Nd:YAG low-level laser treatment in burning mouth syndrome: a pilot study

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Abstract

Background : Burning mouth syndrome (BMS) is chronic disorder characterized by pain/burning sensation in oral cavity. Nd:YAG low-level laser (LLL) has been used in the treatment of pain reduction. The aim of this study was to assess the effectiveness of LLL verse no power placebo with Nd:YAG in the treatment of patients with BMS in pain/burning, numbness and altered taste.

Methods : Forty-two patients with BMS were randomly equally assigned into LLL group and placebo group. The parameters of Nd:YAG irradiation consisted of 100mW power, 3J/cm² energy density, 10 Hz, pulse mode and a 1064nm wavelength emission. The placebo group used the same LLL instrument which was switched off. Each patient underwent one laser irradiation session per week for 4 weeks. Clinical assessment of subjective pain/burning, numbness and altered taste was performed using a visual analogue score (VAS) before each irradiation session and one week after last treatment.

Results : All of patients (21) was showed significant decreasing of VAS value of pain/burning (ranged from 2% ~100%, mean 52%) after 4-weeks LLL treatment. The improvement of VAS value of numbness in LLL group (ranged from 23% ~100%, mean 61%) was significant from the baseline to the end of LLL treatment. Relief of altered taste was found neither in LLL group nor in placebo group. All patients completed this study and none of them reported adverse effects.

Conclusions : Nd:YAG LLL (100mw, 3J/cm² , 10 Hz) was effective for reduction of pain/burning and numbness in patients with BMS.

Background

Burning mouth syndrome (BMS) is a chronic disorder characterized by pain/burning sensation in oral cavity [1]. Some patients also suffer numbness, and/or altered taste [2, 3]. The most affected site of oral cavity is tongue, probably company with lips, and hard palate [4, 5]. The prevalence of BMS is 0.1–3.9% [6] and is relatively higher within the group of pre- and post-menopausal women [7]. The possible causal factors are neuropathy, psychology, oral candidiasis, hormonal disorder related with menopause, and nutritional deficiencies [8]. A trigeminal small-fiber sensory neuropathy in BMS was evidenced by diffuse degeneration of epithelial and sub-papillary nerve fibers of anterior two-third of tongue [9]. Thalamus hypoactivity has been described in BMS [10] and other neuropathic pain conditions [11], which suggesting the CNS in complex pain modulation networks. Even if numerous previous studies are about BMS, its pathogen is still uncertain which related to the difficulty in successfully treating BMS patients. Till now, a variety of drugs, and miscellaneous treatments have been applied in BMS patients [12]; however, the satisfaction of management of this syndrome is still not reached.

Recently, low-level laser (LLL) treatment has showed the benefit in pain relief including patient with BMS [13, 14]. The analgesic effect probably attributes to increasing the pain threshold, decreasing endogenous opiates, and regulating the release of pain mediators [15–17]. Arbabi-Kalati et al treated BMS patients using Iodine-Gallium-Arsenide (IoGaAs) LLL with 810 nm wavelength [18] and showed a significant

improvement of pain relief. Arduino et al selected Aluminum-Gallium-Arsenide (AlGaAs) LLL of with 980 nm wavelength comparing with control of clonazepam treatment in patients with BMS [19]. Patients in AlGaAs LLL group showed a significant decrease of pain/burning sensation, compared with control group did.

The neodymium-doped yttrium aluminum garnet (Nd:YAG) with 1064 nm wavelength has an advantage in penetrating deeply to the target tissue. However, little is known for its effectiveness in managing patients with BMS. The aim of this study was to assess the effectiveness of Nd:YAG LLL verse no power placebo in the treatment of patients with BMS in pain/burning, numbness and altered taste.

Methods

Participants

Patients were recruited at Department of Oral Mucosal Diseases, Shanghai Ninth People's Hospital during July of 2018 to June of 2019. The protocol was approved by Committee of Medical Ethics of the hospital (SH9H-2018-T18-2). The written informed consent was obtained from all patients. And, the trial was registered at Chinese Clinical Trial Registry (ChiCTR1800018834).

Inclusion criteria were as follows: (1) patients diagnosed as BMS in accordance with the International Association for the Study of Pain (IASP) [1] which characterized this syndrome as oral burning sensation without detectable organic lesion in oral cavity; (2) symptom of burning sensation only on the tongue; and (3) ability to complete the clinical trial.

Exclusion criteria: patients (1) with oral pain accompanied with detectable organic lesion in oral mucosa; (2) diagnosed as BMS but symptom of burning sensation was outside the tongue; (3) a history of psychosis; pregnancy or breast-feeding women; and (4) reluctance to give consent to participate.

Laboratory examinations were also performed including blood routine examination, blood glucose, serum iron, total iron binding capacity, iron saturation, vitamin B12, folic acid, 25-OH-D3, fungal culture, and allergic text. All enrolled BMS patients were arranged to have laboratory examinations at the end of treatment. Individuals with abnormal laboratory values were kept as "enrolled participant", but modified diagnosis as "secondary" BMS and treated accordingly.

Study design

Randomization

This randomized controlled trial (RCT) was single-blind, single-center, and parallel study. Patients were assigned to one of two groups by a computer program using simple sequentially numbered randomization table. The assignation number was uniformly kept in a sealed envelope until the moment

of treatment. Participates were allowed to abandon the trial at any time if they no long wanted to receive therapy.

Sample size

Sample size was not estimated because of the lack of any studies using 1064nm Nd:YAG LLL treatment for BMS. Therefore, we arbitrarily decided to enrolled minimum 21 patients in each group for this pilot study.

Treatment modalities

Patients were randomly assigned to two groups: LLL group, the patients were irradiated with a Nd:YAG laser (HSM-Ⅱ, Sichuan Aerospace Sid Control & Guide Co., Ltd, China), according to the manufacturer's instructions, and placebo group, the patients was treated under the same LLL instrument which was switched off.. The tongue was divided into 17 treatment regions (Fig. 1). The number of treatment region was depended on the extents of tongue affected. Before laser irradiation, the treatment areas were cleaned with normal saline and dried with gauze. The probe was applied vertically over mucosa at a distance of about 0.6cm where the irradiation area was 1cm². The parameters of irradiation consisted of 100mW power, 3J/cm² energy density, 10Hz, pulse mode and a 1064nm wavelength emission. Each patient underwent one laser irradiation session per week for 4 weeks.

Clinical assessment

Clinical assessment of subjective pain/burning, numbness and altered taste was performed using a visual analogue score (VAS), which consisting of a 10cm vertical line marked with 0 (absence of symptom) to 10 (the most severe symptom), right before each irradiation session and one week after last treatment.

The primary outcome of the study was the effectiveness of LLL treatment for pain/burning relief between baseline and the last session. The secondary outcomes were the effectiveness of LLL treatment in relief of numbness and altered taste. The effectiveness of LLL treatment was defined as the mean percentage of improvement in symptom and calculated using the following formula:

$$\text{Effectiveness (\%)} = (\text{VAS}_{\text{baseline}} - \text{VAS}_{\text{session}}) \times 100 / \text{VAS}_{\text{baseline}}$$

Statistical analysis

Statistical analysis was performed using SPSS, version 24 (SPSS Inc, Chicago, Illinois). Basic variables including gender, systemic disease and menopause were analyzed using *Chi-square* test. Basic features including age and VAS of symptom were accessed by independent 2-sample *t* test. Non-normal distribution variable, diseases duration, was analyzed by *Wilcoxon rank sum* test. Comparison of VAS in either inter-group or intra-group for each session was analyzed by repeated-measures analysis of variance (ANOVA). Statistically significant deference was established as $P < 0.05$.

Results

General information of the trail

Forty-four BMS patients were screened and 2 patients were not included. One patient declined to participate and one patient had a diagnosis of psychosis. Finally, a total of 42 patients with BMS including 34 (81%) women and 8 (19%) men with average disease duration of 9 months, ranging from 2 to 60 months, were enrolled for the study from October of 2018 to September of 2019 (Table 1). The mean age was 51.69 years, ranging between 19 and 71 years (Table 1). Among these participants, 30 reported systemic disease (supplementary Table 1). Every 21 patients were randomized into LLL and placebo group. After laboratory examination, 10 and 13 participants in LLL and placebo group, respectively. The flow diagram of the trial is showed in Fig. 2.

Table 1
Baseline characteristics

Variables	Total	LLL	Placebo	P
Gender (n)				
Female	34	19	15	0.24
Male	8	2	6	
Age, mean (years)	51.69	56.19	47	0.06
Disease duration, mean (months)	9	11.80	7.00	0.31
Systemic disease (n)				
	30	17	13	0.17
Menopause (n)				
	26	16	10	0.11
Pain/Burning (n)				
	42	21	21	1.00
Numbness (n)				
	22	14	8	0.06
altered taste (n)				
	6	4	2	0.38
Pain/Burning (VAS)	4.29 ± 1.59	4.55 ± 1.67	4.06 ± 1.49	0.33
Numbness (VAS)	3.95 ± 1.70	4.00 ± 1.55	3.86 ± 2.15	0.86
Alter taste (VAS)	3.48 ± 2.54	2.34 ± 1.64	5.75 ± 3.89	0.18
LLL, low-level laser; n, number of patient.				

No significant difference of baseline variables were observed (Table 1). All of them completed the study. No adverse effects were reported. No deviations of trial protocol were made after enrollment.

Primary outcome analysis

All of patients (21) was showed significant decreasing of VAS values of pain/burning (ranged from 2% ~100%, mean 52%) after LLL treatment (Table 2, Supplementary Table 2). The mean VAS value of pain/burning for patients decreased 21%, 22%, 38% and 52%, respectively (Supplementary Table 2), significantly from the baseline session (S_{baseline}) to one week after 1st session (S1), 2nd session (S2), 3rd session (S3) and 4th session (S4) of LLL treatment (Table 2, Supplementary Table 2). The significant

difference of VAS in pain/burning was also observed between LLL and placebo groups at S3 ($P < 0.05$) and S4 ($P < 0.01$) (Fig. 3A, Table 2).

Table 2
Comparison of VAS (mean $\pm$ SD) between two groups & each session

Symptom	S _{baseline}	S1(P ^{S1})	S2(P ^{S2})	S3(P ^{S3})	S4(P ^{S4})
Pain/Burning					
LLL (n = 21)	4.55 $\pm$ 1.67	3.60 $\pm$ 1.69 (< 0.01)	3.56 $\pm$ 1.67 (< 0.05)	2.80 $\pm$ 1.49 (< 0.01)	2.19 $\pm$ 1.15 (< 0.01)
Placebo (n = 21)	4.06 $\pm$ 1.49	3.64 $\pm$ 1.18 (> 0.05)	3.53 $\pm$ 1.22 (> 0.05)	3.80 $\pm$ 1.49 (0.05)	3.64 $\pm$ 1.41 (> 0.05)
p ^g	> 0.05	> 0.05	> 0.05	< 0.05	< 0.01
Numbness					
LLL (n = 14)	4.01 $\pm$ 1.55	4.01 $\pm$ 1.29 (> 0.05)	3.02 $\pm$ 1.19 (< 0.05)	2.91 $\pm$ 1.14 (< 0.05)	1.47 $\pm$ 1.26 (< 0.01)
Placebo (n = 8)	3.86 $\pm$ 2.15	3.81 $\pm$ 1.85 (> 0.05)	3.45 $\pm$ 2.00 (> 0.05)	3.26 $\pm$ 1.78 (> 0.05)	3.55 $\pm$ 2.39 (> 0.05)
p ^g	> 0.05	> 0.05	> 0.05	> 0.05	< 0.05
Altered taste					
LLL (n = 4)	2.34 $\pm$ 1.64	0.70 $\pm$ 1.40 (> 0.05)	0.98 $\pm$ 1.95 (> 0.05)	1.23 $\pm$ 2.45 (> 0.05)	0.87 $\pm$ 1.44 (> 0.05)
Placebo (n = 2)	5.75 $\pm$ 3.89	1.5 $\pm$ 2.12 (> 0.05)	2.00 $\pm$ 2.82 (> 0.05)	2.50 $\pm$ 3.54 (> 0.05)	2.50 $\pm$ 3.54 (> 0.05)
p ^g	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
S, session; LLL, low-level laser; P ^s , P of comparison between baseline and each session for a group itself; P ^g , P of comparison between LLL and placebo group; n, number of patient.					

Secondary outcomes

The mean VAS value of numbness only decreased significantly from the baseline to the end of LLL treatment in LLL group (ranged from 23% ~100%, mean 61%) (Fig. 3B). The significant difference was also observed for inter-group comparison. Relief of altered taste was found neither in LLL group nor in placebo group (Fig. 3C, Table 2).

Discussion

With the properties of analgesic, anti-inflammatory, and bio-stimulation, LLL showed effect in the treatment of pain relief [20–24]. The present study assessed the effectiveness in the Nd:YAG LLL treatment of patients with BMS. BMS patients showed up to 100% pain/burning relief with mean improvement of 52% after 4 weeks Nd:YAG LLL treatment.

The pathology of BMS is complex, and may be caused by oral candidiasis, hormonal disorder related with menopause, and nutritional deficiencies, peripheral and central nervous systems disorders, and psychosocial aspect [8]. The diagnose and classification of BMS are first challenges when a patient complains the symptom of burning/pain in the mouth. According to Headache Classification Committee of the International Headache Society, whether secondary BMS attributed to a local factors such as candidiasis or systemic disorders should be considered as an entity is a matter for debate [25]. As well, it is not clear after eliminating these factors (such as candidiasis, anemia) whether the symptom of pain/burning can be relieved. Therefore, we utilized the BMS definition of IASP, which being burning tongue or other mucous membranes without organic oral lesion [1]. Meanwhile, we performed laboratory test after LLL treatment (blind for secondary BMS) and found that 10 and 13 patients in LLL and placebo were abnormal in laboratory test, respectively. Combining 30 patients with systemic disease in the recruitment, in total 21 and 19 patients in the LLL group and placebo group could be related to “secondary” BMS, respectively. This indicated that Nd:YAG LLL was effective for patients with BMS even if those were with possible systemic conditions.

Different wavelengths, such as 660 nm Indium-Gallium-Aluminum-Phosphorus (InGaAlP) [26–28], 685 nm Gallium-Aluminum-Arsenic (GaAlAs) [29], 790–830 nm Gallium-Aluminum-Arsenide (GaAlAs) [13, 30–34], 910 nm Gallium-Arsenide (GaAs) [35] and 980 nm AlGaAs [19], have been suggested as being effective in managing BMS. Whether laser effect is dependent upon the wavelength of the light is still unclear. Demirkol et al using Nd:YAG laser obtained better results in the treatment of subjective tinnitus related to temporomandibular joint disorders comparing with diode LLL did, probably because of the Nd:YAG laser having a wavelength of 1046 nm that permits it to penetrate deeply and extend readily within tissue [24]. Our study provided the evidence that Nd:YAG LLL treatment was an effective approach for BMS patients relieving pain/burning.

Hansen et al using red diode LLL treating BMS patients with a laser switched-off control group [36]. LLL as well as switch-off Laser decreased symptom of pain in the same manner. Placebo response was also evidenced to be effective in other study approximately 7.3%~50% of the patients [13, 15, 30, 37]. It was suggested that a psychosomatic organ of pain might resulted in the possibility of placebo effect [31]. Therefore, we eliminated the BMS patients with a history of psychosis in our trial screening process. Our data showed significant difference of treatment between LLL and placebo group. And, patients in placebo group did not show clinical significance.

The function of the taste buds depends on the type of papillae and the region in which they are located [38]. In mammals, taste papillae include fungiform papillae, circumvalate papillae and foliate papillae. The fungiform papillae are located at the apex and body of tongue and contains taste buds involving the

sweet and sour tastes, controlled by fibers of the lingual nerve. The circumvallate papillae are distributed at the root of the tongue and its taste buds receives bitter signal through sensory fibers of the glossopharyngeal nerve. The foliate papillae are sit at the lateral surfaces of the posterior tongue. The taste buds of foliate papillae react primarily to the sour taste and are innervated by branches of the chorda tympani nerve and glossopharyngeal nerve. Palatine taste buds are controlled by the branch of the facial nerve [38]. Overall, the largest number of taste buds is at the tongue and palate, while some at the epiglottis, throat and larynx [39]. Our study, irradiation was performed within 17 area (Fig. 1), in which mainly before the circumvallate papillae. This may explain treatment of altered taste was not effective.

Conclusions

It can be concluded that Nd:YAG LLL (3J/cm², 30 s, and 100 mW) was effective for reduction of pain/burning and numbness in patients with BMS.

Abbreviations

BMS: burning mouth syndrome; LLL: low-level laser; RCT: randomized controlled trial; VAS: visual analogue scale; S_{baseline}: baseline session; S1: 1st session; S2: 2nd session; S3: 3rd session; S4: 4th session; Nd:YAG: neodymium-doped yttrium aluminum garnet; I₀GaAs: Iodine-Gallium-Arsenide; AlGaAs: Aluminum-Gallium-Arsenide; InGaAlP: Indium-Gallium-Aluminum-Phosphorus; GaAlAr: Gallium-Aluminum-Arsenic; GaAlAs: Gallium-Aluminum-Arsenide; GaAs: Gallium-Arsenide; IASP: the International Association for the Study of Pain.

Declarations

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

WW Jiang designed and analyzed the study, C Sun contributed to the writing and revision of the manuscript, C Sun and QQ Zhang contributed to statistical analysis, and P Xu contributed to collection of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by Committee of Medical Ethics of Shanghai Ninth People's Hospital (SH9H-2018-T18-2). Written informed consent was obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests

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Figures

Figure 1

Illustration of irradiation regions of the tongue.

Figure 2

Flow diagram of the trial phases.

Figure 3

Improvement of subjective symptom in BMS after treatment between LLL and placebo group. A, VAS of pain; B, VAS of numbness; C, VAS of taste; LLL group, presented as ▲, ■, ●; placebo group, presented as △, □, ●.

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