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CLINICAL INVESTIGATION **Head and Neck**

THE EFFECT OF PILOCARPINE AND BIPERIDEN ON SALIVARY SECRETION DURING AND AFTER RADIOTHERAPY IN HEAD AND NECK CANCER PATIENTS

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Purpose: The influence of parasympathicomimetic pilocarpine and anticholinergic biperiden on salivation in patients irradiated for malignant tumors of the head and neck region was assessed in a prospectively designed clinical study.

Methods and Materials: Sixty-nine patients, irradiated for head and neck cancer with salivary glands included in the irradiation fields, were randomly assigned into three groups (A, B, and C). Group A consisted of patients receiving pilocarpine, group B of those who were receiving biperiden during radiotherapy and pilocarpine for 6 weeks after its completion, while group C comprised patients not receiving any xerostomy prevention therapy during or after radiotherapy. The quantity of secreted unstimulated saliva was measured before the beginning of radiotherapy, after 30 Gy of irradiation, on completed irradiation, and 3, 6, and 12 months after completion of radiotherapy.

Results: Saliva secretion has been found to be the least affected by irradiation treatment in the group of patients receiving biperiden throughout the course of radiotherapy. Six months after completed irradiation, the differences in the quantity of secreted saliva between groups C and B as well as between groups A and B were statistically significant ($P = 0.002$ and 0.05 respectively). In patients receiving pilocarpine during radiotherapy, and those in the control group, further decrease in saliva secretion was observed. One year after completed therapy, the quantity of secreted saliva could only be measured in the patients receiving biperiden during radiotherapy: it amounted to 16% of the average quantity of saliva secreted before the beginning of irradiation.

Conclusion: It seems that the inhibition of saliva production during irradiation treatment and the stimulation after completed radiotherapy may contribute to the preservation of salivary gland function after therapy.

Head and neck, Carcinoma, Radiotherapy, Xerostomy.

INTRODUCTION

Normal salivation is an essential component of oral health due to its important contributions to oral defense mechanisms and digestive functions (1). When irradiating patients with head and neck carcinoma it is often impossible to avoid the irradiation of major salivary glands. During irradiation treatment, patients quickly note reduced production of saliva and increase in its viscosity (2). Lack of saliva may lead to dental caries and mucosal alterations.

The degree of radiation injury to salivary glands depends on the total dose and the proportion of gland that was irradiated. Histopathological studies of irradiated animals showed that acinar cells are the most radiosensitive glandular component. The excretory ducts are relatively insensitive, and the intercalated and striated ducts are of intermediate sensitivity (3). The serous acini of the parotid gland are apparently more radiosensitive than the seromucous acini of the submandibular, and much more than the mucous acini of the sublingual gland (4).

There were many attempts to mitigate the effects of irradiation on salivary glands. Some authors (5, 6) report that pilocarpine given during the irradiation treatment helps to maintain some secretion of saliva. Others found that pilocarpine given after the completion of irradiation treatment improved the salivation (7–12). On the other hand, Ahlner (13, 14) reported that better salivation was achieved in animal experiments if the function of salivary glands had been inhibited during the irradiation. However, the number of patients receiving pilocarpine during the irradiation in these studies was small, and the studies where the salivary glands were inhibited during the irradiation were performed on experimental animals. Thus, the question how to alleviate the irradiation effects on salivary glands in patients irradiated for carcinoma of the head and neck remains unclear.

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Table 1. Distribution of patients by tumor site

	Group			
Localization	A	B	C	Total
Oral cavity	4	5	5	14
Oropharynx	2	16	15	33
Hypopharynx	1	3	4	8
Larynx	2	5	4	11
Other	0	1	2	3
Total	9	30	30	69

The aim of present research was to study the influence that parasympathicomimetic drug (pilocarpine) or parasympathicolytic drug (biperiden) may have on the salivation in patients irradiated for head and neck carcinoma.

MATERIALS AND METHODS

Patients

Sixty-nine patients irradiated for head and neck cancer, and who had the salivary glands included in the irradiation field, entered the study. The patients were randomly assigned into three groups as follows: group A consisted of patients receiving pilocarpine during radiotherapy; patients of group B received biperiden during irradiation and pilocarpine after completed therapy; patients in group C did not receive any treatment for prevention of radiation-induced xerostomy either during or after therapy. Groups B and C consisted of 30 patients each, while there were only 9 patients in group A. Randomization into the latter group was stopped because of ethical reasons.

The patients' age ranged between 32 and 72 years (median 62 years); there were 9 females and 60 males. The distribution of patients in the groups by tumor site is shown in Table 1; the distribution by stage is presented in Table 2. Forty-four patients had postoperative irradiation, and 25 were treated by radiotherapy alone.

Irradiation

All patients were immobilized with thermal plastic cast and were treated with cobalt rays or 5 MeV X-rays. The standard arrangement consisted of opposing lateral portals, loaded 1:1. The portals included gross tumor disease and adjacent tissue of potential tumor spread. In postoperative treatment, primary site and both necks were treated. The computer-generated treatment plan was done in 3 cross-sections through the irradiated volume in such a way that the irradiation dose in the clinical target volume varied from 95% to 105% of the stated dose. Patients were treated with 5×2 Gy per week. The irradiated volume was reduced two times during the irradiation treatment: at 40 Gy for shielding off the spinal cord and at 60 Gy for treating the area of original disease only, up to 70 Gy, where sometimes other beam combinations were used. Postoperatively, patients received 50 Gy–56 Gy with parallel opposed portals only. In case of extracapsular spread and lymph or blood vessels involvement, the affected area was boosted up to 62 Gy–64 Gy, usually with 10 MeV electrons.

Table 2. Distribution of patients by stage (TNM, UICC 1987)

	Group			
Stage	A	B	C	Total
I	0	3	3	6
II	3	8	10	21
III	4	9	14	27
IV	2	10	3	15
Total	9	30	30	69

We did not have the possibility of CT/MR 3D treatment planning and the volume of the salivary glands could not be assessed. Instead, the proportion of salivary gland mass included in the irradiation fields and the dose of irradiation delivered to the salivary glands were assessed in each individual patient. The anatomic position of salivary glands as determined by diagnostic CT or palpation was delineated on the simulation/verification film. By comparison of the delineated glandular mass and borders of the treatment portals with the treatment plan, the irradiated proportion and the dose to the glandular tissue could be approximately assessed. As the sublingual gland was irradiated in only 7 patients from all three groups, and since this gland contributes only 4% to the total saliva secretion, the amount of the received dose and the proportion of the irradiated glandular mass for this site were not calculated separately.

Prior to the beginning of radiotherapy, the patients had their teeth repaired or extracted due to caries or periodontites, and a denture cast/spoon was taken for local fluoride gel application; patients in all three groups were applying fluoride gel onto their teeth for 5 minutes every day throughout the course of radiotherapy. After completed therapy, the fluorination of the teeth was continued three times weekly.

Pilocarpine and biperiden

During irradiation and 6 weeks after completed therapy, the patients in group A received 5 mg pilocarpine hydrochloride perorally three times daily. The time schedule of pilocarpine administration during radiotherapy was adjusted so that the patient received one dose of the drug 1 hour before irradiation.

The patients in group B received two 2-mg tablets of biperiden chloride 1½ hours before irradiation, and pilocarpine hydrochloride for 6 weeks after the completed therapy 5 mg three times daily. The patients in group C received neither pilocarpine nor biperiden during irradiation or after it.

Assessment of acute side effects of irradiation

The degree (severity) of radiomucositis was assessed according to WHO criteria (15): 0—no changes of the mucosa; 1—pain and erythema of the mucosa; 2—erythema and individual ulcerations of the oral mucosa; 3—numerous

Table 3. Mean irradiation dose delivered to the area of salivary glands (in Gy)

	Group		
Salivary gland	A	B	C
Parotid	56.4	57.1	58.5
Submandibular	56.9	56.7	58.3

ulcerations of the oral mucosa; 4—the whole or most of the oral mucosa is covered with ulcerations.

The WHO criteria were also used for the assessment of difficulties on swallowing: 0—no difficulties; 1—minimal difficulties; 2—possible ingestion of pulpy food; 3—possible ingestion of liquid food; 4—ingestion of food is not possible.

The measurement of saliva

The quantity of saliva was evaluated at the beginning of the treatment, at 30 Gy, after completed course of irradiation, and 3, 6, and 12 months after completed therapy. The quantity of secreted saliva was measured in a quiet place, between 8 and 9 a.m. The patients were spitting saliva for 10 minutes into the measuring cylinder. Since we were interested in the total quantity of secreted saliva rather than in the function of individual glands, it was decided to collect all nonstimulated saliva.

Statistical methods

Statistical evaluation of the results was done by means of Student's *t*-test. The differences between individual groups were determined with difference of variance. The study was carried out according to the principles of the Helsinki–Tokyo declaration, and was approved by the medical ethics committee of Slovenia.

RESULTS

Radiation dose to salivary glands

There was no significant difference between the groups in the mean irradiation dose delivered to the salivary glands (Table 3) and in the proportion of the irradiated glandular mass (Table 4).

Table 4. Proportion of irradiated glandular mass

		Group		
Gland	Dose received	A	B	C
Parotid	30 Gy	91%	93%	96%
	>30 Gy	77%	77%	78%
Submandibular	30 Gy	100%	97%	100%
	>30 Gy	100%	96%	98%

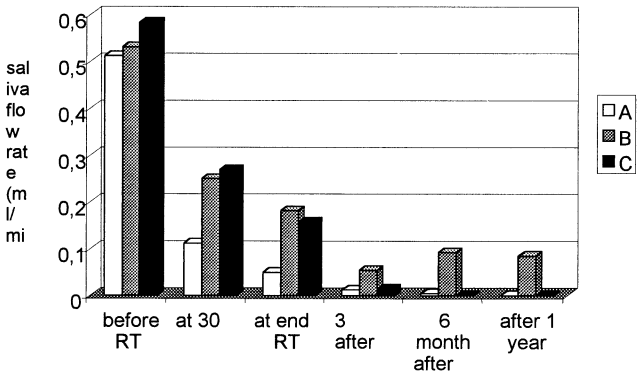

Fig. 1. Mean quantity of secreted saliva in particular groups (ml/min) (RT, radiotherapy).

Quantity of secreted saliva

Group A. In the first group of patients, the mean quantity of saliva secreted before the beginning of irradiation was 0.5 ml per minute (SD 0.2 ml/min). At 30 Gy, total cessation of saliva secretion occurred in 5 patients, whereas in 4 the secretion was still measurable. The mean quantity of saliva secreted in this group at 30 Gy was 0.1 ml per minute (SD 0.13 ml/min), and after completed therapy 0.05 ml per minute (SD 0.05 ml/min). Three months after completed radiotherapy, saliva secretion was detectable in only one patient, the mean value in this group being thus 0.01 ml/min. Six months after completed radiotherapy, the mean quantity of saliva secreted in group A decreased to 0.006 ml/min. One year after completed radiotherapy none of the 7 surviving patients presented with a detectable saliva secretion (Fig. 1).

Group B. Before the beginning of irradiation, the mean quantity of saliva secreted in group B patients was 0.53 ml per minute (SD 0.2 ml/min). During irradiation and after it, the number of patients with measurable saliva secretion was gradually decreasing (Table 5). Thus, at 30 Gy it could be measured in 25 patients, after completed irradiation in 21, and 1 year after treatment in 17 patients. At 30 Gy, saliva secretion decreased to 0.25 ml/min (SD 0.2 ml/min), and after completed therapy to 0.18 ml per minute (SD 0.17 ml/min). Three months after completed radiotherapy, the mean value of saliva secretion in this group was 0.05 ml/min (SD 0.06 ml/min). After 6 months this value was 0.09 ml/min (SD 0.1 ml/min); 1 year after completed therapy, the mean saliva secretion measured in this group was 0.09 ml/min (SD 0.08 ml/min) (Fig. 1).

Group C. In patients of the control group, the mean quantity of saliva secreted before irradiation was 0.58 ml per minute (SD 0.2 ml/min). In this group as well, the number of patients with measurable saliva secretion was gradually decreasing (Table 5). At 30 Gy, the quantity of saliva could be measured in 28 patients, after completed irradiation in 19, and 3 months later in 2. Later on none of the patients in this group presented with measurable saliva secretion. At 30 Gy, saliva secretion decreased on average to 0.27 ml per minute (SD 0.2 ml/min), while at completion

Table 5. Number of patients with measurable saliva in groups A, B, and C

Group	At 30 Gy	After completed irradiation	3 months after completed irradiation	6 months after completed irradiation	1 year after completed irradiation
A	4	4	1	1	—
B	25	21	15	14	17
C	28	19	2	—	—

of radiotherapy only 0.16 ml of saliva per minute was secreted (SD 0.15 ml/min). Three months after completed radiotherapy, measurable saliva secretion was evident in two patients only, the mean quantity being 0.02 ml per minute. Six months and 1 year after completed radiotherapy the quantity of secreted saliva was not measurable any longer (Figure 1).

Acute toxic effects of irradiation

Degree of radiomucositis on completed irradiation is presented in Table 6. Table 7 shows the severity of difficulties on swallowing in surviving patients 1 year after completed therapy.

DISCUSSION

Nonuniform and sometimes even controversial opinions on how to protect salivary gland parenchyma from damage during radiotherapy were the main reason for the present study. The results of this study indicate that the inhibition of the salivation during the irradiation treatment of head and neck carcinoma has some beneficial effect on the production of saliva lasting at least up to 1 year after completion of irradiation treatment.

The hypothesis that—in order to protect salivary function during irradiation—it is better to use agents that inhibit the parasympathetic function rather than stimulate it, is based on the results of Ahlner's tests on animals (13). The author found that although biperiden, an inhibitor of parasympathetic function, actually inhibits saliva production during irradiation, it also diminishes the radiation damage of acinous and ductal cells of the salivary glands, and thus alleviates the adverse effects of salivary gland irradiation.

Although the results of our study are not completely comparable with Ahlner's, owing to the fact that both studies were performed under different conditions, they still indicate that inhibition of salivary secretion during the irradiation period helps to protect later damage of the salivary gland. Namely, our patients in group B, who were receiving biperiden during irradiation, presented with a significantly smaller decrease in the quantity of saliva secreted 3 months ($P = 0.04$), 6 months (0.002), and a year after completed irradiation ($P = 0.0001$), as compared to group C.

The treatment with pilocarpine during irradiation was chosen on the basis of the pilot studies by Wolf (5) and Valdez (6). These authors report that occurrence of postirradiation xerostomy can be prevented or at least diminished by a continuous stimulation of salivary gland secretion during radiotherapy. However, our results obtained after pilocarpine application during radiotherapy do not support their findings. Our patients receiving pilocarpine during irradiation had a considerably diminished salivary secretion: in the middle of irradiation course, the mean quantity of secreted saliva in the group of pilocarpine receiving patients, as compared to that measured before the onset of therapy, was significantly lower than in the control group ($P = 0.04$). Also, at completion of radiotherapy, the decrease in saliva secretion in group A was greater than in the control group ($P = 0.06$). It seems that much more reduced salivary flow during radiotherapy in group A patients compared to that in the control group could be attributed to increased radiosensitivity of pilocarpine stimulated glandular tissue. Under this impression and because of possible side effects of pilocarpine (although 3 months after radiotherapy the mean quantity of secreted saliva was similar to that in the control group) the randomization into the group A was stopped. Because of the limited number of patients in

Table 6. The distribution of patients according to the degree of radiomucositis at the end of irradiation treatment

	Group		
Degree of mucositis	A	B	C
0	—	—	—
1	1 (11%)	12 (40%)	7 (23%)
2	4 (44%)	10 (33%)	13 (43%)
3	4 (44%)	7 (23%)	10 (33%)
4	—	1 (3%)	—
All	9 (100%)	30 (100%)	30 (100%)

Table 7. Swallowing problems in surviving patients 1 year after completed radiotherapy

	Group		
Degree of swallowing problems	A	B	C
0	4	15	13
1	2	13	2
2	—	1	11
3	1	1	4
4	—	—	—
All	7*	30	30

* In group A, 2 patients died within the first year after treatment.

this group, it has not been possible to draw relevant conclusions regarding the influence of pilocarpine administered during irradiation treatment on salivation.

The degree of radiation damage to the salivary glands is influenced by the radiation dose received, as well as by the type and proportion of glands included in the irradiation field (16–21). All our patients received equal dose of irradiation per fraction and per day, i.e. 2 Gy, with the exception of one patient in group A who received a daily dose of 1.8 Gy. Between groups, no significant difference in cumulative irradiation dose to the glands was found. There was also no significant difference in the distribution of patients in the groups regarding the site and stage of disease. Therefore, the comparison of results obtained in individual groups seemed justified. Lack of detailed information on a majority of the above factors in the available reports dealing with the quantity of secreted saliva in irradiated patients, renders the comparison of their results with ours difficult.

In animal experiments, Nagler *et al.* found that early toxic effects of irradiation on salivary glands are partly due to the limited intake of food and water during the immediate postirradiation period (22). This probably also applies to many patients treated for head and neck cancer already before completion of the irradiation course. As there was no statistically significant difference in the degree of radiomucositis among tested groups (Table 6), it could be probably presumed that the difference in the mean amount of saliva secreted among the tested groups is due to different drugs (pilocarpine, biperiden). Postirradiation xerostomy and its adverse effects on the soft and hard dental tissues of the oral cavity after radiotherapy of head and neck cancer patients has been the subject of several reports (8, 23–31). Decrease in the occurrence of radiation-related side effects in those patients who were receiving pilocarpine for alleviation of xerostomy after completed radiotherapy is discussed less frequently (9, 10, 32, 33).

The majority of these authors report on decrease in mouth dryness while the difficulties on chewing and swallowing remained unchanged. Alleviation of difficult chewing and swallowing and minor speech problems in patients receiving pilocarpine after irradiation of head and neck regions was reported by LeVeque (11), Rieke *et al.* (12), and Schuller (34). As the difficulties of swallowing were assessed only on the basis of the patients' subjective observations, and due to different number of patients in individual groups, the intensity of these problems is difficult to compare. However, from our results (Table 7) it does appear that they have been less severe in patients receiving biperiden than in patients from the control group.

The results of the present study indicate that the inhibition of saliva production during irradiation treatment and its stimulation after completed radiotherapy may contribute to the preservation of salivary gland function. However, because of the limited number of patients included, the results should be interpreted with caution.

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