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Evaluation of Radiation-induced Xerostomia in Patients with Nasopharyngeal Carcinomas

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Abstract

Background and aims. Salivary glands are extremely susceptible to radiation injuries. The aim of this study was to evaluate radiation-induced xerostomia in patients with nasopharyngeal carcinomas, referring to Tabriz Imam Khomeini Hospital in 2005-2006.

Materials and methods. Thirty patients with nasopharyngeal carcinomas, who received conventional radiotherapy, were included in the present study. The patients' unstimulated saliva samples were collected at three intervals, i.e. before treatment, 3 weeks after the initiation of treatment and at the end of treatment by spitting, and measured with a graduated pipette.

Results. The differences in the mean values of the patients' salivary flow rates at three afore-mentioned intervals were statistically significant ($p<0.001$). Two-by-two comparison of the mean values of salivary flow rates of all the patients and of males and females, carried out separately, demonstrated statistically significant differences ($p<0.0025$). However, there were no statistically significant differences between males and females before treatment ($p = 0.723$), 3 weeks after the initiation of treatment ($p = 0.724$) and at the end of treatment ($p = 0.595$). There were no statistically significant relationships between age and a decrease in salivary flow rate in the total sample ($p = 0.76$, $r = -0.057$), in males ($p = 0.96$, $r = 0.011$) and in females ($p = 0.539$, $r = -0.208$).

Conclusion. Conventional radiotherapy results in severe xerostomia in 3 weeks in patients with nasopharyngeal carcinomas. Age and sex do not influence radiotherapy-induced xerostomia.

Key words: **Conventional radiotherapy, nasopharyngeal carcinoma, xerostomia.**

Introduction

Saliva plays various important roles in the oral cavity. Proper function of salivary glands is absolutely necessary for oral and dental health. Qualitative and quantitative disturbances in the function of salivary glands are detrimental to the oral environment, adversely influencing patients' quality of life.[1,2] Three pairs of salivary glands, namely parotid, sublingual and submandibular glands, secrete saliva into the oral cavity

through specific ducts. These glands produce 1-1.5 lit of saliva daily.[1]

Salivary glands are extremely susceptible to radiation injuries with parotid glands being more susceptible than others. Serous acini are more susceptible to radiation compared to mucous acini.[1,2] Clinical evaluations have demonstrated that subsequent to a single radiotherapy dose, serous acini are immediately destroyed; however, mucous acini demonstrate no acute histological changes. Therefore, immediately after radiotherapy is initiated, patients' saliva becomes thicker. With the continuation of radiotherapy, mucous cells are also affected and salivary flow rate decreases, depending on the gland that is in the path of direct radiation rays.[2,3] The severity of xerostomia depends on the gland involved, radiation dose and dose rate (the intervals of radiations).

The glands that are partially exposed to radiation demonstrate higher salivation compared to the glands that are completely exposed to radiation. Radiation exposure on one side may not completely affect glands on the other side; therefore, it may not result in severe xerostomia. However, directing rays to the nasopharynx exposes parotid glands to radiation on both sides, leading to severe xerostomia.[2,3,4]

Xerostomia, the most common complication in patients with nasopharyngeal carcinomas following radiotherapy, makes mastication, deglutition and denture wearing difficult for patients. In addition to its constant effect on the patient's daily life, long-term xerostomia predisposes the patient to oral candidiasis. Subsequent to radiotherapy, these patients run a higher risk of dental caries, especially root surface caries. This higher risk is attributed to a decrease in saliva quality and quantity, a shift in the oral flora towards cariogenic microorganisms, and changes in diet. Therefore, it is critically important that dental practitioners have broad knowledge about potential oral complications following radiotherapy procedures in the head and neck region to be able to render efficacious treatment modalities and minimize or eliminate problems.[2,5]

No definitive treatment modalities or preventive measures have been introduced for xerostomia to date. In our community no studies have been carried out about xerostomia; therefore, we decided to evaluate xerostomia in patients under radiotherapy before engaging in an interventional study and comparing various procedures and confounding variables. We decided to use the results of this preliminary study in the following interventional study to determine factors involved in decreasing xerostomia severity. Since, according to some studies, xerostomia and other concomitant complications of radiotherapy begin to manifest themselves approximately in the third week of the procedure we decided to compare the third week data with baseline records.[6]

Materials and Methods

The present study was a self-controlling clinical trial. The study was carried out in the Radiotherapy Department of Tabriz Imam Khomeini Hospital.

All of the patients referring to the Department of Radiotherapy from 22 June 2005 to 21 June 2006, who had the following inclusion criteria, were included in the study:

1. Nasopharyngeal carcinomas with similar stages, i.e. local and local advanced stages
2. No history of surgical removal of salivary glands
3. Absence of any signs and symptoms of distant metastasis
4. No history of saliva-reducing medications, such as anticholinergics and antidepressants
5. Absence of diabetes (evaluated with FBS test before the study)

A questionnaire was filled out for each patient. All the patients granted their informed written consent before sample collection. The patients were asked to refrain form eating, drinking, brushing and smoking at least for two hours before sample collection. In addition, they were given identical hygienic and food regimens. During the study all removable prostheses were removed so that they could not function as foreign bodies which can act as impeding factors in salivation. All the samples were collected in one well-illuminated room while the patients were in a sitting position.

The radiotherapy of these patients was an external procedure, in which the nasopharyax and lymph nodes of the neck received Cobalt 60 (~6MV) radiation with two

lateral fields, which consisted of an initial dose of 4400-4500 cGY in 25 sessions (fractions), comprising 180-200 cGY daily.

The patients received the dose 5 days a week, from Saturday to Wednesday. Then, after a two-day interval, spinal cord was removed from the radiation field and the field was tailored. The treatment continued until the dose increased to 6500-6700 cGY daily. Based on the case involved, the patients received a booster dose, which is a procedure called "conventional radiotherapy."[4]

Saliva samples were collected by spitting method three times, i.e. before treatment, 3 weeks after the initiation of treatment and at the end of treatment.

During sample collection, the patients evacuated their saliva into a glass every 60 seconds for 2-5 minutes and then the volume of the sample was measured with a graduated pipette and recorded in the patients' questionnaires.

Statistical Analysis

One-way ANOVA to test the significance of differences between means, paired sample t-test for the two-by-two comparison of means, independent sample t-test to compare the differences in the mean values between independent groups, and Pearson's correlation coefficient to evaluate the relationship between quantitative variables were used. SPSS 14.0 software was used for data analysis. In the present study $p<0.05$ was defined as statistically significant and means were reported as Mean±SD.

Results

A total of 30 subjects were studied, 63.3% being males and 36.7% females (19 males and 11 females). Mean age of the patients was 51.17±15.44; mean age of females and males were 51.36±14.88 and 51.05±16.16, respectively. Mean values of salivation before radiotherapy in the study population, and in males and females separately, were 1.32±0.37 mL, 1.34±0.41 mL, and 1.25±0.30 mL in 5 minutes, respectively.

Mean values of salivation in the third week after the initiation of treatment in the study population, in males and females separately were 0.84±0.35 mL, 0.85±0.38 mL and 0.80±0.90 mL in 5 minutes, respectively. Means of salivation at the end of treatment in the study population, in males and females separately were 0.42±0.31 mL, 0.44±0.33 mL and 0.38±0.28 mL in 5 minutes, respectively (Tables 1 & 2).

Table 1. The results of one-way ANOVA & independent sample t-test

		t	df	P-Value
Salivation 1	Salivation 2¥	10.23	29	<0.0005
Salivation 1	Salivation 3¥	15.8	29	<0.0005
Salivation 2	Salivation 3¥	10.61	29	<0.0005
Salivation 1	Salivation 2£	8.22	18	<0.0005
Salivation 1	Salivation 3£	11.79	18	<0.0005
Salivation 2	Salivation 3£	7.38	18	<0.0005
Salivation 1	Salivation 2ψ	5.81	10	<0.0005
Salivation 1	Salivation 3ψ	10.34	10	<0.0005
Salivation 2	Salivation 3ψ	8.44	10	<0.0005
Salivation 1	Salivation 1Ч	0.359	28	0.723
Salivation 2	Salivation 2Ч	0.357	28	0.724
Salivation 3	Salivation 3Ч	0.357	28	0.595

Salivation 1: Salivation before radiotherapy ¥: All the subjects
Salivation 2: Salivation 3 weeks after radiotherapy £: Males ψ: Females
Salivation 3: Salivation at the end of radiotherapy Ч:Males compared to Females

Table 2. Percentage of decrease in mean salivation rates

	3 weeks after treatment began	At the end of treatment compared to baseline	At the end of treatment compared to 3 weeks after treatment began
percentage of decrease in all the subjects	36.52%	68%	49.6%
percentage of decrease in males	36.07%	66.6%	47%
percentage of decrease in females	37.32%	70%	52.8%

Pearson's correlation coefficient demonstrated the following: There was no statistical relationship between the decrease in salivary flow rate and all patients' age ($p = 0.76$, $n = 30$, $r = -0.057$), males' age ($p = 0.96$, $n = 19$, $r = 0.011$) and females' age ($p = 0.539$, $n = 11$, $r = -0.208$).

Discussion

Despite great progress in cancer biology and radiotherapy techniques in recent decades, malfunction of salivary glands remains a major and ever-lasting problem subsequent to radiotherapy of head and neck malignancies. The condition usually manifests itself 3 weeks after radiotherapy begins. Despite individual variations, the majority of patients experience severe xerostomia, which adversely influences their quality of life.[7] The present study addressed radiotherapy-induced xerostomia in patients with nasopharyngeal carcinomas. The patients' salivary samples were collected by spitting at three intervals: before treatment, 3 weeks after radiotherapy was instituted, and at the end of treatment. The results demonstrated that differences in the means of salivation 3 weeks after the initiation of radiotherapy compared to baseline data, at the end of radiotherapy compared to baseline data, and at the end of treatment compared to 3 weeks after radiotherapy was initiated, were statically significant. However, there was no relationship between the decreases in the means of salivation and variables such as age and sex. The results of the present study are consistent with the results of studies carried out by Jen Yee-Min et al, 2006; Nagler, 2002; Moller et al, 2004.[1,3,8]

Yee-Min attributed the decrease in salivary flow rate to the destruction of cells in serous acini and to the progression of an acute classic inflammatory process, which takes place 24 hours after receiving a 12.5-Gy radiation dose. The histologic basis for a decrease in salivary flow rate has not been elucidated to data. However, recent molecular evaluations have demonstrated that pro-inflammatory cytokines such as TNF-α result in a decrease in the release of Aquaporin 5 (a group of membrane proteins responsible for the transportation of water through membranes), contributing to a decrease in the production of aqueous solution of saliva. Yee-Min introduced the received radiation does as the most important factor involved in radiotherapy-induced xerostomia.[8]

Nagler reported that the complications of radiotherapy manifested in the salivary glands in the first weeks after the institution of radiotherapy are transient and secondary to oropharyngael syndrome. The syndrome consists of a transient severe mucositis, resulting in dehydration, malnutrition and inadequate chewing of food due to intense pain. These indirect changes lead to a noticeable decrease in parotid gland activity. The changes do not directly affect the secretory parenchyme of the glands. Nagler introduced cell death through apoptosis as an important factor in early radiation-induced xerostomia; this cell death was attributed to injuries to membranes as a result of peroxidation of membrane lipids. In addition, long-term xerostomia was attributed to the damage to DNA, which can be observed during cellular mitosis, and to a decrease in mitotic rate.[3]

Moller, consistent with Nagler's report, attributed the noticeable decrease in salivation to the death of cells in serous acini through apoptosis in the early stages and to cellular necrosis in the late stage. In addition, Moller believed the received dose by salivary glands was an important factor in

determining the severity of xerostomia, pointing out that more than 2/3 of the baseline salivation is lost during radiotherapy.[1] Considering the results of the above-mentioned studies and the almost identical doses used in those studies and our study (approximately 60-65 Gy), we believe similar mechanisms were involved in our subjects. Although we have been unable to find a research study, thoroughly evaluating the effects of age and sex on radiation-induced xerostomia, the results of our study in terms of the influence of age and sex on salivary flow rate are consistent with the results of studies carried out by Yee-Min et al, 2006; Liu et al, 1990; Moller et al, 2004; Shern et al, 1993; Bretz et al, 2001; and Fischer, 1990. However, our results do not coincide with the results of a study carried out by Fenoll-Palomanes, 2004, who reported statistically significant relationship between sex and decrease in salivation and also between age and decrease in salivary flow rate.

Percival attributes the lower rate of salivation in females compared to males, which is statistically significant, to the smaller size of salivary glands in women and hormonal differences. Postmenopausal females have a lower salivary flow rate but this lower rate cannot be attributed to a decrease in estrogen secretion and further comprehensive studies are required.[9]

Fenoll-Palomares believes, in addition to the smaller size of salivary glands in females, higher rate of autoimmune diseases in females compated to males is involved in the lower salivary flow rate in females since autoimmune diseases are important factors involved in xerostomia.[10]

Percival attributes the disparity between the results of his study with the results of studies carried out by Ben-Aryeh et al, 1984, and Heft and Baun, 1984, to differences in sample collection methods.

Ben-Aryeh and Heft and Baun did not find any statistically significant differences between males and females. Percival collected his samples in a 10-minute period (contrary to 5-minute periods in the present study and other studies), which may have resulted in higher volumes of salvation and different results.[9] We, too, attribute lack of significant differences between males and females, in the present study, to differences in the methods employed and recommend further extensive studies to elucidate the role of gender in radiotherapy-induced xerostomia.

There is considerable controversy over the role of age in salivary flow rate and only limited studies have been carried out on the subject. Researchers have attributed the differences in results to differences in the methods used, differences in the criteria for case selection, differences in sample collection and finally inclusion of subjects who were taking medications which influence salivation.[10]

A study by Scott in 1977 demonstrated histologic changes in human submandibular salivary glands due to senescence. Some researchers believe that unstimulated salivary flow rate decreases with age, which can be attributed to the destruction of the parenchyme of the glands due to senescence.[11] On the contrary, some researchers such as Fischer (1999) believe that healthy senile individuals have a salivary flow rate similar to healthy young people and attribute this similarity to the high reserve capacity of salivary glands, especially parotid, which has also been confirmed in the present study.[12]

Conclusion

The present study confirms that patients with nasopharyngeal carcinomas will experience severe xerostomia subsequent to radiotherapy, with no statistically significant differences between males and females.

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