, Blanch L, Amato M, Chen L, Brochard L, Mancebo J; PLeUral pressure working Group (PLUG—Acute Respiratory Failure section of the European Society of Intensive Care Medicine): Esophageal and transpulmonary pressure in the clinical setting: meaning, usefulness and perspectives. Intensive Care Med 2016; 42: 1360-73.

19.The PROVE Network Investigators, for the Clinical Network of the European Society of Anaesthesiology: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): A multicentre randomised controlled trial. Lancet 2014; 384: 495–503.

20.Regli A, Chakera J, De Keulenaer BL, Roberts B, Noffsinger B, Singh B, van Heerden PV: Matching positive end-expiratory pressure to intra-abdominal pressure prevents end-expiratory lung volume decline in a pig model of intra-abdominal hypertension. Crit Care Med 2012; 40: 1879–86.

21.Pelosi P, Foti G, Cereda M, Vicardi P, Gattinoni L: Effects of carbon dioxide insufflation for laparoscopic cholecystectomy on the respiratory system. Anaesthesia 1996; 51:744–9.

22.Diaz-Cambronero O, Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, Olmedilla Arnal LE, Argente Navarro MP, Schultz MJ, Errando CL. IPPColLapSe study group: A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study. Surg Endosc 2019; 33: 252–60.

23.Pereira SM, Tucci MR, Morais CCA, Simões CM, Tonelotto BFF, Pompeo MS, Kay FU, Pelosi P, Vieira JE, Amato MBP. Individual Positive End-expiratory Pressure Settings Optimize Intraoperative Mechanical Ventilation and Reduce Postoperative Atelectasis. Anesthesiology 2018; 129: 1070–81.

24.Cavalcanti AB, Amato MBP, Serpa-Neto A: The Elusive Search for "best PEEP" and Whether Esophageal Pressure Monitoring Helps. JAMA 2019; 321: 839–41.

25.Beitler JR, Sarge T, Banner-Goodspeed VM, Gong MN, Cook D, Novack V, Loring SH, Talmor D; EPVent-2 Study Group: Effect of Titrating Positive End-Expiratory Pressure (PEEP) With an Esophageal Pressure–Guided Strategy vs. an Empirical High PEEP-FiO2 Strategy on Death and Days Free From Mechanical Ventilation Among Patients With Acute Respiratory Distress Syndrome . JAMA 2019; Feb 18. doi:

10.1001/jama.2019.0555. Epub ahead of print.

26.Mazo V, Sabaté S, Canet J, Gallart L, de Abreu MG, Belda J, Langeron O, Hoeft A, Pelosi P: Prospective external validation of a predictive score for postoperative pulmonary complications. Anesthesiology 2014; 121: 219–31.

27.Futier E, Constantin JM, Pelosi P, Chanques G, Kwiatkoskwi F, Jaber S, Bazin JE: Intraoperative Recruitment Maneuver Reverses Detrimental Pneumoperitoneum-induced Respiratory Effects in Healthy Weight and Obese Patients Undergoing Laparoscopy. Anesthesiology 2010; 113: 1310–9.

28.Fahy BG, Barnas GM, Flowers JL, Nagle SE, Njoku MJ: The Effects of Increased Abdominal Pressure on Lung and Chest Wall Mechanics During Laparoscopic Surgery. Anesth Analg 1995; 81: 744–50.

29.Wirth S, Biesemann A, Spaeth J, Schumann S: Pneumoperitoneum deteriorates intratidal respiratory system mechanics: an observational study in lung-healthy patients. Surg Endosc 2017; 31: 753–60.

30.Cortes-Puentes GA, Gard KE, Adams AB, Faltesek KA, Anderson CP, Dries DJ, Marini JJ: Value and limitations of transpulmonary pressure calculations during intra-abdominal hypertension. Crit Care Med 2013; 41: 1870–7.

31.Kubiak BD, Gatto LA, Jimenez EJ, Silva-Parra H, Snyder KP, Vieau CJ, Barba J, Nasseri-Nik N, Falk JL, Nieman GF: Plateau and Transpulmonary Pressure With Elevated Intra-Abdominal Pressure or Atelectasis. J Surg Res 2009; 159: e17–24.

32.Loring SH, Stephen H.Behazin N, Novero A, Novack V, Jones SB, O'Donnell CR, Talmor DS: Respiratory mechanical effects of surgical pneumoperitoneum in humans. J Appl Physiol 2014; 117: 1074–9.

33.Guldner A, Braune A, Ball L, Silva PL, Samary C, Insorsi A, Huhle R, Rentzsch I, Becker C, Oehme L, Andreeff M, Vidal Melo MF, Winkler T, Pelosi P, Rocco PR, Kotzerke J, Gama de Abreu M: Comparative Effects of Volutrauma and Atelectrauma on Lung Inflammation in Experimental Acute Respiratory Distress Syndrome. Crit Care Med. 2016; 44: e854–65.

34.Das A, Haque M, Chikhani M, Cole O, Wang W, Hardman JG, Bates DG: Hemodynamic effects of lung recruitment maneuvers in acute respiratory distress syndrome. BMC Pulm Med 2017; 17: 34.

35.Luecke T, Pelosi P: Clinical review: Positive end-expiratory pressure and cardiac output. Crit Care 2005; 9: 607–21.

36.Moriondo A, Mukenge S, Negrini D: Transmural pressure in rat initial subpleural lymphatics during spontaneous or mechanical ventilation. Am J Physiol Hear Circ Physiol 2005; 289: H263–9.

37.Dellamonica J, Lerolle N, Sargentini C, Beduneau G, Di Marco F, Mercat A, Richard

JC, Diehl JL, Mancebo J, Rouby JJ, Lu Q, Bernardin G, Brochard L: PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intensive Care Med 2011; 37: 1595–604.

38.Olegård C, Söndergaard S, Houltz E, Lundin S, Stenqvist O: Estimation of functional residual capacity at the bedside using standard monitoring equipment: A modified nitrogen washout/washing technique requiring a small change of the inspired oxygen fraction. Anesth Analg 2005; 101: 206–12.

39.Junhasavasdikul D, Telias I, Grieco DL, Chen L, Gutierrez CM, Piraino T, Brochard L: Expiratory Flow Limitation During Mechanical Ventilation. Chest 2018; 154 :948–62.

40.Grieco DL, Anzellotti GM, Russo A, Bongiovanni F, Costantini B, D'Indinosante M, Varone F, Cavallaro F, Tortorella L, Polidori L, Romanò B, Gallotta V, Dell'Anna AM, Sollazzi L, Scambia G, Conti G, Antonelli M. Airway Closure during Surgical Pneumoperitoneum in Obese Patients. Anesthesiology 2019 Jul;131(1):58-73.

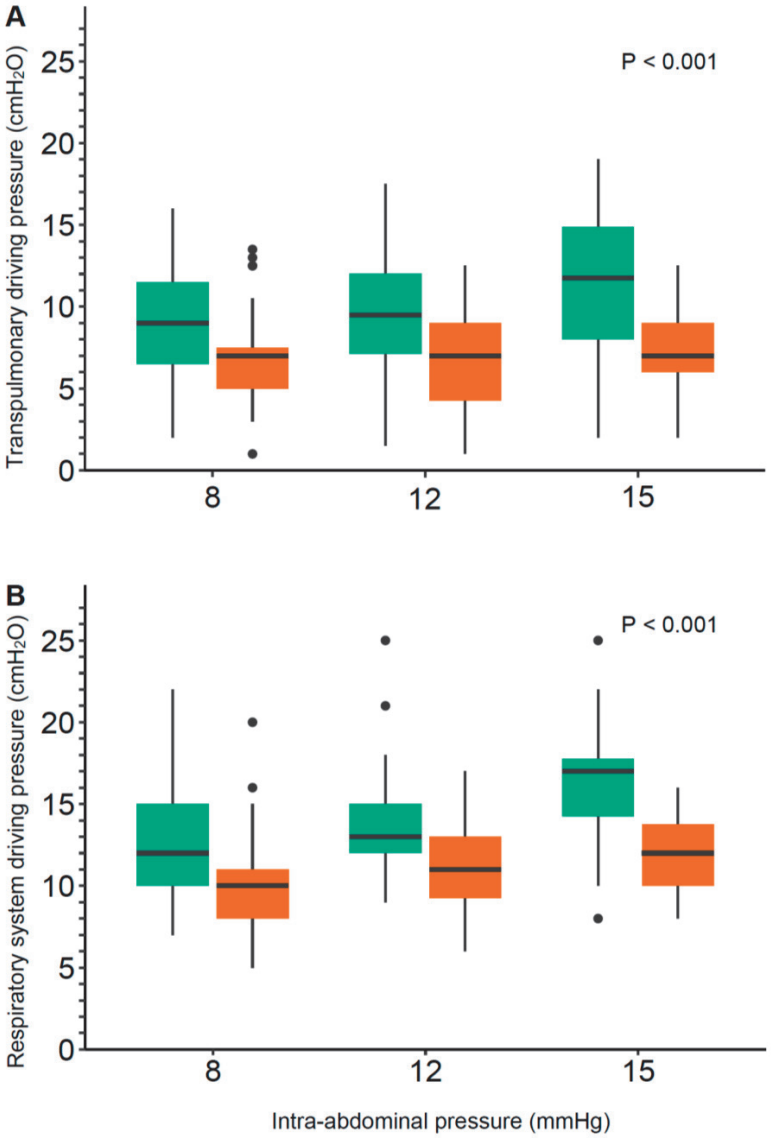


Figure 1. Boxplots for transpulmonary and respiratory system driving pressures by intra–abdominal pressure level at 'standard PEEP' and 'targeted PEEP'. A: Transpulmonary driving pressure; B: Respiratory system driving pressure. Green boxes represent the 'standard PEEP' group, orange boxes the 'targeted PEEP' group. *P* values reported are from the multivariable analysis. Transpulmonary and respiratory system driving pressures are reported in cmH_2O and intra–abdominal pressure in mmHg.

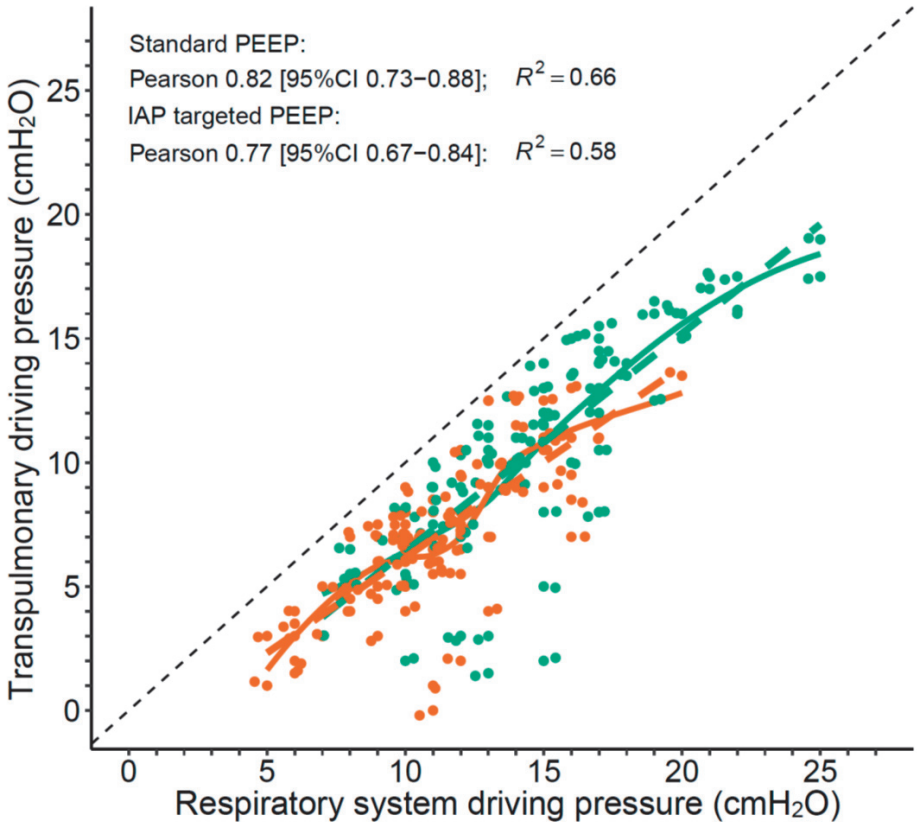


Figure 2. Scatterplots for transpulmonary driving pressure and respiratory system driving pressure and. Solid lines are local polynomial regressions; dashed lines are linear regressions. Green lines represent the 'standard PEEP' group, orange lines the 'targeted PEEP' group. Overall Linear R^2 and Pearson correlation coefficients by group are reported. Transpulmonary and respiratory system driving pressures are reported in cmH_2O. Abbreviations: PEEP, positive end–expiratory pressure.

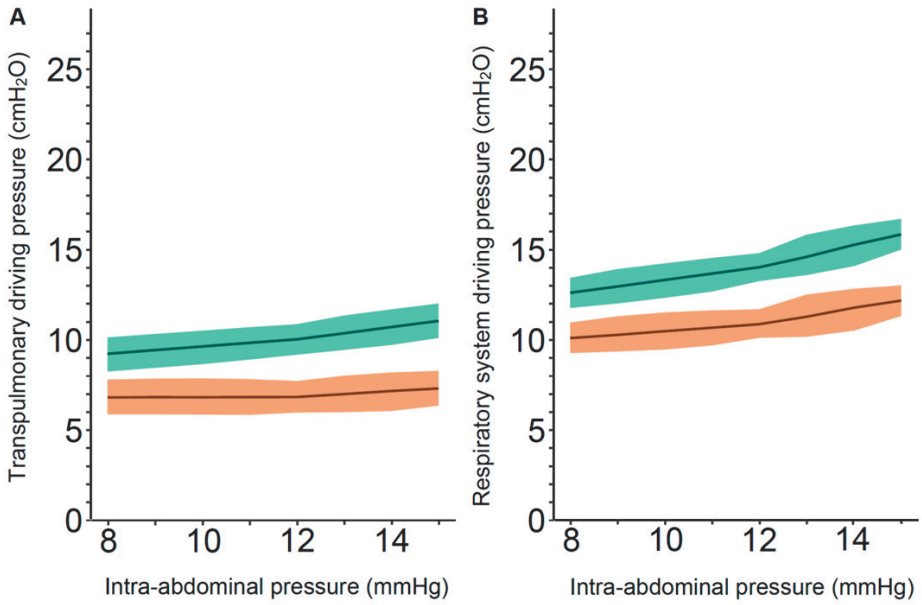


Figure 3. The marginal effect of intra–abdominal pressure from Bayesian multivariable mixed model for A: Transpulmonary driving pressure; B: Respiratory system driving pressure. Green lines represent the 'standard PEEP' group, orange lines the 'targeted PEEP' group. Transparent ribbons are 95% credibility intervals. Transpulmonary and respiratory system driving pressures are reported in cmH_2O and intra–abdominal pressure in mm Hg. Abbreviations: PEEP, positive end expiratory pressure.

Table 1 Baseline characteristics	
Age (Years)	60 [57 – 74]
Gender (Female)	19 (63.3)
Weight (Kg)	72 [65 – 83]
Height (cm)	161 [156 – 166]
ASA	
1	2 (6.7)
2	20 (66.7)
3	8 (26.7)
Previous respiratory disease (Yes)	4 (13.3)
Number of previous pregnancies	
0	14 (46.7)
1	3 (10.0)
2	8 (26.7)
3	4 (13.3)
7	1 (3.3)
Number of previous open surgeries	
0	15 (50.0)
1	7 (23.3)
2	7 (23.3)
3	1 (3.3)
Number of previous laparoscopic surgeries	
0	28 (93.3)
1	1 (3.3)
2	1 (3.3)
Tracheal tube internal diameter (mm)	8 [8 – 8]
Intra–abdominal volume at 15 cmH_20 at first insufflation (L)	5 [4 – 5]
Body mass index (Kg · m^{-2})	27 [25 – 30]
Predicted body weight (Kg)	54 [49 – 61]
V_T (mL)	400 [400 – 450]
Respiratory peak pressure (cmH_2O)	20 [17 – 24]
Respiratory plateau pressure (cmH_2O)	16 [14 – 20]
End–inspiratory esophageal pressure (cmH_2O)	14 [9 – 19]
End–expiratory esophageal pressure (cmH_2O)	10 [6 – 15]
Respiratory driving pressure (cmH_2O)	10 [9 – 15]
Transpulmonary driving pressure (cmH_2O)	8 [5 – 12]
Respiratory system compliance ($mL \cdot cmH_2O^{-1}$)	38 [27 – 48]
Chest wall compliance ($mL \cdot cmH_2O^{-1}$)	124 [100 – 200]
Lung compliance ($mL \cdot cmH_2O^{-1}$)	55 [33 – 85]
Data are reported as number (%) or median [25th–75th percentile]. *ASA*, American Society of Anesthesiologists physical status; V_T, tidal volume.	

Table 2. Ventilation pressures and respiratory mechanics with 'standard PEEP and 'targeted PEEP' at the three predefined intra– abdominal pressure levels

	Intra–abdominal pressure		Standard PEEP	Targeted PEEP	Difference [95% CI]	*P*–value
cmH_2O	mmHg	cmH_2O				
Transpulmonary driving pressure	8	10.8	9 [7 – 11]	7 [5 – 8]	2 [0.5 – 4]	0.010
	12	16.3	10 [7 – 12]	7 [4 – 9]	3 [1 – 5]	0.002
	15	20.4	12 [8 – 15]	7 [6 – 9]	4 [2 – 6]	< 0.001
Respiratory system driving pressure	8	10.8	12 [10 – 15]	10 [8 – 11]	3 [1 – 4]	0.004
	12	16.3	13 [12 – 15]	11 [9 – 13]	3 [1 – 4]	0.001
	15	20.4	17 [14 – 18]	12 [10 – 14]	4 [2 – 6]	< 0.001
Plateau pressure	8	10.8	17 [15 – 20]	20 [18 – 21]	2 [1 – 4]	0.005
	12	16.3	18 [17 – 20]	25 [23 – 27]	6 [5 – 8]	< 0.001
	15	20.4	22 [19 – 23]	29 [27 – 31]	8 [6 – 10]	< 0.001
PEEP	8	10.8	5	10		
	12	16.3	5	14		
	15	20.4	5	17		
End–inspiratory pulmonary pressure	8	10.8	3 [0 – 7]	5 [1 – 8]	2 [0 – 4]	0.189
	12	16.3	4 [-1 – 6]	7 [4 – 9]	4 [1 – 7]	0.003
	15	20.4	2 [-2 – 6]	9 [3 – 13]	6 [3 – 9]	< 0.001
End–expiratory pulmonary pressure	8	10.8	- 7 [-10 – -5]	- 2 [-5 – 0]	4 [2 – 6]	0.001
	12	16.3	- 8 [-11 – -4]	0 [-3 – 1]	7 [5 – 10]	< 0.001
	15	20.4	- 9 [-14 – -4]	1 [-2 – 5]	10 [6 – 14]	< 0.001
End–inspiratory esophageal pressure	8	10.8	15 [14 – 18]	15 [13 – 18]	0 [-2 – 2]	0.867
	12	16.3	17 [14 – 20]	19 [16 – 22]	2 [0 – 4]	0.171
	15	20.4	19 [15 – 23]	22 [17 – 25]	1 [-5 – 2]	0.325
End–expiratory esophageal pressure	8	10.8	12 [10 – 14]	12 [15 – 15]	0 [-3 – 1]	0.605
	12	16.3	13 [9 – 16]	14 [13 – 17]	1 [-4 – 1]	0.293
	15	20.4	14 [9 – 19]	16 [12 – 19]	1 [-5 – 2]	0.374

Data are reported as median [25th–75th percentile]. Airway, transpulmonary, and esophageal pressures are reported in cmH_2O. Abdominal pressure is reported in mm Hg and cmH_2O. Abbreviations: *PEEP*, positive end–expiratory pressure; *IAP*, intra–abdominal pressure; *CI*, confidence interval. *P* values reported for univariate analysis. Wilcoxon rank sum test was applied.

Table 3. Correlation between transpulmonary driving pressure and respiratory system driving pressure by PEEP and intra–abdominal pressure regime

	Standard PEEP	Targeted PEEP	Intra–abdominal pressure	
	Transpulmonary driving pressure		mm Hg	cmH_2O
Respiratory system driving pressure	0.89 [0.78 – 0.95]*	0.90 [0.81 – 0.95]*	8	10.8
	0.77 [0.60 – 0.89]*	0.76 [0.55 – 0.88]*	12	16.3
	0.78 [0.58 – 0.89]*	0.64 [0.36 – 0.81]*	15	20.4

Data are reported as Pearson correlation coefficient [95% Confidence Interval]. Abbreviations: *PEEP*, positive end–expiratory pressure. * $P < 0.001$.

Suplemento Capítulo 5

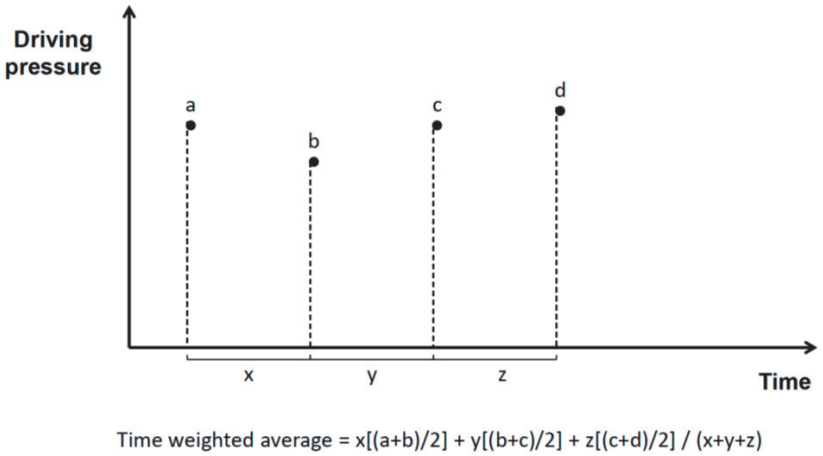
Statistics – Details on covariate balancing propensity score calculation, variable selection process and propensity score matched posthoc analysis.

The association between the main dependent variable (time weighted driving pressure) was tested by fitting a weighted mixed effect logistic regression model with a weighting factor obtained by covariate balancing propensity score (CBPS) and a random intercept by center.

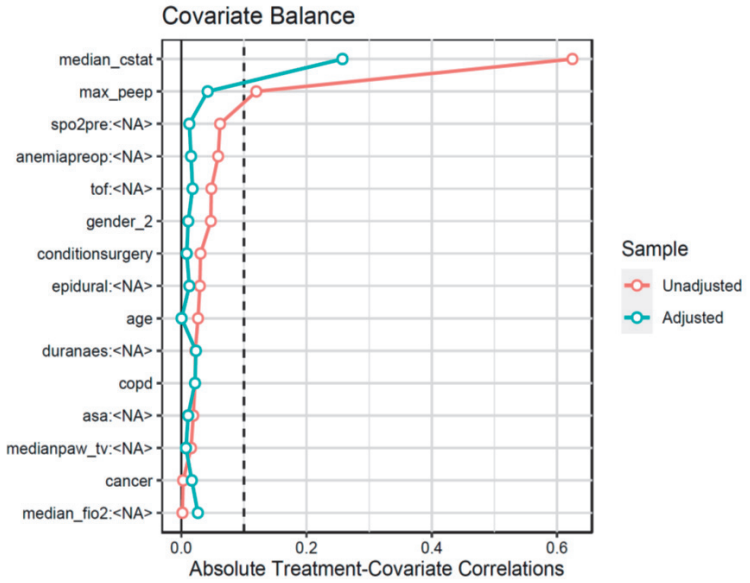
The variable selection process to enter the propensity score calculation was done using the augmented backwards elimination process implemented in the *abe* R package. The variables that finally entered the propensity score calculation for open surgery were: age, gender, body mass index, ASA risk score, functional status, smoker status, baseline comorbidities (chronic obstructive pulmonary disease, oncologic disease, heart failure, chronic kidney disease, obstructive sleep apnea disease, neurologic disease), duration of anesthesia, ARISCAT score (as individual variables) , type of surgery, urgency of surgery, time of surgery, previous and perioperative blood cell transfusion, use of epidural anesthesia, use of recruiting maneuvers, use of neuromuscular monitoring, use of neuromuscular blocking agents reversal, total fluid administration (body weight normalized), total cristalloid administration (body weight corrected), mode of mechanical ventilation, type of anesthetic agent (intravenous vs. halogenated), perioperative mechanical ventilation characteristics (median minute ventilation, median respiratory rate, median fraction of inspired oxygen, median end–tidal CO_2 and median SpO2, median per–actual body weight V_T, median static and dynamic compliance, highest PEEP, lowest PEEP and PEEP coefficient of variation, and driving pressure measures other than the main dependent variable analyzed). The variables that finally entered the propensity score calculation for closed surgery were the same with the addition of antibiotic prophylaxis.

For secondary endpoint (association between driving pressure and intraoperatvie adverse events) a weighted ordinal regression was fitted with *ordinal* R package. We chose this approach to better model the intraoperative adeverse events variables as an ordinal variable where having two events in

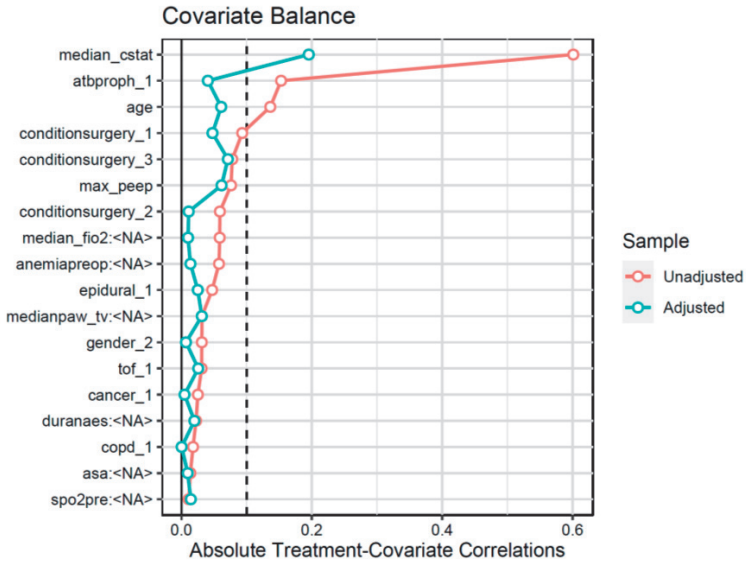
worse than one, three is worse than two etc.. Weighting factor was the propensity score as described in the previous model for PPCs. The propensity score for posthoc matched analysis was calculated with the same covariable structure as the CBPS with the *matchit* package.[2]



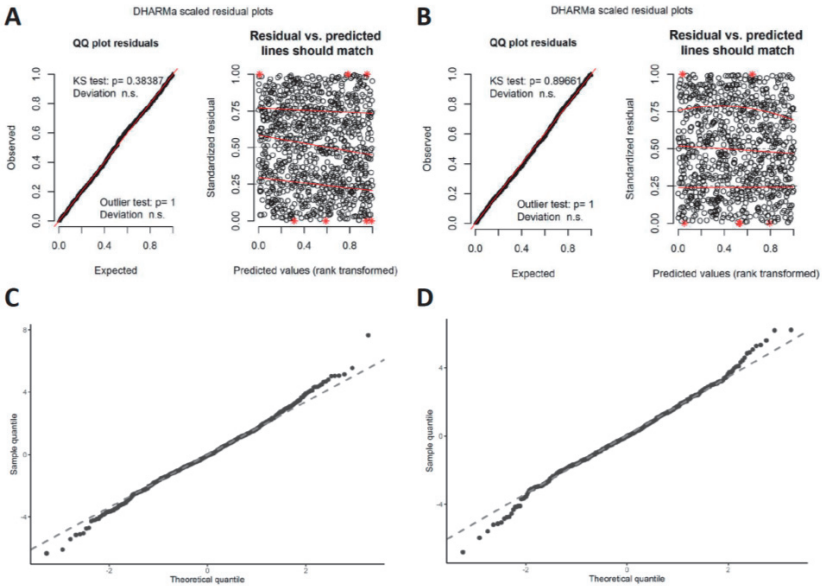
eFigure 1. Time weighted average and coefficient of variation calculation



eFigure 2. Summary plot of covariate balance for time-weighted ΔP before (red line) and after (blue line) conditioning for open surgery.



eFigure 3. Summary plot of covariate balance for time-weighted ΔP before (red line) and after (blue line) conditioning for closed surgery.



eFigure 4. Residuals plot for postoperative pulmonary complications (PPCs) and intraoperative adverse events (AEs). A: PPCs in Open surgery; B: PPCs in closed surgery; C; AEs in open surgery; D: AEs in closed surgery.

eTable 1. Definition of postoperative pulmonary complications	
Single PPC	**Definition**
Unplanned need for oxygen therapy	Supplemental O_2 therapy administered to correct hypoxemia, defined as SpO_2 < 90% in room air or PaO2 < 60 mmHg. This excludes oxygen administration given as a part of standard care, such as routine oxygen administration at the arrival in the PACU.
Respiratory failure	SpO_2 < 90% in room air or PaO2 < 60 mmHg with oxygen therapy, or need for non-invasive mechanical ventilation
Mechanical ventilation	Need for new invasive ventilation after surgery, or unexpected prolonged invasive ventilation after discharge from the operating room
ARDS	According to the Berlin definition
Pneumonia	Lung infiltrates at the chest X-ray or CT, plus at least two among the following three criteria: fever > 38°C (100.4 °F), leucocytosis or leukopenia (WBC count > 12000 or <4000 cells/mm^3), purulent secretions
Pneumothorax	Air in the pleural space without blood presence, as confirmed by chest X-ray
Severe PPC: at least one PPC among respiratory failure, mechanical ventilation, ARDS, pneumonia, pneumothorax, as defined in the Table	

eTable 2. Definition of intraoperative complications	
Intraoperative Complication	**Definition**
De-saturation	SpO_2 < 92%
Need for rescue recruitment manoeuvre	Ventilation strategies aimed at restoring aeration of the lungs
Need for ventilatory pressure reduction	Ventilation strategies aimed at lowering peak and/or plateau pressure
New onset of expiratory flow limitation	End-expiration expiratory flow higher than zero at the visual analysis of the flow curve
Hypotension	Systolic arterial pressure < 90 mmHg for at least 3 minutes
Need for vasoactive drugs	Use of vasoactive drugs to correct hypotension as previously defined
Arrhythmia	Defined as any new onset of atrial fibrillation, sustained ventricular tachycardia, supraventricular tachycardia, or ventricular fibrillation

eTable 3. Patients demographics and surgery–related characteristics in the matched cohort for type of surgery.

	Laparoscopic abdominal surgery (N = 254)	Non–laparoscopic abdominal surgery (N = 344)	SMD
Age, years	54 (18)	55 (16)	0.070
Gender, male (%)	37% (94/254)	41% (143/344)	0.094
BMI (Kg·m^{-2})	25.9 [23.4–30.1]	26.6 [23.3–29.7]	0.015
ASA class, % (n/N)			0.256
1	22% (55/254)	20% (70/344)	
2	56% (143/254)	53% (180/344)	
3	22% (56/254)	24% (84/344)	
4	0% (0/254)	3% (9/344)	
5	0% (0?254)	0% (1/344)	
ARISCAT class, % (n/N)			0.099
< 26	55% (141/254)	51% (174/344)	
26–44	36% (91/254)	40% (137/344)	
> 44	9% (22/254)	9% (33/344)	
Current smoker, %	81% (205/254)	78% (269/344)	0.062
Chronic comorbidity, % (n/N)			
Metastatic cancer	2% (22/906)	10% (116/1.128)	0.141
Chronic kidney failure	1% (13/906)	6% (68/1.128)	0.042
COPD	7.% (83/906)	6% (55/1.128)	0.012
Heart failure	6% (53/906)	8% (90/1.128)	0.050
OSAS	3% (27/906)	1% (15/1.128)	0.022
Neuromuscular disease[a]	1% (6/906)	1% (11/1.128)	0.060
Functional Status, % (n/N)			0.066
Independent	94% (239/254)	93% (323/344)	
Partially dependent	5% (13/254)	5% (16/344)	
Totally dependent	1% (2/254)	2% (5/344)	
Preop transfusion, % (n/N)	1% (3/254)	1% (3/344)	0.031
Surgical procedure[b], % (n/N)			
Lower GI	76% (194/254)	72% (264/344)	0.111
Upper GI, HBP	28% (72/254)	27% (95/344)	0.016
Urological	11% (29/254)	11% (39/344)	0.003
Gynaecological	31% (81/254)	28% (97/344)	0.081
Endocrine surgery	0% (0/254)	0% (1/344)	0.076
Neurosurgery	1% (1/254)	1% (2/344)	0.024
Other procedure	4% (12/254)	4% (15/344)	0.017
Urgency of Surgery[c], % (n/N)			0.017
Elective	83% (212/254)	83% (288/344)	
Urgent	11% (27/254)	11% (37/344)	
Emergency	6% (15/254)	6% (19/344)	
Duration of anesthesia[e], min	109 [78–171]	120 [85–180]	0.111
Time of surgery, % (n/N)			0.001
Daytime[f]	95% (242/254)	95%(328/344)	
Night–time	5% (12/254)	5% (16/344)	
Antibiotic prophylaxis, % (n/N)	82% (662/254)	85% (292/344)	0.091
Intraop. procedures, % (n/N)			
Epidural anesthesia	7% (18/254)	8% (28/344)	0.040
Neuromuscular Monitoring	19% (49/254)	20% (71/344)	0.034
Neuromuscular Reversal	49% (124/254)	49% (171/344)	0.018
TIVA	9% (24/254)	9% (31/344)	0.015
Transfusion	4% (10/254)	5% (19/344)	0.075
Total Fluids (mL· kg^{-1})	22 (15)	23 (14)	0.094
Crystalloids (mL· kg^{-1})	20 (14)	21 (14)	0.076
Ventilation mode, % (n/N)			0.002
Volume–controlled	82% (208/254)	82% (282/344)	
Pressure–controlled	18% (46/254)	18% (62/254)	
Tidal Volume			
Per ABW (ml·kg^{-1})	7 (1)	7 (1)	0.027
Minute ventilation (L·kg^{-1})	6.4 (1.1)	6.4 (1.5)	0.023
Respiratory system compliance			
Dynamic, ml·cm·H_2O^{-1}	27 (9)	27 (9)	0.072
Static, ml·cm·H_2O^{-1}	43 (13)	44 (12)	0.041
Routine recruitment maneuvers, % (n/N)	7% (17/254)	7% (25/344)	0.023
FiO_2, %	55 (13)	55 (13)	0.008
SpO_2, %	99 (1)	99 (1)	0.003
$EtCO_2$, kPa	4.5 (0.6)	4.4 (0.6)	0.106
Airway pressures			
Driving pressure (cm·H_2O)			
Time–weighted average	8.42 (3.55)	8.46 (3.24)	0.009
Maximum value	15.03 (5.03)	14.75 (4.79)	0.058
Minimum value	11.81 (4.20)	11.80 (4.32)	0.002
Coefficient of variation (%)	13.21 (12.83)	12.47 (11.64)	0.061
PEEP (cm·H_2O)			
Maximum value	3.72 (2.45)	3.72 (2.61)	0.001
Minimum value	2.87 (2.29)	2.87 (2.34)	0.001

Data are presented as mean (SD) or median [25th–75th percentile] or % (n/N).

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; ; GI: gastrointestinal; HBP, Hepatobiliopancreatic; SpO_2, peripheral oxygen saturation: CI, confidence interval; SMD, Standardized mean differences.

[a]Neuromuscular disease affecting the respiratory system.

[b]Tha same patient may have more than one surgical indication

[c]Urgency of surgery is defined as *elective*: surgery that is scheduled in advance because it does not involve a medical emergency, *urgent*: surgery required within <48 hours, *emergent*: surgery performed when the patients' life or well being are threatened.

[d]Duration of surgery is the time between skin incision and closure of the incision.

[e]Duration of anaesthesia is the time between start of induction and tracheal extubation or discharge from operation room if the mechanical ventilation is continued.

[f]Daytime surgery is defined as anaesthesia induction between 8:00 a.m. and 19:59 p.m.

eTable 4. Intraoperative and postoperative outcomes in matched cohort for type of surgery.			
	Closed surgery (N = 254)	**Open surgery (N = 341)**	***P*–value**
Severe PPC (composite), % (n/N)	4% (10/254)	7% (22/341)	0.246
Intraoperative complications			
Desaturation	1% (3/254)	4% (16/341)	0.030
Unplanned rescue maneuvers	3% (8/254)	4% (16/341)	0.986
Airway pressure reduction needed	7% (18/254)	1% (4/341)	< 0.001
Expiratory flow limitation	0.3% (4/254)	1% (1/341)	0.215
Hypotension	20% (53/254)	25% (380/341)	0.192
Use of vasopressors	17% (43/254)	20% (68/341)	0.408
New arrhythmia onset	0% (0/254)	1% (3/341)	0.361
Individual PPCs			
Unplanned need for supplementary O_2	13% (33/254)	15% (52/341)	0.509
Acute respiratory failure	3% (9/254)	3% (12/341)	1.000
Need for mechanical ventilation	3% (8/254)	3% (11/341)	1.000
Acute respiratory distress syndrome	0% (0/254)	0.6% (2/341)	0.612
Pneumonia	0% (0/254)	1% (5/341)	0.138
Pneumothorax	0% (0/254)	0.3% 1/341)	1.000
Data are presented as median [25th–75th percentile] or % (n/N).PPC, postoperative pulmonary complications.			

eTable 5. Mixed multivariable logistic regression in matched cohort for postoperative pulmonary complications		
Variables	**OR [L– U 95%CI]**	***P***
Laparoscopic surgery Yes	0.69 [0.39 to 1.21]	0.238
Time–weighted driving pressure	0.44 [0.19 to–0.97]	0.043
Maximum driving pressure	5.714 [1.57 to 20.740]	0.008
Driving pressure coefficient of variation*	0.66 [0.344 to 1.27]	0.210
Minimum driving pressure	0.46 [0.168 to 1.26]	0.130
Maximum PEEP	1.03 [0.66 to 1.60]	0.890
Minimum PEEP	1.47 [0.95 to 2.28]	0.081
Age	1.33 [0.95 to 1.87]	0.100
Gender	0.86 [0.48 to 1.56]	0.621
Asa (Reference: ASA 1)		
Asa 2	1.37 [0.531 to 3.530]	0..516
Asa 3	2.09 [0.71 to 6.07]	0.178
Asa ≥ 4	4.721 [0.63 to 34.946]	0.129
Chronic Bronchitis Yes	3.40 [1.28 to 8.980]	0.014
Cancer Yes	2.33 [1.04 to 5.25]	0.040
Duration of anesthesia	1.96 [1.30 to 2.97]	0.001
ARISCAT score (Reference: Low < 26)		
ARISCAT Intermediate (26 – 44)	0.85 [0.44 to 1.63]	0.621
ARISCAT high (>45)	1.26 [0.48 to 3.30]	0.640
Urgency of Surgery (Reference: Elective)		
Urgent	0.55 [0.18 to 1.68]	0.291
Emergency	3.47 [0.99 to 12.070]	0.051
Epidural anesthesia	1.13 [0.43 to 2.97]	0.797
NMB monitoring Yes	1.52 [0.73 to 3.15]	0.260
TV Per body weight	0.80 [0.59 to 1.10]	0.169
Static Compliance	0.94 [0.56 to 1.58]	0.816
Sd centres. (Intercept)	0.97	
*The driving pressure coefficient of variation was calculated by dividing the standard deviation (SD) by the mean driving pressure level.		

Capítulo 6

Modeling intra-abdominal volume and respiratory driving pressure during pneumoperitoneum insufflation - a patient-level data meta-analysis.

Mazzinari G, Diaz-Cambronero O, *Serpa Neto A, Cañada Martinez A, Rovira L, Argente Navarro MP, Malbrain MLNG, Pelosi P, Gama de Abreu M, Hollmann MW, Schultz MJ, Study Investigators IPPCOLLAPSE.*

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Q1 IF 2.95

Introduction

In laparoscopic surgery, carbon dioxide (CO_2) is insufflated into the peritoneal cavity. Insufflated CO_2 generates a working space for surgeons to monitor and perform the intervention. Intra–abdominal pressure (IAP) during pneumoperitoneum usually exceeds the intra–abdominal hypertension (IAH) syndrome threshold, i.e., 12 mmHg, and thus exposes patients to the harmful effects of increased IAP (18,20).

The abdominal compartment has a combination of rigid borders, including the spine, rib cage and pelvis, and semi–rigid borders like the muscles in the abdominal wall and the pelvis, and the diaphragm. The abdominal compartment shows anisotropic behavior during pneumoperitoneum (8,40,47). Typically, there is an initial phase where marginal gains in volume according to the applied pressure, i.e., abdominal compliance (C_{abd}), follow a linear relationship. (28) Then, according to biomechanics laws, materials undergoing a strain eventually reach their maximum stretching capabilities, i.e., yield stress, after which applying additional pressure leads to diminishing gains in volume (6,15). Identifying this critical point at which gas insufflation should be limited is crucial to maximizing surgical working space while minimizing injurious IAP effects. Such effects include decreased pulmonary function, abdominal perfusion and cardiac output and increased intracranial, thoracic and ocular pressure (31).

A rise in IAP leads to an upward shift of the diaphragm, increasing airway pressures (P_{aw}), and decreasing chest wall compliance (C_{CW}) and lung volumes (11,21,34). The diaphragm shift can be partially outweighed by applying a sufficient positive end–expiratory pressure (PEEP) level during mechanical ventilation, although how much PEEP and when to apply it, i.e., before or after pneumoperitoneum insufflation or lung recruitment maneuvers (49). Previous preclinical trials assessing the effect of IAPs ranging from 5 to 25 mmHg on P_{aw} found that the abdomino–thoracic transmission (ATT) rate, i.e., the proportion of abdominal pressure transmitted to the thorax, for peak and plateau pressure (P_{peak} and P_{plat}) ranges from 40 to 50% in animal models (10,35) and was 20% for P_{plat} (42) and 62% for P_{peak} (50) in physiologic proof of concept trials performed in humans. These studies were carried out after inducing acute

respiratory distress syndrome (ARDS) (28) and without neuromuscular blockade (NMB) (10,35–38,42,50), and none focused on respiratory driving pressure (ΔP).

Nonlinear statistical models can be used to describe a variety of processes in various fields (2). Their advantage resides in that their parameters can easily be linked to biologically meaningful variables. We aimed to determine if a mathematical function can describe IAP and IAV and IAP and ΔP relationships during pneumoperitoneum insufflation by analyzing patient–level data from three previously published studies (13,14,27). The primary objective was to assess the relationship between IAP and IAV, and the secondary objective was to study the relationship between IAP and respiratory driving pressure (ΔP_{RS}).

METHODS

Study design and context

The protocol and statistical analysis plan of this meta–analysis are available in the **Supplement**, and these were planned and prespecified before data opening and registered at clincaltrials.gov (study identifier: NCT04468698). The overall characteristics of the studies are shown in **eTable 1** in **Supplementary Digital Content, https://doi.org/10.6084/m9.figshare.13270118**. IPPColLapSe I was a multicenter cohort study assessing the feasibility of an individualized pneumoperitoneum (IPP) strategy in laparoscopic colorectal surgery (13). IPPColLapSe II was a multicenter randomized clinical trial comparing an IPP strategy with a standard pneumoperitoneum pressure (SPP) strategy with respect to postoperative recovery in laparoscopic colorectal surgery (14). IPPCollapSe III was a single–center crossover trial comparing fixed five cmH_2O positive end–expiratory pressure (PEEP) to IAP targeted PEEP at various IAP levels in laparoscopic cholecystectomies (27). Written informed consent before enrolment and compliance with the Helsinki Declaration and Spanish legislation for biomedical research was mandatory in all studies.

All patients in all three studies underwent an initial standardized insufflation maneuver under deep NMB, which consisted of: i) peritoneum insufflation through a leakproof Hasson trocar (Kii balloon, Applied Medical, Orange County, California, US or VersaOne, Covidien, Dublin, Ireland) up to 15 mmHg of IAP for abdominal wall pre–stretching; ii) patients positioning in 20^{o} Trendelenburg (13,14), or 20^{o} anti–Trendelenburg (27); iii) IAP decrease from 15 down to 12 and then to 11, 10, 9, 8 mmHg (13,14), or IAP increase up from 8 to 12 and then 15 mmHg (27). Insufflation was carried out at constant low flow, i.e., 3 $L \cdot min^{-1}$ to derive the compliance from the slope of the dynamic pressure–volume curve applying a classical technique used in respiratory mechanics (5,33,41). In all studies, patients´ legs were placed in padded leg–holder supports with hips flexed before the initial insufflation. Also, NMB degree was assessed by quantitative monitoring to maintain a post–tetanic count (PTC) between one and five.

During the initial insufflation sequence, mechanical ventilation (Avance or Aisys CS^2, GE Healthcare, Chicago, Illinois, USA) was performed in volume–

controlled mode (VCV) with a tidal volume of 7–8 ml·kg^{-1}, with a respiratory rate of 12 beats per minute, inspiration to expiration (I:E) ratio of 1:2, an inspiratory pause of 20% of the inspiratory time and 5 cmH_2O of PEEP. A lung recruitment maneuver and PEEP settings changes were performed only in IPPcollapse III according to the original protocol; however, only data from 5 cmH_2O PEEP recordings were used for driving pressure analysis.

The details of the insufflation sequence are reported in **eTable 1** in the **Supplementary Digital content**.

Inclusion criteria

Data from patients that participated in the three parent studies were eligible for the current analysis. Patients in whom the initial insufflation procedure was incomplete were excluded.

Data collection

During the initial insufflation maneuver, IAV was recorded at each mmHg of IAP, while during stepwise changes in IAP, P_{plat} was recorded at each IAP level. ΔP was calculated as P_{plat} minus PEEP. The following baseline characteristics were retrieved from the original databases: patients' age, gender, and body mass index (BMI). We also retrieved waist–hip circumference ratio where possible.

Endpoints

The primary objective was the relationship between IAP and IAV, and the secondary objective was the relationship between IAP and respiratory driving pressure (ΔP_{RS}).

Statistical analysis

We included all available data from patients in the trials without formal sample size calculation. Also, as the purpose of the investigation was exploring a physiological hypothesis, we did not specify any *a priori* effect size.

Continuous variables are reported as median [25th–75th percentile]. Normality was checked by quantile–quantile plots examination. Categorical variables are reported as percentages and proportions. In the case of more than 5% of missing data, imputation by chained equations was prespecified.

To determine which function adapted better to data, Bayesian multivariable mixed models with either linear, exponential, or sigmoid response distribution were fitted. Age, gender, BMI, and study, i.e., IPPColLapSe I, II, or

III, were introduced as covariables and patients as a random effect. Full details on the models are reported in the **Statistical Analysis Plan (SAP)** in the **Supplementary Digital Content**. The best–fitting model was chosen by visual inspection of IAP marginal effect and leave-one-out (loo) cross–validation, which is the more robust method in case of weak priors and influential observations (45). We assessed the following functions: linear, logistic for sigmoid response or asymptotic exponential for exponential response. We then estimated the relationship between IAP and IAV and IAP and ΔP_{RS} fitting the selected mathematical function. According to the chosen function, we calculated the dependent variable, i.e., IAV or $\Delta P_{RS,}$ according to the function parameters. According to the function type, the following parameters were determined: i) slope parameter, i.e., the amount of variation in *y* for a unit-increase in *x* was determined for the linear function; ii) maximum reachable *y* value and *y* rate of increase, i.e., half–life parameter, for the asymptotic exponential function; iii) higher asymptote, inflection point, i.e., *x* value halfway between the lower and upper asymptote points, slope parameter and the upper critical point, i.e., *x* value where the slope changes reflecting a decrease in *y* response to *x* increments with three proposed formulas: maximum deceleration point (MDP), asymptotic deceleration point (ADP) (7), Venegas sigmoidal equation (46). Details on mathematical calculations are provided in the **SAP** in the **Supplementary Digital Content,** and a graphical depiction of the used functions and points is shown in **Figure 1**.

To assess the effect of visceral fat on the relation between IAP and IAV we estimated a Bayesian and non–linear model with the same specifications reported for the main analysis in a subsample of patients for which waist–hip circumference ratios were available. We tested the model introducing waist–hip circumference ratio and BMI alternatively.

All analyses were performed with R software version 4.0.2 (R Foundation for Statistical Computing, www.r-project.org). No correction for multiple comparisons was performed. Statistical uncertainty was expressed by showing the 95%–confidence or 95%–credible intervals for frequentist and Bayesian analysis, respectively. Statistical significance was set for two–tailed at $P < 0.05$.

RESULTS

This patient–level meta–analysis included 204 patients undergoing pneumoperitoneum insufflation for laparoscopic surgery under general anesthesia. Baseline characteristics are reported in **Table 1**. In total, 10.866 and 1.065 data points were analyzed for IAV and $\Delta P_{RS,}$ respectively. We did not observe any episode of mean arterial pressure below 60 mmHg during the assessment.

The marginal effects of IAP on IAV and of IAP on ΔP_{RS} for the three fitted Bayesian models are reported in **eFigure 1** and **2** in the **Supplementary Digital Content**. The effect of IAP on IAV followed a sigmoid shape, while the effect of IAP on ΔP_{RS} followed a linear shape. Loo cross–validation results showed that the best fitting model for IAP and IAV relationship was the logistic one while logistic and linear where comparable for IAP and ΔP_{RS} (**eTable 2** in **Supplementary Digital Content**). We finally choose a linear relationship for ΔP_{RS} based on the marginal effect.

By fitting a three–parameter logistic function to IAV data, we found that the inflection point was at an IAP of 6.7 [95%CI 6.6 to 6.8] mmHg, the upper asymptote was at an IAV of 6.0 [95%CI 5.9 to 6.2] L and the scale parameter was 2.3 [95%CI 2.3 to 2.4]. MDP, Venegas and ADP critical points were at IAP of 9.8 [95%CI 9.7 to 9.9], 11.5 [95%CI 11.3 to 11,5] and 12.2 [95%CI 12.0 to 12.3] mmHg respectively. The logistic function fitting curve with critical points and Bayesian estimation are reported in **Figure 2** and full Bayesian and non–linear logistic models' estimation in **eTable 3a and 3b** in **Supplementary Digital Content 2**. Among the introduced covariables, the original study was significant with IPPCollapse III showing higher intra–abdominal volumes (0.64, 95%CI 0.41 to 0.85).

We included 58 patients in the waist–hip ratio sensitivity analysis from IPPCollapse I study, baseline characteristics are reported in eTable 4. Median waist–hip ratio was 0.97 [0.90 to 1.01]. The estimated marginal effects of waist–hip circumference ratio and BMI were small (0.26 [95%–Credible Interval, CI -1.10 to 1.66] and -0.01 [95%CI -0.04 to 0.01] respectively). Full models' estimation is presented in eTable 5–6 in Supplementary Digital Content. Critical points calculated from the logistic function fitting curve were similar (MDP 9.1

[95%CI 8.9 to 9.4] and 9.2 [95%CI 9.1 to 9.2] , Venegas 10.6 [95%CI 10.4 to 10.9] and 10.7 [95%CI 10.6 to 10.7], ADP 11.3 [95%CI 11.0 to 11.6] and 11.3 [95%CI 11.2 to 11.3] for models fitted with waist–hip circumference ratio and BMI respectively, eFigure 3 in Supplementary Digital Content).

By fitting a linear function to ΔP_{RS} data, we found that an increase in IAP was significantly associated with an increase in ΔP_{RS} (effect estimate = 0.65, [95%CI 0.62 to 0.68] and that age and BMI were significantly associated with an increase in ΔP_{RS}. In contrast, the original studies did not show a significant effect. Linear mixed model estimates and fitting to the data are reported in **Table 2** and **Figure 3**.

DISCUSSION

The main findings of this patient–level meta–analysis in subjects undergoing pneumoperitoneum for laparoscopic surgery under general anesthesia can be summarised as follows: during pneumoperitoneum, (i.) the effect of IAP on IAV volume follows a sigmoidal function, and by obtaining the parameters of this function we can (ii.) describe an upper threshold for IAV and (iii.) identify the specific point where marginal gains in volume for each increase in pressure is diminishing; Moreover (iv.) in standard pneumoperitoneum pressure range rising IAP leads to a linear increase in ΔP_{RS}.

This analysis has several strengths. We used a standardized insufflation maneuver in all three studies providing a comparable and granular dataset for models' estimation. Indeed, although this is not the first study on IAV and IAP relationship carried out in humans (28), it analyzes the largest dataset to our knowledge. Moreover, we carried out a multivariable analysis, therefore obtaining less biased effect estimates, and chose the modeling functions by a data–driven process, i.e., by testing several functions on data to pick the best performing one. Moreover, we used non–linear functions with easily interpretable parameters with a clear biological meaning (2,32). Also, the analysis was predefined, and we had no deviations from the original plan.

Our findings show how IAV can be related to an increase in IAP in a non–linear fashion. Higher pressure does not always generate steadily higher volumes. Despite clinical guidelines recommending to set the IAP at the lowest level providing adequate surgical working space during laparoscopy (30), pneumoperitoneum commonly becomes being a iatrogenic IAH condition. IAH and abdominal compartment syndrome (ACS) are well defined clinical conditions proven to be associated with increased morbidity and mortality in critically ill patients (12). IAH can lead to decreased abdominal perfusion and organ injury (22,43,48,50) and increased pressure in other body compartments such as the thorax, eye, or cranium (28,39). Furthermore, animal data show that mechanical ventilation alters diaphragm perfusion by reducing blood flow and increasing vascular resistance. This effect is partially reversed by lowering IAP (17). Altered diaphragm perfusion is already present after thirty minutes of mechanical ventilation (9) and is considered one of the leading causes of

ventilation–induced diaphragm dysfunction (44). For these reasons, the trade-off between additional working space and IAP–related potential injury should be carefully evaluated in each case.

Interestingly, a recent physiologic proof of concept study in robotic laparoscopic surgery has shown how peritoneal capillary circulation may be impaired at IAP above 10 mmHg (1), drawing an interesting physiological parallel with our findings. Recent studies focus on titrating IAP to the minimum effective value as a sensible clinical management of pneumoperitoneum. Indeed, a recent metanalysis showed moderate evidence for better pain scores in patients who underwent surgery with pneumoperitoneum pressure as low as 6 mmHg (31).

According to the fitted model, we found that IAV increases towards a ceiling value of 6.0 [95%CI 5.9 to 6.2] L as IAP rises. This finding is in line with biomechanics reflected in preclinical and clinical studies that showed the anisotropic structure of the abdominal wall muscles with a lower stiffness at the rectus sheath and linea alba level compared to the oblique and transversus abdominis muscles (4,16). The bulk of the response to IAP increments results from reshaping the anterior structures, i.e., rectus muscles and linea alba (40,47), up to a threshold where collagen fibers tissue bonds are stretched to the limit. No further changes are possible, yielding a non–linear stress–strain relationship (23,24,26). Previous studies illustrated that a working space of approximately 3 L is sufficient to ensure optimal surgical field conditions (13,28), thus a considerable safety window to the upper limit volume remains. An initial assessment of the actual volume that grants an adequate surgical field could guide IAP settings during laparoscopic surgery.

Our results show that the pressure–volume (PV) relationship during pneumoperitoneum has some analogies with the respiratory system PV curve during mechanical ventilation (19), confirming the non–linear behavior determined in an animal model of hypertension (38). As in the respiratory system PV curve, we found a sigmoid shape with a linear central portion and an upper inflection point that determines a threshold not to be exceeded to avoid barotrauma. Following the same analogy, IAP levels on the linear part of the PV curve warrant the best $C_{abd,}$ yielding the best volumetric response to IAP rise. Furthermore, we observed bending of the curve at commonly used

pneumoperitoneum pressure levels, i.e., between 10 and 12 mmHg depending on the calculation method. The threshold where the volume expansion is diminishing should be established in each case to ensure the best marginal gains from IAP levels.

We carried out a sensitivity analysis to assess whether the main analysis adjusted estimations could be influenced by a different parameter, e.g., waist–hip circumference ratio as a proxy for visceral fat. Our results show that waist-hip circumference's marginal effect is small and does not yield a considerable change in IAV nor critical points estimation. In general, IAP's marginal effect is far greater than any of the covariables introduced in the model. Of note, we carried out this analysis in a subsample from a single study.

Our data show a linear relationship between IAP and ΔP_{RS}. We found that the ATT is 0.65 [95%CI 0.62 to 0.68], confirming previous estimations from small studies (34). ΔP_{RS} is associated with an increased incidence of postoperative pulmonary complications in patients undergoing mechanical ventilation for surgery (29). Considering the conversion factor between units of measure, i.e., 1 mmHg equals 1.36 cmH_2O, and the linear coefficient estimated from the model for IAP, for each additional mmHg of IAP, we can expect a $1.36 \cdot 0.65 = 0.88$ cmH_2O rise in ΔP_{RS}. A recent large prospective multicenter trial carried out in robotic laparoscopy found that driving pressure was increased in patients at high risk of postoperative pulmonary complications and these patients had a higher incidence of such complications (3). This provides a further reason why each increase in IAP should be justified by corresponding gains in surgical working space during laparoscopy to avoid an unnecessary increase in driving pressure.

Several limitations of this study have to be acknowledged. First, as inherent to any meta–analysis, the results have the internal and external validity of the three original studies. For instance, the exact effect of hip flection or patient positioning could not be assessed. Despite the adjusted analysis, we cannot exclude that all confounding factors have been included. Also, although we did not observe severe arterial hypotension during study assessment, cardiac output or vascular resistance data were not collected; thus, a precise correlation between hemodynamic status and abdominal pressure value cannot be ascertained. Second, during the insufflation maneuver, we did not collect

clinical nor preclinical outcomes; thus, the abdominal and systemic effect of the IAP level could not be assessed. Besides, although leakproof equipment was used, we did not record leak quantitatively during insufflation. Third, we did not collect IAV and airway pressures during the surgery; thus, dynamic changes or the potential effect of other perioperative measures such fluid balance could not be studied. Fourth, the results of the sensitivity analysis on waist–hip circumference ratio have to be confirmed on a more comprehensive sample, and the effect of other variables such parity, abdominal wall, or more extended ranges of BMI values thickness have to be explored. Fifth, we estimated a non–linear model based on a three–parameter logistic function which assumes symmetry. Sixth, the original protocols did not specify IAP measurement through a bladder catheter; therefore, respiratory swings in IAP were not assessed. Seventh, pneumoperitoneum was studied relying on deep neuromuscular blockade; thus, extrapolation to different levels of neuromuscular blockade must be done with great caution. Eighth, oesophageal pressures were only recorded in one of the original studies; hence, a global assessment of transpulmonary driving pressure and lung compliance was not feasible. Ninth, although we introduced patients' positioning in the fitted models since the original protocols prespecified different positions after the initial insufflation, we cannot specifically assess the effect of position changes on driving pressure. Lastly, to limit the heterogeneity of our data, we only used respiratory driving pressure data at 5 cmH_2O of PEEP. Thus, the IAP effect on abdominal volume or respiratory driving pressure at different levels of PEEP must be further investigated as ventilation at different PEEP levels or recruitment maneuvers can influence these associations (25).

In conclusion, during pneumoperitoneum for laparoscopic surgery under general anesthesia, IAV has a non–linear relationship with IAP. There is a threshold of diminishing gains in IAV at commonly used pressure levels. Increase IAP is associated with a linear increase in ΔP_{RS}. IAP during pneumoperitoneum should be kept in the best abdominal compliance range.

REFERENCES

1. Albers K, Polat F, Loonen T, Graat LJ, Mulier JP, Snoeck MM, Panhuizen IF, Vermulst AA, Scheffer GJ, Warlé MC. Visualising improved peritoneal perfusion at lower intra-abdominal pressure by fluorescent imaging during laparoscopic surgery: A randomised controlled study. Int J Surg. 77:8–13. 2020 doi: 10.1016/j.ijsu.2020.03.019.

2. Archontoulis SV, Miguez FE. Nonlinear regression models and applications in agricultural research. Agron J 107:786–98. 2015 doi:10.2134/agronj2012.0506.

3. Assessment of Ventilation during general AnesThesia for Robotic surgery (AVATaR) Study Investigators, for the PROtective VEntilation (PROVE) Network. Ventilation and outcomes following robotic-assisted abdominal surgery: an international, multicentre observational study. Br J Anaesth (August 4, 2020) doi: 10.1016/j.bja.2020.08.058.

4. Axer H, Keyserlingk DG V, Prescher A. Collagen fibers in linea alba and rectus sheaths: II. Variability and biomechanical aspects. J Surg Res 96:239–45. 2001. doi: 10.1006/jsre.2000.6071.

5. Bates JH, Rossi A, Milic-Emili J. Analysis of the behavior of the respiratory system with constant inspiratory flow. J Appl Physiol (1985). 58:1840–8. 1985 doi: 10.1152/jappl.1985.58.6.1840.

6. Becker C, Plymale MA, Wennergren J, Totten C, Stigall K, Roth JS. Compliance of the abdominal wall during laparoscopic insufflation. Surg Endosc. 31:1947–51. 2017. doi: 10.1007/s00464-016-5201-6.

7. de Bem CM, Cargnelutti Filho A, Chaves GG, Kleinpaul JA, Pezzini RV, Lavezo A. Gompertz and Logistic Models to the Productive Traits of Sunn Hemp. J Agric Sci 10:225–238. 2017. doi:10.5539/jas.v10n1p225.

8. Blaser AR, Björck M, De Keulenaer B, Regli A. Abdominal compliance: A bench-to-bedside review. J Trauma Acute Care Surg 78:1044–53. 2015. doi: 10.1097/TA.0000000000000616.

9. Bruells CS, Smuder AJ, Reiss LK, Hudson MB, Nelson WB, Wiggs MP, Sollanek KJ, Rossaint R, Uhlig S, Powers SK. Negative Pressure Ventilation and Positive Pressure Ventilation Promote Comparable Levels of Ventilatorinduced Diaphragmatic Dysfunction in Rats. Anesthesiology 119:652-6. 2013. doi: 10.1097/ALN.0b013e31829b3692.

10. Cortes-Puentes GA, Cortes-Puentes LA, Adams AB, Anderson CP, Marini JJ, Dries DJ. Experimental intra-abdominal hypertension influences airway pressure limits for lung protective mechanical ventilation. J Trauma Acute Care Surg 74:1468–73.

2013. doi: 10.1097/TA.0b013e31829243a7.

11. De Keulenaer BL, De Waele JJ, Powell B, Malbrain MLNG. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? Intensive Care Med 35: 969–76. 2009. doi: 10.1007/s00134-009-1445-0.

12. De Laet IE, Malbrain MLNG, De Waele JJ. A Clinician's Guide to Management of Intra-Abdominal Hypertension and Abdominal Compartment Syndrome in Critically Ill Patients. Crit Care 24:1–9. 2020. doi: 10.1186/s13054-020-2782-1.

13. Diaz-Cambronero O, Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, Olmedilla Arnal L, Argente Navarro MP, Schultz MJ, Errando CL. A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study. Surg Endosc 33:252–60. 2019 doi:10.1007/s00464-018-6305-y.

14. Diaz-Cambronero O, Mazzinari G, Flor Lorente B, Garcia Gregorio N, Robles-Hernandez D, Olmedilla Arnal LE, Martin de Pablos A, Schultz MJ, Errando CL, Argente Navarro MP. Effect of an individualized versus standard pneumoperitoneum pressure strategy on postoperative recovery : a randomized clinical trial in laparoscopic colorectal surgery. Br J Surg Jun 7. Online ahead of print. 2020. doi:10.1002/bjs.11736. (Corrigendum. Br J Surg. 2020 Sep 21. doi: 10.1002/bjs.11932)

15. Förstemann T, Trzewik J, Holste J, Batke B, Konerding MA, Wolloscheck T, Hartung C. Forces and deformations of the abdominal wall-A mechanical and geometrical approach to the linea alba. J Biomech 44:600–6. 2011. doi: 10.1016/j.jbiomech.2010.11.021.

16. Hernández-Gascón B, Mena A, Peña E, Pascual G, Bellón JM, Calvo B. Understanding the passive mechanical behavior of the human abdominal wall. Ann Biomed Eng 41:433–44. 2013 doi: 10.1007/s10439-012-0672-7.

17. Horn AG, Baumfalk DR, Schulze KM, Kunkel ON, Colburn TD, Weber RE, Bruells CS, Musch TI, Poole DC, Behnke BJ. Effects of elevated positive-end expiratory pressure on diaphragmatic blood flow and vascular resistance during mechanical ventilation. J Appl Physiol (1985) 129:626-635. 2020 doi: 10.1152/japplphysiol.00320.2020. Epub 2020 Jul.

18. Kirkpatrick AW, Roberts DJ, De Waele J, Jaeschke R, Malbrain MLNG, De Keulenaer B, Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A, Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C; Pediatric Guidelines Sub-Committee for the World Society of the Abdominal Compartment Syndrome Duchesne J, Bjorck M, Leppaniemi A, Ejike JC, Sugrue M, Cheatham M, Ivatury R, Ball CG, Reintam Blaser A, Regli A,

Balogh ZJ, D'Amours S, Debergh D, Kaplan M, Kimball E, Olvera C. Intra-abdominal hypertension and the abdominal compartment syndrome: Updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. Intensive Care Med 39:1190–206. 2013. doi: 10.1007/s00134-013-2906-z.

19. Lu Q, Rouby JJ. Measurement of pressure-volume curves in patients on mechanical ventilation. Methods and significance. Minerva Anestesiol 66:367–75. 2000. PMID: 10965718.

20. Malbrain MLNG, Wilmer A. The polycompartment syndrome: Towards an understanding of the interactions between different compartments! Intensive Care Med 33:1869–72. 2007. doi: 10.1007/s00134-007-0843-4.

21. Malbrain MLNG, Pelosi P, Quintel M. Effect of intra-abdominal pressure on respiratory mechanics. Acta Clin Belg 62:78–88. 2007. doi: 10.1179/acb.2007.62.s1.011.

22. Malbrain MLNG, Roberts DJ, Sugrue M, De Keulenaer BL, Ivatury R, Pelosi P, Verbrugge F, Wise R, Mullens W. The polycompartment syndrome: A concise state-of-the-art review. Anaesthesiol Intensive Ther 46:433–50. 2014 doi: 10.5603/AIT.2014.0064

23. Malbrain MLNG, Roberts DJ, De Laet I, De Waele JJ, Sugrue M, Schachtrupp A, Duchesne J, Van Ramshorst G, De Keulenaer B, Kirkpatrick AW, Ahmadi-Noorbakhsh S, Mulier J, Ivatury R, Pracca F, Wise R, Pelosi P. The role of abdominal compliance, the neglected parameter in critically ill patients - A consensus review of 16. Part 1: Definitions and pathophysiology. Anaesthesiol Intensive Ther. 46:392–405. 2014. doi: 10.5603/AIT.2014.0062.

24. Malbrain MLNG, De Laet I, De Waele JJ, Sugrue M, Schachtrupp A, Duchesne J, Van Ramshorst G, De Keulenaer B, Kirkpatrick AW, Ahmadi-Noorbakhsh S, Mulier J, Pelosi P, Ivatury R, Pracca F, David M, Roberts DJ. The role of abdominal compliance, the neglected parameter in critically ill patients - A consensus review of 16. Part 2: Measurement techniques and management recommendations Anaesthesiol Intensive Ther 46:406–32. 2014 doi: 10.5603/AIT.2014.0063.

25. Malbrain MLNG. The saga continues: How to set best PEEP in intra-abdominal hypertension? J Crit Care 43:387–9. 2018 doi:10.1016/j.jcrc.2017.11.013.

26. Martins P, Peña E, Jorge NRM, Santos A, Santos L, Mascarenhas T, Calvo B. Mechanical characterization and constitutive modelling of the damage process in rectus sheath. J Mech Behav Biomed Mater 8:111–22. 2012. doi:10.1016/j.jmbbm.2011.12.005

27. Mazzinari G, Diaz-Cambronero O, Alonso-Iñigo JM, Garcia-Gregorio N, Ayas-

Montero B, Ibañez JL Serpa Neto A, Ball L, Gama de Abreu M, Pelosi P, Maupoey J, Argente Navarro MP, Schultz MJ. Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery: An Open-label, Nonrandomized, Crossover, Clinical Trial. Anesthesiology 132:667–677. 2020. doi: 10.1097/ALN.0000000000003146

28. Mulier J, Dillemans B, Crombach M, Missant C, Sels A. On the abdominal pressure volume relationship. Internet J Anesthesiol 21: 1–7. 2009. www.ispub.com/ija/21/1/5221. Last accessed: 24 September 2020.

29. Neto AS, Hemmes SNT, Barbas CSV, Beiderlinden M, Fernandez-Bustamante A, Futier E, Gajic O, El-Tahan MR, Ghamdi AA, Günay E, Jaber S, Kokulu S, Kozian A, Licker M, Lin WQ, Maslow AD, Memtsoudis SG, Reis Miranda D, Moine P, Ng T, Paparella D, Ranieri VM, Scavonetto F, Schilling T, Selmo G, Severgnini P, Sprung J, Sundar S, Talmor D, Treschan T, Unzueta C, Weingarten TN, Wolthuis EK, Wrigge H, Amato MB, Costa EL, de Abreu MG, Pelosi P, Schultz MJ; PROVE Network Investigators. Association between driving pressure and development of postoperative pulmonary complications in patients undergoing mechanical ventilation for general anaesthesia: A meta-analysis of individual patient data. Lancet Respir Med 4:272–80. 2016. doi: 10.1016/S2213-2600(16)00057-6.

30. Neudecker J, Sauerland S, Neugebauer EAM, Bergamaschi R, Bonjer HJ, Cuschieri A, Fuchs KH, Jacobi CA, Jansen FW, Koivusalo AM, Lacy AM, McMahon MJ, Millat B, Schwenk W. The EAES clinical practice guidelines on the pneumoperitoneum for laparoscopic surgery (2002). EAES Guidel Endosc Surg Twelve Years Evidence-Based Surg. 2006. Berlin Springer Verlag. p.39–85.

31. Özdemir-van Brunschot DMD, van Laarhoven KCJHM, Scheffer GJ, Pouwels S, Wever KE, Warlé MC. What is the evidence for the use of low-pressure pneumoperitoneum? A systematic review. Surg Endosc 30(5):2049-65. 2015. doi: 10.1007/s00464-015-4454-9.

32. Passos JR de S, de Pinho SZ, de Carvalho LR, Mischan MM. Critical points in logistic growth curves and treatment comparisons. Sci Agric. 69:308–12. 2012. doi: 10.1590/S0103-90162012000500004.

33. Ranieri VM, Giuliani R, Fiore T, Dambrosio M, Milic-Emili J. Volume-pressure curve of the respiratory system predicts effects of PEEP in ARDS: "occlusion" versus "constant flow" technique. Am J Respir Crit Care Med 149:19–27.. doi: 10.1164/ajrccm.149.1.8111581.

34. Regli A, Pelosi P, Malbrain MLNG. Ventilation in patients with intra-abdominal hypertension: what every critical care physician needs to know. Ann Intensive Care 9: 52. 2019 doi:10.1186/s13613-019-0522-y

35. Regli A, Mahendran R, Fysh ET, Roberts B, Noffsinger B, De Keulenaer BL, Sing B, van Heerden PV. Matching positive end-expiratory pressure to intra-abdominal pressure improves oxygenation in a porcine sick lung model of intra-abdominal hypertension. Crit Care 16:R208. 2012. doi: 10.1186/cc11840.

36. Regli A, Chakera J, De Keulenaer BL, Roberts B, Noffsinger B, Singh B, Van Heerden PV. Matching positive end-expiratory pressure to intra-abdominal pressure prevents end-expiratory lung volume decline in a pig model of intra-abdominal hypertension. Crit Care Med. 2012;40(6):1879–86. doi: 10.1097/CCM.0b013e31824e0e80.

37. Regli A, Hockings LE, Musk GC, Roberts B, Noffsinger B, Singh B, van Heerden PV. Commonly applied positive end-expiratory pressures do not prevent functional residual capacity decline in the setting of intra-abdominal hypertension: A pig model. Crit Care 14:R128. 2010. doi: 10.1186/cc9095.

38. Regli A, De Keulenaer BL, Singh B, Hockings LE, Noffsinger B, van Heerden PV. The respiratory pressure—abdominal volume curve in a porcine model. Intensive Care Med Exp 5:11. 2017 doi: 10.1186/s40635-017-0124-7.

39. Scalea TM, Bochicchio G V., Habashi N, McCunn M, Shih D, McQuillan K, Aarabi B. Increased intra-abdominal, intrathoracic, and intracranial pressure after severe brain injury: Multiple compartment syndrome. J Trauma 62:647–56. 2007 doi: 10.1097/TA.0b013e31802ee542.

40. Song C, Alijani A, Frank T, Hanna G, Cuschieri A. Elasticity of the living abdominal wall in laparoscopic surgery. J Biomech 39:587–91. 2006. doi: 10.1016/j.jbiomech.2004.12.019.

41. Suratt PM, Owens DH, Kilgore WT, Harry RR, Hsiao HS. A pulse method of measuring respiratory system compliance. J Appl Physiol Respir Environ Exerc Physiol 49(6):1116-21. 1980. doi: 10.1152/jappl.1980.49.6.1116.

42. Torquato JA, Jaber Lucato JJ, Antunes T, Barbas CV. Interaction between Intra-Abdominal pressure and Positive-End expiratory pressure. Clinics (Sao Paulo) 64:105–12. 2009. doi: 10.1590/s1807-59322009000200007.

43. Van Damme L, De Waele JJ. Effect of decompressive laparotomy on organ function in patients with abdominal compartment syndrome: A systematic review and meta-analysis. Crit Care 22:1–11. 2018 doi: 10.1186/s13054-018-2103-0.

44. Vassilakopoulos T, Petrof BJ. Ventilator-induced Diaphragmatic Dysfunction. Am J Respir Crit Care Med 169:336-41. 2004 doi: 10.1164/rccm.200304-489CP.

45. Vehtari A, Gelman A, Gabry J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. Stat Comput 27:1413–32. 2017. doi: 10.1007/s11222-016-9696-4

46. Venegas JG, Harris RS, Siman AA comprehensive equation for the pulmonary pressure-volume curve. J Appl Physiol 84:389–95. 1998. doi:10.1152/jappl.1998.84.1.389.

47. Vlot J, Wijnen R, Stolker RJ, Bax K. Optimizing working space in porcine laparoscopy: CT measurement of the effects of intra-abdominal pressure. Surg Endosc 27:1668–73. 2013. doi: 10.1007/s00464-012-2654-0.

48. Wever KE, Bruintjes MHD, Warlé MC, Hooijmans CR. Renal perfusion and function during pneumoperitoneum: A systematic review and meta-analysis of animal studies. PLoS One. 11:1–25. 2016 doi: 10.1371/journal.pone.0163419.

49. Young CC, Harris EM, Vacchiano C, Bodnar S, Bukowy B, Elliott RRD, Migliarese J, Ragains C, Trethewey B, Woodward A, Gama de Abreu M, Girard M, Futier E, Mulier JP, Pelosi P, Sprung J. Lung-protective ventilation for the surgical patient: international expert panel-based consensus recommendations. Br J Anaesth. 123: 898–913. 2019 doi: 10.1016/j.bja.2019.08.017. Epub 2019 Oct 3.

50. Zhou JC, Xu QP, Pan KH, Mao C, Jin CW. Effect of increased intra-abdominal pressure and decompressive laparotomy on aerated lung volume. J Zhejiang Univ Sci B 11:378–85. 2010. doi: 10.1631/jzus.B0900270.

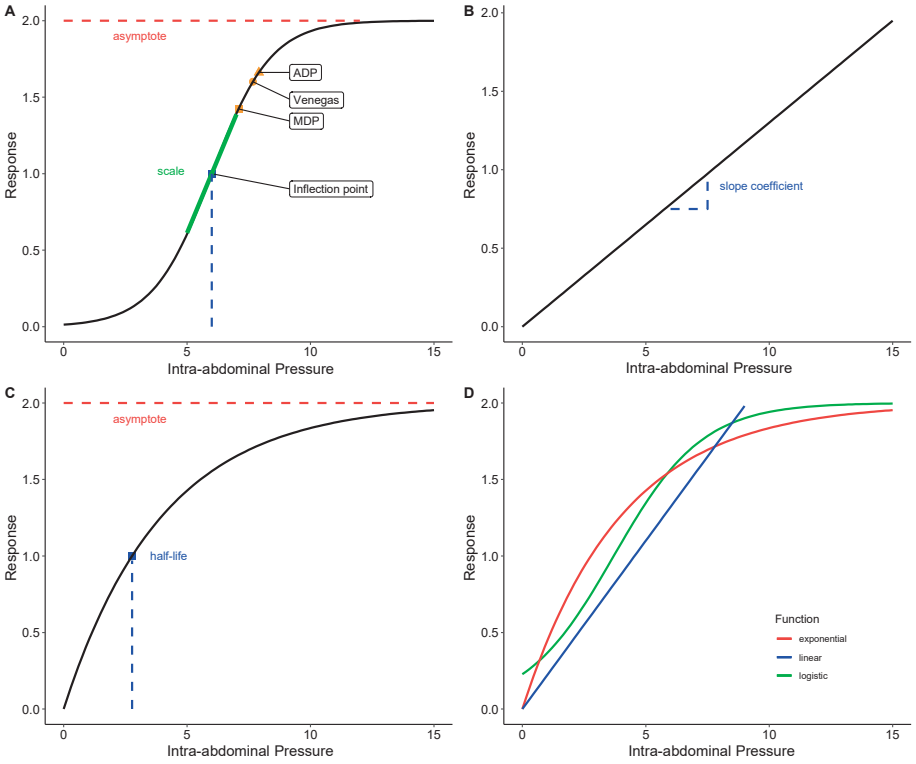


Figure 1.

Graphic representation of the assessed functions. **A**: Logistic function **B**: Linear Function, **C**: Negative exponential, **D**: All functions on the same graph. ADP, asymptotic deceleration point; MDP, maximum deceleration point. *X* and *y* scales are arbitrary and are picked for visual purposes and do not report actual data.

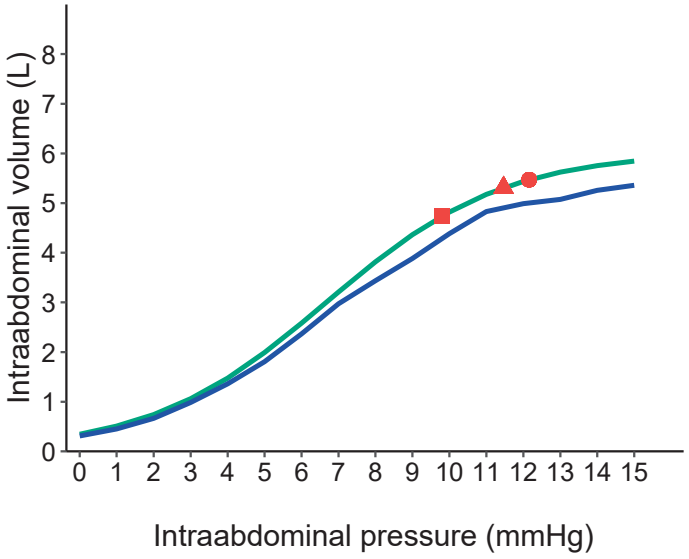


Figure 2.

Scatterplot of Intra–abdominal volume data according to intra–abdominal pressure changes. Green solid line, intra–abdominal pressure effect estimation with three–parameter logistic function. Blue solid line, intra–abdominal pressure Bayesian multivariable mixed model marginal effect estimation with three–parameter logistic function Grey band, 95%credible interval. Red symbols, critical points with change of rate in the function with decreasing *y* response to *x* increase calculated with different formulas. Red square, Maximum deceleration point; Red triangle, Venegas equation (46); Red circle, Asymptotic deceleration point (40).

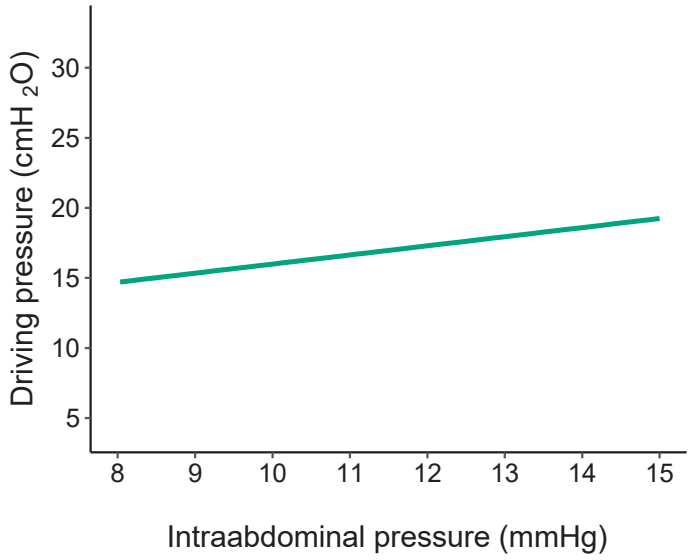


Figure 3.

Scatterplot of respiratory driving pressure data according to intra–abdominal pressure changes. Green solid line, intra–abdominal pressure marginal effect estimates. Grey band, 95%–credible interval.

Table 1 – Baseline Characteristics

	IPPColLapSe I (N = 92)	IPPColLapSe II (N = 85)	IPPColLapSe III (N = 27)	Overall (N = 204)	SMD
Age (years)	66 [58 to 76]	68 [58 to 74]	66 [55 to 74]	67 [58 to 74]	0.184
Gender (Female)	41% (38/92)	32% (27/85)	67% (18/27)	41% (83/204)	0.503
BMI ($Kg \cdot m^{-2}$)	26.6 [23.8 to 29.0]	26.9 [24.2 to 29.8]	27.0 [25.1 to 31.0]	26.8 [24.2 to 29.0]	0.223
Surgical position	Trendelenburg	Trendelenburg	Anti–Trendelenburg	–	–

BMI: Body Mass Index; SMD: standardized mean difference;

Table 2 – Bayesian mixed model with a random factor for individual patient and a linear effect for intraabdominal pressure as main dependent variable with **respiratory system driving pressure** as dependent variable.

Variable	Estimate	Std. Error	Lower 95%CI	Upper 95%CI
(Intercept)	-2.46	2.17	-6.73	1.77
Intraabdominal pressure	0.65	0.01	0.62	0.68
Age	0.05	0.02	0.01	0.10
BMI	0.35	0.07	0.22	0.48
Gender (Female)	0.65	0.59	-0.48	1.80
Study (Reference category IPPCollapse I)				
IPPCollapse II	-0.94	0.60	-2.09	0.23
IPPCollapse III	0.79	0.88	-0.93	2.50

Widely Applicable Information Criterion = 3273.117*; BMI, Body Mass Index; CI, Credible interval; Std, Standard*

Material suplementario Capítulo 6

STATISTICAL ANALYSIS PLAN

Objectives

The primary objective is to determine the relationship between intraabdominal pressure (IAP) and intraabdominal volume (IAV) during pneumoperitoneum insufflation.

The secondary objective is to determine the rate of abdominal–thoracic transmission (ATT) assessing the correlation between IAP and respiratory driving pressure (ΔP_{RS}).

Methods

Design of the 3 clinical trials

Overall characteristics of the studies are shown in **Table 1**. IPPColLapSe I[1] was a multicenter cohort study to assess the feasibility of an individualized pneumoperitoneum (IPP) strategy. IPPColLapSe II[2] was a multicenter randomized study comparing an IPP strategy with a standard pneumoperitoneum pressure (SPP) strategy with respect to postoperative recovery. IPPCollapSe III[3] was a single center crossover trial comparing fixed 5 cmH_2O positive end–expiratory pressure (PEEP) to IAP targeted PEEP at various IAP levels.

The 3 study protocols were approved by the Institutional Review Boards of participating hospitals and registered before patient's enrolment at clinicaltrials.gov (study identifiers: NCT03000465, NCT03435913 and NCT03435913). Written informed consent was obtained from all participating subjects, and all studies complied with the Helsinki Declaration and Spanish legislation for biomedical research**.** This analysis plan is prespecified before data opening and registered at clincaltrials.gov (study indentifier: NCT NCT04468698)

Inclusion and exclusion criteria

We will include in this analysis those patients that i) underwent an initial insufflation procedure with a stepwise change in IAP to record IAV (see **Table 1** for details) and ii) data from insufflation at 5 cmH_2O of PEEP.

Data management

Prior to start of the current analysis, the clinical report forms, data dictionaries, and study protocols will be compared, and similar variables and parameters will be double–checked for consistency across the trials prior to being finally imported into the combined dataset.

The combined database will not contain any patient identifying information. Individual patients will be identifiable only through the unique study number in the original trials.

The following variable and parameters are to be collected: patients' age, gender and body mass index (BMI), plateau pressure (P_{plat}), intraabdominal pressure and volume, participating study. Driving pressure (ΔP_{RS}) will be calculated by subtracting PEEP to P_{plat}.

Power calculation

We will use all available data from patients included in the three trials without formal sample size calculation. Also, as the purpose of the analysis was exploring a physiological hypothesis, we do not specify any *a priori* effect size.

Analysis Plan

Continuous variables are reported as median [25^{th}–75^{th} percentile]. Normality will be checked by examination of quantile–quantile plot. Categorical variables are reported as percentages and proportions. In case of >5% of missing data, imputation will be performed using the *mice* package for R software. Values will be imputed by chained equation with predictive mean matching creating 5 datasets that were jointly used to fit regression models.

To determine which function, adapt better to data we will fit Bayesian mulitvariable mixed models with either linear, exponential or sigmoid response distribution. Age, gender, BMI and study, i.e. IPP 1, 2 or 3, will be introduced as covariables and subject will be introduced in the models as random effect. Models will be fitted with *brms* R package setting a prior distribution for fixed effects using a normal distribution with a mean of 0 and standard deviation (SD) of 5 and a mean of 0 and SD of 20 for IAV and ΔP respectively, with 4 chains of iterations with 3000 post–warm up samples and gaussian, exponential or hurdle log normal prior distribution family for linear, exponential or sigmoid response model. The best fitting model will be chosen by inspection of marginal effects plot, leave-one-out (loo) cross validation and smallest Widely Applicable Information Criterion (WAIC).

According to the best fitting model we will estimate the relationship between IAP and IAV and IAP and ΔP_{RS} fitting the selected function to data. We will examine the following functions: linear, logistic or asymptotic exponential depending on the fitting of the exponential model. According to the selected function we will estimate the dependent variable, i.e. IAV or ΔP_{RS} according to the function parameters.

In a linear equation the relationship between dependent and independent variable is described by the following:

$$y = \beta + \beta_1 x \quad [1]$$

where β is the value of *y* when *x*=0 and β_1 is the slope, i.e. the amount of variation in *y* for a unit-increase in *x*.

In a sigmoid equation, i.e. logistic function the relationship between dependent and independent variable is described by the following:

$$y = \frac{a}{1 + e^{-(x-b)/c}} \quad [2]$$

Where a is the higher asymptote, b is the inflection point, i.e. *x* value half–way between the lower and upper asymptote points, c is the slope around the inflection point. In this parameterization the lower asymptote is assumed to be 0.

A negative exponential growth function where the dependent variable increase until a limit is described by an asymptotic growth with the following parameters:

$$y = a - (1 - e^{-c\,x}) \quad [3]$$

Where a is the maximum reachable value for *y,* and c is a constant proportional to *y* rate of increase.

The linear function will be estimated directly from the coefficients of the multivariable mixed model and exponential and logistic function will be estimated from the predicted values of the respective multivariable mixed model to derive the parameters of each function. Apart for the parameters that define each function, additional critical points where the curve growth phase change will be calculated for logistic regression. Such points will be determined by deriving the growth function with the following methods:[4–6]

1. **Maximum deceleration point (MDP).** At this point, the acceleration of growth has a minimum value. This point is found by equalizing the third derivative of the growth function to zero and can be estimated by the following formula for the predefined logistic function:

$$x = b - (c \cdot 1.3170) \quad [4]$$

b is the inflection point and c is the slope around the inflection point.

2. **Asymptotic deceleration point (ADP).** At this point, the acceleration of growth goes to asymptotic. This point is found by equalizing the fourth derivative of the growth function to zero and can be estimated by the following formula for the predefined logistic function:

$$x = b - (c \cdot 2.2924) \quad [5]$$

b is the inflection point and c is the slope around the inflection point.

3. **Using the classic quasi–static pressure–volume (P-V) curves** which have been used in research and in the clinical setting to quantify the elastic properties of the lungs and respiratory system, the point where the function cease to be linear that can be estimated by the following formula for the predefined logistic function [Venegas]:

$$x = b - (c \cdot 2) \quad [6]$$

b is the inflection point and c is the slope around the inflection point.

All analyses were performed with R software version 3.5.2 (R Foundation for Statistical Computing, www.r-project.org). Statistical significance will be set for two–tailed at $P < 0.05$.

eTable 1 – Characteristics of the included trials

	IPPColLapSe I	IPPColLapSe II	IPPColLapSe III
Number of centres	3	4	1
Eligibility			
Inclusion criteria	1. Age ≥ 18 years 2. ASA < IV 3. Laparoscopic colorectal surgery	1. Age ≥ 18 years 2. ASA < IV 3. Laparoscopic colorectal surgery 4. No cognitive deficits	1. Age ≥ 18 years 2. ASA < IV 3. Laparoscopic cholecystectomy
Exclusion criteria	1. Emergency surgery 2. Absence of written informed consent 3. Allergy or contraindication for rocuronium and/or sugammadex	1. Emergency surgery 2. Absence of written informed consent 3. Allergy or contraindication for rocuronium and/or sugammadex 4. Pregnancy or breastfeeding 5. Immunologic disease 6. Neuromuscular disease 7. Advanced cardiopulmonary disease	1. Pregnancy or breastfeeding 2. Advanced renal disease 3. Advanced hepatic disease 4. Advanced cardiopulmonary disease
Number of patients (total)	92	204/166	30
Number of patients (with stepwise insufflation procedure)	92	85 (intervention arm)	27
Outcome			
Primary	1. Proportion of patients at each level of individualized IAP.	1. Physiologic postoperative recovery as assessed by the Postoperative Quality of Recovery (PQRS) Score	1. Transpulmonary driving pressure
Secondary	1. Airway pressure 2. Intraabdominal volume	1. Overall PQRS 2. Emotive PQRS 3. Nociceptive PQRS 4. Functional PQRS 5. Intraoperative adverse events 6. Plasma inflammation biomarkers course 7. Hepatic perfusion 8. Airway pressure 9. Intraabdominal volume	1. Respiratory mechanics 2. Respiratory driving pressure

Intervention	Single–arm study	Randomized controlled two arm study Control Arm: 1. Moderate neuromuscular blockade 2. IAP set at 12 mmHg Intervention arm: 1. Modified lithotomy position 2. Deep neuromuscular blockade 3. Pre–stretching of the abdominal wall muscles 4. IAP titration to the lowest value that maintain an 'adequate' workspace	Crossover study Intervention A: PEEP at 5 cmH2O Intervention B: PEEP at 2 cmH2O above IAP Intervention A and B repeated at 8, 12 and 15 mmHg IAP
IAP management	1. IAP 15 mmHg for initial abdominal stretching 2. 20° Trendelenburg position. 3. IAP decreased from 15 to 12 mmHg, and then stepwise to 11, 10, 9, and finally 8 mmHg as long as surgical workspace remain adequate	1. IAP 15 mmHg for initial abdominal stretching 2. 20° Trendelenburg position. 3. IAP decreased from 15 to 12 mmHg, and then stepwise to 11, 10, 9, and finally 8 mmHg as long as surgical workspace remain adequate	1. IAP 15 mmHg for initial abdominal stretching 2. 20° anti–Trendelenburg position. 3. The IAP lowered at 8 and then stepwise increased to 12 and 15 mmHg.

IAP: intraabdominal pressure; PEEP: positive end–expiratory pressure; PQRS: Postoperative Quality of Recovery score.

eTable 2 – Bayesian models cross validation results

	ELPD_diff	Se_diff
IAV as dependent variable		
Sigmoid response	0	0
Exponential response	-846.8	173.8
Linear response	-6558.4	92.2
ΔP_{RS} as dependent variable*		
Sigmoid response	-79.2	22.1
Exponential response	0	0
Linear response	-2748.9	38.1

IAV, Intraabdominal volume; ΔP_{RS}, respiratory system driving pressure; ELPD, expected log predictive density*; Se_diff, standard error difference;loo, leave one out.*
**due to observation with Pareto k value > 0.7 parameters in loo cross–validation were achieved through 10–fold cross–validation.*

eTable 3a – Bayesian mixed model with a random factor for individual patient and a spline effect for intra–abdominal pressure as main independent variable and intra–abdominal volume as dependent variable.

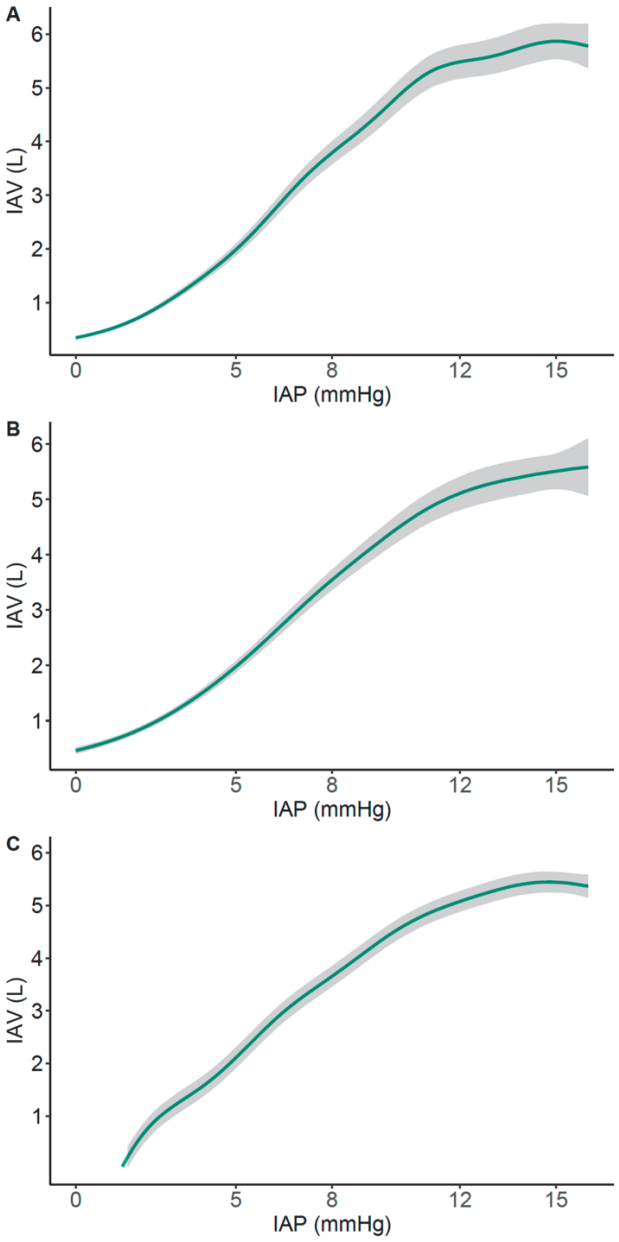
Variable	Estimate	Std Error	Lower 95%CI	Upper 95%CI
(Intercept)	0.69	0.27	0.16	1.20
Intraabdominal pressure	4.41	0.91	2.58	6.13
Age	0.01	0.01	-0.01	0.01
BMI	0	0.01	-0.02	0.02
Gender (Female)	-0.23	0.09	-0.41	-0.06
Study (Reference category IPPCollapse I)				
IPPCollapse II	-0.09	0.08	-0.24	0.07
IPPCollapse III	0.64	0.11	0.41	0.85

Widely Applicable Information Criterion = 13947.71; BMI, Body Mass Index; CI, Credible interval; Std, Standard

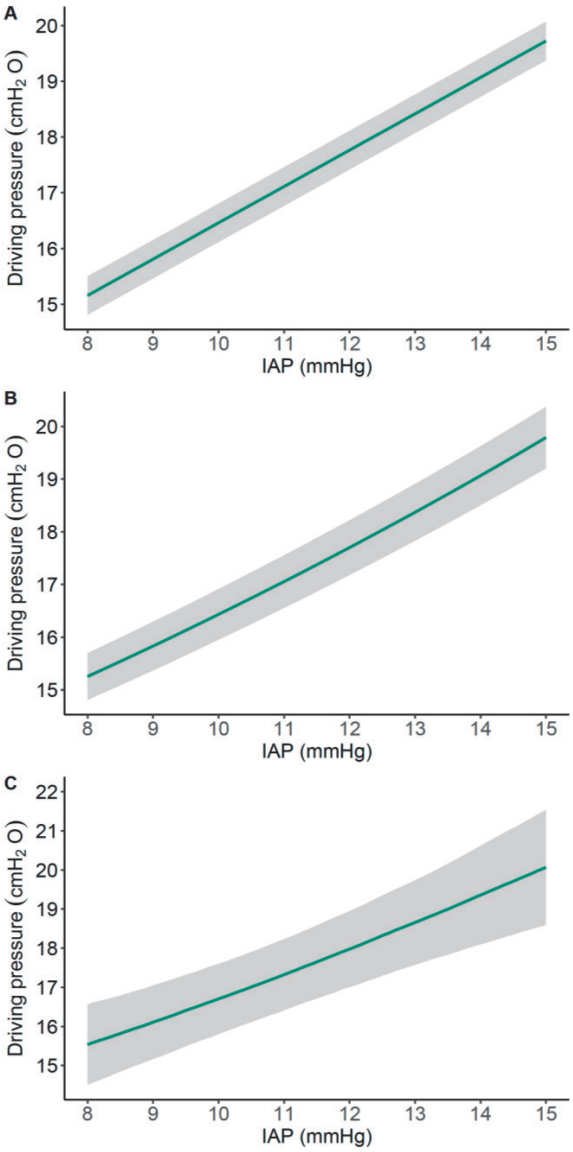
eTable 3b – Non–linear 3 parameters logistic model with intra–abdominal volume as dependent variable and intra–abdominal pressure as main independent variable.

Parameters	Estimate	Std. Error	Lower 95%CI	Upper 95%CI	P Value
Asymptote	6.0	0.01	5.9	6.2	< 0.001
Inflection Point	6.7	0.02	6.6	6.8	< 0.001
Scale	2.4	0.02	2.3	2.4	< 0.001

Std, Standard, CI, Confidence interval



efigure 1 Bayesian marginal effect estimation of intra–abdominal pressure on intra–abdominal volume as estimated wuth three different family functions. **A**: Logistic; **B**: Asymtpotic exponential; **C**: Linear. *IAV,* Intra–abdominal volume; *IAP*, Intra–abdominal pressure



eFigure 2. Bayesian marginal effect estimation of intra–abdominal pressure on respiratory system driving pressure volume as estimated wuth three different family functions. **A**: Logistic; **B**: Asymtpotic exponential; **C**: Linear. *IAP*, Intra–abdominal pressure

REFERENCES

1. Diaz-Cambronero O, Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, et al. A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study. Surg Endosc 2019; 33: 252–60.

2. Díaz-Cambronero O, Mazzinari G, Flor Lorente B, García Gregorio N, Robles-Hernandez D, Olmedilla Arnal LE, Martin de Pablos A, Schultz MJ, Errando CL, Argente Navarro MP, on behalf of the IPPColLapSe II study investigators. Effect of an individualized versus standard pneumoperitoneum pressure strategy on postoperative recovery : a randomized clinical trial in laparoscopic colorectal surgery. Br J Surg 2020 Jun 7. doi: 10.1002/bjs.11736. Online ahead of print.

3. Mazzinari G, Diaz-Cambronero O, Alonso-Iñigo JM, Garcia-Gregorio N, Ayas-Montero B, Ibañez JL, Serpa Neto A, Ball L, Gama de Abreu M, Pelosi P, Maupoey J, Argente Navarro MP, Schultz MJ. Intraabdominal Pressure Targeted Positive End-expiratory Pressure During Laparoscopic Surgery: An Open-label, Nonrandomized, Crossover, Clinical Trial. Anesthesiology 2020; 132:667-677

4. Sebaugh JL, McCray PD. Defining the linear portion of a sigmoid-shaped curve: bend points. Pharm Stat. 2003; 2:167–74.

5. Archontoulis SV, Miguez FE. Nonlinear regression models and applications in agricultural research. Agron J. 2015; 107:786–98.

6. Passos JR de S, de Pinho SZ, de Carvalho LR, Mischan MM. Critical points in logistic growth curves and treatment comparisons. Sci Agric. 2012; 69:308–12.

Estrategia de bloqueo neuromuscular en cirugía laparoscópica

Capítulo 7

Neuromuscular blockade management and postoperative outcomes in enhanced recovery colorectal surgery: secondary analysis of POWER trial

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Introduction

Enhanced recovery programmes in colorectal surgery are being widely implemented, as they have demonstrated lower length of hospital stay (LOS) and fewer complications versus traditional care[1,2,3,4]. Nonetheless, the weight of every single measure on outcomes are not fully established, and new measures as quantitative monitoring and pharmacological reversal of the neuromuscular blockade, were suggested to be considered five years ago in the bundle by Spanish RICA guideline[5] and it also has been recently recommended by ERAS Society guideline[6].

Nowadays, the use of neuromuscular blockade agents (NMBAs) in abdominal surgery is generalised worldwide, mainly in laparoscopic approach. These agents provide better and safer surgical conditions as well as some additional benefit for the patients[7-9]. Nevertheless, NMBAs can be harmful if they are not applied properly leading to poor outcomes and to increased postoperative pulmonary complications[10-12]. Berg and colleagues[13], first suggested that incomplete recovery from muscle paralysis might cause postoperative pulmonary complications. Thereby, reversal of neuromuscular blockade to a train-of-four (TOF) ratio of 90% and even better if it is > 95%, should be desirable in order to avoid residual paralysis, its associated risks[14] and to obtain better postoperative outcomes[15]. Some guidelines and reviews suggest that optimal management of neuromuscular blockade with quantitative monitoring and adequate pharmacological reversal could decrease residual neuromuscular blockade and improve postoperative outcomes[16], but this is still a matter of controversy. Thus, despite those expert recommendations, postoperative residual neuromuscular blockade remains one of the most prevalent complication in the post-anaesthesia care unit (PACU)[17] meaning surgical patient´s safety worldwide is threaten by this reason.

POWER study[18] was a multicentre prospective cohort study of adults scheduled for elective colorectal surgery in Spanish hospitals. It was designed to determine the association between enhanced recovery protocols and outcomes. Our sub-study, conducted with the POWER cohort population, firstly aimed to define the relationship between quantitative neuromuscular blockade monitoring plus pharmacological reversal, and postoperative complications and

LOS in patients undergoing colorectal surgery. Secondary objective was to explore mortality in that population. We hypothesized that optimal neuromuscular blockade management within an enhanced recovery program in colorectal surgery could be associated with better postoperative outcomes.

Materials and Methods

POWER[18] study was an observational prospective 2-month multicentre cohort study in 80 centres in Spain. It was approved by the Instituto Aragonés de Ciencias de la Salud Ethics Committee (Zaragoza, Spain) (C.P.-C.I. P117/017) on February 1st, 2017 and by the Spanish Medical Agency on September 23rd, 2017. It was also registered prospectively at Clinical trials registry (NCT03012802) on January 6th, 2017. Written informed consent was obtained by patients included in the study according to Ethical Review Board in every participating centre. In each collaborating hospital, all consecutive patients aged ≥ 18 years scheduled for elective colorectal surgery with a planned overnight stay, were included during a single period of two months of recruitment between September to December 2017. The follow-up period was 30 days after surgery and it was performed through hospital and primary care medical records. Data were censored at 30 days following surgery for patients who remained in the hospital. Adherence to RICA guideline was suggested, but by protocol it was left at the attending anaesthesiologist criteria. Individual data on 22 Enhanced Recovery Pathways (ERP) items based on the 2013 guidelines[19] of the Enhanced Recovery After Surgery Society in colorectal surgery were also collected prospectively for each enrolled patient.

Our study was a predefined sub-study of POWER study. It has been reported in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE)[20] statement. The primary outcomes were severe-moderate postoperative complications and LOS. Postoperative complications were defined and graded as mild, moderate, or severe as described by European Perioperative Clinical Outcome (EPCO) definitions[21] and recorded as "yes" if any of them appeared in a patient during the 30 days follow up. LOS was defined as days in hospital. Apart from moderate-severe complications we have also evaluated time (in hours) to start feeding per mouth (T1), and time (in

hours) to initiate mobilization (T2), bearing in mind these two variables are highly important when considering functional recovery from an abdominal surgery. Mortality was a secondary outcome and was recorded as “yes” if occurring in any patient during the study following up period. Information regarding NMB was collected prospectively. The use of quantitative neuromuscular monitoring, and pharmacological reversal was recorded as “yes” or “no”. The drug for reversal was recorded as “neostigmine” or “sugammadex”. The total dosage of the administered reversal drugs was not collected and the same was for the TOF ratio counting. ERAS programmes compliance rate was also evaluated in this study.

In this sub-study we defined the following two groups:

1.- Monitoring + Reversal MNB (M+R) group: All patients receiving neuromuscular blockade monitoring plus reversal of it with any drug (neostigmine or sugammadex) were included and 2.- No Monitoring nor reversal NMB (noM+noR) group. In this group all the patients who did not receive monitoring plus reversal of the neuromuscular blockade were allocated. Regarding the drug used for the neuromuscular blockade reversal, we also defined two subgroups in the M+R group in order to assess the impact of the two antidotes on the outcomes. These two subgroups are M+Rsug (including patients who were monitored and reversed with sugammadex) and M+Rneos (including patients who were monitored but in whom the reversal was done with neostigmine).

Statistical analysis

Quantitative variables were explored using Shapiro-Wilks test to assess normality. Mean was used as central tendency measure and standard deviation as dispersion measure. Regarding qualitative variables, the frequencies distribution and their percentages were analysed for each category. Proportions of frequencies were compared when the studied variables were qualitative (Chi square test or Exact´s Fisher test). In the case of quantitative variables with normal distribution, Student T test was performed instead. Otherwise, Mann-Whitney U test was applied if the variable distribution had no a normality pattern. To assess association between the studied groups and postoperative

complications, LOS, time to initiate oral intake and mobilization and mortality, a contrast of hypothesis analysis was performed. Additionally, the statistical analysis was completed with logistic regression models. First, we univariately explored association of complications, LOS, T1, T2, belonging to an ERAS program and mortality with monitoring of the neuromuscular blockade plus its reversal, compared with none of those strategies. The type of the drug used for the reversal was analysed afterwards. For the multivariate analysis all the same variables used for the univariate analyses were included as they all are clinically relevant. Finally, we univariately studied association of all the severe-moderate complications defined by EPCO definitions[21] and the neuromuscular blockade strategy performed together with the type of pharmacological reversal. We admitted as statistically significant those comparisons where p-value and q-value were below 0.05. Data analysis was performed using STATA (StatCorp LP, version 14)[22], and also compare Groups package of R[23].

Results

Once the study period concluded, 2084 candidates were included in POWER for statistical analysis. In our sub-analysis, 803 (38.5%) patients received monitoring of the neuromuscular blockade and 1384 (66.4%) received pharmacological reversal. Optimal neuromuscular blockade management (M+R) was applied in 676 (32.4%) patients, while no neuromuscular blockade strategy (noM+noR) was performed in 458 (21.97%) (Figure I). Basal data of our sub-study population is depicted in table I. Both groups were homogeneous in terms of ASA, comorbidities and type of surgery, with the exception of ASA I and laparoscopic approach which were more frequent in M + R group and Stroke that was developed more often in noM+noR group.

Regarding primary outcomes, neither the development of moderate-severe complications nor LOS, showed statistically significant difference when comparing M+R and noM+noR groups (174(25.7%) vs 124(27.1%); p = 0.607 and (10.8±11.0 vs 11.0 ±12.6) days; p = 0.683 respectively (Table II). T2 was longer in the noM+noR group than in the M+R group (42.7±50.8 vs 36.1±29.0 hours; p = 0.012), while T1 was similar in both groups (34.4±50.7 vs 35.9±49.0 hours; p = 0.183) (These data are not shown in tables). When comparing

patients who were monitored and reversed with neostigmine (M+Rneos) versus the ones who were monitored and reversed with sugammadex (M+Rsug), moderate-severe complications were similar in both groups (24(21.2%) vs 150(26.6%); p = 0.358). Moreover, type of reversal drug was neither linked to LOS, being also similar in both groups (9.5±7.9 vs 11.0±11.6; p = 0.550 days) (Table III). In sugammadex group T1 was longer compared with neostigmine (51.2±76.6 vs 32.8±40.6 hours; p = 0.038) while T2 was not significantly different between both groups (43.9±37.4 vs 34.5±26.7; p = 0.068) (These data are not shown in tables). ERAS programmes were significantly more often implemented in noM+noR group compared with M+R group (326(71.2%) vs 420(62.1%); p = 0.001), being also more implemented in the group reversed with neostigmine (82(72.6%) vs 338(60%); p = 0.030) (Tables II and III). In the univariate analysis, mortality (secondary outcome) was significantly higher in the group reversed with neostigmine compared with the group reversed with sugammadex [OR:0.20(0.04-1.07), p=0.048]. However, in the multivariate analysis mortality presented only a near significant difference when comparing these groups [OR:0.19(0.03-1.10), p=0.052] (Table III). Tables IV and V depict the type of severe-moderate complications and the association with the neuromuscular blockade strategy and the pharmacological reversal. None of the comparisons made in this regard showed statistically significant difference.

Discussion

This prospective observational sub-study examines the occurrence of postoperative complications, LOS and mortality related to neuromuscular blockade monitoring and its pharmacological reversal as part of ERAS programmes, in over 2.000 colorectal surgical patients.

The data suggest that quantitative neuromuscular blockade monitoring during colorectal resection and its reversal at the end of surgery is not associated with a decrease in the occurrence of postoperative moderate-severe complications, LOS or mortality. Nevertheless, both the use of neuromuscular blockade monitoring and the administration of drugs to reverse it have been proposed as strategies to avoid adverse postoperative outcomes[24,25] and reduce the incidence of residual neuromuscular

blockade[26,27]. However, until now it has not been totally demonstrated that this approach by itself leads to a clear clinical improvement what makes this is still a matter of current controversy and debate. So much so that some authors[28,29] suggest that non pharmacological reversal after neuromuscular blockade increases the likelihood of postoperative respiratory complications while some others according to information from POPULAR[12] and previous studies[10,30] assert there is no association between monitoring or pharmacological reversal with improved respiratory outcomes. It is our opinion that optimal neuromuscular blockade management during surgery should include both, quantitative neuromuscular monitoring and pharmacological reversal if needed to achieve a TOFr ≥ 0.9 before tracheal extubation. Regarding quantitative neuromuscular monitoring, it is interesting to remark that under 50% of the anaesthesiologists in Europe[31] acknowledge routine monitoring. Likewise, in our sub-study less than 40 % of patients were properly monitored, suggesting a wide area for improvement. Surprisingly, more than 66% of the anaesthesiologists in our sub-study reversed the neuromuscular blockade with antidotes meaning that a notorious percentage of the reversed patients were not monitored. So, one reason to explain the lack of statistically significant difference between the compared groups when analysing the main variables in this sub-study, may be the loss of patients for the analyses (and so the loss of power of the study). Indeed, all the patients receiving only one of the two strategies (neuromuscular blockade monitoring or reversal but not both of them) were not allocated in the M+R group but discarded. The same happened with patients in the noM+noR group who were only included if both criteria (no monitoring and no reversal) were present. Due to this reason, 950 patients of the all 2084 were not considered for this analysis. Regarding complications associated with neuromuscular blockade management, it still seems to be a controversial matter. So clinicians will have to wait for the current ongoing studies (that are specifically focused on this issue such as PORCzero)[32] to be finished, to obtain extra information. In the medical literature there are no clear data associating neuromuscular blockade management with LOS but there are studies that show prolonged postoperative hospital courses[33] and increased readmission[34] with high doses of NMBAs. It is reasonable to believe that patients with neuromuscular blockade monitoring will receive an appropriate

reversal, and consequently the residual neuromuscular blockade in these cases may decrease and so the complications and LOS related to it. This hypothesis though likely must be ascertained by further studies with an adequate design. **Our data show that patients receiving both quantitative neuromuscular monitoring and reversal initiate mobilization earlier. However, time to initiate oral intake is not modified in this group.** It is not clear for us the reason of these results so more studies with proper design and targeting these two goals should be conducted to clarify it. **Our sub-study also suggests the use of sugammadex is associated with less mortality after surgery than neostigmine, but this study has not been able to find significant difference in the development of severe-moderate complications when comparing these two drugs.** As far as we know, there are no studies demonstrating a clear decrease in mortality when using sugammadex for neuromuscular blockade reversion when compared with neostigmine. However, there are important recently published studies that link a better profile in terms of postoperative complications and safety to sugammadex[35]. At least four meta-analysis have shown better outcomes for sugammadex than for neostigmine as neuromuscular blockade reversal agent. Thus Abad-Gurumeta et al[36] found sugammadex reduced the number of patients with clinical signs of postoperative residual paralysis when compared with neostigmine. A Cochrane review[37] has recently demonstrated that sugammadex has a better safety profile than neostigmine. Following the same line of thought, Carron et al published the association of sugammadex with significantly lower global adverse events and weakness[38] as well as a more accelerated postoperative discharge[39] when compared it with neostigmine.

The two main strengths of the present sub-study is that first, it is multicentre and second, it includes a large sample of patients undergoing colorectal surgery, what means our findings show real life data and may be easily generalizable to patients undergoing colorectal resection elsewhere. This sub-study has some limitations. First, the POWER study was designed not for analysing neuromuscular blockade monitoring and its reversal, but to demonstrate difference in the development of postoperative complications between ERAS versus NO ERAS groups. This fact can be responsible for some uncontrolled bias in our sub-study. Nevertheless, it was indeed planned prospectively to

make a secondary analysis conducting this sub-study to explore that topic. Moreover, we have not focused on respiratory complications only but on a wider range of complications and probably many of them are not associated with neuromuscular weakness. This may have diluted the potential positive effect of neuromuscular monitoring on respiratory postoperative events. Second, TOF ratio after extubating patients in the operating room was not recorded. So, it is not possible to ascertain whether our results are due to residual neuromuscular blockade or to the un-adequate use of the reversal drugs instead. Additionally, it is possible that patients with no neuromuscular blockade monitoring but having blind pharmacological reversion might have better outcomes than those who did not receive any of the two recommended strategies, meaning our sub-study might be statistically significant if we would consider them in the analysis. Something similar happens with patients who were monitored and did not receive reversal drugs. It is very likely that they achieved a TOF ratio ≥ 0.9 meaning that pharmacological reversal was not indicated and so not administered. Including those patients in the final statistical analysis might have changed our results.

Conclusions

Our study suggests there is no association between optimal neuromuscular blockade management (quantitative monitoring and pharmacological reversal) and postoperative complications and LOS during colorectal surgery within an enhanced recovery program. Patients reversed with neostigmine might die more after surgery than those reversed with sugammadex. Further prospective and randomized controlled trials are needed to ascertain these results.

WHAT IS KNOWN

• NMB is associated with pulmonary and non-pulmonary complications after surgery worldwide.
• Anaesthesiologists do not routinely use neuromuscular quantitative monitoring and pharmacological reversion.

WHAT IS NEW

• Quantitative neuromuscular monitoring and pharmacological reversion seems not to be associated with less postoperative complications and LOS during colorectal surgery in enhanced recovery program.

• Pharmacological neuromuscular reversion with sugammadex seems to be associated with less mortality after surgery than neostigmine reversion.

References

1. ERAS Compliance Group. The Impact of Enhanced Recovery Protocol Compliance on Elective Colorectal Cancer Resection: Results From an International Registry. Ann Surg 2015;261:1153–9.

2. Ni X, Jia D, Chen Y, Wang L, Sco J. Is the Enhanced Recovery After Surgery (ERAS) Program Effective and safe in laparoscopic colorectal cancer surgery? A meta-analysis of randomized controlled trials. J Gastrosintest Surg 2019;23:1502-12.

3. Li S, Zhou K, Che G, Yang M, Su J, Shen C, et al. Enhanced recovery programs in lung cancer surgery: systematic review and meta-analysis of randomized controlled trials. Cancer Manag Res 2017;16:657-70.

4. Ripollés-Melchor J, Fuenmayor-Varela ML, Camargo SC, Fernández PJ, Barrio ACD, Martínez-Hurtado E, et al. [Enhanced recovery after surgery protocol versus conventional perioperative care in colorectal surgery. A single center cohort study]. Rev Bras Anestesiol 2018;68:358-68.

5. Calvo-Vecino JM, del Valle Hernández E, Ramírez Rodríguez, Carmelo Loinaz Segurola, Carlos Martín Trapero, Alfredo Rodríguez Antolín et al. Vía clínica de recuperación intensificada en cirugía abdominal (RICA) [Internet]. Ministerio de Sanidad, Servicios Sociales e Igualdad. Instituto Aragonés de Ciencias de la Salud. 2014 [cited 2018 May 26]. Available from: http://portal.guiasalud.es/contenidos/iframes/documentos/opbe/2015-07/ViaClinica-RICA.pdf

6. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, et al. Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS ®) Society Recommendations:2018. World J Surg 2019;43:659-95.

7. Madsen MV, Staehr-Rye AK, Gatke MR, Claudius C. Neuromuscular blockade for optimising surgical conditions during abdominal and gynaecological surgery: a systematic review. Acta Anaesthesiol Scand 2015;59: 1–16.

8. Blobner M, Frick CG, Stauble RB, Feussner H, Schaller SJ, Unterbuchner C, et al. Neuromuscular blockade improves surgical conditions (NISCO). Surg Endosc 2015;29: 627–36.

9. Madsen MV, Istre O, Staer-Rye AK, Springborb HH, Rosenberg J, Lund J et al. Postoperative shoulder pain after laparoscopic hysterectomy with deep neuromuscular blockade and low-pressure pneumoperitoneum. A randomised controlled trial. Eur J Anaesthesiol 2016;33:341-7.

10. Grosse-Sundrup M, Henneman JP, Sandberg WS, Bateman BT, Uribe JV, Nguyen NT et al. Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched

cohort study. BMJ (Clinical Research ed.). 2012 Oct;345:e6329. DOI: 10.1136/bmj.e6329.

11. McLean DJ, Díaz-Gil D, Farhan HN, Ladha KS, Kurth T and Eikermann M. Dose-dependent association between intermediate-acting neuromuscular-blocking agents and postoperative respiratory complications. Anesthesiology 2015;122:1201-13.

12. Kirmeier E, Eriksson LI, Lewald H, Fagerlund MJ, Hoeft A, Hollmann M, and the POPULAR Contributors. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. Lancet Resp Med 2019;7:129-40.

13. Berg H, Roed J, Viby-Mogensen J, Mortensen CR, Engbaek J, Skovgaard LT, et al. Residual neuromuscular block is a risk factor for postoperative pulmonary complications. A prospective, randomised, and blinded study of postoperative pulmonary complications after atracurium, vecuronium and pancuronium. Acta Anaesthesiol Scand 1997;41:1095–103.

14. Murphy GS. Neuromuscular monitoring in the perioperative period. Anesth & analg 2018;126:464-68.

15. Blobner M, Hunter JM, Meistelman C, Hoeft A, Hollman MW, Kirmeier E et al. Use of train-of-four of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data. Br J Anaesth 2020;124:63-72.

16. Fortier LF, McKeen D, Turner K, de Médicis E, Warriner B, PM. Jones, et al. The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade. Anesth Analg 2015;121:366-72.

17. Naguib M, Brull SJ, Kopman AF, Hunter JM, Fulesdi B, Arkes HR et al. Consensus statement on perioperative use of neuromuscular monitoring. Anesth & Analg 2018;127:71-80.

18. Ripollés-Melchor J, Ramírez-Rodríguez JM, Casans-Francés R, Aldecoa C, Abad-Motos A, Logroño-Egea M, et al. Association between use of enhanced recovery after surgery protocol and postoperative complications in colorectal surgery: The postoperative outcomes within enhanced recovery after surgery protocol (POWER) study. JAMA Surg 2019;154:725-36.

19. Gustafsson UO, Scott MJ, Schwenk W, Dermartines N, Roulin D, Francis N, et al. Guidelines for perioperative care in elective colonic surgery: Enhanced Recovery After Surgery (ERAS((R))) Society recommendations. World J Surg 2013;37:259–84.

20.Elm von E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 2007;335:806–8.

21. Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. Eur J Anaesthesiol 2015;32:88–105.

22. A language and evironment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.or/.

23. Isaac Subirana, Hector Sanz, Joan Vila (2014). Building Bivariate Tables: The Compare Groups Package for R. Journal of Statistical Software, 57(12), 1-16. URL http://www.jstatsoft.org/v57/i12/.

24. Rudolph MI, Chitilian HV, Hg PY, Timm FP, Agarwala AV, Doney AB, et al. Implementation of a new strategy to improve the perio-operative management of neuromuscular blockade and its effects on postoperative pulmonary complications. Anaesthesia 2018;73:1067-78.

25. Belcher AW, Leung S, Cohen B, Yang D, Mascha EJ, Turan A, et al. Incidence of complications in the post-anesthesia care unit and associated healthcare utilization in patients undergoing non-cardiac surgery requiring neuromuscular blockade 2005–2013: A single center study. Journal of Clinical Anesthesia 2017;43:33–8.

26. Baillard C, Clec'h C, Catineau J, Salhi F, Gehan G, Cupa M, et al. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth 2005;95:622–26.

27. Murphy GS, Szokol JW, Marymont JH, Greenberg SB, Avram MJ, Vender JS et al. Intraoperative acceleromyographic monitoring reduces the risk of residual neuromuscular blockade and adverse respiratory events in the postanesthesia care unit. Anesthesiology 2008;109:389–98.

28. Bulka CM, Terekhov MA, Martin BJ, Dmochowski RR, Hayes RM, Ehrenfeld JM. Nondepolarizing neuromuscular blocking agents, reversal, and risk of postoperative pneumonia. Anesthesiology 2016;125:647–55.

29. Bronsert MR, Henderson WG, Monk TG, Richman JS, Nguyen JD, sum-Ping JT et al. Intermediate-acting nondepolarizing neuromuscular blocking agents and risk of postoperative 30-day morbidity and mortality, and long-term survival. Anesth Analg 2017; 124:1476–83.

30. Sasaki N, Meyer MJ, Malviya SA, Stalislaus AB, MacDonald T, Doran ME, et al. Effects of neostigmine reversal of nondepolarizing neuromuscular blocking agents on postoperative respiratory outcomes: a prospective study. Anesthesiology 2014;121:959–68.

31. Errando CL, Garruti I, Mazzinari G, Díaz-Cambronero O, Bebawy JF, Grupo Español del Estudio de Bloqueo Neuromuscular. Residual neuromuscular blockade in

the postanesthesia care unit:observational cross-sectional study of a multicenter cohort. Minerva Anestesiol 2016;82:1267-77.

32.https://clinicaltrials.gov/ct2/show/NCT03128151?cond=NCT03128151&draw=2&rank=1

33. Bauer E, Mahida JB, Boomer LA, Lutmer JE, Minneci PC, Deans KJ et al. International Journal of Pediatric Otorhinolaryngology 2016;84:101–05.

34. Thevethasan T, shih SL, Safari KC, berger DL, Burns SM, Grabitz SD, et al. Association between intraoperative non-despolarising neuromusucular blocking agent dose and 30-day readmission after abdominal surgery. BJA 2017;119:595-605.

35. Kheterpal S, Vaughn MT, Dubovoy TZ, Shah NJ, Bash LD, Colquhoun DA, et al. Sugammadex versus Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER): A Multicenter Matched Cohort Analysis. Anesthesiology 2020;132:1371-81. doi: 10.1097/ALN.0000000000003256.PMID: 32282427

36. Abad-Gurumeta A, Ripollés-Melchor J, Casans-Francés R, Espinosa E, Martinez-Hurtado E, Fernandez-Perez C, et al. Evidence Anaesthesia Review Group. A systematic review of sugammadex versus neostigmine for reversal of neuromuscular blockade. Anaesthesia 2015;70:1441-452.

37. Hristovska AM, Duch P, Allingtrup M, Afshari A. The comparative efficacy and safety of sugammdex and neostigmine in reversing neuromuscular blockade in adults. A Cochrane systematic Review with meta-analysis and tiral sequential analysis. Anaesthesia 2018;73:631-641.

38. Carron M, Zarantonello F, Tellaroli P, Ori C. Efficacy and safety of sugammadex compared to neostigmine for reversal of neuromucular blockade: a meta-analysis of randomized controlled trial. J Clin Anesth 2016;35:1-12.

39. Carron M, Zarantonello F, Lazarotto N, Tellaroli P, Ori C. Role of sugammadex in accelarating postoperative discharge: A meta-analysis. J Clin Anesth 2017;39:38-44.

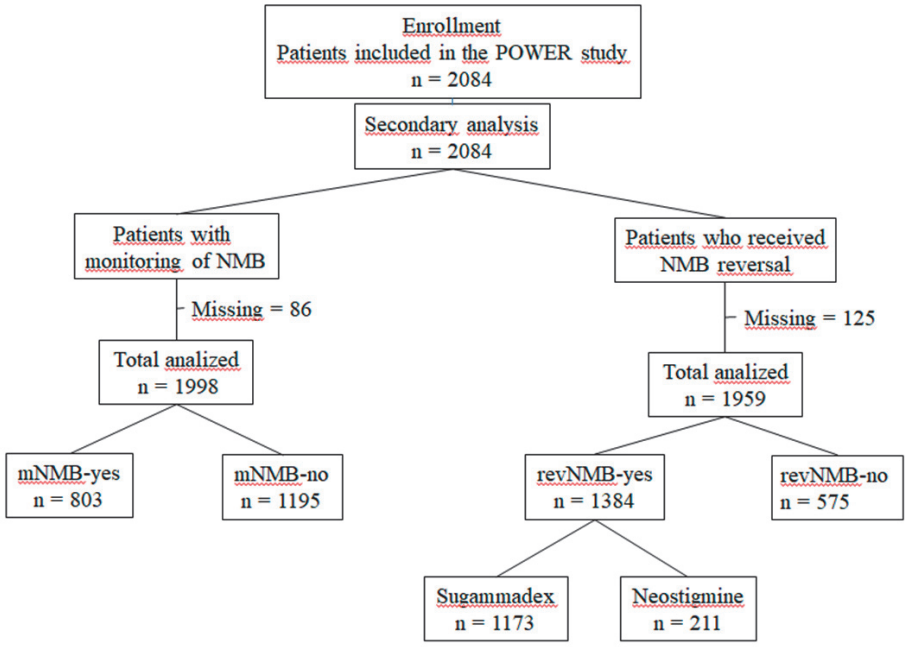

Figure 1.- *Flow chart patients. NMB; neuromuscular blockade, mNMB; monitoring of the neuromuscular blockade, revNMB; reversal of the neuromuscular blockade. M+R; monitoring + reversal neuromuscular blockade. noM+noR; no monitoring+no reversal NMB. Rneos; neostigmine reversal. Rsug; sugammadex reversal.*

Table 1. Basal data

	M+R (N = 676)	noM+noR (N = 458)	ALL (N = 2084)
Age	67.9 (12.8)	66.8 (12.0)	67.5 (12.5)
Male	398 (58.9%)	289 (63.1%)	1286 (61.7%)
BMI	27.0 (4.7)	27.3 (4.5)	27.1 (4.7)
ASA			
I	54 (8.0%)	19 (4.1%)	129 (6.2%)
II	360 (53.3%)	277 (60.5%)	1153 (55.3%)
III	245 (36.2%)	148 (32.3%)	747 (35.8%)
IV	17 (2.5%)	14 (3.1%)	55 (2.6%)
Smoking	126 (18.6%)	98 (21.4%)	399 (19.1%)
Diabetes Mellitus	141 (20.9%)	107 (23.4%)	454 (21.8%)
Congestive heart Failure	43 (6.4%)	29 (6.4%)	129 (6.2%)
Coronary	65 (9.6%)	38 (8.3%)	190 (9.1%)
Cirrhosis	8 (1.2%)	8 (1.7%)	29 (1.4%)
Stroke	30 (4.4%)	33 (7.2%)	118 (5.7%)
COPD	104 (15.4%)	67 (14.6%)	306 (14.7%)
Hypertension	348 (51.5%)	233 (50.9%)	1070 (51.3%)
Surgical procedure			
Abdominal amputation	39 (5.8%)	25 (5.5%)	112 (5.4%)
Anterior rectum resection	167 (24.7%)	123 (27.0%)	490 (23.6%)
Intestinal reconstruction	39 (5.8%)	36 (7.9%)	150 (7.2%)
Left hemicolectomy	49 (7.3%)	37 (8.1%)	168 (8.1%)
Right hemicolectomy	200 (29.6%)	112 (24.6%)	582 (28.0%)
Sigmoidectomy	143 (21.2%)	88 (19.3%)	448 (21.6%)
Subtotal Hemicolectomy	18 (2.7%)	17 (3.7%)	59 (2.8%)
TEM	1 (0.1%)	4 (0.9%)	10 (0.48%)
Total colectomy	11 (1.6%)	5 (1.1%)	33 (1.6%)
Transverse colectomy	8 (1.2%)	9 (2.0%)	26 (1.2%)
Laparoscopic approach	471 (69.7%)	288 (62.9%)	1371 (65.8%)

Data are presented as n (%) or mean (SD) Odds Ratio; 95%CI= 95% Confidence Interval, p value. BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; TEM:Transanal endoscopic microsurgery; M+R; monitoring + reversal of the neuromuscular blockade. noM+noR; no monitoring nor reversal of the neuromuscular blockade.

Table 2 - *Univariate and multivariate analysis. Association of moderate-severe postoperative complications, LOS, mortality and performing ERAS pathways with monitoring of the neuromuscular blockade and its reversal compared with no monitoring nor reversal of the neuromuscular blockade*

	M+R (N = 676)	noM+noR (N = 458)	OR Univariate	OR Multivariate
Moderate severe complications	174 (25.7)	124 (27.1)	1.07 (0.82-1.40, p=0.616)	1.08 (0.80-1.45, p=0.607)
LOS	8.1 (5.6)	8.7 (5.6)	1.02 (1.00-1.04, p=0.125)	1.01 (0.98-1.04, p=0.416)
Mortality	6 (0.9)	5 (1.1)	1.23 (0.35-4.12, p=0.731)	1.13 (0.32-3.85, p=0.840)
ERAS	420 (62.1)	326 (71.2)	1.51 (1.17-1.95, p=0.002)	1.38 (1.05-1.81, p=0.023)

Data are presented as n (%) or mean (SD). OR= Odds Ratio; 95%CI= 95%.Confidence Interval, p value. M+R; monitoring + reversal of the neuromuscular blockade. noM+noR; no monitoring nor reversal of the neuromuscular blockade. Complications (yes): If any of the moderate-severe complications defined by EPCO. LOS: length of hospital stay; ERAS: enhanced recovery after surgery program.

Table 3. *Univariate and multivariate analysis. Association of moderate-severe postoperative complications, LOS, mortality and performing ERAS pathways with monitoring of the neuromuscular blockade and its reversal comparing neostigmine and sugammadex as antidotes*

	M+Rneos (N=113)	M+Rsug (N=563)	OR Univariate	OR Multivariate
Moderate severe complications	24 (21.2)	150 (26.6)	1.35 (0.84-2.23, p=0.232)	1.30 (0.75-2.31, p=0.358)
LOS	9.5 (7.9)	11.0 (11.6)	1.01 (0.99-1.04, p=0.199)	1.01 (0.99-1.03, p=0.550)
Mortality	3 (2.7)	3 (0.5)	0.20 (0.04-1.07, p=0.048)	0.19 (0.03-1.10, p=0.052)
ERAS	82 (72.6)	338 (60.0)	0.57 (0.36-0.88, p=0.013)	0.61 (0.38-0.95, p=0.030)

Data are presented as n(%) or median (SD). OR= Odds Ratio; 95%CI= 95% Confidence Interval. M+Rsug; monitoring + reversal of the neuromuscular blockade with sugammadex. M+ Rneos; monitoring + reversal of the neuromuscular blockade with neostigmine. Complications (yes): If any of the moderate-severe complications defined by EPCO. LOS: length of hospital stay; ERAS: enhanced recovery after surgery program.

Table 4- *Association of moderate- severe complications described by EPCO(21) definitions with monitoring of the neuromuscular blockade and its reversal compared with no monitoring nor reversal of the neuromuscular blockade*

	M+R	noM+noR	OR Univariate
Moderate-severe complication	174 (25.7)	124 (27.1)	1.07 (0.82-1.40, p=0.616)
Complications	256 (37.9)	197 (43.0)	1.24 (0.97-1.58, p=0.083)
Readmission	38 (5.6)	24 (5.2)	1.08 (0.64-1.84, p=0.782)
Reintervention	68 (10.1)	48 (10.5)	0.96 (0.65-1.42, p=0.818)
Mortality Rate	6 (0.9)	5 (1.1)	1.23 (0.35-4.12, p=0.731)
Type of Moderate-severe Complications			
Acute Kidney Injury	26 (3.8)	19 (4.1)	1.08 (0.58-1.97, p=0.798)
Acute Respiratory Distress	7 (1.0)	3 (0.7)	0.63 (0.14-2.28, p=0.505)
Anastomotic Breakdown	44 (6.5)	26 (5.7)	0.86 (0.52-1.41, p=0.568)
Arrhythmia	11 (1.6)	6 (1.3)	0.80 (0.27-2.12, p=0.667)
Cardiopulmonary Edema	0 (0.0)	1 (0.2)	-
Deep vein thrombosis	1 (0.1)	3 (0.7)	4.45 (0.57-90.13, p=0.197)
Gastrointestinal bleeding	14 (2.1)	11 (2.4)	1.16 (0.51-2.58, p=0.710)
Surgical site infection (superficial)	96 (14.2)	68 (14.8)	1.05 (0.75-1.47, p=0.762)
Surgical site infection (Deep)	28 (4.1)	25 (5.5)	1.34 (0.76-2.32, p=0.304)
Surgical site infection (Organ Space)	33 (4.9)	24 (5.2)	1.08 (0.62-1.84, p=0.786)
Infection (Uncertain source)	11 (1.6)	8 (1.7)	1.07 (0.41-2.68, p=0.878)
Infection (bloodstream)	18 (2.7)	22 (4.8)	1.84 (0.98-3.52, p=0.059)
Myocardial infartion	0 (0.0)	0 (0.0)	-
Pneumonia	12 (1.8)	7 (1.5)	0.86 (0.32-2.15, p=0.751)
Paralytic ileus	96 (14.2)	68 (14.8)	1.05 (0.75-1.47, p=0.762)
Postoperative hemorrhage	3 (0.4)	5 (1.1)	2.48 (0.60-12.12, p=0.216)
Pulmonary embolism	1 (0.1)	0 (0.0)	-
Urinary tract infection	11 (1.6)	12 (2.6)	1.63 (0.71-3.78, p=0.249)

Data are presented as n (%). OR= Odds Ratio; 95%CI= 95%.Confidence Interval, p value. M+R; monitoring + reversal of the neuromuscular blockade. noM+noR; no monitoring nor reversal of the neuromuscular blockade. Complications (yes): If any of the moderate-severe complications defined by EPCO.

Table 5.- *Association of moderate-severe postoperative complications defined by EPCO(21) definitions, with monitoring of the neuromuscular blockade and its reversal comparing neostigmine and sugammadex as antidotes*

	M +Rneos (N=113)	M + Rsug (N=563)	OR Univariate
Moderate-severe complication	24 (21.2)	150 (26.6)	1.35 (0.84-2.23, p=0.232)
Complications	41 (36.3)	215 (38.2)	1.08 (0.72-1.66, p=0.703)
Readmission	6 (5.3)	32 (5.7)	0.93 (0.34-2.13, p=0.875)
Reintervention	9 (8.0)	59 (10.5)	0.74 (0.33-1.47, p=0.419)
Mortality Rate	3 (2.7)	3 (0.5)	0.20 (0.04-1.07, p=0.048)
	Type of Moderate-severe complications		
Acute Kidney Injury	4 (3.5)	22 (3.9)	1.11 (0.41-3.84, p=0.853)
Acute Respiratory Distress	1 (0.9)	6 (1.1)	1.21 (0.20-22.90, p=0.863)
Anastomotic Breakdown	5 (4.4)	39 (6.9)	1.61 (0.68-4.75, p=0.329)
Arrhythmia	1 (0.9)	10 (1.8)	2.03 (0.38-37.36, p=0.503)
Cardiopulmonary Edema	0 (0.0)	0 (0.0)	-
Deep vein thrombosis	0 (0.0)	1 (0.2)	-
Gastrointestinal bleeding	2 (1.8)	12 (2.1)	1.21 (0.32-7.84, p=0.806)
Surgical site infection (superficial)	12 (10.6)	84 (14.9)	1.48 (0.80-2.94, p=0.234)
Surgical site infection (Deep)	4 (3.5)	24 (4.3)	1.21 (0.46-4.19; p=0.725)
Surgical site infection (Organ Space)	4 (3.5)	29 (5.2)	1.48 (0.57-5.06, p=0.471)
Infection (Uncertain source)	1 (0.9)	10 (1.8)	2.03 (0.38-37.36, p=0.503)
Infection (bloodstream)	4 (3.5)	29 (5.2)	1.48 (0.57-5.06, p=0.471)
Myocardial infartion	0 (0.0)	0 (0.0)	-
Pneumonia	3 (2.7)	9 (1.6)	0.60 (0.17-2.72, p=0.443)
Paralytic ileus	12 (10.6)	84 (14.9)	1.48 (0.80-2.94, p=0.234)
Postoperative hemorrhage	1 (0.9)	2 (0.4)	0.40 (0.04-8.64, p=0.455)
Pulmonary embolism	0 (0.0)	1 (0.2)	-
Urinary tract infection	1 (0.9)	10 (1.8)	2.03 (0.38-37.36, p=0.503)

Data are presented as n (%). OR= Odds Ratio; 95%CI= 95%.Confidence Interval, p value. M+R; monitoring + reversal of the neuromuscular blockade. noM+noR; no monitoring nor reversal of the neuromuscular blockade. Complications (yes): If any of the moderate-severe complications defined by EPCO.

Estrategia analgésica en cirugía oncológica

Capítulo 8

Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature.

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Introduction

Cancer is a major contributor to morbidity and mortality globally despite advances in prevention, diagnosis, and treatment. Colorectal cancer (CRC) is a global burden, with an estimated annual incidence of more than 140,000 new cases and 50.000 deaths in 2018 in USA.(1) Colorectal cancer therapy is complex, and surgery remains the cornerstone for its treatment, combined with chemotherapy and radiotherapy.

There is a growing interest on the potential effect of perioperative anesthetic management on cancer growth and spread (2–8) since experimental studies demonstrate that anesthetic and analgesic drugs modulate cancer cell behaviors such as proliferation, invasion, and colony formation and induce immune suppression.(8–15) Preclinical studies suggest that opioids could promote direct tumor growth, angiogenesis, metastasis and indirect immunosuppression of cellular and humoral responses, mainly mediated by μ-opioid receptor activation. (16,17) Association between increased expression of μ-opioid receptor and shorter disease free survival (DFS) has been demonstrated in lung, prostate, gastric and esophagus cancers. (18–22) Different retrospective analysis suggested an association between perioperative opioids with a higher recurrence rate/ decreased overall survival of non- small-cell lung cancer and prostate patients.(23–25) Furthermore, a pooled analysis from prospective studies study suggested that methylnaltrexone, a peripherally acting μ-opioid receptor antagonist was associated with increased survival in patients with advanced cancer.(26)

The impact of opioid use as a risk factor for colorectal cancer formation or recurrence after surgery was investigated in different studies. We focused this systematic review of the literature on the long-term impact of perioperative opioids in colorectal cancer recurrence. Specifically, we worked on the hypothesis that opioids are associated to worse long-term oncological outcomes.

Methods

We combined the results of two searching strategies in PubMed/MEDLINE (1950 to 8 April 2018): (i) one with broad search criteria and (ii) and another with more restrictive parameters (see Table 1. Search strategy in PubMed). Two reviewers (ODC and GM) scanned independently all articles identified by these search criteria for relevance by reading title and abstract. In case of disagreement, consensus between the two reviewers was sought. Additionally, the reference lists of eligible studies including narrative reviews and meta-analyses were systematically evaluated to retrieve additional articles. We also searched clinicaltrials.gov website for relevant ongoing trials.

Our research interest was based on a PICO approach:

P: Opioid influence on cancer–related long term outcome in patient undergoing colorectal surgery

I: Opioid drugs administered in the perioperative period with at least partially (intraoperative and/or postoperative) available dose

C: Correlation between dose and/or type of opioid with long term oncologic outcome

O: Disease–free survival (DFS) and/or Overall survival (OS).

Studies that reported only on pre–clinical (e.g. Natural Killer or T lymphocyte activity) or short term outcomes were excluded.

Results

The flowchart following PRISMA guidelines shows the search and selection process of the literature (Figure 1). We finally included 13 papers in the review that fulfilled the predetermined inclusion criteria. Due to the heterogeneity of each study in the design and type of data collection a quantitative meta-analysis to sum the evidence was deemed unfeasible. The characteristics of studies included in this study is showed in Table 2.

Perioperative Opioids administration and long-term outcomes

A recent retrospective analysis on a large cohort (n = 1,679) that used an arbitrary cut-off value of 3 mcg/kg to divide patients in low vs. high opioid use found no association between intraoperative fentanyl administration and DFS or OS.(27)

Another retrospective analysis on a smaller group (n = 157) found that perioperative remifentanyl usage was not associated with cancer recurrence in stage IIIa/IIIb colorectal cancer patients using a Cox proportional hazard model taking into account as covariables: preoperative complications, location of tumor, tumor stage, perioperative remifentanil use, and blood transfusion. (28)

Regional anesthesia study and link with opioid administration

The largest study (n = 42,151) to date was based on a retrospective analysis of an administrative database (Medicare) and found that patients receiving intravenous opioid based analgesia had worse OS but no association was demonstrated with cancer recurrence.(29) Christopherson et al. (30) conducted a secondary analysis from a previously published RCT (31) and investigated the association between epidural analgesia and changes in OS. The authors found that in patient without pathologic evidence of metastasis, the hazard ratio of death was significantly higher in the first 1.46 year of follow–up in patient treated with conventional analgesia (HR: 4.56, 95% CI [1.40, 15.42], $P = 0.012$). The influence of opioids could not be determined because both groups received different opioid medication at different time–points via several routes of administration. Kim et al conducted a RCT in patients undergoing laparoscopic tumor resection to investigate the effect of opioid–based analgesia with pethidine or continuous wound infiltration with local anesthetics on immunological outcomes.(32) CRC recurrence and metastasis at 1 year of

follow–up were secondary outcomes of the study and were not different between both groups of treatment. It is worth noting that the sample size of this study was small and not powered to detect CRC recurrence.(32) Similar results were demonstrated in a female cohort of patients (6).

In a long term follow–up analysis on oncologic patients (the majority of whom were colorectal cancer interventions) from a cohort of subjects who randomized to epidural analgesia or intravenous analgesia (33), Myles et al. (34) found no differences in DFS nor OS between epidural and intravenous analgesia groups. The epidural group received a median of 0 mg equivalent of morphine (interquartile range, 0–31) during the first 72 hours while intravenous group received a median of 107 (44–202). These results are in line with those of another follow–up analysis of a previous single–center RCT.(35)

In a retrospective analysis on a cohort of 655 patients undergoing open colorectal oncologic surgery, Gupta et al. (36) found that patients who received epidural analgesia for rectal resections had a significantly lower mortality than those with opioid intravenous patient controlled analgesia (PCA) while no significant differences were seen in patients with colon cancer. On the contrary a two retrospective study from Gottschalk et al. (37) and Day et al. (38) found no difference in mortality or recurrence between neuraxial anesthesia or analgesia and intravenous analgesia. In these studies, the authors did not report any data on opioid administration.

Ongoing research

By examining the clinicaltrials.gov registry, we found three registered studies (39–41) that plan to assess the impact of opioid administration and cancer recurrence (Table 3. ongoing studies).

Opioids administration and long-term outcomes in the non-perioperative setting

In a population based matched case–control study Naghibzadeh–Tahami et al. found that opioid use was a dose–dependent risk factor for colorectal cancer development.(42) Another study in patients with advanced stage colorectal cancer on last–line chemotherapy found that patients who received opioid formulations have an hazard ratio for death was 3.557 (95% CI, 1.032–12.257; P = 0.044), compared with patients who did not receive them.(43)

Discussion.

Immune response is a critical barrier against cancer progression and metastasis. It is increasingly recognized that impairment of cell-mediated immunity, and mainly natural killer cell function, is a potential risk of cancer dissemination
(44) Furthermore perioperative period is increasingly seen as a critical time window where actions can be undertaken to prevent cancer progression thus improving long term outcomes. To this regard the anesthesiologists' choice of drugs and technique and its potential depressive effects on the host immune system has raised considerable interest in recent years. (2,7,8,10,12,13,45–48)

Opioid drugs are the quintessential example of this line of thought. While they are one of the staple of perioperative treatment numerous *in vitro* studies have showed their potential effect on immune system reaction: (i) they suppress humoral and cellular immunity (ii) they activate cellular migration and angiogenesis through several biochemical pathways. (19,49–53) Although these mechanisms are somewhat questioned lately due to concerns on the animal models used in these studies (54–56) and competing cancer suppressive effects of certain opioids, (57–60) it is generally assumed that, at least in theory, the effects of opioids on the immune system could lead to worse long-term outcomes in patients who receives these medications in the perioperative period.

Despite the physiological rationale it is remarkable how few clinical studies have been performed to investigate this topic. Our review indicates that there is no definitive evidence that the use of opioids in patients undergoing colorectal cancer surgery have a clear deleterious effect as far as long-term outcomes are concerned.

Only the Tai YH et al study, is designed to analyzed the association between perioperative opioid consumption and DFS/OS, and found no association. But this study presents some limitations due to its retrospective design, focus exclusively on intraoperative opioids and highlighting the arbitrary cut-off point between both study groups (high and low doses of intraoperative fentanyl) established in 3 μg/kg. So that the mean low dose group was 2.45 μg/kg and the mean high dose group 3.69 μg/kg. It´s also important highlights a significant

difference between the percentage of epidurals in both groups that could influence the results.

A RCT of Kim SY et al evaluated postoperative pain management on immune function after laparoscopic resection of colorectal cancer. Groups are opioid–based analgesia (fentanyl iv PCA and pethidine as rescue analgesic) or non-opioid based analgesia (continuous 0.5% ropivacaine wound infiltration + tramadol iv PCA and NSAIs as rescue analgesics). Secondary outcomes included CRC recurrence and metastasis at 1 year of follow–up and found also no association between these analgesics and worse long-term outcomes. Main weaknesses was that sample size (59 patients) was not powered to secondary outcomes, tramadol PCA (an opiate derivate) was also used in the non-opioid group and remifentanil perfusion was the main analgesic intraoperative technique in both groups. The studies of Naghibzadeh-Tahami A et al e Imura MK et al are matched case–control and retrospective studies and found positive association of opioids administration with CRC development and worse overall survival, but are not in the perioperative setting.

In line with our findings, studies conducted on different types of cancer do not offer conclusive evidence. A population-based study in breast cancer patients found no association between opioids and cancer recurrence adjusted (HR 1.0, 95% CI 0.92–1.1), (61) while another retrospective analysis conducted in lung cancer patients only demonstrated a decrease in OS in stage I cancer (23).

Our study has several limitations. The studies included in this review have several methodological differences as well as incomplete data reporting that precluded the possibility of a pooled analysis. In some papers only intraoperative opioid was recorded and analyzed (27) and total dose was not reported and the variable was treated in a dichotomic fashion (yes/no) (28). Other reports assessed opioid effects only indirectly as a corrollary of a locoregional techinque (29,30,34–38) Moreover the vast majority of studies were retrospective analysis or follow-up studies on previously published cohorts with heterogenous and often partial inclusion of potenital intraoperative and postoperative confounding factors. For instance, most studies except the work by Gupta et al., have grouped colon and rectal tumors under the same analysis.

It is well known that the prognosis of patients with tumors located in their colon is better than those with rectal malignancies.

The only RCT included (32) has a relatively small sample size probably underpowered to assess long term outcome effects of opioid drugs. The largest study (29) did find a reduction in OS but failed to show any effect on recurrence.

Expert in the field have issued a Consensus Statement (62) that highlights on one hand how current data are insufficient to promote a change of clinical practice and on the other the need for prospective randomized trials to gather definitive proof on the role of opioid on long term outcomes in cancer patients undergoing surgery. Several RCTs are underway and hopefully can shed some light on the matter in the near future.

Our study also demonstrates that many patients undergoing colorectal cancer surgery receive opioids during and after surgery since in all studies opioids were given either in small or large quantities. There has been an increased concerning on whether opioids acting on mu-signaling pathways can promote cancer progression after oncological surgery.. Mu-opioid receptors are expressed in several cancers (i.e. lung and prostate cancer) in which a high level of expression is an independent risk factor of poor survival. (18,22) Nylund et al. (63) have demonstrated that the level of expression of the mu-opioid receptor in human colorectal cancer is high. Unfortunately, the authors did not determine the impact of the expression of the receptor in patients' survival This suggests that opioids could promote metastasis in colorectal cancer however, in vivo experiments have shown that intermittent morphine administration decreases colon metastasis in a rat model but not in mice. (64)

Conclusions

The perioperative period constitutes a promising window where preserving optimal homeostasis anesthesiologists' could theoretically prevent or at least minimize tumor cells spreading and ultimately cancer recurrence. As part of this enhanced perioperative management an opioid-free or opioid-sparing management has been proposed recently.

To this day however there is no conclusive evidence to avoid the use of opioids with the goal of reducing the risk of tumor recurrence in this patients. Anesthesiologists should provide perioperative management based on individual analysis and best available evidence and opioids should continue to be used as a key component of balanced anesthesia.

More studies are needed to demonstrate whether the mu opioid receptor expression in colorectal cancer can be used as an independent risk factor of survival.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin [Internet]. 2018;68(1):7–30. Available from: http://doi.wiley.com/10.3322/caac.214422.

2 Desborough JP. The stress response to trauma and surgery. Br J Anaesth. 2000;85(1):109–17.

3. Cata JP. Can the perioperative anesthesia care of patients with cancer affect their long-term oncological outcomes? Anesth Analg. 2017;124(5):1383–4.

4. Ciechanowicz SJ, Ma D. Anaesthesia for oncological surgery - Can it really influence cancer recurrence? Anaesthesia. 2016;71(2):127–31.

5. Cata JP, Bugada D, De Andrés J. Opioid-less perioperative care. Minerva Anestesiol. 2017;83(3):315–20.

6. Vogelaar FJ, Van Bogerd A, Lemmens VE, Van Linden JC, Cornelisse HGJM, Van FRC, et al. Epidural analgesia e Associated with survival in colon cancer? Eur J Surg Oncol. 2012;38(9):755.

7. Hiller J, Brodner G, Gottschalk A. Understanding clinical strategies that may impact tumour growth and metastatic spread at the time of cancer surgery. Best Pract Res Clin Anaesthesiol [Internet]. 2013;27(4):427–39. Available from: http://dx.doi.org/10.1016/j.bpa.2013.10.003

8. Gottschalk A, Sharma S, Ford J, Durieux ME, Tiouririne M. The role of the perioperative period in recurrence after cancer surgery. Anesth Analg. 2010;110(6):1636–43.

9. Fodale V, D'Arrigo MG, Triolo S, Mondello S, La Torre D. Review Article: Anesthetic techniques and cancer recurrence after surgery. Sci World J. 2014;2014:1–11.

10. Horowitz M, Neeman E, Sharon E, Ben-Eliyahu S. Exploiting the critical perioperative period to improve long-term cancer outcomes. Nat Rev Clin Oncol. 2015;12(4):213–26.

11. Tohme S, Simmons RL, Tsung A. Surgery for cancer: A trigger for metastases. Cancer Res. 2017;77(7):1548–52.

12. Sekandarzad MW, Van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative anesthesia care and tumor progression. Anesth Analg. 2017;124(5):1697–708.

13. Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth [Internet]. 2010;105(2):106–15. Available from: http://dx.doi.org/10.1093/bja/aeq164

14. Jiang L, Nick AM, Sood AK. Fundamental Principles of Cancer Biology: Does It

Have Relevance to the Perioperative Period? Curr Anesthesiol Rep. 2015;5(3):250–6.

15. Yang W, Cai J, Zabkiewicz C, Zhang H, Ruge F, Jiang WG. The Effects of Anesthetics on Recurrence and Metastasis of Cancer, and Clinical Implications. World J Oncol [Internet]. 2017;8(3):63–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29147437%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC5649999

16. Lennon F, Mose J, Singleton P. AND Is There a Direct Effect ? Anesthesiology. 2012;116(4):940'5.

17. Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: A new target for cancer therapy? Cancer. 2015;121(16):2681–8.

18. Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-opioid receptor expression in metastatic lung cancer. Br J Anaesth. 2014;113(SUPPL. 1):103–8.

19. Mathew B, Lennon FE, Siegler J, Mirzapoiazova T, Mambetsariev N, Sammani S, et al. The novel role of the mu opioid receptor in lung cancer progression: A laboratory investigation. Anesth Analg. 2011;112(3):558–67.

20. Yao Y, Yao R, Zhuang L, Qi W, Lv J, Zhou F, et al. MOR1 Expression in Gastric Cancer: A Biomarker Associated With Poor Outcome. Clin Transl Sci [Internet]. 2015;8(2):137–42. Available from: http://doi.wiley.com/10.1111/cts.12246

21. Zhang Y-F, Xu Q-X, Liao L-D, Xu X-E, Wu J-Y, Wu Z-Y, et al. Association of mu-opioid receptor expression with lymph node metastasis in esophageal squamous cell carcinoma. Dis Esophagus [Internet]. 2015;28(2):196–203. Available from: https://academic.oup.com/dote/article-lookup/doi/10.1111/dote.12165

22. Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer. 2013;119(23):4103–10.

23. Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. 2014;3(4):900–8.

24. Maher DP, Wong W, White PF, McKenna R, Rosner H, Shamloo B, et al. Association of increased postoperative opioid administration with non-small-cell lung cancer recurrence: A retrospective analysis. Br J Anaesth. 2014;113(SUPPL. 1):88–94.

25. Forget P, Tombal B, Scholtès J-L, Nzimbala J, Meulders C, Legrand C, et al. Do intraoperative analgesics influence oncological outcomes after radical prostatectomy for prostate cancer? Eur J Anaesthesiol. 2011;28(12):830–5.

26. Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced

cancer. Ann Oncol. 2016 Nov;27(11):2032–8.

27. Tai YH, Wu HL, Chang WK, Tsou MY, Chen HH, Chang KY. Intraoperative Fentanyl Consumption Does Not Impact Cancer Recurrence or Overall Survival after Curative Colorectal Cancer Resection. Sci Rep [Internet]. 2017;7(1):1–8. Available from: http://dx.doi.org/10.1038/s41598-017-11460-1

28. Kurosaki H, Fujii K, Nishikawa K. Does remifentanil affect the incidence of colon cancer recurrence? Anesth Analg [Internet]. 2012;114:S459. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00000539-201205001-00001

29. Cummings KC, Xu F, Cummings LC, Cooper GS. A Comparison of Epidural Analgesia and Traditional Pain Management Effects on Survival and Cancer Recurrence after Colectomy. Anesthesiology [Internet]. 2012;116(4):797–806. Available from: http://anesthesiology.pubs.asahq.org/Article.aspx?doi=10.1097/ALN.0b013e31824674f6

30. Christopherson R, James KE, Tableman M, Marshall P, Johnson FE. Long-term survival after colon cancer surgery: A variation associated with choice of anesthesia. Anesth Analg. 2008;107(1):325–32.

31. Park WY, Thompson JS, Lee KK. Effect of epidural anesthesia and analgesia on perioperative outcome: a randomized, controlled Veterans Affairs cooperative study. Ann Surg [Internet]. 2001;234(4):560-9-71. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1422079&tool=pmcentrez&rendertype=abstract

32. Kim SY, Kim NK, Baik SH, Min BS, Hur H, Lee J, et al. Effects of Postoperative Pain Management on Immune Function After Laparoscopic Resection of Colorectal Cancer. Medicine (Baltimore) [Internet]. 2016;95(19):e3602. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201605100-00043

33. Rigg JR, Jamrozik K, Myles PS, Silbert BS, Peyton PJ, Parsons RW, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. Lancet [Internet]. 2002;359(9314):1276–82. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11965272

34. Myles PS, Peyton P, Silbert B, Hunt J, Rigg JRA, Sessler DI. Perioperative epidural analgesia for major abdominal surgery for cancer and recurrence-free survival: Randomised trial. Bmj. 2011;342(7800):746.

35. Binczak M, Tournay E, Billard V, Rey A, Jayr C. Major abdominal surgery for

cancer: Does epidural analgesia have a long-term effect on recurrence-free and overall survival? Ann Fr Anesth Reanim [Internet]. 2013;32(5):e81–8. Available from: http://dx.doi.org/10.1016/j.annfar.2013.02.027

36. Gupta A, Björnsson A, Fredriksson M, Hallböök O, Eintrei C. Reduction in mortality after epidural anaesthesia and analgesia in patients undergoing rectal but not colonic cancer surgery: A retrospective analysis of data from 655 patients in Central Sweden. Br J Anaesth. 2011;107(2):164–70.

37. Gottschalk A, Ford JG, Regelin CC, You J, Mascha EJ, Sessler DI, et al. Association between Epidural Analgesia and Cancer Recurrence after Colorectal Cancer Surgery. Anesthesiology. 2010;113(1):27–34.

38. Day A, Smith R, Jourdan I, Fawcett W, Scott M, Rockall T. Retrospective analysis of the effect of postoperative analgesia on survival in patients after laparoscopic resection of colorectal cancer. Br J Anaesth [Internet]. 2012;109(2):185–90. Available from: http://dx.doi.org/10.1093/bja/aes106

39. US National Library of Medicine: Epidural Versus Patient-controlled Analgesia for Reduction in Long-term Mortality Following Colorectal Cancer Surgery (EPICOL). Available from: https://clinicaltrials.gov/ct2/show/NCT01318161

40. US National Library of Medicine: Regional Anesthesia in Colon Rectal Surgery. Available from: https://clinicaltrials.gov/ct2/show/NCT00684229

41. US National Library of Medicine: Effects of Different Types of Perioperative Analgesia on Minimal Residual Disease Development After Colon Cancer Surgery. Available from: https://clinicaltrials.gov/ct2/show/NCT02314871

42. Naghibzadeh-Tahami A, Yazdi Feyzabadi V, Khanjani N, Ashrafi-Asgarabad A, Alizaeh H, Borhaninejad VR, et al. Can Opium Use Contribute to a Higher Risk of Colorectal Cancers? A Matched Case-control Study in Iran. Iran J Public Heal [Internet]. 2016;45(10):1322–31. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27957439

43. Imura MK, Wai MI, Sami EU, Eramachi HT, Oshimura TY. Prognostic factors in patients with advanced and recurrent colorectal cancer receiving last-line chemotherapy. Pharmazie. 2018;73:115–9.

44. Sessler D. Long-term Consequences of Anesthetic Management. Anesthesiology. 2010;111(1):1–4.

45. Niwa H, Rowbotham DJ, Lambert DG, Buggy DJ. Can anesthetic techniques or drugs affect cancer recurrence in patients undergoing cancer surgery? J Anesth. 2013;27(5):731–41.

46. Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anesth.

2016;63(2):184–92.

47. Ash SA, Buggy DJ. Does regional anaesthesia and analgesia or opioid analgesia influence recurrence after primary cancer surgery? An update of available evidence. Best Pract Res Clin Anaesthesiol [Internet]. 2013;27(4):441–56. Available from: http://dx.doi.org/10.1016/j.bpa.2013.10.005

48. Watt DG, McSorley ST, Horgan PG, McMillan DC. Enhanced Recovery After Surgery: Which Components, If Any, Impact on The Systemic Inflammatory Response Following Colorectal Surgery? Medicine (Baltimore) [Internet]. 2015;94(36):e1286. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00005792-201509020-00004

49. Singleton PA, Lingen MW, Fekete MJ, Garcia JGN, Moss J. Methylnaltrexone inhibits opiate and VEGF-induced angiogenesis: Role of receptor transactivation. Microvasc Res. 2006;72(1–2):3–11.

50. Fujioka N, Nguyen J, Chen C, Li Y. Morphine-Induced Epidermal Growth Factor Pathway Activation in Non-Small Cell Lung Cancer. 2013;113(6):1353–64.

51. Ecimovic P, Murray D, Doran P, McDonald J, Lambert DG, Buggy DJ. Direct effect of morphine on breast cancer cell function in vitro: Role of the NET1 gene. Br J Anaesth [Internet]. 2011;107(6):916–23. Available from: http://dx.doi.org/10.1093/bja/aer259

52. Farooqui M, Li Y, Rogers T, Poonawala T, Griffin RJ, Song CW, et al. COX-2 inhibitor celecoxib prevents chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality, without compromising analgesia. Br J Cancer. 2007;97(11):1523–31.

53. Liao SJ, Zhou YH, Yuan Y, Li D, Wu FH, Wang Q, et al. Triggering of Toll-like receptor 4 on metastatic breast cancer cells promotes αvβ3-mediated adhesion and invasive migration. Breast Cancer Res Treat. 2012;133(3):853–63.

54. Doornebal CW, Vrijland K, Hau CS, Coffelt SB, Ciampricotti M, Jonkers J, et al. Morphine does not facilitate breast cancer progression in two preclinical mouse models for human invasive lobular and HER2+ breast cancer. Pain. 2015;156(8):1424–32.

55. Doornebal CW, Klarenbeek S, Braumuller TM, Klijn CN, Ciampricotti M, Hau CS, et al. A preclinical mouse model of invasive lobular breast cancer metastasis. Cancer Res. 2013;73(1):353–63.

56. Hooijmans CR, Geessink FJ, Ritskes-Hoitinga M, Scheffer GJ. A systematic reviewand Meta-Analysis of the ability of analgesic drugs to reduce metastasis in experimental cancer models. Pain. 2015;156(10):1835–44.

57. Afsharimani B, Baran J, Watanabe S, Lindner D, Cabot PJ, Parat MO. Morphine

and breast tumor metastasis: The role of matrix-degrading enzymes. Clin Exp Metastasis. 2014;31(2):149–58.

58. Khabbazi S, Nassar ZD, Goumon Y, Parat MO. Morphine decreases the pro-angiogenic interaction between breast cancer cells and macrophages in vitro. Sci Rep [Internet]. 2016;6(April):1–10. Available from: http://dx.doi.org/10.1038/srep31572

59. Koodie L, Ramakrishnan S, Roy S. Morphine suppresses tumor angiogenesis through a HIF-1α/p38MAPK pathway. Am J Pathol. 2010;177(2):984–97.

60. Santamaria LB, Schifilliti D, La Torre D, Fodale V. Drugs of anaesthesia and cancer. Surg Oncol [Internet]. 2010;19(2):63–81. Available from: http://dx.doi.org/10.1016/j.suronc.2009.03.007

61. Cronin-Fenton D, Heide-Jorgenesen U, Ahern T, Lash T, Christianesen O, Ejlertsen B, et al. Opioids and Breast Cancer Recurrence: A Danish population-based cohort study. Cancer. 2016;121(19):3507–14.

62. Buggy DJ, Borgeat A, Cata J, Doherty DG, Doornebal CW, Forget P, et al. Consensus statement from the BJA Workshop on Cancer and Anaesthesia. Br J Anaesth. 2015;114(1):2–3.

63. Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional expression of μ-opioid receptors in the human colon cancer cell line, HT-29, and their localization in human colon. Dig Dis Sci. 2008;53(2):461–6.

*64. Tegeder I, Geisslinger G. Opioids as modulators of cell death and survival--unraveling mechanisms and revealing new indications. Pharmacol Rev. 2004;56(3):351–*69.

Figure 1. PRISMA Flowchart.

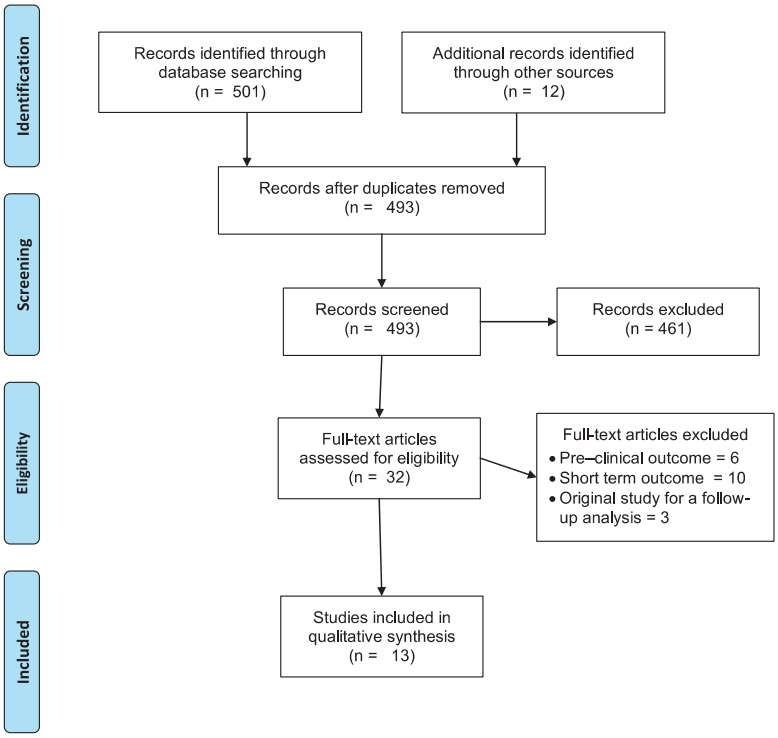

Table 1. Search strategy in PubMed	
#1	**opioid AND ("colorectal" OR "rectal" OR "colon") AND cancer**
#2	**("analgesics, opioid"[Pharmacological Action] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields]) AND ("perioperative"[All Fields] OR "intraoperative"[All Fields] OR "postoperative period"[MeSH Terms] OR ("postoperative"[All Fields] AND "period"[All Fields]) OR "postoperative period"[All Fields] OR "postoperative"[All Fields]) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND ("recurrence"[MeSH Terms] OR "recurrence"[All Fields])**

Table 2. Studies characteristics

First Author	Year of Publication	Study Design	Sample Size	Sample Age	Cancer type	Stage	Follow up (Years)	Opioid effect on OS	Opipid effect on DFS
Christopherson	2008	Follow-up study on a subgroup from an RCT	177	Mean, 68	Colon	0-IV	10	Not assessed specifically	Not assessed specifically
Gottschalk	2010	Retrospective	669	Mean 65	Colon and Rectal	0-IV	Median 1.8	Not assessed specifically	Not assessed specifically
Myles	2011	Follow-up on a subgroup from an RCT	446 (Colon 236)	Mean 70	Colon	Dukes A-C	12	Not assessed specifically	Not assessed specifically
Gupta	2011	Retrospective	655	Mean 71	Colon and Rectal	I-III	Range 1-5	Signficant higher risk of death in rectal cancer	Not significant
Kurosaki	2012	Retrospective	157	N/A	Colon	IIIa-IIIb	Min 2 Max 7	Not significant	Not significant
Cummings	2012	Retrospective	42151	Mean 78	Colon and Rectal	I-III	At least 4	Significantly shorter OS	Not significant
Day	2012	Follow-up study on previous RCT	424	Mean 70	Colon and Rectal	0-IV	Median 1-3	Not assessed specifically	Not assessed specifically
Vogelaar	2012	Follow-up study on a historical cohort	306	Mean 69	Colon	I-III	10	Significantly shorter OS	Not assessed specifically
Binczak	2013	Follow-up study on a previous RCT	132 (Colorectal 55)	Mean 58	Colon and Rectal	0-IV	Median 17	Not assessed specifically	Not assessed specifically
Naghibzadeh-Tahami	2016	Retrospective	525	Only Categorical reported	Colon and Rectal	N/A	N/A	Significant risk factor	N/A
Kim	2016	Randomized controlled	60	Mean 66	Colon and Rectal	I-III	1	Not significant	Not sgnificant
Tai	2017	Retrospective	1679	Mean 68	Colon and Rectal	I-III	Median 2.58	Not significant	Not significant
Imura	2018	Retrospective	47	Only categorical reported	Colon and Rectal	IV	N/A	Significantly shorter	N/A

Table 3. Ongoing randomized controlled trials investigating opioid and cancer long term outcomes relationship in colorectal cancer patients

NCT number	Registration Date	Investigation arm	Current status	Estimated completion date	Calculated sample size
01318161	2011	Epidural ropivacaine + opioid *vs*. Morphine	Recruiting	December 2018	300
00684229	2008	Epidural bupivacaine + fentanyl *vs.* opioid analgesia	Withdrawn		
02314871	2014	Epidural bupivacaine + sufentanyl *vs*. piritramide *vs.* morphine	Recruiting	September 2008	60

Capítulo 9

Mu Opioid Receptor 1 (MOR-1) Expression in Colorectal Cancer and Oncological Long-Term Outcomes: A Five-Year Retrospective Longitudinal Cohort Study.

***Díaz-Cambronero O**, Mazzinari G*, Giner F, Belltall A, Ruiz-Boluda L, Marqués-Marí A, Sánchez-Guillén L, Eroles P, Cata JP, Argente-Navarro MP.*

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Q1 IF 6.37

Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers worldwide [1]. After primary treatment of non-metastatic CRCs, 20%-40% of the patients develop recurrences, which are associated with a poor long-term prognosis [2]. Surgical resection is the cornerstone treatment in CRC, however it is also associated with inflammation, activation of sympathetic nervous system, hypercoagulability, ischemia/reperfusion injury and suppression of the immune system [3–5]. This stress response decreases the host capability to deal with minimal residual disease, thus increasing the potential risk of local recurrences or metastasis [6–9].

Type 1 mu-opioid receptor (MOR-1) agonist drugs such as fentanyl, hydromorphone and morphine are still the mainstay analgesic treatment in oncologic patients undergoing oncologic surgery [10]. Preclinical data suggest that MOR-1 is over-expressed in cancer cells and its activation is linked to cancer progression [11,12]. In addition, analgesics such as opioids may promote cancer recurrence by acting on MOR-1 [13–17].

The current evidence on the impact of MOR-1 over-expression on disease free survival (DFS) or overall survival (OS) is heterogeneous. MOR-1 over-expression is associated to poor DFS in advanced prostate cancer [18], gastric cancer [19] and hepatocellular carcinoma [5] while no association has been found in esophageal squamous cell carcinoma [20]. In CRC, MOR-1 expression has been demonstrated *in vitro* [21] but the association between tumor and non-tumor tissue differences in MOR-1 expression and long-term outcomes in humans has never been assessed. Furthermore, whether opioid use is associated with worse long term outcomes in CRC patients receiving opioids is unknown [22].

The aim of this study was to investigate the association between MOR–1 expression and oncological long-term outcomes in patients with colorectal cancer. We hypothesized that MOR-1 expression is increased in colorectal cancer (versus non-tumor adjacent tissue) and is associated with shorter disease free survival.

Results

Two-hundred and twenty-eight patients were screened for eligibility, 54 patients were excluded due to stage I or postoperative stage IV classification, urgent surgery and poor sample quality, 174 patients were finally included in the study. (Figure S1 in the Supplementary Digital Content). Patients' characteristics are shown in Table 1. Bland–Altman plot of two samples reading is reported in Figure S2, in Supplementary Digital Content. Bias was 0.66 (95%CI, 0.53–0.78) and Limits of agreement were -1.04 (95% CI, -1.26– -0.82) and 2.35 (95%CI, 2.13–2.57) for lower and upper, respectively.

Expression of MOR-1

MOR-1 expression was higher in tumor tissue compared to non–tumor tissue from the same patient (Figure 1). Median MOR-1 expression was 3.5 [95%CI, 2.5–4.5] for tumor tissue and 2 [95%CI, 1.5 – 2.5] for control tissue (difference 1.50, 95%CI 1.49–1.99, *P*<0.001). The correlation between MOR-1 expression and oncological features is showed in Table S1 Supplementary Digital Content. MOR-1 expression was associated with a higher number of metastatic lymph nodes and with stage III. No other significant correlations were observed.

Association between MOR expression and long-term outcomes

The Kaplan Meier analyses are reported in Figure 2. No significant differences were found for DFS or OS (log rank test P=0.81 and P=0.62 respectively).

Thirty patients (22%) experienced a recurrence during the follow–up period and 29 (21%) patients died during follow–up. Univariable analysis showed a HR of 0.85 (95%CI 0.68–1.06, P=0.152) for DFS and a HR of 0.88 (95% CI 0.70–1.11, P=0.270) for OS.

Similarly complete cases multivariable Cox regression (Table 2) showed no significant association between MOR-1 expression, DFS (HR 0.791, 95%CI 0.603–1.039, P=0.092) and OS (HR 1.023, 95%CI 0.784–1.335, P=0.869, Figure 2). Analysis after missing values imputation yielded no significant association between MOR-1 expression and DFS and OS (Table 2). Among the covariables included in the model after the selection process by penalized regression only carcinoembryonic antigen (CEA) value at diagnosis was significantly associated with shorter DFS (HR 1.811, 95%CI 1.245–2.635, P=0.002) and number of metastatic lymph nodes with OS (HR 1.482, 95%CI 1.110–1.978, P=0.008).

Association between MOR expression and postoperative complications

MOR expression was not associated with occurrence of complications in the first 28 postoperative days both in univariable (OR 0.838, 95%CI 0.630–1.105, *P*=0.214) and multivariable logistic regression (Table S2 in Supplementary Digital Content).

Discussion

The main findings of this study can be summarized as follows: in patients with colorectal cancer (stage II-III), (1) expression of MOR-1 receptor was higher in tumor tissue than in normal tissue and (2) this was not associated with shorter DFS or OS.

Increased MOR-1 expression in cancer tissue have been consistently reported in the literature [5,18–20]. Moreover, previous *in vitro* results showed a higher expression of MOR-1 in colorectal cancer tissue than in normal mucosa tissue [21]. The results of our study are in line with these data. On the other hand, the association of MOR-1 over-expression with clinical outcomes is not clearly established with some trials reporting benefits [5,18,19] while other do not [20]. It is difficult to compare our results with preceding studies due to tissue specific considerations and methodological issues as previous data come from other organs' cancers [5,18–20]. Moreover, our study included patients with non-advanced cancer stages, while previous studies frequently including advanced or metastatic cancer disease and MOR-1 over-expression could be a reflection of this advanced stage without any causal relationship. In addition, other factors could influence MOR-1 expression in tumor. For instance, MOR-1 increased expression have been recently linked to intraoperative opioid use [17] and this could explain differences in results. This hypothesis, however, could not be tested in our study since it requires a baseline preoperative assessment of MOR-1.

The method of MOR-1 expression assessment is another source of heterogeneity that hinder comparisons with previous data. Some trials used IHC [18,20] while other relied on real-time quantitative polymerase chain reaction (RT-qPCR) [5,19]. These techniques target different cellular components and although clinical studies supported some correlation [23,24], results are not completely interchangeable. Also, different IHC scoring have been used and the

technique is dependent on the pathologist interpretation. While other studies frequently used a dichotomic score and offer scant details on how they specified such dichotomy, we chose to employ a more gradual scale and carried out repeated blinded assessment of IHC staining.

MOR-1 is encoded by the *OPRM1* gene and polymorphism in the gene locus have been described [25]. Single nucleotide polymorphism A118G have been previously linked with a reduced sensibility to exogenous opioids [26] and decreased cancer specific mortality probably due to the decreased immunosuppression associated with the G allele. Studies in breast and esophageal cancer patients found that the GG and GA alleles provided significant survival benefit compared to the AA allele [27–29]; it was hypothesized that a G allele increased sensitivity to endogenous opioid peptides [30,31]. In our study, we did not assess genetic polymorphism, and this could have contributed to our results, although any allele-specific in colorectal cancer patients remains to be elucidated.

Preclinical investigations appear to indicate that the role of MOR-1 agonists is cell type-, dose- and time-dependent. Morphine has been found to be a suppressor of cells' metastatic behavior [32], inhibitor adhesion molecules (ICAM-1) expression in endothelial cells [33]. Also, chronic administration of morphine inhibited tumorigenesis and metastasis [34] and reduced liver metastasis in animals [35]. Yet, other authors showed that morphine at a concentration of 100 nM stimulated the release of urokinase type plasminogen activator, a factor known to promote metastasis [21] and that the activation of MOR was associated with a significant increase in the release of interleukin-8 [36]. We found no association between total perioperative 96h opioid use with DFS or OS. In previous studies equivalent morphine consumption has contradictory impact upon disease free survival. While it decreased survival on early stages of lung cancer [37] had no impact on colorectal or esophageal cancers [29,38,39].

This study has several strengths. It is the first trial that implement and strictly follow a prespecified analysis plan based on the REMARK benchmark methodology for this type of studies. Furthermore, we used an IHC score that cover all grades of staining without gaps and analyzed it as an ordinal variable without information loss due to dichotomizing process thus maximizing the

power of our analysis. Also, the evaluation of MOR-1 expression was done by blinded repeated readings. Finally, we thoroughly collected potential confounders and analyze the associations with rigorous controlled methodology.

Some limitations have to be nevertheless acknowledged: (1) the retrospective design; (2) the low rate of events which limits the statistical power of any association; (3) the restricted analysis to stage II or III, non-advanced cancer; (4) the lack of evaluation the *OPRM1* gene variant polymorphism and (5) only perioperative opioid use was recorded.(6) No software for IHC evaluation .

CRC adjuvant treatment is guided by an individualized recurrence risk stratification based on oncological features or markers such as CEA or lymph nodes invasion. MOR-1 IHC expression showed promising results and could be potentially incorporated in therapy guidance, however the results from this study did not support such incorporation.

Materials and Methods

This was an investigator–initiated retrospective single center study, conducted according to a protocol reviewed and approved by the Spanish Drugs Regulation Agency on May 4th 2018 and the Institutional Review Board of the Hospital Universitari I Politécnic la Fe, Valencia, Spain on June 27th 2018. The study was registered at clinicaltrials.gov (identifier: Clinical trials - NCT03601351) and conducted in accordance with the Declaration of Helsinki on ethical principles for medical research in human subjects, adopted by the General Assembly of the World Medical Association (1996).

Study population

Patients were eligible for participation if (a) the scheduled colorectal surgery occurred between January 2010 and December 2013; (b) they were age > 18 years and (c) and had suspected colorectal cancer for stage II/III. Exclusion criteria were: (a) non oncologic colorectal surgery; (b) emergency or unplanned surgery; (c) and colorectal cancer for stage I or IV. Patients with poor quality histological samples were not included in analysis. Patients' follow-up was 5

years from the day of surgery and all data were obtained from electronic clinical records.

Primary outcome

The main outcome of this study was to evaluate the impact of MOR-1 expression by immunohistochemistry (IHC) on patients' disease free survival (DFS) 5 years after surgery.

Secondary outcomes

Secondary outcomes included: a) differences in MOR-1 expression in tumor and non-tumor tissue; b) association between MOR–1 expression and oncological features; c) type of recurrence; d) overall five-years survival; and e) any postoperative complications until postoperative day (POD) 28.

Definitions

DFS was calculated according to the National Cancer Institute definition as the length of time after primary treatment (in our study surgery) that the patient survives without any signs or symptoms of cancer progression.

OS was defined the period of time starting from the date of the initial surgery to the time of death any cause or the last date of follow-up if no events were documented. (*https://www.cancer.gov/publications/dictionaries/cancerterms?cdrid=44023)*

Postoperative complications were registered and graded according to European Perioperative Clinical Outcome (EPCO) definitions [40].

Data collected

MOR-1 immunohistochemical studies were performed on paraffin-embedded human histological tissues of colorectal adenocarcinoma. In each case, we selected a sample with colorectal adenocarcinoma and a normal colonic sample.

Human MOR-1 Immunohistochemistry procedure: For antigen retrieval, sections were heated in Envision Flex buffer (pH=9) for 20 min and incubated for 30 min at room temperature with mouse monoclonal MOR-1 antibody (1:100) (Acris®). Slides were developed for ten minutes with 3,3′-diaminobenzidine chromogen and counterstained for ten minutes with hematoxylin. The quantification of MOR-1 Expression in Human Colon Samples was done by microscopic evaluation of MOR-1 immunoreactivity carried out by one experienced pathologist. The observer performed two separate blinded

assessments to evaluate for variability. The standard operation procedure (SOP) for IHC analysis is described in Appendix A. Immunostaining was read in a semi quantitative manner. Positive staining for MOR-1 were defined as those showing brown signals in the cell cytoplasm, nucleus, or membrane. The staining intensity was scored as “0” (no staining), “1” (weakly stained), “2” (moderately stained), or “3” (strongly stained). The percentage of cell positivity was scored as “0” (< 5%, negative), “1” (5%-25%, sporadic), “2” (25%-50%, focal), or “3” (>50%, diffuse). The expression of MOR-1 was scored by adding the intensity staining scores and the percentage area positively stained, producing a total range from 0 to 6. Negative immunostaining score was tested successfully in central nervous system tissue sample without MOR-1 expression. After the first immunostaining reading, the same pathologist conducted a second assessment to minimize interindividual variability.

Other variables recorded were: gender; age; American Society of Anesthesiologists (ASA) physical status; arterial hypertension; diabetes mellitus; history of cigarette smoking; preoperative plasma total protein; anesthetic technique used (intravenous versus halogenated); epidural anesthesia use; amount of opioid drugs administered in the first 96 postoperative hours (in oral morphine equivalents [41]; intraoperative remifentanil use; blood transfusion in the first 96 postoperative hours; duration of surgery; neoadjuvant radiotherapy; neoadjuvant chemotherapy; adjuvant chemotherapy or radiotherapy; preoperative hemoglobin value; stage II or III cancer (%); need for reintervention; MOR-1 expression in non–tumor tissue; carcinoembryonic antigen value at diagnosis; number of positive lymph nodes.

Sample size calculation

To the best of our knowledge, there is no published data in literature on correlation between MOR-1 and DFS rate in colorectal cancer. Thus, we performed our calculation on another digestive tract cancer [19]. Based on published data on MOR-1 expression and mortality in a gastric cancer population and assuming that subjects with positive expression of MOR-1 in the neoplastic tissue had a risk ratio of 2.5 to suffer an event (with a standard deviation of 0.6) we estimated that to detect a statistically significant difference in a sample of 170 patients with a 5-year recurrence rate of 20% and an alpha error of 5% (0.05), power of 80% and a censorship rate of 10%.

Analysis plan

The analysis plan was specified before patients' data retrieval or data analysis. Data are reported as counts and proportions or means (standard deviation, SD) or medians [25^{th} – 75^{th} percentiles] depending on their distribution. Normality of distributions was assessed by inspection of quantile–quantile plots. Logarithm transformation was carried out if severe skewness was observed in any variable distribution. This was performed for carcinoembryonic antigen level at diagnosis and number of positive lymph nodes.

The preliminary analysis on MOR-1 IHC differences between tumor and non–tumor tissue was carried out by paired–sample Wilcoxon rank sum test. The association between MOR–1 IHC expression and oncological features was assessed by Spearman rank correlation (ρ), or Goodman Kruskal's gamma statistic.

The association between MOR-1 IHC expression and DFS and OS was evaluated using the Kaplan-Meier survival curve and the Log-Rank test. For this analysis MOR expression was dichotomized and was defined as positive when tumor tissue had a higher expression than non–tissue tumor in a same patient's samples and negative otherwise. Also, a univariable estimation of association between MOR-1 IHC and both DFS and OS was tested with Cox model after checking for proportional risk assumption and residuals. If scaled Schonfeld residuals plot and test did not fulfill proportional risk assumption a parametric model was fitted choosing the best fitting distribution by Akaike information criterion (AIC) [42].

In addition, a multivariable Cox regression model was estimated to control for potential confounding factors. Variable selection was carried out through Elastic Net with the alpha and lambda parameter estimated by cross-validation. The variables that entered the selection process are detailed in the Table S3 REMARK profile in Supplementary Digital Content.

The relationship between MOR-1 IHC score and complications at 28 postoperative days was assessed by univariable and multivariable logistic regression with variable selection process carried out with Elastic Net with same methodology as for disease free and overall survival analysis (see Table SX REMARK profile in the Supplementary Digital Content for full details).

For outcome analysis (DFS and OS), cases with missing values > 5% in any covariable were included in the analysis using multiple imputation methods. The hazard ratios were derived from the pooled average effect across 10 augmented datasets, with the confidence intervals and significance tests taking into account the uncertainty of the imputations. The multiple imputation was performed by the *mice* package from R software (version 3.5.0).

Statistical significance level will be set at $P < 0.05$. All analysis will be performed with R software (R Foundation for Statistical Computing, Vienna, Austria).

Conclusions

MOR-1 expression is increased in colorectal cancer tissue but there is no association with five years DFS or OS. The results from this study did not support MOR-1 IHC expression incorporation in colorectal cancer recurrence risk stratification markers. More investigations are warranted to evaluate the role of MOR-1 over-expression, perioperative opioid use and long-term oncological outcomes in colorectal patients.

Appendix A

Standard operating procedure (SOP) Immunohistochemical analysis

Immunohistochemical analysis was performed on human tissue from tumoral specimens of colorectal adenocarcinoma from Hospital Universitario y Politécnico La Fe, Valencia, Spain. MOR-1 immunohistochemical staining was performed on the human paraffin-embedded tissue. For each patient, we selected a sample with colorectal adenocarcinoma and a normal colonic sample.

For antigen retrieval, sections were heated in Envision Flex buffer (pH=9) for 20 min and incubated for 30 min at room temperature with mouse monoclonal MOR1 antibody (1:100) (Acris®). Slides were stained for ten minutes with 3,3′-diaminobenzidine chromogen and counterstained for ten minutes with hematoxylin.

The microscopic evaluation of MOR-1 immunoreactivity was carried out by an experienced pathologist without knowledge of patient stage. The

pathologist performed the analysis twice on every sample in a blinded fashion. The Representative pictures of each evaluated area are obtained. The immunostaining was read in a semi quantitative manner. Positive reactions were defined as those showing brown signals in the cell cytoplasm, nucleus, or membrane. The staining intensity was scored as “0” (no staining), “1” (weakly stained), “2” (moderately stained), or “3” (strongly stained). The percent positivity was scored as “0” (< 5%, negative), “1” (5%-25%, sporadic), “2” (25%-50%, focal), or “3” (>50%, diffuse).

The expression of MOR-1 was scored by adding up the intensity scores and the percentage area positively stained, producing a total range of 0–6 (Table 3 and Figure 3).

References

1.Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018, 68 , 394–424; DOI: 10.3322/caac.21492.

2.Sullivan R, Alatise OI, Anderson BO, Audisio R, Autier P, Aggarwal A, et al. Global cancer surgery: Delivering safe, affordable, and timely cancer surgery. Lancet Oncol. 2015 , 16, 1193–224; DOI: 10.1016/S1470-2045(15)00223-5.

3.Snyder GL, Greenberg S. Effect of anaesthetic technique and other perioperative factors on cancer recurrence. Br J Anaesth. 2010, 105, 106–15; DOI: 10.1093/bja/aeq164.

4.Behrenbruch C, Shembrey C, Paquet-Fifield S, Mølck C, Cho HJ, Michael M, et al. Surgical stress response and promotion of metastasis in colorectal cancer: a complex and heterogeneous process. Clin Exp Metastasis. 2018, 35 , 333–45; DOI: 10.1007/s10585-018-9873-2.

5.Chen DT, Pan JH, Chen YH, Xing W, Yan Y, Yuan YF, et al. The mu-opioid receptor is a molecular marker for poor prognosis in hepatocellular carcinoma and represents a potential therapeutic target. Br J Anaesth. 2019, 122, e157–67; DOI: 10.1016/j.bja.2018.09.030.

6.Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. Nat Rev Clin Oncol. 2018, 15, 205–18; DOI: 10.1038/nrclinonc.2017.194.

7.Byrne K, Levins KJ, Buggy DJ. Can anesthetic-analgesic technique during primary cancer surgery affect recurrence or metastasis? Can J Anesth. 2016, 63, 184–92; DOI: 10.1007/s12630-015-0523-8.

8.Missair A, Cata JP, Votta-Velis G, Johnson M, Borgeat A, Tiouririne M, et al. Impact of perioperative pain management on cancer recurrence: An ASRA/ESRA special article. Reg Anesth Pain Med. 2019, 44, 13–28; DOI: 10.1136/rapm-2018-000001.

9.Wall T, Sherwin A, Ma D, Buggy DJ. Influence of perioperative anaesthetic and analgesic interventions on oncological outcomes : a narrative review. 2019;123(June):135–50.

10.Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: An integrative review. J Pain Res. 2016, 9, 515–34; DOI: 10.2147/JPR.S97759.

11.Sekandarzad MW, Van Zundert AAJ, Lirk PB, Doornebal CW, Hollmann MW. Perioperative anesthesia care and tumor progression. Anesth Analg. 2017, 124, 1697–708; DOI: 10.1213/ANE.0000000000001652.

12.Singleton PA, Moss J, Karp DD, Atkins JT, Janku F. The mu opioid receptor: A new target for cancer therapy? Cancer. 2015, 121, 2681–8. DOI: 10.1002/cncr.29460.

13.Connolly C, Buggy DJ. Opioids and tumour metastasis: Does the choice of the anesthetic-analgesic technique influence outcome after cancer surgery? Curr Opin Anaesthesiol. 2016, 29, 468–74; DOI: 10.1097/ACO.0000000000000360.

14.Lennon FE, Moss J, Singleton PA. The μ-Opioid Receptor in Cancer Progression – Is There a Direct Effect? Anesthesiology. 2012, 116, 940–5; DOI: 10.1097/ALN.0b013e31824b9512.

15.Janku F, Johnson LK, Karp DD, Atkins JT, Singleton PA, Moss J. Treatment with methylnaltrexone is associated with increased survival in patients with advanced cancer. Ann Oncol. 2016, 27, 2032–8; DOI: 10.1093/annonc/mdv249.

16.Singleton PA, Mirzapoiazova T, Hasina R, Salgia R, Moss J. Increased μ-opioid receptor expression in metastatic lung cancer. Br J Anaesth. 2014, 113, 103–8; DOI: 10.1093/bja/aeu165.

17.Levins KJ, Prendeville S, Conlon S, Buggy DJ. The effect of anesthetic technique on μ-opioid receptor expression and immune cell infiltration in breast cancer. Br J Anesth. 2018, 32, 792–6; DOI: 10.1007/s00540-018-2554-0.

18.Zylla D, Gourley BL, Vang D, Jackson S, Boatman S, Lindgren B, et al. Opioid requirement, opioid receptor expression, and clinical outcomes in patients with advanced prostate cancer. Cancer. 2013, 119, 4103–10; DOI: 10.1002/cncr.28345.

19.Yao Y, Yao R, Zhuang L, Qi W, Lv J, Zhou F, et al. MOR1 Expression in Gastric Cancer: A Biomarker Associated With Poor Outcome. Clin Transl Sci. 2015, 8, 137–42; DOI: 10.1111/cts.12246.

20.Zhang Y-F, Xu Q-X, Liao L-D, Xu X-E, Wu J-Y, Wu Z-Y, et al. Association of mu-opioid receptor expression with lymph node metastasis in esophageal

squamous cell carcinoma. Dis Esophagus. 2015, 28, 196–203; DOI: 10.1111/dote.12165.

21.Nylund G, Pettersson A, Bengtsson C, Khorram-Manesh A, Nordgren S, Delbro DS. Functional expression of μ-opioid receptors in the human colon cancer cell line, HT-29, and their localization in human colon. Dig Dis Sci. 2008, 53, 461–6; DOI: 10.1007/s10620-007-9897-y.

22.Diaz-Cambronero O, Mazzinari G, Cata JP. Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature. Pain Manag. 2018, 8, 353–61; DOI: 10.2217/pmt-2018-0029.

23.Sinn HP, Schneeweiss A, Keller M, Schlombs K, Laible M, Seitz J, et al. Comparison of immunohistochemistry with PCR for assessment of ER, PR, and Ki-67 and prediction of pathological complete response in breast cancer. BMC Cancer. 2017, 17, 1–10; DOI: 10.1186/s12885-017-3111-1.

24.Zhu GJ, Xu CW, Fang MY, Zhang YP, Li Y. Detection of Her-2/neu expression in gastric cancer: Quantitative PCR versus immunohistochemistry. Exp Ther Med. 2014;8(5):1501–7.

25.Shabalina SA, Zaykin D V., Gris P, Ogurtsov AY, Gauthier J, Shibata K, et al. Expansion of the human μ-opioid receptor gene architecture: Novel functional variants. Hum Mol Genet. 2009, 18, 1037–51; DOI: 10.1093/hmg/ddn439.

26.Fukuda K, Hayashida M, Ide S, Saita N, Kokita Y, Kasai S, et al. Association between OPRM1 gene polymorphisms and fentanyl sensitivity in patients undergoing painful cosmetic surgery. Pain. 2009, 147, 194–201; DOI: 10.1016/j.pain.2009.09.004.

27.Bortsov AV, Millikan RC, Belfer I, Boortz-Marx RL, Arora H, McLean SA. μ-Opioid receptor gene A118G polymorphism predicts survival in patients with breast cancer. Anesthesiology. 2012, 116, 896–902; DOI: 10.1097/ALN.0b013e31824b96a1.

28.Xu X, Mao B, Wu L, Liu L, Rui J, Chen G. A118G Polymorphism in μ-Opioid Receptor Gene and Interactions with Smoking and Drinking on Risk of Oesophageal Squamous Cell Carcinoma. J Clin Lab Anal. 2017, 31, e22018; DOI: 10.1002/jcla.22018.

29.Oh TK, Kim K, Jheon SH, Do S-H, Hwang J-W, Jeon Y-T, et al. Long-Term Oncologic Outcomes, Opioid Use, and Complications after Esophageal Cancer Surgery. J Clin Med. 2018; 7, 33; DOI: 10.3390/jcm7020033.

30.Cieślińska A, Sienkiewicz-Szłapka E, Kostyra E, Fiedorowicz E, Snarska J, Wroński K, et al. μ-Opioid receptor gene (OPRM1) polymorphism in patients with breast cancer. Tumor Biol. 2015, 36, 4655–60; DOI: 10.1007/s13277-015-3113-z.

31.Wang S, Li Y, Liu XD, Zhao CX, Yang KQ. Polymorphism of A118G in μ-opioid receptor gene is associated with risk of esophageal squamous cell carcinoma in a Chinese population. Int J Clin Oncol. 2013, 18, 666–9; DOI: 10.1007/s10147-012-0441-5.

32.Harimaya Y, Koizumi K, Andoh T, Nojima H, Kuraishi Y, Saiki I. Potential ability of morphine to inhibit the adhesion, invasion and metastasis of metastatic colon 26-L5 carcinoma cells. Cancer Lett. 2002, 187, 121–7; DOI: 10.1016/s0304-3835(02)00360-9.

33.Min TJ, Park SH, Ji YH, Lee YS, Kim TW, Kim JH, et al. Morphine attenuates endothelial cell adhesion molecules induced by the supernatant of LPS-stimulated colon cancer cells. J Korean Med Sci. 2011, 26 , 747–52; DOI: 10.3346/jkms.2011.26.6.747.

34.Tegeder I, Geisslinger G. Opioids as modulators of cell death and survival - Unraveling mechanisms and revealing new indications. Pharmacol Rev. 2004, 56, 351–69; DOI: 10.1124/pr.56.3.2.

35.Yeager MP, Colacchio TA. Effect of Morphine on Growth of Metastatic Colon Cancer In Vivo. Arch Surg. 1991, 126, 454–6; DOI: 10.1001/archsurg.1991.01410280056007.

36.Neudeck BL, Loeb JM. Endomorphin-1 alters interleukin-8 secretion in Caco-2 cells via a receptor mediated process. Immunol Lett. 2002, 84, 217–21; DOI: 10.1016/s0165-2478(02)00198-0.

37.Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, et al. A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. Cancer Med. 2014, 3 , 900–8; DOI: 10.1002/cam4.236.

38.Du KN, Feng L, Newhouse A, Mehta J, Lasala J, Mena GE, et al. Effects of intraoperative opioid use on recurrence-free and overall survival in patients with

esophageal adenocarcinoma and squamous cell carcinoma. Anesth Analg. 2018, 127, 210–6; DOI: 10.1213/ANE.0000000000003428.

39.Wu HL, Tai YH, Chang WK, Chang KY, Tsou MY, Cherng YG, et al. Does postoperative morphine consumption for acute surgical pain impact oncologic outcomes after colorectal cancer resection?: A retrospective cohort study. Medicine (Baltimore). 2019, 98, e15442; DOI: 10.1097/MD.0000000000015442.

40.Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: A statement from the ESA-ESICM joint taskforce on perioperative outcome measur. Eur J Anaesthesiol. 2015, 32, 88–105; DOI: 10.1097/EJA.0000000000000118.

41.Gammaitoni AR, Fine P, Alvarez N, McPherson ML, Bergmark S. Clinical application of opioid equianalgesic data. Clin J Pain. 2003, 19, 286–97; DOI: 10.1097/00002508-200309000-00002.

42.Ternès N, Rotolo F, Michiels S. Empirical extensions of the lasso penalty to reduce the false discovery rate in high-dimensional Cox regression models. Stat Med. 2016, 35, 2561–73; DOI: 10.1002/sim.6927.

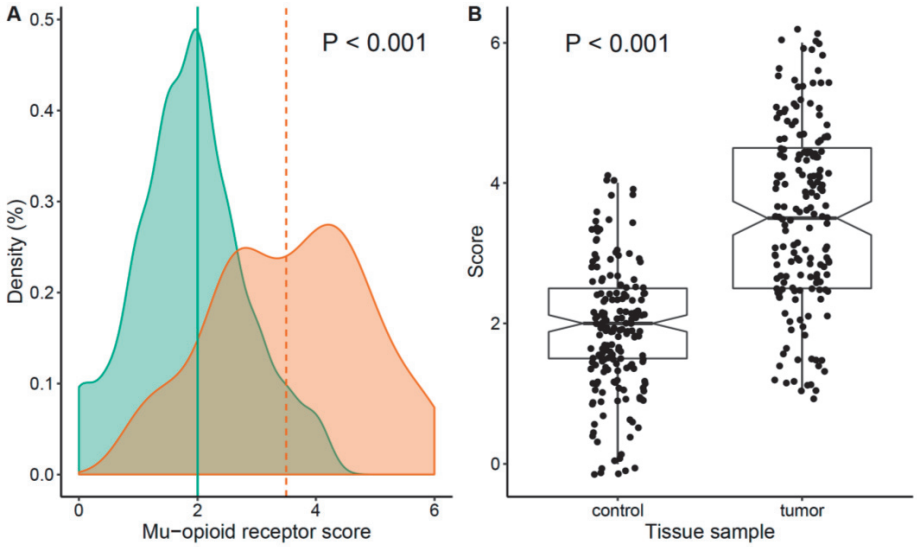


Figure 1. MOR-1 expression: (a) Probability density plot of MOR-1 score, Green: Normal tissue, Orange: Tumor tissue; (b) Scatterplot and Box plot of score distribution by type of sample.

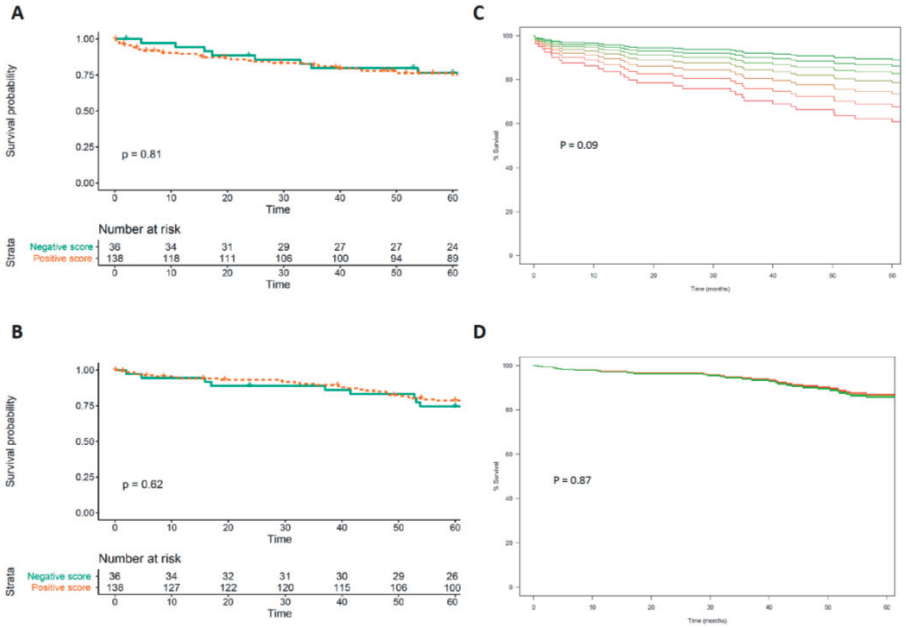


Figure 2. Time to event analysis. Assessment of association between MOR-1 expression in tumor sample and DFS and OS : (a) Kaplan Meier curve assessing MOR-1 expression effect on DFS. MOR-1 score is dichotomized as detailed in text. Missing data are imputed as detailed in text; (b) Multivariable Cox model curve estimation for DFS. MOR-1 score is analyzed as an ordinal variable with 7 levels (from 0 to 6). Different score are showed in colors from green to red with green representing a score of 0 and red a score of 6 (c) Kaplan Meier curve assessing MOR-1 expression effect on OS. MOR-1 score is dichotomized as detailed in text. (d) Multivariable Cox model curve estimation for OS. MOR-1 score is analyzed as an ordinal variable with 7 levels (from 0 to 6). Different score is showed in colors from green to red with green representing a score of 0 and red a score of 6.

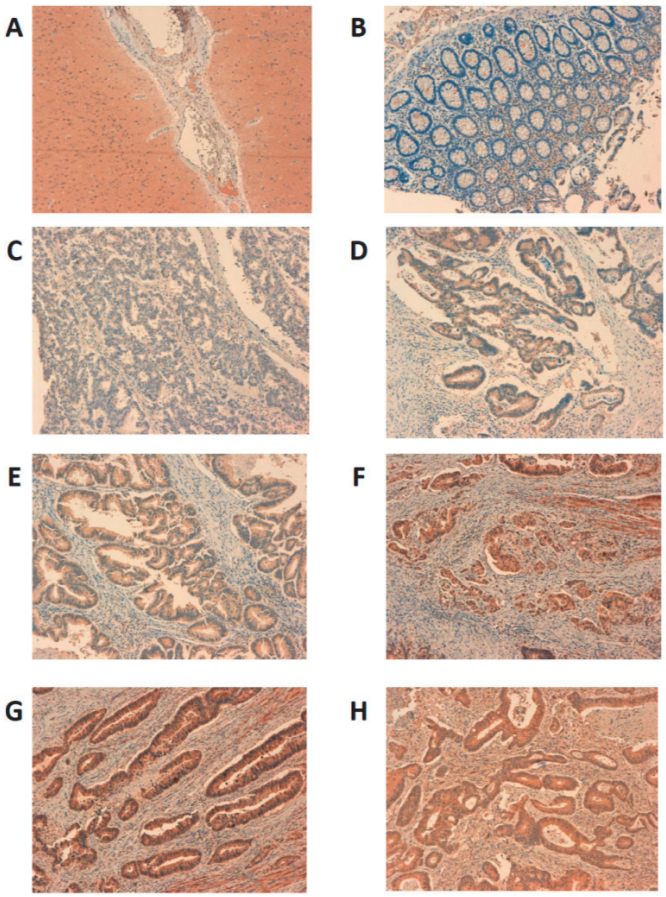


Figure 3. Immunohistochemistry sample to describe scoring. (a) Central nervous system tissue control; (b) Score 0; (c) Score 1; (d) Score 2; (e) Score 3; (f) Score 4; (g) Score 5; (h) Score 6.

Table 1. Patients' characteristics	
N = (174)	
Age (years)	70.5 (11.4)
Gender (female)	42.0% (73)
Complication in the first 28 postoperative days	18.4% (32)
Anesthetic agent	
Halogenated Intravenous Both	75.3% (125) 20.5 % (34) 4.2 % (7)
Intraoperative remifentanyl perfusion	49.1% (81)
First postoperative 96 hours total opioid dose	76.43 (34.76)
Intraoperative Epidural Analgesia (Yes)	16.9% (28)
Red Blood Cell transfusion in the first postoperative 96 hours	30.5% (53)
CEA value at diagnosis (N = 163) ($U \cdot mL^{-1}$)	2.60 [1.60 – 5.10]
Surgical duration (minutes)	217.52 (88.22)
Preoperative total proteins ($g \cdot dL^{-1}$)	7.00 [6.00 – 7.00]
Preoperative Hemoglobin value ($g \cdot dL^{-1}$)	12.03 (2.07)
Number of affected lymph nodes	0 [0 – 2]
Preoperative chemotherapy (Yes)	10.3% (18)
Preoperative radiotherapy (Yes)	9.8% (17)
Postoperative chemotherapy (Yes)	50.9% (87)
Postoperative radiotherapy (Yes)	1.7% (3)
ASA score	
1 2 3 4	7.6% (12) 54.8% (86) 33.8% (53) 3.8% (6)
HTA (Yes)	54.6% (95)
Diabetes Mellitus (Yes)	20.7% (34)
Reintervention Yes)	6.7% (11)
Readmission (Yes)	3.9% (6)
Dukes	
A B C D	1.3% (2) 51.0% (78) 46.4% (71) 1.3% (2)
Oncological Stage (III)	44.8% (78)
Ca 19–9 value at diagnosis ($U \cdot mL^{-1}$) N = 124	11.1 [5.3 – 18.5]
Resection margins (R+) N = 135	19% (25)
Tumoral tissue differentiation N = 169	
Poor/Undifferentiated	12.0% (20)
Moderately differentiated	78% (132)
Well differentiated	10.0 %(17)
Values are reported as mean (standard deviation) or percentage (N) or median [25^{th} – 75^{th} percentile] as appropriate. *HTA*, arterial hypertension; *CEA*, Carcinoembryonic antigen; *ASA*, American Society of Anesthesiology; R+, positive resection margin.	

Table 2. Multivariable Cox regression model for disease free survival and overall survival at 5 years follow–up

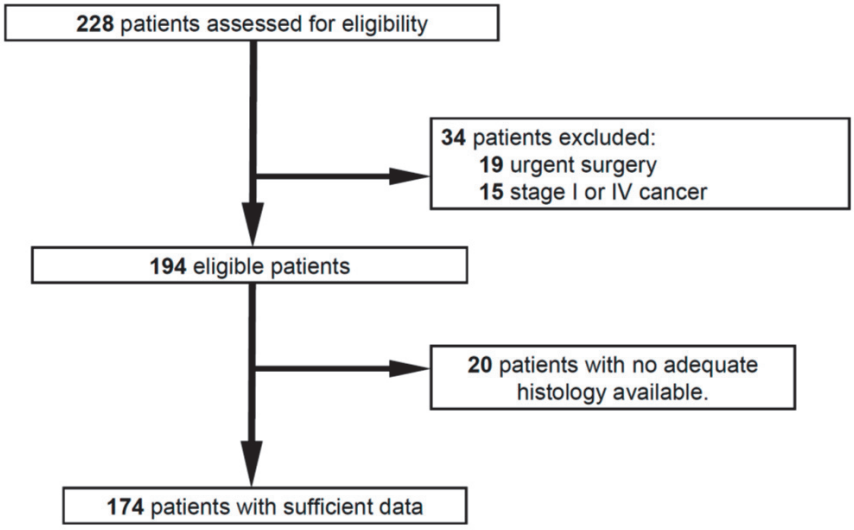
	Complete cases model			Missing data multiple imputation		
Disease free survival model	N = 135 Events = 30			N = 174 Events = 40		
	Hazard Ratio	Lower – Upper 95%CI	P –value	Hazard Ratio	Lower – Upper 95%CI	P –value
MOR expression	0.791	0.603 – 1.039	0.092	1.062	0.930 – 1.212	0.376
First postoperative 96 hours transfusion (yes)	0.991	0.392 – 2.503	0.985	1.060	0.701 – 1.603	0.784
ASA (Reference category = 1)						
2	0.707	0.155 – 3.223	0.654	0.854	0.427 – 1.710	0.657
3	0.936	0.195 – 4.481	0.934	0.994	0.475 – 2.080	0.986
4	1.322	0.159 – 11.007	0.796	0.517	0.129 – 2.069	0.351
Preoperative Hemoglobin ($g \cdot dL^{-1}$)	1.043	0.846 – 1.287	0.693	1.012	0.919 – 1.117	0.807
Number of affected lymph nodes	1.283	0.921 – 1.788	0.141	1.028	0.780 – 1.322	0.828
CEA at diagnosis ($U \cdot mL^{-1}$)	1.811	1.245 – 2.635	0.002	1.058	0.877 – 1.28	0.557
Age (years)	1.010	0.970 – 1.052	0.638	1.005	0.987 – 1.022	0.591
Overall survival model	N = 135 Events = 29			N = 174 Events = 40		
MOR expression	1.023	0.784 – 1.335	0.869	1.031	0.906 – 1.173	0.645
First postoperative 96 hours transfusion (yes)	1.556	0.658 – 3.682	0.314	1.004	0.670 – 1.503	0.986
ASA score (Reference category = 1)						
2	0.954	0.119 – 7.629	0.965	0.898	0.479 – 1.685	0.737
3	1.948	0.247 –15.357	0.527	1.072	0.538 – 2.138	0.843
4	2.375	0.208 – 27.07	0.486	0.832	0.183 – 3.786	0.812
Preoperative Hemoglobin ($g \cdot dL^{-1}$)	0.911	0.729 – 1.139	0.415	1.016	0.925 – 1.115	0.743
Number of affected lymph nodes	1.482	1.110 – 1.978	0.008	0.971	0.774 – 1.218	0.800
CEA at diagnosis ($U \cdot mL^{-1}$)	1.485	1.017 – 2.170	0.041	1.031	0.859 – 1.24	0.746
Age (years)	1.031	0.989 – 1.074	0.147	1.003	0.986 – 1.020	0.746

Table 3. Mu–opioid receptor expression score

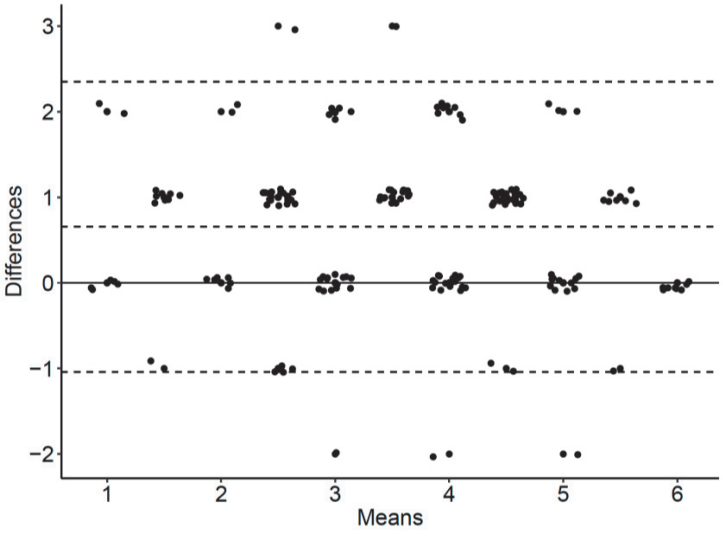
		Staining intensity		
Positivity Percentage	**No Staining**	**Weak**	**Moderate**	**Strong**
Negative (< 5%)	0	1	2	3
Sporadic (5% – 25%)	0	2	3	4
Focal (25%–50%)	0	3	4	5
Diffuse (>50%)	0	4	5	6

Suplemento Capítulo 7

Published as online supplement



eFigure 1. Patients' flowchart



eFigure 2. Bland–Altman plot of ageeement between tow independent readings

eTable 1. Association between Mu–opioid receptor expression score and oncological features				
Characteristics	**N**	**Correlation**	**Lower– Upper 95% CI**	**P value**
Ca 19–9 ($U \cdot mL^{-1}$)	124	- 0.07*	- 0.26 – 0.12	0.448
CEA ($U \cdot mL^{-1}$)	163	0.05*	- 0.09 – 0.22	0.497
Number of positive lymph nodes	174	0.15*	0.003 – 0.29	0.044
Duke stage		0.19**	0 – 0.31	0.119
A	2			
B	78			
C	71			
D	2			
Cancer stage		0.15^^	0 – 0.28	0.053
II	96			
III	78			
Resection margin		0.008**	0 – 0.13	0.926
R+	25			
R0	110			
Tumoral tissue differentiation		0.06**	0 – 0.18	0.717
Poor/Undifferentiated	20			
Moderately differentiated	132			
Well differentiated	17			

Ca 19-9, Gastrointestinal Cancer Antigen ; *CEA*, Carcinoembryonic antigen; *R+*, positive margin ; *R0*, negative margin; *CI*, Confidence interval. * Spearman correlation coefficient. ** square root of ANOVA η^2

eTable 2. Multivariable logistic regression model for complications at 28 postoperative days.			
	Odds Ratio	**Lower – Upper 95%CI**	***P* value**
MOR expression tumor tisues	0.711	0.340 – 1.310	0.305
MOR expression non–tumour tissue	0.555	0.188 – 1.400	0.237
First postoperative 96 hours opioid dose (morphine equivalents)	1.012	0.989 – 1.039	0.342
First postoperative 96 hours transfusion (yes)	0.819	0.123 – 5.055	0.828
Gender (Female)	0.391	0.052 – 2.100	0.299
ASA (Reference category = 1)			
2	-0.147	-2.438 – 1.510	0.996
≥3	0.224	-2.066 – 2.395	0.995
Surgery duration (minutes)	1.004	0.991 – 1.018	0.539
Arterial Hypertension (yes)	4.383	0.717 – 42.894	0.141
Number of affected lymph nodes	3.610	1.546 – 10.789	0.008
Serum total proteins ($g \cdot dL^{-1}$)	1.024	0.832 – 1.920	0.879
Smoker (yes)	0.779	0.026 – 9.585	0.86
Age (years)	1.007	0.921 – 1.107	0.878
MOR, Mu–opioid receptor; *ASA*, American Society of Aensthesiology; *CI*, Confidence Interval.			

Table S3. Study's REMARK profile

A. Patients, treatment and variables

Study and marker	Remarks
Marker	MOR–1: Immunohistochemical cell staining assessed on an ordinal scale from 0 to 6 (see Table 3)in tumour tissue
Further variables	v1= Gender; v2= Anaesthetic agent (intravenous vs. halogenated); v3= Complication in the first 28 postoperative days (yes/no); v4= Amount of opioid drugs administered in the first 96 postoperative hours (in morphine equivalents); v5= Blood transfusion in the first 96 postoperative hours; v6= Epidural analgesia (yes/no); v7= neo–adjuvant radiotherapy; v8 = Neo–adjuvant chemotherapy; v9 = Adjuvant chemotherapy; v10= Adjuvant radiotherapy; v11= ASA risk score; v12 = Duration of surgery; v13= Preoperative Haemoglobin value; v14= Stage III cancer (%); v15 = Reintervention; v16= MOR–1 expression in non–tumor tissue; v17= Carcinoembryonic antigen value at diagnosis (log scale); v18= Number of positive lymph nodes (log scale); v19= Age; v20 = Arterial Hypertension; v21= Diabetes; v23= Smoker; v24= Preoperative Plasma Total Protein

Patients	N	Remarks
Assessed for eligibility	228	*Disease*: Colorectal cancer stage II and III.; *Patients:* Surgery 2010 to 2013, Hospital Universitario la Fe, Valencia, Spain.; *Sample:* Archived specimens available.
Excluded	54	
Included	174	
With outcome events	174	

B. Statistical analyses of outcomes

Analysis	Patients	Events	Variable considered	Results/Remarks
A1: MOR–1 expression in tumor and non–tumour tissue	174	–	MOR–1 , v18	Text (Page 5,Line 76)
A2: DFS Univariable	174	40	MOR–1	Text (Page 4,Line 88)
A3: DFS Multivariable. Variable selection process	109	25	MOR–1,v1 to v24	Elastic net with hyperparameters estimated by cross validation $\alpha = 0.8$ $\lambda = 0.1$

A4a: Adjusted Effect of MOR –1on DFS	135	30	MOR–1,v5,v11,v13,v17 to v19	Table 2
A4b: Adjusted Effect of MOR–1 on DFS with missing values imputation	174	40	MOR–1,v5,v11,v13,v17 to v19	Table 2
A5: OS Univariable	174	40	MOR–1	Text (Page 4, Line 90)
A6: OS Multivariable. Variable selection process	109	26	MOR–1,v1 to v24	Elastic net with hyperparameters estimated by cross validation $\alpha = 0.8$ $\lambda = 0.08$
A7: Adjusted Effect of MOR –1 on OS	135	29	MOR–1,v5,v11,v13,v17 to v19	Table 2
A7b: Adjusted Effect of MOR–1 on OS with missing values imputation	174	40	MOR–1,v5,v11,v13,v17 to v19	Table 2
A8: Complications Univariable	174	32	MOR–1	Text (Page 6, Line 113)
A9: Complications Multivariable	87	11	MOR–1, v1 to v24 omitting v15 which is a complication	Elastic net with hyperparameters estimated by cross validation $\alpha = 0.8$ $\lambda = 0.08$
A10: Adjusted Effect of MOR–1 on complications	74	16	MOR–1, v1,v4,v5,v11,v12,v15, v18,v20,v23,v24	Table S2

Capítulo 10

Discusión general de resultados

La discusión de los resultados se ha agrupado, de igual modo que la introducción, en cuatro bloques principales: estrategia individualizada de neumoperitoneo, ventilación mecánica y bloqueo neuromuscular en cirugía laparoscópica, y estrategia analgésica en cirugía oncológica.

Bloque 1: *Estrategia individualizada de neumoperitoneo en cirugía laparoscópica.*

En el capítulo 2, se detalla el estudio observacional multicéntrico *'Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery' (IPPColLapSe I).* Se reclutaron 92 pacientes y se excluyeron 14 por conversión a cirugía abierta. Se confirma que una estrategia individualizada de presión del neumoperitoneo es factible en todos los pacientes y aceptada por los equipos quirúrgicos. En 61 de los 78 pacientes (78%) se obtuvieron adecuadas condiciones quirúrgicas a la mínima presión intraabdominal (8 mmHg). El análisis de la relación entre la presión del neumoperitoneo y la *"driving pressure"* respiratoria resultó ser casi lineal. El volumen intraabdominal medio estimado con el que se realiza la cirugía laparoscópica colorrectal con adecuadas condiciones fue 3,2 L. Se confirma nuestra hipótesis de que la aplicación de un paquete de medidas permite disminuir la presión del neumoperitoneo utilizada manteniendo unas adecuadas condiciones quirúrgicas en cirugía laparoscópica colorrectal. Esta estrategia individualizada de presión del neumoperitoneo también permite disminuir la *"driving pressure"* respiratoria.

El Capítulo 3 recoge la publicación del protocolo del ensayo clínico con medicamentos, de bajo nivel de intervención, randomizado, multicéntrico, *"Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery versus standard theraphy" (IPPColLapSe II),* no dispone, por tanto, de resultados ni conclusión.

En el capítulo 4, se detalla el ensayo clínico con medicamentos de bajo nivel de intervención, randomizado, multicéntrico, *"Individualized PneumoPeritoneum pressure in Colorectal Laparoscopic Surgery versus standard theraphy" (IPPColLapSe II).* Se reclutaron 166 pacientes, 85 recibieron una estrategia de presión de neumoperitoneo individualizada (IPP) y 81 una estrategia de presión

estándar (SPP). La IPP se asocia a una mayor probabilidad de mejor recuperación medida mediante la escala de calidad de recuperación postoperatoria (PQRS) en el dominio fisiológico [odds ratio (OR) 2,77, IC95% 1,19 a 6,40, p=0,017; risk ratio (RR) 1,82, IC95% 1,79 a 1,87, p=0,049)]. La IPP también se asocia a una mayor probabilidad de mejor recuperación del PQRS en el dominio emocional (p=0,013) y en la recuperación global (p=0,011). Los eventos adversos intraoperatorios fueron asimismo menos frecuentes en el grupo (IPP) (p<0,001), así como la relación neutrófilos-linfocitos en plasma (p=0,029). No hubo diferencias en los otros objetivos. Se confirma nuestra hipótesis de que una estrategia de presión de neumoperitoneo individualizada mejoraría la calidad de recuperación postoperatoria comunicada por el paciente, PQRS, en el día 1 del postoperatorio.

De este modo, la colaboración multidisciplinar con los cirujanos ha permitido demostrar que una estrategia individualizada de presión del pneumoperitoneo en cirugía laparoscópica colorrectal: es factible, permite disminuir la presión intraabdominal a la mínima (8 mmHg) en la mayoría de casos, manteniendo adecuadas condiciones quirúrgicas, presenta menos complicaciones intraoperatorias y menos inflamación, y que, integrando al paciente en la evaluación a través de los resultados por él comunicados, se asocia a una recuperación más rápida, que una estrategia estándar de presión fija.

Bloque 2: Estrategia de ventilación mecánica en cirugía laparoscópica

En el capítulo 5 se detalla el ensayo clínico prospectivo cruzado "*Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery. An open-label, nonrandomized, crossover, clinical trial" (IPPColLapSe III),* donde se incluyeron y analizaron 30 pacientes. La presión positiva al final de la espiración (positive end-expiratory pressure, PEEP) titulada fue 10, 14 y 17 cmH2O para una presión del neumoperitoneo de 8, 12, y 15 mmHg, respectivamente. Comparado con una estrategia de PEEP fija de 5 cmH_2O, la estrategia de PEEP titulada se asocia a menor *"driving pressure"* transpulmonar media a una presión intraabdominal (PIA) de 8 mmHg (7 [5 a 8] frente a 9 [7 a 11] cmH2O; p=0,010; diferencia 2 [IC95% CI 0,5 a 4 cmH2O]);

de 12 mmHg (7 [4 a 9] frente a 10 [7 a 12] cmH2O; p=0,002; diferencia 3 [1 a 5] cmH2O); y de 15 mmHg (7 [6 a 9] frente a 12 [8 a 15] cmH2O; p<0,001; diferencia de 4 [2 a 6] cmH2O). El efecto de una estrategia de PEEP titulada comparado con una estrategia de PEEP fija en la *"driving pressure"* del sistema respiratorio es comparable al efecto en la *"driving pressure"* transpulmonar, a pesar de que la *"driving pressure"* del sistema respiratorio fue mayor que la transpulmonar en todos los niveles de presión intrabdominal del neumoperitoneo. De este modo se confirma la hipótesis de que una estrategia orientada a igualar los niveles de PEEP a los niveles de presión intraabdominal del neumoperitoneo previene el aumento en la *"driving pressure"* transpulmonar y del sistema respiratorio en cirugía laparoscópica.

En el capítulo 6 se incluye el metaanálisis de los estudios *IPPColLapSe I, II y III (*capítulos 2, 3, 4 y 5) en los que se utilizó la misma metodología para la generación del neumoperitoneo y el cálculo de la compliance abdominal, recogiendo datos de la estrategia ventilatoria. Se demuestra que la presión intraabdominal del neumoperitoneo en los rangos habituales utilizados en cirugía laparoscópica tiene una relación no lineal con el volumen intraabdominal alcanzado y una relación lineal con las presiones de vía aérea. El incremento de volumen intraabdominal alcanza una meseta a 6,0 L [IC95% 5,9 a 6,2]. La variación de volumen con relación al aumento de presión intraabdominal disminuye a niveles de presión intraabdominal de 9,8 [IC95% 9,7 a 9,9] a 12,2 [12,0 a 12,3] mmHg. El ratio de transmisión abdomino-torácica fue de 0,65 [IC95% 0,62 a 0,68], de modo que 1 mmHg de PIA aumenta las presiones en vía aérea 0,88 cmH_2O. Se confirma la hipótesis de que se debería identificar esta relación y realizar la cirugía laparoscópica por debajo del umbral de presión intraabdominal en el cual la ganancia de volumen intraabdominal disminuye.

De este modo, una visión integral de la estrategia de ventilación mecánica, entendiendo el impacto de la presión del neumoperitoneo en las presiones del sistema respiratorio, permite, utilizando una estrategia individualizada de neumoperitoneo y una PEEP titulada, disminuir la *"driving pressure"*. Futuros

estudios podrán analizar si permite disminuir las complicaciones pulmonares postoperatorias.

Bloque 3: Estrategia de bloqueo neuromuscular en cirugía laparoscópica

En el capítulo 7 se incluyeron para este subanálisis 2084 pacientes sometidos a cirugía electiva colorrectal que participaron en el estudio *"Postoperative Outcomes Within an Enhanced Recovery After Surgery Protocol (POWER)"*. En el análisis multivariante no se encontraron diferencias en complicaciones moderadas-severas (174 (25,7%) frente a 124 (27,1%); p=0,607), estancia hospitalaria (10,8 ± 11,1 frente a 11,0 ± 12,6) días; p=0,683) y mortalidad (6 (0,9%) frente a 5 (1,1%); p=0,840) entre los grupos que recibieron un manejo óptimo del bloqueo neuromuscular (monitorización cuantitativa y reversión farmacológica) y los que no lo recibieron. En el análisis univariante se encontró que los pacientes revertidos con neostigmina presentaban mayor mortalidad que los revertidos con sugammadex (3 (2,7%) frente a 3 (0,5%); p=0,048). No se puede confirmar la hipótesis de que un manejo óptimo del bloqueo neuromuscular, en el contexto de un programa de recuperación intensificada se asocie a menores complicaciones postoperatorias.

En el contexto de programas recuperación intensificada en cirugía laparoscópica colorrectal en el que se evalúan paquetes de medidas es difícil establecer el peso de cada medida individual en los resultados globales. Esto podría explicar por qué no hemos podido demostrar asociación entre un manejo óptimo y una disminución de las complicaciones.

Bloque 4: Estrategia analgésica en cirugía oncológica

En el capítulo 8 se incluyeron finalmente en la revisión sistemática 13 artículos que cumplieron los criterios preestablecidos. No se realizó un metaanálisis cuantitativo dada la heterogeneidad de los estudios. La revisión indica que no hay evidencia que apoye evitar el uso de opioides perioperatorios con el objetivo de disminuir el riesgo de recidiva tumoral en cáncer colorrectal. De

este modo no se confirma la hipótesis de que los opioides perioperatorios se asocian a peores resultados oncológicos a largo plazo.

En el capítulo 9 se detalla un estudio observacional "*Mu opioid receptor 1 (MOR1) expression in colorectal cancer and disease-free survival relationship (Morocco). Five-year follow-up".* Se incluyeron 174 pacientes. La expresión de MOR1 estaba aumentada en el tumor con respecto al tejido sano adyacente, pero no se relacionó con una menor supervivencia libre de enfermedad (disease free survival-DFS) o con la supervivencia global (overall survival). De modo que, aunque hay un aumento de la expresión de receptor opioide mu tipo 1 (MOR1) en el tejido tumoral, no podemos confirmar la hipótesis ya que no se asocia a una menor supervivencia libre de enfermedad.

Aunque hay múltiples evidencias de investigación básica en las que se asocia de manera general el uso de opioides con inmunosupresión y se demuestra un aumento de la expresión de MOR 1 en el tejido tumoral, en el contexto clínico del cáncer colorrectal no es posible asociar el uso perioperatorio de fármacos opioides con una menor supervivencia libre de enfermedad. De manera que no hay evidencia que sustente la retirada de los fármacos opioides como pilar fundamental en la analgesia multimodal de los pacientes oncológicos con cáncer colorrectal sometidos a un procedimiento quirúrgico.

Capítulo 11

Conclusiones

En medicina perioperatoria en el paciente oncológico:

1. La colaboración multidisciplinar a través de una estrategia individualizada de presión del neumoperitoneo en cirugía laparoscópica colorrectal permite disminuir la presión intraabdominal manteniendo adecuadas condiciones quirúrgicas.
2. Una estrategia individualizada de presión del neumoperitoneo en cirugía laparoscópica colorrectal se asocia a una recuperación más rápida reportada por el paciente.
3. Una estrategia individualizada de presión del neumoperitoneo permite disminuir la *"driving pressure"* del sistema respiratorio.
4. Una estrategia orientada a igualar los niveles de PEEP a los niveles de presión intraabdominal del neumoperitoneo previene el aumento en la *"driving pressure"* transpulmonar y del sistema respiratorio en cirugía laparoscópica.
5. La presión intraabdominal del neumoperitoneo en los rangos habituales utilizados en cirugía laparoscópica tiene una relación no lineal con el volumen intraabdominal alcanzado y una relación lineal con las presiones de vía aérea.
6. Un manejo óptimo del bloqueo neuromuscular (monitorización cuantitativa y reversión farmacológica) no se asocia a menores complicaciones postoperatorias en programas de recuperación intensificada en cirugía colorrectal.
7. El uso de fármacos opioides en la analgesia multimodal perioperatoria de los pacientes oncológicos con cáncer colorrectal no se relaciona con una disminución de la supervivencia libre de enfermedad.

Capítulo 12

Actividad científica vinculada

Líneas de investigación futuras

La elaboración de esta tesis ha contribuido de manera fundamental al desarrollo de esta nueva línea de investigación y a la consolidación del Grupo de Investigación acreditado de Medicina Perioperatoria del Instituto de Investigación Sanitaria la Fe. Podemos destacar como actividad científica vinculada a la realización de la tesis la siguiente:

- **Publicaciones como investigador colaborador.**

1. Garutti I, Errando CL, Mazzinari G, Bellón JM, **Díaz-Cambronero O**, Ferrando C; iPROVE network. Spontaneous recovery of neuromuscular blockade is an independent risk factor for postoperative pulmonary complications after abdominal surgery: A secondary analysis. **Eur J Anaesthesiol. 2020** Mar;37(3):203-211. doi: 10.1097/EJA.0000000000001128. PMID: 32028288.

2. Ferrando C, Suárez-Sipmann F, Librero J, Pozo N, Soro M, Unzueta C, Brunelli A, Peiró S, Llombart A, Balust J, Aldecoa C, **Díaz-Cambronero O**, Franco T, Redondo FJ, Garutti I, García JI, Ibáñez M, Granell M, Rodríguez A, Gallego L, de la Matta M, Marcos JM, García J, Mazzinari G, Tusman G, Villar J, Belda J; Individualized PeRioperative Openlung VEntilation (iPROVE) Network. A noninvasive postoperative clinical score to identify patients at risk for postoperative pulmonary complications: the Air-Test Score. **Minerva Anestesiol 2020** Apr;86(4):404-415. doi: 10.23736/S0375-9393.19.13932-6. Epub 2019 Dec 4. PMID: 31808662.

3. Sanduende-Otero Y, Villalón-Coca J, Romero-García E, **Díaz-Cambronero Ó,** Barach P, Arnal-Velasco D. Patterns in medication incidents: A 10-yr experience of a cross-national anaesthesia incident reporting system. **Br J Anaesth. 2020** Feb;124(2):197-205. doi: 10.1016/j.bja.2019.10.013. Epub 2019 Nov 25. PMID: 31780140.

4. Ferrando C, Aldecoa C, Unzueta C, Belda FJ, Librero J, Tusman G, Suárez- Sipmann F, Peiró S, Pozo N, Brunelli A, Garutti I, Gallego C,

Rodríguez A, García JI, **Díaz-Cambronero O**, Balust J, Redondo FJ, de la Matta M, Gallego- Ligorit L, Hernández J, Martínez P, Pérez A, Leal S, Alday E, Monedero P, González R, Mazzirani G, Aguilar G, López-Baamonde M, Felipe M, Mugarra A, Torrente J, Valencia L, Varón V, Sánchez S, Rodríguez B, Martín A, India I, Azparren G, Molina R, Villar J, Soro M; iPROVE-O2 Network. Effects of oxygen on post-surgical infections during an individualised perioperative open-lung ventilatory strategy: a randomised controlled trial. **Br J Anaesth. 2020,**Jan;124(1):110-120. doi: 10.1016/j.bja.2019.10.009. Epub 2019 Nov 22. PMID: 31767144.

5. Albers KI, **Diaz-Cambronero O**, Keijzer C, Snoeck MMJ, Warlé MC, Fuchs-Buder T. Revisiting the classification of neuromuscular blockade. Aligning clinical practice and research. **Anesth Analg. 2019** Nov;129(5):e176-e178. doi: 10.1213/ANE.0000000000004407. PMID: 31498186.

6. Mazzinari G, Errando CL, **Díaz-Cambronero O**, Martin-Flores M. Influence of tetanic stimulation on the staircase phenomenon and the acceleromyographic time- course of neuromuscular block: a randomized controlled trial. **J Clin Monit Comput. 2019** Apr;33(2):325-332. doi: 10.1007/s10877-018-0157-9. Epub 2018 May 18. PMID: 29777332.

7. Funcke S, Saugel B, Koch C, Schulte D, Zajonz T, Sander M, Gratarola A, Ball L, Pelosi P, Spadaro S, Ragazzi R, Volta CA, Mencke T, Zitzmann A, Neukirch B, Azparren G, Giné M, Moral V, Pinnschmidt HO, **Díaz-Cambronero O**, Estelles MJA, Velez ME, Montañes MV, Belda J, Soro M, Puig J, Reuter DA, Haas SA. Individualized, perioperative, hemodynamic goal-directed therapy in major abdominal surgery (iPEGASUS trial): study protocol for a randomized controlled trial. **Trials. 2018** May 9;19(1):273. doi: 10.1186/s13063-018-2620-9. PMID: 29743101; PMCID: PMC5944092.

8. Ferrando C, Soro M, Unzueta C, Suarez-Sipmann F, Canet J, Librero J, Pozo N,Peiró S, Llombart A, León I, India I, Aldecoa C, **Díaz-Cambronero O**, Pestaña D, Redondo FJ, Garutti I, Balust J, García JI, Ibáñez M, Granell M, Rodríguez A, Gallego L, de la Matta M, Gonzalez R, Brunelli A, García J, Rovira L, Barrios F, Torres V, Hernández S, Gracia E, Giné M, García M, García N, Miguel L, SánchezS, Piñeiro P, Pujol R, García-Del-Valle S, Valdivia J, Hernández MJ, Padrón O, Colás A, Puig J, Azparren G, Tusman G, Villar J, Belda J; Individualized PeRioperative Open-lung VEntilation (iPROVE) Network. Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. **Lancet Respir Med. 2018** Mar;6(3):193-203. doi: 10.1016/S2213-2600(18)30024-9. Epub 2018 Jan 19. PMID: 29371130.

9. Ferrando C, Soro M, Unzueta C, Canet J, Tusman G, Suarez-Sipmann F, LibreroJ, Peiró S, Pozo N, Delgado C, Ibáñez M, Aldecoa C, Garutti I, Pestaña D,Rodríguez A, García Del Valle S, **Diaz-Cambronero O**, Balust J, Redondo FJ, De La Matta M, Gallego L, Granell M, Martínez P, Pérez A, Leal S, Alday K, García P,Monedero P, Gonzalez R, Mazzinari G, Aguilar G, Villar J, Belda FJ; iPROVE-O2 Network Group. Rationale and study design for an individualised perioperative open-lung ventilatory strategy with a high versus conventional inspiratory oxygen fraction (iPROVE-O2) and its effects on surgical site infection: study protocol for a randomised controlled trial. **BMJ Open. 2017** Jul 31;7(7):e016765. doi: 10.1136/bmjopen-2017-016765. PMID: 28760799; PMCID: PMC5642673.

10. Errando CL, Mazzinari G, **Díaz-Cambronero O**, Garutti I; Grupo español de estudio del bloqueo neuromuscular. Residual neuromuscular blockade in the postanesthesia care unit. A secondary analysis of the ReCuSS. Observational cross-sectional study of a multicenter cohort**. Rev Esp Anestesiol Reanim. 2017** Aug-Sep;64(7):419-422. English,

Spanish. doi: 10.1016/j.redar.2017.01.005. Epub 2017 Mar 22. PMID: 28341080.

11. Errando CL, Garutti I, Mazzinari G, **Díaz-Cambronero Ó**, Bebawy JF; Grupo Español De Estudio Del Bloqueo Neuromuscular. Residual neuromuscular blockade in the postanesthesia care unit: observational cross-sectional study of a multicenter cohort. **Minerva Anestesiol. 2016** Dec;82(12):1267-1277. Epub 2016 May 27. PMID: 27232277

Proyectos de investigación coordinados como investigador principal:

Ref: 2019/0033, P.I. Exp. 2016-002162-30

Título del proyecto: Estudio prospectivo, aleatorizado, dobleciego, dobleciego, internacional y multicéntrico sobre la seguridad y la eficacia de la solución 6% Hydroxyethyl starch (HES) comparada con una solución electrolítica en pacientes sometidos a cirugía abdominal.
Entidad financiadora: Propio Grupo

Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 26/04/2019 - Fecha Fin: 25/04/2023

Ref: 2018/0628, P.I. Exp. 2018_0628_PP_DIAZ

Título del proyecto: Evaluación de una estrategia de individualización de la presión de pneumoperitoneo mediante un modelo animal porcino Estudio IPP (presión de pneumoperitoneo individualizada) .Evaluation of an Individualization Pneumoperitoneum Pressure strategy in a porcine model. IPP trial. Entidad financiadora: Propio Grupo
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 28/01/2019 - Fecha Fin: 27/01/2024

Ref: 2020-602-1, P.I. Exp. 2020-602-1_PP_CAMBRONERO

Título del proyecto: Registro español de polimorfismos de RYR1 y CACNA1S y su relación con susceptibilidad a Hipertermia Maligna. Registro RYCA.
Entidad financiadora: Propio Grupo
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 29/10/2018 - Fecha Fin: 28/10/2023

Código Protocolo: EURO-RELAX

Título: IMPACTO DE UNA ESTRATEGIA DE BLOQUEO NEUROMUSCULAR PROFUNDO VERSUS BLOQUEO ESTÁNDAR EN LA SEGURIDAD INTRAOPERATORIA EN CIRUGÍA LAPAROSCÓPICA: ESTUDIO INTERNACIONAL MULTICÉNTRICO EURO RELAX.
Inv. Principal/Servicio: Óscar Díaz Cambronero

Promotor: INSTITUTO DE INVESTIGACION SANITARIA LA FE

Fecha de inicio: 03/03/2020

Código Protocolo: HC-G-H-1505

Título: PRAGMATIC, CONTROLLED, INTERNATIONAL STUDY CONDUCTED IN SEVERAL CENTRES ON THE SAFETY AND THERAPEUTIC EFFECT OF A HYDROXYLETHYL-STARCH (HES) SOLUTION VERSUS AN ELECTROLYTE SOLUTION IN TRAUMA PATIENTS.
Inv. Principal/Servicio: Óscar Díaz Cambronero

Promotor: B. BRAUN MELSUNGEN AG Fecha de inicio: 17/10/2018

Ref: 2020-125-1, P.I. Exp. 2020/VSC/PEA/0075

Título del proyecto: Sistema de actuación mecánica de un respirador manual (AMBU) para su utilización en pacientes con COVID-19. Ensayo preclínico en porcino
Entidad financiadora: Propio Grupo
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 07/04/2020 - Fecha Fin: 06/04/2025

Ref: 2020-086-1, P.I. Exp. 2020-086-1_PP_DIAZ

Título del proyecto: ESTIMACIÓN DE LA DIFERENCIA ENTRE LA TEMPERATURA DEL MICROAMBIENTE PERITONEAL Y LA TEMPERATURA CORPORAL CENTRAL DURANTE LA CIRUGÍA LAPAROSCÓPICA. ESTUDIO PROSPECTIVO OBSERVACIONAL
Entidad financiadora: Propio Grupo

Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 29/01/2020 - Fecha Fin: 28/01/2025

Ref: 2019-226-1, P.I. Exp. 2019-226-1_PP_CALATAYUD-DIAZ

Título del proyecto: Evaluación de la capacidad física en el perioperatorio de pacientes ancianos sometidos a cirugía
laparoscópica colorrectal. Estudio Atlas.
Entidad financiadora: Propio Grupo

Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 20/11/2019 - Fecha Fin: 19/11/2024

Ref: 2019/0262, P.I. Exp. 2019_0262_AVI_Nominativa_DIAZ

Título del proyecto: Nominativa Acción 2019-01. TROCAR: Prueba de concepto trocar multisensor canal unico.
Entidad financiadora:
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 07/05/2019 - Fecha Fin: 31/12/2019

Ref: 2018/0593, P.I. Exp. 2018_0593_PP_DIAZ

Título del proyecto: Registro español de polimorfismos de RYR1 y CACNA1S y su relación con susceptibilidad a Hipertermia Maligna. Registro RYCA.

Entidad financiadora: EUROPEAN MALIGNANT HYPERTHERMIA GROUP
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 05/12/2018 - Fecha Fin: 04/12/2023

Cantidad concedida: 2.500,00 €

Ref: 2018/0502, P.I. Exp. 2018_0502_PP_DIAZ

Título del proyecto: (PORCzero). Bloqueo neuromuscular residual postoperatorio cero.
Entidad financiadora:
Investigador principal: DÍAZ CAMBRONERO, OSCAR
Fecha Inicio: 01/11/2018 - Fecha Fin: 30/11/2020

Ref: 2017/0196, P.I. Exp. 2017_0196_FOR_DIAZ

Título del proyecto: Controversias en bloqueo neuromuscular perioperatorio. Entidad financiadora: Propio Grupo
Investigador principal: DÍAZ CAMBRONERO, OSCAR
Fecha Inicio: 22/03/2017 - Fecha Fin: 31/03/2019

Cantidad concedida: 4.565,09 €

Ref: 2016/0458, P.I. Exp. 2016_0458_CRC_COLAB_UPV-LAFE_DIAZ

Título del proyecto: ACCION PREPARATORIA (C): CAL. CALCULATION OF ABDOMINAL COMPLIANCE IN LAPAROSCOPY
Entidad financiadora: IIS La Fe
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 20/10/2016 - Fecha Fin: 30/09/2017

Ref: 2015/0881, P.I. Exp. 2015_0881_CPC_INV_CLINICA_DIAZ

Título del proyecto: PRESIÓN DE PNEUMOPERITONEO INDIVIDUALIZADA EN CIRUGÍA LAPAROSCÓPICA COLORECTAL.
Entidad financiadora: FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA INSTITUTO DE INVESTIGACIÓN SANITARIA LA FE

Investigador principal: DÍAZ CAMBRONERO, OSCAR Fecha Inicio: 18/09/2015 - Fecha Fin: 17/09/2019

Ref: 2015/0659, P.I. Exp. 2015_0659_CespEC_PI_MERCK_DIAZ

Título del proyecto: INDIVIDUALIZED PNEUMOPERITONEUM PRESSURE IN COLORECTAL LAPAROSCOPIC SURGERY
Entidad financiadora: MERCK SHARP & DOHME DE ESPAÑA S.A.
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 18/02/2016 - Fecha Fin: 17/02/2021

Cantidad concedida: 40.075,20 €

Ref: 2015/0094, P.I. Exp. 2015_0094_PP_DIAZ

Título del proyecto: PRESIÓN DE PNEUMOPERITONEO INDIVIDUALIZADA EN CIRUGÍA LAPAROSCÓPICA COLORRECTAL
Entidad financiadora: Propio Grupo
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 29/05/2015 - Fecha Fin: 28/05/2020

Código Protocolo: CEO-BNM-2014-01

Título: ESTUDIO TRANSVERSAL DE LA INCIDENCIA DE BLOQUEO NEUROMUSCULAR RESIDUAL (BNMR) EN PACIENTES ADULTOS EN LOS HOSPITALES ESPAÑOLES.
Inv. Principal/Servicio: Óscar Díaz Cambronero
Promotor: CARLOS LUIS ERRANDO OYONARTE (HOSPITAL GENERAL UNIVERSITARIO DE VALENCIA)

Fecha de inicio: 15/05/2014 Fecha de fin:15/06/2014

Código Protocolo: IPROVE

Título: REDUCCIÓN DE LAS COMPLICACIONES POSTOPERATORIAS Y DE LA ESTANCIA HOSPITALARIA CON UNA ESTRATEGIA PERIOPERATORIA INDIVIDUALIZADA DE VENTILACIÓN DE PROTECCIÓN PULMONAR. ESTUDIO COMPARATIVO, PROSPECTIVO, MULTICÉNTRICO, ALEATORIZADO Y CONTROLADO.

Inv. Principal/Servicio: Óscar Díaz Cambronero - Lucas Rovira Soriano
Promotor: FUNDACIÓN PARA LA INVESTIGACIÓN DEL HOSPITAL CLÍNICO DE LA COMUNIDAD VALENCIANA (INCLIVA)
Fecha de inicio: 07/05/2015

Código Protocolo: IPPCOLLAPSE-II

Título: PRESIÓN INDIVIDUALIZADA DE INSUFLACIÓN DEL PNEUMOPERITONEO EN CIRUGÍA LAPAROSCÓPICA COLORECTAL FRENTE A TERAPIA ESTÁNDAR.
Inv. Principal/Servicio: Óscar Díaz Cambronero
Promotor: INSTITUTO DE INVESTIGACION SANITARIA LA FE

Fecha de inicio: 04/08/2016 Fecha de fin:19/11/2018

Código Protocolo: IPROVE-O2

Título: REDUCCIÓN DE LA INFECCIÓN DE HERIDA QUIRÚRGICA CON UNA ESTRATEGIA PERIOPERATORIA INDIVIDUALIZADA DE VENTILACIÓN DE PROTECCIÓN PULMONAR CON FRACCIÓN INSPIRATORIA DE OXÍGENO ELEVADA. ESTUDIO COMPARATIVO, PROSPECTIVO, MULTICÉNTRICO, ALEATORIZADO Y CONTROLADO.

Inv. Principal/Servicio: Guido Mazzinari - Óscar Díaz Cambronero
Promotor: FRANCISCO JAVIER BELDA NACHER. HOSPITAL CLÍNICO

UNIVERSITARIO DE VALENCIA.
Fecha de inicio: 31/05/2017

Código Protocolo: IPEGASUS

Título: INDIVIDUALIZED PERIOPERATIVE HEMODYNAMIC GOAL-DIRECTED THERAPY IN MAJOR ABDOMINAL SURGERY (IPEGASUS-TRIAL).
Inv. Principal/Servicio: Óscar Díaz Cambronero
Promotor: UNIVERSITY MEDICAL CENTER HAMBURG-EPPENDORF

Fecha de inicio: 01/11/2017

Código Protocolo: CEO-SUG-2016-01

Título: BLOQUEO NEUROMUSCULAR RESIDUAL POSTOPERATORIO CERO (PORCZERO). Inv. Principal/Servicio: Guido Mazzinari - Óscar Díaz Cambronero
Promotor: INSTITUTO DE INVESTIGACION SANITARIA LA FE
Fecha de inicio: 08/05/2018

Código Protocolo: HC-G-H-1504

Título: ESTUDIO PROSPECTIVO, ALEATORIZADO, DOBLE-CIEGO, INTERNACIONAL Y MULTICÉNTRICO SOBRE LA SEGURIDAD Y LA EFICACIA DE LA SOLUCIÓN 6% HIDROXIETIL ALMIDÓN (HYDROXYETHYL STARCH) (HES) COMPARADA CON UNA SOLUCIÓN ELECTROLÍTICA EN PACIENTES SOMETIDOS A CIRUGÍA ABDMINAL: ESTUDIO PHOENICS.

Inv. Principal/Servicio: Óscar Díaz Cambronero Promotor: B. BRAUN MELSUNGEN AG
Fecha de inicio: 04/07/2018

Proyectos de investigación como investigador colaborador:

Ref: 2019/0049, P.I. Exp. INNCONN00-19-006

Título del proyecto: Unidad Científica de transferencia del conocimiento hacia las empresas del IIS La Fe (UCIE IIS La Fe) - AVI2019
Entidad financiadora: AGENCIA VALENCIANA DE LA INNOVACION (AVI)
Investigador principal: SÁNCHEZ SALVO, SILVIA

Fecha Inicio: 01/01/2019 - Fecha Fin: 31/12/2019

Cantidad concedida: 250.000,00 €

Ref: 2020-652-1, P.I. Exp. PT20/00092

Título del proyecto: Pataforma ISCIII de soporte para investigación clínica. Entidad financiadora: INSTITUTO DE SALUD CARLOS III (ISCIII)

Investigador principal: VENTO TORRES, MÁXIMO
Fecha Inicio: 01/01/2021 - Fecha Fin: 31/12/2023

Cantidad concedida: 297.000,00 €

Ref: 2018/0550, P.I. Exp. 2018_0550_FOR_ARGENTE

Título del proyecto: Puesta al día en Anestesia, Reanimación y Terapéutica del dolor pediátrica y del adulto.
Entidad financiadora: MARCOM MEDICA, SL
Investigador principal: ARGENTE NAVARRO, MARÍA PILAR

Fecha Inicio: 22/10/2018 - Fecha Fin: 21/10/2023

Cantidad concedida: 2.000,00 €

Ref: 2016/0602, P.I. Exp. 2016_0602_PP_MAZZINARI

Título del proyecto: MODIFICACIONES DE LA PRESIÓN DE DISTENSIÓN TRANSPULMONAR CON LA PRESIÓN INTRAABDOMINAL A DIFERENTES NIVELES DE PEEP EN CIRUGÍA LAPAROSCÓPICA.
Entidad financiadora: Propio Grupo

Investigador principal: MAZZINARI, GUIDO

Fecha Inicio: 17/01/2017 - Fecha Fin: 17/01/2022

Ref: 2015/0356, P.I. Exp. 2015_0356_CPC_INV_CLINICA_V_CONVOCATORIA_AYAS

Título del proyecto: APLICACIÓN DE VENTILACIÓN BIPULMONAR CON TUBO SIMPLE Y NEUMOTÓRAX ARTIFICIAL PARA LA REALIZACIÓN DE

ESOFAGUECTOMÍAS TORACOSCÓPICAS EN DECÚBITO PRONO.
Entidad financiadora: IIS LAFE

Investigador principal: Begoña Ayas Montero

Fecha Inicio: 15/06/2015 - Fecha Fin: 14/06/2017

Ref: 2015/0312, P.I. Exp. 2015_0312_CPC_INV_CLINICA_GARCIA

Título del proyecto: DIFUSION DEL ANESTESICO LOCAL EN EL ESPACIO PARAVERTEBRAL TORACICO TRAS BLOQUEO PARAVERTEBRAL: ESTUDIO CON TOMOGRAFIA COMPUTERIZADA CONE BEAM
Entidad financiadora: FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA INSTITUTO DE INVESTIGACIÓN SANITARIA LA FE

Investigador principal: Nuria García Gregorio

Fecha Inicio: 15/06/2015 - Fecha Fin: 14/06/2017

Ref: 2015/0310, P.I. Exp. 2015_0310_CPC_INV_CLINICA_VILA

Título del proyecto: EVALUACION DE LOS NIVELES PLASMATICOS DE HEPCIDINA EN PACIENTES CON ANEMIA FERROPENICA Y CANCER COLORRECTAL
Entidad financiadora: FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA INSTITUTO DE INVESTIGACIÓN SANITARIA LA FE

Investigador principal: Maria Vila Montañes

Fecha Inicio: 15/06/2015 - Fecha Fin: 14/06/2017

Ref: 2015/0309, P.I. Exp. 2015_0309_CPC_INV_CLINICA_MAZZINARI

Título del proyecto: VALORACION DE LA EFICACIA ANALGESICA DEL BLOQUEO SERRATO FRENTE A ANALGESIA CONVENCIONAL EN CIRUGIA DE MAMA
Entidad financiadora: FUNDACION PARA LA INVESTIGACION DEL HOSPITAL UNIVERSITARIO LA FE DE LA COMUNIDAD VALENCIANA INSTITUTO DE INVESTIGACIÓN SANITARIA LA FE

Investigador principal: Guido Mazzinari
Fecha Inicio: 15/06/2015 - Fecha Fin: 14/06/2017

Cantidad concedida: 3.865,62 €

Ref: 2015/0122, P.I. Exp. 2015_0122_PP_AYAS

Título del proyecto: APLICACIÓN DE VENTILACIÓN BIPULMONAR CON TUBO SIMPLE Y NEUMOTÓRAX ARTIFICIAL PARA LA REALIZACIÓN DE ESOFAGUECTOMÍAS TORACOSCÓPICAS EN DECÚBITO PRONO
Entidad financiadora: Propio Grupo

Investigador principal: AYAS MONTERO, BEGOÑA

Fecha Inicio: 09/06/2015 - Fecha Fin: 09/06/2020

Código Protocolo: INC-ACO-2013-01

Título: ESTUDIO OBSERVACIONAL PROSPECTIVO DEL MANEJO PERIOPERATORIO DE LOS ANTICOAGULANTES ORALES DIRECTOS.
Inv. Principal/Servicio: Ma Salomé Matoses Jaén - María Consuelo García Cebrián
Promotor: FUNDACIÓN PARA LA INVESTIGACIÓN DEL HOSPITAL CLÍNICO DE LA COMUNIDAD VALENCIANA (INCLIVA)

Fecha de inicio: 02/05/2014 Fecha de fin:30/01/2018

Código Protocolo: MAR-HIE-2015-01

Título: EVALUACIÓN DE LOS NIVELES PLASMÁTICOS DE HEPCIDINA EN PACIENTES CON ANEMIA FERROPÉNICA Y CÁNCER COLORECTAL.
Inv. Principal/Servicio: María Vila Montañes
Promotor: MARIA VILA MONTAÑÉS. SERVICIO ANESTESIA Y REANIMACIÓN. HOSPITAL LA FE DE VALENCIA.

Fecha de inicio: 11/06/2015 Fecha de fin:11/10/2015

Código Protocolo: NUR-ROP-2015-01

Título: DIFUSIÓN DEL ANESTÉSICO LOCAL EN EL ESPACIO PARAVERTEBRAL TORÁCICO TRAS BLOQUEO PARAVERTEBRAL: ESTUDIO CON TOMOGRAFÍA COMPUTERIZADA CONE BEAM.
Inv. Principal/Servicio: Nuria Garcia Gregorio

Promotor: NURIA GARCÍA GREGORIO. SERVICIO DE ANESTESIOLOGÍA, REANIMACIÓN Y TERAPÉUTICA DEL DOLOR, HUP LA FE
Fecha de inicio: 19/05/2015
Fecha de fin:01/12/2015

- **Innovación / Financiación competitiva**

Ref: 2018/0616, P.I. Exp. INNVAL10/18/056

Título del proyecto: Trocar multisensor para cirugía laparoscópica con presión de pneumoperitoneo individualizada
Entidad financiadora: AGENCIA VALENCIANA DE LA INNOVACION (AVI)
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 01/08/2018 - Fecha Fin: 31/12/2018

Cantidad concedida: 55.000,00 €

Ref: 2020-203-1, P.I. Exp. DTS20/00125

Título del proyecto: Sistema Endoscópico Inteligente. Sistema integral para cirugía endoscópica individualizada de bajo impacto
Entidad financiadora: INSTITUTO DE SALUD CARLOS III (ISCIII)
Investigador principal: DÍAZ CAMBRONERO, OSCAR

Fecha Inicio: 01/01/2021 - Fecha Fin: 31/12/2022

Cantidad concedida: 145.068,00 €

- **Patentes**

PCT NºPCT/EP2020/075580. Título: SISTEMA MODULAR PARA LA MONITORIZACIÓN Y CONTROL DE LA HOMEOSTASIS EN CAVIDADES Y MÉTODO DE GENERACIÓN DE VOLUMEN DE FLUIDO EN UNA CAVIDAD. Fecha de prioridad: 12 Septiembre 2019

De modo que podemos decir que la línea de investigación de Medicina Perioperatoria no muere con esta tesis, sino que contagia de energía a todo el que participa, y expande el concepto de la Anestesiología y Reanimación como eje vertebrador de la asistencia integral al paciente quirúrgico a través de la Medicina Perioperatoria.

Anexo I

Información de los autores.

Filiación, autoría y conflicto de intereses.

La publicación de la tesis "*Medicina Perioperatoria individualizada en cirugía oncológica* "como compendio de publicaciones ha sido posible gracias a la contribución de numerosos autores. A continuación, se adjunta información sobre la filiación, contribución a cada uno de los artículos y conflicto de intereses de cada uno de ellos, tal y como aparece en las publicaciones.

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Capítulo 2.

A multifaceted individualized pneumoperitoneum strategy for laparoscopic colorectal surgery: a multicenter observational feasibility study.

Díaz-Cambronero O, *Flor Lorente B, Mazzinari G, Vila Montañes M, García Gregorio N, Robles Hernandez D, Olmedilla Arnal LE, Argente Navarro MP, Schultz MJ, Errando CL; IPPColLapSe study group et al. Surg Endosc. 2019 Jan;33(1):252-260.*

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Author contributions: *O.D.C: Study design, acquisition, analysis and interpretation of data, drafting and revision of paper. B.F.L: Study design, acquisition, analysis and interpretation of data, drafting and revision of paper. G.M: Study design, analysis and interpretation of data, drafting and revision of paper. M.V.M: Study design, acquisi- tion and interpretation of data, and revision of paper. N.G.G: Study design, acquisition and interpretation of data, and revision of paper. D.R.H: Study design, acquisition and interpretation of data, and revi- sion of paper. L.E.O.A: Study design, acquisition and interpretation of data, and revision of paper. M.P.A.N: Study design, interpretation of data, and revision of paper. M.J.S: Analysis and interpretation of data, drafting and revision of paper. C.L.E.O: Study design, analysis and interpretation of data, drafting and revision of paper.*

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Compliance with Ethical Standards: *Oscar Diaz-Cambronero (oscardiazcambronero@gmail. com) has received speakers' fees and honoraria from Merck Sharp & Dohme for lectures (approximately amount: 8.000 euros) and also received a research grant from Merck Sharp & Dohme of 80.000 euros not related to this study. Blas Flor Lorente (blasflor@hotmail.com) has received speakers' fees and honoraria from Merck Sharp & Dohme for lectures (approximately amount: 3.000 euros). Guido Mazzinari*

(gmazzinari@gmail.com) declares no competing interests. Maria Vila Montañes (mvilamontanes@yahoo.es) declares no competing interests. Nuria Garcia Gregorio (nuriagcia6@gmail.com) declares no competing interests. Daniel Robles Hernandez (drobher@gmail.com) declares no competing interests. Luis Enrique Olmedilla Arnal (lolmedilla@gmail. com) declares no competing interests. Maria Pilar Argente Navarro (argente_marnav@gva.es) has received speakers' fees and honoraria for lectures from Merck Sharp & Dohme (approximately amount: 1.000 euros). Marcus J. Schultz (marcus.j.schultz@gmail.com) declares no competing interests. Carlos L. Errando (errando013@gmail.com) has received speakers' fees and honoraria for lectures from Merck Sharp & Dohme (approximately amount: 1.000 euros).

Capítulo 3.

An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study.

O. Diaz-Cambronero*, G. Mazzinari, C. L. Errando, M. J. Schultz, B. Flor Lorente, N. García-Gregorio, M. Vila Montañés, Daniel Robles-Hernández, L. E. Olmedilla Arnal, A. Martín-De-Pablos, A. Marqués Marí, M. P. Argente Navarro and for the IPPCollapse-II study group. doi: 10.1007/s00464-018-6305-y. Epub 2018 Jun 27. PMID: 29951750*

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Correction to: An individualised versus a conventional pneumoperitoneum pressure strategy during colorectal laparoscopic surgery: rationale and study protocol for a multicentre randomised clinical study.

Díaz-Cambronero O, *Mazzinari G, Errando CL, Schultz MJ, Lorente BF, García-Gregorio N, Montañés MV, Robles-Hernández D, Arnal LEO, Martín-De-Pablos A, Marí AM, Navarro MPA*

et al Trials. 2020 Jan 13;21(1):70.

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Author contributions: *Oscar Diaz Cambronero, Guido Mazzinari, Carlos Luis Errando and Marcus Josepus Schultz designed the study, are on the Steering Committee and drafted and revised the manuscript. Blas Flor Lorente, Nuria García-Gregorio, Maria Vila Montañés, Daniel Robles-Hernández, Luis Olmedilla Arnal, Angel Martín-De-Pablos, Anabel Marqués Marí, Maria Pilar Argente Navarro designed the study and drafted and revised the manuscript; All authors read and approved the final manuscript.*

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La Fe, Valencia, Spain, is the sponsor of this study. The Ministry of Economy and Competitiveness, the Carlos III Health Institute and the National Investigation/ Development/Innovation Plan fund the platform for the Clinical Research and Clinical Trials Units of the Health Research Institute of the Hospital Universitari i Politècnic La Fe (PT17/0017/0035). The Spanish Clinical Research Network provides clinical trial data monitoring and oversees pharmacovigilance.

Compliance with Ethical Standards: *Oscar Diaz-Cambronero received a grant from the Merck Investigator Studies Program Review Committee (MISP-RC), Merck Sharp & Dohme, protocol code #53607 with $109,672 and speakers' fees and honoraria from Merck Sharp & Dohme for lectures (€8.000); Carlos L. Errando received speakers' fees and honoraria for lectures from Merck Sharp & Dohme (€1.000); Blas Flor Lorente received speakers' fees and honoraria from Merck Sharp & Dohme for lectures (€3.000); Maria Pilar Argente Navarro received speakers' fees and honoraria for lectures from Merck Sharp & Dohme (€1.000); Guido Mazzinari, Nuria Garcia Gregorio, Maria Vila Montañes, Daniel Robles Hernandez, Luis Enrique Olmedilla Arnal, Angel Martín de Pablos, Anabel Marques Marí and Marcus J. Schultz declare that they have no competing interests.*

Capítulo 4.

Effect of an Individualized vs Standard Pneumoperitoneum Pressure Strategy on Postoperative Recovery – a randomized clinical trial in laparoscopic colorectal surgery.

Diaz-Cambronero,O, *Mazzinari G, Flor Lorente B,* Robles-Hernández D, Olmedilla Arnal LE, Martín-DePablos A, Schultz MJ, Errando CL, Argente Navarro MP, for the IPPCollapse-II study group***. Br J Surg. 2020** *Nov;107(12):1605-1614.*

doi: 10.1002/bjs.11736. Epub 2020 Jun 7. PMID: 32506481

Q1 IF 5.02

Author response to: Comment on: Effect of an individualized versus standard pneumoperitoneum pressure strategy on postoperative recovery: a randomized clinical trial in laparoscopic colorectal surgery.

Díaz-Cambronero O. Br J Surg. 2020 Nov;107(12): e630-e631.

doi: 10.1002/bjs.11932. Epub 2020 Sep 21. PMID: 32964433

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Compliance with Ethical Standards: *O.D.-C. has received speaker fees for lectures and medical advice from Merck Sharp & Dohme. Disclosure: The authors declare no other conflict of interest.*

Capítulo 5.

Intraabdominal Pressure Targeted Positive End-expiratory Pressure during Laparoscopic Surgery: An Open-label, Nonrandomized, Crossover, Clinical Trial.

Mazzinari G, **Diaz-Cambronero O**, *Alonso-Iñigo JM, Garcia-Gregorio N, Ayas-Montero B, Ibañez JL, Serpa Neto A, Ball L, Gama de Abreu M, Pelosi P, Maupoey J, Argente Navarro MP, Schultz MJ.* ***Anesthesiology. 2020*** *Apr;132(4):667-677.*

doi: 10.1097/ALN.0000000000003146. PMID: 32011334

Q1 IF 5.06

Author contributions: *Guido Mazzinari, Oscar Diaz-Cambronero, Jose Miguel Alonso-Iñigo and Marcus J Schultz helped plan, design, and conduct the study; collect, interpret, and analyze the data; and write and revise the manuscript. Nuria Garcia-Gregorio, Begoña Ayas-Montero, Jose Luis Ibañez, Javier Maupoey, Maria Pilar Argente Navarro helped conduct the study, interpret the data, and revise the manuscript. Ary Serpa Neto, Lorenzo Ball, Marcelo Gama de Abreu, Paolo Pelosi helped interpret the data, and revise the manuscript.*

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Compliance with Ethical Standards: *Oscar Diaz-Cambronero received payment for educational talks and scientific conferences from Merck Sharp & Dohme, Inc. (Kenilworth, New Jersey) and received a grant from Merck Investigator Studies Program, but reports no conflict of interests related to this work. Ary Serpa Neto reports a past financial relationship with Dräger (Lübeck, Germany). Marcelo Gama de Abreu reports past financial relationships with GE Healthcare (Chicago, Illinois), Ambu (Copenhagen, Denmark), Dräger Medical, and GlaxoSmithKline (Brentford, United Kingdom). Jose Miguel Alonso-Iñigo received payment for educational talks and scientific conferences from Vygon (Lansdale, Pennsylvania), but reports no conflict of interests related to the current work. The other authors declare no competing interests.*

Capítulo 6.

Modeling intra-abdominal volume and respiratory driving pressure during pneumoperitoneum insufflation - a patient-level data meta-analysis.

Mazzinari G, ***Diaz-Cambronero O,*** *Serpa Neto A, Cañada Martinez A, Rovira L, Argente Navarro MP, Malbrain MLNG, Pelosi P, Gama de Abreu M, Hollmann MW, Schultz MJ, Study Investigators IPPCOLLAPSE.* ***J Appl Physiol*** *(1985).* ***2020 Dec 24****. doi: 10.1152/japplphysiol.00814.2020. Online ahead of print. PMID: 33357006*

Q1 IF 2.95

Author contributions: *Study concept and design: GM, ODC, LR, MJS. Acquisition of data: GM, ODC, ACM. Analysis: GM, ODC, ASN, LR, MPAN, MGdA, PP, MJS. Interpretation of data: GM, ODC, LR, ASN, MJS. Drafting the manuscript: GM, MLNGM, PP, MWH, MJS. Critical revision for important intellectual content: GM, MGdA, MPAN, MLNGM, PP, MWH, MJS. Statistical analysis: GM, ACM.*

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MGdA had received consulting fees from Ambu, GE Healthcare, and ZOLL. GM, ASN, ACM, LR, MPAN, PP, MWH, and MJS have not conflict of interest related to this study.

Capítulo 7.

Neuromuscular blockade management and postoperative outcomes in enhanced recovery colorectal surgery. Secondary analysis of POWER trial.

Ana B. Serrano, Óscar Díaz-Cambronero, Javier Melchor-Ripollés, Alfredo Abad-Gurumeta, Jose Manuel Ramirez-Rodriguez, Javier Martínez-Ubieto, Miriam Sánchez-Merchante, Rita Rodriguez, Laura Jordá, Silvia Gil-Trujillo, Mercedes Cabellos-Olivares, Daniel Bordonaba-Bosque And César Aldecoa, On Behalf Of Power Group. ***Minerva Anesthesiol 2021*** *Online ahead of print.*
Q2 IF 2.23

Author contributions: *JRM conceived and designed POWER study. ABS and ODC conceived and designed this sub-study. The manuscript was drafted by ABS and revised following critical review by all members of the writing committee and steering committees. All researchers of The POWER Study Investigators Group collected data and provided care for study patients. All authors read and approved the final version of the manuscript.*

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Compliance with Ethical Standards: *JRM reports personal fees from Edwards Lifesciences, and personal fees from Fresenius Kabi, outside the submitted work; ABS and ODC report personal fees from MSD.*

Capítulo 8.

Perioperative opioids and colorectal cancer recurrence: a systematic review of the literature.

***Diaz-Cambronero O**, Mazzinari G, Cata JP.*

Pain Manage.** 2018 Sep 1;8(5):353-361. doi: 10.2217/pmt-2018-0029. **Epub 2018 Sep 13.** **PMID: 30212256

Q2 IF 1.54

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Capítulo 9.

Mu Opioid Receptor 1 (MOR-1) Expression in Colorectal Cancer and Oncological Long-Term Outcomes: A Five-Year Retrospective Longitudinal Cohort Study.

Díaz-Cambronero O, Mazzinari G, Giner F, Belltall A, Ruiz-Boluda L, Marqués-Marí A, Sánchez-Guillén L, Eroles P, Cata JP, Argente-Navarro MP. ***Cancers*** *(Basel) 2020;12(1):134.*

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Author contributions: *Conceptualization: Oscar Díaz-Cambronero, Luis Sánchez-Guillén, Juan Pablo Cata, and María Pilar Argente-Navarro; Data curation: Guido Mazzinari, Amparo Belltall, and Lola Ruiz-Boluda; Formal analysis: Guido Mazzinari, Oscar Díaz-Cambronero, Franicsoc Giner, and Lola Ruiz-Boluda; Funding acquisition: Oscar Díaz-Cambronero and Amparo Belltall; Investigation, Oscar Díaz-Cambronero, Guido Mazzinari, Francisco Giner, Amparo Belltall, Lola Ruiz-Boluda, and Luis Sánchez-Guillén; Methodology: Oscar Díaz-Cambronero, Francisco Giner, Amparo Belltall, Lola Ruiz-Boluda, Anabel Marqués-Marí, Luis Sánchez-Guillén, and Juan Pablo Cata; Project administration, Guido Mazzinari, Francisco Giner, Anabel Marqués-Marí, and María Pilar Argente-Navarro; Supervision: Pilar Eroles and María Pilar Argente-Navarro; Visualization: Guido Mazzinari and Francisco Giner; Writing—original draft, Oscar Díaz-Cambronero, Guido Mazzinari, Francisco Giner, and Juan Pablo Cata; Writing—review and editing: Oscar Díaz-Cambronero, Guido Mazzinari, Francisco Giner, Anabel Marqués-Marí, Luis Sánchez-Guillén, Pilar Eroles, Juan Pablo Cata, and María Pilar Argente-Navarro. All authors have read and agreed to the published version of the manuscript*

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