Association Between Salivary Neuroinflammatory Cytokines and Clinical Manifestations in Burning Mouth Syndrome

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Association Between Salivary Neuroinflammatory Cytokines and Clinical Manifestations in Burning Mouth Syndrome

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감사의 글

아직도 믿겨지지 않지만, 연세대학교 치과병원 구강내과학교실에 입국하던 순간부터 목표했던 척척'박사' 의 순간에 이제 다다른 것 같습니다. 마지막 단추를 채우기 전, 그동안 도움을 주신 모든 분들께 감사의 마음을 전하고자 합니다.

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사랑하는 우리 가족들과 마음의 안식처가 되어준 고마운 친구들, 동기 소라선생님을 포함해서 저를 믿고 지지해준 학선언니에게도 깊은 감사 드립니다.

아무것도 모르던 제가 구강내과 전문의이자 연구자로 성장할 수 있게끔 햇빛이 되어주시고, 그늘이 되어주신 모든 분들께 감사드립니다. 무럭무럭 성장해서 교실에 도움이 되는 큰 나무로 성장할 수 있도록 더더욱 열심히 노력하겠습니다. 감사합니다.

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Purpose: This study aimed to assess the association between salivary neuroinflammatory cytokines and taste disorders, xerostomia, and pain in patients with burning mouth syndrome (BMS).

Methods: A total of 60 participants (male: 4, female: 56) were enrolled. Taste sensitivity was assessed with Taste Strip®. Unstimulated whole saliva was collected using the spitting method to calculate the salivary flow rate. Pain was measured in two settings: spontaneous

pain and pain stimulated with a hot sauce. A 2 ml sample of unstimulated whole saliva was obtained and analyzed using the Human Neuroinflammation ELISA Kit® to assess the levels of salivary cytokines. The BMS group was prescribed topical clonazepam. An independent t-test was performed to compare the BMS and control groups, and a paired t-test was performed to compare the BMS group before and after clonazepam treatment.

Results: The taste sensitivity scores for bitter taste, xerostomia, and stimulated pain intensity were significantly different between the BMS and control groups. The BMS group showed elevated levels of salivary tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) ($P < 0.001$) compared to the control group and the IL-6 levels decreased after one month of clonazepam treatment. Additionally, spontaneous pain and stimulated pain intensity, taste sensitivity score of sweet, bitter, and umami taste, and total sensitivity score showed improvement after clonazepam treatment in the BMS group.

Conclusions: Our study revealed that pain intensity and the levels of salivary IL-6 and TNF-α displayed significant elevation in the BMS group and a subsequent decrease in the level of IL-6 after one-month topical clonazepam treatment. Although changes in the quality and/or quantity of saliva may play a role in the manifestation of BMS symptoms, further studies are needed to explain the manifestations of taste disturbance, xerostomia, and pain.

Keywords: Burning Mouth Syndrome, Cytokines, Taste disorders, Xerostomia, Chronic Pain

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I. INTRODUCTION

Burning mouth syndrome (BMS) is a chronic pain condition with a burning sensation affecting mostly the anterior part of the tongue, the anterior hard palate, and lips, without any local or systemic cause (Scully 2013). There are several definitions of burning mouth syndrome: “a rare chronic neuropathic pain condition characterized by recurring burning pain or dysesthesia in the absence of any local or systemic causes of symptoms” by

International Association for the Study of Pain; "An intraoral burning or dysesthetic sensation, recurring daily for more than 2 hours/day over more than 3 months, without clinically evident causative lesions" by The International Headache Society; and the most recent definition is "idiopathic orofacial pain with intraoral burning or dysesthesia recurring daily for more than 2 hours per day and more than 3 months, without any identifiable causative lesions, with or without somatosensory changes" by International Classification of Orofacial Pain.

The estimated prevalence of burning mouth syndrome was 1.73% in population-based studies and 7.72% in the clinical studies. This condition shows a female predilection and is three times more common than in males. Additionally, it tends to occur more frequently in peri-menopausal and menopausal women (Wu et al. 2022).

Diagnosis relies on ruling out local or systemic factors that could potentially lead to an oral burning sensation or other sensory symptoms. These include hyposalivation, oral candidiasis, allergic reactions, hormonal imbalances, and nutritional deficiencies of vitamin B12, folic acid, and iron (Scully 2013).

Among the four categories of treatments for BMS (anxiolytics/antidepressants, alpha-lipoic acid, photobiomodulation therapy, and phytotherapies such as chamomile), only clonazepam appeared to reduce pain in the latest network meta-analysis (Alvarenga-Brant et al. 2023). The topical use of clonazepam suggested by Greameau-Richard et al. involves sucking a tablet and holding saliva near pain sites in the mouth without swallowing for 3 minutes, followed by spitting (Gremeau-Richard et al. 2004).

Many systematic reviews and meta-analysis studies have revealed that the cardinal features of BMS include taste changes, xerostomia, and burning pain (Eliav et al. 2007). It has been suggested in the literature that changes in the quality and/or quantity of saliva could play a role in the manifestation of BMS symptoms. Hyposalivation itself can possibly cause oral pain.

Although the exact cause of BMS remains elusive, some researchers have proposed that the condition might be a result of somatization, with an increasing body of research concentrating on its potential neuropathic involvement (Jääskeläinen 2012, Kolkka-Palomaa et al. 2015). Studies have been conducted to examine neuropeptides and cytokines, and to find out specific salivary biomarkers for BMS (Boras et al. 2010, Erta, Quintana, Hidalgo 2012, Ji et al. 2017, Lopez-Jornet et al. 2020, Pezelj-Ribarić et al. 2013, Streckfus et al. 2001). Suh et al. reported that BMS is a sub-clinical inflammation resulting in changes in cytokine levels that cause symptoms, such as burning and pain. Although the levels of salivary cytokines vary between studies, the levels of certain cytokines are significantly increased or decreased in patients with BMS. Changes in the levels of cytokines in the saliva may be related to BMS symptoms, such as taste disorders, xerostomia, and pain. The primary outcome of this study was to determine the association of salivary inflammatory cytokines with three clinical symptoms (taste disturbance, xerostomia, and pain) in the BMS group, and the secondary outcome was to observe changes in symptoms and salivary inflammatory cytokines after topical clonazepam treatment.

Ⅱ. SUBJECTS AND METHODS

1. Subjects

A total of 60 participants aged 19 to 65 years were recruited from the Department of Orofacial Pain and Oral Medicine at Yonsei University Dental Hospital in Seoul, Korea, from January 1, 2022, to December 31, 2022. This study included 30 patients diagnosed with BMS by an orofacial pain and oral medicine specialist. The control group was composed of 30 healthy individuals without any discomfort in the oral cavity. All the participants in the BMS group underwent a series of local and systemic investigations. Local investigations were performed to exclude parafunctional activity, such as tongue thrusting, candida infection (smear was taken), oral lichen planus, aphthous ulcers, and periodontal problems. Individuals with systemic diseases that might cause pain, dysgeusia, and xerostomia, such as uncontrolled diabetes, gastroesophageal reflux disease, hypothyroidism, Sjogren's syndrome, history of radiation therapy in the orofacial area, anemia, and anosmia, were excluded. Blood tests, including complete blood count, iron, folate, vitamin B12 levels, liver function tests, erythrocyte sedimentation rate, and C-reactive protein, were performed in the BMS group before the final diagnosis.

The participants were given a verbal description of the study, and written consent was obtained. This study was approved by the Institutional Review Board of the dental hospital (IRB number: 2-2021-0108).

2. Clinical Assessment

All participants were required to answer questionnaires on the subjective senses of symptoms, such as intensity of spontaneous pain, subjective sense of taste disturbance, and xerostomia at every visit. Saliva samples were collected for cytokine analysis, taste sensitivity tests, salivary flow rate tests, and stimulated pain intensity were assessed.

The BMS group was prescribed clonazepam (Rivotril®) powder for topical use in the oral cavity and spit it out thrice daily for one month. After this treatment period, the patients underwent the same set of assessments as during their first visit, except for the salivary flow rate test.

2.1. Taste disturbance

Taste disturbance was assessed using Taste Strips® (Burghart, Wedel Germany) - filter paper strips impregnated with 5 tastes (sweet, sour, salty, umami, and bitter) in 4 different concentrations (sweet: 0.4, 0.2, 0.1, 0.05 g/ml sucrose; sour: 0.3, 0.165, 0.09, 0.05 g/ml citric acid; salty: 0.25, 0.1, 0.04, 0.016 g/ml sodium chloride; umami 0.25, 0.12, 0.06, 0.03 g/ml monosodium L-glutamate; bitter: 0.006, 0.0024, 0.0009, 0.0004 g/ml quinine hydrochloride). The study involved placing strips on the tongue, and participants were asked to identify their tastes using five descriptors (sweet, sour, salty, umami, and bitter). A correct answer earned one point, and the total score, with a maximum of 20, was calculated to assess taste sensitivity. Only one correct answer or false identification for certain taste indicates hypogeusia and no sensation for certain taste indicates ageusia. To avoid bias, taste sensitivity tests were conducted under controlled conditions, which

included participants in a resting state with a two-hour period of no food, water, or toothbrushing before the test.

2.2. Salivary flow rate of unstimulated whole saliva

Hyposalivation was assessed using the salivary flow rate by the spitting method during the daytime. Unstimulated whole saliva was collected for 5 minutes under the following conditions: resting, no smoking, no food, or water intake, and no toothbrushing 1-hour prior visit. The flow rate was calculated in milliliters per minute and with a rate of ≤ 0.1 mg/min indicating hyposalivation. This measurement was performed only during the first visit.

2.3. Spontaneous pain and stimulated pain intensity

Participants were initially questioned about spontaneous pain intensity such as burning pain in the tongue, using a Visual Analog Scale (VAS).

The intensity of stimulated pain was evaluated by placing a drop of Tabasco® sauce on the dorsum of the tongue and using VAS.

3. Enzyme-linked immunosorbent assay (ELISA)

All participants were instructed to provide a 2 ml sample of unstimulated whole saliva into a disposable plastic conical tube during their visits. The time was not considered while collecting the samples. The collected samples were kept at -80℃ until analysis. The assay was performed according to the manufacturer's instructions.

ELISA was used to quantify the levels of inflammatory cytokines in these saliva samples. The following commercially available kit, Human Neuroinflammation ELISA Kit® (Signosis, Santa Clara, USA) was used to evaluate tumor necrosis factor-alpha (TNF-α), interleukin-1 alpha (IL-1α), interleukin-1 beta (IL-1β), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-13 (IL-13), and transforming growth factor-beta (TGF-β).

4. Statistical Analysis

Statistical analysis of participants characteristics of the BMS and control groups was performed using an independent t-test and was evaluated using the Chi-squared test to determine statistical significance. Mean differences in cytokine levels between the BMS and control groups were evaluated using independent t-tests. Changes in clinical symptoms and salivary cytokine levels in the BMS group after treatment were evaluated using paired t-tests.

For all statistical analysis, the SPSS statistics Ver.25.0 (SPSS Inc., Chicago, IL, USA) program was used, and the statistical significance level was set at 5% ($P < 0.05$).

Ⅲ. RESULTS

1. Characteristics of the subjects

A total of 60 subjects, four males (6.7%) and 56 females (93.3%), were enrolled in the study. The BMS group consisted of 30 patients (28 women, mean age 57.0 ± 7.8) and the healthy control group consisted of 30 participants (28 women, 58.2 ± 8.2). All participants were evaluated before enrollment to exclude systemic conditions that could cause taste disturbances, xerostomia, and oral pain.

The subjective sense of taste disturbance was similar in both groups: 30% in the BMS group and 26.7% in the control group. Taste sensitivity scores of sweet, sour, salty, bitter, and umami using Taste Strips for the BMS group and the control group were as follows: for sweet, 3.1 ± 1.0 and 3.3 ± 0.7; for sour, 2.0 ± 0.9 and 1.9 ± 0.9; for salty, 1.9 ± 1.2 and 1.8 ± 1.0; for bitter, 2.1 ± 1.3 and 3.1 ± 1.0; for umami, 1.7 ± 1.4 and 1.6 ± 1.5; total score, 10.8 ± 3.4 and 11.6 ± 3.1.

Sense of xerostomia was positive in 73.3% of the patients in the BMS group and 30% of the participants in the control group. The unstimulated whole saliva flow rate was 0.26 ± 0.15 ml/min for the BMS group and 0.30 ± 0.15 ml/min for the control group.

Spontaneous pain intensity in VAS was 4.2 ± 1.4 for the BMS group and 0 for the control group. Stimulated pain intensity in VAS using hot sauce was 5.8 ± 2.2 and 3.3 ± 1.9 for the BMS group and the control group, respectively.

Participants in the control group who answered positively for subjective taste disturbance and xerostomia after evaluation for enrollment in this study were not excluded because objective results from the taste sensitivity test and salivary flow rate tests were all within the normal range.

Table 1. Participants characteristics according to groups

	BMS group (N = 30)	Control group (N = 30)	P value
Age	57.0 ± 7.8	58.2 ± 8.2	0.585†
Sex			
Male	2 (6.7)	2 (6.7)	1.000‡
Female	28 (93.3)	28 (93.3)	
Spontaneous pain intensity (VAS)	4.2 ± 1.4	0	< 0.001†
Stimulated pain intensity (VAS)	5.8 ± 2.2	3.3 ± 1.9	< 0.001†
Xerostomia			
Yes	22 (73.3)	9 (30.0)	0.001‡
No	8 (26.7)	21 (70.0)	
UWS flow rate	0.26 ± 0.15	0.30 ± 0.15	0.315†
Subjective taste disturbance			
Yes	9 (30.0)	8 (26.7)	0.774‡
No	21 (70.0)	22 (73.3)	
Taste sensitivity score			
Sweet	3.1 ± 1.0	3.3 ± 0.7	0.361†
Sour	2.0 ± 0.9	1.9 ± 0.9	0.673†
Salty	1.9 ± 1.2	1.8 ± 1.0	0.635†
Bitter	2.1 ± 1.3	3.1 ± 1.0	0.002†
Umami	1.7 ± 1.4	1.6 ± 1.5	0.716†

Total score	10.8 ± 3.4	11.6 ± 3.1	0.389†

†Independent t-test, Mean ± standard deviation.

‡Chi-square test, N (%).

2. Differences in salivary cytokine levels between BMS and control group

Mean differences in cytokine levels of BMS and the control groups are: for TNF-α, 0.33 ± 0.08 and 0.22 ± 0.04, IL-1α 0.16 ± 0.04 and 0.14 ± 0.03, IL-1β 0.14 ± 0.02 and 0.14 ± 0.02, IL-4 0.14 ± 0.02 and 0.14 ± 0.02, IL-6 0.43 ± 0.10 and 0.18 ± 0.04, IL-10 0.15 ± 0.04 and 0.14 ± 0.02, IL-13 0.13 ± 0.02 and 0.13 ± 0.01, and TGF-β 0.14 ± 0.02 and 0.13 ± 0.02, respectively (Table 2). Level of TNF-α and IL-6 were significantly different ($P < 0.001$) according to groups.

All 30 patients in the BMS group underwent analysis whereas only randomly chosen 15 participants in the control group underwent analysis.

Table 2. Mean differences in cytokine levels according to groups.

Cytokines	BMS group (N = 30)	Control group (N = 15)	P-value
TNF-α	0.33 ± 0.08	0.22 ± 0.04	< 0.001
IL-1α	0.16 ± 0.04	0.14 ± 0.03	0.112
IL-1β	0.14 ± 0.02	0.14 ± 0.02	0.521
IL-4	0.14 ± 0.02	0.14 ± 0.02	0.755
IL-6	0.43 ± 0.10	0.18 ± 0.04	< 0.001
IL-10	0.15 ± 0.04	0.14 ± 0.02	0.231
IL-13	0.13 ± 0.02	0.13 ± 0.01	0.594
TGF-β	0.14 ± 0.02	0.13 ± 0.02	0.797

Independent t-test, Mean ± standard deviation.

3. Changes after topical clonazepam treatment in the BMS group

3.1. Taste disturbance and pain

Taste sensitivity score before and after treatment with topical clonazepam demonstrated the following changes: Sweet: Before 3.1 ± 1.0 and after 3.4 ± 0.9 (P = 0.009); Sour: Before 2.0 ± 0.9 and after 2.0 ± 0.9; Salty: Before 1.9 ± 1.2 and after 2.0 ± 1.2; Bitter: Before 2.1 ± 1.3 and after 2.7 ± 1.2 (P = 0.005); Umami: Before 1.7 ± 1.4 and after 2.6 ± 1.2 (P = 0.001); Total score: Before 10.8 ± 3.4 and after 12.6 ± 3.4 (P < 0.001). Statistically significant differences were observed in the total score of Taste Strips® and in the taste sensitivity for sweet, bitter, and umami tastes.

Spontaneous pain intensity in VAS significantly decreased, from 4.2 ± 1.4 to 3.4 ± 1.8 (P = 0.002). Stimulated pain intensity in VAS before and after clonazepam treatment significantly decreased from 5.8 ± 2.2 to 2.9 ± 2.4 (P < 0.001) respectively (Table 3).

The salivary flow rate test to assess hyposalivation was not repeated after clonazepam treatment, because there was no actual hyposalivation in the BMS group at baseline.

Table 3. Changes in clinical symptoms after treatment in the BMS group (N = 30)

	Before treatment	After treatment with clonazepam	P-value
Spontaneous pain intensity (VAS)	4.2 ± 1.4	3.4 ± 1.8	0.002
Stimulated pain intensity (VAS)	5.8 ± 2.2	2.9 ± 2.4	< 0.001
Taste sensitivity score			
Sweet	3.1 ± 1.0	3.4 ± 0.9	0.009
Sour	2.0 ± 0.9	2.0 ± 0.9	0.869
Salty	1.9 ± 1.2	2.0 ± 1.2	0.690
Bitter	2.1 ± 1.3	2.7 ± 1.2	0.005
Umami	1.7 ± 1.4	2.6 ± 1.2	0.001
Total score	10.8 ± 3.4	12.6 ± 3.4	< 0.001

Paired t-test, Mean ± standard deviation.

3.2. Salivary cytokine levels

TNF-α and IL-6 were two cytokines that exhibited differences in the BMS group compared to the control group. Therefore, subsequent evaluations of their levels before and after treatment were analyzed.

The cytokine levels before and after treatment with clonazepam were: TNF-α 0.33 ± 0.08 and 0.31 ± 0.06 ($P = 0.117$); IL-6 0.43 ± 0.10 and 0.23 ± 0.05 ($P < 0.001$), respectively. Change in the IL-6 level was statistically significant (Table 4).

Table 4. Changes in cytokine level after treatment in the BMS group (N = 30)

Cytokines	Before treatment	After treatment with clonazepam	*P*-value
TNF-α	0.33 ± 0.08	0.31 ± 0.06	0.117
IL-6	0.43 ± 0.10	0.23 ± 0.05	<0.001

Paired t-test, Mean ± standard deviation.

IV. DISCUSSION

We studied 30 patients with BMS and compared them to 30 healthy, age- and sex-matched controls. All participants underwent assessments for taste disturbance, and salivary pain analyses. Taste analysis was based on the taste sensitivity of five basic tastes (sweet, sour, bitter, salty, and umami). Salivary analyses included flow rate and immunological evaluation using an enzyme-linked immunosorbent assay. Pain was evaluated in two settings: spontaneous pain and pain stimulated with a hot sauce. Our study findings revealed that significant differences were observed in the intensity of pain (both spontaneous pain and stimulated pain), the increased levels of two cytokines (TNF-α and IL-6) in the BMS group, increased total scores of taste sensitivity, and decreased level of two cytokines after clonazepam treatment in BMS group. Our study aimed to determine the association between salivary neuroinflammatory cytokines in patients with BMS and three clinical manifestations (taste disturbance, xerostomia, and pain) of BMS, and to determine the effect of clonazepam treatment on cytokines and symptom association. There have been studies on salivary and/or serum cytokines with each symptom of BMS, but not one with all three symptoms.

Cytokines regulate host responses to infection, immune modulation, and inflammation. Pro-inflammatory cytokines worsen disease, whereas anti-inflammatory cytokines induce inflammatory processes and promote healing. They act as potential neuromodulators of nociceptive signals and cause neuropathic pain and/or hyperalgesia (Kishore et al. 2019).

Cross-sectional studies highlighting the significance of cytokines in BMS have shown

conflicting results. In a systematic review by Kishore et al., results of high-quality Newcastle Ottawa Scale assessment had outcomes, such as: De Souza et al. studied 30 BMS and 32 controls on three salivary cytokines (TNF- α, IL-6, and IL-10) and IL-6 was increased and TNF- α was decreased in BMS compared to healthy controls; Pekiner et al. studied 30 BMS and 30 controls on two salivary cytokines (IL-2, IL-6) with no remarkable differences, but another study of six serum cytokines (IL-2, IL-4, IL-6, IL-10, TNF- α, IFNγ) showed decreased level of IL-2 and TNF- α, while others showed no difference compared to healthy controls; Simcic et al. studied 30 BMS and 30 controls on two salivary cytokines (IL-2, IL-6) and both showed increase in BMS compared to controls. IL-6 is a pleotropic cytokine that influences both antigen-specific immune responses and inflammatory reactions. Furthermore, it plays a role in modulating pain and inducing hyperalgesia. Pain resulting from subclinical inflammation and depression constitutes a significant aspect of BMS. TNF- α is involved in the pathogenesis of many autoimmune and inflammatory diseases and its products induce immune complexes, substance P, IL-1, etc. Sustained elevation of cytokine levels causes permanent changes in neurotransmitter function, contributing to neuropsychiatric dysfunction, especially depression.

The patients' taste disturbances did not align with the outcomes of the taste sensitivity tests, reinforcing the findings of earlier research on taste disorders (Heckmann et al. 2009). In a study involving 48 patients with BMS, an electrical taste threshold test revealed a notably higher threshold in patients with BMS (Eliav et al. 2007). In another study on the subjective sensation of taste alteration in BMS patients with 51 participants, there was a

discrepancy between the subjective sense and objective assessments of taste sensitivity. However, taste sensitivity for bitterness yielded similar results in both studies, such that patients with BMS showed a higher sensitivity for bitterness (Park, Kho 2022). Taste sensitivity, whether in the presence or absence of BMS, remains an area marked by uncertainty and contradictory findings. Taste perception and understanding of it remain enigmatic. Alterations in taste associated with inflammatory conditions such as cancer and acute inflammatory diseases have also been documented (Schalk et al. 2018, Sherry 2002). Transient receptor potential channel dysfunction associated with neuropathic pain, inflammation, and taste sensitivity have been reported (Aroke et al. 2020).

Our findings are consistent with the theory that subclinical inflammation plays a role in the development of spontaneous pain in patients with BMS. Furthermore, the pain exacerbated by the stimulation with hot sauce was associated with an increase in inflammatory cytokines TNF-α and IL-6 in the BMS group, which displayed significant differences when compared to the control group. The study by Pezelj-Ribaric et al. revealed elevated levels of TNF-α and IL-6 in the saliva of patients with BMS and the level de creased after treatment with low-level laser therapy (LLLT), and it corresponds to the clinical improvement in pain. Effect of LLLT in inhibiting inflammatory mediator sec retion has been reported. It is suggested that active LLLT decreased the level of saliv ary proinflammatory cytokines in the BMS group compared to the control group (Pez elj-Ribarić et al. 2013).

Benzodiazepines are GABA-A receptor agonists that bind to both peripheral and central

receptor sites. This activation initiates the descending pain inhibitory pathway in both the peripheral and central nervous systems by opening the chloride channels. They enhance serotonergic descending pain inhibition and mitigate spontaneous hyperactivity in central neurons that occur after differentiation. Clonazepam is a benzodiazepine that enhances the neural inhibition facilitated by gamma-aminobutyric acid (GABA). Its efficacy in patients with BMS has been reported previously; however, changes in salivary cytokine levels before and after treatment have not been reported. Only one study with low-level laser therapy by Pezelj-Ribarić et al. revealed a decrease in salivary levels of TNF- α and IL-6 after treatment with one month of low-level laser therapy (Pezelj-Ribarić et al. 2013). By far, our study is the first study to assess the effect of clonazepam on changes in salivary cytokine levels after treatment in patients with BMS.

Taste disorders, xerostomia, and pain are considered the clinical triad of burning mouth syndrome, which disturbs the quality of life. Considering its suspected etiopathogenesis involving subclinical inflammation, our analysis included the assessment of salivary cytokines, along with a concurrent analysis of the main symptoms. Our study revealed that pain intensity and the levels of salivary IL-6 and TNF-α displayed significant elevation in the BMS group.

To improve these results and overcome the limitations of this study, it is crucial to conduct further high-quality integrated studies with a substantial number of participants, involving a greater number of salivary inflammatory cytokines including serum cytokines. These

studies should comprehensively assess the clinical symptoms with inflammatory cytokine levels.

V. CONCLUSION

1. Out of 60 participants, 4 were males and 56 were females. The mean age of the BMS group was 57.0 ± 7.8 and the control group was 58.2 ± 8.2 years. Spontaneous pain intensity and stimulated pain intensities were higher in the BMS group ($P < 0.001$). Xerostomia was higher in the BMS group ($P < 0.001$); however, the unstimulated whole-saliva flow rate was not significantly different ($P = 0.315$). The subjective sense of taste disturbance showed no difference between the groups ($P = 0.774$) or for the taste sensitivity test (sweet, sour, salty, bitter, and umami) between the groups. However, taste sensitivity to bitterness showed differed between the groups ($P=0.002$).

2. Salivary cytokine levels of two cytokines (TNF-α and IL-6) were elevated in the BMS group compared to the control group ($P < 0.001$).

3. Changes after clonazepam treatment in the BMS group showed differences in spontaneous pain intensity ($P = 0.002$), stimulated pain intensity ($P < 0.001$), and the total score of taste sensitivity test score ($P < 0.001$). Taste sensitivity test scores increased for sweet ($P = 0.009$), bitter ($P = 0.005$), and umami ($P = 0.001$) after clonazepam treatment.

4. Salivary cytokine levels of TNF-α and IL-6 decreased after clonazepam treatment with $P=0.117$ and $P<0.001$ for TNF-α and IL-6, respectively.

Based on this limited study, association of salivary neuroinflammatory cytokines and three clinical symptoms in BMS was determined. The study also unveiled changes in both symptoms and salivary neuroinflammatory cytokines following the topical clonazepam treatment. These findings will contribute to the groundwork for future research in BMS and its association with neuroinflammatory cytokines.

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Abstract (in Korean)

구강작열감증후군에서 타액 신경염증성 사이토카인과 임상 증상과의 상관관계

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홍 유 리

연구목적: 본 연구는 구강작열감 증후군 환자의 임상 증상(미각 이상, 구강 건조, 통증)과 타액 사이토카인을 분석하고자 하였다.

연구대상 및 방법: 만 19세에서 65세 이하 성인을 대상자로 모집하였으며, 구강작열감증후군으로 진단된 환자 30명과 건강한 성인 30명 총 60명(남성: 4명, 여성: 56명)의 데이터를 분석하였다. 타액 분비량은 비자극성 타액을 5분간 수집하여 계산했고, 비자극성 타액 2ml를 수집하여 효소결합면역흡착제분석을 통해 타액 염증성 사이토카인 발현량을 분석하였다. 통증은 자발통과

Tabasco® 를 이용한 자극 시 통증 강도를 시각 통증 척도로 기록했으며, 미각 민감도는 Taste Strip®을 이용하여 측정하였다. 환자군은 치료를 위해 한 달간 국소적 클로나제팜을 처방했고, 치료 후 타액 재수집 및 미각민감도 검사, 통증 검사를 재시행하여 치료 전후 차이를 비교하였다. 대조군과 실험군 비교를 위해 독립 표본 t-검정을 사용하였고, 클로나제팜을 이용한 치료 전후 차이 비교를 위해 대응 표본 t-검정을 사용하였다.

연구결과: 대조군과 실험군에서 자극 시 통증, 구강건조감, 쓴맛에 대한 미각 민감도에 통계적으로 유의한 차이를 보였다. 구강작열감증후군 환자에서 증가된 TNF-α와 IL-6를 보였고 ($P<0.001$), 환자군에서 클로나제팜 사용에 따른 IL-6의 감소를 보였다. 환자군에서 클로나제팜 사용 후 자발통과 자극 시 통증, 단맛, 쓴맛, 감칠맛의 미각민감도도 큰 차이를 보였다.

결론: 구강작열감증후군 환자에서 증가된 TNF-α와 IL-6 발현량을 보였고, 환자군에서 클로나제팜 국소적 사용에 따른 IL-6의 발현량 감소를 보였다.

핵심어 : 구강작열감증후군, 사이토카인, 미각 이상, 구강 건조, 만성 통증