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Comparison of intraoral somatosensory thresholds between atypical odontalgia and inflammatory toothache and its clinical implication

비정형 및 염증성 치통의 구강내 감각 역치에 관한 비교연구

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ABSTRACT

Comparison of intraoral somatosensory thresholds between atypical odontalgia and inflammatory toothache and its clinical implication

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This study aimed to compare the characteristics of intraoral quantitative sensory testing (QST) among atypical odontalgia (AO), inflammatory toothache (IT), and healthy controls and find out how to apply QST characteristics in AO diagnosis and treatment. The QST results and clinical symptoms of 43 subjects (14 AO, 14 IT, 15 healthy controls) were analyzed. QST was performed on the attached gingiva of painful and control teeth based on the modified German Research Network on Neuropathic Pain protocol. QST measurements were statistically compared among groups, and abnormality was evaluated by z-score. Mechanical pain threshold (MPT, $p = 0.003$), mechanical pain sensitivity (MPS, $p = 0.006$), and pressure pain threshold (PPT, $p = 0.011$) showed significant differences. The abnormal z-score rate was highest in the AO group (AO, 78.6%; IT, 14.3%; control, 26.7%) and the most frequent abnormal parameter was MPT. The proportion of subjects with bilateral abnormality was relatively high in the AO group. Treatment prognosis differed slightly according to the unilaterality of the abnormalities.

In conclusion, AO had a distinctive QST characteristics that could be applied in the diagnosing and also predicting disease prognosis.

With further research it would be possible to establish a clinical diagnostic

guideline based on QST and clinical characteristics of AO.

Key words: Atypical odontalgia, Quantitative sensory testing, Toothache, Pain threshold, Somatosensory sensitivity

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비정형 및 염증성 치통의 구강내 감각 역치에 관한 비교연구

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-CONTENTS-

I. INTRODUCTION

Toothaches are the most common condition encountered by dentists. However, not all toothaches are resolved by invasive treatment such as root canal treatment (RCT) or extraction. Therefore, invasive treatment should not be administered to a patient who complains of tooth pain before non-odontogenic toothache, including atypical odontalgia (AO), is thoroughly ruled out based on cautious assessments. AO is characterized by continuous pain without an objective lesion or causative inflammation in the teeth or surrounding dentoalveolar structure[1,2]. In the past, the terms phantom tooth pain and idiopathic toothache were used interchangeably. More recently, persistent idiopathic dentoalveolar pain (PIDP) has replaced these terms[3]. And according to the International Classification of Headache Disorders (ICHD-3 beta version) and the International Classification of Disease (ICD-11), PIDP is defined as persistent dentoalveolar area pain recurring daily for more than two hours/day, over three months, in the absence of any clinical neurological deficit and abnormal clinical and radiographic signs[4–7].

According to the diagnostic criteria for the international Headache Society, AO pain generally has a dull, aching, or nagging quality[1,6]. However, the expression of pain shows wide inter-person variability, and such characteristics are also observed in an inflammatory toothache (IT), such as pulpitis[8]. Moreover, radiological abnormalities are sometimes absent during the initial stages of IT[9]. Therefore, AO is difficult to diagnose through routine clinical examinations, including radiographic examinations, electric pulpal, percussion, bite, ice, and heat tests. Considering that misdiagnoses lead to inappropriate treatment, the most important

aspect of diagnosing and treating AO is accurate differentiation from IT.

Although AO is diagnosed based on the exclusion of other diseases, a precise and specific clinical test to diagnose AO in relation to pulpitis or periodontitis remains unestablished. Various forms of sensory testing have been investigated to confirm their validity for such purposes[10–12], and the German Research Network on Neuropathic Pain (DFNS; Deutscher Forschungsverbund Neuropathischer Schmerz) devised a collective quantitative sensory testing (QST) protocol consisting of parameters to standardize the QST process[13,14]. The protocol consists of measuring somatosensory thresholds and pain responses to temperature, mechanical, vibration, and pressure stimuli, which can then be used to evaluate the function of the A-β, A-δ, and C-fibers. It has been used to discriminate patients with neuropathic pain from healthy individuals and to differentiate between different types of neuropathic pain[15,16]. Several previous studies have reported that AO patients show somatosensory abnormalities distinct from those associated with other odontogenic toothache patients[1,15,17–19]. Such evidence implies that QST results may be used to distinguish AO from IT or a healthy status. However, QST results have not been established as a decisive factor in AO diagnosis until now.

In this study, we hypothesized that intraoral QST of AO patients would have different features from those of IT and healthy controls. Therefore, the primary aim of this study was to compare intraoral QST characteristics among AO, IT, and healthy control groups. Furthermore, this study aimed that explore the possibility of diagnosing and treating AO with these features.

II. REVIEW OF LITERATURE

1. Atypical odontalgia

AO is challenging and difficult to diagnose because of persistent complaints of pain in the tooth and in the alveolar bone area around the tooth without noticeable local lesions[20,21]. According to Malacarne et *al*.[7], part of "of nervous pains in the jaw" John Hunter's book described AO for the first time in 1778[22]. John described the disease that as not a tooth-related disease, although, seems to be caused by teeth, so the healthy teeth may be extracted by a mistake[22]. The term AO was coined in 1979[23]. It has also been called phantom tooth pain (PTP)[24] and, more recently, persistent dentoalveolar pain (PDAP)[3,7,25] and persistent idiopathic dentoalveolar pain (PIDP)[26]. Considering the change in classification, PDAP[25] and painful posttraumatic trigeminal neuropathy (PTTN)[27] were observed in the literature in 2012[7]. According to this classification, PTTN is an obvious injury that causes pain in the trigeminal nerve area[4,6,26]. In a previous definition, AO did not clearly distinguish PDAP and PTTN[28]; however, considering diverse clinical features, the current concept of AO is more similar to PDAP[7]. In 2020, the International Classification of Orofacial Pain (ICOP) established PIDP as a classification and subdivided it according to somatosensory changes[26]. In recent literature, AO, PDAP, and PIDP have been used together[7]. The current review includes AO, PADP, and PIDP as search terms, and all terms were unified and used as AO.

1) An overview of the epidemiology and clinical characteristics

AO is characterized by a persistent toothache without observed local pathologic

lesions and without findings in clinical and radiological examinations[5]. In addition, there is a possibility of false positives in general tests such as ice, pressure, and percussion tests[21,29,30]. This situation is important for understanding the clinical features[31].

AO is predominant in females[3,7,31,32]. According to *t al.*[34], the male-to-female ratio is approximately 2:1. The age of onset is usually between 40 and 50 years[1,7,31,34], with an average age of approximately 55[33,35]. Prevalence is reported differently in each study[34,36,37]; however, it was reported as 0.8%–3.2 %[35].

According to this systematic review, AO occurs after a traumatic event[8,21,38] RCT, extraction, apicoectomy, crown preparation, etc.) in approximately 65% of cases, and pain occurs spontaneously in approximately 35% of cases[7]. According to Nixford *et al.*[39], it occurs in 5% to 5.3% of cases after an RCT. A point to consider here is that AO was not clearly distinguished from PTTN previously; therefore, this should be taken into account during the literature review.

Pain is more prevalent in the premolars and molars and is usually localized around the teeth[40,41]. The intensity of pain is approximately 5 to 6 on the basis of numeric rating scale (NRS, 0~10)[2,3,7,25,38,42]. Although there is an increase or decrease in pain intensity, its characteristic is that it is continuous[43]. Pain affects falling asleep but not waking up and does not interrupt sleep[44,45]. Each individual describes pain differently: dull, aching, burning, sharp, throbbing, tingling, itching[46], pulling/dragging, pulsating, and pressing[3,42]; therefore, it is difficult to distinguish AO from neuropathic pain or IT[47]. In addition, AO is accompanied by psychological problems more[48], than healthy controls, and Miura *et al.*[49], explains that 46.2% of people with AO experience psychological problems. There are

various psychological problems, such as depression, anxiety, and somatization[8,40,45,50–52], but 15.4% and 10.1% of psychological problems mostly involve depression and anxiety disorders, respectively[38,49].

As mentioned above, it is important to identify the clinical characteristics of AO diagnosis[31,34,46]. Summarized the clinical characteristics of patients via interviews[31]. According to this summary[31], the characteristics of AO are as follows: 1) persistent pain; 2) a generally dull feeling; 3) possibility of changes in pain intensity (increase and return to the usual level); 4) change in pain with changes in air pressure; 5) localization of pain around the teeth; 6) deep pain sensation; 7) feeling of pressure; 8) difficulty in pain description; 9) some complaints of itching, tingling, and pricking; and 10) described as a different pain feeling than before.

2) Etiology and pathophysiology

There is still no clear hypothesis explaining the mechanism of pain in AO[25,35,53,54]. However, there are several hypotheses that explain this mechanism via clinical characteristics, application of topical materials such as lidocaine or capsaicin[55,56], and neurophysiological examination results such as QST[3,7,21,42,57]. Hypotheses related to the neuromatrix theory[58] and psychogenic origin have been discussed[8,40,45,51,52], but the most accepted hypothesis was that of neuropathic pain caused by deafferentation[141].

The hypothesis related to psychogenic factors is based on the fact that psychogenic problems/disorders such as depression, anxiety, somatization, and hypochondriacal psychosis are observed at a higher rate in the AO group than in the normal control group[8,40,50–52,59,60]. However, given that there was no difference

in the psychological test results[61] between the AO and the normal control groups in some studies and considering that controversial or questionable results were also reported, it was difficult to support this hypothesis[41,62–64]. However, continuous pain tends to increase psychological problems[65], such as depression or anxiety, and psychological problems interfere with pain treatment, which has been proven by previous studies to affect the chronicity of pain[66]. Ciaramella *et al.*[67], explained that the pain threshold of patients with psychological predispositions changes because of specific psychological events, and AO pain arises accordingly.

In the neuropathic pain mechanism, trauma that can cause nerve damage is a prerequisite[41,68]. Trauma includes extraction, apicoectomy, RCT, and crown treatment[7,8,45]. On the basis of this dental treatment process, when a nerve is traumatized, neurotransmitters, cytokine secretion, etc., cause the sensitization of nociceptive fibers around the trauma, as well as the sprouting and activation of afferent somatic fibers, ephaptic crosstalk between damaged afferent fibers, formation of neuroma, induction of central nervous system (CNS) changes, inhibition of inhibitory pathways, and increase and redistribution of sodium channel expression[41,46,61,64,68–74]. The chronicity of pain and peripheral and central sensitization may be explained via this pathogenesis, and hypo/hyperalgesia or allodynia features are explained in patients with AO[19,21,41]. The degree of difference in these processes is explained by the difference in the degree of clinical characteristics of each individual. In addition, delayed blinking reflex[75,76], prolonged cold response[77], abnormalities observed at high rates in QST–allodynia, and temporal summation[19] are also described as having the characteristics of neuropathic pain.

However, this hypothesis cannot fully explain the pain generation mechanism of AO because 1) there are patients who spontaneously develop pain without any traumatic event, and 2) there are aspects that do not perfectly match the definition of neuropathic pain in the International Association for the Study of Pain (IASP)[78,79]. According to the IASP definition[78,80], neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system." Here, AO cannot be completely explained because no obvious neurological deficits or lesions were observed. Thus, IASP defined nociplastic pain by distinguishing it from nociceptive and neuropathic pain[78,80]. Nociplastic pain[79,81] is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for the disease or lesion of the somatosensory system causing pain neuroplasticity pain." This definition is more suitable for describing AO[78].

3) Diagnosis and differential diagnosis

Diagnosis of AO is generally established by excluding possible diseases through the evaluation of the clinical characteristics and imaging studies[51,53] such as X-ray, cone beam computed tomography (CT)[82], or magnetic resonance imaging[83]; however, differentiating odontogenic pain remains a challenge for dentists[20,47,51]. Although the diagnostic criteria differ according to terminology changes such as AO, idiopathic pain, PTP, PDAP, and PIDP[4,7,24,35,84,85], among others, these terms refer to "continuous pain," "without local/pathologic lesions," and "localized in the tooth and its surrounding tissue." The ICOP diagnostic criteria are as follows[26].

"Diagnostic criteria"

A. Intraoral dentoalveolar pain fulfilling criteria B and C

B. Recurring daily for >2 hours/day for >3 months

C. Pain has both of the following characteristics:

1. localized to a dentoalveolar site (tooth or alveolar bone)

2. deep, dull, pressure-like quality

D. Clinical and radiographic examinations are normal, and local causes have been excluded.

E. Not better accounted for or by another ICOP or ICHD-3 diagnosis.

According to previous studies, the diseases that should be considered for differential diagnoses include pulpal toothache, trigeminal neuralgia, temporomandibular joint disorder, myofascial pain, sinusitis, cracked tooth syndrome, neuralgia, acute herpes zoster, and postherpetic neuralgia[1,9,43,51,86,87]. Among these disease entities, AO is the most difficult to distinguish from pulp disease[88]. For pain induced by an inflammatory disease, an increase or decrease in pain is observed over time, whereas pain caused by AO is characterized as persistent pain[89], and despite repeated dental treatments, symptoms do not improve[31,90]. In addition, since peripheral sensitization occurs in AO depending on the patient, false-positive reactions can be observed even in odontogenic tests such as hot and cold tests or during percussion[29,30]. Generally, an equivalent response to local anesthesia is known in AO patients[41]; however, it is challenging to distinguish because significant pain relief is also observed in some AO patients[55]. According to, approximately 54% of AO patients reported a 50% or more pain reduction with lidocaine injection[91]. In radiological examinations, periapical bone lesions are observed in approximately 17% of AO patients (X-ray and CBCT), and bony scars may appear as a result of no of previous inflammatory lesions[82]. Therefore, the

differential diagnosis can be difficult to rule out using these imaging studies.

Compared with odontogenic pain in healthy controls, in the QST of AO patients, hyperalgesia, hypoalgesia, and allodynia are observed at a higher rate[19,92]. However, since there are also AO patients whose somatosensory changes are not observed and odontogenic pain patients whose somatosensory changes are noted, there are limitations in using this as a stand-alone differential diagnostic tool[19,92,93]; therefore, caution is warranted when analyzing the results. As mentioned above, it takes an average of 19.3 months before AO can be diagnosed[88], and thus, receiving appropriate treatment can be delayed because it is difficult to differentiate AO from other diseases, especially odontogenic pain[88].

4) Treatment and prognosis

AO is characterized by persistent complaints of pain, and pain management is important in AO treatment[75]. First, unnecessary additional treatment was not performed after AO diagnosis[21,34]. This included repeat RCTs, extractions, and dental surgeries. The repetition of these procedures can exacerbate pain the repetition and intensification of the trauma event process[21,60]. The treatment of AO patients includes counseling and education about the disease, topical/oral medication, and Botox injection[7,35,51,94].

However, there are few qualified randomized controlled study and long-term follow-up studies on this topic[90,95,96]; therefore, it is difficult to predict the prognosis and possibility complete pain relief can be achieved. Systematic and long-term studies on treatment prognosis are also lacking, but according to Pigg *et al*.[90], as a result of the long-term 7-year follow-up of AO patients, significant pain

reduction and complete pain reduction was observed in 35% and 14% of patients, respectively. However, the remaining patients showed persistent or exacerbated pain. The predictive value in this study was a low baseline pain intensity.

Therefore, when one first meets a patient with AO, the first thing to do is to explain the clinical characteristics of AO so that they can reduce the psychiatric problem due to persistent pain and obtain a realistic treatment goal[1,34,35,50,97]. Chronic pain and psychological problems interact with one another[3,65,98]. Therefore, this process will have a positive effect on pain management by reducing anxiety about unexplained persistent pain and increasing the understanding of the treatment. The drugs mainly used for symptom relief are antidepressants (tricyclic antidepressant, TCA; serotonin and norepinephrine reuptake inhibitors, SNRI) and anticonvulsant drugs (gabapentin or pregabalin); antidepressants are generally used first[21,34,53,75,99,100]. It is explained that the pain-relieving mechanism of affects the endogenous pain inhibitory pathway by blocking the reuptake of noradrenaline and serotonin, and the pain-relieving mechanism of antiepileptic drugs is achieved via interactions with voltage-gated Ca2+ channels[43,101]. The TCAs or SNRIs used for treatment include nortriptyline; amitriptyline; imipramine; duloxetine; and anticonvulsants such as gabapentin, pregabalin, clonazepam, and baclofen[102,103]. In addition, opioid narcotic analgesics, including oxycodone, meperidine, and ketamine, are also used[75,104]. According to Tu *et al.*[102], after 4 weeks of drug treatment, 65.9% of the subjects reported the effect of drug treatment, and this effect was accompanied by a decrease in pain intensity, and a decrease in depression and catastrophizing score. In the case of duloxetine, significant symptom improvement was observed in 77.0% of the subjects, and the predictive

value in this case was observed as a short disease duration[105]. The points to be aware of when using these drugs include the use of an appropriate dose for pain management, observation and management of various side effects that may occur, and the need for tapering when stopping the drug[21,46,51,103,106]. The typical side effects of these drugs include drowsiness, dizziness, dry mouth, anorexia, vomiting, sexual dysfunction, headache, suicide, weakness, skin rash, insomnia, and blurred vision[35,103,106].

Although the results vary from study to study, the application of topical drugs reportedly provides pain relief[107]. According to previous study[46], approximately 60% of patients reported pain relief during application of lidocaine and prilocaine, while 63% experienced pain relief during capsaicin 0.025% application.

As for the application of Botox in the oral cavity, few well-designed studies were published, and each study had fewer than 10 participants. According to Dawson *et al*.[108], pain reduction of more than 25%[109], three out of four participants reported that pain almost disappeared[94], and reported a pain reduction of more than 50%[110]. Thus, Botox could be a possible treatment option for relieving pain in AO, with few side effects[108].

2. Quantitative sensory testing protocol of the German research network on neuropathic pian

QST is a method of quantifying and evaluating somatosensory changes/ abnormalities[19,92,111]. It is called a psychophysiological examination because it gives various stimuli—temporal, mechanical, pressure, and vibration stimuli—and measures the threshold through the patient's response[112]. It has the advantage of being able to identify somatosensory abnormalities—both gain of function and loss

of function—of A-delta, A-beta, and C-fibers at once in a non-invasive method[14,113]. However, the QST results are easy to affect, depending on the patient's state as well as the examiner's skill, the accuracy of the test instrument, and the test environment[14,114]. Therefore, it was necessary to standardize the test methods and instruments in order to increase the scientific basis of test results and to make objective comparisons for each study. To this end, DFNS standardized the test protocol[13]. After establishing the DFNS protocol, reference data were obtained for each body site, gender, and age, at the same time reliability was studied[93,115,116]. Through these studies, it was confirmed that the DFNS protocol has acceptable reliability, the threshold values are different not only for each body part but also for each gender and age[93,115–117]. The standardized QST protocol is used to diagnose, evaluate prognosis and study underlying pathogenesis mechanisms in the various types of pain - neuropathic, neuralgia, skeletal muscle pain, odontogenic/non-odontogenic pain, etc.—by confirming somatosensory abnormality[17,19,47,92,112,118,119]. It is also used for early diagnosis of abnormal findings in patients with early asymptomatic neuropathy[120].

The QST protocol by DFNS consists of 13 parameters in 7 tests—cold detection threshold (CDT), warm detection threshold (WDT), thermal sensory limen (TSL), paradoxical heat sensation (PHS), cold pain threshold (CPT), heat pain threshold (HPT), mechanical detection threshold (MDT), mechanical pain threshold (MPT), mechanical pain sensitivity (MPS), dynamic mechanical allodynia (DMA), wind-up ratio (WUR), vibration detection threshold (VDT), and pressure pain threshold (PPT), and the detailed method below was summarized according to the DFNS manual and previous literature[14,19,92,112,114,121,122].

1) Thermal detection and pian thresholds

This test includes a total of six parameters: CDT, WDT, TSL, PHS, CPT, and HPT. Thermal Sensory Analyzer II (TSA 2001-II Thermal Sensory Analyzer, Medoc, Israel) and MSA Thermal Stimulator (SOMEDIC, H¨orby, Sweden) are used for most tests. There are two types of thermode used for cutaneous (SOMEDIC: 20X20 mm and Medoc: 30X30 mm, both square surfaces) and intraoral (SOMEDIC: 9X9 mm square surface; Me-doc: 6 mm diameter round surface). When the thermode contact surface temperature continuously increases or decreases, a threshold value can be determined by pressing a stop button connected to a computer unit (temperature change of 1 ℃/s)—starting from a baseline temperature of 32 ℃ (intraoral 37℃). This device automatically stops measurements when it reaches a temperature of 0 °C or 50 °C for preventing tissue damage. An arithmetic average of three repeated measurements is used to determine the threshold. The order of measurement is CDT, WDT, TSL, CPT, HPT, and PHS is recorded during TSL. All thermal tests start at the basic temperature (32 ℃ or 37 ℃), CDT is the temperature at which the temperature is first felt cold when the temperature is decreased, and WDT is the temperature at which the temperature is first felt when the temperature is increased. In addition, CPT is the temperature at which pain is first felt when the temperature is decreased, and HPT is the temperature at which pain is first felt when the temperature is increased. In the CPT and HPT test, feeling of pain includes sensations of “burning”, “stinging”, “drilling” or “aching”. During TSL measurement, the increase and decrease of the temperature of the device appear alternately. TSL is the arithmetic mean value of the difference between the temperature at which you first feel warm when the

temperature rises and the temperature at which you first feel cool or temperature change when the temperature decreases. At this time, the PHS records the number of "warm", "hot" or "painfully hot" during cold stimulation in the TSL test.

2) Mechanical detection threshold

DFNS QST protocols use standardized von Frey filaments (OptiHair2, MARSTOCKnervtest, Marburg, Germany) for measuring mechanical detection thresholds. The von Frey filament set consists of 12 monofilaments (0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, and 512 mN), and the diameter is about 1 mm^2, which is the same. And the tip is blunt to measure the threshold for mechanical stimulation. The filament is applied perpendicular to the test site for 1-2 seconds, and when the intensity is lowered starting with 16mN, the intensity at which stimulation is not felt for the first time is subthreshold, and the intensity is gradually increased again to be suprathreshold at the intensity when stimulation is felt first. After repeating this process 5 times, the geometric mean of the 5 trials is set as the final threshold.

3) Mechanical pain threshold

For MPT measurement according to the DFNS protocol, a custom-made weighted pinprick stimulator is used (Johannes Gutenberg University of Mainz, Mainz, Germany: The Pin Prick; at Aarhus University, Aarhus, Den-mark; and at University of Washington, Seattle, USA)[19]. It consists of a set of 7 stimulators (6, 32, 64, 128, 256, and 512 mN), with a tip diameter of 0.25 mm. The measurement method is to apply it vertically to the test area for 1-2 seconds and increase the intensity from 8mN stimulator until the sense of touch is felt as "sharp", "pricking"

or "painful"; this intensity is recorded with suprathreshold. And then decrease the intensity, until the sense of "sharp" or "painful" changes to "blunt" or "non-painful; this intensity is recorded with subthreshold. The above process is performed five times as in MDT, and the geometric average is determined as the final threshold.

4) Stimulus/response functions—mechanical pain sensitivity and dynamic mechanical allodynia

For MPS measurement, the pinprick stimulator used in MPT is used, and for DMA measurement, a cotton wisp (3 mN), a cotton wool tip (Q-tip, 100 mN), toothbrush (Top Dent, Meda AB, Solna, Sweden, 200 ~400 mN) is used. 7 pinprick stimulators and 3 tactile stimulators are applied 5 times in one set, and the intensity of pain upon application is recorded as NRS (0-100). At this time, MPS is the geometric mean of NRS recording during pinprick stimuli, and DMA is the geometric mean of NRS recording during tactile stimuli.

5) Wind-up ratio

For WUR measurement, the pinprick stimulator used in MPT measurement is used. In the test the NRS (0-100 rating) is obtained after a single pinprick stimulus is applied to the subject, and then 10 times after the pinprick stimuli are applied. This process is repeated 5 times (or 3 times), and when applying the stimulus 10 times, it should be applied with the same force at intervals of 1 second. The final threshold of this test is determined by dividing the arithmetic mean of NRS obtained by stimulating 10 times by the arithmetic mean of NRS obtained by stimulating once. Starting with 218 mN, but if pain is not felt by applying 128 mN

first, 256 mN and 512 mN are applied in increments. Generally, 256 mN is used, and for the face, 128 mN is applied. If no pain is felt even at 512 mN, this test is not performed. This test is to see the effect of temporal summation by WDR neuron sensitization, because when repetitive C-fiber input is received more than once within 3 seconds from the spinal cord[123].

6) Vibration detection threshold

To determine the vibration threshold, a Rydel-Seiffer tuning fork (64 Hz, 8/8 scale) is used. To determine the threshold value, the tuning fork is applied to bony prominence such as ankle, mandible or maxilla, and the scale (0~8) s recorded when the subject no longer feels the vibration. The final threshold is determined by the arithmetic average of three measurements.

7) Pressure pain threshold

An electronic algometer is used to determine the PPT (SOMEDIC Algometer, SOMEDIC Sales AB, Sweden). Continuously increasing pressure in increments of 50 kPa/s. The pain threshold is measured by increasing the pressure at 50 kP/s by contacting the rubber tip to the skin (surface area 1 cm^2) or oral mucosa (surface area 0.8 cm^2). A PPT is measured as a kPa value, which represents the point at which pressure becomes painful for the first time. Following three repeated measurements, the PPT is calculated as an arithmetic mean.

8) Analyzing QST data to evaluation somatosensory abnormalities

To evaluate somatosensory abnormalities through QST data, z-score should be calculated through the following formula. Here, the reference group generally means the data of the normal (healthy) group. If the z-score is positive, it is called gain of function, and if it is negative, it is called loss of function, when the z-score is over +1.96 or below -1.96, it is evaluated that there is somatosensory abnormality.

$$(\text{Individual value} - \text{Mean}_{\text{reference group}}) / \text{Standard deviation (SD)}_{\text{reference group}}$$

Therefore, the first thing to do before z-score calculation is to check whether each parameter data has a normal distribution, and if not, log transformation should be performed for analysis. Gain of function means hyperesthesia, hyperalgesia, and allodynia, and loss of function means hypoesthesia and hypoalgesia. In addition, because DMA is to feel pain on tactile stimulation, it is evaluated as gain of function, and PHS is evaluated as loss of function in cold detection.

III. METHODS

1. Subjects

The subjects were consecutive patients who visited the Department of Oral Medicine, Conservative Dentistry or Periodontics in Seoul National University Dental Hospital (SNUDH) from February 2017 to February 2019. A healthy control group was recruited through a research recruitment notice, and their gender and age were configured similarly to AO patients. Initially, 47 individuals (17 AO patients, 15 IT patients, and 15 healthy controls) participated; of these, 2 AO patients and 1 IT patient were excluded following the exclusion criteria during the follow-up period, and 1 AO patient wanted to stop the QST and excluded (Figure 1). Finally, 43 individuals were analyzed in this study, including 14 AO (2 males and 12 females, mean age: 42.5 ± 10.4 years), 14 IT (6 males and 8 females, mean age: 39.4 ± 13.2 years), and 15 healthy controls (2 males and 13 females, mean age: 43.9 ± 11.2 years).

AO patients were those who came to the SNUDH with a toothache, and were referred from local clinics, Conservative Dentistry, or Periodontics due to the absence of subjective inflammatory symptoms. Specific inclusion criteria were as follows[5,6,41] first, the pain was in the dentoalveolar area without any other systemic pain; second, the pain (more than fifteen days a month) persisted more than three months; third, radiographic and clinical examination- including percussion, bite, ice, and electric pulp testing, probing depth assessment- results normal, and the normal results were confirmed by the Department of Conservative Dentistry or Periodontics.

The IT group included patients who had toothache with apparent signs of inflammation in the radiographic and clinical examination including thermal and electric pulp testing, probing depth assessment. The Department of Conservative Dentistry or Periodontics evaluated the inflammatory signs and confirmed that the toothache was caused by inflamed lesions, and in the IT group, 8 patients had pain of pulpal origin and 6 patients had pain of periodontal origin. The healthy control group comprised individuals without orofacial pain, including toothache, in the last 6 months.

The exclusion criteria for all groups were individuals with neuromuscular disorders, uncontrolled diabetes mellitus, neoplasms, psychological disorders that could affect the study results, temporomandibular joint disorders, oral mucosal lesions, and other neuropathic pain conditions.

The study protocol was reviewed and approved by the Institutional Review Board of SNUDH (# CRI17001) and was conducted in accordance with the Code of Ethics of the World Medical Association for experiments involving humans. All procedures were performed in accordance with the ethical standards of the institutional research committee and Helsinki Declaration of 1964 and its later amendments or other equivalent ethical standards. Written informed consent was obtained from all participants.

2. Clinical assessment

Clinical assessment was conducted through patient interviews, radiographic, and oral examinations. The patient's age, gender, medical history, such as medications and diseases, as well as pain location, intensity (NRS:0-10), and duration from onset (months) were confirmed through chart recording and interviews. Oral and

radiographic examinations were evaluated based on clinical signs (e.g., signs of inflammation) and plain radiographic findings. Additional imaging tests, such as cone-beam computed tomography, were performed only when the diagnosis could not be made clearly by plain radiography. Additional radiological examinations were not performed in the healthy control group. The healthy controls were done oral examinations, palpation, percussion, and thermal tests to confirm the soundness of the tooth and surrounding tissue or the absence of inflammation.

3. Psychological evaluation

Symptom checklist-90-revision (SCL-90-R) and graded chronic pain scale (GCPS) were used to assess the psychological profile and disability. The SCL-90-R evaluates the psychological profile by a self-report assessment consisting of nine symptomatologic dimensions and three global distress indices[124]. The nine symptomatologic dimensions are somatization (SOM), obsessiveness-compulsiveness (O-C), interpersonal sensitivity (I-S), depression (DEP), anxiety (ANX), hostility (HOS), phobic anxiety (PHOB), paranoid ideation (PAR) and psychoticism (PSY), and the three global distress indices are global severity Index (GSI), positive symptom total (PST), positive symptom distress index (PSDI).

GCPS is a pain assessment tool that evaluates the severity of pain as a combination of pain intensity and pain-related disability and is divided into four grades according to the scoring rule—Grade 1, low disability and low intensity; Grade 2, low disability and high intensity; Grade 3, high disability and moderately limiting; Grade 4, high disability and severely limiting[125].

4. Quantitative sensory testing

QST was performed according to the DFNS version 2.1 protocol[13,14,119] with some modifications. The specific organization and methods are described below. In the patient groups, the non-painful site was examined first, followed by the painful site.

Thermal detection and pain threshold

Temperature-related tests were performed using Thermal Sensory Analyzer (TSA type II; Medoc Ltd. Advanced Medical Systems, Ramat Yishai, Israel) with an intraoral probe (6-mm diameter). The rate of change in temperature was 1 °C/s.

1) CDT and WDT

   Starting at 32 °C, CDT was defined as the first temperature at which the subject perceived coldness, and the WDT was defined as the first temperature at which warmness was perceived. Based on three repeated measurements, the arithmetic mean was determined as the threshold.

2) TSL and PHS

   While increasing and decreasing the temperature, the temperatures that an individual feels warm and cold were recorded. This process was repeated three times. TSL was the average temperature difference between the cold and warm thresholds. The complaint of heat pain during cold temperatures is called PHS, and the number of reactions during the three tests is the PHS value.

3) CPT and HPT

   Starting at 32 °C, the CPT was defined as the first temperature at which pain was felt during the application of a cold stimulus, and the HPT was

defined as the first temperature at which pain was felt during the application of a hot stimulus. As a threshold, three repeated measurements were used to calculate the arithmetic mean. To prevent tissue damage, the TSA temperature was set not to rise above 50 °C

Tactile detection threshold – mechanical detection threshold

The test was performed using a Von Frey filament (Touch Test Sensory Evaluators Semmes-Weinstein von Frey Aesthesiometers; Stoelting Europe, Dublin, Ireland) and the threshold value was determined using a modified limit method. The examiner started with the 0.16 g probe intensity at which a sensation was first felt in the MDT test. Then, the intensity gradually increased. The intensity at which pain was felt for the first time was recorded. Subsequently, the intensity was decreased, and the intensity at which no pain was felt was recorded. This procedure was performed five times, and the final threshold was determined by the geometric mean of the supra- and sub-thresholds.

Mechanical pain threshold

The test was performed using a Von Frey filament (Touch Test Sensory Evaluators Semmes-Weinstein von Frey Aesthesiometers; Stoelting Europe, Dublin, Ireland), and the threshold value was determined by performing a modified limit method. The start was with the probe intensity at which the patient first felt; in the MDT test, then gradually increased the intensity, then recorded the intensity at which you felt pain for the first time, and then recorded the intensity you did not feel pain by decreasing the intensity again. This procedure was performed five times, and the final threshold was determined by the geometric mean of the supra-

and subthreshold.

Stimulus / Response functions – mechanical pain sensitivity and dynamic mechanical allodynia

Von Frey filament (Touch Test Sensory Evaluators Semmes-Weinstein von Frey Aesthesiometers; Stoelting Europe, Dublin, Ireland) 1.0, 1.4, 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, 26.0, 60.0, 100.0, 180.0, and 300.0 g probes were used as stimuli, and cotton wisps, Q-tips, and toothbrushes were used as dynamic innocuous stimuli. The pain intensity during stimulation was graded using the NRS (0-100) and recorded. The measurement was repeated five times, and the geometric mean was recorded as the final result. MPS was the mean NRS score during stimulation with a Von Frey filament, and DMA was the mean NRS score during stimulation with a cotton wisp, Q-tip, and toothbrush.

Wind-up ratio

Using 180 g of the Von Frey filament (Touch Test Sensory Evaluators Semmes-Weinstein von Frey Aesthesiometers; Stoelting Europe, Dublin, Ireland), the NRS (0-100) after ten times stimuli (repetition rate of 1/s) was divided by a single stimuli NRS (0-100). The procedure was repeated five times, and the final WUR was determined as the arithmetic mean of the above value.

Vibration detection threshold

VDT was measured using the 64 Hz Rydel-Seiffer tuning fork (Rydel–Seiffer; Martin, Tuttlingen, Germany). A tuning fork is applied to the gingival area and

recorded on an 8/8 scale when they did not feel the vibration. This test was repeated thrice, and the arithmetic mean of these values was recorded as the final result.

Pressure pain threshold

The PPT was measured using an electronic pressure algometer (SOMEDIC Algometer, SOMEDIC Sales AB, Hörby, Sweden) with a 1 cm^2 probe. Pain intensity applied to the gingival area was recorded. The same test was performed thrice, and the arithmetic mean of these values was used as the final result.

5. Categorization of AO patients according to the LossGain coding system

The LossGain coding system applies the method used in previous studies to evaluate somatosensory loss and gain of function through QST[16,19]. The LossGain coding system consists of the loss-of-function (L0, L1, L2, and L3) and gain-of-function (G0, G1, G2, and G3) scores. L0 indicates no loss of function; L1, loss of function in the thermal parameters alone (e.g., CDT, WDT); L2, loss of function in the mechanical parameters alone (e.g., MDT, VDT, PPT); and L3, loss of function in both the thermal and mechanical parameters. The G0, G1, G2, and G3 scores are defined similarly to the L0–L3 scores (G0: no gain of function, G1: gain of function in only the thermal parameters, G2: gain of function in only the mechanical parameters, and G3: gain of function in both). If the DMA is not zero, it means allodynia for mechanical stimuli; thus, it was included in the gain of function category (G2 or G3).

6. Data evaluation

First, Shapiro-Wilk test was performed to verify the normal distribution. If the raw data were not a normal distribution, the data were converted to log transformation. In general, ANOVA (post hoc comparisons through Tukey) or an independent t-test was used to compare the mean values of AO, IT, and control; however, if the data were not a normal distribution, the Kruskal-Wallis test (post hoc comparisons through Mann-Whitney U test with Bonferroni correction) or Mann-Whitney U test was used. Categorical variables were analyzed by Fisher's exact test because the sample size in each group was small. Site differences (within-subjects) QST thresholds between the painful and non-painful sites and group differences (between-subjects) in thresholds between AO and IT groups were analyzed using mixed-ANOVA. In the analysis, a P-value less than 0.05 was considered significant. Z-score ($[Value_{individual} - Mean_{controls}]/ SD_{controls}$) was calculated to compare the abnormality of QST results. The abnormal z-score range was $Z>1.96$ or $Z<-1.96$; above 1.96 means gain of function (hyperalgesia, hyperesthesia, allodynia) below -1.96 means loss of function (hypoalgesia, hypoesthesia). These statistical analyses were performed using the SPSS 25.0 software (SPSS; IBM, Armonk, NY, USA)

IV. RESULTS

1. Comparisons of clinical characteristics

Forty-three subjects (14 AO, 14 IT, and 15 control) were analyzed. The mean age and gender distributions of each group are shown in Table 1. Although the ratio of men in the IT group was higher, the difference in gender distribution (p = 0.141) and age was not statistically significant among the groups (p = 0. 779).

The pain intensity was higher in the AO group than in the IT group ($p < 0.001$). There was no statistically significant difference in the duration from pain onset (p = 0.134); however, AO patients had experienced significantly more pain days in the preceding 6 months ($p < 0.001$).

2. Comparisons of disability and psychological profiles

According to the GCPS results, the number of patients with low and high disability was similar in the IT group, while all patients in the AO group showed high disability (p = 0.006).

Psychological profiles were analyzed using the SCL-90-R. The scores of the patient groups (AO and IT) were higher than those of the healthy control group. When the three groups were compared, there were statistically significant differences in somatization ($p < 0.001$), anxiety (p = 0.006), and psychoticism (p = 0.013). However, in the post-hoc analysis based on these results, there was no statistically significant difference between the AO and IT groups (Table 2).

3. Comparisons of the intraoral quantitative sensory testing profiles

The intraoral QST parameters and analysis results of the groups are shown in Tables 3 and 4. There were no significant differences among the non-painful sites in the three groups ($p > 0.064$), except for the VDT ($p = 0.054$). There were significant differences between the painful and non-painful sites (within-groups) in terms of MPT ($p = 0.003$), MPS ($p = 0.006$), and PPT ($p = 0.011$) values. The TSL ($p = 0.017$) and PPT ($p = 0.001$) values were significantly different between the AO and IT groups (between-groups). The AO group showed lower MPT (42.8 ± 36.6 and 42.8 ± 62.5 g *vs.* 93.5 ± 85.8 and 59.3 ± 63.8 g) and higher MPS (20.3 ± 17.3 and 26.5 ± 17.6 g, *vs* 16.9 ± 18.3, and 18.3 ± 16.2 g) and PPT (82.6 ± 79.0 and 55.9 ± 25.9 kPa *vs*. 40.4 ± 13.0 and 29.0 ± 14.7 kPa) values than the IT group, regardless of the site (painful and non-painful) (Table 3). The MPT showed little difference between the painful and non-painful sites in the AO group (Table 3). However, there was no interaction between the site and group ($p > 0.065$).

PHS and DMA—non-zero PHS and DMA values—were higher in the AO (PHS, 21.4%; DMA, 28.6%) group than in the IT (PHS, 0%; DMA, 21.4%) and control groups (PHS, 0%; DMA, 0%). However, these differences were not statistically significant (Table 5).

4. Comparisons of the frequency and distribution of abnormal z-scores

The abnormal z-score distribution in each group is shown in Table 6, Fig. 2-A, and Fig. 2-B. The rate of abnormal z-scores was highest in the AO group (78.6%), regardless of the site (painful and non-painful) (Table 5); however, a few subjects in the IT (14.3%) and control groups (26.7%) also had abnormal z-scores.

The AO group showed many different LossGain coding results (such as L0G1, L0G3, L1G0, L1G2, L2G0, L2G3, and L3G2), whereas the IT and control groups showed only L0G1, L0G2, L0G3, and L1G2 results (Table 7).

V. DISCUSSION

The main finding of this study was that AO patients had more somatosensory abnormalities than did the IT and healthy control groups and that the AO group has QST characteristics that distinguish it from the other two groups.

Z-scores were used to evaluate abnormalities in QST results, and values less than -1.96 or greater than 1.96 (95% CI; confidence interval) were considered abnormal[13]. According to previous studies based on intraoral QST values, AO patients showed hyperalgesia or allodynia in response to mechanical stimuli, especially pin-prick stimuli and noxious thermal stimuli (e.g., CPT and HPT), and hypoesthesia for non-noxious thermal stimuli (e.g., CDT and WDT)[19,90]. Another multicenter study reported gain of function or hyperalgesia in 87.3% of AO patients in response to mechanical and thermal stimuli[19].

In this study, the overall proportion of abnormal z-scores in AO patients was higher (78.6%) than that in the other groups. In the AO group, the ratio of gain of function in terms of the MPT and loss of function in terms of the CDT was high, and the frequency of DMA and PHS was also high. Because DMA is considered allodynia and PHS is considered hypofunctional in cold detection[11,13], the results of this study revealed a trend similar to that of previous studies. Comparing the means of the QST results confirmed that the MPT, MPS, and PPT values were statistically different across within-group sites (painful and non-painful sites); in addition, the MPT values were lower while the MPS and PPT values were higher than those in the IT group. Moreover, there was little difference in the QST results between painful and non-painful sites in patients with AO. Considering this, together with

the z-score abnormality results, it can be assumed that both peripheral and central sensitization are present in AO patients[2,90].

This sensitization process can be considered in relation to the GCPS results. In this study, pain intensity and duration (from pain onset to QST date), and pain days were investigated using the GCPS questionnaire. Pain intensity scores measured using the numeric rating scale (NRS, 0–10) were significantly different among the groups, with a mean score of 5.9 ± 1.8 in the AO group and 3.3 ± 1.5 in the IT group. The pain intensity scores of the AO patients were similar to those in a previous study[2,38] however, it was difficult to obtain consent to proceed with QST in IT patients with moderate or high pain intensity, which should be considered when interpreting the results. There was no significant difference in pain duration (from pain onset to QST date) between the AO and IT groups, but there was a statistically significant difference in constant pain duration. While quantifying the "duration of symptoms from onset" simply involves counting the days from pain onset to the QST date, quantifying “pain days” involves counting all days the patient experienced pain. This study revealed that AO patients experienced pain that interfered with their daily activities almost every day over the course of the preceding six months, while this was not the case for IT patients.

Many previous studies have reported that patients with AO show the pain characteristic of sensitization[2,13,55,126,127]. They demonstrated unique features, such as recognition of pain not only in the affected area but also on the contralateral side, and allodynia, hyperalgesia, light dynamic pain, and conditioned pain modulation[18,126]. The appearance of these symptoms in patients with chronic pain is considered to be caused by long-term exposure to persistent pain[126]. Therefore, we

can assume that persistent pain-induced neuroplastic changes are responsible for the central sensitization or somatosensory abnormalities seen in AO patients[2,7,128]. As sensitization is also observed in the inflammation process[8], the PPT of the IT group was considered lower than that of the AO group. This low PPT observed in inflamed gingivitis was similarly found in a previous study[129], and it should be noted that the PPT is lowered without MPT abnormalities in gingivitis patients. This can be attributed to the different reactions of the inflamed gingiva to pinprick and blunt stimuli. According to Wang *et al.*[129], the area examined when determining the MPT is too small to reflect the gingival inflammation-related condition as a whole.

Although the differences in QST results between AO and IT patients have been demonstrated, AO is still difficult to diagnose, as QST abnormalities are not observed in all AO patients. This is thought to be a result of the complex pain mechanism in AO patients, which is not yet fully understood. Therefore, it is not advisable to diagnose AO solely based on QST results, even though a high rate of abnormal z-scores was observed in the AO group compared to the other groups. Nevertheless, QST results still reveal special clinical features according to the various types of pain, including AO[127]. Therefore, QST can be helpful for differential diagnoses if used in conjunction with other clinical features.

QST results have also been applied to explain the underlying mechanism of AO pain and evaluate its prognosis according to phenotype[2,32]. However, no promising results have been observed in prognostic evaluation. In this study, AO patients were phenotyped according to LossGain coding[13,19], however, there was no significant difference in prognostic evaluation. However, it was confirmed that the

prognosis for drug treatment differed depending on whether the patient's abnormality was bilateral or unilateral, and subjects with bilateral problems were more likely to have a poor prognosis (Table 8). In the evaluation of prognosis, there were no differences according to the drugs used or LossGain code distributions. Since not many samples were analyzed, additional studies with larger sample sizes are needed in the future.

This study had some limitations. First, the sample size might have been small to detect significant differences in some QST parameters among groups. Also, in this regard, although no statistically significant difference was observed in the gender distribution among the groups, it is believed that the low female ratio in the IT group also affected the results. According to previous studies[130,131], females generally tend to have lower QST thresholds than males.

Second is heterogeneity in the composition of the AO and IT group. According to the International Classification of Orofacial Pain (ICOP) classification, AO is described as a previous term for PIDP[3]. In this classification, PIDP does not include post-traumatic trigeminal neuropathy (PTTN) that appears after trauma; however, AO has been used interchangeably to diagnose patients without a strict distinction between PIDP and PTTN[3]. Accordingly, a limitation may be that the state of the AO patients before dental treatment, the degree of trauma during surgical procedures such as RCT or extraction, and the possibility of iatrogenic events was not thoroughly evaluated. However, within the definition of AO, we attempted to standardize the composition of the AO group. Therefore, those who experienced an accident or surgery or who took antiepileptic drugs or antidepressants for more than 1 week were excluded. And IT group consisted of

patients with pupal and periodontal pain. Pulpal pain is visceral pain, and periodontal pain is deep somatic pain of the musculoskeletal type[41]. Therefore, the clinical features of pain are different in some aspects. So, it can be assumed that this may affect the intraoral QST, but previous studies on the QST difference between the two categories of pain have not been reported.

The upper limit for hot stimulation was set at 50 ℃ to prevent tissue damage. However, unlike other oral mucosal areas, the gingiva has a high temperature threshold[47] and often starts to feel pain at temperatures near 50 ℃. The CPT measurement was set to drop the temperature at a rate of 1 ℃/s. However, as the temperature approached 0 ℃, due to the effect of body temperature, it was observed that this rate decreased slightly. As a result, the third limitation is that the HPTs recorded could have been below the actual thresholds, and the CPTs recorded could have been somewhat higher than the actual thresholds.

A fourth limitation is that most of the methods in this study were conducted according to the DFNS protocol; however, when measuring the mechanical detection and pain thresholds, a von Frey filament was used instead of the recommended device. Although the method used in this study was based on previous studies[2,47,132,133], it should be considered when interpreting the results.

Despite these limitations, this study confirmed intraoral QST features of AO pain that were different from those of IT or helathy controls through various analysis methods. In addition, it evaluated treatment prognosis according to the bilaterality of the abnormality using z-scores.

VI. CONCLUSIONS

The intraoral QST clinical characteristics of AO patients differ from those of patients with IT or healthy controls. AO patients had 1) a higher rate of abnormal z-scores in both affected and non-affected sites and 2) a wide distribution of more various types of LossGain codes than IT and control group. And more, this study confirmed that their treatment prognoses differ depending on whether their abnormal z-scores are bilateral. However, there were variations among individuals and considering that AO patients without somatosensory changes exist, the findings must be used in conjunction with other additional clinical information. So, with further research it would be possible to establish a clinical diagnostic guideline based on the distinctive QST profile of AO patients and their clinical characteristics.

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Table 1. Clinical characteristics

	AO (n=14)	IT (n=14)	Control (n=15)	*P*-value
Female (%)	12 (85.7)	8 (57.1)	13 (86.7)	0.141[a]
Age (years)	42.5 ± 10.4	39.4 ± 13.2	43.9 ± 11.2	0.779[b]
Pain intensity (NRS: 0-10)	5.9 ± 1.8	3.3 ± 1.5	N/A	<0.001[c]
Duration of symptom (months)	10.8 ± 8.4	9.2 ± 15.4	N/A	0.134[d]
Pain days in the last 6 months (days)	133.2 ± 44.9	30.5 ± 46.7	N/A	<0.001[d]
Pain days that make usual activities difficult (days)	106.4 ± 67.1	25.6 ± 40.8	N/A	0.002[d]

AO, atypical odontalgia; IT, inflammatory toothache; NRS, numeric rating scale; N/A, not applicable
[a] P-value was obtained from Fisher's exact test.
[b] P-value was obtained from Kruskal-Wallis.
[c] P-value was obtained from independent t-test.
[d] P-values were obtained from Mann-Whitney *U* test.
Values are given as mean ± SD

Table 2. Psychological characteristics

	AO	IT	Control	*P*-value
GCPS (%)				
Low disability				
Low intensity (I)	0	5 (35.7)	N/A	N/A
High intensity (II)	0	3 (21.4)	N/A	
High disability				
Moderate limiting (III)	5 (35.7)	3 (21.4)	N/A	0.006[a]
Severe limiting (IV)	9 (64.3)	3 (21.4)	N/A	
Symptom dimension				
SOM	46.9 ± 8.9	44.7 ± 6.4	38.1 ± 1.9	<0.001[b]
O-C	43.4 ± 10.1	44.9 ± 8.0	40.1 ± 6.7	0.160[b]
I-S	44.8 ± 10.0	44.7 ± 7.2	40.9 ± 9.4	0.154[b]
DEP	44.5 ± 9.3	45.1 ± 9.5	39.4 ± 3.5	0.120[b]
ANX	44.4 ± 10.3	44.1 ± 7.2	38.4 ± 5.7	0.006[b]
HOS	45.2 ± 10.3	45.4 ± 8.7	42.6 ± 8.4	0.357[b]
PHOB	45.9 ± 9.6	44.5 ± 3.3	41.9 ± 3.4	0.060[b]
PAR	44.1 ± 11.0	44.2 ± 5.9	42.5 ± 9.4	0.208[b]
PSY	45.3 ± 10.5	45.1 ± 5.5	40.4 ± 5.4	0.013[b]
Global index				
GSI	43.9 ± 11.0	44.4 ± 7.6	38.3 ± 5.8	0.031[b]
PSDI	43.1 ± 7.9	43.9 ± 6.1	41.5± 6.3	0.278[b]
PST	44.9 ± 13.8	45.6 ± 10.6	35.8 ± 7.2	0.029[b]

AO, atypical odontalgia; IT, inflammatory toothache; N/A, not applicable
GCPS, graded chronic pain scale; SCL-90-R, symptom check-list-90-R; SOM, somatization; O-C, obsessive-compulsive; I-S, interpersonal-sensitivity; DEP, depression; ANX, anxiety; HOS, hostility; PHOB, phobic anxiety; PAR, paranoid ideation; PSY, psychoticism; GSI, global severity index; PSDI, positive symptom distress index; PST, positive symptom total
Note) Significant difference were observed in SOM, ANX, and PSY between patient groups (AO and IT) and control group.

Values are given as mean ± SD

[a] P-values were obtained from Fisher's exact test.
[b] P-values were obtained from Kruskal-Wallis test.

Table 3. Intraoral quantitative sensory testing values

	AO (n=14)		IT (n=14)		Control (n=15)
	Non-painful site	Painful site	Non-painful site	Painful site	
CDT (℃)	11.5 ± 7.9	11.9 ± 6.5	10.6 ± 3.8	11.7 ± 5 6	8.9 ± 5.2
WDT (℃)	13.8 ± 5.8	15.8 ± 3.2	16.3 ± 4.1	15.6 ± 4.9	13.4 ± 6.3
TSL (℃)	10.4 ± 9.6	9.7 ± 9.1	17.2 ± 6.4	17.19 ± 8.68	10.6 ± 12.3
CPT (℃)	13.4 ± 5.6	16.6 ± 4.7	14.7 ± 5.7	15.4 ± 4.0	12.3 ± 5.5
HPT† (℃)	49.5 ± 3.3	47.2 ± 5.4	49.8 ± 3.1	50.8 ± 2.2	49.7 ± 3.2
MDT† (℃)	15.1 ± 21.4	19.9 ± 34.7	10.9 ± 7.1	14.9 ± 26.5	23.6 ± 29.8
MPT†(g)	42.8 ± 36.6	42.8 ± 62.5	93.5 ± 85.8	59.3 ± 63.8	89.2± 73.8
MPS†	20.3 ± 17.3	26.5 ± 17.6	16.9 ± 18.3	18.3 ± 16.2	14.5 ± 14.2
WUR†	1.1 ± 0.7	1.1 ± 0.6	1.2 ± 0.6	1.0 ± 0.5	1.0 ± 0.7
VDT (/8)	7.1 ± 0.6	6.6 ± 1.2	6.4 ± 0.9	6.4 ± 0.6	6.5 ± 1.0
PPT†(kPa)	82.6 ± 79.0	55.9 ± 25.9	40.4 ± 13.0	29.0 ± 14.7	59.7 ± 45.9

AO, atypical odontalgia; IT, inflammatory toothache; CDT, cold detection threshold (difference from 32 ℃); WDT, warm detection threshold (difference from 32 ℃); TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity (NRS 0-100); WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold

† HPT, MDT, MPT, MPS, WUR, and PPT values underwent logarithmic transformation to obtain normal distribution.

Table 4. ANOVA of intraoral quantitative sensory testing

Factor	Site (1)		Group (2)		Interaction		Control site
Parameter	F^a	P^a	F^a	P^a	F^a	P^a	P^b
CDT (℃)	0.370	0.548	0.074	0.788	0.066	0.800	0.479
WDT (℃)	0.382	0.542	0.670	0.420	1.823	0.189	0.320
TSL (℃)	0.037	0.848	6.525	0.017	0.046	0.831	0.128
CPT (℃)	3.209	0.085	0.001	0.980	1.363	0.254	0.529
HPT† (℃)	0.676	0.418	3.188	0.086	3.674	0.066	0.976
MDT† (℃)	0.001	0.975	0.135	0.716	0.100	0.755	0.341
MPT†(g)	10.727	0.003	3.756	0.064	0.301	0.588	0.064
MPS†	8.918	0.006	1.200	0.284	0.060	0.809	0.292
WUR†	0.036	0.852	0.127	0.725	0.423	0.523	0.953
VDT (/8)	2.609	0.118	2.318	0.140	3.698	0.065	0.054
PPT†(kPa)	7.570	0.011	13.630	0.001	0.462	0.503	0.097

CDT, cold detection threshold (difference from 32 ℃); WDT, warm detection threshold (difference from 32 ℃); TSL, thermal sensory limen; CPT, cold pain threshold; HPT, heat pain threshold; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity (NRS 0-100); WUR, wind-up ratio; VDT, vibration detection threshold; PPT, pressure pain threshold

Note)
† HPT, MDT, MPT, MPS, WUR, and PPT did log transformations because the original data were not normal distribution.

F^a and P^a-values were obtained from mixed ANOVA between AO and IT groups. Factor 1 is site (painful site and non-painful site) and factor 2 is group (AO and IT)
P^b-values were obtained from one-way ANOVA among AO (non-painful site), IT (non-painful site) and control groups.

Table 5. Comparisons of frequency of positive PHS, DMA, and abnormal z-score

	AO (n=14)	IT (n=14)	Control (n=15)	*P*-value
PHS (%)	3 (21.4)	0 (0)	0 (0)	0.059
DMA (%)	4 (28.6)	3 (21.4)	0 (0)	0.074
abnormal z-score subject (%)	11 (78.6)	2 (14.3)	4 (26.7)	0.005

AO, atypical odontalgia; IT, inflammatory toothache; PHS, paradoxical heat sensations; DMA, dynamic mechanical allodynia

Note1) Positive PHS and DMA mean the non-zero PHS and DMA values. And, if at least one parameter showed the abnormal z-score, they were considered abnormal z-score subjects.
P-values were obtained from Fisher's exact test.

Table 6. Frequency of abnormal Z-score of quantitative sensory testing values

	AO (n=14)				IT (n=14)				Control (n=15)	
	Non-painful site		Painful site		Non-painful site		Painful site			
n (%)	<-1.96	>1.96	<-1.96	>1.96	<-1.96	>1.96	<-1.96	>1.96	<-1.96	>1.96
CDT	4 (29)	0	3 (21)	0	0	0	1 (7)	0	0	0
WDT	0	0	0	0	0	0	0	0	0	1 (7)
TSL	0	1 (7)	0	0	0	0	0	0	0	1 (7)
CPT	0	1 (7)	0	1 (7)	0	1 (7)	0	0	0	0
HPT	0	1 (7))	0	3 (21)	0	1 (7)	0	0	0	1 (7)
MDT*	0	0	1 (7)	2 (14)	0	1 (7)	0	1 (7)	0	0
MPT*	0	2 (14)	0	4 (29)	0	1 (7)	0	0	0	1 (7)
MPS*	0	0	0	0	0	0	0	0	0	0
WUR	0	1 (7))	1 (7)	0	0	0	0	0	1 (7)	0
VDT	0	0	0	0	0	0	0	0	0	0
PPT	1 (7)	0	0	0	0	0	0	0	0	0

Table Source: LossGain Coding system from L. Baad-Hansen et al., *Intraoral somatosensory abnormalities in patients with atypical odontalgia—a controlled multicenter quantitative sensory testing study.* PAIN 154 (2013) 1287–1294

AO, atypical odontalgia; IT, inflammatory toothache; CDT, cold detection threshold (°C, difference from 32 °C); WDT, warm detection threshold (°C, difference from 32 °C); TSL, thermal sensory limen (°C); CPT, cold pain threshold (°C); HPT, heat pain threshold (°C); MDT, mechanical detection threshold (g); MPT, mechanical pain threshold (g); MPS, mechanical pain sensitivity (NRS 0-100); WUR, wind-up ratio; VDT, vibration detection threshold (/8); PPT, pressure pain threshold (kPa)

Table 7. LossGain distribution by LossGain coding system

	Non-painful site and control site					Painful site in AO and IT groups				
	Gain					Gain				
Loss	G0	G1	G2	G3	All	G0	G1	G2	G3	All
AO patients										
L0		3			3		1	1	2	3
L1	2		2		4	1		2	1	4
L2	1				1				1	1
L3								2		2
All	3	3	2	0	8	1	2	4	3	10
IT patients										
L0		1	1		2			3		3
L1					0			1		1
All	0	1	1	0	2	0	0	4	0	4
Control group										
L0		2		1	3					
L2	1				1					
All	1	2	0	1	4					

Table Source: LossGain Coding system from L. Baad-Hansen et al., *Intraoral somatosensory abnormalities in patients with atypical odontalgia—a controlled multicenter quantitative sensory testing study.* PAIN 154 (2013) 1287–1294

Note) LossGain score combines a score of somatosensory loss of function (L0, L1, L2, or L3) with a score of somatosensory gain of function (G0, G1, G2 or G3). The number after the letter L or G indicated that, 1. abnormality is related to the thermal modalities alone, 2. mechanical modalities alone, 3. mixed (thermal and mechanical)

Table 8. Clinical characters according to the presence of abnormal z-score

No.	Gender	Age (years)	Onset	Pain days	NRS	GCPS	LG 1) pain site 2) non-painful site	Pain site	RCT	Medication (after diagnosis)	F/U (months)	Prognosis
A group												
1	F	45	19	160	8	3	1)L1G3 2)L2G0	#45	yes	clonazepam and nortriptyline	6	relief of some symptom NRS: 8→2
2	F	58	21	180	8.5	4	1)L0G3 2)L1G2	#47	yes	nortriptyline, gabapentin, and duloxetine	6	symptoms increase after some relief NRS: 8.5→4→8
3	M	24	8	160	8	4	1)L0G1 2)L0G1	#37	no	clonazepam and duloxetine prn) NSAIDs	22	symptoms increase after some relief NRS: 8→2.5→7 treatment with department of anesthesiology and pain medicine
4	F	33	3	90	7.5	4	1)L3G2 2)L1G0	#35	no	clonazepam	4	relief of symptom NRS: 7.5→1
6	F	54	3	60	6	4	1)L3G2 2)L1G2	#46	yes	[carbamazepine and clonazepam] change to [pregabalin and carbamazepine]	12	symptoms decrease at the beginning of treatment, then no longer decrease NRS: 4 →2~3
14	F	55	7	180	3	4	1)L1G2 2)L0G2	#45	yes	nortriptyline	Only 1st visit	unknown
B-1 group												
7	F	44	6	180	5	3	1)L0G3 2)L0G0	#27	yes	gabapentin	8	pain relief after medication f/u loss NRS: 5→2~3

No.	Gender	Age (years)	Onset	Pain days	NRS	GCPS	LG 1) pain site 2) non-painful site	Pain site	RCT	Medication (after diagnosis)	F/U (months)	Prognosis
8	F	44	3	180	5.5	4	1)L1G2 2)L0G0	#26	yes	nortriptyline and gabapentin	12	pain relief after medication NRS: 5.5→2~3
10	M	27	7	120	4.5	4	1)L0G2 2)L0G0	#26	yes	gabapentin, clonazepam, and carbamazepine	3	symptom improvement NRS: 4.5→2~3 treatment with department of neurology
11	F	49	3.5	100	5	4	1)L1G0 2)L0G0	#27	yes	clonazepam prn) NSAIDs with physical therapy (moist hot pack)	16	initial symptom almost decreased
B-2 group												
5	F	33	4	100	3.5	3	1)L0G0 2)L1G0	#46	yes	nortriptyline	2	almost symptom improvement NRS: 3.5→2
9	F	43	24	85	7	3	1)L0G0 2)L0G1	#16	yes	NSAIDs	3	symptom improvement so she didn't have to take medicine NRS: 7→1~2
C group												
12	F	36	24	90	3.5	3	1)L0G0 2)L0G0	#14	yes	nortriptyline	16	symptom improvement and remaining the state; considering drug dose reduction NRS: 3.5→1~2
13	F	48	18	180	7	4	1)L0G0 2)L0G0	#35	yes	nortriptyline	Only 1st visit	unknown

NRS, numeric rating scale; GCPS, graded chronic pain scale; LG, Loss and Gain coding system; RCT, root canal treatment; F/U, follow up; NSAIDs, non-

steroidal anti-inflammatory drugs

Note 1) No, Serial number given at test; Onset, duration from first appearance of pain to QST day (month); Pain days, persistent pain days during last 6 months; NRS, pain intensity at QST day (0-10); Pain site, main pain area tooth FDI number

Note 2) LossGain score combines a score of somatosensory loss of function (L0, L1, L2, or L3) with a score of somatosensory gain of function (G0, G1, G2 or G3). The number after the letter L or G indicated that, 1. abnormality is related to the thermal modalities alone, 2. mechanical modalities alone, 3. mixed (thermal and mechanical)

Note 3) A group, abnormal QST results on both sides; B group, abnormal QST results on only one side (B-1, abnormal QST results at the painful site; B-2, abnormal QST results at the non-painful site); C group, normal QST results on both sides

Figure legend

Figure 1. Flow diagram

Figure 2.

A. Individual z-score profile at the painful site and control group

B. Individual z-score profile at the non-painful site and control group

Z score = (individual value – mean control group)/SD control group

Normal range: -1.96 < z < 1.96

Above 1.96: gain of function (hyperalgesia, hyperesthesia, allodynia)

Below -1.96: loss of function (hypoalgesia, hypoesthesia)

AO, atypical odontalgia group; IT, inflammatory toothache group

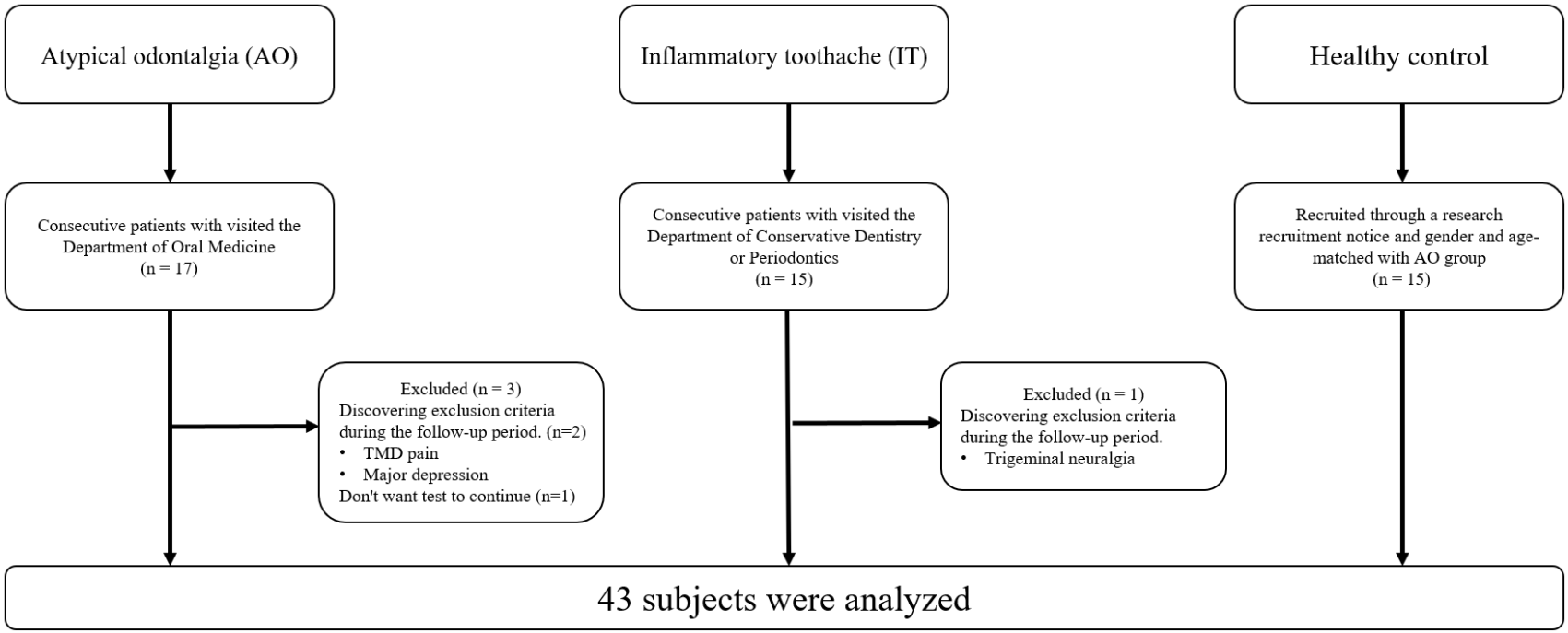
Atypical odontalgia (AO)
Inflammatory toothache (IT)
Healthy control
Consecutive patients with visited the Department of Oral Medicine (n = 17)
Consecutive patients with visited the Department of Conservative Dentistry or Periodontics (n = 15)
Recruited through a research recruitment notice and gender and age-matched with AO group (n = 15)
Excluded (n = 3)
Discovering exclusion criteria during the follow-up period. (n=2)
• TMD pain
• Major depression
Don't want test to continue (n=1)
Excluded (n = 1)
Discovering exclusion criteria during the follow-up period.
• Trigeminal neuralgia
43 subjects were analyzed

Figure 1.

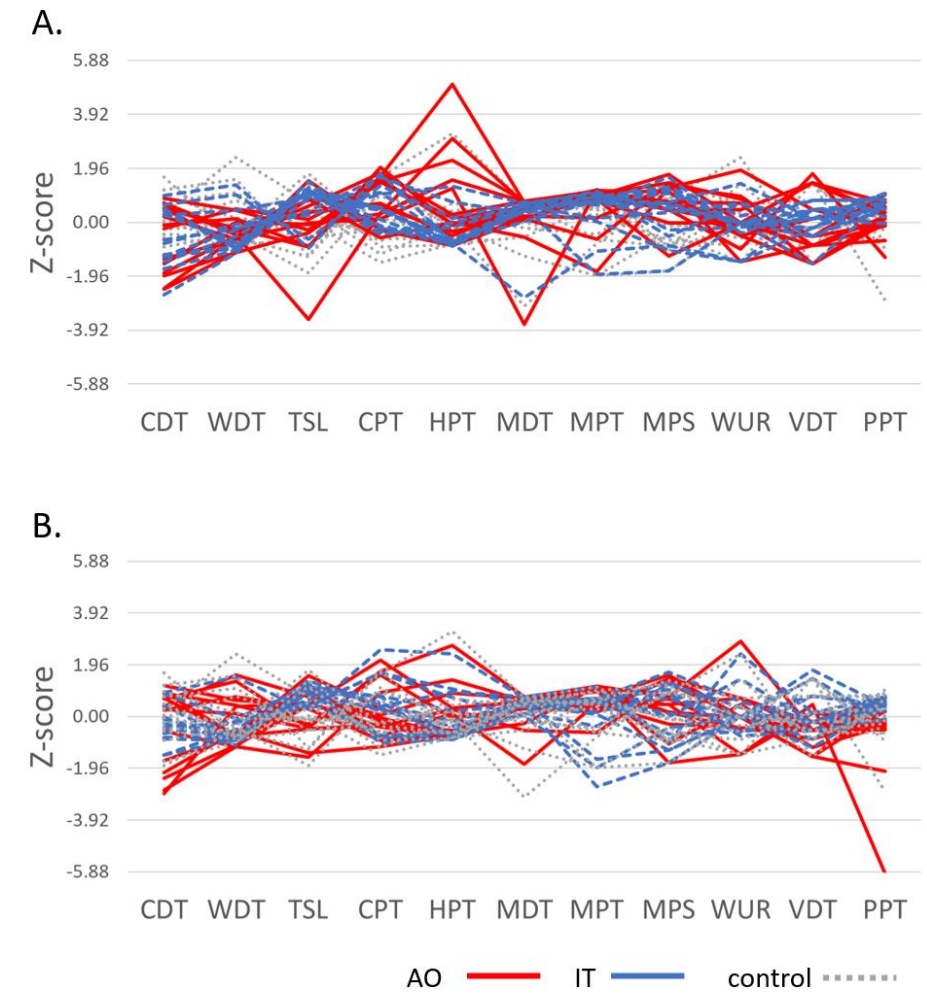
A.
5.88
3.92
1.96
0.00
-1.96
-3.92
-5.88
Z-score
CDT WDT TSL CPT HPT MDT MPT MPS WUR VDT PPT
B.
5.88
3.92
1.96
0.00
-1.96
-3.92
-5.88
Z-score
CDT WDT TSL CPT HPT MDT MPT MPS WUR VDT PPT
AO
IT
control

Figure 2.

국문초록

비정형 및 염증성 치통의 구강내 감각 역치에 관한 비교연구

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장 지 희

비정형 치통은 비치성 치통중의 하나로 염증성 병변이 원인인 치수염이나 치주염으로 인한 치성 통증과는 다르다. 하지만 비정형 치통과 치성 통증 모두 치아와 그 주변조직에서 통증이 발생하고, 비정형 치통의 경우 방사선사진과 같은 객관적인 임상검사에서 뚜렷한 감별진단 소견이 관찰되지 않으므로 잘못된 진단과 비가역적인 치료로 환자와 의사에게 큰 문제를 초래할 수 있다.

정량적 감각검사는 비침습적인 검사방법으로 굵은 유수신경섬유, 가는 유수신경섬유 (A-δ 섬유) 및 무수신경섬유 (C 섬유)의 이상을 모두 평가할 수 있어 통증 환자의 감각 역치 연구에 주로 적용되며, 통증의 종류에 따라 다양한 형태의 특징이 나타나므로 비정형 치통과 염증성 치통을 구분하는 데 적용해 볼 수 있다.

따라서 본 연구의 목적은 비정형 치통, 염증성 치통 및 건강한 대조군 간의 구강 내 정량적 감각검사의 특징을 비교하고 이러한 정량적 감각검사의 특성을 비정형 치통의 진단 및 치료 과정에 적용하는 방법을 찾는 것이다.

본 연구에서는 총 43 명의 대상자 (비정형 치통 14 명, 염증성 치통 14 명, 건강한 대조군 15 명)의 정량적 감각검사 결과 및 임상 증상을 분석하였다. 정량적 감각검사는 German Research Network on Neuropathic Pain protocol 을 기반으로 하되 일부 방법을 수정하여

통증이 있는 치아와 대조 치아의 부착 치은에서 수행하여 그룹간 차이를 통계적으로 비교하였으며, 정량적 감각검사의 비정상 여부는 z-score 로 평가하였다.

기계적 통증 역치(mechanical pain threshold, p=0.003), 기계적 통증 민감도 (mechanical pain sensitivity, p=0.006) 및 압력 통증 역치 (pressure pain threshold, p=0.011)에서 유의한 차이를 보였으며, 비정상 z-score 비율은 비정형 치통 군에서 가장 높았다 (비정형 치통, 78.6%; 염증성 치통, 14.3%; 건강한 대조군, 26.7%). 정량적 감각검사 항목 중 비정형 치통 그룹에서 가장 높은 빈도로 비정상 소견을 보인 것은 기계적 통증 역치였으며, 비정형 치통 그룹에서는 통증 부위 뿐만 아니라 통증이 없는 부위에서도 비정상 범위의 z-score 비율이 다른 군에 비하여 높았다.

이러한 결과를 통하여 비정형 치통 환자군이 염증성 치통이나 건강한 대조군과 구별되는 구강내 정량적 감각검사 특징을 가지고 있다는 것을 확인할 수 있었다. 다만, 체성감각 이상소견을 보이지 않는 비정형 치통 환자도 있으므로 이를 임상적으로 활용하기 위해서는 정량적 감각검사 결과와 다른 임상적 특징을 함께 활용해야 하며, 위의 결과와 추가 연구를 통하여 QST 와 AO 의 임상적 특성에 기반한 임상 진단 지침을 수립할 수 있을 것이다.

주제어: 비정형 치통, 정량적 감각검사, 치통, 통증 역치, 체성감각 민감도

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