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ORIGINAL ARTICLE

CORRELATION BETWEEN HYPOSALIVATION AND XEROSTOMIA IN PATIENTS WITH HEAD AND NECK CANCER

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Abstract:

Introduction: Saliva plays an important role in maintaining oral homeostasis. However, cancer treatment can induce transient or permanent adverse effects on the salivary glands. **Objective:** This study aimed to evaluate the correlation between xerostomia and salivary flow velocity (SFV) in patients undergoing antineoplastic treatment for head and neck cancer (HNC), under the Public Health System in the city of Salvador-BA. **Materials and Methods:** This cross-sectional observational study evaluated medical records of patients diagnosed with HNC and treated by the Oncology Service of the High Complexity Unit in Oncology Nossa Senhora de Fátima - Irmã Dulce Social Works - dental team between January 2019 and March 2020. After anamnesis, stimulated saliva was collected at the 1st and 24th radiotherapy sessions to quantify SFV, and a xerostomia questionnaire was administered for assessments based on a visual analogue scale (VAS). Descriptive statistics were performed, and categorical variables are presented as means, percentages, and coefficients of variation. **Results:** Medical records of 200 patients were assessed and 16 patients were included in the study. The sociodemographic profile showed a predominance of men (62.50%), aged between 46 and 70 years (56.25%), of mixed ethnicity (43.75%), with incomplete primary education (43.75%), alcoholics (56.25%), and non-smokers (56.25%). Tumor and treatment data showed a predominance of exclusive radiotherapy (50%), location in the larynx (31.25%), and T1/T2 staging (56.25%). The mean SFV of patients was 1.75 mL/min and 0.71 mL/min at the 1st and 24th session, respectively, revealing that irradiation reduced SFV. All domains of the xerostomia scale showed an increase in the means obtained, which indicated worsening of xerostomia between the 1st and 24th sessions. **Conclusions:** An inverse correlation was observed between the mean VAS scores and SFV in patients with HNC. Further studies to correlate hyposalivation (objective sign) with xerostomia (subjective symptoms) are recommended.

Keywords: saliva. xerostomia. head and neck neoplasms

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INTRODUCTION

Saliva is an aqueous solution that bathes the entire oral cavity and is composed of water, electrolytes, alpha amylase, lingual lipase, kallikrein, and mucus, with high concentrations of potassium and bicarbonate. It is secreted by three pairs of major salivary glands: the parotid, submandibular, and sublingual glands, as well as by the minor glands. The latter are distributed over the oral mucosa, formed by mucous and serous cells, and the total daily secretion of saliva is approximately 1.0L[1-3].

Saliva plays a fundamental role in oral homeostasis, as it acts as a lubricant, has defense factors such as antibodies, contains salivary buffers for the regulation of the pH of the oral environment, initiates starch digestion, moistens and dilutes food, and has an antimicrobial action[4,5]. In addition, it is a fast and non-invasive medium for the detection and recognition of pathological processes and therapeutic follow-up[6].

Changes in the pattern of saliva production, whether qualitative and/or quantitative, can be due to multiple causes, including systemic disorders, autoimmune conditions, side effects of medications, infectious processes, involvement of the glandular parenchyma in diseases, and radiotherapy to the head and neck region. Reduced saliva can cause numerous disorders in the oral cavity and oropharynx[7], such as carious lesions, periodontitis, fungal infections, halitosis, and patient discomfort[4].

Objective evidence of reduced saliva production is required for the diagnosis of hyposalivation, which is a disorder in which there is an effective decrease in salivary flow rate. In contrast, xerostomia is a term used to designate the subjective sensation of dry mouth, which may or may not be associated with hyposalivation and is induced especially by the imbalance in the composition of the saliva.[3,4,7,8].

Head and neck cancer (HNC) is highly prevalent in Brazil, and the indicated therapeutic modalities, including surgery, radiotherapy, chemotherapy, or any combination of these, cause significant changes to the patient's quality of life[9].

Radiotherapy is one of the treatment modalities for HNC, and depending on the dose and location of the irradiated field, radiation may result in long-term or irreversible, quantitative and qualitative changes in the composition of saliva[3,10]. Therefore, monitoring of salivary parameters is necessary for early intervention to reduce side effects caused by hyposalivation and/or xerostomia.

Therefore, this study aimed to evaluate salivary flow velocity (SFV) and xerostomia in patients undergoing antineoplastic treatment for HNC, under the Public Health System in the city of Salvador-BA.

MATERIAL AND METHODS

Ethics Committee

This study was approved by the Research Ethics Committee of the Hospital Santo Antônio/ Irmã Dulce Social Works (OSID) (no. 1,215,616). In addition, all patients provided written informed consent, as per the criteria in resolution 466/12 of the National Health Council.

Study population

This observational cross-sectional study included patients diagnosed with malignant head and neck neoplasms between January 2019 and March 2020, who had not started radiochemotherapy or exclusive radiotherapy treatment, through free demand, assisted and monitored by the dentistry team, from the Oncology Service of the High Complexity Unit in Oncology Nossa Senhora de Fátima – Irmã Dulce Social Works (UNACON-OSID).

Data regarding the type of neoplasm, staging, and proposed treatment, including the dose and number of radiotherapy sessions were obtained from the medical records and stored in a standardized Excel spreadsheet. The socioeconomic and cultural characteristics of the population, including age, sex, and socioeconomic status, were obtained using a questionnaire.

Inclusion criteria

Individuals monitored by the UNACON-OSID Dental Service who were diagnosed with malignant head and neck neoplasms, had not started the proposed treatment protocol (radiochemotherapy or exclusive radiotherapy) that included at least 28 radiotherapy sessions, and were at least 18 years old at the beginning of the study were included.

Exclusion criteria

Individuals with decreased salivary flow, due to the use of medications or diseases, such as diabetes mellitus and autoimmune diseases; people with cognitive disabilities or whose general health conditions prevented them from understanding the guidelines or performing the necessary procedures; and individuals who missed more than two consultations/assessments were excluded.

Procedures

Consenting participants completed the socioeconomic questionnaire and underwent anamnesis and physical examination at their first dental appointment. Data on tumor location, clinical staging, and total radiation dose to be applied were collected. Stimulated saliva was collected at the first and 24th sessions of radiotherapy.

At the 24th session, the oral cavity was examined again, and the established xerostomia questionnaire was administered. Radiotherapy for the head and neck region is usually performed 5 times a week for 7 weeks. Considering that in each session there was an irradiation of 200 cGy (2 Gy), at the end of the 35th session, each patient would have received a total of 7,000 cGy or 70 Gy of ionizing radiation. The minimum irradiation dose to participate in the research protocol was 5600 cGy or 56 Gy, which is equivalent to 28 radiotherapy sessions.

Determination of SFV

Stimulated saliva was collected for 5 min according to the methodology proposed by Krasse (1998)[11]. Before collection, the researcher instructed the participants to perform two sequenced folds in paraffin film (Parafilm ® M - 4", Bemis Company, Winsconsin, USA), in order to better accommodate it in the mouth. The film was placed on the tongue for 1 min and participants swallowed all the saliva present in the oral cavity. Finally, they chewed the film for the proposed time, spitting out all the saliva secreted during the examination into a millimeter container. After keeping the sample at rest for 10 min, stimulated SFV was calculated up to at least two decimal places by dividing the total volume of saliva collected, by the examination time.

Patients were classified according to the classification proposed by Thylstrup and Fejerskov (1995)[12] for stimulated saliva.

1) normal flow rate: between 1.0 mL/min and 2.0 mL/min;
2) reduced flow rate: >0.7mL/min but <1.0 mL/min;
3) hyposalivation: ≤0.7 mL/min.

Application of the xerostomia questionnaire

The xerostomia questionnaire was developed and evaluated by Pai et al. (2001)[13] and was based on previous objective and subjective assessments of salivary function. Two main aspects of saliva production were subjectively investigated: (1) dryness of the oral mucosa (lips, mouth, tongue, and throat) and (2) decreased functional capacity caused by this dryness (difficulty in swallowing and speaking). In addition, dryness of the mouth in general (amount of saliva in the mouth) and the level of thirst were evaluated. All assessments were based on a visual analog scale (VAS). Patients were instructed to quantify each item by marking a vertical line on a horizontal scale of 100 mm immediately after saliva collection.

Statistical analysis

A database in Excel 2016 was created for descriptive analyses (mean, percentage, and coefficient of variation) to identify the general and specific characteristics of the study population.

RESULTS

After analyzing a total of 200 medical records of patients treated between January 2019 and March 2020 (start of the coronavirus pandemic) by the dental team, 20 patients who met the inclusion/exclusion criteria were enrolled in the study. However, for the results presented here, data from 16 patient, who correctly and completely filled out their information, were considered. Table 01 presents the sociodemographic data of the 16 patients included in this study.

Table 01. Sociodemographic profile of patients (Dental Service, UNACON-OSID – 2019/2020).

CHARACTERISTICS	(n=16)	(%)
SEX		
Male	10	62.50%
Female	6	37.50%
AGE GROUP		
Age 30–45	2	12.50%
Age 46–70	9	56.25%
Age >70	5	31.25%
SKIN COLOR (SELF-DECLARED)		
White	3	18.75%
Brown	7	43.75%
Black	6	37.50%
SCHOLARITY		
Illiterate	1	6.25%
Incomplete elementary school	7	43.75%
Complete elementary school	3	18.75%
Incomplete high school	0	0%
Complete high school	5	31.25%
University education	0	0%
ETHYLIST		
Yes	9	56.25%
No	7	43.75%
SMOKER		
Yes	7	43.75%
No	9	56.25%

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Table 02 presents data related to tumors and treatment of the same individuals.

Table 02. Tumor and treatment data (Dental Service, UNACON-OSID - 2019/2020).

CHARACTERISTICS	(n=16)	(%)
TYPE OF TREATMENT		
Radiotherapy	8	50.00%
Radiotherapy/Chemotherapy	6	37.50%
Radiotherapy/Surgery	2	12.50%
Radiotherapy/Chemotherapy/ Surgery	0	0%
PRIMARY TUMOR LOCATION		
Soft palate	2	12.50%
Hard palate	1	6.25%
Glottis	1	6.25%
Larynx	5	31.25%
Tongue	2	12.50%
Mandible	1	6.25%
Oropharynx	3	18.75%
Parotid	1	6.25%
STAGE		
T1 / T2	9	56.25%
T3 / T4	5	31.25%
TX	2	12.50%

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The number of radiotherapy sessions ranged from 28 to 35, with an average of 33 sessions among 16 patients, consistent with 66 Gy of radiation at the end of treatment. The number of chemotherapy sessions ranged from 3 to 8, with an average of 5 among the 6 patients who received chemotherapy combined with radiotherapy. SFV values at the beginning (1st session) and end (24th session) of treatment were included.

As shown in Table 3, at the 1st radiotherapy session, 08 (50.0%), 01 (6.3%), and 07 (43.7%) patients had normal SFV (between 1.0 mL/min and 2.0 mL/min), reduced SFV (> 0.7mL/min and < 1.0mL/min) and hyposalivation (≤0.7mL/min), respectively. At the 24th radiotherapy session, four (28.6%), 01 (7.1%), and 09 (64.3%) patients had normal VFS, reduced SFV, and hyposalivation, respectively. Data of two patients were not obtained as they failed to attend the service.

Table 03. Distribution of the number and percentage of patients according to the classification of Thylstrup e Fejerskov (1995)[12] for salivary flow velocity at the 1st and 24th radiotherapy treatment sessions (Dental Service, UNACON-OSID – 2019/2020).

SFV	1st session (n)	24th session (n)
Normal (between 1.0 mL and 2.0 mL/min)	8 (50.0%)	4 (28.6%)
Reduced (> 0.7 mL/min and < 1.0 mL/min)	1 (6.3%)	1 (7.1%)
Hyposalivation (≤0.7 mL/min)	7 (43.7%)	9 (64.3%)
Total of patients	**16**	**14**

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Note: It was not possible to obtain data from two patients who did not attend the evaluation of the Dentistry team at the Service at the 24th session.

Table 4 presents the means of the VAS domains of xerostomia questionnaire at the 1st and 24th radiotherapy sessions. Analyses revealed an increase in the average values of all variables between the 1st and 24th sessions of radiotherapy.

As shown in Table 5, data analysis showed extremely high coefficients of variation.

DISCUSSION

In this study, evaluation of the sociodemographic profile of the sample showed that there was a predominance of men (62.50%), aged between 46 and 70 years (56.25%), of self-declared mixed race (43.75%), who had not completed elementary school (43.75%), and consumed alcohol (56.25%). These factors were correlated as the main causes of increase in HNC[14]. The sociodemographic profile of this sample is in agreement with that reported in the literature[9,14,15]. Smoking is one of the main risk factors associated with tumors in this region. It is noteworthy that, unlike most previous studies on HNC[9,14,15], 43.75% of the participants were smokers, which can be explained by the fact that patients who stopped smoking after the diagnosis did not indicate the smoking habit prior to the diagnosis, although information was collected carefully during the anamnesis by the members of the research group.

Tumor-related data showed that the predominant treatment was radiotherapy (50.00%), followed by radiotherapy associated with chemotherapy (37.50%) and surgery associated with radiotherapy (12.50%).

Table 04. Mean VAS scores for stimulated SFV and xerostomia for each patient at the 1st and 24th radiotherapy sessions (Dental Service, UNACON-OSID - 2019/2020).

Nº patient	SFV (mL/min)		DM		DL		DT		Dth		DS		DSp		AS		HL	
	1ª Session	24ª Session	1ª Session	24ª Session	1ª Session	24ª Session	1ª Session	24ª Session	1ª Session	24ª Session	1a Session	24ª Session	1a Session	24ª Session	1a Session	24ª Session	1ª Session	24ª Session
1	2	0.66	0	0	2	3	0	0	0	0	0	2	0	4	2	9	0	0
2	0.64	0.32	0	0	3	3	0	0	5	0	0	6	0	0	0	9	5	0
3	0,2	0	0	2	0	1	0	0	0	0	0	0	0	0	0	10	0	8
4	1.86	0	0	5	0	5	0	5	0	0	0	0	0	0	7	5	0	2
5	0.64	0.92	0	0	0	2	0	0	0	2	0	4	0	0	10	4	0	7
6	2.2	0.3	6	5	1	2	3	4	5	5	5	5	5	5	6	4	8	6
7	2,2	1.8	0	0	0	0	0	0	6	10	2	8	0	0	6	0	9	10
8	2.26	2.4	0	0	0	0	0	0	0	0	0	4	0	0	0	0	5	6
9	0	0	NI	4	NI	6	NI	3	NI	4	NI	0	NI	2	NI	8	NI	0
10	1.2	0	0	8	1	1	0	1	0	8	0	7	0	3	10	8	0	1
11	0.5	0.22	2	5	2	5	3	0	0	5	1	8	0	2	0	5	3	5
12	3	1	0	0	0	2	0	0	0	0	0	0	0	0	0	4	0	4
13	2.06	1.72	2	2	9	2	2	2	0	2	0	2	5	2	8	6	3	3
14	0.6	NI	5	NI	1	NI	0	NI	0	NI	0	NI	0	NI	0	NI	0	NI
15	0.74	NI	1	NI	3	NI	1	NI	0	NI	0	NI	0	NI	0	NI	1	NI
16	0	0.6	NI	0	NI	0	NI	0	NI	0	NI	0	NI	0	NI	5	NI	0
Mean	**1.25**	**0.1**	**1.1**	**2.2**	**1.6**	**2.3**	**0.6**	**1.1**	**1.1**	**2.6**	**0.6**	**3.3**	**0.7**	**1.3**	**3.5**	**5.5**	**2.4**	**3.7**

SFV, salivary flow velocity; DM, dryness of the mouth; DL, dryness of the lips; DT, dryness of the tongue; DTh, dry throat; DS, difficulty swallowing; DSp, difficulty speaking; AS, amount of saliva; HL, headquarters level; and NI, no information;
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Table 05. Distribution of variables (Dental Service, UNACON-OSID – 2019/2020).

VARIABLE	(n)	MEAN	MAXIMUN	MINIMUN	COEFFICIENT OF VARIATION
Salivary flow	16	0.81	1.90	0.05	82.09
Dry mouth	16	2.66	6.50	0	80.38
Dry lips	16	2.62	6.50	0	70.57
Tongue dryness	16	1.31	3.70	0	105.02
Dry throat	16	2.52	9.20	0	98.05
Difficulty swallowing	16	2.26	7.40	0	79.60
Difficulty speaking	16	1.63	4.50	0	94.88
Amount of saliva	16	4.89	8.60	0	39.65
Headquarters level	16	3.43	9.80	0	79.15

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In this sample, there were no cases of exclusive surgery. Although surgery is the main treatment option for HNC, depending on the location of the tumor and the margins of necessary resections, surgical procedures can permanently compromise vital structures and essential functions[16]. For example, removal of the salivary glands could have influenced the results of this study due to the reduction in SFV due to the absence of the producing gland. Although it is known that both radiotherapy and chemotherapy cause side effects in these organs, surgical removal of the glands directly affects salivary production.

The most common site of tumor was the larynx (31.25%), a finding that corroborates the study of Rocha et al. (2017)[14], followed by the oral cavity (31.25%), which comprises the anterior 2/3 of the tongue, floor of the mouth, lips, hard palate, gums, salivary minor glands, and oral mucosa. Previous studies have shown a predilection for primary cancer in the oral cavity due to direct exposure to carcinogens and harmful habits[9,15,17]. Regarding staging, the majority of tumors were categorized as T1 or T2 (56.25%). This result differs from those of previous studies, which

show greater involvement of the tumor due to late diagnosis, usually resulting from the location of the lesion, absence of symptoms in the initial stage, and difficulty in accessing health care[9,14,15,17,18], especially when it comes to public health service. This difference may be explained by the fact that the information about tumor staging was absent in 12.50% of medical records in our sample, which hinders a more assertive interpretation of the numbers.

The mean SFV at the 1st session was normal (1.25 mL/min), but reduced at the 24th session (0.71 mL/min). This considerable decrease demonstrates that, although none of the analyzed patients underwent surgical excision of the salivary glands, the treatment of choice may have caused indirect injury to the salivary glands, which resulted in a reduction in SFV during the treatment period. This result is similar to that of a study by Silva et al. (2017)[19] who, using the technique of spontaneous sialometry, found that reduced salivary flow before radiotherapy was present in 35% of 20 patients, and 100% of the patients had some degree of reduction in salivary flow at the end of radiotherapy. It is noteworthy that in the present study, SFV was evaluated using stimulated saliva. In the study of stimulated SFV by Lima et al. (2004)[10], 40% of 42 patients had SFV classified as hyposalivation prior to radiotherapy. During radiotherapy, this percentage increased to 82% and reached 97.3% at the end of the treatment. In addition, they found that hyposalivation persisted for up to six weeks post-radiotherapy. Similar to the studies by Silva et al. (2017)[19] and Lima et al. (2004)[10], in the present study, the daily dose of irradiation was 200 cGy, and although the final treatment dose varied, it was always > 4,000 cGy; therefore, it was capable of causing permanent damage to the salivary glands[20].

Regarding the analysis of the observed pattern of salivary dysfunction using the VAS for xerostomia, there was an increase in the mean scores at the 24th session compared to the initial session of radiotherapy. This increase in mean VAS scores reveals that a higher VAS score associated with a reduction in the SFV results in more interference in the functional capacity and, consequently, in the patient's quality of life. Silva et al. (2017), by applying the EORTC H&N35 questionnaire, showed significant differences in the domains irritation in the mouth ($p = 0.0020$), choking ($p = 0.0005$) and sticky saliva ($p = 0.0313$), before and after radiotherapy.

CONCLUSION

This study showed that there was an inverse correlation between average score on the xerostomia scale (VAS) and SFV between the 1st and 24th radiotherapy treatment sessions in patients with HNC; that is, an increase in VAS scores corresponded to a worsening of SFV. Thus, serial evaluation of SFV and the use of a questionnaire-based VAS are important for the correct diagnosis, monitoring, and prognosis of oral conditions, especially in risk groups.

Further studies with a larger sample size would allow a more accurate analysis of data, with more reliable statistical results to correlate hyposalivation (objective) with xerostomia (subjective).

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