Original Article

JOMP
Journal of Oral Medicine and Pain

pISSN 2288-9272 eISSN 2383-8493
J Oral Med Pain 2016;41(1):1-6
http://dx.doi.org/10.14476/jomp.2016.41.1.1

Effects of Pregabalin in Primary Burning Mouth Syndrome Patients Unresponsive to Topical Clonazepam Treatment: A Retrospective Pilot Study

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Received February 15, 2016
Revised March 9, 2016
Accepted March 9, 2016

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This study was supported by Clinical Research Grant, Pusan National University Dental Hospital (2014).

Purpose: To investigate the efficacy of pregabalin for patients with primary burning mouth syndrome (BMS) who are unresponsive to topical clonazepam therapy.

Methods: By searching the clinical electronic records from the Department of Oral Medicine, Pusan National University Dental Hospital from 2012 to 2014, a retrospective analysis was performed on patients with primary BMS who were treated with topical clonazepam therapy during this period. Of the patients who were unresponsive to this therapy, 19 patients who were subsequently treated with pregabalin were included in the study. A pain assessment was performed using the 11-point numerical rating scale at first visit, following topical clonazepam therapy, and again after pregabalin therapy. The treatment outcomes were statistically analyzed using the Wilcoxon signed rank test.

Results: Following additional pregabalin administration, the mean pain score was slightly reduced. A total of 7 patients reported a marked response (>50% pain reduction), and 3 patients reported a slight reduction in pain. Pain reduction following pregabalin therapy was statistically significant ($p<0.05$).

Conclusions: Pregabalin has a slight therapeutic effect on patients with primary BMS. Therefore, we recommend pregabalin as an alternative drug for BMS patients who are unresponsive to topical clonazepam therapy.

Key Words: Burning mouth syndrome; Clonazepam; Pregabalin

INTRODUCTION

Burning mouth syndrome (BMS) is a chronic pain condition with no identifiable dental or medical causes. It manifests as a burning dysesthesia, or a similar pain, in the oral cavity.[1)] Owing to the vague diagnostic criteria, the exact prevalence rates of BMS are uncertain and can vary from 0.7% to 15%.[2-4)] Elderly postmenopausal women are the most commonly affected.[5)] The tongue is the most affected site in the majority of cases, but BMS can also involve the lips, palate, and gingiva.[6,7)] Scala et al.[8)] classified BMS into two clinical forms based on the presence of identifiable causes: primary BMS and secondary BMS. These two forms can be distinguished from one another with careful clinical examinations and diagnosis or if thetreatment eliminates etiologic factors that are associated with secondary oral burning. Secondary BMS has better clinical outcomes than primary BMS.[9)] The exact etiology of primary BMS is unclear,[10)] but current neurophysiological, psychophysical, neuropathological, and functional imaging studies suggest that primary BMS may be a chronic neuropathic pain disorder with peripheral and central mechanisms.[11-19)]

To date, the treatment of primary BMS has been largely empirical and has depended on the patient's condition and

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clinician's preference. The treatment of primary BMS has traditionally focused on symptom relief and has employed the same pharmacological medications that are used for other neuropathic pain disorders.[20] Such medications for primary BMS include antidepressants, anticonvulsants, capsaicin, and benzodiazepines.[10] Of these medications, it has been reported that clonazepam can be effective for primary BMS, and is widely accepted as the primary BMS treatment.[21] Clonazepam is an anticonvulsant medication enhanced by the neuronal inhibition of gamma-amino butyric acid. This medication is approved by the U.S. Food and Drug Administration (FDA) for treating seizures and panic disorders. In addition, it is used off-label for several neuropathic paindisorders, including primary BMS.[22] However, clonazepam is not always effective for all cases of primary BMS.[21] Therefore, if a patient with primary BMS does not respond to this medication, alternative medications should be considered.

Pregabalin is a new anticonvulsant drug that binds to a subunit of the calcium channel and consequently reduces neuronal activity. It is similar to gabapentin and its use is approved by the FDA forneuropathic pain.[23] Considering that primary BMS has a possible neuropathic component, pregabalin can potentially be effective as a second-line medicine for primary BMS. Thus, we performed this retrospective pilot study to investigate the efficacy of pregabalin for patients with primary BMS who were unresponsive to topical clonazepam therapy.

MATERIALS AND METHODS

1. Subjects and Data Selection Criteria

The clinical electronic records from the Department of Oral Medicine, Pusan National University Dental Hospital (Yangsan, Korea) from 2012 to 2014 were searched using the key word "primary BMS". A total of 252 outpatients had been diagnosed with primary BMS during this time.

The following primary BMS diagnostic criteria[10] were used:

- The patient had experienced a burning sensation in the mouth for more than 4 months
- An absence of detectable oral mucosal changes based on a careful oral examination
- Normal salivary flow rate (unstimulated whole saliva >0.1 mL/min and stimulated whole saliva >0.7 mL/min)
- An oral swab culture yielded negative findings for candidiasis
- Blood test was normal (complete blood count, blood glucose, and serum iron, ferritin, vitamin B12, folic acid, Zn, thyroid hormone)
- No history of a systemic conditionthat could possibly be associated with an oral burning sensation (e.g., uncontrolled diabetes, hypertension, thyroid disease, and autoimmune disease)

Of the 252 patients that were identified, 132 were treated with topical clonazepam therapy. When based on a pain reduction of 50%,[24] 85 patients responded to topical clonazepam therapy. These patients were continued on a treatment of topical clonazepam. A total of 47 patients were unresponsive to topical clonazepam and were subsequently treated with antidepressants (e.g., nortriptyline and amitriptyline) and anticonvulsants (e.g., gabapentin and pregabalin). Among these, 19 patients that were treated with pregabalin were included in this study (Fig. 1). When choosing these medication, we obtained informed consent to treatment for each patient. The study protocol was approved by the Institutional Review Board of Pusan National University Dental Hospital (PNUDH-2015-004).

2. Treatment Protocol and Pain Assessment

At the first visit, a medical history, clinical examination (including sialometry and oral swab culture), panoramic

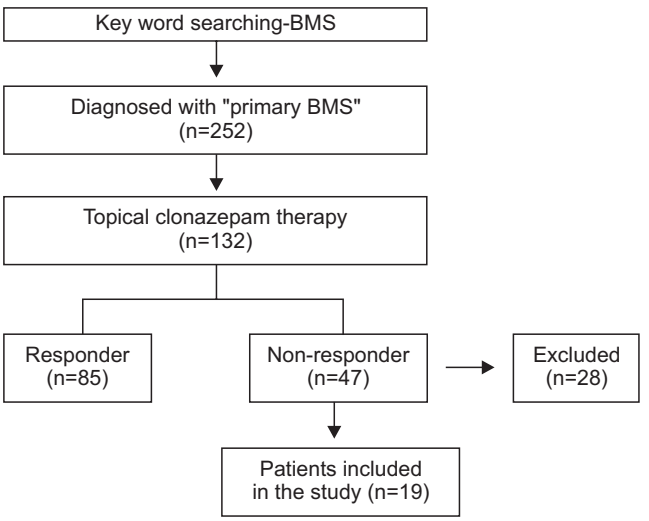

Fig. 1. Flow diagram. BMS, burning mouth syndrome.

radiograph, and a blood test were performed on all patients. After primary BMS was diagnosed, patients were started on an initial therapy of topical clonazepam (0.5 mg; Roche Korea, Seoul, Korea). Patients were instructed to dissolve one tablet orally, without swallowing, three times a day for 2 weeks. When patients experienced symptom relief, the same dose was maintained for the remaining treatment period. If a >50% reduction in pain was not achieved, or the patient was unresponsive to the dose, the clonazepam dose was escalated to two tablets at a rate of three times a day for 2 weeks. In this manner, 132 patients were prescribed with topical clonazepam. Of these, 85 patients (64%) were responsive to topical clonazepam therapy (i.e., pain was improved by more than 50%). If patients had no response to topical clonazepam following 4 weeks of therapy (i.e., pain was improved by less than 50%), other medications (including pregabalin) were administered, depending on the patients' medical conditions.

Pregabalin was administered with a starting dose of 150 mg/day, twice a day. The dose was gradually increased up to 300 mg/day, twice a day, depending on patients' response. Side effects were monitored. All patients were treated for at least 4 weeks.

Pain assessment was performed using the 11-point numerical rating scale (NRS); 0 was defined as no pain and 10 as the worst pain imaginable for the treatment period. Pain was assessed at the first visit (NRS0), following topical clonazepam therapy (NRS1), and following pregabalin therapy (NRS2) (Fig. 2).

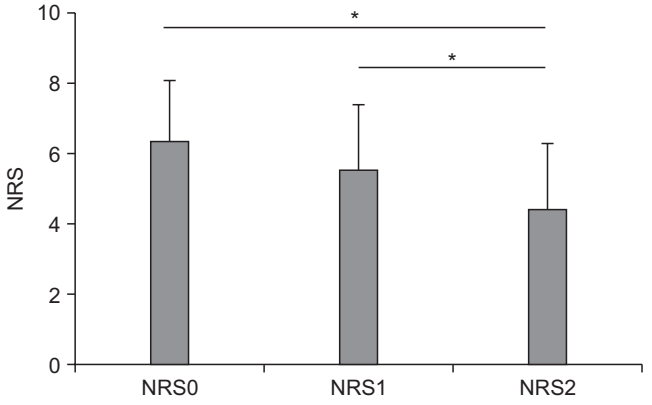

Fig. 2. Treatment outcome in primary burning mouth syndrome patients. NRS0, numerical rating scale (NRS) at first visit; NRS1, NRS after topical clonazepam therapy; NRS2, NRS after pregabalin therapy. p-values were analyzed by Wilcoxon signed rank test. *p<0.05; statistically significant.

3. Statistical Analyses

The categorical variables were summarized as counts and percentages; numerical variables as the mean±standard deviation. The treatment outcomes were statistically analyzed using the Wilcoxon signed rank test. All statistical analyses were performed using IBM SPSS Statistics version 21.0 software (IBM Co., Armonk, NY, USA). p-values less than 0.05 were considered statistically significant.

RESULTS

Following the previously mentioned clinical record review process, 19 patients were included in this study (17 female and 2 male). The mean age was 63.8±7.9 years. The mean symptom duration was 13.0±13.8 months. All patients experienced a burning pain of the tongue. A total of nine patients presented with isolated pain in the tongue, whereas ten patients presented multiple site pain (including gingiva, palate, and lip). The mean daily dose of prescribed topical clonazepam was 2.2±0.9 mg, and the mean treatment duration was 11.7±8.1 weeks. The mean pretreatment pain score (NRS0) was 6.5±1.6. Following topical clonazepam therapy, the mean pain score (NRS1) was 5.5±1.9. Of the 19 patients, 11 patients reported a slight reduction in pain, four patients reported no improvement, and four patients reported the pain to have worsened. None of these patients achieved an NRS1 pain score that equated to a >50% reduction in pain compared with the pretreatment score. Furthermore, no significant relationship was detected in the pain before and after topical clonazepam therapy (p>0.05).

Table 1. Patients demographic data

Variable	Value
Age (y)	63.8±7.9
Symptom duration (mo)	13.0±13.8
Affected site (n=19)	
Tongue	10
Multiple site	9
Clonazepam dose (mg)	2.2±0.9
Clonazepam treatment period (wk)	11.7±8.1
Pregabalin dose (mg)	213.1±76.1
Pregabalin treatment period (wk)	6.8±5.1

Values are presented as mean±standard deviation or number only.

Following additional pregabalin administration, the mean pain score (NRS2) was 4.4±1.8. The mean prescribed dose was 213.1±76.1 mg, and the mean treatment duration was 6.8±5.1 weeks. A total of seven patients reported a marked response (>50% pain reduction), and three patients reported a slight reduction in pain. However, nine patients experienced either no improvement or a worsening of the pain. The reduction in pain following pregabalin therapy was statistically significant ($p<0.05$) (Table 1).

DISCUSSION

To date, the standardized treatment method for primary BMS patients has not been established.[10] The treatment is very difficult and spontaneous remission is rare.[25] The purpose of BMS therapy is symptom relief, and several drugs for neuropathic pain therapy are widely used. Among these medications, the efficacy of topical clonazepam has been demonstrated for BMS patients. Woda et al.[26] reported that topical clonazepam had potential therapeutic effect for idiopathic BMS patients. Thereafter, a multicenter randomized control trial (RCT) demonstrated that topical clonazepam therapy improved symptoms of burning pain in two-thirds of the study subjects.[27] In addition, systemic clonazepam and the combined therapy of both sucking and swallowing clonazepam have been reported to be effective for BMS patients.[28-30]

Based on this evidence, in our clinic, topical clonazepam is used as the first drug of choice for patients with BMS. Patients are instructed to suck one clonazepam tablet (0.5 mg) until fully dissolved three times a day, and are not to swallow it.[27] According to patients' responses, the clonazepam dose was increased to 3 mg/day if necessary. However, this regimen is not always effective for all BMS patients. As patients with primary BMS not only have a peripheral neuropathic component but also have a central component, topical application of medication may be a limitation.[31] In these cases, a second-line medication is also needed. These second-line drugs with central-acting mechanisms include anxiolytics, antidepressants, anticonvulsants, etc. When choosing an alternative drug, the systemic condition of the patient and the side effects of the drug should be considered.

Pregabalin is widely used off-label for several neuropathic pain disorders. The starting dose of pregabalin is 150 mg/day and the maximum dose is 600 mg/day after titration and adjustment. As this drug does not usually incur drug-drug interactions, and has few side effects, pregabalin is also a first-line medication for the elderly or when tricyclic antidepressants are contraindicated. Although the etiopathogenesis of BMS is complex, because BMS has a possible neuropathic component, pregabalin is likely to be a promising therapy. However, to our knowledge, no clinical study has reported the efficacy of pregabalin in patients with primary BMS. Only two case reports that utilize pregabalin exist.[32,33] There are a few reports on the efficacy of gabapentin, which is similar to pregabalin, in BMS patients but the results are contradictory.[34,35] In this study, 19 patients who were unresponsive to topical clonazepam treatment were retrospectively analyzed. Our results suggest that pregabalin has potential effects on patients with primary BMS. Nearly half of the patients included in the study demonstrated improvements in their symptoms, and 70% of these patients had marked symptom relief. However, the remaining patients did not improve. This study also suggests that the treatment of primary BMS requires several combined medications, such as with other neuropathic pain disorders, and should not depend on only one medication.

The limitations of our study include the small sample size and the fact that it is a retrospective study without adequate control group. However, we considered that a retrospective pilot study on pregabalin efficacy for BMS patients was needed before a prospective RCT study could be performed. Furthermore, there was not a sufficient 'wash-out' period between clonazepam and pregabalin treatments. We reasoned that as topical clonazepam has no systemic effect,[27] any synergistic effects of these drugs could be discounted.

The results of the present study demonstrate that pregabalin has a therapeutic effect on patients with primary BMS. Therefore, we recommend that pregabalin is used as an alternative drug in any BMS patient who is unresponsive to topical clonazepam therapy. Future RCT studies with large sample sizes are needed to further identify the efficacy of pregabalin on primary BMS patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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