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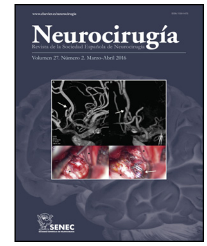

Clinical Research

Intraoperative brain mapping during awake surgery in symptomatic supratentorial cavernomas

Ricardo Prat-Acín[a,d,*], *Inma Galeano-Senabre*[a,d], *Pilar López-Ruiz*[b], *Daniel García-Sánchez*[a], *Angel Ayuso-Sacido*[c], *Raul Espert-Tortajada*[b]

[a] *Servicio de Neurocirugía. Hospital Universitario I Politècnic La Fe, Valencia, Spain*
[b] *Departmento de Psicobiología, Universidad de Valencia, Spain*
[c] *Fundación de investigación HM Hospitales, Madrid, Spain*
[d] *Unidad Mixta Nanomedicina y Sensores: Fundación Hospital La Fe, Universidad Politécnica de Valencia, Spain*

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ABSTRACT

Background: Complete resection of symptomatic supratentorial cavernoma (SCA) and removal of the surrounding gliotic area is recommended to minimize the risk of persistent seizures or (re)bleeding. Surgery of SCA located in an eloquent area, can carry out severe postoperative neurological morbidity. We report a study aimed to assess feasibility, extent of resection and outcome after surgical removal of CA by cortico-subcortical intraoperative brain stimulation (ioBS) in the awake patient.

Methods: Six patients diagnosed of symptomatic SCA located on an eloquent area and operated on while awake under local anaesthesia ioBS, were included. Preoperative planning included neuropsychologic assessment of language-related functions, sociocognitive functions and executive functions. Intraoperatively, we recorded the results achieved in the planned neuropsychological tasks when stimulation was applied (cortical and subcortical). Postoperative control 3D MRI was scheduled at 1 month after surgery to calculate extent of resection. Neuropsychological assessment at 6 months after surgery was performed in all cases.

Results: Six patients (5 females, 1 male) aged 24–48 years were included in our study. Locations of the lesions were right insular ($n = 1$), left insular ($n = 1$), left temporo-insular ($n = 1$), left temporal ($n = 2$) and left frontal ($n = 1$). In all patients, positive findings were obtained during ioBS. In 5 patients, complete surgical resection was achieved. Two patients had postoperative transient neurological deficits, one case of hemiparesis, one case of dysnomia, both cleared over a 6-month period. Clinical follow-up revealed that all patients experienced complete recovery from preoperative symptoms within a year and five patients with seizures showed marked improvement and eventually quit antiepileptic drugs. Neuropsychological assessment at 6 months provided normal results compared to preoperative baseline in all domains.

Abbreviations: CA, cavernoma; ioBS, intraoperative brain stimulation; SCA, supratentorial cavernoma; PPTT, Pyramid and Palm Trees Test; RME, Reading the Mind in the Eyes test; AED, antiepileptic drugs.

* *Corresponding author.*
E-mail address: ricprat@hotmail.com (R. Prat-Acín).

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Conclusions: Our study suggests that ioBS in the awake surgery of symptomatic SCA located in eloquent areas, allows to increase the rate of complete resection, minimizing postoperative neurological and neuropsychological deficit, and improving postoperative seizures control.

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Mapeo cerebral intraoperatorio con paciente despierto en la cirugía de cavernomas supratentoriales sintomáticos

Keywords:
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RESUMEN

Antecedentes y objetivo: La resección completa de los cavernomas supratentoriales (SCA) sintomáticos, incluyendo el área gliótica perilesional, es el tratamiento de elección para evitar la persistencia de crisis y el resangrado. La cirugía de los SCA localizados en áreas elocuentes puede asociar graves complicaciones neurológicas. Presentamos un estudio cuyo objetivo es documentar la viabilidad de la estimulación corticosubcortical intraoperatoria (ioBS) en el paciente despierto y su impacto en el grado de exéresis y el resultado clínico final.

Materiales y métodos: Incluimos 6 pacientes diagnosticados de SCA sintomático localizado en área elocuente, que fueron intervenidos mediante ioBS en el paciente despierto. El estudio preoperatorio incluyó una valoración neuropsicológica de funciones lingüísticas, sociocognitivas y ejecutivas. Durante la realización de la ioBS en el paciente despierto registramos los resultados obtenidos por los pacientes en las tareas neuropsicológicas planificadas. El grado de exéresis se estimó en una RM realizada un mes tras la cirugía. A los 6 meses de la cirugía se realizó una evaluación neuropsicológica de control.

Resultados: Cinco mujeres y un hombre con edades comprendidas entre los 24 y 48 años fueron incluidos en el estudio. Las localizaciones de los cavernomas fueron insular derecha (n = 1), insular izquierda (n = 1), temporo-insular izquierda (n = 1), temporal izquierda (n = 2) y frontal izquierda (n = 1). En todos los pacientes se encontraron hallazgos tras la ioBS. Se obtuvo una exéresis completa en 5 casos. Dos pacientes presentaron déficit neurológico transitorio, un caso de hemiparesia y un caso de disnomia, que mejoró a los 6 meses. El seguimiento clínico mostró que todos los pacientes presentaron al cabo de un año una recuperación completa de los síntomas por los que fueron diagnosticados. Los 5 pacientes con crisis de inicio pudieron dejar los fármacos antiepilépticos. La evaluación neuropsicológica a los 6 meses de la cirugía mostró una evolución normal en todos los dominios estudiados.

Conclusiones: Nuestro estudio sugiere que la ioBS con paciente despierto en la cirugía de SCA sintomático en área elocuente permite conseguir resecciones completas, reduciendo el riesgo de déficit neurológico y neuropsicológico posquirúrgico y mejorando el control de las crisis epilépticas.

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Introduction

Cavernomas (CA) account for 5–15% of intracranial vascular malformations,[1–3] being seizures (25% of patients) and neurological symptoms related to a haemorrhagic event (25% of patients) the most common clinical presentation. Complete resection of supratentorial cavernoma (SCA) and removal of the surrounding gliotic area (or hemosiderin rim) is recommended to minimize the risk of postoperative persistent seizures or (re)bleeding. When this aim is obtained, it usually implies patient's cure, however, when an eloquent brain is involved, total, safe SCA removal is still a challenge, and surgery can carry out severe postoperative neurological morbidity. Moreover, incomplete resection due to conservative surgery can bring along persistence of severe risks, including recurrent haemorrhage and persistent activity of the epileptogenic foci. Hence, meticulous planification of surgery, including cortico-subcortical intraoperative brain stimulation (ioBS) in the awake patient, also known as awake brain mapping, has been advised so that the less hazardous approach to cavernoma could be chosen.[1,4,5] Intraoperative language mapping under local anaesthesia has been probed to minimize the risk of postoperative language deficit[6,7] in brain tumour patients. Nevertheless, not only language-related functions but other higher functions, including visuospatial cognition, sociocognitive functions and executive functions can be tested intraoperatively by means of ioBS[8,9] thus contributing to improve postoperative clinical outcome and quality of life.[10]

We report a study based on a series of 6 cases of brain supratentorial hemispheric CA aimed to assess feasibility, extent of resection and outcome after surgical removal of CA by cortico-subcortical intraoperative brain stimulation (ioBS) in the awake patient.

Material and methods

Patient selection

Six patients diagnosed of symptomatic SCA located on an eloquent area and operated on while awake under local anaesthesia ioBS, were included. Diagnosis was made using magnetic resonance imaging and angiography. The preoperative planning included neuropsychologic assessment of language-related functions, sociocognitive functions and executive functions. All 6 patients were operated by the same senior neurosurgeon. Written informed consent was obtained from each patient.

Stimulation

All patients underwent asleep-awake-asleep surgery. Intraoperative brain stimulation (ioBS) in the awake phase of surgery was performed with bipolar stimulation, frequency of 60 Hz, pulse duration 1 ms and intensity range from 2 to 4 mA. We used the method developed by Ojemann and Mateer,[11] including that electrical stimulation was applied to the cortical or subcortical studied area of the brain for less than 5 s, it was never consecutively applied twice at the same location, and the result of a task in one location was recorded when the same result was obtained during three non-consecutive ioBS in that location. A task was considered as performed incorrectly if an error or the absence of response was observed three non-consecutive times and it was registered as a "positive finding" in that location. In all cases neuronavigation system was used

Intraoperative neuropsychological tasks

Intraoperatively, we recorded the results achieved for the patients in the planned tasks when stimulation was applied on a specific location (cortical or subcortical). Intraoperative tasks[12,13] included number counting 1–10 to record areas of speech arrest, D-80 oral picture as naming task, the Pyramid and Palm Trees Test (PPTT) as nonverbal semantic association task, a simultaneous task of left arm movement and naming was performed to check working memory and attention, the modified version of the "Reading the Mind in the Eyes" (RME) test,[14,15] to check mentalizing (i.e., the sociocognitive function that enables human beings to attribute mental states to others),[16] and a famous faces recognition task to check memory.[12]

Postoperative follow-up

Postoperative control 3D MRI was scheduled at 1 month after surgery to calculate percentage of resection. Neuroradiologists were blinded to whether electrical stimulation was applied during surgery.

Neuropsychological assessment at 6 months after surgery was performed. A patient was considered to have deficit if a decrease of performance of each task was observed compared to preoperative evaluation.

Results (Table 1)

Six patients (5 females, 1 male) aged 24–48 years were included in our study. Clinical onset presentations included seizures ($n = 5$), headache ($n = 4$),and haemorrhage ($n = 4$, including two cases of hemiparesis and two cases of dysphasia) Prior conventional subtotal resection of CA had been performed in one patient, and a history of prior haemorrhage was found for two patients. Four CA were in the left dominant hemisphere. Locations of the lesions were right insular ($n = 1$), left insular ($n = 1$), left temporo-insular ($n = 1$), left temporal ($n = 2$) and left frontal ($n = 1$). In all patients, positive findings were obtained during ioBS, leading the neurosurgeon to modify surgical approach according to intraoperative brain mapping. In 5 patients, complete surgical resection was achieved as demonstrated by postoperative magnetic resonance imaging studies. In one patient, harbouring a right insular cavernoma, subtotal resection consistent on a small remnant affecting corticospinal tract was achieved. Critical tract location was identified during subcortical ioBS (Fig. 1). Two patients had postoperative transient neurological deficits, one case of hemiparesis, one case of dysnomia, both cleared over a 6-month period. There was no related mortality to the procedure. Histological diagnosis was consistent with cavernous angioma in all cases. Clinical follow-up revealed that all patients experienced complete recovery from preoperative symptoms within a year and five patients with seizures showed marked improvement and eventually quit antiepileptic drugs (AED). One patient remained free of seizures one year after surgery under AED. Neuropsychological assessment at 6 months provided normal results compared to preoperative baseline in all domains.

Illustrative case (Fig. 2)

A 48-year-old right-handed woman harboured a left temporal-posteroinsular CA, revealed by generalized seizures following a bleed confirmed on MRI. Afterwards, the patient remained neurologically intact but suffered bad control of seizures even under three AED. Surgical indication to remove SCA by using awake brain mapping was established, and informed consent from the patient was obtained. The patient underwent asleep-awake-asleep surgery aimed to attempt CA complete resection and control of seizures. Large left frontotemporal craniotomy was performed exposing the temporal lobe, frontal lobe, and sylvian vein. Cerebral sulci and gyri (in special Sylvian fissure and superior temporal gyrus) and its topographical relationship with cavernous angioma, were identified using intraoperative neuronavigation. In the awake patient, intraoperative functional mapping using direct cortico-subcortical electrical stimulation was performed under local anaesthesia. Cortico-subcortical ioBS allowed the identification of language areas (positive findings for speech arrest, D80 and

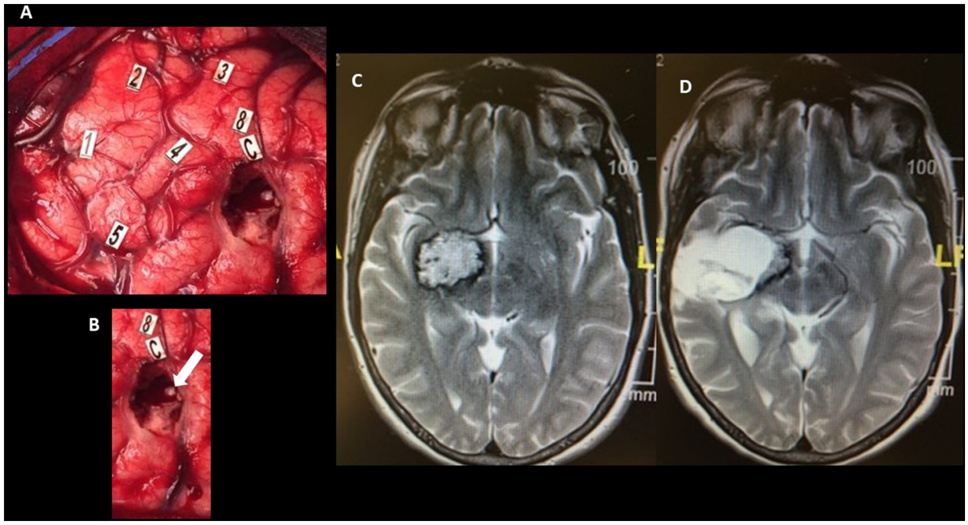

Fig. 1 – (A) The surgical field in a patient with right insular CA, after performing ioBS. Cortical projection of the inferior limit of CA (label C), Speech arrest areas (labels 1–3). Incorrect Reading the Mind in the Eyes test (label 8), working memory and attention (label 5) famous faces recognition task (label 4). (B) Detail of surgical field after subcortical ioBS, identification of corticospinal tract (white arrow) and CA subtotal resection. (C) Preoperative axial T2-weighted MRI with a right insular CA. (D) Postoperative axial T2-weighted MRI, showing CA remnant and right peduncular hemosiderin rim.

Table 1 – Clinical characteristics and findings of 6 patients harbouring brain cavernoma who underwent ioBS during awake brain surgery. SA = speech arrest, D80 = oral picture naming task, PPTT = Pyramid and Palm Trees Test, WM = working memory and attention, RME = Reading the Mind in the Eyes test, FFRT = famous faces recognition task, M = motor function.

Case Nr	Age/sex	Side/location	Extent of resection	IOP positive findings
1	48/F	L temporoinsular	Complete	SA, D80, PPTT, WM, M
2	45/F	R insular	Subtotal	SA, RME, WM, FFRT M
3	40/F	L temporal	Complete	SA, D80, FFRT, WM
4	42/F	L frontal	Complete	SA, D80, WM, M
5	24/F	L temporal	Complete	SA, FFRT, WM
6	38/M	L insular	Complete	SA, D80, PPTT, WM, M

PPTT tests), cognitive functions regions (positive findings for working memory tests) and motor structures (identification of cortico-spinal tract). Using that functional information, a transcortical T1 approach was performed to preserve the previously identified eloquent area and total removal of both CA and pericavernomatous gliosis was achieved, as shown on repeated postoperative MRIs. There was no postsurgical permanent deficit, nor recurrence of seizures after removal of AED (follow-up: 3 years).

Discussion

Although ioBs in the awake patient is increasingly considered as a crucial technique to the safe surgical resection of tumours (mainly low grade gliomas) located in eloquent areas, this technique is not as broaden used as expected as regards the surgical management of SCA in eloquent areas. It has been recently reported that only 58% of cases of SCA benefit from intraoperative direct electrostimulation, with only 66% of the cases undergoing awake craniotomy.[1] One of the main alleged drawbacks of the procedure is its complexity and the supposed procedure-related discomfort for the patient. Nevertheless, in our experience, far from being uncomfortable, technically difficult, or time-consuming procedure, ioBs in the awake patient turns to be an efficient, feasible tool in the safe management of eloquent brain areas.[17,18] Doubtless, to obtain excellence results requires that the procedure be performed by an experienced team, involving well-trained anaesthesiologists, neuropsychologists, neurophysiologists, nurses, and neurosurgeons. In our experience, and due to pre-established organizational structures, that for instance do not cover the presence of neuropsychologist in operating room, the formation of a specialized working group can be the main challenge to overcome.

Based on our results and those of the revised literature, faster recovery, low rate of adverse postoperative events and short length of stay are usually related to this procedure in SCA.[17,19] Moreover, given the fact that SCA are mainly subcortical-located lesions, ioBS provides precise intraoperative functional information that integrated with exhaustive anatomical knowledge may allow the surgical procedure to be performed in a safe, straightforward manner.

Up to 50% of cavernomas are symptomatic when discovered on MR examination[20] including neurological deficit in 34%, seizures in 70%, (of which uncontrolled seizures in 34%),

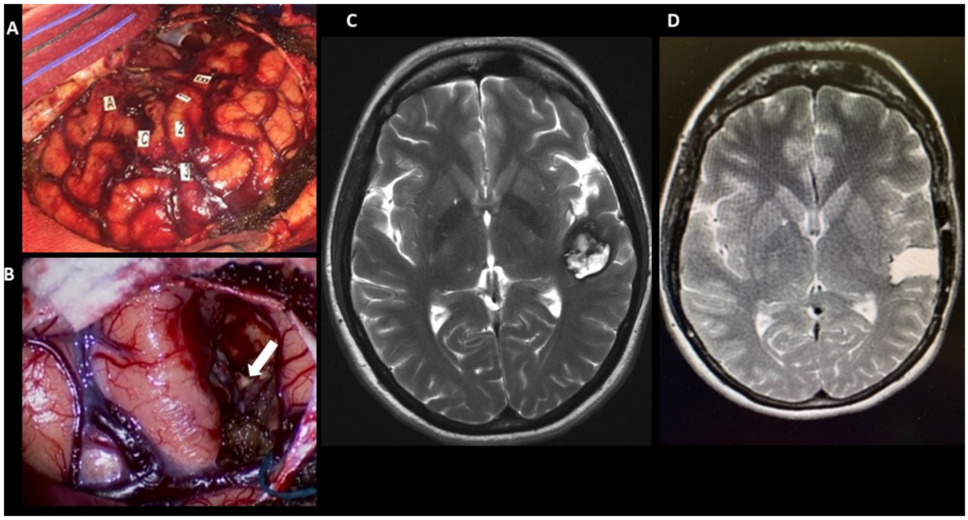

Fig. 2 – (A) The surgical field in a patient with left temporal-posteroinsular CA, after performing ioBS. Cortical projection of the superior limit of CA (label B), Speech arrest area (label 1). Incorrect D80 test (label 2). Semantic disturbances on PPTT (label C and A) Incorrect working memory task (label 3). (B) Surgical field under microscope after subcortical ioBS of corticospinal tract (white arrow) and CA resection. (C) Preoperative axial T2-weighted MRI with a left temporal-posteroinsular CA. (D) Postoperative axial T2-weighted MRI, showing a complete CA and pericavernomatous gliosis resection.

reduced Karnofsky Performance Status score of 70 or less in 24% and inability to work in 52%.[17] In those cases, patients should be advised to underwent early surgery aimed to completely resect SCA and hemosiderin rim. Complete resection has been probed to prevent rebleeding (and associated neurological morbidity) and control intractable epileptic seizures.[21] However, in the subset of symptomatic patients harbouring deep-located SCA or SCA located near so-called "eloquent areas", attempting complete resection surgery may cause severe postoperative disability that may permanently affect quality of life and clinical outcome, due to neurological and neuropsychological impairment. The above-mentioned surgical risk implies that surgical attempt to remove SCA located within or near a suspected eloquent area is not as frequent as expected,[19] and conservative management is frequently favoured to avoid surgical complications.[1] However, since no therapeutic alternative or associated treatment has proved to be that effective,[22] complete resection of SCA remains the main goal in SCA treatment.[18]

In this setting, establishing secure surgical corridors to reach subcortical, sometimes deep-seated SCA and finding safe functional boundaries of resection, seems of paramount importance to attempt complete resection. In our series, ioBS proved to be helpful to do so obtaining valuable intraoperative response in all cases. Based in our study and the revised literature, ioBS and neuropsychological tasks validation, can precisely localize neurological and cognitive functions allowing the neurosurgeon to accurately select the safer surgical approach for SCAs involving eloquent areas.[23] Moreover, with the help of brain mapping subcortical stimulation, decision can be made whether or not safely remove the pericavernomatous hemosiderin rim.[24] Supporting this consideration, it has been reported that a complete removal of the hemosiderin rim was more frequently observed (87% vs 53%) if surgery involved functional brain mapping in the awake patient.[1] Since seizures control and rebleeding seem to be closely related with extensive resection of pericavernomatous hemosiderin rim, SCA patients undergoing ioBS experienced better postoperative outcome and improved quality of life. However, fast recovery should not always be expected. In previous studies on ioBS in awake surgery patients, it has been reported a decline of neurological and neuropsychological functions immediately after surgery, with a sustained improvement between 3 to 6 months postoperatively.[13,25] This recovery, mostly observed in language functions, has been linked to mechanisms of brain plasticity[26] that might also become activated in the case of other cognitive functions.[13,27] According to these findings, in all patients SCA of our study, neuropsychological assessment at 6 months after surgery provided normal results in all domains studied compared to preoperative baseline.

Although cognitive functions have been poorly studied in the specific field of SCA, neurosurgical patients usually suffer postoperative cognitive disorders when functions, such as visuospatial cognition and executive functions, are not tested intraoperatively, either in awake or non-awake patients.[28–30] For this reason, we systematically included in SCA surgery, intraoperative tasks to test non-verbal functions such as working memory and attention, mentalizing and memory with promising results. We consider that avoid these postoperative deficits may deeply affect the quality of life of patients and their fast reintegration to previous work.[31]

Conclusions

Our study suggests that intraoperative cortical-subcortical stimulation in awake patients represents a valuable adjunct to routinely performed image-guided surgery for symptomatic

SCA involving eloquent areas. ioBS in awake surgery of symptomatic SCA allows to increase the rate of complete resection, including pericavernomatous rim, minimizing postoperative neurological and neuropsychological deficit, reducing rebleeding rate and improving postoperative seizures control. Potential additional advantages of the procedure linked to greater safety, include reduced morbidity, shorter length of stay, and subsequently better outcome. In our opinion, awake surgery with ioBS should be considered more frequently as a useful tool in the surgical management of symptomatic SCA in eloquent areas.

Informed consent

This study was conducted in accordance with the ethical principles stated in the Helsinki Declaration and approved by the institution's ethics committee, Biomedic Research Ethics Committee (2014/0202).

Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

None of these authors has any conflict of interest to disclose.

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