

The low level laser therapy in the management of neurological burning mouth syndrome. A pilot study

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Summary

The low level laser therapy in the management of neurological burning mouth syndrome. A pilot study.

Background and objective. Burning Mouth Syndrome (BMS) is a common disease but still a diagnostic and therapeutic challenge for clinicians. Despite many studies its nature remains obscure and controversial; nowadays there is no consensus about definition, diagnosis and classification. BMS is characterized clinically by burning sensations in the tongue or other oral sites, often without clinical and laboratory findings. According to the etiology, BMS cases should be subdivided into three subtypes: BMS by local factors (lfBMS), BMS by systemic factors (sfBMS) and neurological BMS (nBMS), the most frequent, in which the symptom is caused by central or peripheral neurological malfunctions affecting in particular the taste pathway. To establish the type of BMS, both anamnesis and clinical examination, including laboratory tests, are necessary; nBMS cases will be recognized by exclusion of any other type. In case of lfBMS or sfBMS, the treatment of the main pathology will be resolutive; in nBMS cases many Authors proposed different pharmacological trials without satisfactory results and the current opinion is that a multidisciplinary approach is required to keep the condition under control.

This pilot study aimed to investigate whether the biostimulative effect of Low Level Laser Therapy (LLLT) could enhance the symptoms of nBMS cases, improving patients' quality of life.

Study design/materials and methods. Among 160 patients affected by oral burning sensation attending to the Oral Pathology Complex Operative Unit of the De-

partment of Stomatological Sciences of Sapienza University of Rome, 77 resulted affected by nBMS. Twenty-five of these patients, 16 females and 9 males, were randomly selected for low level laser applications. All the patients were irradiated with a double diode laser (Lumix 2 Prodent, Italy) emitting contemporarily at 650 nm and 910 nm, with a fluence of 0.53 J/cm² for 15 minutes twice a week for 4 weeks. The areas of irradiation were the sides of the tongue on the path of taste fibers. A NRS (numerical rating scale) evaluation of maximum and minimum pain was registered before and after the treatment. In each case to the total value of NRS rates registered before the treatment was deducted the total NRS rate registered after the treatment. The difference was estimated effective if over two points. The Kruskal-Wallis test revealed the significance of the study ($p < 0.0001$) and the Dunn's Multiple Comparison test, applied to compare NRS rates before and after the treatment, showed that there is not a statistically relevant difference between min NRS ratings before and after treatment, while there are statistically significant differences between max NRS ratings ($p < 0.05$).

Results. All the patients agreed the treatment confirming the general good compliance related to laser treatments. No side effects were registered and all the patients completed the therapy without interruption. Seventeen patients (68%) had relevant benefits from the treatment with valid reduction of NRS ratings. In 8 cases the differences of NRS rates were not relevant being under the limit of reliability established in study design. In no case there was a worsening of the symptoms.

Conclusions: According to the results of this pilot study it is reasonable to suppose that LLLT may play an important role in the management of nBMS cases, more investigations are needed to clarify, by a greater number of cases and a placebo control group, the real effectiveness of this innovative LLLT application.

Key words: oral pain, BMS, LLLT, laser dentistry.

Objectives and background

Burning Mouth Syndrome (BMS) is a common disease that represents a diagnostic and therapeutic challenge for clinicians. Despite many studies tried to investigate this particular disorder, its real nature remains still obscure and controversial, and at this moment there is no consensus about even the diagnosis and the classification of BMS. A lot of terms are used to describe similar situations, such

as glossodynia, glossopyrosis, stomatodynia, and oral dysesthesia.

Affected patients often present with multiple oral complaints, including burning, xerostomia and taste alterations. The prevalence of BMS is 1.8-19% in the general population (1-4) and it is higher in middle-aged post-menopausal women (Male:Female ratio = 1:7), while children are never affected. The anterior two third of the tongue is the most frequently affected site, followed by hard palate, lips and gums (5-9).

Many causes, local or systemic, can raise these particular oral sensations creating great problems in diagnosis and treatment.

Many patients affected by this pathology present evidence of anxiety, depression and personality disorders, but it is unresolved if the pain led to the psychological disorder or vice versa (10-14).

As a first, BMS patients should be sub-divided into two categories, the first including all the cases presenting clinical mucosal signs; the second one including all those patients without mucosal affections. Seventy-five per cent of BMS cases belong to this second category (15).

The symptoms vary from different entity of burning sensation, to pain, dry mouth (xerostomia), unpleasant and altered taste sensation and itching (16). Symptoms involve tongue, palate, lips, and gums often in relation with removable dentures. Patients awaken without pain and refer increasing symptoms through the day and into the evening. Symptoms often decrease during meals and working activity. The onset is sudden and sometimes related to dental procedures. Most patients suffer from the pathology for long time, ranging from months up to years. According to its etiology, BMS should be differentiated into three subtypes: BMS by local factors (lBMS), BMS by systemic factors (sBMS) and idiopathic BMS (iBMS) (17); lBMS is caused by various pathologies affecting oral mucosa, such as erosive lichen planus, acute or chronic candidiasis, allergies, trauma, geographic tongue, trigeminal neuralgia and parafunctions. The sBMS occurs as oral sign of systemic conditions such as Sjögren syndrome nutritional deficiencies (e.g.: iron and B complex), type II diabetes (formerly known as no-insulin dependent), hormonal changes, as during menopause (18), hypothyroidism (19), and drug induced xerostomia.

The iBMS differs from the two previous conditions by lack of local signs and being often associated with neurological disturbances like anxiety, hypochondriasis and especially depression, so many Authors consider the main psychological factors responsible for this situation. In iBMS salivary flow rates seems to keep into normal values as demonstrated by Zhao et al (20). Recent studies about iBMS have pointed to dysfunction of several cranial nerves associated with taste sensation (16) or reduction of density of epithelial nerve fibers (21), as possible causes of the pathology, for this reason it should be reasonable to call this particular form neurological BMS (nBMS) (Fig. 1).

Nowadays the diagnostic approach to BMS patients is still very difficult and needs a wide knowledge of the various aspects of this pathology. In order to establish what kind of BMS is affecting the patient, both anamnesis and clinical examination, including laboratory tests are necessary. In case of lBMS or sBMS the treatment of local or systemic pathology will be resolute.

In nBMS patients a multidisciplinary approach has been proposed to keep the condition under better control. In low

dosages, benzodiazepines, tricyclic antidepressant or anticonvulsants may be effective; in patients with nBMS, however it must be considered that a long period treatment with these drugs may induce a xerostomia worsening the oral distress.

Topical capsaicin has been used in some trials (22); Femiano and coll. (23) registered an enhancement of oral pain in nBMS with α -lipoic acid, confirming the neurological involvement of this kind of BMS.

The aim of this study is to verify whether the biostimulative effect of low level laser therapy (LLLT) may enhance the symptoms of nBMS cases improving patients quality of life.

Materials and methods

The study was realized at the Department of Stomatological Sciences of Sapienza University of Rome in the period between January 2004 and April 2009.

In this period 160 patients affected by oral burnings attended to the Oral Pathology Complex Operative Unit. In order to identify the exact kind of the oral burning, in each case a clinical examination was performed and a series of laboratory tests was requested. The complete series of laboratory tests requested is reported in Table 1. After this first screening, only 77 patients could be recognized as affected by nBMS (Tab. 2).

Amongst these cases, 25 patients, 16 females and 9 males, were randomly selected for low level laser applications. In every case a written informed consent to LLLT was requested and obtained.

All the patients were irradiated with a double Gallium Arsenide (GaAs) laser (Lumix 2 by Prodent, Italy). This device emits contemporarily at two wavelengths, 650 nm and 910nm, in the red and near infrared respectively. The biostimulative trial was performed by a cycle of 15 minutes of irradiating time, repeated twice a week for 4 weeks. The fluence (F) irradiated was 0.53 J/cm². According to the hypothesis of peripheral nerve damage in nBMS cases, the irradiation areas were the sides of the tongue on the anatomical path of taste fibers. A NRS evaluation of maximum and minimum pain was registered before the first application and after the whole treatment.

In each case to the total value of NRS rates registered before the treatment was deducted the total NRS rate registered after the treatment. The difference was estimated effective if over two points.

Results

All the patients completed the treatment confirming the general excellent compliance of laser treatments. The results obtained are reported in Table 3; in 17 cases (68%, 10 females and 7 males) a clear reduction of total NRS rates was registered (total difference over 2 points). In remaining 8 cases (32%, 6 females and 2 males) the results were under the limit of efficacy established in study design (total difference between 0 and 2 points) and were considered ineffective. In no case a worsening of symptoms was registered. The Kruskal-Wallis test revealed the significance of the study ($p < 0.0001$) and the Dunn's Multiple Comparison test, applied to compare NRS rates before and after the treatment, showed that there is not a statistically

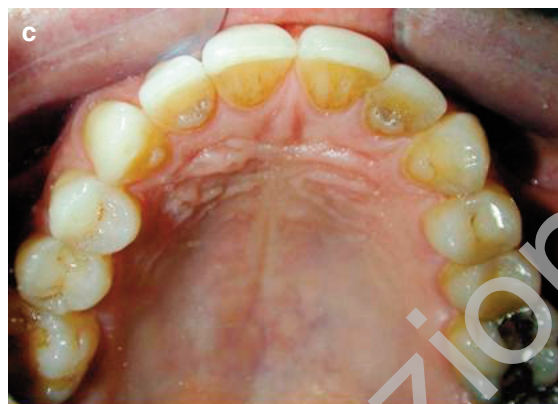
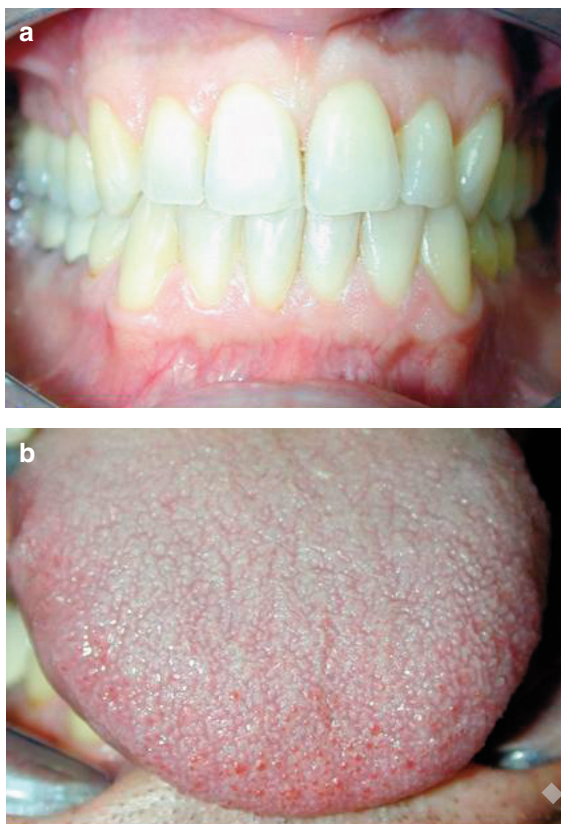


Figure 1a, b, c - Clinical normal appearance of a nBMS patient.

relevant difference between min NRS ratings before and after treatment, while there are statistically significant differences between max NRS ratings ($p < 0.05$)

Discussion

The effectiveness of low level laser irradiation in peripheral nerve regeneration was demonstrated in several studies (24) both *in vitro* and in animal trials. One of the most interesting results in this research pathway was obtained by

Rochkind and coll. (25) that tested in rats the efficacy of 780 nm laser phototherapy versus non irradiated controls on the acceleration of axonal growth and the nerve regeneration after peripheral nerve reconstruction by polyglycolic acid neurotube. The study demonstrated that the nerves were morphologically reconstructed in both groups, but the Sciatic Functional Index and the total number of myelinated axons were higher in laser treated group. Ihsan and co. (26) in 2007 in rabbits, showed the efficacy of 901 nm low level irradiation versus control, in regenerative processes after surgical induced peroneal nerve sections. The evaluation was registered in the short and middle period after surgery. Compared to the control groups, thicker nerve fibers, more regular myelin layers and clearer Ranvier nodes were observed in treated group. The differences between two groups were yet relevant in a short period, 2 weeks after surgery, and highly significant in mid period, 6 and 8 weeks, after surgery. Oron and coll. (27) investigated *in vitro* whether low level diode laser irradiation could enhance the ATP production in cultured normal human neural progenitor (NHNP). The results showed an almost double ATP production in irradiated cells versus non lased controls (7513 ± 970 units vs. 3808 ± 539 units), supporting the hypothesis of a good effectiveness of low level laser irradiation in human neuronal cells too. A peripheral nerve dysfunction, especially of taste pathway,

Table 1 - Laboratory tests for clinical screening.

CBC	Stomatological Patch Test
SGOT	Serum H.Pylori
SGPT	T3
LDH	T4
ESR	TSH
AST	Thyroid antibodies
CK	Thyroid Ecography
Serum iron, ferritin, transferrin	MSG Scintigraphy
Total IgE (PRIST)	Res Oral Candidiasis



Figure 2 - Low level laser irradiation of tongue.

in the aetiology of nBMS is long lasting, since Fox first observations in 1931 (28). Many studies related the lack of function of taste in predisposed subjects, the so-called supertasters, with the burnings typical of the syndrome (29, 30). The reliability of this hypothesis was showed as a first by histological study by Suarez and coll. (21) that showed in tongue biopsies a relevant lower density of epithelial nerve fibres in BMS patients versus controls. Similarly Lauria and coll. (31) demonstrated that BMS patients tongue, compared to normal ones, shows a reduction of trigeminal small fibres.

Table 2 - Diagnosis after clinical and laboratory screening.

Patients with Oral Burnings	160
BMS	77
Candidiasis	17
Oral Lichen Planus	18
Leukoplakia	7
G-Oe-Reflux	4
Local Hypersensitivity	4
Aphthous Ulcers	4
Thyroid Dysfunction	3
No BMS-related pathologies	26

According with these observations we designed this pilot study to investigate whether neurological biostimulative effects of LLLT could enhance oral nBMS patients' complaints by a reduction of symptoms. For this first observation the site of irradiation was arbitrarily established in the tongue sides, according to the anatomic distribution of taste fibers (Fig. 2), independently from the referred sites of symptoms. The obtained results of 68% effectiveness are encouraging together with no worsening cases and good patients' compliance. The study was also statistically significant by

Table 3 - Minimum and maximum NRS rates registered before and after LLLT.

	Name	Sex	NRS mM bef LLLT		NRS mM aft LLLT		Differ.
1	V. R.	F	4	8	3	5	4
2	R. M.	F	3	5	2	3	3
3	L. L.	F	1	5	0	3	3
4	D. G.	M	2	5	1	2	4
5	I. S.	M	4	7	2	3	6
6	P. E.	M	4	6	3	5	2
7	G. MP.	F	4	8	4	8	0
8	P. R.	F	4	6	0	1	9
9	D. PM.	F	4	6	1	5	4
10	A. A.	F	4	6	3	6	1
11	M. M.	F	0	4	0	2	2
12	S. A.	F	3	6	3	6	0
13	T. G.	M	6	10	4	6	6
14	S. M.	F	3	6	2	4	3
15	V. N.	F	3	5	2	4	2
16	B. G.	M	1	3	5	0	2
17	C. L.	F	1	3	5	2	5
18	T. M.	M	1	2	5	2	4
19	P. A.	F	3	5	2	4	2
20	L'O. G.	M	2	4	0	3	3
21	N. F.	F	5	8	1	3	9
22	C.L.	F	3	9	2	6	4
23	A. A.	M	3	6	2	4	3
24	D.S. V.	F	5	10	4	8	3
25	G. G.	M	2	4	0	2	4

Kruskall-Wallis test ($p < 0,0001$); the comparative Dunn's test showed significant results for Max NRS rates differences ($p < 0,005$) between pre and post treatment evaluation, while min NRS rates differences were not significant. This difference could be explained with the difficulty to establish clearly an exact value of minimum pain level, while it is easier for a patient to be accurate in establishing the maximum pain evaluation rate.

Conclusion

This is only the first step of a research pathway that previews further investigations, in order to clarify the other questions still unresolved at the moment. As a first a higher number of cases are mandatory to obtain statistically significant results and versus control study is necessary to avoid placebo effects. At last, it could be necessary to apply multiple system of pain evaluation to prevent subjective bias in records.

According to this pilot experience it is reasonable to presume that LLLT biostimulative effects may play an effective role in the management of nBMS cases, however further studies are needed to establish whether it can be clearly considered the resolution of this long lasting clinical dilemma.

References

1. Elad S, Czerninski R, Eliav E: Burning Mouth Syndrome. *Hafuah* 2002; 141(4): 407.
2. Forman R, Settle RG. Burning mouth symptoms, part II: a clinical review. *Compendium* 1990; 11(3): 140-144.
3. Forman R, Settle RG. Burning mouth symptoms: a clinical review part I. *Compendium* 1990; 11(2): 74-78.
4. Zakrzewska JM, Forsell H, Glenn AM. Interventions for the treatment of Burning mouth syndrome. *Cochrane database Syst Review* 2005(1); CD002779.
5. Ship JA, Grushka M, Lipton JA, Mott AE, Sessle BJ, Dionne RA. Burning mouth syndrome: an update. *JADA*; 1995; 126(7): 842-53
6. Rhodus NL, Carlson CR, Miller CS. Burning mouth (syndrome) disorder. *Quintessence Int.* 2003; 34(8): 587-93.
7. Mignogna MD, Fedele S, Lo Russo L, Leuci S, Lo Muzio L. The diagnosis of Burning mouth syndrome represents a challenge for clinicians. *J Orofac Pain*; 2005; 19(2): 168-73.
8. Lamey PJ. Burning mouth syndrome. *Dermatol Clin.* 1996; 14(2): 339-54.
9. Lamey PJ, Lamb AB. Lip component of burning mouth syndrome. *Oral Surg Oral Med Oral Pathol*; 1994; 78(5): 590-3.
10. Al Quaran FA. Psychological profile in Burning mouth syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2004; 97(3): 339-44.
11. Brody HA, Nesbitt WR. Psychosomatic oral problems. *J Oral Med.* 1967; 22(2): 43-6.
12. Grushka M, Epstein JB, Gorski M. Burning mouth syndrome and other oral sensory disorders: a unifying hypothesis. *Pain Res Manag.* 2003; 8(3): 133-5.
13. Maina G, Albert U, Gandolfo S, Vitalucci A, Bogetto F. Personality disorders in patients with Burning mouth syndrome. *J Pers Disord.* 2005; 19(1): 84-93.
14. Popper F. Psychogenic aspects of the Burning mouth. *J Dent Assoc S Afr.* 1968; 23(10): 357-8.
15. Pindborg JJ. Atlas of diseases of the oral mucosa. Munksgaard ed (COPENHAGEN) 1992; 238.
16. Eliav E, Kamran B, Schaham R, Czerninski R, Gracely R, Benoliel R. Evidence of chorda tympani dysfunction in patients with Burning mouth syndrome *JADA*; 2007; 138(5): 628-33.
17. Balasubramaniam R, Klasser GD, Delcanto R. Separating oral burning from burning mouth syndrome: unravelling a diagnostic enigma. *Aust Dent J* 2009; 54: 293-99.
18. Del Vecchio A, Podda G, Rossi L, Francalanci P. Burning Mouth Syndrome: indagine immunistoichimica sulla presenza nelle mucose orali di recettori specifici per gli estrogeni. In *Atti II Simposio SIOG Padova* 1992; 255.
19. Femiano F, Lanza A, Bonaiuto C, Gombos F, Nunziata M, Cuccurullo L, Cirillo N. Burning mouth syndrome and Burning mouth in hypothyroidism: proposal for a diagnostic and therapeutic protocol. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2008; Jan 105(1): e22-7.
20. Zhao M, Chen Q, Lin M. Relationship between the symptom of xerostomia and non-stimulated salivary flow rates in patients with burning mouth syndrome. *Hua Xi Kou Qiang Yi Xue Za Zhi.* 2001; 19(3): 169
21. Suarez P, Clark GT. Burning mouth syndrome an update on diagnosis and treatment methods. *J Calif Dent Assoc.* 2006; Aug; 34(8): 611-22.
22. Grushka M, Epstein JB, Gorsky M. Burning Mouth Syndrome. *Am Fam Phys* 2002; 65(4): 615-20.
23. Femiano F, Scully C. Burning mouth syndrome (BMS): double blind controlled study of alpha-lipoic acid (thioctic acid) therapy. *J Oral Pathol Med* 2002; 31(5): 267.
24. Tuner J, Hode L: *The laser therapy Handbook* Prima Books AB Ed (Grängesberg – SWEDEN); 2007; 161-2.
25. Rochkind S, Leider-Trejo L, Nissan M, Shamir RH, Kharenko O, Alon M: Efficacy of 780-nm Laser Phototherapy on Peripheral Nerve Regeneration after Neurotube Reconstruction Procedure (Double-Blind Randomized Study). *Photomed Las Surg.* 2007;25(3):137-43.
26. Ihsan FR, Al-Mustawfi N, Kaka LN: Promotion of Regenerative Processes in Injured Peripheral Nerve Induced by Low Level Laser Therapy. *Photomed Las Surg.* 2007; 25(2): 107-111.
27. Oron U, Ilic S, De Taboada L, Streeter J: Ga-As (808 nm) laser Irradiation enhances ATP Production in Human Neuronal Cells in Culture. *Photomed Las Surg.* 2007;25(3):180-2.
28. Fox AL: The relation between chemical constitution and taste. *Proc. Natl. Acad. Sci. USA.* 1931; 18:115-20
29. Lamey, P.J., R.S. Hobson, and R. Orchardon, Perception of stimulus size in subjects with burning mouth syndrome. *Journal of Oral Pathology and Medicine*, 1996: 25: 420-423.
30. Grushka M, Sessle BJ. Burning mouth syndrome. *Dent Clin North Am.* 1999; 35(1):171-84.
31. Lauria G, Maiorana A, Borgna M, Lombardi M, Penza P, Padovani A, Sapelli P.: Trigeminal small-fiber sensory neuropathy causes burning mouth syndrome *Pain* 2005; 115: 332-7.