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Oral signs of intravenous chemotherapy with 5- Fluorouracil and Leucovorin calcium in colon cancer treatment

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Abstract

Several studies have shown how cytostatics may cause hypofunction of salivary glands but failed to elucidate any potentially related side effects. Keeping in mind the sialochemical assistance and the role of saliva on the homeostasis of the stomatognathic system, the aim of this study was to establish potential gland disorders in patients submitted to 5- Fluorouracil (5-Fu) and Leucovorin calcium(LV) as well as their correlation with certain oral health disorders that diminish the quality of life.

Materials and methods: the focus of this research was observational and longitudinal. Twenty-five patients diagnosed with colon cancer at an initial, intermediate and late phase submitted to specifically devised therapy were assessed. Clinical history, oral health indexes and basal or stimulated saliva samples were recorded.

Results: Basal and stimulated flow dropped in the intermediate stage. Stimulated saliva pH decreased during treatment. On basal saliva, urea, sodium and potassium rose during the intermediate phase. Löe and Silness rates as well as simplified bleeding increased during therapy but reverted by the end of the treatment. Depth index of the vestibular gingival sulcus rose during the intermediate phase but did not return.

Conclusion: This treatment caused functional salivary gland disorders as evidenced by basal and stimulated hyposialia, and acidification of stimulated saliva pH during the intermediate phase. Increase in basal urea may be due to proteic catabolism arising from plasma or glands. Variation in Na+ and K+ of basal saliva concentrates might be assumed as a possible duct disorder. Recovery of bleeding and Löe and Silness rates may point to a transient inflammatory effect associated to a decrease in salivary flow. Increase in the depth rates of the periodontal vestibular sulcus could be correlated with a higher risk of periodontal disease.

Key words: *5- Fluorouracil + Leucovorin Calcium, salivary glands, dysfunction, xerostomia, oral health indexes.*

Introduction

Numerous side effects in the oral cavity are caused by chemotherapy, which should be minimized to relieve discomfort and maintain its healthy performance.

It is hard to reach definite conclusions about the influence of chemotherapy over salivary gland activity due to the limited or lack of suitable methods of recording small samples, short time of assays, and variety of management for different types of cancer.

Among the various therapeutical schemes, 5-Fluoruracil (5-Fu) and Leucovorin Calcium (LV), are two widely used drugs for the treatment of colon and rectum cancer (1-5). 5-Fu is classified as an analogue of pyrimidine bases that adds a fluor atom in position 5, replacing a hydrogen and damaging malignant cells two ways: by inhibiting thymidylate synthetase and by RNA bonding.

On the other hand, Leucovorin calcium, acts as a modulator of 5-Fu amplifying its range of action. Concomitant use of both drugs enhances the therapeutical and toxic effects of 5-Fu (6). An alternative in the administration of these cytostatics is the ambulatory management, with six I.V. cycles during five consecutive days and a twenty-five day intermission.

The administration of these drugs is designed keeping in mind the body surface of the patient. This way, pharmacological induction of 5- Fu and LV can be extended for approximately six months.

This treatment exerts deleterious effects on several organic systems. Within the oral cavity, it initiates morphologic, structural and ultra structural disorders that promote dysfunctions, namely, salivary gland hypofunction (7,8).

Several authors claim these drugs would directly affect glands and thereby the product of their secretion, while others suggest that saliva would become the vehicle of such drugs inside the oral cavity, thus causing cytotoxicity (9).

Clinical assessment may elicit a subjective response from the patient such as dry mouth sensation or xerostomia or objective findings like flow and sialochemical assays. Dry mouth sensation does not necessarily agree with objective evaluations (10).

Based on these records and keeping in mind the relevant role of this complex exocrine secretion vital to the homeostatic balance of the stomatognathic system (11), the aim of the present work was to assess within a therapeutical frame work, the possible alterations in human saliva and their impact on oral health of colon cancer patients during the different stages of their treatment.

Material and Methods

The observational and longitudinal study was performed on twenty –five patients from the Oncology Unit of Sanatorio Allende, Cordoba, Argentina diagnosed with colon cancer and submitted to 5-Fu and LV treatment during six cycles of five consecutive days with a twenty –one day intermission between them.

Patients were assessed based on the following scheme:

1- Initial phase: Prior to treatment.

2- Intermediate phase: Prior to the fourth drug administration.

3- Late phase: Twenty-one days after the end of the treatment.

Patients of both sexes between 21 and 75 years of age with colon cancer diagnosis and no previous stomatologic complaints were included in this survey. Patients exposed to neck and head radiation suffering from metabolic and mental disorders were not included in this survey.

Clinical management warranted risk free procedures or any discomfort inflicted on the patients, complying with anonymity, and confidentiality policies.

Once the written consent was granted and signed according to the standard model approved by the ethical committee of Sanatorio Allende, a clinical history was made. Oral exam of the mouth and samples of basal and stimulated saliva were collected in the morning so as not to disturb the circadian rhythm of secretion (12-14).

The following oral health parameters were assessed for each patient:

a- odontogram

b- Löe and Silness rates (14,15)

c- simplified bleeding indexes (16)

d- Ramfjord index (17)

e- plaque index (18).

f- Probing depth of the vestibular sulcus of the elements 13-23-33 and 43 plus 16-26-36 and 46.

Collection of stimulated and basal saliva was carried out for five minutes using a 1 square cm inert rubber piece (19,20). Samples were maintained at -4^0C for further assay. The following assays were made:

a- Salivary flow and pH.

b- Organic components: whole proteins, salivary amylase, Ig A and urea.

c- Inorganic components: ionogram in saliva (Na+, K+, Cl-), Ca++, PO4=.-

Statistical Analysis: data were analyzed by Student "T" test for paired data to compare the different stages of treatment, setting a P value< 0.05 for statistical significance.

Results

Mean age of the patients with colon cancer was 55 years old, with 43% and 57% of subjects respectively younger or older than the mean. Regarding genetic predisposition, only 36% reported cancer history (only first and second degree line ancestors were taken into account).

Both basal and stimulated flow dropped significantly in the intermediate stage as compared with the initial phase but reverted 21 days after treatment had ended. ($p> 0.05$ and $p> 0.01$ respectively). (Fig.1). As regards pH,

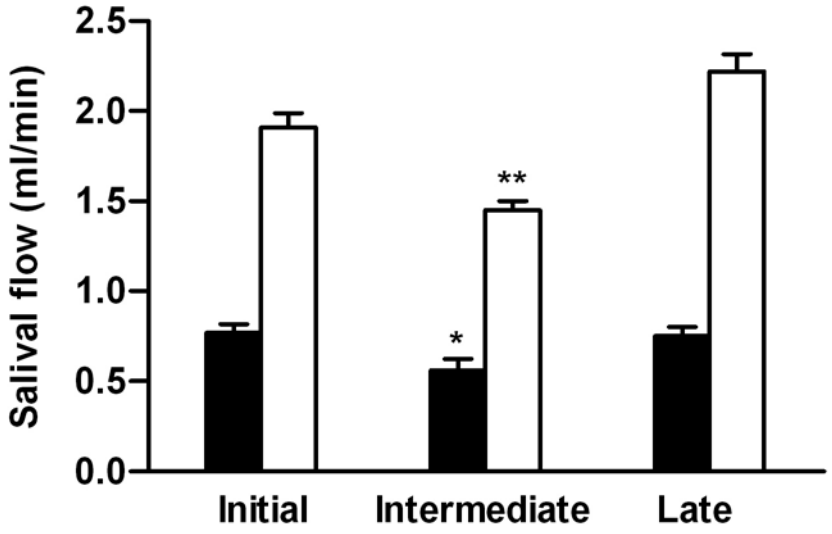


Fig. 1. Effect of 5 – FU and LV over basal and stimulated saliva flow from patients at diferent treatment phases: basal flow; : stimulated flow. (*): p< 0.05: intermediate basal flow versus initial and final; (**): p< 0.01 intermediate stimulated flow versus initial and final.

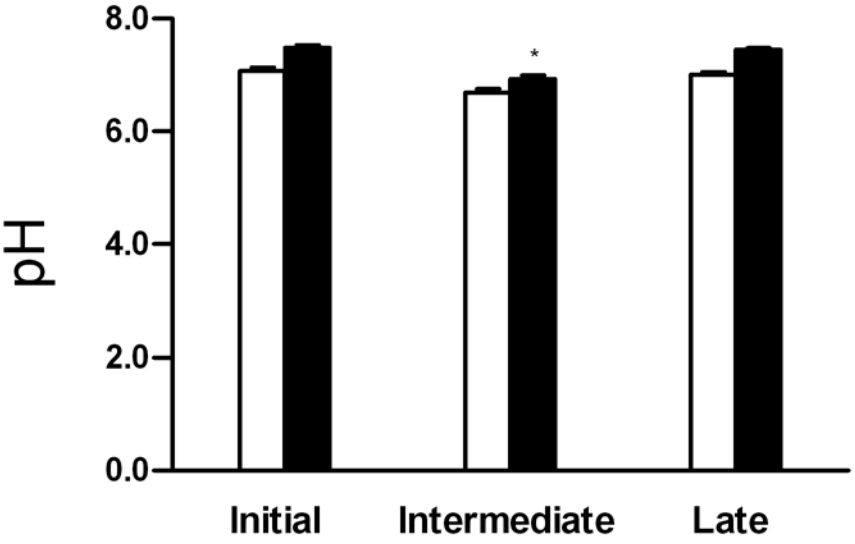
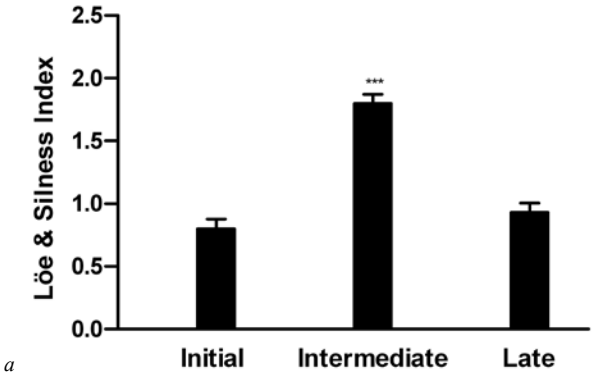
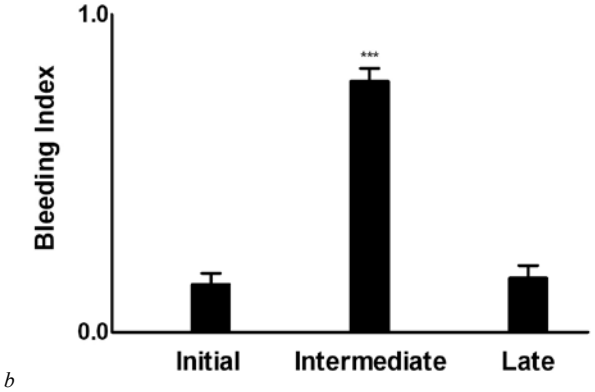


Fig. 2. Effect of 5 – FU and LV over basal and stimulated saliva pH of patients at different treatment phases. : basal flow; :stimulated flow. (*): p< 0.05: intermediate, stimulated flow versus initial and final.



a



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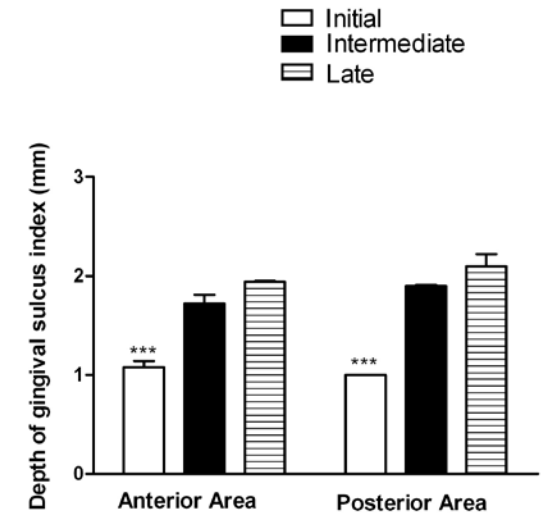

c

Fig. 3. Effect of 5 – FU and LV over Löe and Silness index, bleeding index and depth of gingival sulcus index of patients at different treatment phases. (***): p< 0.0001: intermediate versus initial and final (a and b); initial phase anterior and posterior areas, versus intermediate and final (c).

basal saliva showed no statistically significant changes, but stimulated saliva acidified in the intermediate as compared with the initial phase. This effect reverted during the final stage, when mechanical stimulation promoted saliva secretion with a pH similar to that of the initial stage ($p< 0.05$) (Fig.2).

As for basal saliva composition, inorganic components such as Na+ and K+ increased during the intermediate unlike the initial stage but recovered in the final phase.

Among organic components, only a significant increase in urea concentration was evidenced during cytostatics administration that reverted in the late stage. (Table 1)

Oral health indexes yielded the following results:

Gingival inflammatory response, evaluated by Löe and Silness rates, increased in the intermediate unlike the initial stage ($p< 0.0001$), and reverted by the end of the treatment (Fig.3a). The simplified bleeding index exhibited a rise over the periodontal probing in the intermediate as compared with the initial phase ($p< 0.0001$). Such an effect was reverted in the late stage (Fig.3b).

Depth index of the vestibular sulcus of anterior and posterior elements significantly increased in the intermediate phase but did not revert at the end of the treatment ($p <0.0001$) (Fig.3c). Odontogram, plaque and Ramfjord indexes revealed no significant differences in the studied sample.

Conclusions

It is well known that many cytostatic drugs disturb the health status of the stomatognathic system but their real impact on gland tissue is not fully elucidated.

The current paper ratified the deleterious effect of these drugs discarding certain issues that complicate data analysis such as interpersonal variations since every individual in the survey was evaluated during the different stages of the therapy. The schedule of treatment applied mainly caused stimulated salivary glands disorders and basal hyposalivation. This might be the cause of xerostomia or dry mouth sensation with burning, dorsal lingual distress, lips and corners of the mouth cracking, discomfort in the use of removable dentures, and impaired swallowing and chewing in addition to dysgeusia (21). Basal and stimulated saliva pH was affected differently. Even though basal saliva pH experienced no changes, stimulated saliva pH acidified in the intermediate stage. This finding, along with a drop in the amount of flow released, would modify healthy flora (22-24).

Many physiologic processes involved in electrolyte exchange are susceptible to chemotherapy effects. As regards inorganic substances, increase in Na+ and K+, would suggest a disorder in duct transport mechanisms during ions re- arrangement which occurs during secondary saliva formation.

Urea, which rose in the intermediate stage was the only

Table 1. Effect of 5-FU and Leucovorin Calcium over organic and inorganic components of basal and stimulated saliva of patients at different stages of treatment.

saliva	Basal			Stimulated		
	Treatment phases					
	Initial	Intermediate	Final	Initial	Intermediate	Final
Na^+ mEq/l	5.5±2.3	9.66±3.2 (**)	5.0±2.1	11.1±1.5 (###)	11.6±2.04	9.5±2.4
Cl^- mEq/l	15.3±1.5	16.5±1.4	13.2±1.1	23.0 ± 1.5 (#)	21.1± 1.7	20.9 ±2.6
K^+ mEq/l	17.2±1.3	22.6±4.8 (**)	16.3±4.0	11.3±1.6 (#)	16.3±0.9	10.7±2.0
Phosphate mg/dl	24.6±2.0	22.4±2.3	18.2±1.4	12.6±1.8 (###)	9.9±1.1	9.4±1.0
Ca^{++} mg/dl	3.3±0.3	3.8±0.3	3.1±0.3	5.7±2.3	3.1±0.2	2.5±0.4
whole proteins mg/dl	145±12.9	167±12.9	153±10.9	88.7±31 (##)	79.7±21.0	50.7±5.0
IgA_s mg/dl	25.8±4.9	24.3±5.3	19.1±6.6	15.8±2.7 (##)	20.3±3.3	17.8±2.3
α amylase UA/µl	38.0±7.9	55.7±8.8	40.9±5.8	27.3±6.7	38.0±6.2	32.3±10.9
Urea mg/dl	29.8±4.8	47.6±4.2 (*)	25.4±2.9	20.1±3.2 (##)	19.9±3.0	17.8±4.5

(*): p< 0.05 intermediate Urea versus initial and final; (**): p<0.001: intermediate Na+ and K+ versus initial. (#): p<0.5: Chlorine and potassium initial stimulated saliva versus basal. (##): p<0.01: whole proteins, IgAs and urea initial stimulated saliva versus basal; (###): p<0.0001: Sodium and phosphate initial stimulated saliva versus basal.

organic component that exhibited significant difference. This change may be a catabolic protein effect arising either from blood plasma or from the gland itself. Results related to whole protein concentration and salivary alpha amylase among patients were variable. This finding might be due to countless factors, such as age, sex, diet, stress, medication or habits.

Changes in stimulated saliva composition over basal saliva were detected. Such modifications would not necessarily depend on drug action but rather on the increase in salivary flow since no significant differences in either the concentration of organic or in the inorganic stimulated saliva were found at different times of therapy.

Current results let us suggest the finding of pathogenic bacteria increase would enhance the risk of periodontal disease as evidenced by the depth of the vestibular sulcus; the single oral health index that did not revert after treatment. This result is particularly relevant since it will draw patients' awareness to the need of developing therapeutical care at the very start of therapy, thus preventing complications that jeopardize the health of the stomatognathic system during oncologic management (25,26).

Although some results are in agreement with scientific reviews, we cannot ignore contradictory reports due to the different types of cancer and consequently varied therapeutical protocols, lack of standardized methods and relatively short follow-up lapses which limit the possibility of gathering consistent results (27,28).

Including dental dentistry specialists in the interdisciplinary oncologic team will aid cancer treatment.

The prevention and screening of oral disorders detected during cytostatic treatment will potentially prevent those side effects which may negatively affect the patients' quality of life.

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