

Evaluation of Salivary Flow Rate in Patients undergoing Chemotherapy for Solid Tumors

Avaliação de Fluxo Salivar em Pacientes Submetidos à Quimioterapia para Tumores Sólidos

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Abstract

Chemotherapy for cancer treatment offers the possibility of eradicating neoplastic cells, however, its use can result in systemic and oral adverse effects, with emphasis on the qualitative-quantitative modification of saliva. To evaluate the stimulated salivary flow rate (SFR) in patients undergoing chemotherapy for treatment of solid malignancies. This was a cross-sectional study with twenty patients diagnosed with solid tumors undergoing chemotherapy with cytotoxic drugs. Subjects were submitted to stimulated sialometry in the 1st cycle of chemotherapy (baseline, 7th day and 14th day). Additionally, sociodemographic data regarding these patients were collected in a standardized questionnaire. Descriptive and inferential statistical analysis were performed, with a significance level of $p < 0.05$. There was a predominance of women (75%) aged over 40 years old (90%). The most prevalent tumor location was breast (55%), followed by ovaries (15%), and the most used drug was cyclophosphamide (50%). In the sample, no statistically significant result was observed with regard to SFR ($p > 0.05$) in the studied periods. The data suggest that the 1st cycle of chemotherapy was not able to induce significant changes in the SFR. New studies need to be performed for the prospective identification of potential changes in salivary parameters.

Keywords: Antineoplastic Agents. Neoplasms. Saliva.

Resumo

A quimioterapia para tratamento do câncer oferece possibilidade de erradicação das células neoplásicas, todavia, seu emprego pode resultar em efeitos adversos sistêmicos e em cavidade oral, com destaque para modificação quali-quantitativa da saliva. Avaliar a velocidade de fluxo salivar (VFS) estimulado em pacientes sob quimioterapia para tratamento de neoplasias malignas sólidas. Tratou-se de um estudo transversal, no qual vinte pacientes com tumores sólidos sob regime quimioterápico com drogas sabidamente citotóxicas, foram submetidos à sialometria estimulada no 1º ciclo de quimioterapia (baseline, 7º dia e 14º dia). Adicionalmente, foram coletados dados referentes às características sociodemográficas desses pacientes. Foi realizada análise estatística descritiva e inferencial, com nível de significância $p < 0,05$. Observou-se predominância de mulheres (75%) em idade acima dos 40 anos (90%). A localização do tumor mais prevalente foi a mama (55%), seguida de ovários (15%) e a droga mais utilizada foi a ciclofosfamida (50%). Na amostra não foi observado resultado estatisticamente significativo no que diz respeito à variável VFS ($p > 0,05$) nos períodos estudados. Os dados sugerem que o 1º ciclo de quimioterapia não foi capaz de induzir alterações significativas na VFS. Novos estudos precisam ser realizados para a identificação prospectiva de potenciais alterações nos parâmetros salivares.

Palavras-chave: Antineoplásicos. Neoplasias. Saliva.

1 Introduction

Chemotherapy for cancer treatment offers the possibility of eradication of neoplastic cells, containment of tumor growth or control and relief of symptoms through the use of medicines. These drugs can operate at different times of the cell cycle and are classified as to the mechanism of action in alkylating agents, antimetabolites, antitumor antibiotics, mitotic inhibitors, hormones and various drugs¹.

Although chemotherapy drug therapy offers a benefit in cancer control, it is known that the use of these drugs often results in complications, which derive from the low specificity with neoplastic cells². The most severe side effects are myelosuppressive, nephrotoxicity, peripheral neuropathies,

increased risk for leukemia, nausea, vomiting and diarrhea, alopecia, hyperpigmentation of skin and hemorrhages^{1,3}.

Patients on chemotherapy may also suffer oral alterations and complain of pain, sensations of oral burning or numbness of the lower lip, xerostomia, paresthesia, dysesthesia, dysgeusia, gingival bleeding, difficulty in food intake, trismus, feeling of tension in the masticatory muscles², in addition to qualitative-quantitative changes in saliva^{2,4-8}.

Saliva is an exocrine secretion composed of water, ions, proteins (enzymes, albumin, glycoproteins, polypeptides and immunoglobulins), glucose, urea and ammonia. The content of this fluid is composed of both non-stimulated and stimulated saliva, which differ as to the compositions and volumes secreted daily. In the absence of diseases or the use of drugs

that interfere with the flow, total salivary production varies between one liter and one and a half a day. Due to the complex composition, saliva actively participates in the maintenance of oral homeostasis and performs multiple functions, among them: protection and lubrication of oral soft tissues, which maintains the viscoelasticity of the mucosa and allows the functions of chewing, speech and swallowing remain in perfect functioning; modulation of the demineralization-rem mineralization cycle in the hard tissues of the oral cavity through the presence of free ions of calcium, phosphate, fluoride and bicarbonate; beginning of carbohydrate digestion by alpha-amylase enzyme; antibacterial properties and inhibition of the formation of dental calculus^{8,9}.

The reduction of salivary secretion makes the oral mucosa more susceptible to mechanical trauma. This factor, in association with the low regenerative power of oral epithelium derived from biological events that culminate in lesion and apoptosis of basal layer epithelial cells, may facilitate the penetration of microorganisms into tissues and blood vessels^{2,10} possible risk factors for the development of mucositis were identified. Patients were treated with chemotherapeutic regimens appropriate to tumor type and disease stage on an in- or out-patient basis. Mucositis was scored using the World Health Organization (WHO¹¹). In addition, a deficient immune response can favor the processes of spread of pathogens, considering that the oral cavity is a gateway for infections. Thus, patients with hyposalivation also present increased risk for periodontal diseases, caries lesions, erythema and ulceration in the mucosa, fungal infections, tongue papillae atrophy, dysphagia, dysarthria, taste disorders, intolerance to acidic or spicy foods, halitosis, bacterial sialoadenitis, malnutrition and reduction of quality of life⁸.

Due to the negative influence of chemotherapeutic drugs on the oral environment and its possible consequences for patients submitted to this treatment, the aim of this study was to evaluate possible changes in salivary flow velocity (SFV) stimulated resulting from chemotherapy for the treatment of solid malignant neoplasms.

2 Material and Methods

2.1 Ethical aspects, study population, inclusion and exclusion criteria

Cross-sectional study, conducted at the Dentistry Service of the High Complexity Unit in Oncology Nossa Senhora de Fátima das Obras Sociais Irmã Dulce (UNACON-OSID), located at Hospital Santo Antônio, Salvador, BA, Brazil, in 2017. It obtained approval from the Research Ethics Committees of the Bahia State Foundation for the Development of Sciences, under protocol number CAAE 46909315.1.0000.0047 and Hospital Santo Antônio/OSID number CAAE: 68263317.8.0000.0047. In addition, it is in accordance with the latest version of the Helsinki Declaration of 2013 and with Resolutions number 466/2012 and 510/2016

of the National Health Council.

To compose the sample, 20 patients with malignant neoplasms were selected at any anatomical site, with a minimum age of 18 years, whose treatment protocol established by the medical team included chemotherapy every 21 days, using at least one of the following drugs known to be cytotoxic to the oral mucosa: capecitabine, carboplatin, cyclophosphamide, cisplatin, docetaxel, doxorubicin, fluorouracil, oxaliplatin and paclitaxel. In order to verify the isolated action of chemotherapies on the salivary glands, it was decided not to include patients with hematological malignant neoplasms, since the treatment for this group of diseases often associates high doses of chemotherapeutics with other therapeutic modalities; or patients with head and neck cancer, considering the known role of radiotherapy in the therapeutic approach of this group and the deleterious role of radiation on the salivary glands, which is already well established by the literature¹². Diabetic patients, with cognitive impairments, autoimmune diseases, due to possible interference in the amount of saliva produced, in addition to those with the presence of erosive lesions of the mucosa prior to the service or whose general state of health prevented the understanding of the guidelines or carrying out the salivary collection procedures were excluded.

After consenting to the participation in the study through the signing of the Free and Informed Consent Form, clinical dental examination was performed at the first consultation prior to the 1st cycle of chemotherapy and data on the anatomical site, sex, age, schooling, smoking and/or ethyl habits and salivary flow rate were collected.

2.2 Stimulated salivary flow scan

All collections were performed in the morning and patients were instructed not to eat, drink, smoke or brush their teeth during the 60 minutes prior to the examination, in order to avoid external influences on the results.

The stimulated saliva collection was performed in 3 different moments: *baseline*, corresponding to the time of the first chemotherapy infusion, and the other collections after 7 and 14 days of *baseline*, with regular intervals of 1 week between them. Stimulated saliva collection was performed for 5 minutes, according to the methodology proposed by Krasse (1988)¹³. It should be noted that all patients were instructed regarding the need for minimum water intake of 2 liters per day.

Prior to the examination, as instructed by the researcher, the participants performed two folds in the paraffin film to present an area of 4cm² (*Parafilm*[®] M, Bemis Company, Wisconsin, USA), in order to better accommodate it in the mouth. After positioning it on the tongue, they kept it at rest for 1 minute and then swallowed all saliva present in the oral cavity. Finally, they chewed *the Parafilm*[®] for 5 minutes, ejecting all the saliva secreted in a millimetered specimen.

VFS was determined by the ratio between the total amount of saliva collected (in mL) by the time of the examination (in minutes), after the sample was kept at rest for 10 min.

Patients were classified according to the classification proposed by Thylstrup and Fejerskov¹⁴. Normal flow speed: between 1.0mL/min and 2.0mL/min; reduced flow speed: above 0.7mL/min and below 1.0mL/min; Hyposalivation: <0.7 ml/min.

2.2. Statistical analysis

Student T test was applied to compare the mean VFS. The analyzes were performed using SPSS software (version 21.0) with a confidence level established at 95% (p<0.05).

3 Results and Discussion

Regarding the level of education, a considerable percentage of the sample (50%) declared complete/incomplete elementary school. Regarding the associated risk factors (smoking and/or alcohol consumption), 50% of the sample reported not using tobacco or alcohol (Table 1). Regarding the sociodemographic profile and tumor characteristics, it was possible to identify the majority composition of malignant breast neoplasms (55%) followed by ovaries (15%), which justifies the predominance of women (75%) aged over 40 years (90%) (Table 2). In relation to the most used chemotherapeutic drugs, cyclophosphamide occupied the 1^a place (50%), followed by cisplatin (15%), as shown in Chart 1.

Table 1 - Socio-demographic description of the sample

Variables	n	%
Sex		
Male	5	25.0
Female	15	75.0
Age		
18-29	1	5.0
30-39	1	5.0
40-49	6	30.0
50-59	3	15.0
60-69	5	25.0
70-79	2	10.0
80-89	2	10.0
Schooling		
Never studied	1	5.0
Complete/incomplete elementary school	10	50.0
Complete/incomplete high school	7	35.0
Complete/incomplete high school	2	10.0
No information	-	-
Associated risk factors		
No tobacco or alcohol	10	50.0
Tobacco	1	5.0
Alcohol	3	15.0
Alcohol and tobacco	5	25.0
No information	1	5.0

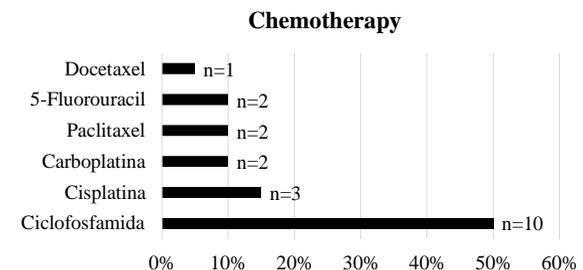
Source: UNACON/OSID-HSA (2017)

Table 2 - Distribution of the sample according to the location of the primary site

Location of primary site (n=20)	% (n)
Breast	55.0 (11)
Ovaries	15.0 (3)
Colon	10.0 (2)
Testicles	5.0 (1)
Cervix	5.0 (1)
Prostate	5.0 (1)
Lung	5.0 (1)

Source: UNACON/OSID-HSA (2017).

Chart 1 - Distribution of chemotherapeutic drugs



Source: UNACON/OSID-HSA (2017).

Regarding the mean VFS, it was possible to observe the maintenance of normality at all moments of salivary examination, with a slight increase in flow on the 14th day, however, without statistical significance (Table 3).

Table 3 - Comparison of initial, final averages and variation (Δ) of salivary flow velocity (mL/min) in the sample

	baseline	7 days	14 days	Δ	p value
mean \pm SD	1.17 \pm 0.65	1.21 \pm 0.70	1.24 \pm 0.70	0.07	0.448

Source: UNACON/OSID-HSA (2017).

The VFS through the collection of stimulated saliva was not affected by the different types of cytotoxic chemotherapies for the oral cavity. A possible justification for the non-occurrence of hyposalivation in the present study is due to the fact that the standard therapeutic protocol used was cycles with an interval of 21 days between infusions, which possibly attenuates the side effects in the oral cavity, including hyposalivation, compared to cycles that have a shorter delivery range. In addition, it is also necessary to consider that the differences in the protocols used for the various types of solid tumors are based on specific characteristics, such as the histological type, clinical stage and general health status of each individual.

The composition profile of the sample corroborates the data from the literature¹⁵, with predominance of women (51%), and a significant proportion of breast tumors (18.5%) or gynecological tumors (10%) and age above 50 years. The predominance of breast tumors shows agreement with epidemiological data presented by the National Cancer Institute (INCA), which point to them as the most frequent type of cancer in women after non-melanoma skin cancer¹⁶.

In the present study, it was chosen not to include patients with hematological malignant neoplasms, since these commonly affect younger individuals and use myeloablative

drugs at high concentrations, which leads to disorders of dental development, lesions in the oral mucosa, deficient oral hygiene and greater experience of caries lesions¹⁷. Regarding the exclusion of patients with head and neck cancer, this decision was based on the routine use of radiotherapy in this region, mainly for disease control in the most advanced stages (III and IV). According to the study conducted by Brandão et al.¹⁸, at least 96% of patients diagnosed with oral cavity squamous cell carcinoma are submitted to head and neck radiotherapy, commonly in association with chemotherapy or surgery. The deleterious effects of this treatment modality on the salivary glands are already well described in the literature¹⁹⁻²².

To date, few studies have been carried out to evaluate, in an isolated way, the role of chemotherapies in salivary function^{2,4-7}. In 1998, a study was carried out to investigate the differences in VFS among healthy women, women with breast carcinomas under CMF therapy (cyclophosphamide, methotrexate and fluorouracil) or under no therapy. The results showed a statistically significant difference between healthy women and those in chemotherapy treatment. Despite this finding, the mean salivary flow in patients under chemotherapy with CMF for at least one month remained slightly less than 1.0mL/min, pointing to reduced salivary flow, but still insufficient to achieve hyposalivation. Still, this study evaluated IgA levels, without statistically significant differences among the three groups⁴. In the present study, although the patients were exposed to known cytotoxic chemotherapeutic drugs for the oral cavity²³, especially cyclophosphamide and cisplatin, hyposalivation cannot be observed in this group of patients.

In a study carried out by Jensen et al. (2008)⁵, the authors evaluated salivary alterations in 45 women during chemotherapy treatment for breast cancer. The authors describe that hyposalivation was present between the second and third week after chemotherapy infusion. Therefore, these results disagree with the data presented in the present work. This divergence can be justified by the difference among the moments when salivary collections were performed in both studies. In this study, the collection occurred in a unique way after the 1st cycle of chemotherapy, while in the one by Jensen et al.⁵, salivary examination was performed between 6 and 7 treatment cycles. According to Sonis²⁴, patients who perform the first cycle of chemotherapy have a reduced probability of developing alterations in the oral cavity, such as mucositis, due to the low cumulative effect of the drug, which can also justify the result observed in the present study. That is, the more chemotherapy cycles the patient is submitted, the greater chance of developing these adverse effects. However, it is important to point out that, although this probability is reduced in comparison to more advanced cycles, the possibility of developing oral alterations is not eliminated, and its early management favors a better quality of life for the oncological patient, since it does not interfere in daily activities, as food and speech, besides avoiding the appearance of mucositis

lesions and those resulting from opportunistic infections, reducing the risk of morbidity and mortality.

In the study by Mazzeo et al.⁶, it was aimed to evaluate the influence of 5-fluorouracil on several salivary parameters, including the stimulated flow, concentration of organic and inorganic components, and pH. The results showed a statistically significant reduction in salivary flow between the initial averages and after the fourth cycle of administration of the drug. Regarding the qualitative changes, there was a record of increasing concentration of ions in , K and urea, and reduction of salivary pH, making acid saliva, but unable to reach the critical points for demineralization of dental tissues. The authors describe that the changes recorded were transient, with recovery of base levels about 20 days after completion of treatment.

Another study performed the evaluation of stimulated VFS of patients under chemotherapy (0.81 mL/min) compared to healthy patients of the same age group (2.11 mL/min). A statistically significant difference was observed between the means of the two groups. It should be noted that the authors evaluated patients using the same group of drugs as the present study and under the same salivary examination methodology performed in the work described here. Although this difference was noted, the reduction in the salivary secretion generated was mild and insufficient to achieve a condition of hyposalivation. In addition, the authors do not describe at what time of treatment the salivary examination was performed, which limits the comparison with other studies².

The same study evaluated oral complications related to chemotherapy and found that 82.76% of the sample complained of oral dryness, with the same rate being reached by the percentage of reports of nausea and/or vomiting. Other manifestations were also identified in a significant number of the sample, such as dysgeusia (72.41%), oral mucositis (60.34%), fungal lesions (50%), difficulty eating food (41.38%) and burning sensation of the mucosa (31.0%)². Although such complications are frequent and important, Frowen et al.¹⁵ emphasize that patients with breast cancer usually have a low prevalence of dysphagia for solids and liquids, as well as a lower prevalence of voice, dental and prosthetic problems, in relation to patients with head and neck cancer. However, both authors warn of the need to evaluate the influence of the amount of chemotherapeutic infusions on the prevalence of oral complications, due to the cumulative effect of drugs, as already mentioned above^{2,15}.

Although no significant quantitative changes have been found in the present study, it is of paramount importance to consider that saliva can be affected by the direct effect of cytotoxic drugs on glandular tissue, secondary systemic changes, as protein catabolism and/or disorders in the mechanisms of secretion of salivary ducts in the course of treatment. It is emphasized that salivary disorders that occur during chemotherapy can directly affect the balance of the oral environment, which favors the installation or progression of

periodontal disease, caries lesions, acid erosion, xerostomia and reduction of the quality of life of these patients⁶. Therefore, the follow-up of this population by the dentist is indispensable, in order to intervene early when detecting oral alterations.

Since the drugs evaluated in the aforementioned studies were similar to the present study, long-term evaluations may corroborate the findings of reduction of VFS, since patients may present varying degrees of local and systemic changes at different times of treatment.

As limitations of the study, its cross-sectional character is emphasized, and it is not possible to detect salivary changes in the long term; limited sample size, which makes extrapolation of the results impossible. In addition, the heterogeneity of the characteristics of age, sex, habits, diet, stress levels and different treatment protocols should be considered, which is a limitation imposed on most studies that are willing to evaluate effects caused by chemotherapy. However, studies such as the one presented here help in the increasingly understanding of the clinical manifestations of antineoplastic treatment, which bases the professional to adjust the clinical management, acting early and leading to the improvement of the quality of life of the oncological patient.

4 Conclusion

According to the methodology used in the present study, it was possible to conclude that the 1st cycle of chemotherapy with cytotoxic drugs for the oral environment was not able to induce significant changes in salivary flow velocity. However, the role of these drugs in salivary composition remains uncertain. It is suggested to carry out new studies with extended sample size and standardized treatment protocols for the prospective identification of potential changes in salivary parameters.

Sources of Funding

Foundation for Research Support of the State of Bahia (FAPESB/Red0025/2014).

Acknowledgements

Social Works Sister Dulce (OSID).

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