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Effectiveness and Safety of Clonazepam, Pregabalin, and Alpha Lipoic Acid for the Treatment of Burning Mouth Syndrome

ORIGINAL ARTICLE

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ABSTRACT

Objective: Burning mouth syndrome is characterized by pain in the oral mucosa with no visible organic pathology. Few treatment options are available; however, none of them are gold-standard. Here we evaluated the effectiveness and safety of clonazepam, pregabalin, and alpha lipoic acid for treating burning mouth syndrome.

Materials and Methods: Patients were divided into three groups. Clonazepam (2 mg/day) was administered to the patients in the first group, pregabalin (150 mg/day) to those in the second group, and alpha lipoic acid (600 mg/day) to those in the third group. Each group consisted of 30 patients. The intensity of oral pain in each group was measured before and at the end of the treatment (fourth month) using the visual analog scale. The study was carried on for four months.

Results: Significant improvement was observed in the clonazepam and pregabalin groups; no effects were observed in the alpha lipoic acid group. No serious side effects were noted in any of the patients.

Conclusion: Systemic clonazepam and pregabalin are viable options for the treatment of burning mouth syndrome.

Keywords: Alpha lipoic acid, burning mouth syndrome, clonazepam, pregabalin, visual analog scale

INTRODUCTION

Burning mouth syndrome (BMS), also known as stomatodynia, is characterized by pain or discomfort in the oral mucosal without a known cause (1). Burning, itching, paresthesia, and dysesthesia can be the disturbing symptoms in patients with BMS. Xerostomia can accompany the oral symptoms (2). There are three subtypes of BMS. In type I, the symptoms are absent early in the morning, but start and worsen throughout the day. In type II, the symptoms are continuous throughout the day. In type III, the symptoms are intermittent (3).

The etiopathogenesis of BMS is unclear. A neuropathic etiology, mostly trigeminal dysfunction, is commonly observed (4). Physicians find difficulty in diagnosing BMS. BMS is diagnosed after ruling out any organic pathology (5). BMS mostly occurs in the middle-aged and elderly population with female dominance (4).

There is no gold-standard treatment option for BMS (6). Many topical and systemic agents have been used with different success rates. Alpha lipoic acid (ALA) is a natural antioxidant that increases the production of nerve growth factor; therefore, it is used for the treatment of diabetic neuropathy and BMS (7). Clonazepam is a benzodiazepine used to treat seizures and panic disorders. It is effective in treating BMS as it suppresses nerve excitability and relieves anxiety (8). Pregabalin is an antiepileptic agent that slows down the impulses in the brain. Pregabalin also acts on chemicals which send pain signals across the nervous system. Therefore, it is used for treating pain caused by nerve damage in diabetes, herpes zoster, and BMS (9).

Here we aimed to compare the effectiveness and safety of clonazepam, pregabalin, and ALA for treating BMS.

MATERIALS and METHODS

The study was conducted at Dermatology and Venereology Department, Erciyes University Faculty of Medicine between November 2015 and November 2017. The study was approved by the Erciyes University Ethics Committee (approval number: 2014656). Informed and written consents were collected from all patients.

Burning mouth syndrome (BMS) was diagnosed after ruling out all possible organic causes. Patients aged >18 years were enrolled. Patients with a known chronic systemic or oral mucosal disease or those who underwent treatment for BMS in the last 6 months were excluded. Also, patients having metallic implants were excluded to rule out any possible reaction due to the implanted metal.

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After a strict evaluation, patients who agreed to participate in the study were randomly divided in three groups. In the first group, patients were systemically administered clonazepam. In the second and third groups, patients were administered pregabalin and ALA, respectively. The daily doses of clonazepam, pregabalin, and ALA were 2, 150, and 600 mg, respectively. All patients were evaluated for the intensity of burning using the visual analog scale (VAS) The pain calculation by using the VAS scale was done at the beginning of the study and at the end of the study (Fourth month). At each visit, any possible side effects were asked and noted. Complete blood count and biochemical values were investigated at the beginning and at each visit to detect any possible side effects due to drug use. Any change in the VAS score of <50% was considered as no effect. Any reduction in the VAS score between 50% and 75% was considered as "mild effect" and >75% as "great improvement."

Statistical Analysis

The Wilcoxon test was used to assess the change in each group before and after the treatment. Kruskal–Wallis test was used to compare the three groups in terms of effectiveness. P<0.01 was considered significant. All analyses were made using PASW Statistics 18 software (SPSS, Chicago, IL, USA).

RESULTS

Of the 90 patients who fulfilled the inclusion criteria, 75 were enrolled in the study. The mean ages of the three groups were similar [clonazepam group (43±2.25 years), pregabalin group (45±2.75 years), and ALA group (42±2.75 years)]. There was female dominance in each group (16, 17, and 15 in the clonazepam, pregabalin, and ALA groups, respectively). The mean duration of the symptoms was as follows: 18.24±3.25 days (clonazepam group), 17.76±2.98 days (pregabalin group), and 16.48±3.11 days (ALA group). No statistically significant difference was observed among the groups with respect to disease duration.

The mean VAS score of the clonazepam group was 8.04±1.14 before treatment and 3.96±0.78 at the end of the study (fourth month). The mean VAS score of the pregabalin group was 8.12±1.03 before treatment and 3.44±0.74 after the treatment. The mean VAS score of the ALA group was 7.16±1.21 before treatment and 6.44±0.98 after the treatment. The decrease in mean VAS scores of the clonazepam and pregabalin groups was statistically significant (p<0.001). There was nearly 20% decrease in the mean VAS score of the ALA group, which was not statistically significant. The mean VAS score decrement was similar in the clonazepam and pregabalin groups.

The total number of systemic treatment options used by the patients for ≥6 months before the beginning of the study was considered for each group, but there was no correlation.

Eight patients in the clonazepam group (four reported dizziness, two transient diarrhea, and two myalgia), six patients in the pregabalin group (three reported increased appetite, one transient vertigo, one mild nausea, and one diarrhea), and three patients in the ALA group (two reported mild nausea and one myalgia) experienced side effects. No serious side effect was stated by any patient in any group.

Table 1. Topical, systemic, and other treatment options for BMS

Topical agents	Systemic agents	Others
Capsaicin	ALA	Acupuncture
Aloe vera	Pregabalin	LLLT
Anesthetics	Clonazepam	Cognitive therapy
Clonazepam	Vitamin B	Botulinum toxin injection
	Iron	Catuama
	Amitriptyline	
	SSRIs	

ALA; alpha lipoic acid, BMS, burning mouth syndrome; LLLT; low-level laser therapy, SSRIs; selective serotonin reuptake inhibitors.

DISCUSSION

The etiology of BMS is still unclear. Some local factors, such as contact allergens, prostheses, caffeine intake, smoking, presence of xerostomia or candidal infections, and consumption of hot and spicy food, have been emphasized (10–13). The systemic factors associated with BMS are menopause; nutritional deficiencies such as iron, folic acid, and vitamin B; diabetes mellitus; hypothyroidism; and some systemic drugs (14). Anxiety, depression, and fear of cancer also account for BMS symptoms in some patients (15). Neurological factors are also believed to cause BMS. Lingual nerve hyperfunction due to chorda tympani alterations may be a possible cause (16). Tinastepe and Oral reported cases of BMS after dental procedures such as tooth extraction and endodontic treatment (17).

As the etiopathogenesis of BMS is not fully understood, there is no universally accepted treatment option. Topical capsaicin, aloe vera, clonazepam, and anesthetics can be used locally for treatment (18). Systemic treatment options include ALA, clonazepam, gabapentin, selective serotonin reuptake inhibitors, pregabalin, amitriptyline and vitamin B and iron supplements (1,19). Topical agents are primarily preferred, and in cases of failure, systemic ones are used. In some rare studies, low-level laser treatment, acupuncture, botulinum toxin injections, and Catuama (Brazilian herbal product) have been used with different success rates (20–22). Table 1 summarizes the treatment options for BMS.

There is no objective measurement of pain in BMS; therefore, VAS has been used widely. VAS is a validated research pain scale. In this method, patients are asked to give points between 1 and 10 to state their degree of pain. Higher scores in VAS indicate severe pain (23). Although there are some methods to evaluate the intensity of pain such as painDETECT, all are either based on VAS or not accepted widely (24). In our study, we used VAS to evaluate the intensity of pain as in most of the studies in the literature.

Alpha lipoic acid (ALA), a natural antioxidant, has been used for pain control in many diseases. Palacios-Sanchez et al. reported beneficial effects of ALA in patients with BMS. The authors claimed 64% success rate with 600 mg/day ALA (6). Likewise, Femiano and Scully reported improvement in 97% of the patients after ALA treatment (25). But in both studies, the improvement in the placebo groups was almost 40%. In our study, 17 patients in the ALA

group (68%) declared improvement with varying rates. But only five (20%) patients declared ≥50% improvement with VAS.

Clonazepam inhibits pain pathways in the spinal cord and peripheral nerves and has anxiolytic and analgesic effects (26). Satisfactory results with clonazepam have been reported in the treatment of BMS. Fenelon et al. reported 6% improvement after 3 months of clonazepam treatment and claimed that clonazepam was an effective treatment option in BMS (27). In a randomized, placebo-controlled study, 23 of 33 (70%) patients who used clonazepam demonstrated >50% improvement (8). In the same study, 15% of the patients stated complete resolution of BMS symptoms. In our study, 21 patients (84%) stated an improvement to a degree, but only 13 patients (52%) had >50% improvement. Furthermore, none of our patients noted complete remission.

Pregabalin is derived from GABA and acts by binding to the alpha-2/delta-1 subunit of the voltage-gated calcium channels in central nervous system and spinal cord. Thus, it has analgesic effects and is used in pain control (28). Ito et al. reported five cases of BMS who were unresponsive to serotonin-noradrenaline reuptake inhibitors. All of the patients declared complete remission after pregabalin use (29). Likewise, Lopez et al. reported complete remission of BMS after pregabalin use (50 mg/day) (30). The authors claimed that pregabalin was effective in every repetitive use (30). In our study, pregabalin appeared to be the most effective drug for the treatment of BMS. All of the patients (96%), except one, stated some degree of improvement. Nineteen patients (76%) had >50% improvement in the VAS score.

Our study had one limitation. We were not able to re-evaluate the patients after a treatment-free period. To the best of our knowledge, there are no previous studies that compared the effectiveness and safety of clonazepam, pregabalin, and ALA in the same study. Therefore, we believe our study can be useful.

There are many studies on the management of BMS with different treatment options. However, we found clonazepam and pregabalin to be effective. Pregabalin appeared to be even more effective with fewer side effects than clonazepam. Unlike many studies, we found ALA ineffective, but it seemed to be the safest drug with the fewest side effects. On the basis of our results, we state that clonazepam and pregabalin can be used for the treatment of BMS. They also seem to be safe when used for a short period.

CONCLUSION

The number of patients with BMS is increasing in recent years. However, the pathogenesis of the disease is still unclear. Therefore, the evidence for therapeutic intervention is still weak and there is no evidence-based first-line treatment for BMS. More studies with larger groups are required to establish treatment guidelines.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Erciyes University (Approval no: 2014656).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: SLÇ, DK, MB. Performed the experiments or case: SLÇ, TP. Analyzed the data: DK, MB, TP. Wrote the paper: SLÇ. All authors have read and approved the final manuscript.

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