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Original Article

Assessment of the Preventive Effect of Pilocarpine on Radiotherapy-Induced Xerostomia in Patients with Head and Neck Cancers

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Abstract

Introduction
Xerostomia is one of side-effects of radiotherapy for head and neck cancers. No definitive method has been proposed for the treatment of this condition. However, pilocarpine is considered effective for the management of chronic xerostomia. The purpose of the present study was to assess the preventive effect of pilocarpine.

Materials and Methods
This study was performed on 34 patients with head and neck cancers, undergoing radiation therapy (5000 cGy). The patients were randomly divided into two groups. The case group was administered 16 drops of pilocarpine (2%) eye drops per day, while the control group received normal saline; the treatment plan continued for four weeks. Unstimulated whole saliva flow rate was measured at four stages: two weeks before radiotherapy (baseline), the first day of radiotherapy, and two and four weeks after the initiation of radiotherapy.

Results
At baseline and the first day of radiotherapy, no significant differences were observed in the amount of saliva between the case and control groups ($P<0.76$ and $P<0.054$, respectively). However, by starting radiotherapy, a statistically significant improvement was reported in saliva production in the case group, compared to the control group ($P<0.00$); this trend continued during the next four weeks of radiotherapy ($P<0.003$). Generally, a significant difference was observed between the two groups at all stages of data evaluation ($P<0.00$).

Conclusion
According to the findings, pilocarpine was found to be effective for the prevention of xerostomia. Moreover, it could restrain the decline in the amount of saliva and reduce the rate of xerostomia.

Keywords: Head and Neck Neoplasms, Pilocarpine, Radiotherapy, Saliva, Xerostomia

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1. Introduction

Radiotherapy is one of the most frequently used treatments for head and neck cancers [1]. This treatment modality plays a significant role in the management of some cancers and can increase the chance of survival in patients; moreover, it can be a definite treatment in some cases.

Despite its obvious advantages, head and neck radiotherapy is accompanied by inevitable side-effects such as xerostomia and decreased salivary flow, which can persist for a lifetime in some cases [1-3]. In most cases, it is impossible to avoid radiation-induced damages, which are caused by the destruction of serous acinar cells in the salivary glands.

Radiation leads to a vigorous decline in the amount of saliva in patients undergoing radiotherapy [4]. Xerostomia may cause significant disorders such as severe pain, speech disorders, dysphasia, increased rate of dental damages, mucosal infections, atrophic change of tongue papillae, lobulated tongue, halitosis, cervical caries, disorders in nutrition and taste, and susceptibility to oral diseases [5, 6].

Xerostomia has significant adverse effects on the quality of life in patients undergoing radiotherapy [7-10]. Moreover, it can limit the patients' social activities and promote depression among them [11]. This condition can also lead to or exacerbate mucositis, which might limit the application of radiation therapy in patients [12].

Several methods have been proposed for the prevention of radiation-induced xerostomia. Frequent intake of liquids and use of sugar-free gums and candies might stimulate the remaining salivary cells. Moreover, systemic sialogogues, which have all the natural ingredients and protective functions of saliva, can help stimulate saliva. In addition, bethanechol and cevimeline have been reported to be effective for the treatment of xerostomia [13].

Among sialogogues, pilocarpine has been introduced as the best available option.Pilocarpine is a parasympathomimetic agent, which mainly affects muscarinic cholinergic receptors in the acinar cells of salivary glands. This agent can increase the amount of saliva if used three times a day at a dosage of 5-10 mg; it should be mentioned that cardiovascular side-effects are limited at this dose range [2].

Use of pilocarpine has been approved for the treatment of chronic xerostomia [14-16]. If used during radiotherapy, pilocarpine can be effective and reduce the rate of xerostomia to some extent[17-20] . Therefore, this agent can reduce the occurrence of many oral disorders, resulting from radiotherapy, and increase the patient's quality of life. Pilocarpine, as a prophylactic agent, can be useful for the management of xerostomia and may reduce the rate of radiation-induced xerostomia. Therefore, in this clinical trial, we aimed to evaluate the preventive effect of pilocarpine on xerostomia.

2. Materials and Methods

In this double-blinded, randomized, clinical trial, the study population consisted of 34 patients with head and neck cancers (i.e., locally advanced laryngeal cancer, locally advanced hypopharyngeal cancer, and nasopharyngeal cancer). The subjects underwent radiotherapy (5000 cGy), using an accelerator device(Neptun 10PC,IPJ-ZdAJ,Swierk,Poland) and a protective oral radiation shield at Ramezanzadeh Radiotherapy Center, Yazd, Iran.

The table of random numbers was used for randomization. The case and control groups each consisted of 17 patients. The control group received training on massage therapy of salivary glands and adequate hydration. They were administered lemon tablets, containing normal saline, four times a day as placebo.

In addition to the previously mentioned training, the case group received four pilocarpine 2% eye drops, containing 2 g of pilocarpine in 100 ml pilocarpine hydrochloride (Mina Daroo Company, Iran) four times a day. The intervention continued for two weeks after radiotherapy.

The inclusion criteria were as follows: 1) head and neck cancers; 2) locally advanced

laryngeal cancer, hypopharyngeal cancer, and nasopharyngeal cancer; 3) undergoing conventional radiotherapy with doses more than 50 Gy; and 4) no prior history of cardiovascular diseases, glaucoma, asthma, or gastrointestinal diseases.

The exclusion criteria were as follows: 1) changes in the patient's treatment protocol or the process of receiving therapeutic radiation therapy; 2) lack of patient cooperation in the study process; and 3) unwillingness to cooperate in the sampling process at the specified time. 4) prior history of cardiovascular diseases, gastrointestinal disorders, or asthma.

Unstimulated whole saliva flow rate was measured at four stages: two weeks before the first session of radiotherapy (baseline), the first day of radiation therapy, and two and four weeks after the initiation of radiotherapy. For this purpose, the spitting method was applied in which patients avoided to drink or eat anything 90 minutes before sampling. Then, after 5 minutes, the subjects were asked to spit their saliva into a graded test tube once or twice within a minute [21].

The amount of saliva (millilitres in 5 minutes) was calculated and recorded by a trained nurse. During the study, the patients and the nurse, who collected the samples, were not aware of the type of medications; therefore, we could ensure the double-blinded design of the study. At the beginning, the number of patients was 40, although it reduced to 34 cases by the end of the study. In fact, one subject died during the treatment process, three cases left the treatment due to lack of motivation, and two samples did not continue radiotherapy.

The gathered data were analyzed by SPSS version 18. Independent and paired t-tests, Chi-square, and repeated measures analysis Of variance were applied for data analysis. P-value less than 0.05 was considered statistically significant.

3. Results

The purpose of this study was to evaluate the preventive effect of pilocarpine on radiation-induced xerostomia in patients with head and neck cancers. The results showed that the amount of saliva was not significantly different between the case and control groups two weeks before radiotherapy ($P<0.761$).

By starting radiotherapy, the case group experienced a lower rate of decline in the amount of saliva, compared to the control group ($P<0.00$). This protocol continued during the next four weeks of radiotherapy ($P<0.003$). The results are presented in Table 1, which indicates the analysis of unstimulated whole saliva flow rates (ml/min) in both groups at two weeks before the start and four weeks after the onset of radiotherapy.

Furthermore, according to repeated measures analysis, at different intervals during the study, the difference in the saliva amount was significant, regardless of the grouping ($P<0.00$). Generally, significant differences were observed in the amount of saliva between the two groups at all stages of evaluation ($P<0.00$). These findings showed that pilocarpine was effective in restraining the decline in the amount of saliva during radiotherapy and decreased the rate of xerostomia in patients undergoing head and neck radiotherapy.

Table 1. Analysis of unstimulated whole saliva flow rates (ml/min) in the case and control groups

Sampling Periods	Control Group		Case Group		P-value
	Average	Standard Deviation	Average	Standard Deviation	
Two weeks before radiotherapy	1.3059	0.57279	1.3588	0.42139	0.761
The first day of radiotherapy	1.3294	0.56099	1.7000	0.51841	0.054
Two weeks after the initiation of radiotherapy	0.8765	0.38976	1.5176	0.52943	0.001
Four weeks after the initiation of radiotherapy	0.5588	0.29803	0.9235	0.35449	0.003

4. Discussion

This double-blinded, randomized, placebo-controlled study was conducted to assess the effectiveness of oral pilocarpine in preventing xerostomia among patients receiving radiotherapy for head and neck cancers. The results showed that the prophylactic oral use of pilocarpine could reduce the rate of radiation-induced xerostomia and dry mouth in these patients. Patients undergoing pilocarpine therapy experienced less reduction in the unstimulated salivary flow during radiotherapy, compared to the control group.

The obtained results were not far from expectation, as pilocarpine is a parasympathomimetic agent. The prophylactic use of this agent reduces the extent of damage to the salivary gland tissues. It also increases the salivary flow rate by affecting muscarinic cholinergic receptors of acinar cells in the salivary glands and stimulating the remaining salivary tissues [22, 23]. Cell damage is due to the leakage of intracellular granules containing proteolytic enzymes. In fact, sialogogues can prevent damage by reducing the number of intracellular granules [24].

Stimulation of salivary gland secretion by pilocarpine was studied in 1964 for the first time [25]. Over the past decade, the effect of pilocarpine at 2.5-10 mg doses has been evaluated in two different studies, with the results showing an obvious improvement in xerostomia in 30-40% of patients. The best outcomes were obtained by the use of 5 mg pills three times a day. Despite the decreased rate of xerostomia in patients, absence of significant changes in the salivary flow was notable in these studies [14, 15]. Moreover, in previous studies, the positive effect of pilocarpine in improving xerostomia was noted among patients undergoing radiotherapy [3, 16].

Contrarily, some previous studies have noted the inefficiency of pilocarpine, which is probably due to the assessment of stimulated salivary flow rate[26-28]. This discrepancy may be also related to the evaluation of quality of life as a determining factor in the mentioned studies. In fact, quality of life may affect the results, since various factors such as patients' cultural background, mental status, and attitude are involved. For instance, a previous study reported no difference in xerostomia among patients who received pilocarpine, despite an increase in the stimulated saliva. In the mentioned study, a questionnaire was used for assessing the patients' quality of life [29].

In the majority of previous surveys, pilocarpine has been used as a 5 mg pill three times a day [3, 20, 19, 27, 28, 30, 31, 37]. Considering the unavailability of pilocarpine pills in our country, we had to use pilocarpine 2% eye drops (four times a day, four drops each time) in our study. At this dosage, pilocarpine seems to be adequately effective, without causing any side-effects. Although some patients complained of palpitations or excessive sweating, their conditions were not severe enough to lead to withdrawal from the study.

Different time periods for pilocarpine prescription such as two weeks [12], six and twelve weeks [30], six months [31], and six weeks, six months, and twelve months [4] have been considered for evaluating the effectiveness of pilocarpine. In our study, the subjects were studied for a six-week period, since it takes at least four weeks to assess the therapeutic effects of pilocarpine [32]. Unstimulated salivary flow rate was measured two weeks before radiotherapy until four weeks after the initiation of radiotherapy. In fact, multiple points of time were considered for assaying the patients in our study, which is one of its strengths.

The amount of saliva on the first day of treatment with pilocarpine was recorded as the baseline. During the second week of the study by starting radiotherapy, despite an increase in the amount of saliva in the case group, no significant difference was observed between the two groups. Considering the proximity of the obtained P-value to the significance threshold (P=0.054), the difference might have

been statistically significant by increasing the number of study samples.

In our study, two and four weeks after the initiation of radiotherapy, patients who took pilocarpine experienced a decline in the amount of saliva during radiotherapy. However, the amount of saliva was higher in these subjects, compared to the control group, which showed the efficiency of pilocarpine.

In a previous study, injection of pilocarpine caused an increase in the amount of saliva and protected the salivary glands against radiation in animals [33]. Furthermore, in another study, pilocarpine prescription during radiotherapy could increase the salivary flow rate in the case group, compared to the control group [32].

In our study, pilocarpine was used before and during radiotherapy to evaluate its prophylactic and therapeutic effects. Based on previous research, efficiency of pilocarpine ends as the patient ceases to use this medication [32]. However, we observed significant differences in the salivary flow rate between pilocarpine and control groups four weeks after the onset of radiotherapy (two weeks after the cessation of pilocarpine treatment); this can be a result of long-term observation in our study.

Other methods such as acupuncture and hyperbaric oxygen therapy have been also proposed for reducing xerostomia and increasing the salivary flow rate [34, 35, 38, 39]. However, considering the scarcity of controlled studies, it is not currently possible to assess the efficiency of these methods. Amifostine has been also evaluated as a preventive method and has been shown to be effective in protecting the salivary glands. However, severe toxicity was reported in 7% of patients; also, its intravenous injection before radiotherapy was challenging. Therefore, use of pilocarpine seems to be the best available option due to its effectiveness and fewer side-effects[36].

In the present research, the sample size was more limited than some previous studies which was due to the low number of patients referring to the studied center. We decided not to include several centers in order to reduce the influence of confounding factors [4, 19, 20, 27, 30].

5. Conclusion

In our study, preventive use of pilocarpine reduced radiation-induced xerostomia in patients suffering from head and neck cancers; moreover, it led to no serious side-effects in patients. Therefore, prescription of pilocarpine might minimize the serious adverse side-effects of radiotherapy in patients and increase their quality of life.

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