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A randomized pilot study to assess the safety and the value of low-level laser therapy versus clonazepam in patients with burning mouth syndrome.

Abstract

Comparison between low-level laser therapy (LLLT) and clonazepam for treating Burning Mouth Syndrome (BMS) patients has never been documented; the aim of this study was to assess the effects of LLLT photobiomodulation versus medical therapy with clonazepam on BMS. Thirty-three patients (25 female, 8 male, mean age = 67.12) were randomly allocated to 2 different groups: the first one (Group A, 18 patients) underwent two laser irradiation sessions weekly for 5 weeks, whereas the second one (Group B, 15 patients) received topical clonazepam therapy [half a tablet (2 mg) in the mouth without swallowing for 3 min, three times a day for 21 days]. LLLT was delivered with a continuous wave 980-nm AlGaAs diode laser, and the output of 300 mW, delivering a Fluence of 10 J/cm^2, using a "spot technique", with an average Power Density of about 1W/cm^2. The laser probe was held perpendicularly at a distance of about 2 mm from the mucosa. Visual Analogue Scale (VAS), McGill Pain Questionnaire, Present Pain Intensity (PPI), and Oral Health Impact Profile (OHIP-49) assessed sensation of pain. Hospital Anxiety and Depression Scale, and Geriatric Depression Scale assessed levels of anxiety and depression.

Twelve weeks after the end of treatment, patients treated with LLLT experienced a decrease in pain sensation reported for all the parameters analysed: VAS (P=0.004), McGill Pain Questionnaire (P=0.002), PPI (P=0.002) and OHIP-49 (P=0.010). The group treated with clonazepam had less favourable results for VAS (P=0.33), McGill Pain Questionnaire

two groups, LLLT appeared to be superior in improving pain perception, but statistically only at 8 weeks after the end of the protocol proposed (P=0.026). Based on this preliminary trial, LLLT is capable of reducing the symptoms of patients with burning mouth syndrome with a constant and long-lasting effect, experienced since the end of the first applications.

Introduction

The International Headache Society has defined the Burning Mouth Syndrome (BMS) as “an intraoral burning sensation for which no medical or dental cause can be found” [1]. Patients usually describe it as a painful burning sensation of the oral cavity, in the absence of clinically apparent mucosal alterations, more commonly occurring in middle-aged and elderly women [2]. Its possible cause has not been yet established, and diagnosis and therapy are fairly controversial [3]. BMS management should be directed to reduce symptoms and pains, but no therapy has been shown to be more effective [4]. Primary patients’ treatment has been based on the avoidance of possible causes of oral irritation and the provision of psychological support [3]. Clonazepam is a benzodiazepine having an inhibitory effect on the central nervous system, commonly used as an anxiolytic agent. Topical clonazepam has showed good short-term results for the relief of pain in BMS, though this was not presented as a conclusive cure [4,5].

Low-Level Laser Therapy (LLLT) is an approach increasingly used in medicine, which has potential analgesic, anti-inflammatory and biostimulating effects also if applied to oral tissues. To date, some reports have been published describing the usefulness of LLLT in reducing the symptoms of patients with BMS [6-9].

The aim of this prospective study was to estimate the effects and the efficacy of LLLT versus conventional medical therapy with clonazepam on the outcome of BMS patients.

The present trial is reported according to the CONSORT statement for improving the quality of reports of randomised controlled trials (http://www.consort-statement.org/).

Patients and methods

Study population

Consecutive Caucasian patients, attending the Oral Medicine Section of the CIR - Dental School, Turin, Italy, from November 2010 and June 2013, were selected for the present study.

The inclusion criteria were: a) oral burning sensation, at least in the last six months; b) no detection of oral mucosal lesions; c) ability to complete the present clinical trial.

The exclusion criteria were: a) diagnosis of Sjögren Syndrome on the basis of AECG criteria [10]; b) previously head and neck radiotherapy; c) diagnosed lymphoma; d) hepatitis C infection; c) pregnant or breast-feeding women; d) patients taking antidepressant, anxiolytic or anticonvulsant drugs.

Routine serological analyses were also performed, including quantification of different serum vitamins (B1, B2, B6 and B12), folic acid, iron (Fe^{++}), fasting blood glucose, Zinc, and full blood count. Individuals with one or more values not in range were also excluded.

Different treatment options were discussed, and all patients submitted written informed consent. Investigations were performed according to the Declaration of Helsinki on Biomedical Studies Involving Human Subjects. The ethics

committee of the CIR-Dental School, University of Turin, Italy, approved the protocol.

Assessment of pain and associated variables

Subject had their unstimulated whole salivary flow (UWS) measured mid morning, at least two hours after the last food intake. They were asked to allow saliva to drain into a plastic glass by drooling or gentle spitting; they were instructed not to chew, swallow or speak. Saliva was collected for a period of 15 minutes, and the flow expressed in ml/min.

Levels of USW pH were measured using an Oakton ph5/6® pH meter (Eutech Instruments Europe B.V., Landsmeer, The Netherlands) with a Hamilton Minitrode® electrode.

The subjective sensation of pain reported was assessed by Visual Analogue Scale (VAS) [consisting of a 100 mm-vertical line, marked wit 0 (=no pain) to 100 (=most severe pain experienced)], McGill Pain Questionnaire, Present Pain Intensity (PPI), and by Oral Health Impact Profile (OHIP-49).

Levels of anxiety and depression were assessed by Hospital Anxiety and Depression Scale (HADS), and Geriatric Depression Scale (GDS).

A single physician (M.G.), unaware of collocation, recorded all outcome measures.

Randomization and treatment modalities (Table 1)

Allocation to treatment arms was performed using sequentially numbered randomization table. RANCODE (version 3.6) was used to generate the randomization sequence. Investigators had a closed envelope for each patient

to establish the assigned treatment. Only one external investigator, not involved in the study, was aware of the sequence and could have access to the file.

Patients were randomly allocated to 2 different groups: the first one (Group A) underwent LLLT, whereas the second one (Group B) received topical clonazepam therapy.

A) Laser irradiation

LLLT was delivered with a 980-nm Aluminium Gallium Arsenide (AlGaAs) diode laser (DM980, distributed by DMT S.r.l., Via Nobel 33, 20035, Lissone, Italy). The device was used according to the manufacturer's instructions. A probe with a diameter of 0.6 cm and a spot size of 0.28 cm^2, delivering a Gaussian collimated beam, was used. The output power was 300 mW, continuous wave emission, verified using the calibrating door of the laser device. Each session was performed delivering a Fluence of 10 J/cm^2, using a "spot technique", with an average Power Density of about 1W/cm^2, and the probe, protected with a transparent plastic sleeve, was held perpendicularly at a distance of about 2 mm. The time of delivery, 10 seconds per point, was calculated using the formula Fluence = Power Density x Time, and all the mucosal burning sites were irradiated, up to 0.5 cm beyond the borders.

Each patient underwent two laser irradiation sessions weekly for 5 weeks.

B) Medical treatment

In Group B, the patients were instructed to suck half a tablet of 2 mg of clonazepam and hold their saliva near the pain sites in the mouth without swallowing for 3 min, and then to spit. This protocol has to be repeated three times a day for 21 days.

Follow-up schedule

Follow-up visits were conducted at 3 (T2), 8 (T3) and 12 weeks (T4) after the end of the protocol study.

At T2, T3 and T4, patients were asked to complete the VAS scale, the PPI and McGill Pain questionnaires, whereas, only at T4, they had also to fill the OHIP-49, the HADS and the GDS.

Sample size calculation

Sample size was not estimate based on the lack of any previously reported changes for BMS patients treated with these regimens. We arbitrarily decided to include at least 15 subjects in each group for this preliminary examination, in order to test the null hypothesis that LLLT was not superior to clonazepam therapy for treatment of newly diagnosed BMS patients.

Statistical analysis

The primary outcome measure was the decrease of oral pain reported at the end of the protocol and during 12 weeks of follow-up. Secondary outcome measures were the variation of levels of anxiety and depression; the reported adverse events possibly due to the clonazepam treatment; and the post-operative complications of LLLT.

Wilcoxon's signed rank was used to calculate the significance of the outcome data for reported symptoms (VAS, McGill and PPI) and depressive anxious state (HADS, GDS). P-values ≤ 0.05 were considered to be statistically significant.

SPSS (SPSS for windows, version 11, SPSS inc, Chicago, IL, USA) statistical software was utilized.

Results

General information

Initially 76 patients were screened; 25 of these patients were not included in the trial because presenting exclusion criteria (20 patients under medication with banned drugs; 4 with diabetes and 1 with anaemia). Eighteen patients refused to be part of this study. Fig. 1 shows the flow diagram for patients' enrolment and selection.

Thirty-three patients were finally randomised and treated, of whom 25 were women (75.75%); the mean age at presentation was 67.12 years (± 8.58). Group A consisted of 18 patients, while Group B of 15 patients. No deviations from the operative protocol occurred after enrolment.

The two groups were similar at baseline for age, gender and all clinical data analysed (Table 1).

None of the patients treated with LLLT reported adverse effects; 32% of patients treated with clonazepam reported dizziness, fever, headache and lack of appetite.

Evaluation of subjective sensation of pain reported

At T4, patients treated with LLLT experienced a decreasing sensation of pain reported for all the parameters analysed: VAS (P=0.004), McGill Pain Questionnaire (P=0.002), PPI (P=0.002) and OHIP-49 (P=0.010). At the same time, group treated with clonazepam had less favourable results for VAS (not

statistical significant, P=0.33), McGill Pain Questionnaire (P=0.005), PPI (P=0.013) and OHIP-49 (not statistical significant, P=0.25) (data not showed).

The Wilcoxon's signed rank was also used to calculate the significance of the outcome data only for reported symptoms (VAS) in LLLT group before and after every single session; a significant lessening of pain perception was detailed in all 10 sessions for each patient (P<0.05, data not shown).

Table 2 reported statistical differences between the 2 groups in different times of follow-up period. LLLT appeared to be superior in improving pain perception, but statistically only in VAS and PPT score at T3 (P=0.026 and P=0.0379 respectively), if compared with medical therapy.

Analysis of anxiety and depression

Levels of anxiety and depression did not changed statistically in both groups before and after treatment provided (data not showed), and also comparing the two groups (Table 2).

Discussion

Currently employed therapies for the treatment of BMS include hormone replacement therapy, anticonvulsants, antidepressants, capsaicin, benzodiazepines, analgesics, alpha-lipoic acid, LLLT and cognitive therapies. However, none of them appeared to be better than others [5]. This wide-ranging diversity should require more detailed studies to assess which treatment should be the gold standard for this quite common condition.

To the best of our knowledge, comparison between LLLT and clonazepam in BMS patients has never been documented.

The clinical features of patients in our survey share many similarities with those reported previously. Usually, BMS has been described to be more prevalent in middle-aged and older women (5th to 7th decade), with a female to male ratio varying from 3:1 to 16:1 [7]. Mainly for this reasons the female predominance is so evidence in our series.

Patients with BMS cannot have any signs of oral mucosal pathology; moreover, clinical diagnosis relies on a detailed review of patient' s medical and dental histories, and a careful analysis of data obtained from physical and laboratory examinations [2]. For these reasons, our exclusion criteria were so strictly.

The essential principle of LLLT is based upon the belief that irradiation, at a detailed wavelength, could alter cellular behaviour, resulting in analgesic, anti-inflammatory and biostimulating effects. LLLT can induce different intracellular biological reactions to stimulate regenerative abilities, without undesired adverse effects, reducing also the pharmacological support [11, 12].

LLLT has been showed to promote an increase in the synthesis and release of serotonins and β-endorphins, with reduced sensory nerve conduction, with optimal results also in patients with BMS [8, 9, 13-15]. Moreover, recent study provided direct evidence that the reduction of the salivary TNF-α and IL-6 after LLLT corresponds to improvement in pain perception in patients with BMS [7].

Moreover, for reported symptoms controlling, LLLT has also been used in dentistry as an alternative treatment modality in the management of masticatory muscle pain [16], in reducing pain after major oral surgery [17], and during orthodontic therapy [18] or surgery [19].

In our series, LLLT appeared to be effective in reducing pain reported in BMS patients. Three months after the end of the protocol, subjects treated with LLLT still experienced a significant decreasing sensation of pain reported.

Challenging results of laser effectiveness in the treatment of pain or inflammation are to date present; even if the majority of the studies demonstrated that the reduction of pain is effective, the physiological mechanisms underlying the reduction in pain after LLLT are still unknown [7,20].

Despite the possible side effects that may occur at low doses (e.g. xerostomia and sleepiness above all) [4], clonazepam has shown promising results for relief of symptoms in BMS patients, ranging form 69% to 80% [21-23]. In our experience, only 58.3% of the total population studied reported a significant reduction in symptoms, with a good long lasting action.

Originally, in this report we also tried to determine changing in the levels of anxiety and depression of BMS patients after proposed therapies. Values bigger than 8 of HADS [24] and bigger than 4 of GDS [25] has been reported to be appropriate for diagnosing anxiety and depression. Our BMS patients had baseline median values representing a pathological depressive condition, reflecting a well-known aspect already reported in literature [26-28]. However, none of the therapies provided did improved levels of anxiety and depression.

This finding is not surprising; in fact, such short-time topical therapy cannot modify or change the psychological trait of the patient. A similar finding has already been showed [29].

Salivary flow rate and salivary pH were also initially analysed in order to exclude true hyposalivation and condition leading to acid ph values, conditions in which patients could suffer of oral burning sensations [30].

Even if both LLLT and clonazepam have been previously demonstrated to be superior versus placebo for pain relief in BMS patients, conclusions drawn from this study are limited by its design; the main limitation was the lack of any inactive substance or false biostimulating laser used as control. Additionally, the number of patients treated was too small to allow generalized conclusions. However, the results do offer encouragement for further study of acupuncture as a treatment for pain relief in BMS patients.

It is possible to preliminary assume that LLLT is capable of reducing the symptoms of patients with BMS with a constant and long-lasting effect, experienced since the end of the first applications. LLLT appeared to offer therapeutic results slightly more consistent than those obtained with clonazepam therapy, with no adverse effects.

Further bigger and properly defined randomized controlled trials, with also different therapeutic approaches or placebo-controlled, are however needed in order to achieve the aim of ascertaining the clinical efficacy of LLLT compared with medical therapy for BMS patients.

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