Evaluation of the effect of acupuncture in relieving xerostomia (dry mouth): study protocol

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Abstract
Malignant neoplasia in the head and neck area (HNA) represent a diverse group of diseases, each with distinct epidemiological, anatomical, and pathological features. Therapeutic approaches of this type of lesions are sometimes provided with a certain complexity due to the intricacy of anatomical structures and severity of side effects, such as xerostomia.

This study aims to evaluate the effect of acupuncture in relieving xerostomia induced by radiation (XIR) and to study the feasibility of clinical research protocol in obtaining preliminary data for the foundation of a posterior randomized controlled study. Thus, the main research question is: Does acupuncture objectively improves xerostomia?

Therefore, with the use of acupuncture points ST44 (Neiting), LI2 (Erjian), ST6 (Jiache) and CV24 (Chengjiang), in the experimental group, there was a significant improvement in the amount of secreted saliva and increase of salivary flow with and without salivary induction when compared with the control group. This therapeutic program by acupuncture may indeed be a significant method to consider in reducing accentuated levels of dryness in the mouth caused by radiation therapy.

Keywords: xerostomia, acupuncture, radiotherapy, clinical case

Introduction
Head and neck neoplasia (HNA) represent the 6th most common neoplasia in the world, representing 6% of all diagnosed neoplasia (1). Worldwide, incidence level is approximately 500,000 new cases, with a yearly mortality of 300,000 cases (2). Radiotherapy (RT) used in head and neck disorders can have an effect on secretions, especially on the saliva, leading to a decrease of salivary production on the parotid glands, a pH reduction and an alteration of salivary consistency. These changes can cause symptoms such as: swallowing difficulties, complications to chew, anosmia, dysgeusia, dysarthria, halitosis, gingivitis, sialadenitis, flushing, difficulty to speak, localized pain, feeling of oral burning, irritability in the mouth, insomnia, increased risk of tooth decay, susceptibility to infections in the oral cavity (Candida) and osteoradionecrosis (3, 4).

Nederfors et al. suggest that salivary dysfunctions can be divided into three aspects: xerostomia as a subjective change in salivary flow, hyposalivation as an objective reduction in salivary flow, and changes in salivary composition (5). These changes may happen due to several factors: drugs, systemic diseases, aging, and radiation (5).

In humans, depending on the irradiation locations, a rapid decrease in salivary flow rate is observed during the first RT week and then there is a gradual continuous decrease to less than 10% of the initial flow rate (6). Brosky et al. acquiesce that total reduction in saliva may vary depending on the radiation field: bilateral RT may result in reductions up to 80%, while unilateral RT results in a reduction of 50%-60% (6). So, xerostomia causes a significant morbidity in patients with head and neck cancer treated with RT, adversely interfering with the patients’ quality of life and comfort.

Treatments for xerostomia are restricted (4). Current therapies consist of oral hygiene with fluoride, pilocarpine (alkaloid, cholinergic agonist) amifostite (made hydrophilic), salivary substitutes (oral lubri-
Currently, cancer patients seek non-conventional therapies, such as Traditional Chinese Medicine (TCM) as a complementary or alternative form to drugs or other conventional therapies. TCM comprises a variety of clinical practices that share common concepts of Medicine developed in China and are based on a tradition that has existed for over 5000 years, with its main objective being to promote the individual’s self-healing. TCM offers various methods of treatment such as acupuncture.

Acupuncture can be defined as the practice of inserting needles distributed over certain points on the skin with therapeutic purposes. It is a method of treatment that consists in sensory stimulation, causing local and distant release of neuropeptides with involvement of the central and peripheral nervous system.

In this context, the main objective of this study is to evaluate the effect of acupuncture in specific points to minimize the reducing action of radiotherapy (RT) used in head and neck disorders, especially on the decrease of salivary production of the parotid glands. For this purpose, patients with these clinical features and in a radiotherapeutic treatment program will be recruited.

Methodology

Sample -The initial sample of this study was based in 2 clinical cases, randomly selected, with malignant neoplasia in the head and neck area, submitted to RT treatment between October 2014 and May 2015 in the RT service of Hospital de São João at Porto.

Study Design - A clinical study was conducted, comparing an experimental group (EG) with a control group (CG). Just before the start of the first week (W1) of the acupuncture program, which was considered the baseline for all patients, (W1, baseline) measurement tests were applied to assess saliva levels (sialometry and Schimer test modified) in order to obtain baseline data, pre-intervention.

Subsequently, EG is subjected to 8 sessions of acupuncture treatment (2x per week). CG is not subjected to acupuncture.

After 4 weeks (W4), new saliva level tests are performed in order to evaluate xerostomia.

Radiotherapy Protocol - All patients in this study (n = 2) were subjected to RT treatment (using photon energies: 6Mv), with daily doses of 2Gy/fraction from Monday to Friday over a period of 5 to 7 weeks with a total of 25 to 35 sessions thus making a prescription dose from 50Gy to 70Gy. Treatment field includes the lesion and surrounding tissues, as well as the parotid with medium doses exceeding 20Gy at least on one of them.

Study participants underwent a treatment of RT linear accelerators Clinac 600C Varian brand or Primus from Siemens in the RT service of Hospital de São João do Porto (HSJ) with 3D-CRT and IMRT techniques.

Acupuncture Protocol - The manual acupuncture protocol was developed in accordance with the Heidelberg model of Traditional Chinese Medicine with the support of the Institute of Biomedical Sciences Abel Salazar.

Only two patients were selected for the clinical study. In the RT service HSJ, the experimental group patient (EG) has done acupuncture treatment twice a week for a 4 week period, with a total of 8 sessions, beginning after the first saliva collection (W1). Each session lasted 20 minutes. The control group patient (CG) was not subjected to any acupuncture session during the same period. The acupuncture protocol includes: at the lower limbs, the ST44 point (Neiting); in the upper limbs, the LI2 point (Erjian); and at the head, the ST6 points (Jiach ) and CV24 (Chengjiang).

Disposable acupuncture needles 0.22x13mm, stainless steel and coated with silicon (Tewa®) were used for this intervention. Puncture depth was approximately 5mm and tried to get the "De Qi" effect.

Measuring devices - Objective measurements of this study are based in two tests. The first test is called modified Schimer test developed from Schimer tear test and the second test is sialometry. The modified Schimer test consists in measuring mouth moisture (ml). It is used a band of Schimer with a millimetric scale of 0-35mm (Schimer-Plus®). Patients elevate the tongue towards the hard palate (so the band does not touch the tongue) and a Schimer band is placed vertically on the left or right side of the frenulum for 5 minutes. Saliva absorption by the band is measured and recorded in the first, second, third, and fifth minute. The patient is requested not to swallow the saliva during the test in order for it to be more accurate.

Sialometry is the functional evaluation of the salivary glands. The sialometry test appears in the study by Braga et.al, and it is based on total saliva collection without and with salivary induction (using something sweet). The patient is instructed to expel saliva accumulated in the mouth every minute into a glass over a period of 6 minutes without swallowing saliva. Both tests are carried out for 5 minutes, with the 5th minute being the sum of saliva production.

Results

Clinical and Socio-demographic characterization - In the following study, both clinical cases (EG vs CG) have malignant neoplasia in the head and neck and share similar clinical characteristics. The patient, a female, belonging to EG is 67 years old and has a malignant stage I tumour in the nasopharynx (T1N1xM0R0). This means the tumour may consist in dimensions up to 2 cm without extra-parenchymal extension; regional nodes cannot
be assessed and there are no metastases in the distance. 70Gy in 35 fractions (2Gy/fx) has been prescribed for RT treatment, having finished it in February 2015 with 3D-CRT technique. This patient discontinued RT treatment on the 4th day due to high degree of xerostomia and returned shortly after to complete the remaining treatment. The CG patient, a female, is 57 years old and has a stage II malignant neoplasia on her vocal cords (T2NxM0), meaning the tumour is bigger than 2 cm but not larger than 4 cm in its greatest dimension, no extra-parenchymal extension, regional nodes cannot be assessed and were not found metastases in the distance. She received RT treatment with 3D-CRT technique with a prescribed dose of 50Gy in 25 fractions (2Gy/fx).

Analysis of objective tests results

Modified Schimer test
Comparing the clinical cases (EG vs CG), there were no significant differences in W1 (baseline) in the modified Schimer test up to 5 minutes (Table 1; Figure 1). However, significant differences were found between CG and EG after 4 weeks: the amount of saliva was higher in EG compared to CG (at 5 minutes + 12ml). So, patients subjected to acupuncture have more 12mm of saliva, meaning there was an improvement of 54.55%.

In EG, a significant increase in the amount of saliva after 8 acupuncture sessions was observed, when comparing W1 vs W4, the measurement at 5min, with an improvement of about 83.89%.

Sialometry Test
Comparing EG with CG, without or with salivary induction, a small difference of 0.9mm in W1 (baseline) was observed. After the 4-week evaluation (W4), an increase in salivary flow on EG compared to CG was observed, without salivary induction (+ 2.8mm) and with salivary induction (+ 12mm). This ascertains that patients who perform acupuncture treatment have an improved salivary flow with or without stimulation (Table 2, Figure 2).

The EG, after 8 acupuncture sessions, shows there was a significant increase without salivary induction (+ 2mm) or after salivary induction (+ 5mm) when comparing W1 vs W4. This determines there was an improvement of 50 % (W1 vs W4).

Discussion
Radio-induced injuries change the volume, consistency, and pH of saliva, which in its turn originates other complications that may impact on the quality of life of the cancer patient. Salivary glands are highly susceptible to radiation, with the parotid being the most sensitive. Doses higher than 20Gy under the parotid can decrease salivary flow and doses above 50Gy can lead to its dysfunction. This study appears in a context where there is a growing use of knowledge of TCM in cancer patients, yet it still lacks scientific validation. The existence of other clinical studies and meta-analyses of literature suggest the benefit of acupuncture treatment of patients with XIR. Pilocarpine is the only drug approved by the FDA (Food and Drug Administration) for XIR. However, pilocarpine is contraindicated in individuals with asthma, acute iritis, or glaucoma and should be used with caution in patients suffering from COPD (chronic obstructive pulmonary disease) and cardiovascular diseases. Therefore, not all patients with head and neck cancer can be prescribed this drug. These drugs have fallen into disuse, opting only for administering artificial saliva substitutes. However, due to the great complexity of saliva, very few have been evaluated adequately. Significant progress of techniques in RT (3D CRT,
IMRT) allow a better conformation of the target volume by avoiding a larger volume of surrounding tissue to be irradiated, including the parotid itself. Nevertheless, to date, it is still not possible to prevent XIR in all patients. Marije Vergeer R. et al. has found the IMRT technique resulted in a significant reduction of the average dose in the parotids when compared to 3D-CRT technique (IMRT: 27 Gy and 3D CRT: 43 Gy; p < 0.001).

The mechanisms underlying acupuncture are not clear. It is possible acupuncture, at certain points, can directly stimulate the nerves that innervate the salivary glands.

Up to this date and to our present knowledge, this research study appears to be the first study on acupuncture for relief of XIR in patients with head and neck cancer conducted at the Portuguese National Health Service.

Firstly and objectively, a decrease in XIR when the patient performs acupuncture (EG) was observed. This positive trend was perceived in the amount of saliva present in the oral cavity and the production of salivary flow in the EG vs CG and between W1 vs W2. Secondly, there were no side effects related to the practice of manual acupuncture.

Apart from the above, the study also noted some limitations that we would like to correct in a posterior study:
1. There is a possibility the results could have occurred by chance because of the small sample size;
2. Blinding was not applied to patients and acupuncturists;
3. Results evaluation was carried out by the researcher, which may be an evaluation bias;
4. Points selection is usually individualized based on the acupuncture model used;
5. There have been no questionnaires done to the patients involved, only objective tests.

In the future, these limitations should be overcome.

Conclusion

The results seem to be promising for therapeutic action of acupuncture, as suggested by recent studies. Regarding this study, the use of points ST44 (Neiting), LI2 (Erjian), ST6 (Jiache), and CV24 (Chengjiang) in the experimental group led to a significant improvement in accented levels of dry mouth caused by the effect of radiation therapy. Thus, despite of caution in interpreting the results because of several limitations, the study suggests acupuncture reduces XIR.

A study of larger dimensions, preferably double-blind, with a larger sample size controlled by a waiting list and the inclusion of objective tests with subjective tests (questionnaire) will be needed to clarify modulatory effects of acupuncture on XIR in patients with cancer of the head and neck. If the benefit of acupuncture is established at last, then this treatment is likely to be included in therapeutic offers in addressing XIR in patients with cancers of the head and neck, and promoting the quality of life of cancer patients.

It is essential that clinical practice is a reflexive practice, where researchers can apply their knowledge. This relates to holding of scientific knowledge but also with necessary clinical supervision.

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