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Original Article

Prospective Phase II Study of the Efficacy of Transcutaneous Electrical Nerve Stimulation in Post-radiation Patients

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Abstract

Aims: To evaluate the effectiveness of transcutaneous electrical nerve stimulation (TENS) delivered using an extra-oral device in patients with radiation-induced xerostomia.

Materials and methods: Thirty oral cavity and oropharyngeal cancer patients post-adjuvant ($n = 26$) or definitive radiotherapy ($n = 4$) were enrolled in this study. The TENS electrode pads were placed externally on the skin overlying the parotid glands. Unstimulated whole saliva was collected for 5 min into graduated tubes using the low forced spitting method. The TENS unit was then activated and stimulated saliva was collected for an additional 5 min. The difference between unstimulated and stimulated saliva output was measured using the paired *t*-test. Linear regression was used to determine factors significantly influencing the improvement in salivary output.

Results: Twenty-nine of 30 patients showed increased saliva flow during stimulation. A statistically significant improvement in saliva production ($P < 0.05$) during stimulation was noted. The mean unstimulated saliva flow was 0.056 ml/min and the mean stimulated saliva flow was 0.12 ml/min with a median increase of 0.06 ml/min. The interval to the application of TENS after radiotherapy significantly influenced the improvement in salivary flow.

Conclusion: Extra-oral application of TENS is effective in increasing the whole salivary flow in most of the post-radiated oral cavity/oropharyngeal cancer patients with xerostomia. TENS therapy may be useful as an effective supportive treatment modality in post-radiated oral cancer patients.

Key words: Head and neck cancer; intensity-modulated radiotherapy; radiotherapy; transcutaneous electrical nerve stimulation (TENS); xerostomia

Introduction

Radiation-induced xerostomia is one of the most common and debilitating complications of radiotherapy to the head and neck region [1]. The palliative management of xerostomia includes topical agents such as saliva substitutes, increased water intake, application of lip moisturisers, chewing sugar-free gums, sucking lemon drops, paraffin and citric acid-containing lozenges and rinses [2]. Systemic agents, such as pilocarpine and cevimeline, stimulate salivary flow, but often have unfavourable side-effects, such as profuse sweating, rhinitis, dyspepsia, increased episodes of micturition, etc [3]. Acupuncture has also been shown to improve xerostomia [4].

Transcutaneous electrical nerve stimulation (TENS) is a well-known physical therapy, which is useful for the relief of pain. It uses surface electrodes through which an electric current is passed [5]. It is non-invasive, safe, easy to master and generally well accepted by patients [6]. The results of recent preliminary investigations of non-invasive electronic stimulation of reflex salivation in patients with xerostomia have been encouraging [7]. The present study was planned as a prospective study to evaluate the effectiveness of an externally applied TENS device in improving salivary output in head and neck cancer patients with post-radiation xerostomia.

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Materials and Methods

This prospective study was approved by the institutional review board after complete ethical review as TENS has not been approved by the Food and Drug Administration (FDA) for the treatment of radiation-induced xerostomia to date. The protocol was registered on the Clinical Trial Registry of India (CTRI: CTRI/2014/03/004475). Patients with cancer in the oral cavity or oropharynx who had received conformal radiotherapy in the definitive or adjuvant setting were included in this study. At the time of TENS, patients should have had complete healing of the radiation mucositis and should have been free of locoregional disease. Exclusion criteria were patients with any pre-existing salivary gland disorder, patients with any implants or pacemakers, autoimmune disease, pregnancy and on any medication that induced xerostomia. None of the patients were on any sialogogue therapy before or during the procedure.

Written informed consent was obtained from all participants. They were informed to refrain from eating, drinking, chewing gum, smoking and oral hygiene procedures for at least 1 h before the appointment. Saliva samples were collected at a standardised time of the day (9.00–11.00 am). The TENS machine used for the study was MEDIHIGHTEC 8000 combo (MEDIHIGHTEC Medical Company. Ltd, Taiwan). The settings of the TENS machine were as follows: the pulse rate was fixed at 50 Hz, the pulse duration was fixed at 250 μs, the time was fixed for 5 min and the unit was used in normal mode. The electrode pads were placed externally on the skin, 1 cm in front of the tragus of the ear, over the parotid region with the TENS unit in the off position.

The patient was asked to sit in an upright position with their head bent down to allow saliva to drool into the measuring cup using the 'low force spit' method [8]. The TENS unit was then activated and the intensity control switch was adjusted for patient comfort by turning up one increment at a time, at 5 s intervals until the optimal intensity level was reached, which was indicated by the patient by raising their hand. Optimal intensity is defined as the maximum intensity that the subject still perceived to be comfortable. Stimulated saliva was then collected for 5 min into a separate calibrated cup. After the completion of treatment, the TENS machine was turned off completely and a log of adverse effects was kept.

This study was planned as a pilot study to gain baseline data about the efficacy of TENS in patients with xerostomia after radiotherapy. In a study involving 50 patients with xerostomia, Mittal *et al.* [9] had shown that salivary output can increase by 0.045 ± 0.02 ml/min after the application of TENS. As our study population was patients post-radiotherapy, we expected the increase to be much less. Using the paired difference model, a sample size of 25 at an alpha of 0.01 had a power of 80% to detect an increase of 0.015 ml/min after the application of TENS with a standard deviation of difference of 0.02 ml/min [10]. In order to account for potential incompliance, the sample size was increased to 30.

The study was conducted between 10 June 2013 and 10 July 2013. Data regarding salivary output were prospectively recorded; patient and radiation data were taken retrospectively from the treatment planning system. The database was locked for analysis on 1 October 2013. A statistical analysis was carried out using SPSS version 16.0 (IBM, Armonk, NY, USA) and the comparison between unstimulated and stimulated saliva was carried out using the paired Student *t*-test. The median and interquartile range of continuous variables are reported. A linear regression analysis was conducted using the enter method to determine the factors that significantly influenced the increase in salivary output after TENS application. A *P* value of 0.05 or less was considered statistically significant.

Results

The demographic profile of the population, including the treatment parameters, is noted in Table 1. As can be seen, 90% of the patients had a tumour in the oral cavity, whereas the rest had a tumour in the oropharynx. Twenty-nine patients (96.7%) had undergone treatment with Rapidarc intensity-modulated radiotherapy (IMRT), whereas one patient with buccal mucosa carcinoma had undergone 3DCRT (3 Dimensional Conformal Radiotherapy). Twenty-six patients had received adjuvant radiotherapy to a dose of 60–66 Gy in 30–33 fractions. Four patients had received definitive chemoradiation of whom two had oropharyngeal cancers (base of tongue) treated with SIB (Simultaneous Integrated Boost) IMRT (to a dose of 69.3 Gy in 33 fractions) and one had received sequential IMRT to a dose of 70 Gy in 35 fractions. One patient with upper alveolar cancer had received definitive chemoradiotherapy to a dose of 70 Gy in 35 fractions with 3DCRT (due to financial reasons). Patients treated with definitive chemoradiation had received weekly cisplatin at the dose of 40 mg/m^2. Figure 1 shows the median dose volume histograms of ipsilateral, contralateral and both parotid glands for all 30 patients.

All patients completed the procedure after due consent and saliva could be collected in all patients. The median unstimulated saliva flow was 0.05 ml/min (interquartile range: 0.04–0.08 ml/min). The median stimulated saliva flow after TENS was 0.12 ml/min (interquartile range: 0.08–0.16 ml/min). The median increase in the saliva flow after TENS was 0.06 ml/min (0.04–0.08 ml/min). This increase represented a median increase of 130% (interquartile range 65–200%) over the baseline salivary outflow. The difference in between the unstimulated versus the stimulated saliva flow was statistically significant with a *P* value of <0.0001.

Twenty-nine of 30 patients showed improvement in salivary flow rate, whereas one patient showed no change in salivary flow from the baseline. Two patients had no salivary flow at baseline, but showed an improvement in salivary flow rate after electrostimulation. There were no major side-effects with the use of TENS noticed in the study subjects. Four subjects had slight twitching of facial musculature during the application of TENS, which was transient and ceased immediately once the device was turned off.