Clinical Features Affecting the Efficacy of Systemic Clonazepam for Management of Burning Mouth Syndrome.

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Burning mouth syndrome(BMS) is defined as chronic, painful burning sensation in the oral mucosa. Treatments for BMS include medication and psychiatric interventions. Capsaicin, alpha-lipoic acid, and topical and systemic clonazepam showed more effective in reducing the symptoms of BMS in the previous studies.

The purpose of this study is to evaluate of the therapeutic efficacy of systemic clonazepam in BMS and to elucidate the relationships between such a efficacy and various clinical features, including age, pain intensity, pain duration, previous dental history and condition of oral mucosa.

A retrospective clinical records audit was performed of patients diagnosed with BMS between January 2011 and August 2012. Patients were prescribed 0.5 mg clonazepam two times daily. Pain was assessed by patients on an 11-point numeric rating scale (NRS; 0 to 10) before and 1-2 weeks after systemic administration of clonazepam. The efficacy of clonazepam was evaluated in terms of patient's age, initial pain intensity, pain duration, presence or absence of precipitating event, condition of the tongue, presence or absence of denture.

A total of 50 patients (46 women, 4 men) were included in this study. The patients were divided into two or three groups according to above clinical features. The amount of mean NRS reduction in patients with severe initial pain was 3.33±2.74, whereas that in patients with mild initial pain was 1.64±1.54. The amount of mean NRS reduction in oldest patients was 3.53±1.94 (≥70yrs), and those in another younger patients were 2.88±1.80(< 60yrs) and 1.54±2.86(60yrs ≤ age < 70yrs), respectively.

It was concluded that the older patients and the patients with higher intensity of initial pain tend to show better efficacy of clonazepam. However, There were no statistically significant differences according to pain duration, presence or absence of precipitating events, tongue fissuring, and wearing dentures.

Key words : Burning mouth syndrome, clonazepam

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I. INTRODUCTION

Burning mouth syndrome (BMS) is defined as chronic, painful complaint, characterized by burning sensation or dysesthesia in the tongue or oral mucosa in the absence of clinical or laboratory findings. The burning sensation often occurs in more than one oral site, including the anterior tongue, the anterior hard palate, lower lip and gingiva[1]. The burning pain is moderate to severe in

intensity, and the pain is continuous or fluctuant for a daytime. Mostly the pain gradually increases throughout the day, but it rarely disturbs sleep. Many studies have suggested that burning sensation is frequently accompanied by other symptoms, including dry mouth and altered taste with or without the presence of salivary hypofunction. These symptoms appear suddenly with no identified precipitating factors in more than a half of patients. Approximately one third of patients reported previous dental treatments, illness and antibiotic therapy before the onset of BMS[2]. The factors that cause BMS include oral candidiasis, hyposalivation, drugs, nutritional deficiencies, ill-fitted denture, endocrinopathies, parafunctions such as tongue thrusting and bruxism. The secondary BMS symptoms disappear with treatment of the underlying causes, but no single treatment is universally effective for all patients with primary BMS[3].

Possible treatments for primary BMS include medications and psychiatric interventions. Topical medications including clonazepam, lidocaine, capsaicin and doxepine have been considered to be of more benefit in primary BMS. Systemic medications of possible benefit in primary BMS include gabapentin, pregabalin, amitriptyline, nortriptyline, paroxetine, sertraline, alpha-lipoic acid, clonazepam, chlordiazepoxide, olanzapine, and pramipexole[4]. Among these medications, therapies that used capsaicin, alpha-lipoic acid, and topical and systemic clonazepam have been reported to be more effective in reducing symptoms of BMS[5,6].

The purpose of this study is to evaluate of therapeutic efficacy of systemic clonazepam in BMS and to elucidate the relationships between the efficacy and age, pain intensity, pain duration, previous dental practice and condition of oral mucosa.

Ⅱ. METHODS

This study was carried out at the Department of Oral medicine in Kyungpook National University Hospital. A retrospective clinical records audit was performed of patients diagnosed with BMS between January 2011 and August 2012. A group of 50 patients (4 males; ages 53-73years, 46 females; ages 38-89years) with a complaint of burning pain in the oral area without any causative signs included in the study.

In first visit, patient history was taken by interview and questionnaire. Burning pain intensity of individuals was measured using an 11-point numeric rating scale (NRS). Patients were asked to choose a number between 0 and 10. In this scale, the former indicate no pain the latter most severe pain.

Panoramic pantographs, measurement of unstimulated whole salivation by spitting method were conducted. Laboratory tests were performed if there was any suspicion of systemic diseases. Once patients were diagnosed with BMS, they were prescribed 0.5 mg clonazepam(Rivotril®.5mg, Roche) twice a day, and instructed to swallow with water and not to dissolve the pills orally. One or two weeks later, pain intensity was evaluated by NRS again. At the same time, adverse effects were investigated.

To define the clinical characteristics of patients affecting the efficacy of systemic clonazepam, patients were divided into two or three subgroups by age, pain duration, initial pain intensity, precipitating events, clinical features of tongue and denture condition or quality.

Changes in pain intensity between first and second visit were compared among each subgroups using one way ANOVA test, Mann-Whitney U-test and two sample t-test (SPSS 18.0.0., 2009). All of data are expressed as mean±SD, and the significance level was set to $P < 0.005$.

Ⅲ. RESULTS

Of the 50 patients enrolled in the study, 46 were female (mean age 63.46±10.88) and 4 were male (mean age 63.50±8.23). Patients suffered from BMS for 1.41±2.08 years. 42 patients (84%) reported burning pain and 6 patients (12%) described as

tingling pain but 2 patients (1%) complained dull pain in oral area. Most of patients reported burning pain in the tongue (96%), especially tip of tongue. Some patients had oral discomfort in the lips (22%), palate (16%) and gingiva (8%). 20 patients (40%) reported subjective oral dryness and 3 patients (6%) complained taste alteration.

To evaluate the influence of age on efficacy of systemic clonazepam therapy, the patients were divided into three groups by the following age criteria: group 1 (age < 60, n=17), group 2 (60 ≤ age < 70, n=19) and group 3 (age ≥ 70, n=14). The amount of NRS reduction was compared among the groups using one way ANOVA test. The mean NRS reduction were 2.88±1.80 in group 1, 1.54±2.86 in group 2 and 3.53±1.94 in group 3. In spite of the lowest reduction in group 2, the mean NRS reduction between group 1 and group 2 showed no significant difference, whereas the mean NRS reduction in group 3 with oldest age was significantly higher. The mean initial NRS were 5.85±2.26, 6.37±1.98 and 6.39±1.90 in 3 groups, respectively.

To identify the effect of initial pain intensity to the therapeutic outcome, the patients were divided into two groups according to the initial NRS. The mean initial NRS of all patients was 6.20±2.03, so patients grouping was achieved based on the mean score: group 1 (initial NRS ≥ 6.20, n=27) and group 2 (initial NRS < 6.20, n=23). The mean NRS reduction were 3.33±2.74 in group 1 and 1.64±1.54 in group 2. There was significant difference in NRS reduction between both groups.

Considering the initial NRS, the influence of age on the reduction of NRS was evaluated. At the mean initial NRS range (4.17 ≤ NRS < 8.23), the patients were divided into good responder and poor responder based on the mean NRS reduction score (2.56±2.40). The mean age of the good responder group (2.56 ≤ NRS reduction) was 62.22±11.18 and that of the poor responder group (NRS reduction < 2.56) was 66.28±8.76. There were no statistically significant differences in mean ages between two groups.

Regarding relationship between the pain duration and the therapeutic effect, the patients were divided into two groups by chronicity: group 1 (pain duration ≤ 6 months, n=26) and group 2 (6months < pain duration, n=24). The mean initial NRS of group 1 was 5.94±2.20 and that of group 2 was 6.48±1.84. There was the trend toward more reduction in mean NRS of the group 2 (1.92±2.44 in group 1, 3.24±2.21 in group 2), but this did not reach statistical significance.

To investigate the relationship between NRS reduction and previous dental treatment as precipitating factor, the amount of NRS reduction in group with previous dental history as precipitating factor was compared to that in group without the onset-related events. The patients with previous dental history as precipitating factor showed less reduction in the mean NRS when compared to the patients without onset-related events. The mean NRS reduction in group with previous dental history was 2.39±2.16 (n=9) and that in group without onset-related events was 2.17±2.42 (n=29), but there was no significant difference.

To estimate the response to clonazepam according to the condition of oral mucosa, the difference of the mean NRS reduction between fissured tongue group and normal tongue group was examined. The mean NRS reduction in fissured tongue group was 3.09±3.14 (n=11) and that in the normal tongue group was 2.27±2.23 (n=34). However, there was no statistically significant.

To evaluate the influence of oral dentures on the outcome clonazepam therapy, a comparison of the mean NRS reduction between the patients wearing dentures and those not wearing dentures was made. The mean NRS reduction in patients with denture was 3.00±2.89 (n=13), that in patients without denture was 2.40±2.22 (n=37), but the difference was no statistically significant.

Table 1. Relationship of various clinical features to pain reduction by systemic clonazepam medication

Factors		Groups	n	Mean±SD	Median	P value	
Age	1	age < 60yrs group	17	2.88±1.80	3.0	2	0.196
						3	0.711
	2	60yrs ≤ age < 70yrs	19	1.54±2.86	1.0	1	0.196
						3	0.044*
	3	70yrs ≤ age	14	3.53±1.94	3.0	1	0.711
						2	0.044*
Initial pain intensity	1	initial NRS ≥ 6.20	23	3.33±2.74	3.5	0.011*	
	2	initial NRS < 6.20	27	1.64±1.54	1.5		
Pain duration	1	duration ≤ 6months	26	1.92±2.44	1.5	0.068	
	2	duration > 6months	24	3.24±2.21	3.0		
Precipitating event	1	with dental practice	9	2.39±2.16	2.5	0.501	
	2	without dental practice	29	2.17±2.42	2.0		
Condition of oral mucosa	1	with fissured tongue	11	3.09±3.14	2.0	0.345	
	2	without fissured tongue	34	2.27±2.23	2.0		
Dentures	1	with denture	13	3.00±2.89	3.0	0.375	
	2	without denture	37	2.40±2.22	2.0		

Age : P calculated from one way ANOVA test, Initial pain intensity : P calculated from two sample t-test, Pain duration: P calculated from Mann-Whitney test, Initiating factor: P calculated from Mann-Whitney test, Oral mucosa: P calculated from two sample t-test, Dentures: P calculated from Mann-Whitney test
SD: Standard Deviation
* P < 0.05

Ⅳ. DISCUSSION

Although pathophysiology of BMS is yet unclear, but recent studies suggested that BMS patients showed the significant loss of epithelial and sub-papillary nerve fibers in the tongue, and decreased density of unmyelinated nerve fibers within the epithelium and diffuse axonal derangement[7]. And some authors reported that TRPV1 and nerve growth factor (NGF)-positive nerve fibers were significantly increased in the tongue of BMS patients[8]. Some studies demonstrated that BMS patients exhibit higher dopamine D2 receptor availability in the putamen than control group and that reflects depletion of endogenous dopamine[9]. These findings suggested that BMS is not only trigeminal small-fiber neuropathy in peripheral nervous system, but also presynaptic dysfunction of the nigrostriatal dopaminergic pathway in central nervous system[10].

$GABA_A$receptors are distributed widely throughout the peripheral and central tissues[11]. Clonazepam binds γ-subunit of $GABA_A$ receptor and potentiate GABAnergic inhibition, and bind more to central than to peripheral receptor[12,13,14]. Many literatures presented that even low doses of topical or systemic clonazepam reduced BMS pain[15,16]. In our study, the pain intensity after administration of clonazepam was reduced compared initial pain intensity. The mean NRS reduction of all patients was 2.56±2.40. And 42 patients (82%) experienced improvement of symptoms. In addition to GABAnergic inhibition in CNS and PNS, clonazepam have antidopaminergic effect on striatum in basal ganglia by which clonazepam may be adverse to BMS patients who lack dopamine in

the striatum[17]. That may be the one of possible explanations for the diversity in response to clonazepam.

Aging has been thought as risk factor of BMS[18]. The number of GABA/benzodiazepine receptor binding site as a target of clonazepam decreases with increasing age, that may correspond to cell loss and/or differential expression of mRNAs coding[19]. Through above results, we presumed that age may be determination factor or predictor of efficacy to clonazepam. But in this study, the efficacy in elder patients group was unexpectedly better than in younger patient group. Elderly patients often have variable drug absorption, decreased plasma protein drug binding due to decreased albumin concentrations, and the reduced hepatic and renal clearance. Then, the sensitivity of older patient to clonazepam may be increased than that of younger adults[20]. This fact may explain the present result of greatest reduction of NRS in oldest patients by the systemic application of clonazepam. But further investigations are needed to clarify the effect of age on the outcome of systemic medication for BMS.

The longer symptoms persisted, the less epithelial nerve fibers density in the tongue presented in BMS patients[7]. It is assumed that the extent of histological changes depending on pain duration may affect the efficacy of the drug. However, the result of this study showed that the duration of symptoms was not significant factor.

Many patients reported that the onset of BMS is followed by dental practices. It was suggested that chemical irritation or allergic reaction of dental materials and galvanic current may be causative factors, but this hypothesis has not supported[21]. In this study, dental practice did not affect the response to clonazepam in patients with BMS. In spite of our result, when there was the temporal relation between dental practice and onset of BMS, patients were apt to suspect the dental malpractice. Overall, suspicion about dental treatments and wish for compensation may interfere the recovery in some BMS patients.

Fissured tongue is that painless multiple fissures occur on the dorsal area of the tongue[22]. It has been proposed that irritants, such as black tea and tobacco use, may be an etiologic factor and that fissured tongue with smooth-surfaced papillae was transmitted as a dominant characteristics[23,24]. Recent study demonstrated a higher prevalence of geographic tongue and fissured tongue in BMS patients compared with a control group of patients with temporomandibular joint[25]. It has been shown that the presence of fissured tongue did not influence the effects of clonazepam in this study.

Mechanical irritation caused by dentures and contact allergy of denture materials such as methyl methacrylate may be causative factors in some patients[26,27]. Oral mucosa can be irritated by ill-fitted base and flange of dentures. Moreover, in some patients with orofacial dystonia, dentures can make multiple sore spots as well as BMS symptoms. In the study, it did not found the difference between patients with and without denture, but more extensive studies should be established.

In conclusion, it was shown the more NRS reduction in both oldest patients and patients with high initial pain intensity after administration of systemic clonazepam. On the other hand, there were no significant difference of mean NRS reduction according to pain duration, precipitating factors, fissured tongue and wearing dentures.

These results indicated that the clinical outcomes following the systemic application of clonazepam to BMS seemed to be influenced by initial pain intensity and age. These findings suggested that the initial pain intensity and age could be one of important factors in the prognosis for patients with BMS during the systemic application of clonazepam.

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국문초록

구강작열감증후군의 치료를 위한 전신적 클로나제팜의 투여 시 환자의 임상적 특징에 따른 효능의 차이에 관한 연구

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구강작열감증후군은 구강점막의 만성통증성 작열감이다. 구강작열감증후군의 치료로는 약물치료, 심리치료가 있다. 과거의 연구를 통해 캡사이신, 알파-리포산, 도포용 클로나제팜, 전신적 클로나제팜이 구강작열감증후군 증상의 감소에 효과적임이 보고되었다. 이 연구의 목적은 구강작열감증후군 환자에게 전신적 클로나제팜을 투여하여 치료 효과를 평가하고 약제의 효능과 연령, 통증의 강도, 통증의 기간, 과거의 치과병력, 구강점막 상태 등의 다양한 임상적 특징과의 관계를 밝히는 것이다. 이 연구는 2011년 1월과 2012년 8월 사이에 구강작열감증후군으로 진단된 환자를 대상으로 후향적 임상자료 분석을 통해 이루어졌다. 환자들에게 0.5mg 클로나제팜을 하루 2회 처방하였다. 통증은 전신적 클로나제팜의 투여 전과 투여 1-2주 후에 11-점 숫자등급척도(11-point numeric rating scale, NRS)를 통해 측정되었다. 클로나제팜의 효능은 환자의 연령, 초기 통증 강도, 통증 지속기간, 유발인자의 존재유무, 혀의 상태, 의치착용 유무에 따라 평가되었다.

총 50명의 환자(여성 46명, 남성 4명)가 연구에 참여하였다. 환자들은 상기의 임상적 특징에 따라 2-3개의 군으로 나누었다. 강한 초기 통증 환자들의 평균 NRS 감소량은 3.33±2.74인 반면에 경도 혹은 중등도 초기 통증 환자들의 평균 NRS 감소량은 1.64±1.54였다. 70세 이상의 가장 높은 연령의 환자군의 평균 NRS 감소량은 3.53±1.94였으며, 60세 이하 환자군에서는 2.88±1.80, 60세에서 70세 사이 환자군에서는 1.54±2.86의 감소량을 보였다.

결론적으로 높은 연령의 환자들과 강한 초기 통증을 가진 환자들에게서 클로나제팜의 효능이 뛰어난 경향이 있다. 그러나 통증 기간, 유발인자 유무, 열구설 유무, 의치 장착 유무에 의한 클로나제팜의 효능의 차이는 통계학적 유의성이 없었다.

주제어: 구강작열감증후군, 클로나제팜