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The efficiency of alpha-lipoic acid in the treatment of burning mouth syndrome: a systematic review

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Abstract. – OBJECTIVE: Burning mouth syndrome (BMS) is generally characterized by oral mucosa burning in the absence of any medical and dental reasons. The findings of previous studies or reviews are generally ambiguous. Therefore, the aim of this study was to review the findings of previous studies of randomized controlled trials (RCTs) for pain as evaluated by Visual Analogue Scales (VAS). VAS is a validated, subjective measure for acute and chronic pain

MATERIALS AND METHODS: A search of PubMed/MEDLINE/ScienceDirect and Embase up to 2020.

RESULTS: By following the criteria of exclusion and inclusion, the papers were examined and divided into two categories, one based on BMS and the other that used alpha-lipoic acid to treat BMS. The reviewed results were compared in terms of methodology, size of sample, outcomes, and results.

CONCLUSIONS: Some studies showed positive results of using ALA to treat the BMS, but these findings need more improvements, and more investigations are required.

Key Words:
Burning mouth syndrome, Alpha-lipoic acid, Tomatodynia, Glossopyrosis, Glossodynia, Oral dysesthesia.

Introduction

Burning mouth syndrome (BMS) is a chronic condition which is characterized by a feeling of burning of intraoral mucosa in lack of presence of a systemic or local reason. The World Health Organization (WHO) adds that Burning Mouth Syndrome (BMS) is characterized by a significant disturbance in functions of the mouth and facial or emotional distress[1]. The definition of burning mouth syndrome according to the International Headache Society (IHS) is, "a numbness or burning sensation in the oral mucosa that occurs for more than two hours/day over three months or more with no presence of clinical variations". These sensations may be associated with paresthesia, dysgeusia and xerostomia. The commonly affected part is the tongue tip. It mainly affected women during and after menopause[2].

Historically, there is important heterogeneity in BMS definitions which are used in literature; with many studies[1,3] having patients whose sensation of burning is capable of being attributed to a basic condition. After its appearance in the 1800s in literature[4], the BMS is referred to as tomatodynia, glossopyrosis, burning mouth, glossodynia and oral dysesthesia[1,5]. The rate of BMS prevalence varies worldwide; the range can be reported from 0.7% to 8% based on various data[3]. It appears in women 7 times more than in men[6]. Almost all subjects who have BMS are peri and post-menopausal women having symptoms exhibiting between 3-12 years with the inception of menopause[3,7]. BMS rarely happens before 30 years and the mean age is between 59 and 61 years[5].

In terms of etiology, BMS is poorly managed and understood. It is generally characterized by discomfort and oral pain with no systemic or local symptoms connected with stomatodynia. This condition due to various factors makes its diagnosis very difficult. The present knowledge about BMS treatment and causes was detailed. It is an idiopathic, painful, and chronic condition characterized by pain, itching, burning, or scalding of mucosa with no evident symptoms[8]. Patients having BMS can be categorized into three groups: (i) patients who have neuropathy of peripheral small

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fibre, (ii) patients with neuropathy of sub-clinical central trigeminal and (iii) patients who experienced inhibitory dopaminergic deficiency[9]. That is why much attention has been paid to peripheral and central nervous system dysfunction recently.

The most observed disorders in patients who have BMS are depression, anxiety[10] and poor sleep[11,12]. It is interesting to observe that in a study of 200 BMS patients[12], disturbance in sleep is positively correlated with depression and anxiety. However, more work is required to check the relation between sleep disturbance and BMS.

Treatments for BMS

Currently, there are no effective treatments available to manage BMS, however, hormone replacement therapy (HRT); anticandida agents; medicine for ulcers; psychotherapy; benzodiazepines; inhibitors of serotonin uptake and antidepressants are used to treat BMS[13]. Available treatments can be grouped into three categories: topical, systemic, and behavioral treatments[14].

Clonazepam has been used both systemically and topically to treat BMS, and it has been shown to minimize symptoms in both the long term and the short term[3,5,7,15,16]. However, it can cause psychological and physiological dependence[3]. Other side effects include fatigue, xerostomia and lethargy[16]. A neuropeptide, which is extracted from chili peppers called Capsaicin, can be topically used to manage BMS. It binds to TRPV1, reduces the number of their receptors, and leads to long term numbness of pain receptors against heat[5,7,17]. This method provides long-term relief despite the fact that it may increase burning soon after treatment[15]. Gabapentine, which is used to treat the conditions of neuropathic pain successfully, when used with Alpha-lipoic acid (ALA), reduces the symptoms of BMS[5,7,15]. In some cases, it has been shown that ALA, an antioxidant has a role in nerve repair, improves the symptoms of BMS but these studies possess heterogeneity and inconsistency[3,5,15]. The use of ALA is preferred as first-line therapy, especially for those who do not want regular prescriptional medicines[3].

Alpha-Lipoic Acid

ALA Alpha-lipoic acid is produced in humans in small quantities. It is essential for the function of many oxidative enzymes, which are involved in metabolism. It is currently known for various biochemical activities and it also acts as a metal chelating agent and biological anti-oxidant, it reduces the oxidized forms of anti-oxidants i.e., GSH (glutathione), vitamins E and C, and it acts as a modulator for signal transduction of many pathways[18].

Alpha Lipoic acid is also present in different food like meats, broccoli, and spinach. It acts as a coenzyme for various chemical reactions, while involving in glycolysis, it converts sugar into energy and regenerates the damaged liver tissues. ALA provides protection to nerve tissues and the brain, it crosses the barrier of the hematoencephalic, and it also plays a neuro regeneration role[19].

Alpha-lipoic acid is a mitochondrial coenzyme that bears neuroprotective and antioxidant properties which can excite the production of neural growth factors[20]. It has the ability to eradicate the free radicals and help in nerve repairing[21]. Various clinical trials used this substance to treat the BMS and investigated its efficiency but the results are not consistent[22].

Role of Lipoic acid in treating BMS

The results of the Cochrane Collaboration systematic review showed that ALA may be used systemically to treat patients. ALA may use to manage the burning mouth syndrome[23]. ALA is an important antioxidant. It acts by reducing the nervous system oxidative damage therefore used in the treatment and prevention of diabetic neuropathy[24]. However, its role in the treatment of BMS is not clear. The use of ALA showed improvements in the intensity of pain in single-blinded and unblended studies, while 2 out of 5 double-blinded cases when ALA was associated with placebo reported the difference in mean scores of pain[20,25]. Gastric upset and headache are the most observed side effects of this method, although they are not significant when compared with placebo[25]. Many studies[26,27] revealed that ALA use did not provide many benefits for mouth burning when compared with placebo. Hence more investigations and studies are needed to describe the effectiveness of Alpha-lipoic acid. This review presents the efficiency of ALA in the treatment of BMS.

Materials and Methods

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) instructions were used, and the standards of IOM (Institute of Medicine) for systematic reviews were observed as a guideline[28,29].

Search Strategy

A search of PubMed/Science Direct/MEDLINE from 2000 to 2020 was carried out with the Mesh terms 'burning mouth syndrome' and 'lipoic acid' and subheadings, 'prevention and control', and 'therapy'. This search was limited to the English language. For the entire database of the Cochrane Library, a similar search with the same terms was also conducted.

Study Selection

Studies or experiments were excluded initially on the basis of relevance of abstract and title proposed by an independent author, studies that did not involve the clinical outcomes about the efficacy of ALA in the management of BMS and those studies which met the criteria i.e., BMS diagnosis, randomization, placebo-controlled trial, and the studies that described the efficacy of ALA in the management of BMS were included in this review (Figure 1). The eligible abstracts were reviewed by the authors and disagreements were solved by consensus, otherwise, the study was not included. Each study was abstracted. The primary and secondary outcomes were considered as a change in pain and relief in related symptoms.

Results

The results included the eleven studies[9,18,19,23,27,30,31,33,34,38,39], which used the ALA (Alpha-lipoic acid) to treat the burning mouth syndrome. One study out of 10 used ALA without and with CPT (cognitive psychotherapy), one assessed the ALA effect with gabapentin, as well as without gabapentin and one study used ALA without vitamins and with vitamins[23,30,31] (Table I). The regime of these studies[18,23,27,31-34] generally contained 200 to 800 mg ALA on daily basis for two months. The studies[23,27,34] which used the comparison of the change in pain between placebo and ALA showed no difference significantly.

In terms of improvements, five studies[18,19,30,31,33] presented a significant variation between placebo and ALA. Two studies[30,31] that combined the ALA with other treatments (CPT and gabapentin) also showed improvements in symptoms more than the results of only ALA, not combined with other treatment. In two studies[27,34], gastric upset and headache were the commonly reported effects of ALA but their occurrence rates were not different from that of placebo.

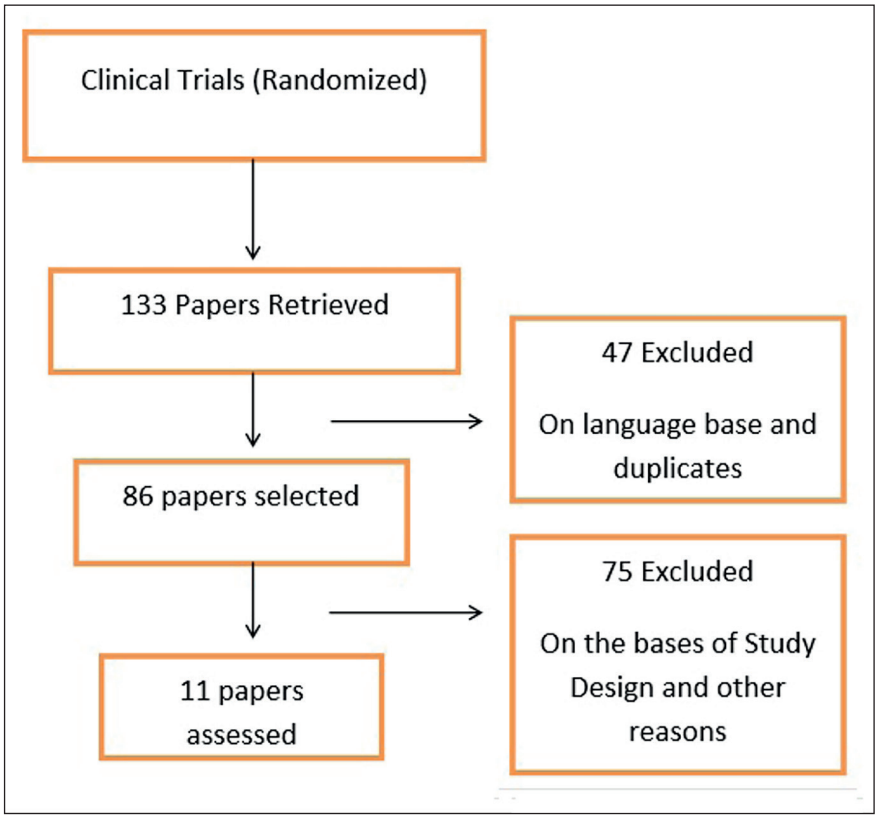

Figure 1. The search process.

Table I. Summary of studies reviewed sorted by year and author.

Author	Regime	Number of subjects	Outcome	Results summary
Femiano et al[19] 2000	600 mg/day for 20 days, then 200 mg/day for 10 days; placebofor 30 days. Crossover: placebo treated with test regime	42	Symptoms (Non-specific) at 30 days Symptoms of burning	76% improvements (63% in crossover with placebo) 14% was significant 40% placebo *vs.* 97%
Femiano and Scully 2002[33]	200 mg TID for 2 months	60	(non- specific VAS) at 2 and 12 m	Improvement at 2 m weakening of symptoms in 27% *vs.* 100% placebo at 12 m (significant)
Femiano et al 2004[30]	Group A: use tranquillizer Group B: not use tranquillizer Each group was given 200 mg (3 times/day) with a gastroprotector (150 mg ranitidine per day) for the duration of two months	40	Had BM for between 2-12 months, and hypochondriacal with a visible cancerophobia	In group A: 4 patients showed improvements in symptoms with ALA, 7 patients exhibited a aminor decrease in burning, 2 showed a deteriorating and 7 had showed no change. In group B: 11 patients exhibited a complete resolve, 4 reported improvements in symptoms, 3 observed a Small reduction and 2 reported no change
Lopez-Jornet et al 2009[34]	800 mg per day for eight weeks	39	Burning VAS at 1 and 2 m	Not improved significantly
Carbone et al 2009[23]	Group 1: 400 mg ALA+ Vit Group 2: 400 mg ALA Group 3: placebo 2 times per day (Duration of treatment was 8 weeks with the follow-up of 2 months	52	VAS T0 = baseline T1 = two weeks, T2=four weeks T3 = four weeks, T4 = end Then 2 months of follow-up	Both groups exhibited improvement, but no difference was reported in groups
Cervigon et al 2009[39]	Oral application of Alpha-lipoic acid (600 mg per day) and γ-linoleic acid (360 mg per day) was given for 8 weeks.	10	4 patients had severe symptoms, 5 had moderate and 1 had mild symptoms	3 patients improved slightly while the remaining showed no improvements
Cavalcanti and da Silveira 2009[27]	TID (200 mg) for thirty days, then washing for 20 days, then treatment of placebo for 30 days crossover: tx with placebo switched groups and cycle wasrepeated	31	Symptoms (Non-specific) and VAS score at 30, 50 and 80 d	Not improved significantly

Continued

Discussion

In terms of treatment and etiology, BMS is not clearly understood. This condition is described as pain in the mouth without any observable symptoms. To understand the risk factors for BMS many factors have been considered as possible reason including systemic, psychological and local characteristics[35,36]. Due to the lack of well-defined and correct etiology, many methods have been proposed and used to treat patients with BMS. However, such treatments do not consider the causes of BMS in the mouth. Furthermore, a completely effective treatment method for BMS is currently not available.

As mentioned earlier, ALA is important for the functioning of many oxidative enzymes, although it produces in very small quantities in the human body[18,33]. It acts as a coenzyme, improves the metabolism of glucose and produces energy in the form of ATP[37].

Table I *(Continued)*. Summary of studies reviewed sorted by year and author.

Author	Regime	Number of subjects	Outcome	Results summary
Marino et al 2010[38]	Group 1: 250 mg capsaicin in 50 ml of water Group 2: ALA 400 mg two times per day Group 3: rinse orally with lysozyme lacto-peroxidase 5 times per week Group 4: rinse orally 3 times per day with 0.05 g boric acid (dissolved in 100 ml of DW) for the period of 8 weeks	28	After 2 months, VAS baseline	Groups 1, 2, and 3 showed that they are superior to group 4 (placebo) but group 1 was the only group that showed improvements after 2 months
Lopez-Jornet et al 2013[9]	TID (200 mg) for thirty days, then washing for 20 days, then treatment of placebo for 30 days crossover: tx with placebo switched groups and cycle wasrepeated	31	Symptoms (Non-specific) and VAS score at 30, 50 and 80 d	Not improved significantly
Lopez-D'alessandro and Escovich, 2011[31]	Group 1: 600 mg ALA per day Group 2: 300 mg GABA per day Group 3: ALA + GABA Group 4, 5 and 6: 100 mg starch placebo per day 100 mg/day for the period of 2 months	20 in each group	0 = no burning, 1 = burning only at 1 place of the Tongue 2 = burning at two places (tongue and gums, tongue and lips, and tongue and palate) 3 = three areas 4 = burning in whole mouth	Groups 1, 2, and 3 showed more improvements than 4, 5 and 6 (placebo)
Palacios-Sanchez et al 2015[18]	TID (200 mg) for two months placebo: 29 participants/ treated: 25 participants	54	VAS score of burning at 2 m	64% improvement with ALA *vs.* 27.6% improvement with placebo, significant

When ALA was compared with placebo, improvements were observed. These studies[23,27] also suggested that psychological factors related to BMS must be considered. Other studies compared ALA with placebo, as well as other groups i.e., capsaicin[38] and GABA[31] showed positive findings. Cavalcanti and da Silveria[27] maintained treatment only for a month while other studies compared treatments for two months. However, this duration did not affect the treatment, because the only study with no positive effects of ALA for BMS[34] was used for 2 months[38].

Conclusions

The efficiency of ALA is still controversial because only some studies showed positive results greater than placebo. More studies could provide more knowledge about its effectiveness.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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