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ORIGINAL ARTICLE

Efficacy of pilocarpine for the prevention of radiation induced xerostomia evaluated by semi-quantitative ^{99m}Tc -pertechnetate scanning in a randomized trial

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ABSTRACT

Background: Radioisotope scanning by Technetium-99m Pertechnetate is the best method for objective assessment of salivary gland function. Thus it was used in a randomized placebo-controlled trial to assess the preventive effect of concomitant pilocarpine with head and neck radiotherapy for prevention of radiation-induced xerostomia.

Methods: Salivary gland scintigraphy was performed immediately before and 6 months after the end of radiotherapy. Salivary gland function was measured by excretion fraction (EF) of Technetium-99m Pertechnetate.

Results: Twenty patients underwent salivary scintigraphy before radiotherapy, and also 21 post-radiotherapy scans were obtained. Mean parotid EF was 61% in the pre-radiotherapy and 9% in the post-radiotherapy scans ($P < 0.001$). The means for submandibular glands in the pre-and post-radiotherapy scans were 41% and 11%, respectively ($P < 0.001$). Also the mean EF in the pilocarpine and placebo groups was 15% and 4% for parotid glands ($P = 0.06$) and 18% and 5% for submandibular glands ($P = 0.05$) respectively.

Conclusion. Salivary gland scintigraphy was a valuable method for evaluation of xerostomia after head and neck radiotherapy, quantitatively demonstrating the protective effect of pilocarpine compared to placebo on salivary glands.

Keywords: Scintigraphy, salivary glands, radiotherapy, xerostomia, pilocarpine.

INTRODUCTION:

Radiotherapy is a successful modality for treatment of head and neck cancer, leading to local control and long term survival in a large proportion of the affected patients. Virtually all patients who undergo radiotherapy of the head and neck have some degree of xerostomia as a result of damage to the salivary

Glands [1]. Xerostomia caused by reduced salivary gland function is one of the disturbing chronic side-effects of radiotherapy to the head and neck region, and is responsible for a lower quality of life among the irradiated long-term cancer survivors [2].

Although the effects of radiation on salivary glands have been recognized as a significant clinical problem for more than 80 years, the specific mechanisms responsible for radiation-induced salivary gland dysfunction are still not well understood [3]. Irradiation of the major salivary glands leads to a reduction in the salivary flow, changes in electrolyte and immunoglobulin composition of saliva, reduction of its pH, and repopulation of the mouth by cariogenic microflora. Consequences of xerostomia include feeding disturbances, impaired taste feeling and predisposition to dental and oral diseases.

Because management of xerostomia is rarely effective, prevention is paramount. Several strategies have been developed to avoid radiation-induced salivary dysfunction without compromising

definitive oncologic treatment. These include salivary gland-sparing radiation techniques, such as 3-dimensional conformal or intensity-modulated radiotherapy, concomitant cytoprotectants, and surgical salivary gland transfer [4]. Oral pilocarpine has been approved for treatment of xerostomia in the chronic phase, but some studies suggest that its use concurrent with radiation could also be beneficial for prevention or reduction of the subsequent radiation-induced xerostomia [3,5-6]. The protective effect of pilocarpine on salivary glands might be pharmacologically mediated. This can occur through depletion of secretory granules in serous cells; intracellular leakage of proteolytic enzymes in secretory granules after radiation-induced peroxidative membrane damage may be responsible for serous cell injury [6].

Salivary gland scintigraphy is the method of choice for qualitative (visual) and quantitative evaluation of salivary gland function, and it can be used to accurately assess the effect of radiation on salivary glands [7-9]; thus we undertook to test the prophylactic effect of pilocarpine on radiation-induced xerostomia by radioisotopic method in a randomized clinical trial which originally used subjective scoring by patients and objective assessment by physicians for this purpose.

METHODS:

Patients with head and neck cancer participating in a randomized, double-

blind, placebo-controlled trial of concomitant pilocarpine with head and neck irradiation for prevention of radiation-induced xerostomia were eligible for radioisotopic assessment of salivary function. The above-mentioned trial has been reported separately [10]; inclusion criteria were age 18-70 and planning for irradiation to the head and neck, with both parotid glands in the radiation fields of minimum 40 Gy. Patients received either oral pilocarpine 5mg or placebo three times daily in a randomized double-blind setting, starting with irradiation and continued until 3 months after the end of radiotherapy. This trial used a visual analog scale questionnaire for subjective assessment of xerostomia, and also an objective evaluation according to objective grades of Late Effects of Normal Tissues Subjective, Objective, Management and Analytic (LENT SOMA) scale, with both assessments performed 6 month after the end of radiotherapy [10].

This radioisotopic study (in addition to the original randomized trial) was approved by Tehran University of Medical Sciences' Ethical Committee. The patients giving informed consent to the radioisotopic study were referred to our nuclear medicine center, once before radiotherapy for a baseline scan and once six months after its termination.

Salivary scans were performed by the intravenous (IV) administration of 185 MBq of ^{99m}Tc -pertechnetate. Dynamic images 1 min per frame were acquired for 30 min by an ADAC (Genesis, USA) camera equipped

with a low energy all purpose (LEAP) collimator, on the anterior and posterior projections from head and neck area. At the 15th min of the study, 6ml of lime juice was poured in the patient's mouth as a salivary gland stimulator. Image processing was performed by the "Euro Custom Menu" software program. Regions of Interest (ROIs) were drawn for each of the parotid and the submandibular glands. ROIs of the background activity for the parotid glands were drawn over the temporal bone and for the submandibular glands over the neck soft tissue (avoiding the subclavian vasculature). For analysis, anterior and posterior images were conjugated. Time-activity curves were then created for each salivary gland on the basis of region of interest (ROI) located on it. Salivary excretion fraction (EF) was obtained by the percentage fall between maximum and minimum background-corrected counts for each gland.

Comparison between pre-radiotherapy and post-radiotherapy EFs was made by paired-samples t-test. Post-radiotherapy EFs of the parotid and the submandibular glands in pilocarpine and placebo groups were compared by independent samples t-test. Correlation of the scan results with the subjective and objective xerostomia findings in the original trial was sought. The effect of different variables on post-radiotherapy EF was assessed by the linear regression method.

RESULTS:

Twenty salivary scans were done before

radiotherapy; also 21 post-radiotherapy scintigraphies were performed in 10 pilocarpine and 11 placebo patients. The scanned patients' age was 18-70 years with a median of 39 years. Male to female ratio was 1.21. Patients had mostly nasopharyngeal (76%) and then tonsillar carcinomas (14%); other tumors included tongue and base of tongue cancers. Radiation dose was 45-70 Gy with a median of 60 Gy, given by standard fractionation (1.8-2 Gy per day, 5 days per week). Parotid and submandibular glands were inside the radiation fields in all patients, but a small anterior part of the mouth and the lips were not. Mean parotid dose was 58 Gy (range 45-70 Gy).

There was no significant difference between the age, sex and radiation dose of the scanned patients in the pilocarpine and placebo groups ($P>0.1$).

Mean parotid EF was 61% (39%-79%) in the pre-radiotherapy group and 9% (0%-44%) in the post-radiotherapy group ($P<0.001$, figure 1). The means for the submandibular glands in the pre- and post-radiotherapy scans were 41% (24-63%) and 11% (0-49%), respectively ($P<0.001$, figure 2). The parotid and submandibular EFs were positively correlated ($p=0.01$).

The mean post-radiotherapy EF was 15% (0%-44%) in the pilocarpine group and 4% (0%-18%) in the placebo group for parotid glands ($P=0.06$, figure 3), and 18% (0%-49%) and 5% (0%-21%) respectively for the submandibular glands ($P=0.05$, figure 4).

The effects of age and the dose delivered to the salivary glands on the post-radiotherapy EF were not significant ($P>0.1$).

In patients undergoing the radioisotopic scan, mean subjective xerostomia as measured by the analog-scale questionnaire was 39.7 mm in the pilocarpine group and 56.1 mm in the placebo group; the difference between two groups was statistically significant ($p=0.04$). Also mean objective xerostomia grade was 2.0 in the pilocarpine group and 2.6 in the placebo group; this difference too was statistically significant ($p<0.001$). The correlation of post-radiotherapy parotid and submandibular EF was near statistical significance with the objective grades of xerostomia ($P=0.06$, figure 5), but not with the subjective scores ($P>0.1$).

DISCUSSION:

Salivary gland scintigraphy is a noninvasive, rather easy, sensitive, and accurate test to assess the functional status of the salivary glands in both healthy subjects and patients with dry mouth symptoms [7,11-12]. The destructive effect of ionizing radiation on salivary gland function has been well demonstrated by salivary gland scintigraphy [8-9].

Our results, showing marked drop of salivary EFs after radiotherapy, indicate the ability of scintigraphy to demonstrate the destructive effects of ionizing radiation on the salivary glands.

Pilocarpine has been shown to reduce the symptoms of established radiation-induced xerostomia, but it has also been suggested that its use during radiotherapy may reduce salivary gland dysfunction afterwards [5-6]. The results of the randomized trial from which our patients originated also confirmed this hypothesis, and were in agreement with our radioisotopic findings. The subjective scores and objective grades of xerostomia found in the scanned patients (subjective scores of 39.7 mm in the pilocarpine and 56.1 mm in the placebo group, $p=0.04$, and objective grades of 2.0 in the pilocarpine and 2.6 in the placebo group, $p<0.001$) were very close to those found in the whole patient population of the original trial (40.3 versus 57.0 mm for the subjective scores and 2.2 versus 2.6 for objective grades, respectively), with the same statistical significance. For details, please see our separate report on the original randomized trial [10]. Radioisotopic scanning in the parotid and the submandibular glands demonstrated a smaller decrease of EFs in the patients receiving pilocarpine compared to placebo, further confirming the prophylactic effect of pilocarpine in this setting. The scan results showed a nearly significant correlation with the objective grades of xerostomia.

Both of the previous studies on the prophylactic effect of pilocarpine on xerostomia [5-6] and our study used the drug during and until 3 months after radiotherapy, and thus some of the

observed drug's benefit might be due to post-radiation component of therapy. In contrast, another trial with pilocarpine or placebo prescribed during radiotherapy and until 1 month after radiotherapy failed to detect a beneficial effect of pilocarpine on radiation-induced xerostomia [13].

Nearly all our patients had both their parotid glands and submandibular glands completely treated to a minimum of 45 Gy, and the drug's effect could still be shown, but of course the minor salivary glands in the anterior parts of the mouth and lips were outside the radiation fields, and their stimulation by pilocarpine may have contributed to the reduction of xerostomia [10]. The current study also reveals that the dysfunctional status of salivary glands will last for at least 6 months after the termination of radiotherapy and is independent of age and dose for doses higher than 45 Gy. Although in the study performed by Tsujii et al [14] the parotid glands were more sensitive to radiotherapy than the submandibular glands, our study did not show any significant difference in this regard between these two salivary glands. Jellema et al too have shown that the risk of developing xerostomia in irradiated patients is influenced by both the mean parotid and submandibular radiation dose [15].

The most frequent adverse effects reported with the use of oral pilocarpine include sweating, nausea, and lacrimation. In our original radiotherapy trial no significant side-effect was observed for pilocarpine;

nausea was equally distributed in the pilocarpine and placebo groups and could have been produced by radiotherapy, and only one complaint of lacrimation was reported [10].

In conclusion, salivary gland scintigraphy in our study showed the significant salivary gland dysfunction after radiation and quantitatively demonstrated the protective effect of pilocarpine compared to placebo

used during radiotherapy. Radioisotopic scanning may well evaluate xerostomia after head and neck radiotherapy.

Acknowledgment:

This study was approved and monitored by Tehran University of Medical Sciences' Research Council and Ethical Committee, to whom we are very thankful.

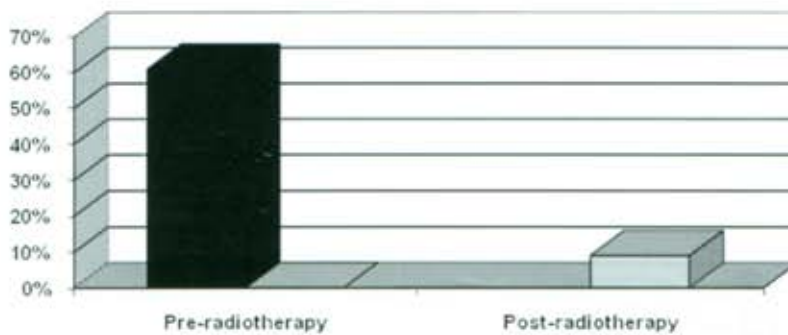


Figure 1. Parotid EF in the pre- and post-radiotherapy scans.

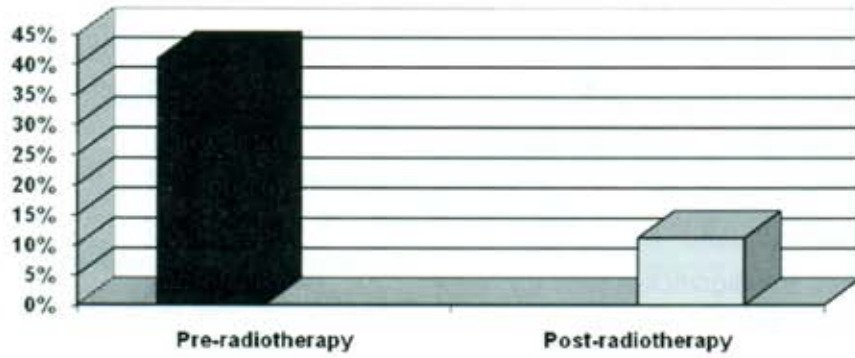


Figure 2. Submandibular EF in pre- and post-radiotherapy scans.

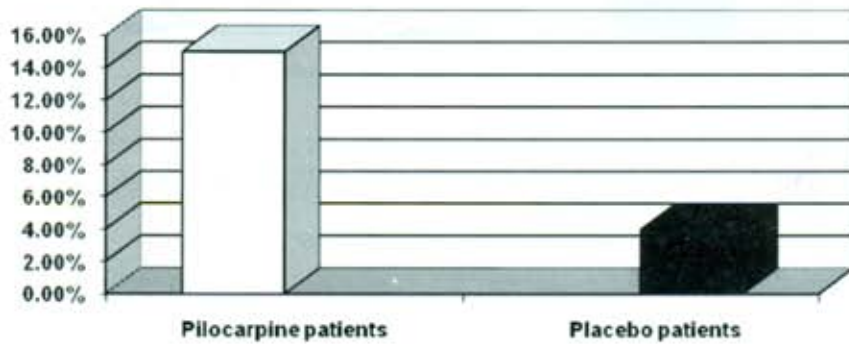


Figure 3. Parotid EF at the end of radiotherapy in the pilocarpine and placebo patients.

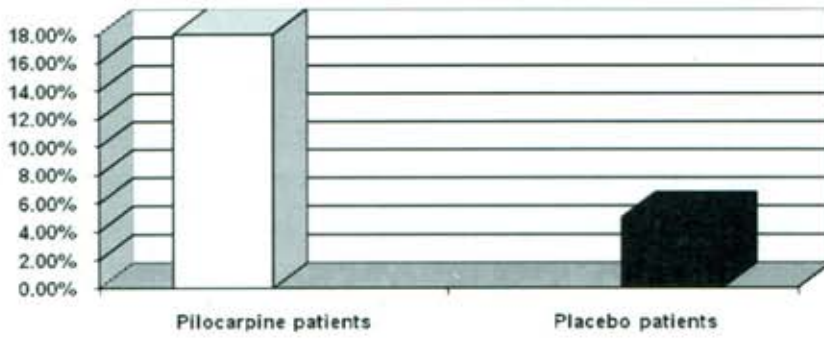
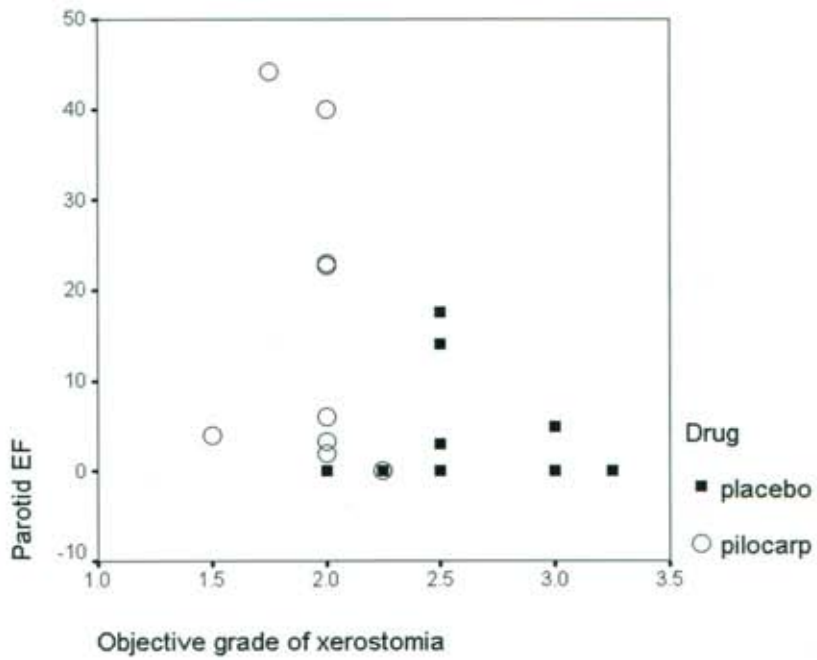


Figure 4. Submandibular EF at the end of radiotherapy in the pilocarpine and placebo patients.



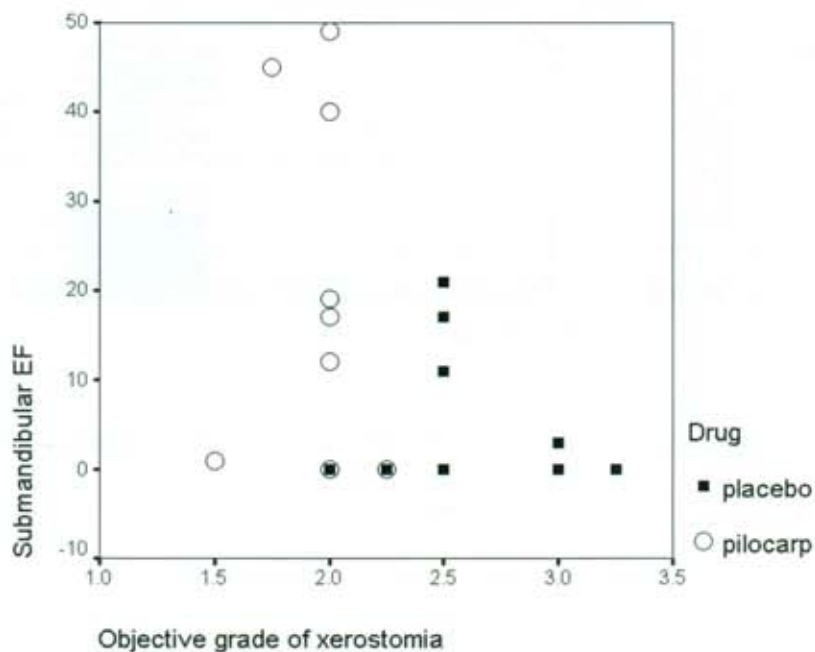


Figure 5. Objective grade of xerostomia versus parotid and submandibular ejection fraction after

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