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Outcome predictors affecting the efficacy of clonazepam therapy for the management of burning mouth syndrome (BMS)

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ABSTRACT

BMS is a common condition characterized by chronic oral mucosal pain condition and primarily affects elderly women. Although clonazepam therapy has been widely used due to its efficacy, it is not always effective because of the complexity of BMS pathogenesis. In this study, we have investigated outcome predictors of clonazepam therapy in patients with BMS. One hundred patients with BMS (7 men and 93 women, mean age 58.5 ± 10.8 years) were instructed to take 0.5 mg of clonazepam once or twice daily for 4 weeks. The patients were sub-grouped according to psychological status, salivary flow rate, presence of psychiatric medications, symptom area and duration, symptom severity, presence of oral parafunctions, and accompanying oral complaints. The changes in symptoms were analyzed and compared between the sub-groups. Subjects with *T*-scores ≤50 for each psychological symptom dimension, a greater degree of initial symptoms (visual analog scale (VAS) ≥ 5), and accompanying oral complaints, such as xerostomia and taste disturbance, displayed greater decreases in symptoms compared with their counterparts. In conclusion, psychological status, initial symptom severity, and the presence of xerostomia and/or taste disturbance can serve as outcome predictors of clonazepam therapy for patients with BMS.

1. Introduction

BMS is characterized by a painful burning sensation or other dysesthesias of the oral mucosa, with no visible mucosal abnormalities upon clinical examination (Grushka et al., 2002). BMS occurs predominantly in older women and is often accompanied by xerostomia and dysgeusia (Scala et al., 2003; Patton et al., 2007; Lopez-Jornet et al., 2010).

The etiology of BMS is unclear and multifactorial, probably involving a complex interaction among local, systemic, and/or psychogenic factors (Patton et al., 2007; Lopez-Jornet et al., 2010). As far as local factors are concerned, there is strong evidence for local nerve trauma, oral parafunctional habits, and salivary gland dysfunction (Scala et al., 2003; Patton et al., 2007; Lopez-Jornet et al., 2011). Among systemic factors, menopausal disorders, diabetes, and nutritional deficiencies are regarded as significant predisposing conditions (Bergdahl and Anneroth, 1993; Ship et al., 1995; Scala et al., 2003). Personality and mood changes, especially anxiety and depression, have consistently been reported in patients with BMS, leading to the suggestion that BMS is a psychogenic problem (Grushka et al., 2000). BMS has also been suggested as a complex somatoform disorder due to the high prevalence of unexplained extraoral comorbidities (Mignogna et al., 2011). Based on recent findings (Forssell et al., 2002; Lauria et al., 2005), BMS is now believed to be a neuropathic pain entity.

The treatment of BMS typically focuses on symptom relief and is the same as medical management for other neuropathic pain conditions (Grushka et al., 2002). Among pharmacological options including benzodiazepines, tricyclic antidepressants, anticonvulsants, capsaicin, and alpha lipoic acid (Patton et al., 2007; Lopez-Jornet et al., 2010), clonazepam therapy is the most widely accepted. Clonazepam is an anticonvulsant which potentiates the neural inhibition mediated by gamma-amino butyric acid (GABA) (Grisius, 2000). It also has a longer half-life than many of the other benzodiazepines, which causes it to have fewer withdrawal effects on discontinuation of the medication (Grushka et al., 1998). The efficacy of topical clonazepam (Woda et al., 1998; Gremeau-Richard et al., 2004), systemic clonazepam (Grushka et al., 1998), and a combined topical and systemic clonazepam regimen (Amos et al., 2011) has been reported in BMS patients. However, clonazepam therapy is not always effective in all BMS patients due to the complexity of BMS pathogenesis (Forssell et al., 2002; Gremeau-Richard et al., 2010). Therefore, the identification of outcome predictors is necessary in order to aid clinicians in choosing the most appropriate treatment course for individual patients. The aim of this study was to identify outcome predictors of clonazepam therapy in patients with BMS.

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2. Materials and methods

2.1. Participants

From the BMS patients who had visited the Department of Oral Medicine, Seoul National University Dental Hospital with a complaint of burning or painful sensation in the mouth without any visible causative signs from 1st July, 2006 to 28th February, 2011, 107 patients were included in this study. All patients were without systemic diseases or conditions affecting oral burning pain, did not respond to the initial treatment with the application of topical lubricant and parafunctional habit control (Kho et al., 2010; Ko et al., 2011), and completed the 4-week systemic clonazepam therapy. Seven patients had to be excluded because a topical antifungal and/or corticosteroid therapy was administered for the management of their concomitant oral mucosal diseases. Ultimately, 100 patients were included in this study (7 men and 93 women, mean age 58.5 ± 10.8 years). The research protocol was approved by the Institutional Review Board of the University Hospital (CRI11024).

2.2. Clinical evaluation

Clinical evaluation procedures included an oral examination, an interview, panoramic radiography, a comprehensive questionnaire, a simplified psychological evaluation (SCL-90-R; Symptom Checklist-90-Revision), blood tests, and a measurement of salivary flow rate. The questionnaire used to evaluate subjective symptoms included questions about duration of suffering, area of symptoms, type of discomfort (burning, aching, stinging, itching, numbness, bad taste, taste alteration, xerostomia, and sore throat), and the effect of oral complaints on daily life (Eff-life). The intensities of oral complaints and Eff-life were measured using a VAS (0–10 cm, with 10 being the worst possible). Oral parafunctional habits, such as pressing the tongue against the teeth, tooth clenching during the day, tongue or mucosal biting, and nocturnal clenching or bruxing were also inquired.

2.3. Measurement of stimulated and unstimulated whole salivary flow rates

Saliva was collected by a standard, reproducible method (Birkhed and Heintze, 1989). Briefly, samples from the subjects were collected between 9:00 and 11:00 a.m., to minimize diurnal variability. All subjects abstained from smoking, eating, and drinking for 2 h prior to the measurement of salivary flow rate. Unstimulated whole saliva (UWS) was collected for 10 min by the spitting method. Stimulated whole saliva (SWS) was collected for 5 min by habitual chewing 1 g of gum base. SWS could not be collected from 7 subjects who were unable to chew the gum base due to the loss of posterior teeth. The flow rate of whole saliva was expressed as mL/min.

2.4. Laboratory tests

Laboratory tests were performed to rule out the possibility of systemic diseases that could affect oral sensation, such as diabetes mellitus, anemia, etc. The tests included complete blood counts with leukocyte differential counts, erythrocyte sedimentation rate, blood glucose, liver function tests (total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, and cholesterol), kidney function tests (blood urea nitrogen and creatinine), thyroid function tests (T3, free T4, and TSH), calcium, phosphorus, ferritin, vitamin B_{12}, and folate levels.

2.5. Psychological evaluation

The SCL-90-R (Derogatis, 1977) was used to evaluate the psychological characteristics of the patients. The SCL-90-R is a 90-item self-report measure that has been used to assess psychological symptoms; it comprises of nine symptom dimensions, including somatization (SOM), obsessive–compulsive (O–C), interpersonal sensitivity (I-S), anxiety (ANX), depression (DEP), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR), and psychoticism (PSY), as well as three global indices of functioning, including a global severity index (GSI), a positive symptom distress index (PSDI), and a positive symptom total (PST). GSI is the average score of the 90 items of the questionnaire and is suggested to be the best single indicator of the current level of the disorder. PST is the number of items scored above zero. PSDI is the average score of the items scored above zero and also assesses the response style of the patient, i.e. whether the patient is "augmenting" or "attenuating" his or her symptoms. The SCL-90-R was administered to every patient except for 2 elderly patients who could not understand the SCL-90-R questionnaire. A total of 98 patients completed the SCL-90-R.

2.6. Treatment protocol

At the first visit, an oral examination, panoramic radiography, and a blood test were performed on each patient and the questionnaire was provided to the patients. At the second appointment, scheduled in the morning, the salivary flow rate was measured, the SCL-90-R was administered, and the questionnaire was checked by the staff to ensure the completion of any omitted sections. Patients were then interviewed by one doctor (HSK) and received an explanation regarding the possible etiology and management strategies for BMS. The initial treatment with the application of topical lubricant and parafunctional habit control (Kho et al., 2010; Ko et al., 2011) was provided to all patients for 2 weeks. Patients who did not respond to the initial approach were re-evaluated using the same questionnaire and were administered systemic clonazepam. The severity of the subjective symptoms at this point was used as a baseline reference for the evaluation of the efficacy of the systemic clonazepam.

Patients were instructed to take 0.5 mg clonazepam (Roche) nightly for the first 2 weeks. When patients experienced significant pain relief, the same dosage was maintained for another 2 weeks. Otherwise, clonazepam was prescribed twice daily (morning and night) for the next 2 weeks. If untoward side effects (in particular, severe drowsiness and/or dizziness) occurred, patients were instructed to take half of a tablet. In the present study, 59 patients experienced significant pain relief after 2 weeks, thus the same dosage was maintained for another 2 weeks (mean daily dose: 0.5 mg). However, 39 patients did not experience pain relief, therefore clonazepam was prescribed twice daily for the next 2 weeks (mean daily dose: 0.75 mg). Two patients experienced untoward side effects. One patient maintained half of a tablet during whole 4 weeks (mean daily dose: 0.25 mg), but the other patient could tolerate one whole tablet for the next 2 weeks (mean daily dose: 0.375 mg). The changes in subjective symptoms were examined using the same questionnaire after 4 weeks (Fig. 1).

2.7. Statistics

VAS scores were compared using the Wilcoxon-signed rank test to evaluate the effects of clonazepam therapy. To explore possible contributing factors affecting the treatment outcome, the subjects were divided into two to four groups according to the following related factors: the *T*-score for each dimension in the SCL-90-R, salivary flow rate, the presence of self-reported parafunctional habits, the use of psychiatric medication, the duration of oral discomfort, initial symptom severity, the symptom area, and accompanying oral complaints. We then analyzed changes in median VAS scores for burning sensation (Burning) and Eff-life in each group using the Wilcoxon-signed