UNIVERSIDADE DE SÃO PAULO
FACULDADE DE ODONTOLOGIA DE BAURU

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Comparative Evaluation of Somatosensory Mechanisms involved in Orofacial Somatic, Visceral and Neuropathic Pain.

Avaliação Comparativa dos Mecanismos Somatossensoriais Envolvidos na Gênese das Dores Orofaciais de Origem Somática, Visceral e Neuropática.

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Orientador: Prof. Dr. Paulo César Rodrigues Conti

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Sam Harris

ABSTRACT

Comparative Evaluation of Somatosensory Mechanisms involved in Orofacial Somatic, Visceral and Neuropathic Pain.

Orofacial pain conditions can be classified into somatic, visceral or neuropathic pain. Somatic pain is triggered by a noxious stimulus generally inducted by peripheral traumas, such as dental implants surgeries (IMP). Visceral pain initiates within internal body tissues and is normally triggered by inflammation, as in inflammatory toothaches (IT). The third condition is neuropathic pain, which results from persistent injury to the peripheral nerve as in Atypical Odontalgia (AO). The aims of this study were: 1- to investigate somatosensory abnormalities, using mechanical, painful, and electrical quantitative sensory testing (QST), in somatic (IMP patients), visceral (IT) and neuropathic pain (AO); 2- to quantify how accurately QST discriminates an IT or AO diagnosis; and 3- to investigate the influence implant surgeries or pulpectomy may have on somatosensory system and sensory nerve fibers. Sixty subjects were divided in three groups: IMP (n = 20), IT (n = 20) and AO group (n = 20). A sequence of five QSTs and the Conditioned Pain Modulation Test (CPM) were performed one month and three months after dental implant surgery (IMP group) or pulpectomy (IT group). AO group was evaluated only at baseline. QST comprehended Mechanical Detection Threshold (MDT), Mechanical Pain Threshold (MPT), Dynamical Mechanical Allodynia (DMA), Current Perception Threshold (CPT) for A-beta (frequency of 2000Hz), A-delta (250Hz) and C fibers (5Hz) and Temporal Summation Test (TS). “Z” score transformation were applied to the data, and within and between groups were statistically analyzed using two-way ANOVA. In addition, the receiver operating characteristic curve analysis, diagnostic accuracy, sensitivity, specificity, likelihood ratios, and diagnostic odds ratio of QSTs were calculated (α = 5%). The findings of this study proved that: 1- loss of function for touch threshold and electrical threshold of C fibers is present in inflammatory toothache; 2- allodynia, hyperalgesia, gain of function for touch and pain thresholds and impaired pain modulation is detected in atypical odontalgia; 3- some QSTs may be used as complementary tests in the differential diagnosis of atypical odontalgia and inflammatory toothache with strong accuracy; 4- the most accurate QSTs for differential diagnosis between subjects with AO and IT were MDT, MPT and DMA where touch threshold forces

> 1 g/mm2 and pain threshold forces > 10g/mm2 can be used to accurately discriminate AO from IT; and 5- no somatosensory modification is found after implant surgery and reduced electrical threshold in C fiber is found for patients with inflammatory toothache after 3 months of pulpectomy.

Keywords: Dental Implants; Somatic Pain; Dental Pulp Diseases; Visceral Pain; Pulpectomy; Neuropathic Pain; Somatosensory Disorders; Quantitative Sensory Testing; Diagnostic Accuracy.

RESUMO

Avaliação Comparativa dos Mecanismos Somatossensoriais Envolvidos na Gênese das Dores Orofaciais de Origem Somática, Visceral e Neuropática.

As dores orofaciais podem ser classificadas em dores somáticas, viscerais ou neuropáticas. A dor somática está relacionada a um estímulo nocivo evidente, geralmente associada a um trauma periférico, como por exemplo, nas cirurgias de implantes (IMP). As dores viscerais têm origem dentro dos órgãos e cavidades internas do corpo e são ativadas pela inflamação, como no exemplo da dor de dente do tipo Pulpite Aguda (PA). A terceira condição é a dor neuropática, que resulta de uma lesão persistente ao nervo periférico, como ocorre na Odontalgia Atípica (OA). Os objetivos deste estudo foram: 1- avaliar as alterações somatossensoriais, por meio do uso de Testes Sensoriais Quantitativos (TSQ) mecânicos, dolorosos e elétricos em dores somáticas (pacientes IMP), viscerais (PA) e neuropáticas (OA); 2- quantificar a acurácia dos TSQs na descriminação diagnóstica de uma PA ou OA; e 3- investigar alterações somatossensoriais e nas fibras nervosas sensoriais após cirurgia de instalação de implantes dentários ou pulpectomia. Sessenta sujeitos foram divididos em três grupos: IMP (n = 20), PA (n = 20) e OA (n = 20). Uma sequência de cinco TSQs e o teste de Controle da Modulação da Dor (CMD) foram realizados um mês e três meses após cirurgia de implantes (grupo IMP) ou pulpectomia (grupo PA). No grupo OA, os testes foram realizados somente uma vez no início do estudo. Os TSQs englobaram o Limiar de Detecção Mecânica (LDM), Limiar de Dor Mecânica (LDoM), Alodinia Mecânica Dinâmica (AMD), Limiar de Percepção de Corrente (LPC) para fibras A-beta (frequência de 2000Hz), A-delta (250Hz) e C (5 Hz), e o teste de Somação Temporal (ST). A transformação em escores de "Z" foi aplicada aos dados, e diferenças intra e inter-grupos foram analisadas usando ANOVA de medidas repetidas. Ainda, a acurácia diagnóstica dos TSQs foi medida por meio da sensibilidade, especificidade, razão de verossimilhança e razão de chances para diagnóstico (α = 5%). Os resultados deste estudo mostraram que: 1- perda da função em limiar táctil e limiar elétrico de fibras C está presente na Pulpite Aguda; 2- alodinia, hiperalgesia, ganho de função nos limiares de tato e de dor, e modulação da dor prejudicada são encontrados em pacientes com odontalgia atípica; 3- alguns TSQs podem ser usados como testes

diagnósticos complementares ao diagnóstico diferencial entre PA e OA; 4- os TSQs com maior acurácia para o diagnóstico diferencial entre indivíduos com PA e OA foram LDM LDoM e AMD, onde uma força maior que 1 g/mm2 para limiar de tato e maior que 10 g/mm2 para limiar de dor podem ser usados com precisão; e 5- nenhuma alteração somatossensorial é encontrada após cirurgia de implantes e uma redução no limiar elétrico em fibras C é encontrado em pacientes com PA após 3 meses da pulpectomia.

Palavras-chave: Implantes Dentários; Dor Somática; Doenças da Polpa Dentária; Dor Visceral; Pulpectomia; Dor Neuropática; Distúrbios Somatossensoriais; Teste Sensorial Quantitativo; Acurácia Diagnóstica.

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1 Introduction

1 INTRODUCTION

Pain may be defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (OKESON, 2005; LEEUW., 2008). Orofacial pain refers to soft and mineralized associated tissues of head, face, and neck, and can be defined as pain and dysfunction affecting sensory and motor transmission in the trigeminal nervous system (LEEUW., 2008).

Pain seriously affects millions of people worldwide and its pathophysiologic mechanisms involve a sequence of events from peripheral to central courses (GRAVEN-NIELSEN et al., 2010; FORNASARI, 2012). First, noxious stimulus is transformed into action potentials from peripheral nerve fibers and are transferred to the central nervous system (CNS) for their cortical integration and interpretation by the cerebral cortex as pain (ROCHA, 2007). From the peripheral region, primary afferent neurons conduct nerve impulses toward the CNS (PERTES, 2005). These primary afferent neurons have axons of different diameters and its thickness plays a role on impulse conduction speed. These afferent fibers may be sub-divided into A-alpha fibers (diameter: 13-20μm, conduction speed: 70-120m/s), A-beta (diameter: 6-13μm, conduction speed: 40-70m/s), A-delta (diameter: 1-5μm, conduction speed: 5-15m/s), and C fibers (diameter: 0,5-1μm, conduction speed: 0,5-2m/s) (GUYTON, 2002; OKESON, 2005). This kind of fiber is also related to somatosensory transmission; A-alpha and A-beta fibers lead to proprioceptive and touch stimuli, while A-delta and C fibers conduct painful stimuli (ROCHA, 2007).

Essentially, painful phenomenal can be classified into acute or chronic pain or, more specifically, into somatic, visceral, or neuropathic pain (OKESON, 2005; ROCHA, 2007). Acute pain is usually related to tissue changes such as damage or trauma (AUVENSHINE, 2007). It is an unpleasant sensation of short duration, limited to normal healing time of initiators or etiological factors (LEEUW., 2008). Acute pain is usually initiated by an identifiable tissue damage and plays a role in protecting the body over any impending danger (PERTES, 2005).

Acute pain may be completely resolved with conventional therapy, but when it persists, it often becomes chronic and complex (LEEUW., 2008). Chronic pain is

more influenced by the CNS and symptoms become less local and more widespread (OKESON, 2000). The mechanisms involved in pain genesis and its chronicity are still poorly understood; besides, studies have demonstrated that chronicity processes are related to abnormal reduced nerve thresholds and changes in genetic expression (OKESON, 2005; ROCHA, 2007). Chronic pain is then triggered by non-painful stimuli, requiring minimal awareness nociceptive impulses. In this process, patients may experience somatosensory abnormalities expressed clinically by allodynia, hyperalgesia, and pain exacerbation by thermal, mechanical, and/or chemical stimuli (LIST; LEIJON; SVENSSON, 2008; ZAGURY et al., 2011) (BAAD-HANSEN, 2008).

Somatic pain is related to an obvious noxious stimulus and may affect mostly superficial and deep tissues such as bone and dentoalveolar tissues (LEEUW., 2008). Somatic pain is more precise and is generally inducted by peripheral traumas, such as surgeries, installation of dental implants, or temporomandibular disorders (OKESON, 2005; ROCHA, 2007).

Visceral pain originates within internal organs and cavities of the body and is generally activated by inflammation. Visceral pain is associated with diffuse discomfort, possible swelling, and affects mainly abdominal and pelvic viscera. In dentistry, the dental pulp is also considered a viscera and acute pulpitis (AP) may be an example of visceral pain (OKESON, 2005; ROCHA, 2007).

Neuropathic pains occur in the absence of any obvious noxious stimulus and are possibly associated with a nerve lesion (WODA; PIONCHON, 1999; PERTES, 2005; LEEUW., 2008). Neuropathic pain, as well as chronic pain conditions, are related to peripheral and central sensitization, associated to some sort of somatosensory abnormality (LIST; LEIJON; SVENSSON, 2008). Specifically in dentistry, there is a subclassification of neuropathic pain known as Atypical Odontalgia (AO), which is a continuous pain of moderate to severe intensity, localized in dentoalveolar region, not caused by another disease, identified through clinical, dental, neurological, and image examinations (CAMPBELL; PARKS; DODDS, 1990; GRAFF-RADFORD; SOLBERG, 1992; VICKERS et al., 1998; NIXDORF et al., 2012).

Studies have demonstrated that AO patients have difficulties to accept their pain condition, related to multiple and repetitive ineffective dental procedures the patients undergo (NIXDORF et al., 2012; GAUL; ETTLIN; PFAU, 2013; PIGG et al.,

2013; TARCE; BARBIERI; SARDELLA, 2013). Furthermore, studies have identified a number of mechanisms as potential factors contributing to the etiology and pathophysiology of such entity. Trauma in orofacial structures, like periodontal surgery, endodontic therapy, apicectomy, traumatic injury, tooth extraction, or even anesthetic blocks may alter the nerve continuity, which may creates a deafferentation process and reproduce a persistent neuropathic pain (MARBACH, 1993a; MATWYCHUK, 2004; MELIS; SECCI, 2007). AO occurs in 3 to 6% of patients who receive dentistry management (MARBACH et al., 1982; CAMPBELL; PARKS; DODDS, 1990; MARBACH, 1993b, 1993a; VICKERS et al., 1998; MATWYCHUK, 2004; MELIS; SECCI, 2007).

Somatosensory abnormalities may be assessed using Quantitative Sensory Testing (QST), which comprehensively evaluates the nervous system (BAAD-HANSEN, 2008; PIGG et al., 2010). QST uses mechanical (static or dynamic), thermal, electrical, and chemical tests. The static mechanical test detects thresholds to innocuous and/or harmful stimuli, and the dynamic mechanical test explores allodynia and temporal summation. Thermal detection thresholds evaluate innocuous and/or harmful thermal stimuli (cold, warm, or hot) (ROLKE et al., 2006a; ROLKE et al., 2006b; SVENSSON et al., 2011).

Besides mechanical touch QST which evaluates nerve conduction of A-beta, A-delta, and C fibers, another sensitive and reliable QST may be performed through somatosensory Current Perception Threshold testing (CPT). CPT may be very helpful for diagnosis of peripheral nerves damage. Nerve conduction may be assessed with the aid of a Neurometer®, a painless electrodiagnostic sensory nerve testing equipment (Baltimore, Maryland, USA). Therefore, it is possible to obtain quantitative measurements of direct sensory nerve function. The eletrodiagnostic test identifies nerve conduction threshold through an automated painless procedure (OGURA et al., 2006; CAISSIE et al., 2007; OGURA et al., 2007).

The literature is clear about the possibility of stimulating each of the specific sensory fibers (A-beta, A-delta, and C fibers). Each type of sensory fiber responds to a specific frequency of electrical stimulation: 2000 Hz specifically stimulates A-beta, 250 Hz stimulates A-delta and 5 Hz C fibers (OGURA et al., 2006; CAISSIE et al., 2007; OGURA et al., 2007).

Noxious stimuli cause peripheral and CNS changes; however, the actual mechanisms of pain conduction and the involvement of the peripheral fibers are still poorly understood. Therefore, a complete quantitative sensory evaluation of nerve fibers in patients with different pain classifications, such as somatic, visceral, and neuropathic pain, is essential for assimilation of these distinctive painful phenomena.

Based on the above, the aims of this study were: 1 - to investigate somatosensory abnormalities, using mechanical, painful, and electrical quantitative sensory testing (QST), in somatic (IMP patients), visceral (IT), and neuropathic pain (AO); 2 - to quantify how accurately QST discriminates an IT or AO diagnosis; and 3 - to investigate the influence implant surgeries or pulpectomy may have on somatosensory system and sensory nerve fibers.

2 Articles

2 ARTICLES

The articles presented in this Thesis were written according instructions and guidelines for articles submission of the *Journal of Endodontics* (Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain) and *Clinical Oral Implants Research* (Somatic, Visceral and Neuropathic Pain Present Different Somatosensory Profiles).

2.1 ARTICLE 1

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain.

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ABSTRACT

Differential diagnosis between inflammatory toothache (IT) and intraoral neuropathic pain is challenging. The aim of this diagnostic study was to quantify somatosensory function of subjects with IT (acute pulpitis), atypical odontalgia (AO, intraoral neuropathic pain) and healthy volunteers, and to quantify how accurately Quantitative Sensory Testing (QST) discriminates an IT or AO diagnosis. The sample consisted of 60 subjects equally divided (n = 20) into three groups: 1) IT, 2) AO, and 3) Control. A sequence of four Quantitative Sensory Tests (QSTs) was performed over the dentoalveolar mucosa in the apical maxillar or mandibular area: Mechanical Detection Threshold (MDT), Pain Detection Threshold (PDT), Dynamical Mechanical Allodynia (DMA), and Temporal Summation (TS). One-way analysis of variance, Tukey's post hoc analyses, and the "Z" score transformation were applied to the data. In addition, the receiver operating characteristic curve analysis, diagnostic accuracy, sensitivity, specificity, likelihood ratios, and diagnostic odds ratio of QSTs were calculated (α = 5%). The results showed that somatosensory abnormalities were found for the AO group, which is consistent with low detection threshold to touch and pain, and the presence of mechanical allodynia. For the IT group, no somatosensory abnormality was observed when compared with the control group. The most accurate QST to discriminate the diagnostic differences between IT and healthy individuals is the PDT. The diagnostic differences between AO and healthy individuals and between IT and AO are best discriminated with MDT, PDT, and DMA. We concluded that the proposed QSTs may aid in the differential diagnosis between IT and AO with strong accuracy and may be used as complementary diagnostic tests.

Key words: Inflammatory Toothache; Intraoral Neuropathic Pain; Persistent Pain; Quantitative Sensory Testing; Diagnostic Accuracy.

INTRODUCTION

Traumatic injuries such as endodontic therapy, apicectomy, tooth extraction, tooth preparation, or inferior alveolar nerve block may damage nerve fibers and disrupt peripheral afferent nerve impulses (1-4). Due to a possible lack of healing on the apical root tissues after some of these traumatic injuries, 3–6% of patients who

undergo endodontic management may experience chronic persistent pain, which is classified as a neuropathic condition (3-5).

Persistent pain after root canal therapy may be related to odontogenic and nonodontogenic etiologies (6, 7). Odontogenic causes result from untreated or incompletely obturated root canal, root fracture, failure of the apical seal, or pain referred from an adjacent tooth or structure (6). Nonodontogenic causes are trigeminal neuralgia, maxillary sinusitis, temporomandibular disorders, tension-type headaches, and atypical odontalgia (AO) (3, 5, 8-10). AO is a continuous neuropathy of moderate to severe intensity, occurs in the orofacial region and is localized to the dentoalveolar region, is not caused by another disease, and can be identified by clinical, dental, neurological, and image examination (1, 2, 8, 11).

Although infrequent, when AO cases manifest in the dental office, they are often treated through numerous dental procedures with no pain relief (2, 12). AO patients have difficulties accepting their pain condition because of misdiagnoses and repeated ineffective dental procedures that the patients endure (8, 13-15). The differential diagnosis between intraoral AO and inflammatory toothache (IT) is challenging. In patients with AO, pain is continuous, unchanging over weeks or months, with an absence of any local or systemic cause. Furthermore, local tooth provocation does not promote consistent alterations in pain, and repeated endodontic or dental procedures fail to relieve pain (10, 16-18).

The sensory abnormalities such as allodynia, hyperalgesia, and pain exacerbation by thermal, mechanical, and/or chemical stimuli are frequent in AO patients (9, 19). Quantitative Sensory Testing (QST) methods are appropriate tools to access these abnormalities (9, 20). QST comprehensively evaluates the nervous system and may involve static or dynamic mechanical, thermal, electrical, and chemical tests (12, 21). Static mechanical tests detect thresholds to innocuous and/or harmful stimuli, whereas dynamic mechanical tests explore allodynia and temporal summation; thermal detection thresholds evaluate innocuous and/or harmful thermal stimulus (cold, warm, or hot) (22-24). Although QSTs were proposed to be used as diagnostic tools (21, 23), their accuracy for differential diagnosis between intraoral neuropathic pain and inflammatory toothache has not yet been tested.

Based on the above, the aim of this study was to quantify the somatosensory function of subjects with IT, AO, and healthy volunteers, to quantify how accurately

QSTs discriminate tooth pain as an IT or AO, and to learn if QSTs may assist the endodontic specialist in the assessment and differential diagnosis of such conditions.

SAMPLE AND METHODS

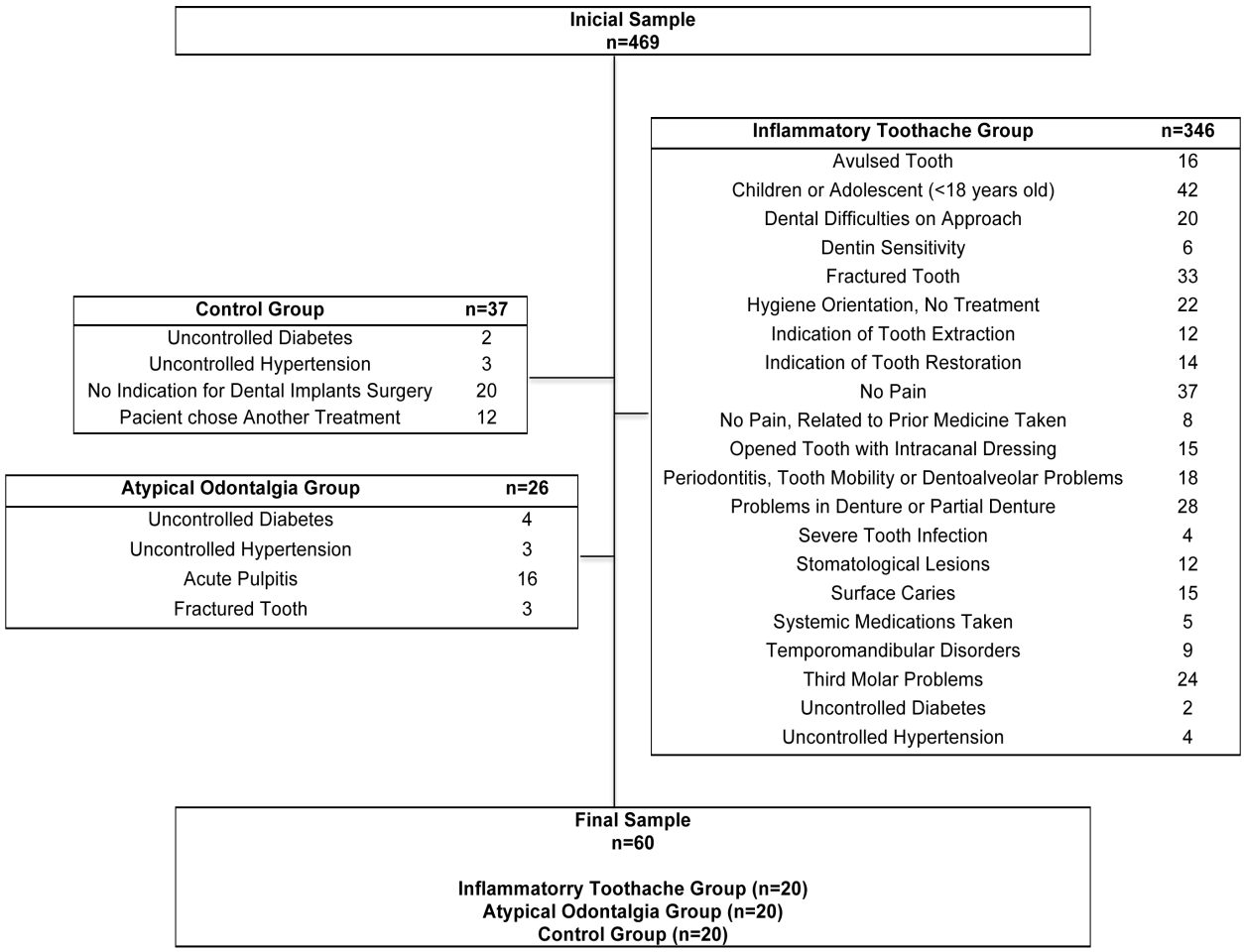
Study Population

This diagnostic study was conducted from December 2013 to November 2014. Subjects were recruited at three different services at the Bauru School of Dentistry, University of São Paulo, Brazil: 1) Emergency and Screening Service (Stomatology Department), 2) Orofacial Pain Service (Prosthodontics Department), and 3) Integrated Service of Oral Rehabilitation and Dental Implants (Prosthodontics Department). This study was conducted in accordance with Helsinki guidelines and was approved by the local ethics committee (Certificate of Presentation for Ethical Consideration #19840113.2.0000.5417). Written informed consent was obtained from all participants.

Prior to study enrollment, all subjects underwent anamnesis and physical examination. Anamnesis included history taken about personal data, chief complaint, and medical and dental history. The dental history included questions related to the main complaint, pain severity and quality, worsening and improvement factors, accompanying symptoms, and previous treatments.

The initial sample consisted of 469 subjects, then 346 subjects were excluded from the IT group, 26 from the AO group, and 37 from the control group (C). A flowchart of the exclusion criteria for the selected subjects can be observed in Figure 1. All the subjects were then eligible and agreed to initiate the study.

Figure 1: Flowchart of exclusion criteria for the selected subjects.



The IT group consisted of 20 subjects (14 women, 35.1 ± 8.68 years old) with acute pulpitis. Individuals were assessed following the mandatory diagnosis criteria (10, 16):

- Acute pain in dental pulp;
- Pain related to a dental inflamed pulp;
- Moderate or severe intensity;
- Pain intensity could vary over time, passing through asymptomatic periods;
- Pain could be caused by a stimulus or occurred spontaneously;
- Pain was intermittent or continuous;
- Pain was affected by time or body position.

Periapical radiography was always used for differential diagnosis. The IT group consisted solely of cases with acute pulpitis; cases with apical periodontitis were excluded. Individuals with previous use of analgesics and/or anti-inflammatory agents

were included in the study. Subjects were excluded if they had no pain at the time of evaluation, or if they were taking analgesics and had residual pain <50 mm on a Visual Analogue Scale (VAS).

The AO group consisted of 20 subjects (15 women, 57.84 ± 13.42 years old) diagnosed with intraoral neuropathic pain by orofacial pain specialists (A.L.P., Y.M.C., J.S.B.) during the first patient consultation, which was prior to enrollment in the study. Subjects with AO were diagnosed using currently published and accepted criteria:(8, 10, 16)

- Persistent pain present at least 8 h/day, ≥15 days per month for ≥ 3 months;
- Localized in the dentoalveolar area, where the maximum pain is defined within an anatomical area;
- Not caused by another disease or disorder, through dental and neurological examination and imaging.

A Computed Tomography Cone-Beam (CBCT) image was requested for patients when any diagnostic doubt remained after the complementary exams and periapical radiographs (25). Patients taking pain medications were also included in this group.

The control group consisted of 20 healthy subjects (14 women, 50.22 ± 6.67 years old) without painful dental pathology at the time of assessment. Individuals could not have had previously received a neuropathy diagnosis and needed to be free from any type of pain and dental pathology for at least 6 months (26).

For the three groups, the subjects were excluded in cases of systemic conditions such as uncontrolled hypertension, uncontrolled diabetes, leprosy, and/or disabling neurological and psychological disorders, previously diagnosed by a qualified physician (27).

Study Design

Subjects from all groups were comfortably installed in a quiet room (room temperature 22–25°C) and a sequence of four QSTs was performed at baseline. QSTs were applied over the dentoalveolar mucosa in the apical area of maxillar or mandibular regions. This dentoalveolar area was approximately 10 mm^2. For the IT group, tests were performed in the toothache apical area on the dentoalveolar region. For the AO group, tests were applied in the painful dentoalveolar area. For the control group, QSTs were performed in a random dentoalveolar area.

A trained researcher (A.L.P.) executed QSTs, testing participants through the entire procedure to ensure consistency. The duration of all exams for each person was approximately 45 min.

The assessment of pain intensity at baseline was recorded using a VAS (22). The VAS consisted of a horizontal line, 100 mm long, anchored by word descriptors at each end; the far left read “no pain” and the right read “worst pain imaginable.” Patients were requested to make a vertical mark on the VAS line at the point that they felt represented their perception of their current pain state (28).

The sequence explained below was the order of QST used in this study:

- *Mechanical Detection Threshold (MDT)*

This test used von Frey monofilaments that were adapted to define tactile fiber thresholds (29). Twenty von Frey nylon monofilaments with different diameters were used and calibrated to exert specific forces when bending. Monofilament force varied from 0.008 g/mm^2 to 300 g/mm^2 (29).

Each monofilament was applied perpendicularly to the dentoalveolar region, and a slight pressure was applied until the filament bent. The method of limits was used in which approximately 6–8 ascending/descending stimuli were applied, and the average force was calculated (30). MDT estimated the light touch detection threshold, i.e., the lowest von Frey nylon monofilament force that individuals were able to appropriately detect (29).

- *Pain Detection Threshold (PDT)*

This test estimated the lowest von Frey filament force for which subjects reported a painful sensation. The method of limits used in MDT was also applied for PDT. Patients identified the filament, and their pain intensity was recorded using VAS (22).

- *Dynamical Mechanical Allodynia (DMA)*

A slight vibration of a cotton swab was applied to the alveolar mucosa for 10 s and the pain intensity was recorded with VAS (22). The stimulus area was approximately 2 mm^2 for the cotton swab.

- *Temporal Summation (TS)*

This test was conducted using repeated application of the 5.46 g von Frey filament in a continuous 30-s sequence (force of 26 g/mm^2, approximately 1 stimulus/s). Subjects rated the pain intensity four times on an NRS (numeric rating scale) at 1 s, 10 s, 20 s, and 30 s. The NRS is a 0-10 point scale, and patients were

asked to rate their pain from 0 to 10. A score of 0 indicated “no pain,” and 10 was the “worst pain imaginable” (31, 32). TS was determined using subtraction calculations (painfulness train of 30 seconds of pinprick stimulations minus the first second of pinprick) and a single value was established.

Data reduction and analysis

The “Z” score transformation was performed to standardize the QST values and obtain a single value for each test for comparison with the control subjects (24).

(“Z” score calculation = $X_{\text{single patient}} - \text{Mean}_{\text{controls}}/\text{Standard Deviation}_{\text{controls}}$).

In this analysis, the “X” value was used for the IT group and the AO group, and the controls were healthy subjects (control group).

QST values from each patient were transformed to “Z” scores as described by Rolke et al, 2006 (24). A score >1.96 or <−1.96 fell outside the 95% confidence interval of the mean reference value, and these scores were considered sensory abnormalities. Abnormalities were subsequently categorized as a sensory gain or sensory loss.

All analyses were performed on a personal computer using STATISTICA for Windows, version 10.0 (StatSoft Inc., Tulsa, OK, USA) and MedCalc (MedCalc Software, Ostend, Belgium). QST statistical analysis was performed using a one-way analysis of variance (ANOVA). QST parameters that were not normally distributed were analyzed after log transformation. When appropriate, Tukey’s post hoc analyses were used to determine significant differences between groups.

Receiver operating characteristic (ROC) curve analysis (33) was used to quantify how accurately QSTs discriminate a tooth pain as IT or AO. Therefore, diagnostic accuracy (area under the curve, AUC), sensitivity, specificity, likelihood ratios (LR), and diagnostic odds ratio (DOR) of QSTs were calculated (34). The results were considered significant at a level of 5%.

RESULTS

Patient characteristics, such as age, gender, the evaluated areas, and pain intensity can be observed in Table 1.

Table 1: Within-groups characteristics.

	Inflammatory Toothache Group		Atypical Odontalgia Group		Control Group	
Age (SD)	35.1 (8.68)		57.84 (13.42)		50.22 (6.66)	
Gender	14 W	70%	15 W	75%	14W	70%
	6 M	30%	5 M	25%	6 M	30%
Evaluated Region	0 Incisor	0%	2 Incisor	10%	2 Incisor	10%
	2 Canine	10%	3 Canine	15%	2 Canine	10%
	4 Premolar	20%	7 Premolar	35%	10 Premolar	50%
	14 Molar	70%	8 Molar	40%	6 Molar	30%
Pain Intensity (SD) in a VAS	68.6 (22.99)		62.5 (23.47)		0 (0)	

Legend: SD: Standard Deviation; W: Women; M: Men; VAS: Visual Analogue Scale.

In the IT group, all patients were nonsmokers, and only one individual had hypertension controlled with medications. Due to strong and sharp pain that affects patients with IT, five subjects had previously taken painkiller drugs (three analgesic and muscle relaxant formulation and two Dipyrone®). However, no improvement in pain intensity was observed.

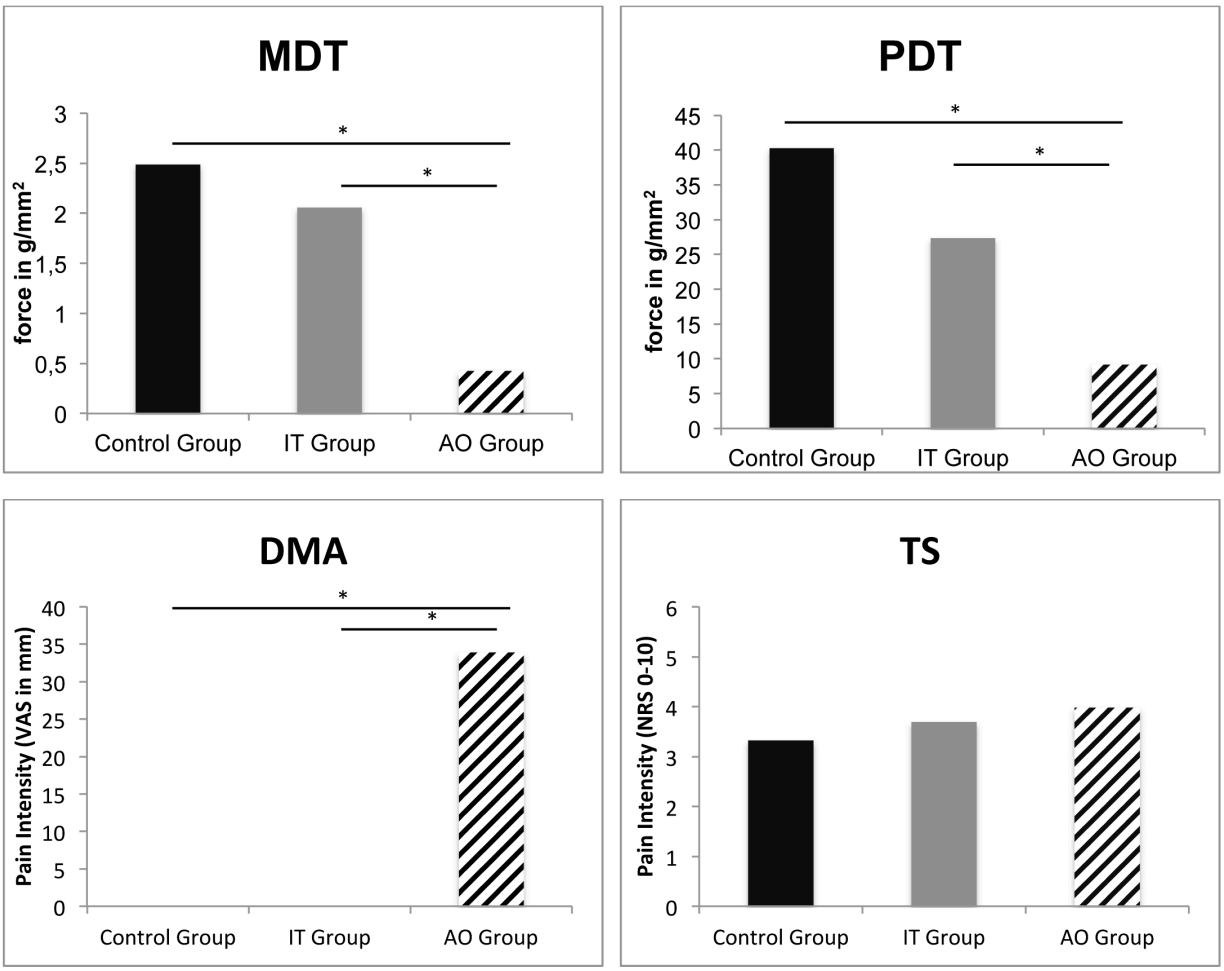
In the AO group, three subjects mentioned cholesterol problems, eight reported controlled hypertension, two arthritis and/or osteoarthritis, two controlled diabetes mellitus type II, and one hypothyroidism. Prior medication for pain and associated symptoms was used by six subjects and involved 25 mg amitriptyline® (1 subject), 300 mg gabapentin® or more (6 subjects), ≥200 mg Carbamazepine® (three subjects), 30 mg Duloxetine® (2), and 25 mg Topiramate® (1). However, pain intensity had not relief in any of the 6 subjects. CBCT was performed to assist in the differential diagnosis of 13 AO subjects. CBCT was required due to the visualization difficulty of possible dental or bone alterations after conventional and panoramic radiographs.

Between-groups QST Differences

The results of all tests are shown in Figure 2.

Figure 2: QST data for all groups.

Legend: MDT: Mechanical Detection Threshold; PDT: Pain Detection

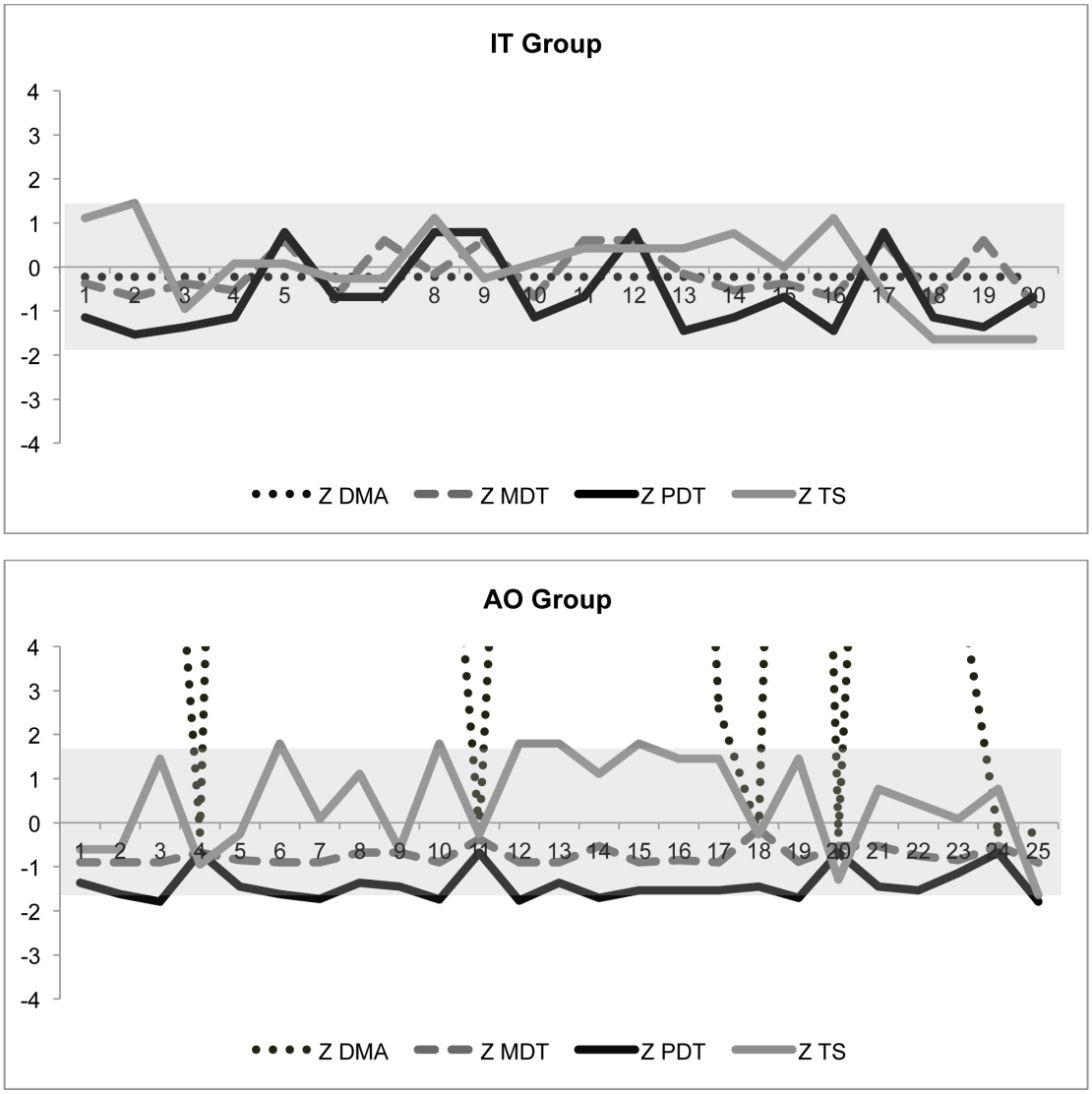


Threshold; DMA: Dynamical Mechanical Allodynia; TS: Temporal Summation; IT: Inflammatory Toothache; AO: Atypical Odontalgia; VAS: Visual Analogue Scale; NRS: Numeric Rating Scale; * $p<0.05$.

Somatosensory abnormalities were detected in the AO group, consistent with low detection threshold to touch and pain, and the presence of mechanical allodynia, when compared to the control group and when compared to IT group ($p < 0.05$). The IT group had no somatosensory abnormalities.

Figure 3 shows the Z Score for the IT and AO groups, when compared with control group. No sensory gain or loss was found for the IT group. A gain in function for dynamical tests as DMA and TS was perceived in the AO group.

Figure 3: Z Score Transformation values for all Quantitative Sensory Testing in IT and AO group compared to Control group.



Legend: Z: Z Score Transformation; DMA: Dynamical Mechanical Allodynia; MDT: Mechanical Detection Threshold; PDT: Pain Detection Threshold; TS: Temporal Summation.

QST Diagnostic Accuracy

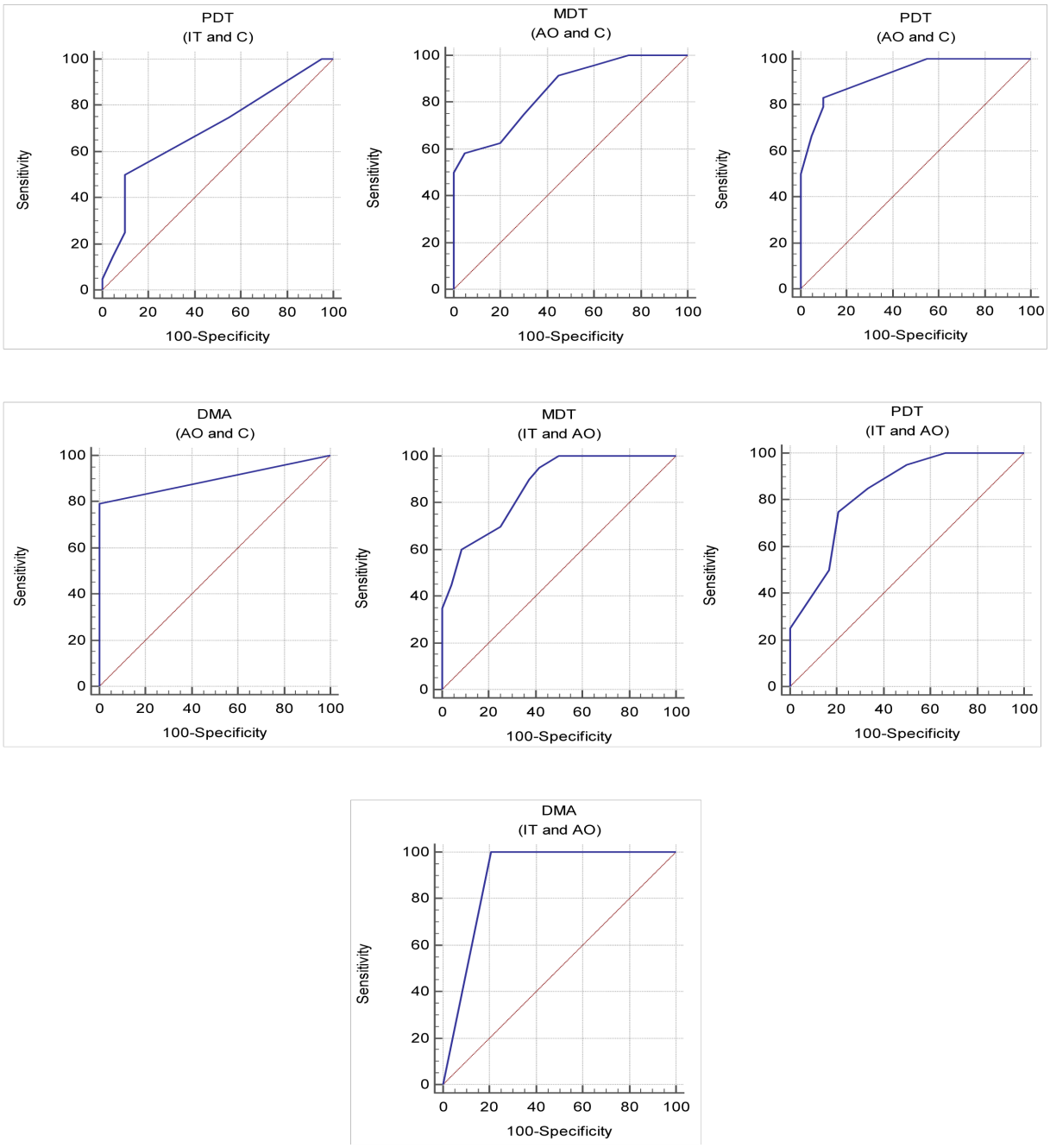
The results of the ROC analysis, with a between-group response and discrimination, are displayed in Table 2 and Figure 4.

Table 2: Calculation of the likelihood ratios (LR), area under the curve (AUC) of Receiver Operator Characteristic test (ROC) and Diagnostic Odds Ratio (DOR) for QSTs of Inflammatory Toothache, Atypical Odontalgia Group and Control Group.

Legend: MDT: Mechanical Detection Threshold; PDT: Pain Detection Threshold; DMA: Dynamical Mechanical Allodynia; TS: Temporal Summation; IT: Inflammatory Toothache; AO: Atypical Odontalgia; *p < 0.05.

	Criterion	Sensitivity	CI	Specificity	CI	+LR	CI	-LR	CI	AUC	SE	CI	Z value	p	DOR
IT and C															
MDT	>2	35.00	15.4 - 59.2	75.00	50.9 - 91.3	1.40	0.5 - 3.7	0.87	0.6 - 1.3	0.513	0.094	0.356-0.672	0.132	0.89	1.615
PDT	≤15	50.00	27.2 - 72.8	90.00	68.3 - 98.8	5.00	1.3 - 20.0	0.56	0.4 - 0.9	0.696	0.082	0.531-0.831	2.394	0.016	9.00
DMA	≥0	100.00	83.2 - 100.0	0.00	0.0 - 16.8	1.00	1.0 - 1.0	-	-	0.500	0.0	0.338-0.662	-	1	-
TS	>7	31.25	11.0 - 58.7	85.00	62.1 - 96.8	2.08	0.6 - 7.4	0.81	0.6 - 1.2	0.592	0.0966	0.416-0.752	0.954	0.34	2.424
AO and C															
MDT	≤0.16	58.33	36.6 - 77.9	95.00	75.1 - 99.9	11.67	1.7 - 81.2	0.44	0.3 - 0.7	0.849	0.055	0.709-0.939	6.289	<0.0001	26.60
PDT	≤8	66.67	44.7 - 84.4	95.00	75.1 - 99.9	13.33	1.9 - 92.0	0.35	0.2 - 0.6	0.928	0.033	0.808-0.984	12.70	<0.0001	38.00
DMA	≥0	100.00	85.8 - 100.0	0.00	0.0 - 16.8	1.00	1.0 - 1.0	-	-	0.896	0.042	0.766-0.967	9.349	<0.0001	-
TS	>7	45.83	25.6 - 67.2	85.00	62.1 - 96.8	3.06	1.0 - 9.5	0.64	0.4 - 1.0	0.656	0.0833	0.498-0.793	1.876	0.0607	4.795
IT and AO															
MDT	>1	60.00	36.1 - 80.9	91.67	73.0 - 99.0	7.20	1.8 - 28.5	0.44	0.3 - 0.8	0.867	0.0514	0.730-0.950	7.133	<0.0001	16.71
PDT	>10	75.00	50.9 - 91.3	79.17	57.8 - 92.9	3.60	1.6 - 8.2	0.32	0.1 - 0.7	0.834	0.0591	0.692-0.929	5.658	<0.0001	76.00
DMA	≤0	100.00	83.2 - 100.0	79.17	57.8 - 92.9	4.80	2.2 - 10.5	0.00	-	0.896	0.0423	0.766-0.967	9.349	<0.0001	130.45
TS	≤8	93.75	69.8 - 99.8	37.50	18.8 - 59.4	1.50	1.1 - 2.1	0.17	0.02 - 1.2	0.590	0.0902	0.423-0.743	0.997	0.3190	-

Figure 4: Receiver Operator Characteristic test (ROC) Curves of significant QSTs from Inflammatory Toothache, Atypical Odontalgia Group and Control Group.



Legend: MDT: Mechanical Detection Threshold; PDT: Pain Detection Threshold; DMA: Dynamical Mechanical Allodynia; IT: Inflammatory Toothache; AO: Atypical Odontalgia; C: Control.

The most accurate QST to discriminate IT patients from healthy individuals is the PDT. Based on the ROC curve, the cut-off point on PDT values, which provided a

good balance between sensitivity and specificity, was ≤ 15 g/mm^2. Diagnostic differences between AO and healthy individuals are best discriminated with MDT, PDT, and DMA. Respectively, values ≤ 0.16 g/mm^2, ≤ 8 g/mm^{2,} and ≥ 0 on pain intensity by VAS had a strong and significant effectiveness to discriminate them. MDT, PDT, and DMA are accurate QSTs for discriminating the differences between IT and AO with strong and significant effectiveness with values of > 1 g/mm^2, > 10 g/mm^2, and ≥ 0 on pain intensity, respectively.

DISCUSSION

This is one of relatively few studies that have examined somatosensory features in inflammatory toothache and intraoral neuropathic pain. The clinical differential diagnosis of IT and AO is still challenging, and it is extremely important to avoid establishing an incorrect treatment plan. Based on the results of the present diagnostic study, it is suggested that QSTs are usable tools to discriminate such conditions. The results indicated that 1) the AO group has decreased detection threshold to touch and pain when compared with the IT control groups, 2) the presence of mechanical allodynia was a specific feature of AO subjects; 3) touch threshold forces > 1 g/mm^2 and pain threshold forces > 10g/mm^2 can be used to accurately discriminate AO from IT, and 4) MDT, PDT, and DMA can be used to discriminate IT and AO.

In accordance with epidemiological studies, 70% to 75% of this sample was women. The literature is clear in asserting that women are more likely to face a variety of recurrent, severe, and persistent pains (9, 27, 35-38). Some AO subjects were taking pain medications, like anticonvulsants, antidepressants, and/or ansiolytics. This fact appears to not influence initial pain severity (62.5 mm). A similar study evaluated pain intensity in AO subjects who were either taking or not taking unsupervised pain medications at first consultation, and no differences were found between those groups (27).

Somatosensory abnormalities are common in AO patients and intraoral QST can detect these sensory disturbances, however, they have not been completely tested in IT individuals (9, 20). Our study found a tendency for lower pain detection threshold for IT subjects compared with healthy individuals. This means that a minor stimulus is needed to activate pain responses in IT patients, indicating a peripheral

primary hyperalgesia situation, however, this PDT test was not statically significant (39, 40). For the IT group, although we could perceive peripheral hyperalgesia, the PDT test was not a useful tool for detecting this hyperalgesia abnormality.

Typically, hyperalgesia ceases when peripheral inflammation disappears. However, sometimes genetic defects and/or repetitive nerve injury can result in allodynia phenomena, where tactile stimuli are interpreted as painful stimuli. Allodynia reflects the presence of central sensitization, usually in patients with chronic disorders (12, 16). Dynamic Mechanical Testing assesses allodynia through the activation of low-threshold mechanoreceptors (41), and allodynia may be explained by anatomical and physiological changes related to synaptic disorganization, distension of afferent endings, spatial distribution and sprouting of new nerve endings leading to sensory gain in receptive fields (42-44). In this study, allodynia was only observed in the AO group and should be used for differential diagnosis from both IT and AO conditions.

The use of DMA testing is simple to implement in a clinical setting. The professional may carry it out by vibrating only the bristles of a toothbrush or a cotton swab on the region where the patient reports pain and observe a pain report or increased sensation after this stimuli (45). For clinical purposes, the professional could control his/her force and evaluate the response of the patient by comparing the results with a contralateral nonpainful side.

Rapid and long-term changes can occur in parts of the central nervous system that are involved in pain transmission and modulation. Peripheral and central sensitizations of sensory nerve fibers are the main reasons for pain hypersensitivity after injury, and occur mainly in neuropathic pain (46). Persistent abnormal somatosensory processing may initiate neuroplastic changes that perpetuate central sensitization, resulting in chronic pain (47).

It is difficult to accurately diagnose AO. However, for IT, comprehensive medical and dental history associated with visual inspection, imaging, and response to stimuli application (pulp tests) are effective for inferring a possible diagnosis (48). Studies have demonstrated that some additional evaluation should be performed in any patient for discrimination between an IT or AO situation, including pulp tests, periapical and panoramic images, head and neck examination for other maxillofacial disease, and CBCT for incomplete tooth fracture (25, 49, 50). Also, looking for any

abnormalities, such as a nerve examination including QST, is suggested for discriminating between IT and AO (19, 51).

In this study, an additional test with reasonable accuracy to discriminate IT diagnosis was the PDT. In a clinical setting, the most similar approach to PDT may be the pinprick test. This test may be easily performed with very simple instruments before referral to specialized management (52). In the pinprick test, the sensitivity to a painful stimulus is evaluated on the painful gingival site and the corresponding, nonpainful, contralateral site. This painful stimulus is applied with a dental examination probe with moderate force. After the stimulus, patients are asked to report hypersensitivity, hyposensitivity, or normal sensitivity in comparison with nonpainful control side (52).

Although some studies have shown significant diagnostic profiles of AO and IT that could increase the diagnostic capability of clinicians, these profiles were established by considering AO or IT patients individually (9, 10, 45, 50). No study has been published on the association between IT and AO. The present findings showed that three QSTs (MDT, PDT, and DMA) could be used to help discriminate between AO and IT when doubts remain after the initial examination.

Although this study demonstrated a strong accuracy for some QSTs as diagnostic tests, it is clear that QST examinations cannot be performed alone and must be used in combination with medical history, physical examination, and imaging technics in order to improve the accuracy of differential diagnosis (21).

Z score analysis is used for looking at individual patients and how their data are distributed within the normal range for each QST parameter. This study indicated sensory gain (positive Z scores) for allodynia and temporal summation tests (DMA and TS) for the AO group only. A gain in function indicates that dynamical stimuli of innocuous or noxious intensity are able to overexcite nociceptors and provoke a more intense pain response. As a chronic neuropathy, the expected presence of central sensitization may explain the results of dynamical tests of allodynia and summation (41).

There are some limitations to performing the QST testing. Firstly, the time taken to carry out the tests in all areas, which may result in the subject becoming fatigued. Secondly, mechanical stimulation tests can confuse some individuals because they may require a long explanation and repeated testing. Thirdly, QSTs on painful areas are difficult to perform and may have to be explained very carefully to the subjects

prior to examination. Fourthly, although we suggested pinprick as a similar QST to be performed in a clinical setting, this test was not evaluated in this study, and further studies must be done to indicate the pinprick for IT and AO discrimination.

We conclude that some QSTs might aid in the differential diagnosis of AO and IT with strong accuracy, and some QSTs may be used as complementary diagnostic tests. To date, the most accurate QSTs to use for differential diagnosis between AO and IT subjects are the mechanical detection threshold test, the pain detection threshold test, and dynamical mechanical allodynia.

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CONFLICT OF INTEREST

There were no conflicts of interest reported for this study.

REFERENCES

1. Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. Oral Surg Oral Med Oral Pathol 1990;69(3):287-290.

2. Vickers ER, Cousins MJ, Walker S, Chisholm K. Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85(1):24-32.

3. Matwychuk MJ. Diagnostic challenges of neuropathic tooth pain. J Can Dent Assoc 2004;70(8):542-546.

4. Melis M, Secci S. Diagnosis and treatment of atypical odontalgia: a review of the literature and two case reports. J Contemp Dent Pract 2007;8(3):81-89.

5. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part I: Evidence derived from pathophysiology and treatment. Oral Surg Oral Med Oral Pathol 1993;75(1):95-105.

6. Vena DA, Collie D, Wu H, Gibbs JL, Broder HL, Curro FA, et al. Prevalence of persistent pain 3 to 5 years post primary root canal therapy and its impact on oral health-related quality of life: PEARL Network findings. J Endod 2014;40(12):1917-1921.

7. Khan AA, Maixner W, Lim PF. Persistent pain after endodontic therapy. J Am Dent Assoc 2014;145(3):270-272.

8. Nixdorf DR, Drangsholt MT, Ettlin DA, Gaul C, De Leeuw R, Svensson P, et al. Classifying orofacial pains: a new proposal of taxonomy based on ontology. J Oral Rehabil 2012;39(3):161-169.

9. List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: A case-control study. Pain 2008;139(2):333-341.

10. Okeson JP. Bell`s orofacial pains. ed 6 ed. Chicago: Quintessence; 2005.

11. Graff-Radford SB, Solberg WK. Atypical odontalgia. J Craniomandib Disord 1992;6(4):260-265.

12. Baad-Hansen L. Atypical odontalgia - pathophysiology and clinical management. J Oral Rehabil 2008;35(1):1-11.

13. Tarce M, Barbieri C, Sardella A. Atypical odontalgia: an up-to-date view. Minerva Stomatol 2013;62(5):163-181.

14. Pigg M, Svensson P, Drangsholt M, List T. Seven-year follow-up of patients diagnosed with atypical odontalgia: a prospective study. J Orofac Pain 2013;27(2):151-164.

15. Gaul C, Ettlin D, Pfau DB. [Persistent idiopathic facial pain and atypical odontalgia]. Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen 2013;107(4-5):309-313.

16. Leeuw. Rd. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management. American Academy of Orofacial Pain. 4th ed: Quintessence; 2008.

17. Koratkar H, Pedersen J. Atypical odontalgia: a review. Northwest Dent 2008;87(1):37-38, 62.

18. Bosch-Aranda ML, Vazquez-Delgado E, Gay-Escoda C. Atypical odontalgia: a systematic review following the evidence-based principles of dentistry. Cranio 2011;29(3):219-226.

19. Porporatti AL, Costa YM, Stuginski-Barbosa J, Bonjardim LR, Conti PC, Svensson P. Quantitative methods for somatosensory evaluation in atypical odontalgia. Brazilian oral research 2015;29(1).

20. Cruccu G, Anand P, Attal N, Garcia-Larrea L, Haanpaa M, Jorum E, et al. EFNS guidelines on neuropathic pain assessment. Eur J Neurol 2004;11(3):153-162.

21. Pigg M, Baad-Hansen L, Svensson P, Drangsholt M, List T. Reliability of intraoral quantitative sensory testing (QST). Pain 2010;148(2):220-226.

22. Svensson P, Baad-Hansen L, Pigg M, List T, Eliav E, Ettlin D, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. J Oral Rehabil 2011;38(5):366-394.

23. Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain 2006;10(1):77-88.

24. Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain 2006;123(3):231-243.

25. Pigg M, List T, Petersson K, Lindh C, Petersson A. Diagnostic yield of conventional radiographic and cone-beam computed tomographic images in patients with atypical odontalgia. Int Endod J 2011;44(12):1092-1101.

26. Rocha APCea. Dor: Aspectos Atuais da Sensibilização Periférica e Central. Rev Bras Anestesiol 2007;57(1):94-105.

27. Zagury JG, Eliav E, Heir GM, Nasri-Heir C, Ananthan S, Pertes R, et al. Prolonged gingival cold allodynia: a novel finding in patients with atypical odontalgia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111(3):312-319.

28. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. Pain 2011;152(10):2399-2404.

29. Levin S, Pearsall G, Ruderman RJ. Von Frey's method of measuring pressure sensibility in the hand: an engineering analysis of the Weinstein-Semmes pressure aesthesiometer. J Hand Surg Am 1978;3(3):211-216.

30. Hansson P, Backonja M, Bouhassira D. Usefulness and limitations of quantitative sensory testing: clinical and research application in neuropathic pain states. Pain 2007;129(3):256-259.

31. Brunelli C, Zecca E, Martini C, Campa T, Fagnoni E, Bagnasco M, et al. Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. Health Qual Life Outcomes. 2010;8:42.

32. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113(1-2):9-19.

33. Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation 2007;115(5):654-657.

34. Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. BMJ 2004;329(7458):168-169.

35. Baad-Hansen L, Juhl GI, Jensen TS, Brandsborg B, Svensson P. Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. Pain 2007;129(1-2):46-54.

36. Baad-Hansen L, List T, Jensen TS, Svensson P. Increased pain sensitivity to intraoral capsaicin in patients with atypical odontalgia. J Orofac Pain 2006;20(2):107-114.

37. List T, Leijon G, Helkimo M, Oster A, Svensson P. Effect of local anesthesia on atypical odontalgia--a randomized controlled trial. Pain 2006;122(3):306-314.

38. Girard-Tremblay L, Auclair V, Daigle K, Leonard G, Whittingstall K, Goffaux P. Sex differences in the neural representation of pain unpleasantness. J Pain 2014;15(8):867-877.

39. Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. World J Gastroenterol 2007;13(27):3699-3704.

40. Olesen AE, Upton R, Foster DJ, Staahl C, Christrup LL, Arendt-Nielsen L, et al. A pharmacokinetic and pharmacodynamic study of oral oxycodone in a human experimental pain model of hyperalgesia. Clin Pharmacokinet 2010;49(12):817-827.

41. Walk D, Sehgal N, Moeller-Bertram T, Edwards RR, Wasan A, Wallace M, et al. Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. Clin J Pain 2009;25(7):632-640.

42. Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet 1999;353(9168):1959-1964.

43. Conti PC, Pertes RA, Heir GM, Nasri C, Cohen HV, Araujo Cdos R. Orofacial pain: basic mechanisms and implication for successful management. J Appl Oral Sci 2003;11(1):1-7.

44. Vickers ER, Cousins MJ. Neuropathic orofacial pain part 1--prevalence and pathophysiology. Aust Endod J 2000;26(1):19-26.

45. Baad-Hansen L, Pigg M, Ivanovic SE, Faris H, List T, Drangsholt M, et al. Intraoral somatosensory abnormalities in patients with atypical odontalgia-a controlled multicenter quantitative sensory testing study. Pain 2013.

46. Fornasari D. Pain mechanisms in patients with chronic pain. Clinical drug investigation 2012;32 Suppl 1:45-52.

47. Kwon M, Altin M, Duenas H, Alev L. The Role of Descending Inhibitory Pathways on Chronic Pain Modulation and Clinical Implications. Pain practice : the official journal of World Institute of Pain 2013.

48. Ricucci D, Loghin S, Siqueira JF, Jr. Correlation between Clinical and Histologic Pulp Diagnoses. J Endod 2014;40(12):1932-1939.

49. Clark GT. Persistent orodental pain, atypical odontalgia, and phantom tooth pain: when are they neuropathic disorders? J Calif Dent Assoc 2006;34(8):599-609.

50. Levin LG. Pulp and periradicular testing. Pediatr Dent 2013;35(2):113-119.

51. Trowbridge HO, Franks M, Korostoff E, Emling R. Sensory response to thermal stimulation in human teeth. J Endod 1980;6(1):405-412.

52. Baad-Hansen L, Pigg M, Ivanovic SE, Faris H, List T, Drangsholt M, et al. Chairside intraoral qualitative somatosensory testing: reliability and comparison between patients with atypical odontalgia and healthy controls. J Orofac Pain 2013;27(2):165-170.

2.2 ARTICLE 2

Somatic, Visceral and Neuropathic Pain Present Different Somatosensory Profiles

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ABSTRACT

Objectives: The aim of this study was to investigate somatosensory abnormalities, using quantitative sensory testing (QST), in somatic (dental implant patients - IMP), visceral (inflammatory toothache - IT) and neuropathic pain patients (atypical odontalgia - AO). **Methods:** Sixty subjects were divided into three groups: IMP (n=20), IT (n=20) and AO Group (n=20). A sequence of QSTs were performed at baseline, one month and three months after dental implant surgery (IMP group) or pulpectomy (IT group). Statistical analyses were completed with one-way and two-way ANOVA, and "Z" score transformations (α=5%). **Results:** The main findings of this study indicated that: 1- loss of function for touch threshold and electrical threshold of C fibers were found at baseline in IT subjects; 2- somatosensory abnormalities compatible with alodynia, reduced touch and pain threshold detection, and impaired pain modulation were only found in AO group; 3- no somatosensory alterations after implant surgery were found; and 4- a reduction on electrical threshold of C fiber was reported after 3 months of pulpectomy. **Conclusions:** This study showed that somatosensory abnormalities are compatible with AO; and with IT subjects, even after 3 months of pulpectomy. Indeed, no somatosensory modification is seen after implant surgery.

Keywords (MESH): Dental Implants; Somatic Pain; Dental Pulp Diseases; Visceral Pain; Pulpectomy; Neuropathic Pain; Somatosensory Disorders.

INTRODUCTION

Dental pain or pain in the dentoalveolar region is regarded as the most common orofacial pain disorder.(Lipton et al., 1993) Orofacial pain conditions can be classified into somatic, visceral or neuropathic pain.(Carver and Foley, 2003; Okeson, 2005; Rocha, 2007) Somatic pain is triggered by a noxious stimulus, generally induced by peripheral traumas, such as dental implant placement surgeries. Somatic pain is generally pinpointed by the patient and described as aching, gnawing, throbbing, or cramping.(Carver and Foley, 2003; Okeson, 2005; Rocha, 2007) Visceral pain initiates within internal body tissues and is normally triggered by inflammation. It is associated with diffuse discomfort, possible swelling and affects the dental pulp in inflammatory toothaches.(Carver and Foley, 2003;

Okeson, 2005; Rocha, 2007) The third condition is neuropathic pain, which results from persistent injury to the peripheral nerve.(Leeuw., 2008; Porporatti et al., 2015a) Atypical Odontalgia (AO) is a continuous neuropathic pain diagnosed by exclusion of other possible diseases, identified through clinical, dental, neurological and image examination.(Nixdorf et al., 2012) AO is usually described as diffuse, throbbing and burning.(Vickers et al., 1998)

Quantitative Sensory Testing (QSTs) are standardized methods to assess the clinical manifestations and somatosensory abnormalities of the peripheral and Central Nervous System.(Baad-Hansen, 2008; Cruccu et al., 2004; Svensson et al., 2011) Their results indicate alterations on myelinated A fibers (A-beta and A-delta fibers) and unmyelinated C fibers.(Abd-Elmeguid and Yu, 2009; Rolke et al., 2006a; Svensson et al., 2011)

Sensory sensitization processes have been reported, e.g., allodynia, hiperalgesia and pain exacerbation by thermal, mechanical and/or chemical stimuli, in patients with AO.(Baad-Hansen, 2008; Porporatti et al., 2015a; Zagury et al., 2011) However, QST has not been fully explored in orofacial somatic and visceral pain. In addition, the effect of tissue and nerve damage on somatosensory system after trauma from dental treatment warrants further investigation.

This study sought to investigate somatosensory abnormalities, by means of mechanical, painful and electrical QST, in intraoral somatic (dental implant patients), visceral (inflammatory toothache) and neuropathic pain (atypical odontalgia), and to evaluate the sensorial and neural changes resulting from dental implant placement surgery or pulpectomy.

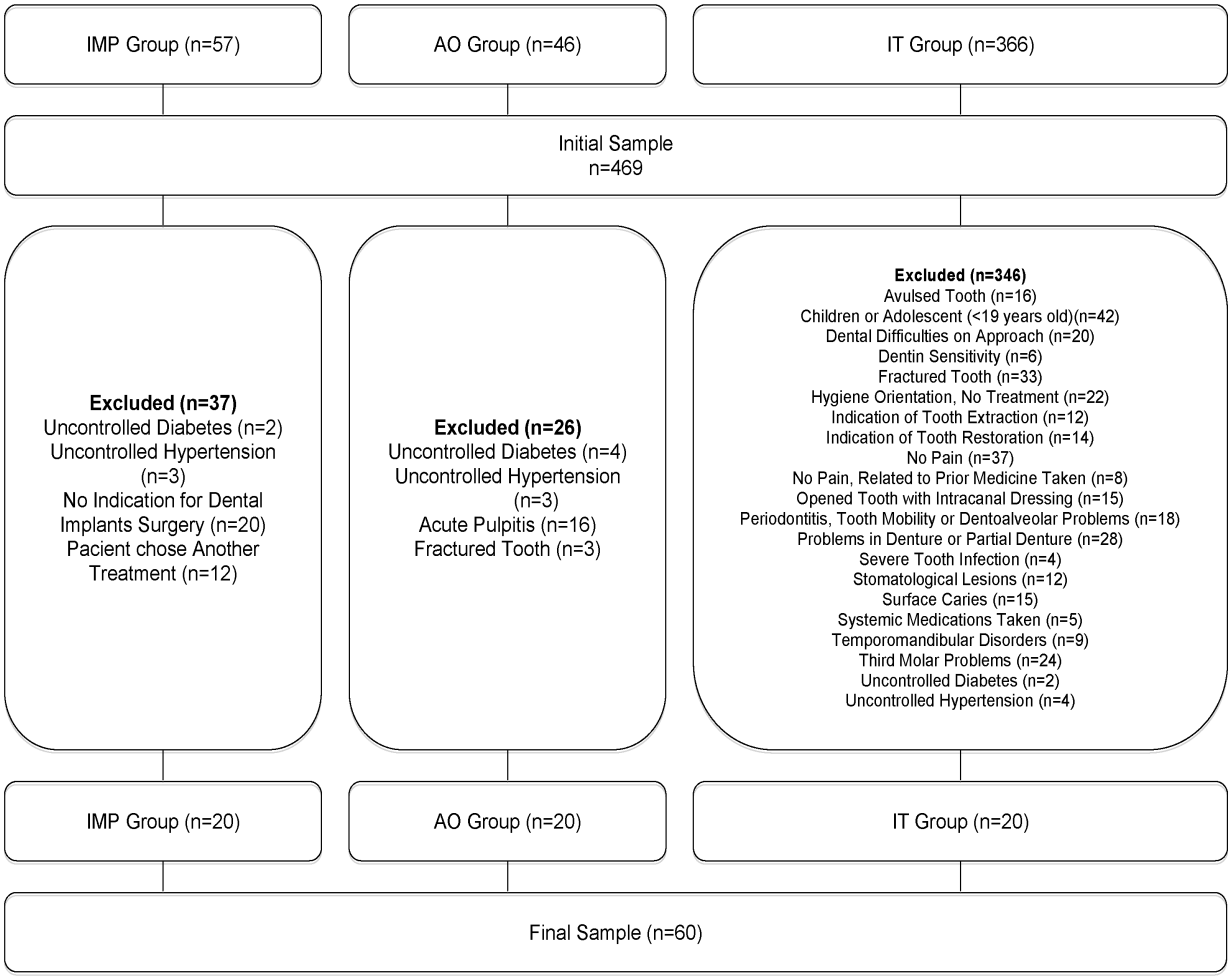
METHODS

This work was supported by the São Paulo Research Foundation – FAPESP (Number 2013/15496-1). There were no conflicts of interest in the performance of this study. This study was conducted in accordance to Helsinki guidelines and was approved by the local ethics committee (Certificate of Presentation for Ethical Consideration #19840113.2.0000.5417). Written informed consent was obtained from all participants.

Subjects

Subjects were recruited at Bauru School of Dentistry, University of São Paulo, Brazil, from December 2013 to January 2015. Accordingly, 469 subjects were eligible and 409 subjects were excluded (Figure 1).

Figure 1: Flowchart of exclusion criteria for the selected subjects



Legend: IMP: Implant group; IT: Inflammatory Toothache group; AO: Atypical Odontalgia group.

Potential sources of bias were managed individually for each group and was explained below. Sixty subjects, at least 19 years old and from both genders, agreed to participate and were allocated into one of the three groups, as follows:

- Implant (IMP) Group (Somatic Pain): 20 healthy subjects who had undergone dental implants installation.

Healthy adults could not had previously received a neuropathy diagnosis and needed to be free from any type of pain and dental pathology for at least six months.(Rocha 2007) This group had undergone a delayed implant placement into non-grafted areas and delayed loading protocol (3 months) based on general patient indications including: 1- sufficient and adequate bone quantity and quality; 2- single, multiple partial units (fixed dental prostheses); or 3- full-arch supported prostheses. single tooth replacement or replacement of two or three teeth.(Rocha 2007, Rosenlicht 2011)

Local anesthesia (articaine 4% and epinefrin 1:100.000) was used during standardized surgery procedures. One hour after implant installation, a medication protocol was started and standardized regarding drug class and dosage. The protocol followed the same guidelines for all subjects and consisted of antibiotic (Amoxicillin® 500mg 8/8 hours for 7 days) and anti-inflammatory drug (Nimesulide® 100mg 12/12hours for 3 days). The diameter and length of dental implants were individualized for each case based on patient`s bone dimensions.

- Inflammatory Toothache (IT) Group (Visceral Pain): 20 subjects with Acute Pulpitis who had undergone pulpectomy.

Individuals were diagnosed following the mandatory criteria of acute toothache related to a dental inflamed pulp with moderate or severe intensity, which could vary over time and go through asymptomatic periods. Pain could be provoked by a stimulus or evoked spontaneously. It could also be intermittent or continuous and affected by time or body position.(Leeuw. 2008) Periapical radiography was always used for differential diagnosis and cases with apical periodontitis were excluded.

Individuals under previous use of analgesics and/or anti-inflammatory drugs were included in the study, if moderate to severe pain still remained. Subjects were excluded if they had no pain at the time of evaluation, or if after taking analgesics they presented remaining pain intensity lower than 50 mm on a Visual Analogue Scale (VAS). VAS consisted of a horizontal line, 100 millimeters long, anchored by word descriptors at each end where the far left read “no pain” and the right read “worst pain imaginable”. Subjects were requested to make a vertical mark on the VAS line at the point that they felt represented the perception of their current pain state.(Ferreira-Valente, et al. 2011)

The dental implant installation and pulpectomy procedures were performed/supervised by experienced faculty from Bauru School of Dentistry at the University of São Paulo.

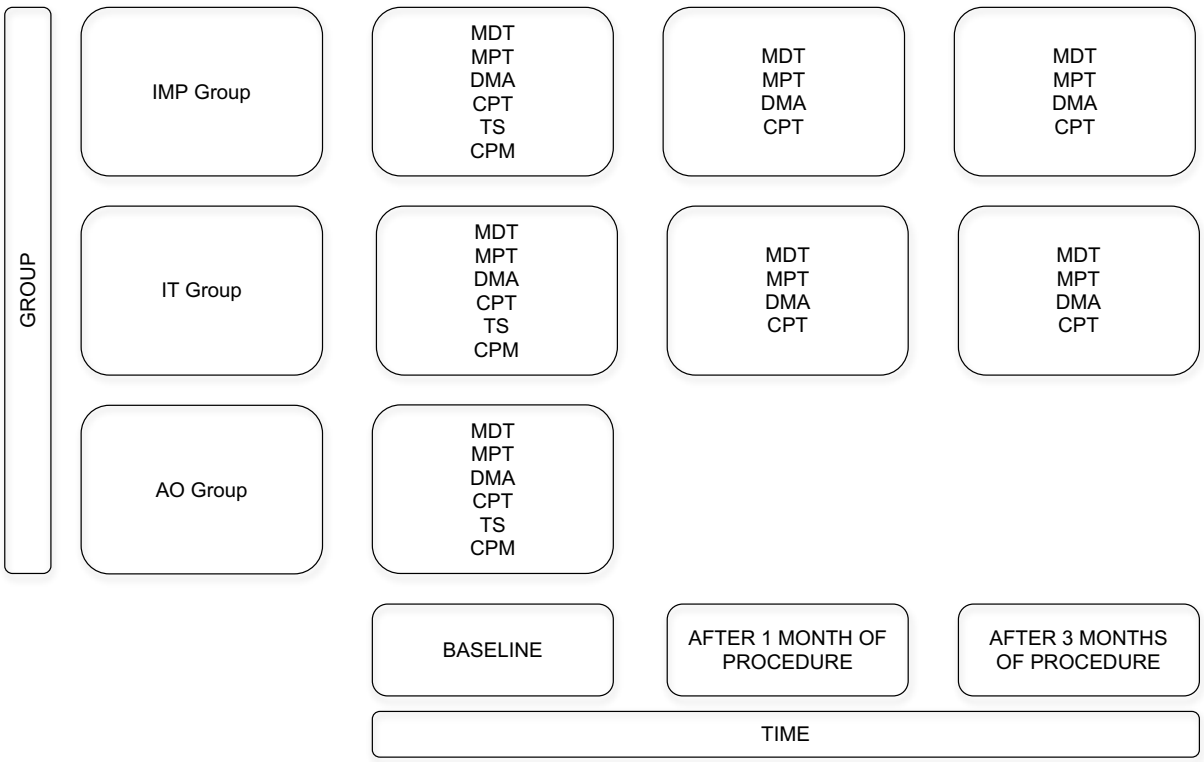
- Atypical Odontalgia Group (Neuropathic Pain): comprised by 20 subjects diagnosed with neuropathic pain classified as AO.

Prior to patient's enrollment in the study, orofacial pain specialists (A.L.P., Y.M.C., J.S.B.) diagnosed AO based on the currently published and accepted criteria for this condition: persistent pain present at least 8 hours per day, during 15 days or more per month for at least 3 months; localized in dentoalveolar area, within a defined anatomical area; and not caused by another disease or disorder excluded by dental and neurological examination and imaging.(Leeuw. 2008, Nixdorf, Drangsholt, Ettlin, Gaul, De Leeuw, Svensson, Zakrzewska, De Laat, Ceusters & International 2012, Okeson 2005) Panoramic or periapical radiography was requested for all patients and a Cone-Beam Computed Tomography (CBCT) image was performed in patients when any diagnostic uncertainty remained after the complementary exams and radiographs.(Pigg, et al. 2011) Patients taking pain medications were also included in this group when pain persisted.

Study Design

A sequence of five QSTs and the Conditioned Pain Modulation Test (CPM) were performed in all subjects, comfortably installed in a quiet room with settled temperature of 22°C to 25°C. The duration of all tests was approximately 45 minutes. An experienced researcher (A.L.P.) performed all procedures, and oriented participants through the entire process to ensure accuracy. Tests were applied over the dentoalveolar-attached mucosa, the closest region to the tooth, within an area of approximately 10 mm^2.(Lu, et al. 2013, Svensson, Baad-Hansen, Pigg, List, Eliav, Ettlin, Michelotti, Tsukiyama, Matsuka, Jaaskelainen, Essick, Greenspan, Drangsholt & Special Interest Group of Oro-facial 2011) Region was group-dependent and comprised the area where the implant was installed (IMP group), toothache reported area (IT group) or the painful reported region (AO group). Pain intensity report, as well as QSTs, were performed preoperatively (at baseline) and postoperatively one month and three months after tissue trauma following implant installation (IMP group) or pulpectomy (IT group). AO group was examined once, at baseline. A diagram with the follow-up of the experimental protocol is depicted in Appendix 1.

Appendix 1: Sequence of the experimental protocol for all groups.



Legend: IMP: Implant group; IT: Inflammatory Toothache group; AO: Atypical Odontalgia group; MDT: Mechanical Detection Threshold; MPT: Mechanical Pain Threshold; DMA: Dynamical Mechanical Allodynia, CPT: Current Perception Threshold; TS: Temporal Summation.

Variables

- Mechanical Detection Threshold (MDT)

This test was performed to estimate the least force at the moment subjects appropriately recognized as light touch and not pain.(Levin, et al. 1978) This force was executed with a kit of 20 von Frey nylon monofilaments with different diameters, calibrated to exert specific forces when bending, ranging from 0.008 g/mm^2 to 300 g/mm^2.(Levin, Pearsall & Ruderman 1978) The monofilament was applied perpendicularly and maintained over the dentoalveolar region within the monofilament bended for 1 to 1.5 seconds.(Hansson, et al. 2007) The method of limits was used in which approximately 6 to 8 ascending/descending monofilament stimuli were applied, and the average force was calculated.(Hansson, Backonja & Bouhassira 2007)

- Mechanical Pain Threshold (MPT)

The same protocol for MDT was executed, however at this time the least von Frey monofilament stimuli should appropriately be recognized by the subjects as a painful sensation and not touch.(Svensson, Baad-Hansen, Pigg, List, Eliav, Ettlin, Michelotti, Tsukiyama, Matsuka, Jaaskelainen, Essick, Greenspan, Drangsholt & Special Interest Group of Oro-facial 2011)

- Dynamical Mechanical Allodynia (Meier, et al.)

Ten seconds of slight vibration of a cotton swab was applied to dentoalveolar mucosa (estimated area of 2 mm^2) and, immediately after, pain intensity was recorded with the aid of a VAS.(Svensson, Baad-Hansen, Pigg, List, Eliav, Ettlin, Michelotti, Tsukiyama, Matsuka, Jaaskelainen, Essick, Greenspan, Drangsholt & Special Interest Group of Oro-facial 2011)

- Current Perception Threshold (CPT)

CPT was performed with the aid of Neurometer® (Painless Electrodiagnostic Sensory Nerve Testing Equipment, Baltimore, Maryland, USA) and is defined as the mean of the minimum detected intensity of an electrical stimulus that was consistently detected by the subjects. The CPT device is a transcutaneous electrical stimulator, based on automated procedure to quantitatively measure the conduction and functional integrity of three main sensory fibers with three different electrical frequencies: A-beta (2000Hz), A-delta (250Hz) and C fibers (5Hz). For each frequency, the current intensity was slowly increased from 0.01 mA (output intensity range of 0.01 to 9.99 mA) until the patient perceived an electrical sensation and not pain.(Lee, et al. 2007, Masson & Boulton 1991, Murina, et al. 2010, Nogami & Taniguchi 2015)

Two small gold-plated electrodes (10 mm each) coated with 0.3 ml of electroconductive gel were placed on the dentoalveolar region and during the three different frequencies, the subjects patients held a remote control used to stop the electrical stimulus.(Masson & Boulton 1991, Nogami & Taniguchi 2015)

- Temporal Summation Test (TS)

A repeated painful stimulus of 26 g/mm^2 during a continuous 30-seconds sequence, using one von Frey monofilament (approximately one stimulus per second, frequency of 1 Hz) was applied to the structures. At the 1^{st} second, 10^{th} second, 20^{th} second and 30^{th} second, subjects rated their pain intensity on a

Numeric Rating Scale (NRS). The NRS is a 0-10 point scale, where 0 indicates "no pain", and 10 the "worst pain imaginable".(Brunelli, et al. 2010, Dworkin, et al. 2005) Patients were asked to write their responses on a paper. NRS was used based on difficulties found for the patients report pain on VAS during the TS Test. For statistical analysis, a single ratio of TS was determined using subtraction calculations (pain intensity after 30 seconds of pinprick stimulations minus pain intensity at the first second of pinprick).

- Conditioned Pain Modulation (CPM)

Five minutes after TS, subjects were submitted to a conditioned stimulus (CS) for 30 seconds, in which the non-dominant hand was immersed, up to the wrist with fingers apart, in a container with water at 47ºC. With the hand still immersed in the container, TS was applied a second time and pain was rated again within the 30-seconds sequence.(Svensson, Baad-Hansen, Pigg, List, Eliav, Ettlin, Michelotti, Tsukiyama, Matsuka, Jaaskelainen, Essick, Greenspan, Drangsholt & Special Interest Group of Oro-facial 2011) Inclusion of non-dominant hand in a container with water in a temperature of 47°C has the purpose to elicit a painful thermal conditioned stimulus.

For statistical analysis, a single value of CPM ratio was determined using subtraction calculations (pain intensity of 30 seconds of pinprick stimulations after CS minus pain intensity of the first second of pinprick stimulations before CS). Also, the degree (percent of reduction in the train of 30 seconds) in pain rating after CS compared to before CS was evaluated.

Data reduction and analysis

All analyses were performed using STATISTICA for Windows, version 10.0 (StatSoft Inc., Tulsa, OK, USA) and MedCalc (MedCalc Software, Ostend, Belgium). Between-group characteristics, pain intensity, baseline QST values, CPM ratio and CPM degree were analyzed using one-way analysis of variance (ANOVA). QSTs and CPM variation over time (1 and 3 months) were performed with repeated-measures two-way ANOVA, in which group and time were the two factors. When appropriate, Tukey's post hoc analyses were used to determine significant differences between groups. The results were considered significant at a level of 5%.

Furthermore, raw QST values from each patient were transformed to “Z” scores to obtain a single value for each test for comparison with control.(Rolke, Baron, Maier, Tolle, Treede, Beyer, Binder, Birbaumer, Birklein, Botefur, Braune, Flor, Huge, Klug, Landwehrmeyer, Magerl, Maihofner, Rolko, Schaub, Scherens, Sprenger, Valet & Wasserka 2006)

“Z” score calculation index = ($X_{single\ patient}$ - $Mean_{reference}$) / Standard $Deviation_{reference}$

In this study, three “Z” score transformations were performed: 1- the “X” value was used for the IT and AO patient; and the “reference” were the IMP group at baseline; 2) the “X” value was the IMP and IT patient after 1 month of the procedure; and the “reference” were the IMP and IT group at baseline, respectively; and 3) the “X” value was the IMP and IT patient after 3 months of the procedure; and the “reference” were the IMP and IT group at baseline, respectively.

A score above 1.96 or below -1.96 fell outside the 95% confidence interval of the mean were considered sensory abnormalities. Abnormalities were subsequently categorized as a gain (above 1.96) or loss (below -1.96) of function.

RESULTS

Group Characteristics

Sample characteristics, such as age, gender, the evaluated areas, pain intensity, systemic conditions and previous medications are presented in table 1.

There were no complications during or after the procedures for IMP and IT group. In the IMP group, there were no reports of adverse events or need for extra intake of medication. Average implant diameter was 3.75 mm (3.25-5.00) and length was 10 mm (8.50-13.50). All implants were external hexagon, 10 from Neodent® (Curitiba, PR, Brazil) and 10 from SIN® (São Paulo, SP, Brazil). There were no reports of adverse events in the IT group, except for three reports of intake of painkiller after pulpectomy, only once in the first day.

Table 1: Groups characteristics at baseline

	IMP Group	IT Group	AO Group
Age (SD)	50.22 (6.66)	35.1 (8.68)	57.84 (13.42)
Gender	14W 6 M	14 W 6 M	15 W 5 M
Evaluated Region	2 Incisor 2 Canine 10 Premolar 6 Molar	0 Incisor 2 Canine 4 Premolar 14 Molar	2 Incisor 3 Canine 7 Premolar 8 Molar
Pain Intensity (SD) in VAS	0 (0)	68.6 (22.99)	62.5 (23.47)
Systemic Conditions	None	1 controlled hypertension	3 cholesterol problems 8 controlled hypertension 2 controlled diabetes mellitus type II 1 hypothyroidism
Previous Medications	None	3 analgesic and muscle relaxant formulation 2 Dipyrone®	1 Amitriptyline® (25mg) 6 Gabapentin® (300mg) 3 Carbamazepine® (200mg), 2 Duloxetine® (30mg) 1 Topiramate® (25mg)

Legend: IMP: Implant; IT: Inflammatory Toothache; AO: Atypical Odontalgia; SD: Standard Deviation; W: Women; M: Men; VAS: Visual Analogue Scale.

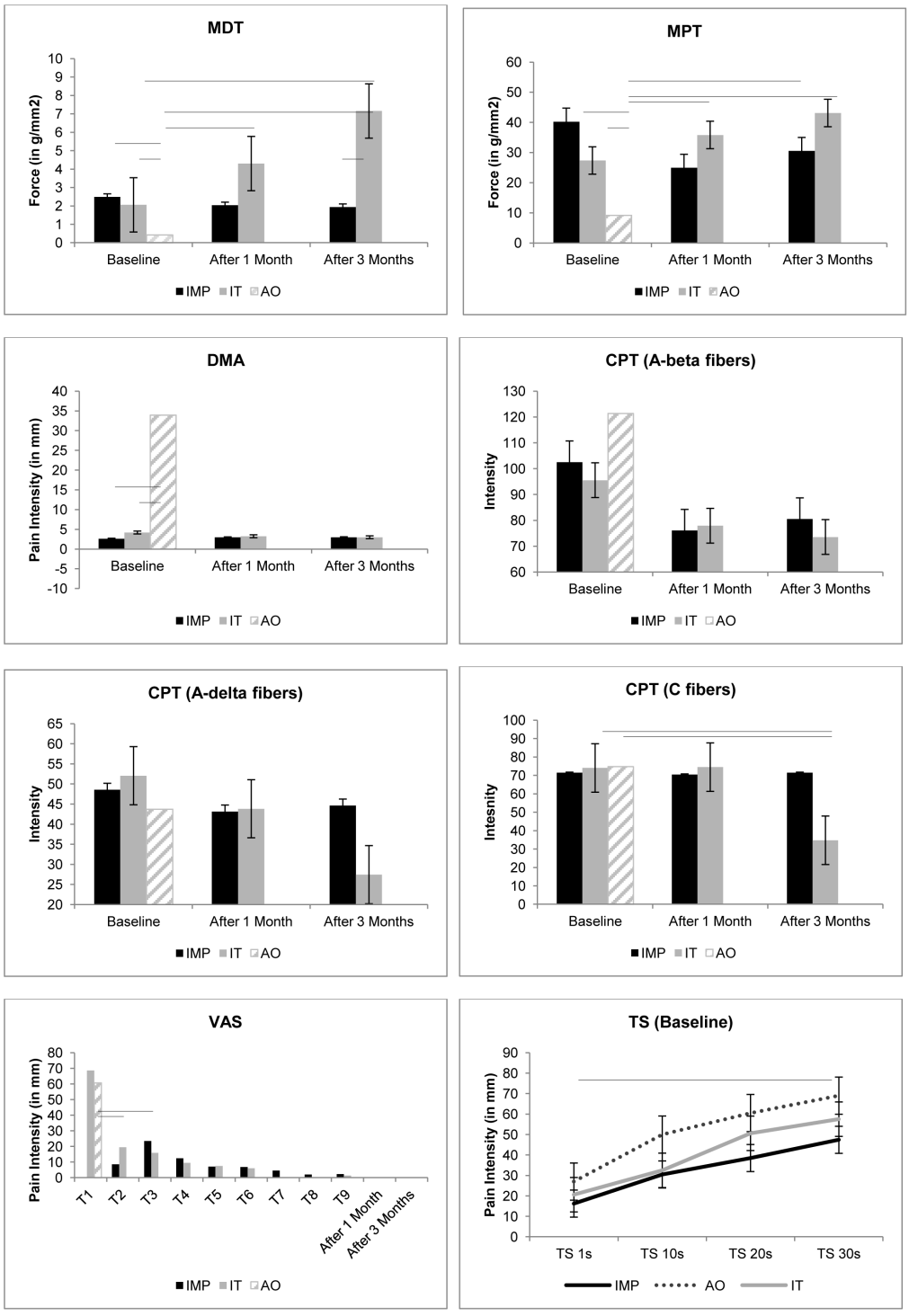
All the sixty eligible subjects who meet the inclusion and exclusion criteria agreed to participate. However, eighteen subjects withdrew from the study, because they did not attend the appointments after recurrent calls. In the IMP group, 16 subjects completed the first appointment (1 month) and 13 completed the second one (3 months). In the IT group, 12 and 9 subjects completed the first and second appointment, respectively.

In 13 AO subjects, CBCT was performed to assist in the differential diagnosis. CBCT was required due to the visualization difficulty of possible dental or bone alterations after conventional and panoramic radiographs.

Baseline Analysis

Values for all QSTs are shown in Figure 2.

Figure 2: QST differences between groups by time: at baseline, after 1 month and after 3 months; and pain intensity evaluated by a visual analogue scale in differents intervals.



Legend: QST: Quantitative Sensory Testing; IMP: Implant group; IT: Inflammatory Toothache group; AO: Atypical Odontalgia group; MDT: Mechanical Detection Threshold; MPT: Mechanical Pain Threshold; DMA: Dynamical Mechanical

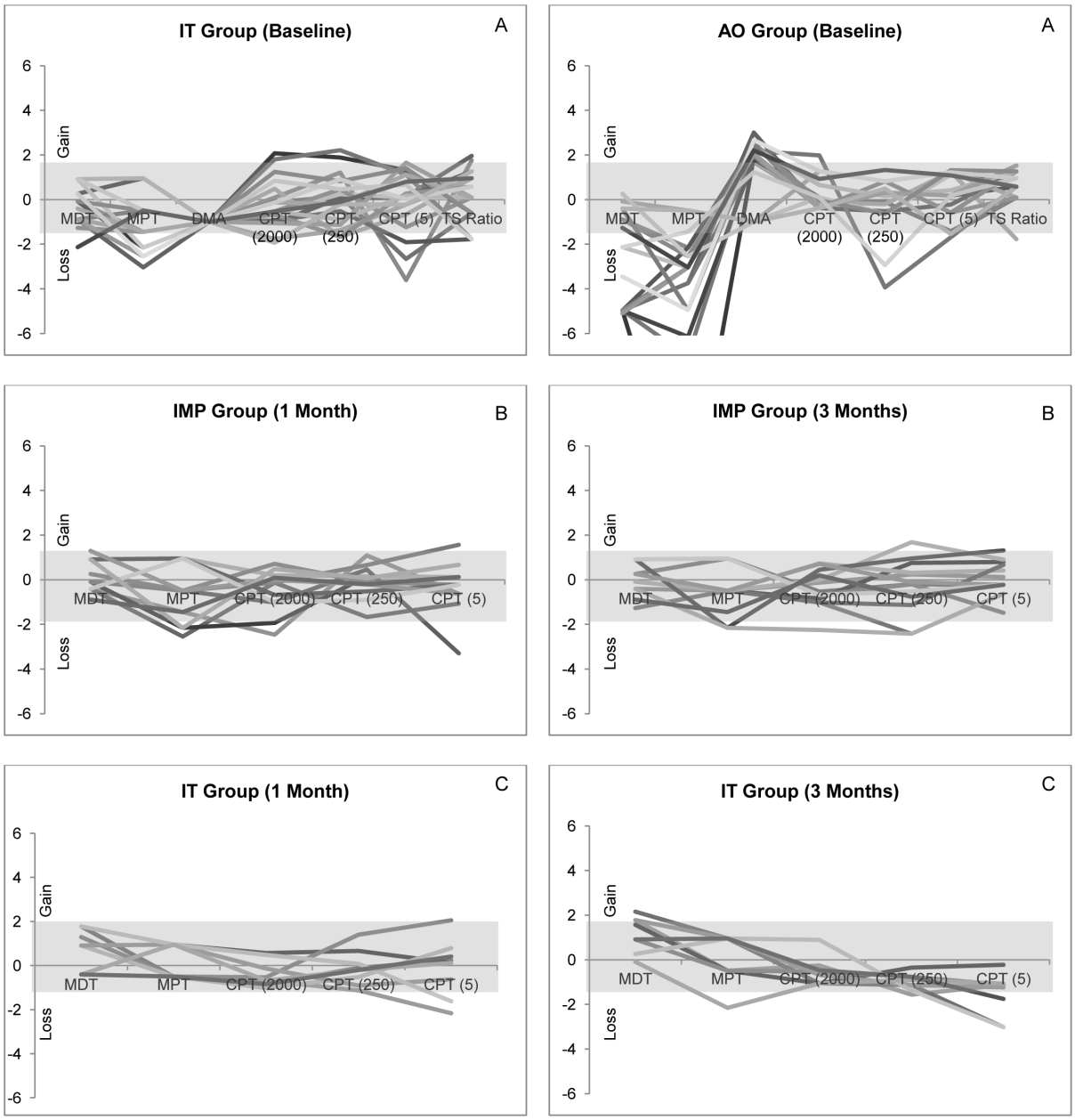
Allodynia, CPT: Current Perception Threshold; TS: Temporal Summation; VAS: Visual Analogue Scale; s: Seconds; mm: millimeters; T1: at baseline; T2: during the procedure (implant installation or pulpectomy procedure); T3: one hour after the procedure; T4: two hours after the procedure; T5: three hours after the procedure, T6: four hours after the procedure; T7: five hours after the procedure; T8: one day after the procedure; T9: one week after the procedure; —— $p<0.05$.

Patients with AO presented decreased threshold to touch ($F=24.44$, $P<.001$) and pain ($F=16.88$, $P<.001$) compared to subjects with IT or IMP. Only subjects with AO reported pain (33.9 mm on a VAS) after vibration of a cotton swab. No differences in CPT at any type of fiber (A-beta, A-delta and C fibers) and TS test were found between or among groups.

After “Z” transformation, loss of function for touch threshold and electrical threshold of C fibers was found in patients with IT; and for touch, pain and electrical threshold of A-delta fibers in AO subjects. Also, a gain of function was observed for allodynia test in AO subjects (Figure 03-A).

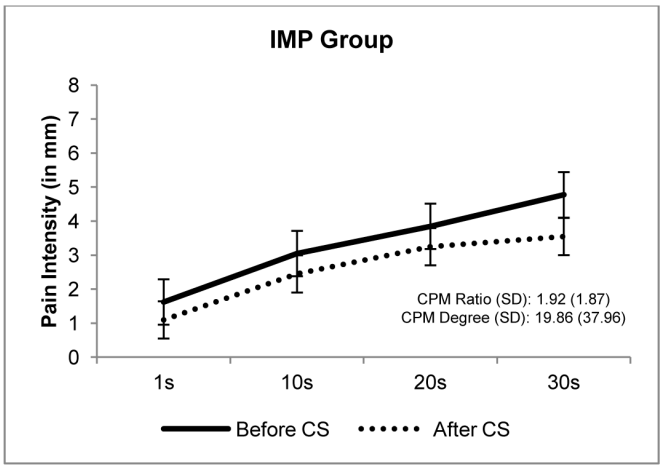
AO subjects presented ineffective endogenous pain modulation measured through CPM test. IMP and IT subjects showed higher CPM degree and lower CPM ratio than AO patients, suggesting an undamaged internal modulatory system ($F=17.88$, $P<.001$) (Figure 4). The overall pain amelioration after conditioned stimulus for AO group was only 7.84% (SD: 30.56), where IMP and IT have 19.86% (37.96) and 48.76% (41.54), respectively ($F=5.27$, $P=.006$).

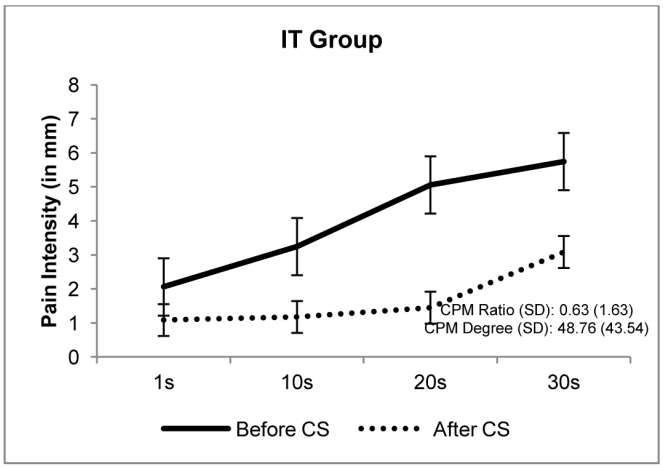
Figure 3: A- “Z” score sensory profiles at baseline for IT and AO compared to IMP group; B- ”Z” score sensory profiles for IT and IMP after 1 month respectively compared to itself at baseline; C- ”Z” score sensory profiles for IT and IMP after 3 months respectively compared to itself at baseline.

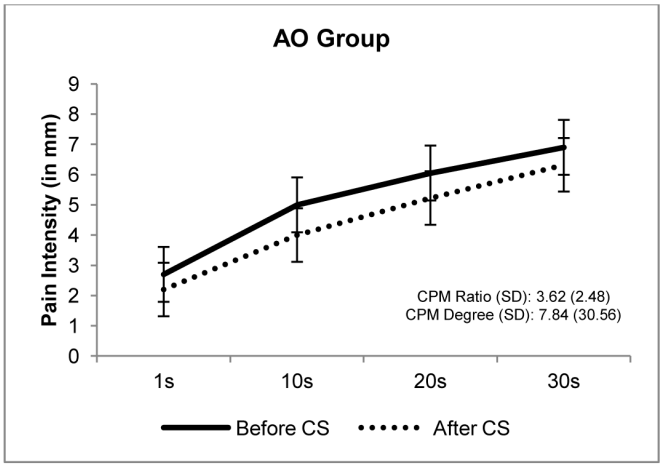


Legend: IMP: Implant group; IT: Inflammatory Toothache group; AO: Atypical Odontalgia group; MDT: Mechanical Detection Threshold; MPT: Mechanical Pain Threshold; DMA: Dynamical Mechanical Allodynia, CPT: Current Perception Threshold; (2000): A-beta fibers; (250) A-delta fibers; (5): C fibers; TS: Temporal Summation; Gain: Gain in Function; Loss: Loss in Function.

Figure 4: Conditioned pain modulation protocol, before and after a conditioned stimulus (immersed hand in a container with water at 47ºC).







Legend: CPM: Conditioned Pain Modulation; IMP: Implant group; IT: Inflammatory Toothache group; AO: Atypical Odontalgia group; s: seconds; mm: millimeters; SD: Standard Deviation; CS: Conditioned Stimulus; * $p<0.05$.

Between-time Analysis

For IMP group, pain started during implant installation (VAS: 8.5 mm) and increased in intensity one hour after the procedure (VAS: 23.4 mm)(F=13.00, P=.003)(Figure 02). Two hours later, pain reduced (VAS: 12.4mm) and it was no different from baseline (F=76.19, P<.001). For IT group, pain was moderate at baseline (VAS: 68.6mm) and decreased immediately after pulpectomy (VAS: 19.5mm), with progressive pain relief until four hours after pulpectomy (F=76.19, P<.001). After five hours, no pain was observed for all IT patients.

No somatosensory alterations after implant surgery were found (F=6.29, P=.99). An increased threshold to touch for IT group was observed after 3 months of pulpectomy and this threshold was significantly higher than IMP and AO group (F=6.29, P<.001). Also after 3 months, IT subjects expressed reduced electrical threshold for the stimulation of C fibers than IMP and AO subjects (F=6.30, P<.001). IMP and IT subjects have no differences in pain threshold and electrical threshold for the stimulation of A-beta and A-delta fibers (F=1.17, P=.32).

Furthermore, in “Z” scores, no loss or gain of function were observed after 1 or 3 months of implant surgery (Figure 03-B) and for only two subjects with IT, a loss in function was seen in electrical threshold of C fibers after 1 and 3 months of pulpectomy (Figure 03-C).

DISCUSSION

This is one of relatively few studies that have examined somatosensory features in intraoral somatic, visceral and neuropathic pain. Evaluation of somatosensory function is a significant field exponentially growing in research and clinical practice of dentistry. It is trusted that QST provides better understanding of sensory mechanisms underlying a variety of pain conditions.(Pigg, et al. 2010, Rolke, et al. 2006) Studies have shown that after intraoral damages to the nervous system, three situations can follow. The first and most common one is that after the healing courses, the peripheral inflammation and pain are ceased and sensory system may work as formerly.(Meier, Widmayer, Abazi, Brugger, Lukic, Luchinger & Ettlin 2015) In the second situation, pain may be evoked by innocuous or nociceptive stimulus and the third condition comprises an opposite effect with hypoesthesia, hypoalgesia, parestesia and analgesia sensations. (Porporatti, et al. 2015, Svensson, Baad-

Hansen, Pigg, List, Eliav, Ettlin, Michelotti, Tsukiyama, Matsuka, Jaaskelainen, Essick, Greenspan, Drangsholt & Special Interest Group of Oro-facial 2011)

Epidemiological studies provide evidence that this nerve damage may persist in 3-6% of patients who receive dental care such as endodontic procedures in a situation of intra-oral neuropathic pain. Cases of post-implant neuropathic pain are less explored and seems to be around 13%.(Ellies & Hawker 1993) In this study, no patient developed persistent pain or parestesia after implant surgery or pulpectomy. This is in contrast to other studies where patients receiving dental implants experienced some sensory disturbances such as parestesia in 7-39%.(Al-Sabbagh, et al. 2015, Shavit & Juodzbalys 2014).

Allodynia, hyperalgesia and decreased touch and pain thresholds (gain of function) were seen in the present study for patients with AO. However, no somatosensory alterations were found in IMP patients at baseline. This finding is in accordance with the current literature, since IMP patients were not exposed to direct trauma at baseline.(Cruccu, Anand, Attal, Garcia-Larrea, Haanpaa, Jorum, Serra & Jensen 2004, Ellies & Hawker 1993, Juhl, et al. 2008)

An important result of this study was the possible impaired pain modulation in AO patients. A recent study concluded similar results on patients with persistent post-endodontic pain (PPEP), which suggested a reduced function of the inhibitory endogenous pain system for PPEP patients.(Nasri-Heir, et al. 2015) However, our results were also contradictory to previous published data, where the effect of pain modulation was tested using the nociceptive blink reflex as the TS protocol and capsaicin application as the conditioned stimulus.(Baad-Hansen, et al. 2006) The authors concluded that no signs of disturbances in endogenous pain inhibitory systems were found for atypical odontalgia and healthy participants.(Baad-Hansen, List, Kaube, Jensen & Svensson 2006) Also, to the author's knowledge, this is the first study assessing conditioned pain modulation in IMP and IT patients, supporting the idea that modulation system is working efficiently in these individuals. This is an expected finding in patients where the pain sensation was supposed to be protective to an acute event (implant insertion or bacterial infection), and no long-term central alterations are present.

This study found no somatosensory alterations and no changes on electrical stimulation of nerve fiber after implant surgery, suggesting the absence of persistent

damage to sensory nerves or of a restructuration of the sensory innervation around the implant. The present study also revealed, through current perception threshold tests, changes in C fiber after 3 months of pulpectomy in patients with IT. A plausible explanation for this reduced threshold of electrical stimulation could be the result of sprouting of C fiber after pulp extirpation. Studies have showed that C fibers are located in the core of the pulp, or in the pulp itself, while A fibers are mainly located at the pulp-dentin boundaries at the coronal portion of the pulp and concentrated at the pulp horns.(Abd-Elmeguid & Yu 2009, Holland 1995).

The location of C fiber in the central region of the pulp leads to a less excitability and a higher threshold, which will require more intense stimuli for activation.(Narhi, et al. 1979, Shimazaki, et al. 2012) Since the QST electrical stimuli were applied on mucosa and not on dental pulp itself, this could provide evidence of possible changes on tooth apical root. Moreover in this area after pulpectomy, evidence of formation of a disorganized group of sprouting and branching axons was found in literature, sharing some features in common with neuromas.(Holland 1995)

The concept of neurogenic inflammation after pulpectomy is well established in the pulp tissue, which means that inflammatory vascular changes may occur, with release of substance P and calcitonin gen-related peptide (CGRP), and consequently the activation of afferent nerves. A study in the canine of ferrets proved that considerable histological evidence of periapical inflammation, sprouting and expression of CGRP in injured tissues was still present after three months of endodontic treatment.(Holland 1995, Holland 1996)

CPT is part of the quantitative sensory testing and has been proposed based on its non-invasiveness and nerve selectiveness.(American Association of Electrodiagnostic 1999) Accordingly, this test was proposed for nerve evaluation after implant surgery or pulpectomy, however there are no validation and no estimation of normal values for Neurometer® CPT in intra-oral conditions yet. Studies on diabetic neuropathy showed that CPT might be a useful screening instrument to comprehensively assess the functional integrity of different nerve fiber populations.(Lv, et al. 2015, Masson & Boulton 1991) These studies concerning the selective ability to distinct different nerve function are based primarily upon studies correlating with other examination techniques, such as thermal and vibration threshold tests. However it is likely that more than one type of sensory fibers are being stimulated simultaneously, resulting in subjective sensations described by the

patient. Further studies should focus on the sensitivity and specificity of CPT to establish and compare it to an appropriate standard test, for instance microneurography.(Ikeda & Suda 2003, Shen, et al. 2008)

Furthermore, in this study some limitations are highlighted, including the absence of somatosensory evaluation immediately after implant surgery or pulpectomy. However, some difficulties were observed when this approach was attempted on a pilot study. Subjects reported pain after surgery or they were uncooperative after pulpectomy, which lead to suspension of the research tests. Also as a limitation, although the IMP group at baseline was used as a control, a QST comparison between time was not performed in healthy subjects, not exposed to any procedure, which could limit the extrapolation of our results.

In essence, this study showed that somatosensory abnormalities compatible with loss of function for touch threshold and electrical threshold of C fibers is present in inflammatory toothache. Allodynia, hyperalgesia, gain of function for touch and pain thresholds associated to impaired pain modulation are detected in atypical odontalgia subjects. No somatosensory modification was seen after implant surgery, in opposite to reduced electrical threshold in C fibers in patients with inflammatory toothache, after 3 months of pulpectomy.

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REFERENCES

Abd-Elmeguid, A. & Yu, D. C. (2009) Dental pulp neurophysiology: Part 1. Clinical and diagnostic implications. *J Can Dent Assoc* **75**: 55-59.

Al-Sabbagh, M., Okeson, J. P., Khalaf, M. W. & Bhavsar, I. (2015) Persistent pain and neurosensory disturbance after dental implant surgery: Pathophysiology, etiology, and diagnosis. *Dent Clin North Am* **59**: 131-142.

American Association of Electrodiagnostic, M. (1999) Guidelines in electrodiagnostic medicine. Technology review: The neurometer current perception threshold (cpt). *Muscle Nerve Suppl* **8**: S247-259.

Baad-Hansen, L. (2008) Atypical odontalgia - pathophysiology and clinical management. *J Oral Rehabil* **35**: 1-11.

Baad-Hansen, L., List, T., Kaube, H., Jensen, T. S. & Svensson, P. (2006) Blink reflexes in patients with atypical odontalgia and matched healthy controls. *Exp Brain Res* **172**: 498-506.

Brunelli, C., Zecca, E., Martini, C., Campa, T., Fagnoni, E., Bagnasco, M., Lanata, L. & Caraceni, A. (2010) Comparison of numerical and verbal rating scales to measure pain exacerbations in patients with chronic cancer pain. *Health Qual Life Outcomes* **8**: 42.

Carver, A. & Foley, F. (2003) Types of pain In: Kufe, D., Pollock, R., Weichselbaum, R. & al., e., eds. *Holland-frei cancer medicine.* 6th edition. BC Decker.

Cruccu, G., Anand, P., Attal, N., Garcia-Larrea, L., Haanpaa, M., Jorum, E., Serra, J. & Jensen, T. S. (2004) Efns guidelines on neuropathic pain assessment. *Eur J Neurol* **11**: 153-162.

Dworkin, R. H., Turk, D. C., Farrar, J. T., Haythornthwaite, J. A., Jensen, M. P., Katz, N. P., Kerns, R. D., Stucki, G., Allen, R. R., Bellamy, N., Carr, D. B., Chandler, J., Cowan, P., Dionne, R., Galer, B. S., Hertz, S., Jadad, A. R., Kramer, L. D., Manning, D. C., Martin, S., McCormick, C. G., McDermott, M. P., McGrath, P., Quessy, S., Rappaport, B. A., Robbins, W., Robinson, J. P., Rothman, M., Royal, M. A., Simon, L., Stauffer, J. W., Stein, W., Tollett, J., Wernicke, J., Witter, J. & Immpact (2005) Core outcome measures for chronic pain clinical trials: Immpact recommendations. *Pain* **113**: 9-19.

Ellies, L. G. & Hawker, P. B. (1993) The prevalence of altered sensation associated with implant surgery. *Int J Oral Maxillofac Implants* **8**: 674-679.

Ferreira-Valente, M. A., Pais-Ribeiro, J. L. & Jensen, M. P. (2011) Validity of four pain intensity rating scales. *Pain* **152**: 2399-2404.

Hansson, P., Backonja, M. & Bouhassira, D. (2007) Usefulness and limitations of quantitative sensory testing: Clinical and research application in neuropathic pain states. *Pain* **129**: 256-259.

Holland, G. R. (1995) Periapical neural changes after pulpectomy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **80**: 726-734.

Holland, G. R. (1996) Steroids reduce the periapical inflammatory and neural changes after pulpectomy. *J Endod* **22**: 455-458.

Ikeda, H. & Suda, H. (2003) Sensory experiences in relation to pulpal nerve activation of human teeth in different age groups. *Arch Oral Biol* **48**: 835-841.

Juhl, G. I., Jensen, T. S., Norholt, S. E. & Svensson, P. (2008) Central sensitization phenomena after third molar surgery: A quantitative sensory testing study. *Eur J Pain* **12**: 116-127.

Lee, Y. S., Kho, H. S., Kim, Y. K. & Chung, S. C. (2007) Influence of topical capsaicin on facial sensitivity in response to experimental pain. *J Oral Rehabil* **34**: 9-14.

Leeuw., R. d. (2008) Orofacial pain: Guidelines for assessment, diagnosis, and management. American academy of orofacial pain. 4th edition: Quintessence.

Levin, S., Pearsall, G. & Ruderman, R. J. (1978) Von frey's method of measuring pressure sensibility in the hand: An engineering analysis of the weinstein-semmes pressure aesthesiometer. *J Hand Surg Am* **3**: 211-216.

Lipton, J. A., Ship, J. A. & Larach-Robinson, D. (1993) Estimated prevalence and distribution of reported orofacial pain in the united states. *J Am Dent Assoc* **124**: 115-121.

Lu, S., Baad-Hansen, L., List, T., Zhang, Z. & Svensson, P. (2013) Somatosensory profiling of intra-oral capsaicin and menthol in healthy subjects. *Eur J Oral Sci* **121**: 29-35.

Lv, S. L., Fang, C., Hu, J., Huang, Y., Yang, B., Zou, R., Wang, F. Y. & Zhao, H. Q. (2015) Assessment of peripheral neuropathy using measurement of the current perception threshold with the neurometer((r)) in patients with type 1 diabetes mellitus. *Diabetes Res Clin Pract* **109**: 130-134.

Masson, E. A. & Boulton, A. J. (1991) The neurometer: Validation and comparison with conventional tests for diabetic neuropathy. *Diabet Med* **8 Spec No**: S63-66.

Meier, M. L., Widmayer, S., Abazi, J., Brugger, M., Lukic, N., Luchinger, R. & Ettlin, D. A. (2015) The human brain response to dental pain relief. *J Dent Res* **94**: 690-696.

Murina, F., Bianco, V., Radici, G., Felice, R. & Signaroldi, M. (2010) Electrodiagnostic functional sensory evaluation of patients with generalized vulvodynia: A pilot study. *J Low Genit Tract Dis* **14**: 221-224.

Narhi, M., Virtanen, A., Kuhta, J. & Huopaniemi, T. (1979) Electrical stimulation of teeth with a pulp tester in the cat. *Scand J Dent Res* **87**: 32-38.

Nasri-Heir, C., Khan, J., Benoliel, R., Feng, C., Yarnitsky, D., Kuo, F., Hirschberg, C., Hartwell, G., Huang, C. Y., Heir, G., Korczeniewska, O., Diehl, S. R. & Eliav, E. (2015) Altered pain modulation in patients with persistent post-endodontic pain. *Pain*.

Nixdorf, D. R., Drangsholt, M. T., Ettlin, D. A., Gaul, C., De Leeuw, R., Svensson, P., Zakrzewska, J. M., De Laat, A., Ceusters, W. & International, R. D. C. T. M. D. C. (2012) Classifying orofacial pains: A new proposal of taxonomy based on ontology. *J Oral Rehabil* **39**: 161-169.

Nogami, K. & Taniguchi, S. (2015) Stellate ganglion block, compared with xenon light irradiation, is a more effective treatment of neurosensory deficits resulting from orthognathic surgery, as measured by current perception threshold. *J Oral Maxillofac Surg* **73**: 1267-1274.

Okeson, J. P. (2005) Bell`s orofacial pains. ed 6 edition, Chicago: Quintessence.

Pigg, M., Baad-Hansen, L., Svensson, P., Drangsholt, M. & List, T. (2010) Reliability of intraoral quantitative sensory testing (qst). *Pain* **148**: 220-226.

Pigg, M., List, T., Petersson, K., Lindh, C. & Petersson, A. (2011) Diagnostic yield of conventional radiographic and cone-beam computed tomographic images in patients with atypical odontalgia. *Int Endod J* **44**: 1092-1101.

Porporatti, A. L., Costa, Y. M., Stuginski-Barbosa, J., Bonjardim, L. R. & Conti, P. C. (2015) Effect of topical anaesthesia in patients with persistent dentoalveolar pain disorders: A quantitative sensory testing evaluation. *Arch Oral Biol* **60**: 973-981.

Porporatti, A. L., Costa, Y. M., Stuginski-Barbosa, J., Bonjardim, L. R., Conti, P. C. & Svensson, P. (2015) Quantitative methods for somatosensory evaluation in atypical odontalgia. *Braz Oral Res* **29**.

Rocha, A. P. C. e. a. (2007) Dor: Aspectos atuais da sensibilização periférica e central. *Rev Bras Anestesiol* **57**: 94-105.

Rolke, R., Baron, R., Maier, C., Tolle, T. R., Treede, R. D., Beyer, A., Binder, A., Birbaumer, N., Birklein, F., Botefur, I. C., Braune, S., Flor, H., Huge, V., Klug, R., Landwehrmeyer, G. B., Magerl, W., Maihofner, C., Rolko, C., Schaub, C., Scherens, A., Sprenger, T., Valet, M. & Wasserka, B. (2006) Quantitative sensory testing in the german research network on neuropathic pain (dfns): Standardized protocol and reference values. *Pain* **123**: 231-243.

Rolke, R., Magerl, W., Campbell, K. A., Schalber, C., Caspari, S., Birklein, F. & Treede, R. D. (2006) Quantitative sensory testing: A comprehensive protocol for clinical trials. *Eur J Pain* **10**: 77-88.

Rosenlicht, C. A. B. J. A. H. J. T. K. J. L. (2011) Dental implants the art and science. 2nd edition: Elsevier.

Shavit, I. & Juodzbalys, G. (2014) Inferior alveolar nerve injuries following implant placement - importance of early diagnosis and treatment: A systematic review. *J Oral Maxillofac Res* **5**: e2.

Shen, J., Wang, H. Q., Zhou, C. P. & Liang, B. L. (2008) Magnetic resonance microneurography of rabbit sciatic nerve on a 1.5-t clinical mr system correlated with gross anatomy. *Microsurgery* **28**: 32-36.

Shimazaki, T., Otsuka, T., Akimoto, S., Kubo, K. Y., Sato, S. & Sasaguri, K. (2012) Comparison of brain activation via tooth stimulation. *J Dent Res* **91**: 759-763.

Svensson, P., Baad-Hansen, L., Pigg, M., List, T., Eliav, E., Ettlin, D., Michelotti, A., Tsukiyama, Y., Matsuka, Y., Jaaskelainen, S. K., Essick, G., Greenspan, J. D., Drangsholt, M. & Special Interest Group of Oro-facial, P. (2011) Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. *J Oral Rehabil* **38**: 366-394.

Vickers, E. R., Cousins, M. J., Walker, S. & Chisholm, K. (1998) Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **85**: 24-32.

Zagury, J. G., Eliav, E., Heir, G. M., Nasri-Heir, C., Ananthan, S., Pertes, R., Sharav, Y. & Benoliel, R. (2011) Prolonged gingival cold allodynia: A novel finding in patients with atypical odontalgia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **111**: 312-319.

3 Discussion

3 DISCUSSION

The two studies presented in this thesis feature relevant data about the somatosensory function of three different pain conditions: somatic, visceral, and neuropathic pain. To the best of the author's knowledge, both studies featured completely unpublished new data and revealed that the suggested QSTs are useful tools to discriminate inflammatory toothache and atypical odontalgia, where touch threshold forces > 1 g/mm2 and pain threshold forces > 10g/mm2 were the most accurate cut-off values. Also, we discovered loss of function for touch threshold and electrical threshold of C fibers in inflammatory toothache (IT); and somatosensory abnormalities compatible with allodynia, reduced touch and pain thresholds, and impaired pain modulation system found only in atypical odontalgia (AO). As an important result of this study, no somatosensory alterations after implant surgery (IMP group) were found; and a reduction on electrical threshold of C fiber was reported after 3 months of pulpectomy.

The clinical differential diagnosis between inflammatory toothache and neuropathic pain is still challenging; however, for IT, the clinical diagnosis is well documented and valuable. A histological study evaluated 95 extracted teeth, which were clinically categorized as having normal pulps, reversible pulpitis, or irreversible pulpitis. The results presented show that clinical diagnosis of normal pulp/reversible pulpitis matched the histologic diagnosis in almost 97% of cases. For the diagnosis of irreversible pulpitis, it occurred in 85% of cases. This study proved that the classification of pulp conditions as normal pulps, reversible pulpitis, and irreversible pulpitis has high chances of guiding the correct therapy in the vast majority of cases (RICUCCI; LOGHIN; SIQUEIRA, 2014).

Diagnostic methods for inflammatory toothache are based on data from subjective examination (chief complaint and dental history), visual inspection, radiographic examination, and response to stimuli application (pulp tests) (RICUCCI; LOGHIN; SIQUEIRA, 2014). The accuracy of different pulp tests was evaluated in a study comparing clinical accuracy, reliability, and repeatability of laser Doppler flowmetry, an electric pulp test, and thermal pulp sensibility tests such as CO2, EndoFrost, and ice. Pulp tests were performed in 121 teeth of 20 subjects and the results showed CO2, electric, and laser tests were reliable and the most accurate tests. EndoFrost was reliable but not as accurate as electrical tests and CO2. Ice was

the most repeatable but the least accurate and least reliable test (CHEN; ABBOTT, 2011).

In addition to that, another study presented values of accuracy for Endo Ice results showed sensitivity of 0.92, specificity of 0.89, positive predictive value of 0.86, and negative predictive value of 0.94. The results for electrical tests showed sensitivity of 0.84, specificity of 0.74, positive predictive value of 0.58, and negative predictive value of 0.90. This study concluded that pulpal sensibility testing with Endo Ice and electrical tests are accurate and reliable methods of determining pulpal vitality (JESPERSEN et al., 2014).

When pain persists after endodontic treatment, it frequently becomes a torturing phase for the patients. In a recent review, the authors presented a case of Atypical Odontalgia, where the patients visited innumerous dentists and repeated and unnecessary dentistry procedures, trying to relieve the pain without success (KHAN; MAIXNER; LIM, 2014).

> Middle-aged woman visited a clinician with the chief complaint that her tooth hurt despite having been treated several times by an endodontist to whom she had been referred. Over the previous year, the endodontist had performed nonsurgical endodontic therapy on her maxillary right first molar and six months later performed surgical endodontic therapy (that is, an apicectomy and a retrograde root canal filling) in an attempt to resolve her pain. However, this treatment was unsuccessful. The patient then sought a second opinion from another dentist, who advised her to have the tooth extracted and an implant placed; however, she chose not to pursue these treatment options. The patient reported that her pain intensity had not changed since she underwent the original endodontic treatment. Analgesics such as ibuprofen and acetaminophen had little or no effect on her pain. The clinical examination did not reveal any dental pathology. A periapical radiograph of the tooth and a cone-beam computed tomographic scan of the quadrant failed to identify any pathological lesion that could have contributed to her pain (KHAN; MAIXNER; LIM, 2014).

In a study, adults from a private clinic who received endodontic therapy were evaluated after periods from 3 to 5 years to check for remaining pain. Persistent pain here was defined as pain occurring spontaneously or elicited by percussion, palpation, or biting. The results showed that 5% of the patients reported persistent pain. Of all persistent pain cases, 38% were due to an odontogenic pain (periapical pathosis and/or root fracture) and in 62% no obvious odontogenic cause was found. Also, no association was found between persistent non-odontogenic pain and sex, age, tooth type, type of dentist (specialists or generalists), or arch (mandible or

maxilla). Lastly, 3.1% of patients experience persistent pain not attributable to odontogenic causes 3-5 years after endodontics, which impacts their quality of life (VENA et al., 2014).

Regarding the possible complications and survival characteristic for endodontic procedures, a systematic review investigated the effect of therapy characteristics on reported tooth survival after root canal treatment. Fourteen longitudinal human clinical studies published up to 2007 were included. The results revealed a pooled percentage of reported tooth survival over 8-10 years following 87% of cases. Furthermore, a meta-analysis was performed with four studies and four conditions were found to significantly improve tooth survival. The prognostic characteristics presented were crown restoration after endodontics, tooth having both mesial and distal proximal contacts, tooth not functioning as an abutment for removable or fixed prosthesis, and tooth type or specifically non-molar teeth (NG; MANN; GULABIVALA, 2010).

Tooth retention with root canal treatment and tooth replacement with implant treatment are well documented in literature, and both techniques have their own indications; however, sometimes clinicians have difficulty to choose between keeping the tooth or replacing it with an implant. In order to address this procedural dilemma, a study was carried out to compare nonsurgical root canal treatment and single delayed implant therapy with regards to the degree of preoperative and postoperative pain, complications, and patient satisfaction. Twenty-four patients had initial nonsurgical root canal treatment, and another 24 had single implant treatment in healed sites and the results proved that no significant difference in pain, complications, or overall satisfaction was noted between the 2 groups in a 12-month follow-up period (TORABINEJAD et al., 2014).

Indeed all the most sophisticated and accurate method for diagnostics, the clinicians must have in mind that persistent tooth pain after denstistry procedures is possible related to odontogenic or nonodontogenic etiologies. Whereas odontogenic pain usually resolves after endodontic therapy, dentistry therapy, or even surgeries, nonodontogenic pain is best managed by an orofacial pain expert, and the treatment should include medications and sometimes corticoid infiltration (KHAN; MAIXNER; LIM, 2014).

The approach of somatosensory function in patients with intra-oral neuropathic pain is a relatively new one, and therefore only a few studies have been published so

far. New studies and further research on quantitative and qualitative sensory tests are mandatory. Somatosensory evaluation is an essential method to understand the sensation perception, alteration on nerve fibers, and maintenance of pain and modulation systems, which amplify our knowledge about this painful neuropathic condition.

Based on the collected sample of this thesis, the jaw was the most affected region of AO with 64% of cases. This was in accordance to other studies that showed the jaw as the most prevalent with 80% (BAAD-HANSEN et al., 2007), 65,7% (BAAD-HANSEN et al., 2006), and 56% (LIST; LEIJON; SVENSSON, 2008).

Atypical Odontalgia is a continuous chronic pain, which is very distressing and painful for the patient, lasting for months or even years. The average pain duration of AO group in this study was 3 and a half years (42.3 months), and this is not only evidence of the harsh reality of AO patients, but also a reason to seek a better understanding of the basic mechanisms of pain. Vickers, when analyzing 50 patients with AO, found a mean duration of 4.9 years, ranging from 3 months to 32 years (VICKERS et al., 1998).

A better understanding of pain mechanisms is extremely important, as well as conducting an accurate differential diagnosis. Dentists need to understand about differential diagnosis of odontogenic and non-odontogenic pain in order to carry out a more appropriate approach for both types of patients. The differential diagnosis is an essential part and the use of complementary methods of diagnosis was fundamental here. The performance of conventional radiographs (periapical and panoramic radiographies) is a basic approach for better differentiation of AO pain and dental problems such as cavities, periodontal problems, and bone problems. However, possibly due to the precision required to complete the AO diagnosis, performed by excluding any other possible pathology, the use of more sophisticated radiographic images may become necessary. In this study 65% of patients with suspected AO performed a cone-beam computed tomographic (CBCT) to aid in the differential diagnosis.

The periapical and panoramic radiographic techniques have been used as parameters for the images examination in the OA diagnosis (PORPORATTI et al., 2015). For an improved diagnostics, the use of cone-beam computed tomographic (CBCT) imaging has been shown to increase the frequency of detection of periapical radiolucencies over conventional periapical radiography (ESTRELA et al., 2008).

Additionally, it was recently noticed that the use of CBCT in patients with suspected AO improves the differentiation between AO and Symptomatic Apical Periodontitis (SAP). In the study of Pigg and colleagues, the additional diagnostic examination of the CBCT on the use of conventional radiographs in patients with initial suspicion of AO was tested. Also, the hypothesis that CBCT improves the differentiation between AO and SAP was evaluated. SAP is a continued and recurrent pain that originates from the persistent inflammation of the tooth's periodontic region (PIGG et al., 2011). In this study, 25 patients were analyzed, with 20 patients were diagnosed with OA and 5 with SAP. It was concluded that CBCT was able to assess 17% more periapical bone destruction compared to conventional radiographs. CBCT should be an important image method to aid in the diagnosis of OA, and should be requested more frequently in all suspected patients of intra-oral neuropathic pain (PIGG et al., 2011).

A recent systematic review searched reliable methods for somatosensory evaluation in patients with atypical odontalgia. This review included data analysis of the databases PubMed, LILACS, Cochrane (including Central Cochrane), and Current Controlled Trials, from January 1990 to August 2011, in English, Portuguese, or Spanish. As conclusions of the 4 studies included in this systematic review, the reliability of some quantitative sensory tests were certified such as the dynamical mechanical tests (DMA) with cotton swab and toothbrush, the wind-up ratio test (WUR), and the heat pain threshold test. In addition, additional QSTs appear to be helpful when the patients were compared to healthy controls, such as mechanical tests (allodynia, tactile, and pain threshold tests) and heat thermal tests (PORPORATTI et al., 2015).

Due to difficulties in diagnosis, often the AO patient seek several professionals in an attempt to relieve the pain. In our study, some of the research subjects were already using pain medications. One patient was using Amitriptyline® (25mg), 6 Gabapentin® (300mg), 3 Carbamazepine® (200mg), 2 Duloxetine® (30mg), and one Topiramate® (25mg). For these patients, however, no significant reduction in pain was achieved. In the initial consultation, mean pain intensity was 62.5 +- 23.47 on a visual analog scale. In a similar study, Zagury and collaborators evaluated AO patients, and 55% of them were under use of medications for neuropathic pain, such as opioids, antidepressants, anticonvulsants, or combinations. Pain intensity was not

different between patients taking medications and those who were not taking any (ZAGURY et al., 2011).

In a clinical setting, it is important to know how a result of diagnostic tests discriminates diseased patients from healthy ones. The first paper presented in this thesis aimed to evaluate how accurately QST discriminates a diagnosis of inflammatory toothache or atypical odontalgia. To the best of the author`s knowledge, this is the first study to validate QST for AO and IT differential diagnosis, as well as to determine the best cut-off values for the QST presented. Sensitivity, specificity, likelihood ratio, and ROC curves analysis were used here for the diagnostic accuracy. These data play a central role in evaluating diagnostic ability of tests to discriminate healthy patients from diseased ones (ZOU; O'MALLEY; MAURI, 2007). ROC curves allow finding the cut-off values of each test. The greater the area under the ROC curve, the higher the capacity to discriminate AO from IT or healthy individuals, and the more useful is the method (ZOU; O'MALLEY; MAURI, 2007). Touch threshold forces > 1 g/mm^2 (AUC=0.867, Sensitivity 60%, Specificity 91.67%) and pain threshold forces > 10g/mm^2 (AUC=0.834, Sensitivity 75%, Specificity 79.17%) were found in our study to be used accurately for discrimination between AO from IT.

Although not always possible, the best test should cover both highly sensitive and highly specific. When we change cut-off point between a diseased patient from healthy one, e.g. to increase either sensitivity or specificity, usually a concomitant decrease takes place in the other (AKOBENG, 2007). Highly sensitive tests are particularly important in the diagnosis of illnesses that might lead to death or irreversible damage (AKOBENG, 2007). In our study, we focused in high specificity QST to discriminate a diagnosis of IT or AO. Low specificity tests could lead to overtreatment, with possible biological, psychological, and financial damage to the individual (AKOBENG, 2007).

In our study, all the QST tested presented specificity ranging from 75% to 95%, which was acceptable. Only for Temporal summation test the specificity was low (37.5%), however this test did not prove to be an accurate QST for the diseases studied here.

The QST used in this study had already been tested. The reliability of comprehensive intra-oral QST protocol has been examined in patients with atypical odontalgia and healthy controls in a multicenter study. They evaluated 45 patients

with AO and 68 healthy controls and the results showed no differences in reliability measures, nor was within-session variability detected between patients with AO and the healthy reference group. They concluded intra-oral QST is sufficiently reliable for use as a part of a comprehensive evaluation of somatosensory function of neuropathic pain (BAAD-HANSEN et al., 2015).

A recent research presented stratified values of QST for gender, age, and sites in trigeminal region. The study evaluated 70 healthy individuals, which were divided into two groups according to age: younger group (16 female, 16 male, age 24-40 years old) and elder group (20 female, 18 male, age 41-69 years old). The 13 standardized QST battery developed by the German Research Network were performed bilaterally over the infraorbital, mental, and hand regions. Their results revealed women were more sensitive than men for most of the QST. Also, the younger group was more sensitive for heat pain threshold (HPT), warmth detection threshold (WDT), mechanical detection threshold (MDT), pressure pain threshold (PPT), cold pain threshold (CPT), cold detection threshold (CDT), and wind-up ratio (WUR). For the sites, infraorbital and mental were more sensitive than the hand for CDT, HPT, WDT, thermal sensory limen (TSL), MDT, MPT, MPS, and PPT (YANG et al., 2015).

Evaluation of somatosensory function is a significant field exponentially growing in research and clinical practice of dentistry. It is believed that QST provides better understanding of sensory mechanisms underlying a variety of pain conditions (ROLKE et al., 2006; PIGG et al., 2010). After damages to nervous system, the patient can face three situations: the most common one is that peripheral inflammation and pain are ceased and sensory system may work as usual again (MEIER et al., 2015); as a second situation, pain may be evoked by innocuous and nociceptive stimulus, leading to allodynia and hyperalgesia; and the third condition clues to hypoesthesia, hypoalgesia, parestesia and analgesia sensations (SVENSSON et al., 2011; PORPORATTI et al., 2015).

This nerve damage may persist in 3-6% of patients who receive dentistry management such as endodontic procedures and around 13% in cases of post-implant neuropathic pain (ELLIES; HAWKER, 1993). In this study, no patient developed persistent pain or parestesia after implant surgery or pulpectomy. After two hours of surgery, pain relieved in the IMP group, and after 5 hours of pulpectomy in the IT group. Our results are contradictory to studies that showed patients

receiving dental implants and then experienced sensory disturbances such as parestesia in 7-39% of cases (SHAVIT; JUODZBALYS, 2014; AL-SABBAGH et al., 2015).

Also, these surgical nerve injuries may lead to neuropathic pain. Recent evidence evaluated 46 patients scheduled for iliac crest bone harvest two days and three months after surgery, and a possible association between partial nerve lesions and more intense neuropathic pain was found instead of that with total nerve lesion. Additionally, preoperative pain and opioid use were higher in patients who developed neuropathy (MARTINEZ et al., 2015). In our study, no patients submitted to installation of dental implants presented somatosensory abnormalities after one and three months of surgery.

Studies have shown that blockade of myelinated fibers (A-beta, A-Delta) was not capable of reducing mechanical hyperalgesia in patients with neuropathic pain, revealing that unmyelinated C fibers are partially responsible for these hyperalgesia symptoms (OCHOA; YARNITSKY, 1993).

Another frequent sensory phenomenon in patients with neuropathic pain is allodynia, which can be interpreted as pain report due to an innocuous stimulus (not painful) (BAAD-HANSEN, 2008; LEEUW., 2008). Dynamic mechanical testing assesses the presence of allodynia. This test activates low-threshold mechanoreceptors (Meissner corpuscle, Pacine corpuscle, and hair follicle), and A-Beta fibers nerve impulses are triggered to the Central Nervous System (CNS). When in the CNS, increased neural excitability in subnucleus region of the trigeminal nerve succeeds (WALK et al., 2009).

Trigeminal subnucleus caudalis is very affected by injuries from peripheral afferent neurons. Anatomical and physiological changes are related to a synaptic disorganization, sprouting the spatial distribution of intact afferent endings in the peripheral and subnucleus region. Due to the sprouting of new nerve endings, the receptive fields are increased, which leads to the perception of tactile stimuli as painful (WOOLF; MANNION, 1999; VICKERS; COUSINS, 2000; CONTI et al., 2003).

In our study, Dynamic Mechanical Allodynia tests showed significantly higher values when comparing the somatic and visceral groups. The light vibration of a cotton swab on the dentoalveolar region of patients proved those who reported pain had it identified as neuropathic pain and those who did not report pain had it identified as inflammatory toothache. Allodynia here reflects the presence of central

sensitization in patients with AO and demonstrates that peripheral nerve impulses alone do not explain the constant pain in these patients, suggesting a dysfunction in sensory nociceptive pathways more amplified and centralized.

The use of allodynia tests is simple to perform. They are inexpensive and can be carried out by professionals in a clinical setting. For this, the professional should only vibrate a cotton swab (for 10 seconds) in the region where the patient reports pain. To compare the sensory change and the intensity of pain reported, clinicians might use the contralateral side of the patient without pain as control.

Mechanical detection threshold and mechanical pain threshold tests are important methods to evaluate the mechanical impulses from peripheral fibers. MDT evaluates low-threshold mechanoreceptors, such as Ruffini endings, hair follicles, Merkel disks, and Meissner corpuscles. These receptors trigger the touch impulses through myelinated A-Beta fibers. PDT evaluates high-threshold mechanoreceptors, such as unencapsulated receptors, leading to impulses to CNS through C and A-delta fibers (WALK et al., 2009). Our results revealed loss of function for MDT tests and electrical threshold of C fibers in IT subjects, and also reduced touch and pain thresholds in AO subjects.

The present study findings may help understand the mechanisms involved in somatic, visceral, and neuropathic pain, especially when it comprises clinical differential diagnosis between inflammatory toothache and intra-oral neuropathic pain and embraces peripheral mechanisms on origin of nerve transmission from myelinated and unmyelinated fibers of somatic, visceral, and neuropathic pain.

When a patient visits a clinician with the chief complaint of persistent pain after root canal treatment, there are some difficulties for the dentist to discriminate if pain persists because the root canal was not well treated or because the patient had developed a neuropathic pain. So, the present study had the importance to propose some complementary diagnostic quantitative sensory testing, which will help dentists to distinguish an inflammatory toothache patient from a patient with neuropathic pain. The other results presented were more technical and were key features to detail somatosensory alterations in nerve fibers for somatic pain after implant surgery and for visceral pain after pulpectomy. Three of the four existing nerve fibers in the orofacial region were studies: A-beta, A-delta, and C fiber. Furthermore, by knowing exactly which of these fibers may became damage after procedures, it will be possible to develop specific drugs to treat nerve disease more accurately.

This study showed that somatosensory abnormalities are compatible with AO and with IT subjects, even after 3 months of pulpectomy, and no somatosensory modification is seen after implant surgery. In addition, the most accurate QSTs to discriminate diagnostic differences between IT and AO were MDT, PDT, and DMA. The proposed QSTs may aid in the differential diagnosis with strong accuracy, and may be used as complementary diagnostic tests. This study plays an important role on basic mechanisms of pain from different pain conditions, which could help clinicians to better understand the prognosis of diverse dentistry therapies.

4 Conclusions

4 CONCLUSIONS

Based on the results presented in this thesis, it can be concluded that:

1. Some Quantitative Sensory Testing might aid in the differential diagnosis of atypical odontalgia and inflammatory toothache with strong accuracy;
2. Some Quantitative Sensory Testing may be used as complementary diagnostic tests;
3. The most accurate Quantitative Sensory Testing for differential diagnosis between subjects with atypical odontalgia and inflammatory toothache are the mechanical detection threshold test, the pain detection threshold test, and dynamical mechanical allodynia test;
4. Touch threshold forces > 1 g/mm^2 and pain threshold forces > 10g/mm^2 can be used to accurately discriminate atypical odontalgia from inflammatory toothache;
5. Loss of function for touch threshold and electrical threshold of C fibers is present in inflammatory toothache;
6. Allodynia, hyperalgesia, gain of function for touch and pain thresholds and impaired pain modulation is detected in atypical odontalgia;
7. No somatosensory modification is found after implant surgery;
8. Reduced electrical threshold in C fiber is found in patients with inflammatory toothache after 3 months of pulpectomy.

References

REFERENCES

Akobeng AK. Understanding diagnostic tests 3: Receiver operating characteristic curves. Acta Paediatr. 2007 May;96(5):644-7.

Al-Sabbagh M, Okeson JP, Khalaf MW, Bhavsar I. Persistent pain and neurosensory disturbance after dental implant surgery: pathophysiology, etiology, and diagnosis. Dent Clin North Am. 2015 Jan;59(1):131-42.

Auvenshine RC. Temporomandibular disorders: associated features. Dental clinics of North America. 2007 Jan;51(1):105-27, vi.

Baad-Hansen L. Atypical odontalgia - pathophysiology and clinical management. J Oral Rehabil. 2008 Jan;35(1):1-11.

Baad-Hansen L, Juhl GI, Jensen TS, Brandsborg B, Svensson P. Differential effect of intravenous S-ketamine and fentanyl on atypical odontalgia and capsaicin-evoked pain. Pain. 2007 May;129(1-2):46-54.

Baad-Hansen L, List T, Jensen TS, Svensson P. Increased pain sensitivity to intraoral capsaicin in patients with atypical odontalgia. J Orofac Pain. 2006 Spring;20(2):107-14.

Baad-Hansen L, Pigg M, Yang G, List T, Svensson P, Drangsholt M. Reliability of intra-oral quantitative sensory testing (QST) in patients with atypical odontalgia and healthy controls - a multicentre study. J Oral Rehabil. 2015 Feb;42(2):127-35.

Caissie R, Landry PE, Paquin R, Champigny MF, Berthod F. Quantitative method to evaluate the functionality of the trigeminal nerve. J Oral Maxillofac Surg. 2007 Nov;65(11):2254-9.

Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. Oral Surg Oral Med Oral Pathol. 1990 Mar;69(3):287-90.

Chen E, Abbott PV. Evaluation of accuracy, reliability, and repeatability of five dental pulp tests. J Endod. 2011 Dec;37(12):1619-23.

Conti PC, Pertes RA, Heir GM, Nasri C, Cohen HV, Araujo Cdos R. Orofacial pain: basic mechanisms and implication for successful management. J Appl Oral Sci. 2003 Mar;11(1):1-7.

Ellies LG, Hawker PB. The prevalence of altered sensation associated with implant surgery. Int J Oral Maxillofac Implants. 1993 8(6):674-9.

Estrela C, Bueno MR, Leles CR, Azevedo B, Azevedo JR. Accuracy of cone beam computed tomography and panoramic and periapical radiography for detection of apical periodontitis. J Endod. 2008 Mar;34(3):273-9.

Fornasari D. Pain mechanisms in patients with chronic pain. Clinical drug investigation. 2012 Feb 22;32 Suppl 1(45-52.

Gaul C, Ettlin D, Pfau DB. [Persistent idiopathic facial pain and atypical odontalgia]. Zeitschrift fur Evidenz, Fortbildung und Qualitat im Gesundheitswesen. 2013 107(4-5):309-13.

Graff-Radford SB, Solberg WK. Atypical odontalgia. J Craniomandib Disord. 1992 Fall;6(4):260-5.

Graven-Nielsen T, Arendt-Nielsen L, Madeleine P, Svensson P. [Pain mechanisms in chronic musculoskeletal conditions]. Ugeskr Laeger. 2010 Jun 14;172(24):1824-7.

GUYTON AC, HALL, J.E Tratado De Fisiologia Médica. Rio de Janeiro: Guanabara Koogan; 2002.

Jespersen JJ, Hellstein J, Williamson A, Johnson WT, Qian F. Evaluation of dental pulp sensibility tests in a clinical setting. J Endod. 2014 Mar;40(3):351-4.

Khan AA, Maixner W, Lim PF. Persistent pain after endodontic therapy. J Am Dent Assoc. 2014 Mar;145(3):270-2.

Leeuw. Rd. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management. American Academy of Orofacial Pain. 4th ed: Quintessence; 2008.

List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: A case-control study. Pain. 2008 Oct 15;139(2):333-41.

Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part I: Evidence derived from pathophysiology and treatment. Oral Surg Oral Med Oral Pathol. 1993a Jan;75(1):95-105.

Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part II: Psychosocial considerations. Oral Surg Oral Med Oral Pathol. 1993b Feb;75(2):225-32.

Marbach JJ, Hulbrock J, Hohn C, Segal AG. Incidence of phantom tooth pain: an atypical facial neuralgia. Oral Surg Oral Med Oral Pathol. 1982 Feb;53(2):190-3.

Martinez V, Uceyler N, Ben Ammar S, Alvarez JC, Gaudot F, Sommer C, et al. Clinical, histological and biochemical predictors of post-surgical neuropathic pain. Pain. 2015 Jul 7;

Matwychuk MJ. Diagnostic challenges of neuropathic tooth pain. Journal. 2004 Sep;70(8):542-6.

Meier ML, Widmayer S, Abazi J, Brugger M, Lukic N, Luchinger R, et al. The human brain response to dental pain relief. J Dent Res. 2015 May;94(5):690-6.

Melis M, Secci S. Diagnosis and treatment of atypical odontalgia: a review of the literature and two case reports. J Contemp Dent Pract. 2007 8(3):81-9.

Ng YL, Mann V, Gulabivala K. Tooth survival following non-surgical root canal treatment: a systematic review of the literature. Int Endod J. 2010 Mar;43(3):171-89.

Nixdorf DR, Drangsholt MT, Ettlin DA, Gaul C, De Leeuw R, Svensson P, et al. Classifying orofacial pains: a new proposal of taxonomy based on ontology. J Oral Rehabil. 2012 Mar;39(3):161-9.

Ochoa JL, Yarnitsky D. Mechanical hyperalgesias in neuropathic pain patients: dynamic and static subtypes. Ann Neurol. 1993 May;33(5):465-72.

Ogura K, Kimoto S, Kobayashi K, Yamaguchi H, Saito T. [Reliability of the measurement of current perception thresholds in the palatal mucosa]. Nihon Hotetsu Shika Gakkai zasshi. 2006 Jul;50(3):432-40.

Ogura K, Kimoto S, Yamaguchi H, Kobayashi K. Perception thresholds for electrical stimulation of the palatal mucosa. Int J Prosthodont. 2007 Jul-Aug;20(4):423-31.

Okeson J. Sinais e sintomas das Desordens Temporomandibulares. In: Tratamento das Desordens Temporomandibulares e Oclusão. 4a. edOkeson J, editor. São Paulo: Artes Médicas; 2000. p. 141-80.

Okeson JP. Bell`s orofacial pains. ed 6 ed. Chicago: Quintessence; 2005.

Pertes RAG, Sheldon G. Tratamento clínico das disfunções temporomandibulares e da dor orofacial.: Quintessence; 2005. 368 p.

Pigg M, Baad-Hansen L, Svensson P, Drangsholt M, List T. Reliability of intraoral quantitative sensory testing (QST). Pain. 2010 Feb;148(2):220-6.

Pigg M, List T, Petersson K, Lindh C, Petersson A. Diagnostic yield of conventional radiographic and cone-beam computed tomographic images in patients with atypical odontalgia. Int Endod J. 2011 Dec;44(12):1092-101.

Pigg M, Svensson P, Drangsholt M, List T. Seven-year follow-up of patients diagnosed with atypical odontalgia: a prospective study. J Orofac Pain. 2013 Spring;27(2):151-64.

Porporatti AL, Costa YM, Stuginski-Barbosa J, Bonjardim LR, Conti PC, Svensson P. Quantitative methods for somatosensory evaluation in atypical odontalgia. Brazilian oral research. 2015 29(1):

Ricucci D, Loghin S, Siqueira JF, Jr. Correlation between Clinical and Histologic Pulp Diagnoses. J Endod. 2014 Dec;40(12):1932-9.

Rocha APCea. Dor: Aspectos Atuais da Sensibilização Periférica e Central. Rev Bras Anestesiol. 2007 57(1):94-105.

Rolke R, Baron R, Maier C, Tolle TR, Treede RD, Beyer A, et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): standardized protocol and reference values. Pain. 2006a Aug;123(3):231-43.

Rolke R, Magerl W, Campbell KA, Schalber C, Caspari S, Birklein F, et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. Eur J Pain. 2006b Jan;10(1):77-88.

Shavit I, Juodzbalys G. Inferior alveolar nerve injuries following implant placement - importance of early diagnosis and treatment: a systematic review. Journal of oral & maxillofacial research. 2014 Oct-Dec;5(4):e2.

Svensson P, Baad-Hansen L, Pigg M, List T, Eliav E, Ettlin D, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. J Oral Rehabil. 2011 May;38(5):366-94.

Tarce M, Barbieri C, Sardella A. Atypical odontalgia: an up-to-date view. Minerva Stomatol. 2013 May;62(5):163-81.

Torabinejad M, Salha W, Lozada JL, Hung YL, Garbacea A. Degree of patient pain, complications, and satisfaction after root canal treatment or a single implant: a preliminary prospective investigation. J Endod. 2014 Dec;40(12):1940-5.

Vena DA, Collie D, Wu H, Gibbs JL, Broder HL, Curro FA, et al. Prevalence of persistent pain 3 to 5 years post primary root canal therapy and its impact on oral health-related quality of life: PEARL Network findings. J Endod. 2014 Dec;40(12):1917-21.

Vickers ER, Cousins MJ. Neuropathic orofacial pain part 1--prevalence and pathophysiology. Aust Endod J. 2000 Apr;26(1):19-26.

Vickers ER, Cousins MJ, Walker S, Chisholm K. Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1998 Jan;85(1):24-32.

Walk D, Sehgal N, Moeller-Bertram T, Edwards RR, Wasan A, Wallace M, et al. Quantitative sensory testing and mapping: a review of nonautomated quantitative methods for examination of the patient with neuropathic pain. Clin J Pain. 2009 Sep;25(7):632-40.

Woda A, Pionchon P. A unified concept of idiopathic orofacial pain: clinical features. J Orofac Pain. 1999 Summer;13(3):172-84; discussion 85-95.

Woolf CJ, Mannion RJ. Neuropathic pain: aetiology, symptoms, mechanisms, and management. Lancet. 1999 Jun 5;353(9168):1959-64.

Yang GJ, Cao Y, Zhang L, Qin XY, Xie QF. [Data of the quantitative orofacial somatosensory functions of healthy subjects and its influence factors analysis]. Beijing da xue xue bao Yi xue ban = Journal of Peking University Health sciences. 2015 Jun 18;47(3):521-8.

Zagury JG, Eliav E, Heir GM, Nasri-Heir C, Ananthan S, Pertes R, et al. Prolonged gingival cold allodynia: a novel finding in patients with atypical odontalgia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011 Mar;111(3):312-9.

Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation. 2007 Feb 6;115(5):654-7.

Annexes

ANNEX A

Relatório Inicial Comitê de Ética em Seres Humanos

Faculdade de Odontologia de Bauru – Universidade de São Paulo

FACULDADE DE ODONTOLOGIA DE BAURU-USP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação Comparativa dos Mecanismos Somatossensoriais Envolvidos na Gênese das Dores Orofaciais de Origem Somática, Visceral e Neuropática.

Pesquisador: André Porporatti

Área Temática:

Versão: 3

CAAE: 19840113.2.0000.5417

Instituição Proponente: Universidade de Sao Paulo

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DO PARECER

Número do Parecer: 682.359

Data da Relatoria: 09/06/2014

Apresentação do Projeto:

Informa o pesquisador que de acordo com sua origem, as dores orofaciais podem ser divididas em somáticas, viscerais e neuropáticas. A dor somática está relacionada à um estímulo nocivo evidente, sendo uma dor mais precisa e definida, geralmente relacionadas à um trauma periférico, como por exemplo, nas cirurgias de implantes. As dores viscerais têm origem dentro dos órgãos e cavidades internas do corpo e são ativadas pela inflamação, como no exemplo de uma Pulpite Aguda Irreversível (PAI). Já as dores neuropáticas ocorrem na ausência de qualquer estímulo nocivo óbvio e estão possivelmente associadas à uma lesão em fibra nervosa com alteração de sensibilidade, como ocorre na dor da Odontalgia Atípica (OA). O impacto dessas condições na vida do individuo pode ter a importante participação do comportamento de catastrofização. Os objetivos deste estudo serão: 1) Avaliar mecanismos periféricos e centrais de condução neural de pacientes saudáveis com necessidade de tratamento com implantes dentários e pacientes com PAI antes, 01 dia após, 1 mês e 3 meses após a realização do procedimento cirúrgico de implantodontia (estímulo somático) e pulpectomia, respectivamente; 2) Avaliar mecanismos periféricos e centrais de condução neural de pacientes com dores de OA; e 3) Avaliar a influência da catastrofização na percepção de dor. Um total de 60 indivíduos serão incluídos, sendo 20 sujeitos saudáveis, com necessidade de tratamento com implantes dentários

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FACULDADE DE ODONTOLOGIA DE BAURU-USP

(Grupo 01 -Somática), 20 sujeitos com PAI (Grupo 02 - Visceral) e 20 sujeitos com OA(grupo 03 - Neuropática). Os sujeitos da pesquisa serão avaliados por meio do teste sensorial quantitativo (QST) e do teste de condução neural (CPT), além de relatos de dor e questionários de atastrofização. Serão aplicados os testes de Limiar de Detecção Mecânica (MDT), Limiar de Sensibilidade Dolorosa Mecânica (PDT), Teste Mecânico de Alodinia com cotonete (DMA1) e escova dental (DMA2), o Teste de Somação Temporal (WUR) e o Teste de Controle da Modulação da Dor (CPM). A análise estatística será feita através da ANOVA de medidas repetidas com o intuito de se verificar diferenças estatisticamente significativas intra e inter-grupos, considerando um nível de significância de 5%.

Objetivo da Pesquisa:

Objetivo Primário:

Avaliar os mecanismos periféricos e centrais de condução neural de pacientes, antes, 01 dia após, 1 mês e 3 meses após a realização de procedimentos cirúrgicos de implantodontia (estímulo nociceptivo ou somático);Avaliar os mecanismos periféricos e centrais de condução neural de pacientes com dores viscerais do tipo Pulpite Aguda Irreversível, antes, 01 dia após, 1 mês e 3 meses após a realização de procedimentos de pulpectomia;Avaliar os mecanismos periféricos e centrais de condução neural de pacientes com dores neuropáticas crônicas persistentes de Odontalgia Atípica; Objetivo Secundário: Investigar a interação entre a intensidade de dor percebida e sintomas de catastrofização em pacientes com dores somáticas, viscerais e neuropáticas.

Avaliação dos Riscos e Benefícios:

Riscos:

Informa o pesquisador que há risco mínimo aos sujeitos da pesquisa, apenas aqueles inerentes aos procedimentos realizados.

Benefícios:

Este estudo possibilita auxílio aos pesquisadores e profissionais da área de dor orofacial, na avaliação dos pacientes portadores de dores orofaciais de origem somática, visceral e neuropática, objetivando o conhecimento mais aprimorado sobre a qualidade da dor, a percepção sensorial, as alterações na sensibilidade somatossensorial e a capacidade modulatória da dor destes sujeitos.

Endereço: DOUTOR OCTAVIO PINHEIRO BRISOLLA 75 QUADRA 9
Bairro: VILA NOVA CIDADE UNIVERSITARIA **CEP:** 17.012-901
UF: SP **Município:** BAURU
Telefone: (14)3235-8356 **Fax:** (14)3235-8356 **E-mail:** cep@fob.usp.br

FACULDADE DE ODONTOLOGIA DE BAURU-USP

Continuação do Parecer: 682.359

Comentários e Considerações sobre a Pesquisa:

Não há.

Considerações sobre os Termos de apresentação obrigatória:

Referido projeto de pesquisa foi considerado APROVADO por este CEP, e em emenda realizada o pesquisador adiciona o nome dos outros pesquisadores que fazem parte da equipe de pesquisa.

Recomendações:

Tendo em vista a inclusão de outros pesquisadores na equipe, recomenda-se que o pesquisador anexe o currículo dos mesmos.

Conclusões ou Pendências e Lista de Inadequações:

Tendo em vista a emenda realizada apenas para adicionar o nome dos outros pesquisadores que fazem parte da equipe de pesquisa, sou de parecer favorável a modificação informada.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

O CEP reunido extraordinariamente no dia 9.6.2014, com base nas normas éticas da Resolução CNS 466/12, acata o parecer APROVADO emitido pelo relator, referente à EMENDA apresentada. Ao término da pesquisa o CEP-FOB/USP exige a apresentação de relatório final. Os relatórios parciais deverão estar de acordo com o cronograma e/ou parecer emitido pelo CEP. Alterações na metodologia, título, inclusão ou exclusão de autores, cronograma e quaisquer outras mudanças que sejam significativas deverão ser previamente comunicadas a este CEP sob risco de não aprovação do relatório final. Quando da apresentação deste, deverão ser incluídos todos os TCLEs e/ou termos de doação assinados e rubricados.

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FACULDADE DE ODONTOLOGIA DE BAURU-USP

Continuação do Parecer: 682.359

BAURU, 10 de Junho de 2014

Assinado por:
Izabel Regina Fischer Rubira Bullen
(Coordenador)

Endereço: DOUTOR OCTAVIO PINHEIRO BRISOLLA 75 QUADRA 9
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ANNEX B

Aceite Relatório Final Comitê de Ética em Seres Humanos

Faculdade de Odontologia de Bauru – Universidade de São Paulo

FACULDADE DE ODONTOLOGIA DE BAURU-USP

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Avaliação Comparativa dos Mecanismos Somatossensoriais Envolvidos na Gênese das Dores Orofaciais de Origem Somática, Visceral e Neuropática.

Pesquisador: André Porporatti

Área Temática:

Versão: 3

CAAE: 19840113.2.0000.5417

Instituição Proponente: Universidade de Sao Paulo

Patrocinador Principal: FUND COORD DE APERFEICOAMENTO DE PESSOAL DE NIVEL SUP

DADOS DA NOTIFICAÇÃO

Tipo de Notificação: Envio de Relatório Final

Detalhe:

Justificativa: Envio o Relatório final de Pesquisa

Data do Envio: 03/08/2015

Situação da Notificação: Parecer Consubstanciado Emitido

DADOS DO PARECER

Número do Parecer: 1.198.676

Apresentação da Notificação:

Envio de relatório final e TCLEs.

Objetivo da Notificação:

Idem acima.

Avaliação dos Riscos e Benefícios:

Não se aplica.

Comentários e Considerações sobre a Notificação:

Relatório final condizente com metodologia e objetivos.

Considerações sobre os Termos de apresentação obrigatória:

TCLEs assinados e rubricados num total de 60.

Endereço: DOUTOR OCTAVIO PINHEIRO BRISOLLA 75 QUADRA 9
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FACULDADE DE ODONTOLOGIA DE BAURU-USP

Continuação do Parecer: 1.198.676

Recomendações:

Conclusões ou Pendências e Lista de Inadequações:

Nenhuma.

Considerações Finais a critério do CEP:

O CEP reunido ordinariamente no dia 19.08.2015 acata por unanimidade o parecer APROVADO, emitido pelo relator, sobre o relatório final da pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Envio de Relatório Final	Relatorio Final.pdf	02/08/2015 23:19:13		Aceito
Envio de Relatório Final	TCLE IMPLANTE 01-02.pdf	02/08/2015 23:57:48		Aceito
Envio de Relatório Final	TCLE IMPLANTE 03-05.pdf	02/08/2015 23:58:25		Aceito
Envio de Relatório Final	TCLE IMPLANTE 06-10.pdf	02/08/2015 23:59:12		Aceito
Envio de Relatório Final	TCLE IMPLANTE 11-15.pdf	02/08/2015 23:59:53		Aceito
Envio de Relatório Final	TCLE IMPLANTE 16-20.pdf	03/08/2015 00:00:34		Aceito
Envio de Relatório Final	TCLE OA 01-02.pdf	03/08/2015 00:00:55		Aceito
Envio de Relatório Final	TCLE OA 03-05.pdf	03/08/2015 00:01:29		Aceito
Envio de Relatório Final	TCLE OA 06-10.pdf	03/08/2015 00:02:07		Aceito
Envio de Relatório Final	TCLE OA 11-12.pdf	03/08/2015 00:02:29		Aceito
Envio de Relatório Final	TCLE OA 13-15.pdf	03/08/2015 00:03:00		Aceito
Envio de Relatório Final	TCLE OA 16-17.pdf	03/08/2015 00:03:30		Aceito
Envio de Relatório Final	TCLE OA 18-20.pdf	03/08/2015 00:04:02		Aceito
Envio de Relatório Final	TCLE Pulpite 01-05.pdf	03/08/2015 00:04:42		Aceito
Envio de Relatório Final	TCLE Pulpite 06-10.pdf	03/08/2015 00:05:16		Aceito
Envio de Relatório Final	TCLE Pulpite 11-15.pdf	03/08/2015 00:05:55		Aceito

Endereço: DOUTOR OCTAVIO PINHEIRO BRISOLLA 75 QUADRA 9
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FACULDADE DE ODONTOLOGIA DE BAURU-USP

Continuação do Parecer: 1.198.676

Envio de Relatório Final	TCLE Pulpite 16-20.pdf	03/08/2015 00:06:32		Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

BAURU, 25 de Agosto de 2015

Assinado por:
Izabel Regina Fischer Rubira Bullen
(Coordenador)

Endereço: DOUTOR OCTAVIO PINHEIRO BRISOLLA 75 QUADRA 9
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ANNEX C

Email de Submissão Journal of Endodontics (ARTICLE 1)

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain.

De: **The Journal of Endodontics** ees.joe.0.31aa60.9b32f922@eesmail.elsevier.com
Assunto: Submission Confirmation for DIAGNOSTIC ACCURACY OF QUANTITATIVE SENSORY TESTING TO DISCRIMINATE INFLAMMATORY TOOTHACHE AND INTRAORAL NEUROPATHIC PAIN.
Data: 2 de junho de 2015 17:46
Para: andreporporatti@yahoo.com.br

TJ

Dear Dr. Porporatti,

Your submission entitled "DIAGNOSTIC ACCURACY OF QUANTITATIVE SENSORY TESTING TO DISCRIMINATE INFLAMMATORY TOOTHACHE AND INTRAORAL NEUROPATHIC PAIN." has been received by the Journal of Endodontics.

You will be able to check on the progress of your paper by logging on to the Journal of Endodontics web site as an author.

The URL is http://ees.elsevier.com/joe/

Your username is: andreporporatti@yahoo.com.br

If you need to retrieve password details,
please go to: http://ees.elsevier.com/joe/automail_query.asp

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to the Journal of Endodontics.

Kind regards,

Journal of Endodontics

ANNEX D

Email da Primeira Revisão Journal of Endodontics (ARTICLE 1)

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain.

De: **The Journal of Endodontics** ees.joe.0.328ef1.42bbdca8@eesmail.elsevier.com
Assunto: Submission Confirmation for JOE 15-552R1
Data: 13 de julho de 2015 09:00
Para: andreporporatti@yahoo.com.br

TJ

Ref.: Ms. No. JOE 15-552R1
DIAGNOSTIC ACCURACY OF QUANTITATIVE SENSORY TESTING TO DISCRIMINATE INFLAMMATORY TOOTHACHE AND INTRAORAL NEUROPATHIC PAIN.

Dear Dr. Porporatti,

The Journal of Endodontics has received your revised submission.

You may check the status of your manuscript by logging onto the Journal of Endodontics web site.

The URL is http://ees.elsevier.com/joe/

Your username is: andreporporatti@yahoo.com.br

If you need to retrieve password details,
please go to: http://ees.elsevier.com/joe/automail_query.asp

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ANNEX E

Carta aos Revisores Journal of Endodontics (ARTICLE 1)

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain.

06-Jul-2015

Dear Dr.Ken Hargreaves
Editor, Journal of Endodontics

We appreciate the insightful critiques of our manuscript. We carefully considered the Reviewers' suggestions and revised the manuscript "DIAGNOSTIC ACCURACY OF QUANTITATIVE SENSORY TESTING TO DISCRIMINATE INFLAMMATORY TOOTHACHE AND INTRAORAL NEUROPATHIC PAIN, (Ref.: Ms. No. JOE 15-552) accordingly. Specific itemized responses to the Reviewers' comments are listed below. All suggestions and corrections into the text were made using "Text Highlight Color Tool" of Microsoft Office Word.

We would like to inform that we made a professional english review by an specialized association to ensure a better understanding for all of the paper. Furthermore some grammatical changes were performed, which did not compromise the meaning of our study.

We hope that you will now find the manuscript acceptable for publication in Journal of Endodontics

Sincerely and with best Regards
André Luís Porporatti, on behalf of all the authors

Reviewer(s)' Comments to Author:

Reviewer #1: This manuscript touches upon a very important and clinically relevant topic. I have minor comments which I mainly provide to satisfy my (and maybe others) curiosity than to improve on the already excellent data.
Response: Thank you for your kind comments.

1) In authors' experience, are AO and IT mainly prevailing in females?

Response: Sure, in our experience we assist mainly women with dental pain (even AO or IT) in about a proportion of 2-3 women for 1 man. Also literature is clear in asserting that women are more likely to face a variety of recurrent, severe and persistent pain.

References:

- Porporatti AL, Costa YM, Stuginski-Barbosa J, Bonjardim LR, Conti PC.Effect of topical anaesthesia in patients with persistent dentoalveolar pain disorders: A quantitative sensory testing evaluation.Arch Oral Biol. 2015 Jul;60(7):973-81.
- T. List, G. Leijon, M. Helkimo, A. Oster, P. Svensson. Effect of local anesthesia on atypical odontalgia – a randomized controlled trial. Pain, 122 (3) (2006), pp. 306–314
- Vena DA, Collie D, Wu H, Gibbs JL, Broder HL, Curro FA, et al. Prevalence of persistent pain 3 to 5 years post primary root canal therapy and its impact on oral health-related quality of life: PEARL Network findings. J Endod 2014;40(12):1917-1921.
- Girard-Tremblay L, Auclair V, Daigle K, Leonard G, Whittingstall K, Goffaux P. Sex differences in the neural representation of pain unpleasantness. J Pain 2014;15(8):867-877.
- Prevalence of Persistent Pain 3 to 5 Years Post Primary Root Canal Therapy and Its Impact on Oral Health–Related Quality of Life: PEARL Network Findings

2) Why MDT is not named "light touch detection threshold"?

Response: Even your suggestion is clearly understandable, MDT is an initial previously described and defined on published guidelines. We accepted you suggestion and we added this information when describing the MDT test (page 6) . Thanks

Reference:

- Svensson P, Baad-Hansen L, Pigg M, List T, Eliav E, Ettlin D, et al. Guidelines and recommendations for assessment of somatosensory function in oro-facial pain conditions--a taskforce report. J Oral Rehabil 2011;38(5):366-394.

3) Almost all AO patients had comorbidity of pain condition and some other conditions. Is this normal?

Response: Sure, this is a normal situation in clinical setting. As a chronic pain condition, other comorbidities can be present more frequently.

Reference:

- Abiko Y1, Matsuoka H, Chiba I, Toyofuku A. Current evidence on atypical odontalgia: diagnosis and clinical management. Int J Dent. 2012;2012:518-548.

All-in-all, this is a truly outstanding study.
Response: Thank you for your kind comments.

Reviewer #2: This research examined the use of Quantitative sensory testing to differentiate neuropathic pain from acute pulpitis. While the testing is promising, several suggestions are offered:

1) Table 1 - Use "Incisor" instead of "Incisive" to match with other terms of Canine, Premolar, Molar
Response: Ok. Changes made accordingly. Thanks

2) Fig 2 - No y axis legends
Response: Ok. Changes made accordingly. Thanks

3) References need correcting Ref #3 Journal name left off and #31 needs correct abrev. title of journal
Response: Ok. Changes made accordingly. Thanks

4) Unclear if IT group consisted solely of acute pulpitis or was included cases with apical periodontitis
Response: IT group consisted solely of acute pulpitis and cases with apical periodontitis were excluded. This was made clear on text (page 5). Thanks.

5) Analgesics allowed with some patients and while may not influence initial pain severity, it may influence diagnostic testing. Please explain
Response: Although we agree with you, the proposed tests needed to be performed in AO or IT patients when, even if some had analgesics, they had remaining pain greater than 50mm on a VAS. Subjects were excluded if they had no pain on time of evaluation. This method was based in a similar study, where the levels of pain of atypical odontalgia patients were not statistically significant regardless of pain medication status. This was made clear on the text (page 5). Thanks.

Reference:

- Zagury JG, Eliav E, Heir GM, Nasri-Heir C, Ananthan S, Pertes R, et al. Prolonged gingival cold allodynia: a novel finding in patients with atypical odontalgia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2011;111(3):312-319.

6) Pg 7 "01th second" do you mean 1/100th of a second?
Response: Sorry, that was written wrong. Actually we mean "the first second", and the sentence should be this: *"painfulness train of 30 seconds of pinprick stimulations minus the first second of pinprick"*. Changes made accordingly (page 7). Thanks for this consideration.

7) Pg 9 2nd paragraph - when you state "...pain intensity had not improved..." I think it would be cleaner to say "..pain intensity had not decreased..."
Response: Sure. We agree with you. Changes made accordingly.

8) Many grammatical/spelling errors need correcting
Response: We would like to inform that we made a professional english review by an specialized association to ensure a better understanding for all of the paper. Furthermore some grammatical changes were performed, which did not compromise the meaning of our study. Thanks

9) You state on pg 12 that "the accuracy of diagnosis methods for IT is very limited". I disagree with this statement as these are very well defined. The accuracy of diagnosis for AO however is limited.
Response: We totally agree with you. Changes made accordingly in the text. Thanks.

10) Discussion 1st paragraph - Unclear what is meant by 3) pain threshold cutoff forces of ≤15 g/mm2 and ≤ 8 g/mm2 have reasonable accuracy to discriminate individually IT and AO diagnosis..."
Response: We agree with you and we chose to change this sentence. Thanks
Touch threshold forces > 1 g/mm2 and pain threshold forces > 10g/mm2 can be used to accurately discriminate AO from IT.

ANNEX F

Carta de Aceite Journal of Endodontics (ARTICLE 1)

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain.

De: **Elsevier - Article Status** Article_Status@elsevier.com
Assunto: Track your article [JOEN_3195] submitted to Journal of Endodontics
Data: 20 de julho de 2015 05:08
Para: andreporporatti@yahoo.com.br

EA

Please note this is a system generated email from an unmanned mailbox.
If you have any queries we really want to hear from
you via our 24/7 support at http://help.elsevier.com

Dear Mr. Porporatti,

Your article DIAGNOSTIC ACCURACY OF QUANTITATIVE SENSORY TESTING TO DISCRIMINATE INFLAMMATORY TOOTHACHE AND INTRAORAL NEUROPATHIC PAIN. will be published in Journal of Endodontics.

To track the status of your article throughout the publication process, please use our article tracking service:

http://authors.elsevier.com/TrackPaper.html?trk_article=JOEN3195&trk_surname=Porporatti

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[T-12a-20131309]

ANNEX G

Artigo Publicado Journal of Endodontics (ARTICLE 1)

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain

Clinical Research

Diagnostic Accuracy of Quantitative Sensory Testing to Discriminate Inflammatory Toothache and Intraoral Neuropathic Pain

André Luís Porporatti, DDS, MSc, Yuri Martins Costa, DDS, MSc,*† Juliana Stuginski-Barbosa, DDS, PhD,* Leonardo Rigoldi Bonjardim, DDS, PhD,‡ Marco Antônio Hungaro Duarte, DDS, PhD,§ and Paulo César Rodrigues Conti, DDS, PhD**

Abstract

Introduction: A differential diagnosis between inflammatory toothache (IT) and intraoral neuropathic pain is challenging. The aim of this diagnostic study was to quantify somatosensory function of subjects with IT (acute pulpitis) and atypical odontalgia (AO, intraoral neuropathic pain) and healthy volunteers and to quantify how accurately quantitative sensory testing (QST) discriminates an IT or AO diagnosis. **Methods:** The sample consisted of 60 subjects equally divided (n = 20) into 3 groups: (1) IT, (2) AO, and (3) control. A sequence of 4 QST methods was performed over the dentoalveolar mucosa in the apical maxillar or mandibular area: mechanical detection threshold, pain detection threshold (PDT), dynamic mechanical allodynia, and temporal summation. One-way analysis of variance, Tukey post hoc analyses, and z score transformation were applied to the data. In addition, the receiver operating characteristic curve analysis, diagnostic accuracy, sensitivity, specificity, likelihood ratios, and diagnostic odds ratio of the QST methods were calculated (α = 5%). **Results:** Somatosensory abnormalities were found for the AO group, which is consistent with a low detection threshold to touch and pain and the presence of mechanical allodynia. For the IT group, no somatosensory abnormality was observed when compared with the control group. The most accurate QST to discriminate the diagnostic differences between IT and healthy individuals is the PDT. The diagnostic differences between AO and healthy individuals and between IT and AO are best discriminated with the mechanical detection threshold, PDT, and dynamic mechanical allodynia. **Conclusions:** The proposed QST methods may aid in the differential diagnosis between IT and AO with strong accuracy and may be used as complementary diagnostic tests. *(J Endod 2015;41:1606–1613)*

Key Words

Diagnostic accuracy, inflammatory toothache, intraoral neuropathic pain, persistent pain, quantitative sensory testing

Traumatic injuries such as endodontic therapy, apicectomy, tooth extraction, tooth preparation, and inferior alveolar nerve block may damage nerve fibers and disrupt peripheral afferent nerve impulses (1–4). Because of a possible lack of healing of the apical root tissues after some of these traumatic injuries, 3%–6% of patients who undergo endodontic management may experience chronic persistent pain, which is classified as a neuropathic condition (3–5).

Persistent pain after root canal therapy may be related to odontogenic and non-odontogenic etiologies (6, 7). Odontogenic causes result from an untreated or incompletely obturated root canal, root fracture, failure of the apical seal, or pain referred from an adjacent tooth or structure (6). Nonodontogenic causes are trigeminal neuralgia, maxillary sinusitis, temporomandibular disorders, tension-type headaches, and atypical odontalgia (AO) (3, 5, 8–10). AO is a continuous neuropathy of moderate to severe intensity; occurs in the orofacial region and is localized to the dentoalveolar region; is not caused by another disease; and can be identified by clinical, dental, neurologic, and image examination (1, 2, 8, 11).

Although infrequent, when AO cases manifest in the dental office, they are often treated through numerous dental procedures with no pain relief (2, 12). Patients with AO have difficulties accepting their pain condition because of misdiagnoses and repeated ineffective dental procedures that the patients endure (8, 13–15). The differential diagnosis between intraoral AO and inflammatory toothache (IT) is challenging. In patients with AO, pain is continuous, unchanging over weeks or months, with an absence of any local or systemic cause. Furthermore, local tooth provocation does not promote consistent alterations in pain, and repeated endodontic or dental procedures fail to relieve pain (10, 16–18).

Sensory abnormalities such as allodynia; hyperalgesia; and pain exacerbation by thermal, mechanical, and/or chemical stimuli are frequent in AO patients (9, 19). Quantitative sensory testing (QST) methods are appropriate tools to assess these abnormalities (9, 20). QST comprehensively evaluates the nervous system and may involve static or dynamic mechanical, thermal, electrical, and chemical tests (12, 21). Static mechanical tests detect thresholds to innocuous and/or harmful stimuli, whereas dynamic mechanical tests explore allodynia and temporal summation; thermal detection thresholds evaluate innocuous and/or harmful

From the Departments of *Prosthodontics, †Biological Sciences, and §Endodontics, Bauru School of Dentistry, University of São Paulo, Bauru, Brazil; and ‡Section of Orofacial Pain and Jaw Function, Department of Dentistry, Aarhus University, Aarhus, Denmark.

Address requests for reprints to Dr André Luís Porporatti, Department of Prosthodontics, Bauru School of Dentistry, University of São Paulo, Al Octávio Pinheiro Brizolla 9-75, CEP 17012-901 Vila Universitária, Bauru, SP, Brazil. E-mail address: andreporporatti@yahoo.com.br

0099-2399/$ - see front matter

http://dx.doi.org/10.1016/j.joen.2015.07.006

thermal stimulus (cold, warm, or hot) (22–24). Although QST methods are proposed to be used as diagnostic tools (21, 23), their accuracy for differential diagnosis between intraoral neuropathic pain and inflammatory toothache has not yet been tested.

Based on this information, the aim of this study was to quantify the somatosensory function of subjects with IT, AO, and healthy volunteers; to quantify how accurately QST discriminates tooth pain as IT or AO; and to learn if QST may assist the endodontic specialist in the assessment and differential diagnosis of such conditions.

Sample and Methods

Study Population

This diagnostic study was conducted from December 2013 to November 2014. Subjects were recruited at 3 different services at the Bauru School of Dentistry, University of São Paulo, São Paulo, SP, Brazil:

1. Emergency and Screening Service (Stomatology Department)
2. Orofacial Pain Service (Prosthodontics Department)
3. Integrated Service of Oral Rehabilitation and Dental Implants (Prosthodontics Department)

This study was conducted in accordance with Helsinki guidelines and was approved by the local ethics committee (Certificate of Presentation for Ethical Consideration #19840113.2.0000.5417). Written informed consent was obtained from all participants.

Before study enrollment, all subjects underwent anamnesis and physical examination. Anamnesis included a history taken about personal data, chief complaint, and medical and dental history. The dental history included questions related to the main complaint, pain severity and quality, worsening and improvement factors, accompanying symptoms, and previous treatments.

The initial sample consisted of 469 subjects, and then 346 subjects were excluded from the IT group, 26 from the AO group, and 37 from the control group (C). A flowchart of the exclusion criteria for the selected subjects can be observed in Figure 1. The remaining subjects were eligible and agreed to participate in the study.

The IT group consisted of 20 subjects (14 women, 35.1 ± 8.68 years old) with acute pulpitis. Individuals were assessed for the following mandatory diagnosis criteria (10, 16):

1. Acute pain was in dental pulp.
2. Pain was related to a dental inflamed pulp.
3. Pain was moderate or severe in intensity.
4. Pain intensity could vary over time, passing through asymptomatic periods.
5. Pain could be caused by a stimulus or occur spontaneously.
6. Pain was intermittent or continuous.
7. Pain was affected by time or body position.

Periapical radiography was always used for the differential diagnosis. The IT group consisted solely of cases with acute pulpitis; cases with apical periodontitis were excluded. Individuals previously using analgesics and/or anti-inflammatory agents were included in the study. Subjects were excluded if they had no pain at the time of evaluation or if they were taking analgesics and had residual pain <50 mm on a visual analog scale (VAS).

The AO group consisted of 20 subjects (15 women, 57.84 ± 13.42 years old) diagnosed with intraoral neuropathic pain by orofacial pain specialists (A.L.P., Y.M.C., or J.S.B.) during the first patient consultation, which was before enrollment in the study. Subjects with AO were diagnosed using the following currently published and accepted criteria (8, 10, 16):

1. Persistent pain was present at least 8 h/d ≥15 days per month for ≥3 months.
2. Pain was localized in the dentoalveolar area where the maximum pain is defined within an anatomic area.

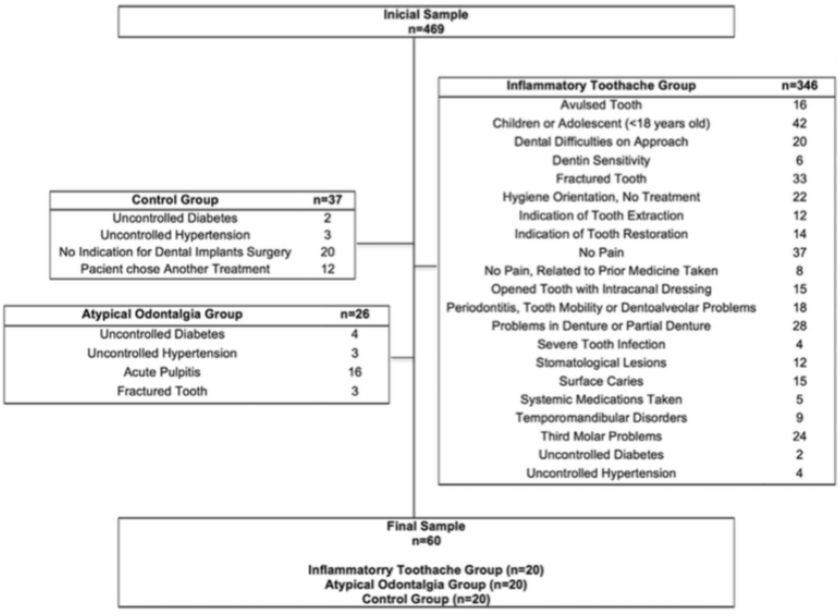

Figure 1. A flowchart of the exclusion criteria for the selected subjects.

3. Pain was not caused by another disease or disorder, confirmed through dental and neurologic examination and imaging.

Cone-beam computed tomographic (CBCT) imaging was requested for patients when any diagnostic doubt remained after the complementary examinations and periapical radiographs (25). Patients taking pain medications were also included in this group.

The control group consisted of 20 healthy subjects (14 women, 50.22 ± 6.67 years old) without painful dental pathology at the time of assessment. Individuals could not have had previously received a neuropathy diagnosis and needed to be free from any type of pain and dental pathology for at least 6 months (26).

For the 3 groups, the subjects were excluded if they had systemic conditions such as uncontrolled hypertension, uncontrolled diabetes, leprosy, and/or disabling neurologic and psychological disorders previously diagnosed by a qualified physician (27).

Study Design

Subjects from all groups were comfortably installed in a quiet room (room temperature 22°C–25°C), and a sequence of 4 QST methods was performed at baseline. QSTs were applied over the dentoalveolar mucosa in the apical area of the maxillar or mandibular regions. This dentoalveolar area was approximately 10 mm^2. For the IT group, tests were performed in the toothache apical area on the dentoalveolar region. For the AO group, tests were applied in the painful dentoalveolar area. For the control group, QST methods were performed in a random dentoalveolar area.

A trained researcher (A.L.P.) executed the QST methods, testing participants through the entire procedure to ensure consistency. The duration of all examinations for each person was approximately 45 minutes.

The assessment of pain intensity at baseline was recorded using a VAS (22). The VAS consisted of a horizontal line, 100-mm long, anchored by word descriptors at each end; the far left read "no pain," and the right read "worst pain imaginable." Patients were requested to make a vertical mark on the VAS line at the point that they felt represented their perception of their current pain state (28).

The following sequence was the order of QST used in this study.

Mechanical Detection Threshold. This test used von Frey monofilaments that were adapted to define tactile fiber thresholds (29). Twenty von Frey nylon monofilaments with different diameters were used and calibrated to exert specific forces when bending. The monofilament force varied from 0.008 g/mm^2–300 g/mm^2 (29).

Each monofilament was applied perpendicularly to the dentoalveolar region, and slight pressure was applied until the filament bent. The method of limits was used in which approximately 6 to 8 ascending/descending stimuli were applied, and the average force was calculated (30). The mechanical detection threshold (MDT) estimated the light touch detection threshold (ie, the lowest von Frey nylon monofilament force that individuals were able to appropriately detect) (29).

Pain Detection Threshold. This test estimated the lowest von Frey filament force for which subjects reported a painful sensation. The method of limits used in MDT was also applied for the pain detection threshold (PDT). Patients identified the filament, and their pain intensity was recorded using a VAS (22).

Dynamical Mechanical Allodynia. A slight vibration of a cotton swab was applied to the alveolar mucosa for 10 seconds, and the pain intensity was recorded with a VAS (22). The stimulus area was approximately 2 mm^2 for the cotton swab.

Temporal Summation. This test was conducted using repeated application of the 5.46-g von Frey filament in a continuous 30-second sequence (force of 26 g/mm^2, approximately 1 stimulus per second). Subjects rated the pain intensity 4 times on a numeric rating scale at 1, 10, 20, and 30 seconds. The numeric rating scale is a 0- to 10-point scale, and patients were asked to rate their pain from 0 to 10. A score of 0 indicated "no pain," and 10 was the "worst pain imaginable" (31, 32). Temporal summation (TS) was determined using subtraction calculations (pain train of 30 seconds of pinprick stimulations minus the first second of pinprick), and a single value was established.

Data Reduction and Analysis

The z score transformation was performed to standardize the QST values and obtain a single value for each test for comparison with the control subjects (24).

$$\left(\text{“}z\text{” score calculation} = \frac{X_{\text{single patient}} - \text{mean}_{\text{controls}}}{\text{standard deviation}_{\text{controls}}}\right)$$

In this analysis, the "X" value was used for the IT group and the AO group, and the controls were healthy subjects (control group).

QST values from each patient were transformed to z scores as described by Rolke et al (24). A score >1.96 or ≤1.96 fell outside the 95% confidence interval of the mean reference value, and these scores were considered sensory abnormalities. Abnormalities were subsequently categorized as a sensory gain or sensory loss.

All analyses were performed on a personal computer using STATISTICA for Windows, version 10.0 (StatSoft Inc, Tulsa, OK) and MedCalc (MedCalc Software, Ostend, Belgium). QST statistical analysis was performed using 1-way analysis of variance. QST parameters that were not normally distributed were analyzed after log transformation. When appropriate, Tukey post hoc analyses were used to determine significant differences between groups.

Receiver operating characteristic (ROC) curve analysis (33) was used to quantify how accurately QST methods discriminate tooth pain as IT or AO. Therefore, diagnostic accuracy (area under the curve), sensitivity, specificity, likelihood ratios, and diagnostic odds ratio of

TABLE 1. Within-group Characteristics

	Inflammatory toothache group	%	Atypical odontalgia group	%	Control group	%
Age (SD)	35.1 (8.68)		57.84 (13.42)		50.22 (6.66)	
Sex	14 W	70	15 W	75	14 W	70
	6 M	30	5 M	25	6 M	30
Evaluated region	0 incisors	0	2 incisors	10	2 incisors	10
	2 canines	10	3 canines	15	2 canines	10
	4 premolars	20	7 premolars	35	10 premolars	50
	14 molars	70	8 molars	40	6 molars	30
Pain intensity (SD) on a VAS	68.6 (22.99)		62.5 (23.47)		0 (0)	

M, men; SD, standard deviation; VAS, visual analog scale; W, women.

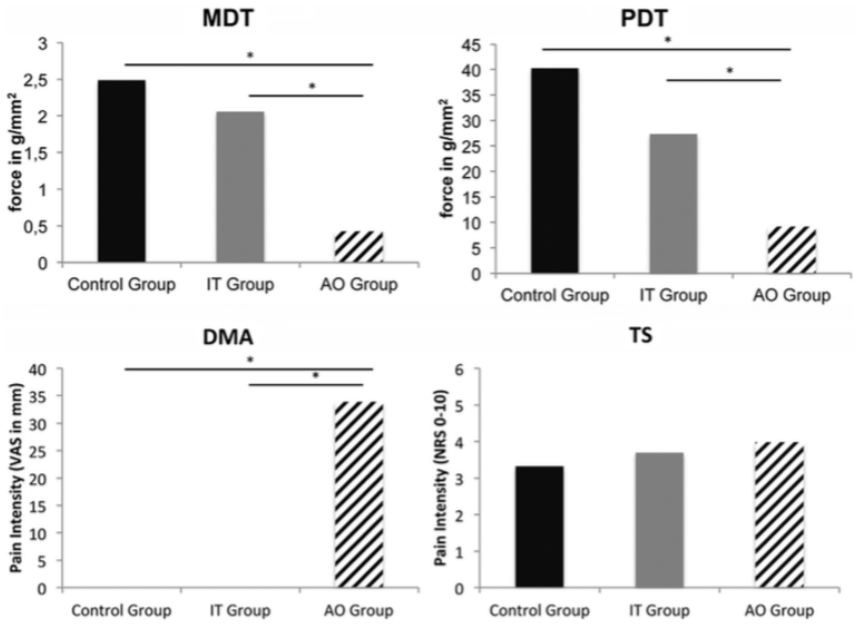

Figure 2. QST data for all groups. NRS, numeric rating scale. *$P < .05$.

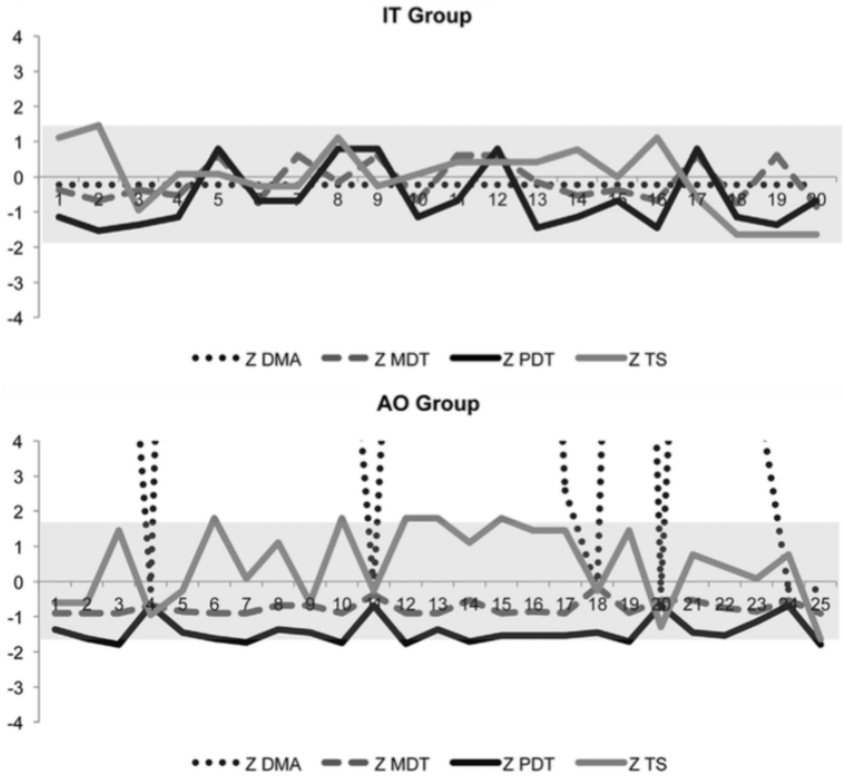

Figure 3. *z* score transformation values for all quantitative sensory testing in the IT and AO groups compared with the control group. Z, *z* score transformation.

QST methods were calculated (34). The results were considered significant at a level of 5%.

Results

Patient characteristics such as age, sex, the evaluated areas, and pain intensity can be observed in Table 1. In the IT group, all patients were nonsmokers, and only 1 individual had hypertension controlled with medications. Because of strong and sharp pain that affects patients with IT, 5 subjects had previously taken painkiller drugs (3 analgesic and muscle relaxant formulations and 2 Dipyrone [Sanofi-Aventis Farmacêutica Ltda, Suzano, SP, Brazil]). However, no improvement in pain intensity was observed.

In the AO group, 3 subjects mentioned cholesterol problems, 8 reported controlled hypertension, 2 arthritis and/or osteoarthritis, 2 controlled diabetes mellitus type 2, and 1 hypothyroidism. Prior medication for pain and associated symptoms was used by 6 subjects and involved 25 mg amitriptyline (1 subject), 300 mg gabapentin or more (6 subjects), ≥200 mg carbamazepine (3 subjects), 30 mg duloxetine (2 subjects), and 25 mg topiramate (1 subject). However, pain intensity was not diminished in any of the 6 subjects. CBCT imaging was performed to assist in the differential diagnosis of the 13 AO subjects. CBCT imaging was required because of the visualization difficulty of possible dental or bone alterations after conventional and panoramic radiographs.

Between-group QST Differences

The results of all tests are shown in Figure 2. Somatosensory abnormalities were detected in the AO group, consistent with a low detection threshold to touch and pain and the presence of mechanical allodynia, when compared with the control group and the IT group ($P < .05$). The IT group had no somatosensory abnormalities.

Figure 3 shows the z score for the IT and AO groups when compared with the control group. No sensory gain or loss was found for the IT group. A gain in function for dynamic tests such as dynamic mechanical allodynia (DMA) and TS was perceived in the AO group.

QST Diagnostic Accuracy

The results of the ROC analysis with a between-group response and discrimination are displayed in Table 2 and Figure 4. The most accurate QST to discriminate IT patients from healthy individuals is the PDT. Based on the ROC curve, the cutoff point on PDT values, which provided a good balance between sensitivity and specificity, was ≤15 g/mm^2. Diagnostic differences between AO and healthy individuals are best discriminated with MDT, PDT, and DMA. Respectively, values ≤0.16 g/mm^2, ≤8 g/mm^2, and ≥0 on pain intensity measured using a VAS had a strong and significant effectiveness to discriminate them. MDT, PDT, and DMA are accurate QST methods for discriminating the differences between IT and AO with strong and significant effectiveness with values >1 g/mm^2, >10 g/mm^2, and ≥0 on pain intensity, respectively.

Discussion

This is one of the relatively few studies that have examined somatosensory features in ITs and intraoral neuropathic pain. The clinical differential diagnosis of IT and AO is still challenging, and it is extremely important to avoid establishing an incorrect treatment plan. Based on the results of the present diagnostic study, it is suggested that QST methods are usable tools to discriminate such conditions. The results indicated that

1. The AO group has a decreased detection threshold to touch and pain when compared with the IT control groups.

TABLE 2. Calculation of the Likelihood Ratios (LRs), Area under the Curve (AUC) of the Receiver Operator Characteristic (ROC) Test, and Diagnostic Odds Ratio (DORs) for QST Methods of the Inflammatory Toothache (IO), Atypical Odontalgia (AO), and Control (C) Groups

	Criterion	Sensitivity	CI	Specificity	CI	+LR	CI	−LR	CI	AUC	SE	CI	z value	*P* value	DORs
IT and C															
MDT	>2	35.00	15.4–59.2	75.00	50.9–91.3	1.40	0.5–3.7	0.87	0.6–1.3	0.513	0.094	0.356–0.672	0.132	.89	1.615
PDT	≤15	50.00	27.2–72.8	90.00	68.3–98.8	5.00	1.3–20.0	0.56	0.4–0.9	0.696	0.082	0.531–0.831	2.394	.016	9.00
DMA	≥0	100.00	83.2–100.0	0.00	0.0–16.8	1.00	1.0–1.0	—	—	0.500	0.0	0.338–0.662	—	1	—
TS	>7	31.25	11.0–58.7	85.00	62.1–96.8	2.08	0.6–7.4	0.81	0.6–1.2	0.592	0.0966	0.416–0.752	0.954	.34	2.424
AO and C															
MDT	≤0.16	58.33	36.6–77.9	95.00	75.1–99.9	11.67	1.7–81.2	0.44	0.3–0.7	0.849	0.055	0.709–0.939	6.289	<.0001	26.60
PDT	≤8	66.67	44.7–84.4	95.00	75.1–99.9	13.33	1.9–92.0	0.35	0.2–0.6	0.928	0.033	0.808–0.984	12.70	<.0001	38.00
DMA	≥0	100.00	85.8–100.0	0.00	0.0–16.8	1.00	1.0–1.0	—	—	0.896	0.042	0.766–0.967	9.349	<.0001	—
TS	>7	45.83	25.6–67.2	85.00	62.1–96.8	3.06	1.0–9.5	0.64	0.4–1.0	0.656	0.0833	0.498–0.793	1.876	.0607	4.795
IT and AO															
MDT	>1	60.00	36.1–80.9	91.67	73.0–99.0	7.20	1.8–28.5	0.44	0.3–0.8	0.867	0.0514	0.730–0.950	7.133	<.0001	16.71
PDT	>10	75.00	50.9–91.3	79.17	57.8–92.9	3.60	1.6–8.2	0.32	0.1–0.7	0.834	0.0591	0.692–0.929	5.658	<.0001	76.00
DMA	≤0	100.00	83.2–100.0	79.17	57.8–92.9	4.80	2.2–10.5	0.00	—	0.896	0.0423	0.766–0.967	9.349	<.0001	130.45
TS	≤8	93.75	69.8–99.8	37.50	18.8–59.4	1.50	1.1–2.1	0.17	0.02–1.2	0.590	0.0902	0.423–0.743	0.997	.3190	—

CI, confidence interval; DMA, dynamic mechanical allodynia; MDT, mechanical detection threshold; PDT, pain detection threshold; TS, temporal summation.
*$P < .05$.

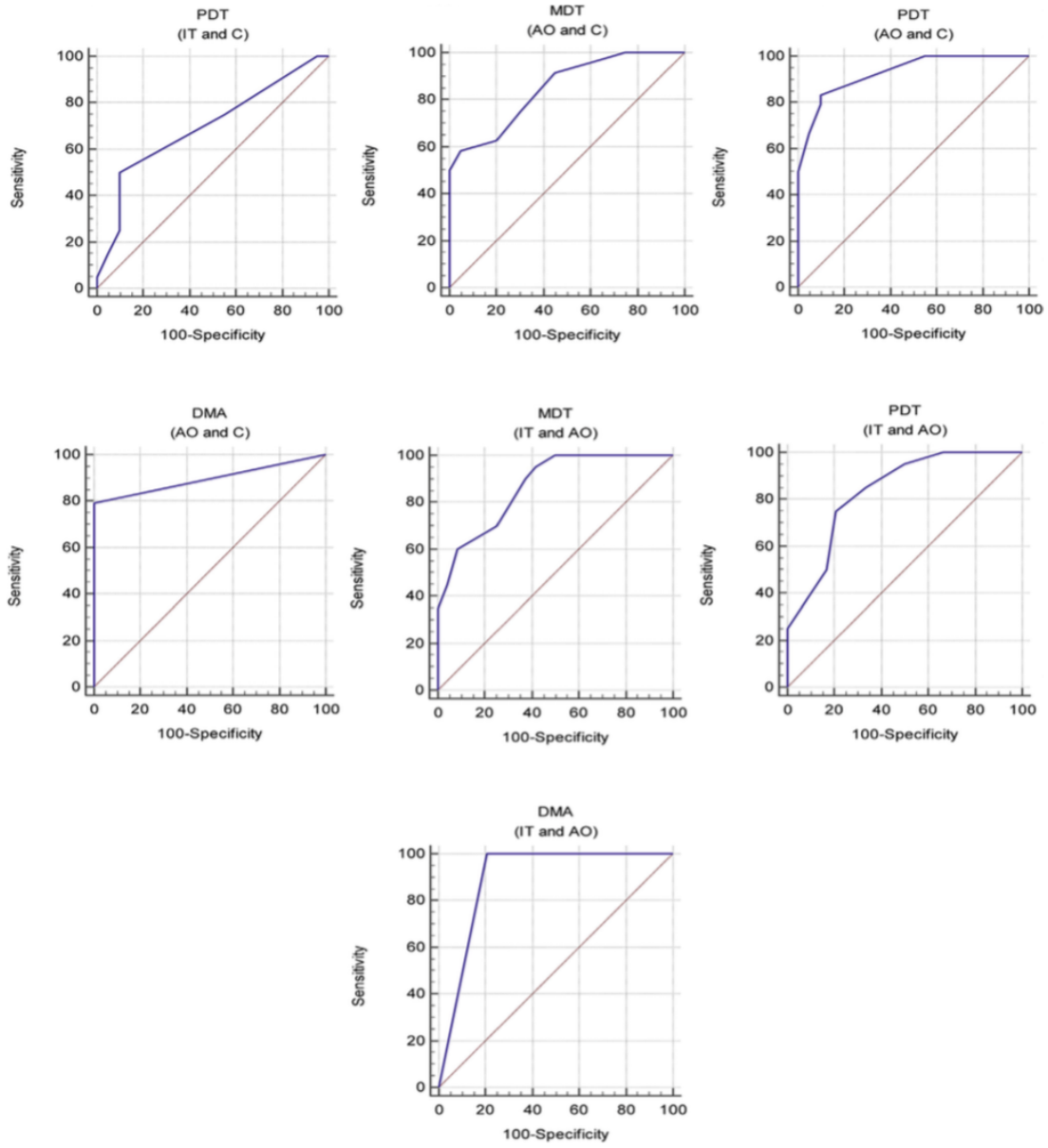

Figure 4. ROC curves of significant QST methods from the IT, AO, and control (C) groups.

2. The presence of mechanical allodynia was a specific feature of AO subjects.
3. Touch threshold forces >1 g/mm^2 and pain threshold forces >10 g/mm^2 can be used to accurately discriminate AO from IT.
4. MDT, PDT, and DMA can be used to discriminate IT and AO.

In accordance with epidemiologic studies, 70%–75% of this sample was women. The literature is clear in asserting that women are more likely to face a variety of recurrent, severe, and persistent pain (9, 27, 35–38). Some AO subjects were taking pain medications such as anticonvulsants, antidepressants, and/or anxiolytics. This fact appears to not influence the initial pain severity (62.5 mm). A similar study evaluated pain intensity in AO subjects who were either taking or not taking unsupervised pain medications at first consultation, and no differences were found between those groups (27).

Somatosensory abnormalities are common in AO patients, and intraoral QST can detect these sensory disturbances; however, they have not been completely tested in individuals with IT (9, 20). Our study found a tendency for a lower pain detection threshold for subjects

with IT compared with healthy individuals. This means that a minor stimulus is needed to activate pain responses in patients with IT, indicating a peripheral primary hyperalgesia situation; however, this PDT test was not statically significant (39, 40). For the IT group, although we could perceive peripheral hyperalgesia, the PDT test was not a useful tool for detecting this hyperalgesia abnormality.

Typically, hyperalgesia ceases when peripheral inflammation disappears. However, sometimes genetic defects and/or repetitive nerve injury can result in allodynia phenomena in which tactile stimuli are interpreted as painful stimuli. Allodynia reflects the presence of central sensitization, usually in patients with chronic disorders (12, 16). DMT assesses allodynia through the activation of low-threshold mechanoreceptors (41), and allodynia may be explained by anatomic and physiological changes related to synaptic disorganization, distension of afferent endings, spatial distribution, and sprouting of new nerve endings leading to sensory gain in receptive fields (42–44). In this study, allodynia was only observed in the AO group and should be used for differential diagnosis from both IT and AO conditions.

The use of DMA testing is simple to implement in a clinical setting. The professional may perform it by vibrating only the bristles of a toothbrush or a cotton swab on the region where the patient reports pain and observing a pain report or increased sensation after this stimulus (45). For clinical purposes, the professional could control his or her force and evaluate the response of the patient by comparing the results with a contralateral nonpainful side.

Rapid and long-term changes can occur in parts of the central nervous system that are involved in pain transmission and modulation. Peripheral and central sensitizations of sensory nerve fibers are the main reasons for pain hypersensitivity after injury and occur mainly with neuropathic pain (46). Persistent abnormal somatosensory processing may initiate neuroplastic changes that perpetuate central sensitization, resulting in chronic pain (47).

It is difficult to accurately diagnose AO. However, for IT, comprehensive medical and dental history associated with visual inspection, imaging, and response to stimuli application (pulp tests) are effective for the inference of a possible diagnosis (48). Studies have shown that some additional evaluation should be performed in any patient for discrimination between an IT or AO situation, including pulp tests, periapical and panoramic images, head and neck examination for other maxillofacial disease, and CBCT imaging for incomplete tooth fracture (25, 49, 50). Also, looking for any abnormalities, such as a nerve examination including QST, is suggested for discriminating between IT and AO (19, 51).

In this study, an additional test with reasonable accuracy to discriminate IT diagnosis was the PDT. In a clinical setting, the most similar approach to PDT may be the pinprick test. This test may be easily performed with very simple instruments before referral to specialized management (52). In the pinprick test, the sensitivity to a painful stimulus is evaluated on the painful gingival site and the corresponding, nonpainful, contralateral site. This painful stimulus is applied with a dental examination probe with moderate force. After the stimulus, patients are asked to report hypersensitivity, hyposensitivity, or normal sensitivity in comparison with the nonpainful control side (52).

Although some studies have shown significant diagnostic profiles of AO and IT that could increase the diagnostic capability of clinicians, these profiles were established by considering AO or IT patients individually (9, 10, 45, 50). No study has been published on the association between IT and AO. The present findings showed that 3 QST methods (MDT, PDT, and DMA) could be used to help discriminate between AO and IT when doubts remain after the initial examination.

Although this study showed strong accuracy for some QST methods as diagnostic tests, it is clear that QST examinations cannot be performed alone and must be used in combination with medical history, physical examination, and imaging technics to improve the accuracy of the differential diagnosis (21).

z score analysis is used for looking at individual patients and how their data are distributed within the normal range for each QST parameter. This study indicated sensory gain (positive *z* scores) for allodynia and TS tests for the AO group only. A gain in function indicates that dynamic stimuli of innocuous or noxious intensity are able to overexcite nociceptors and provoke a more intense pain response. As chronic neuropathy, the expected presence of central sensitization may explain the results of dynamic tests of allodynia and summation (41).

There are some limitations to performing QST. The first is the time it takes to perform the tests in all areas, which may result in the subject becoming fatigued. Second, mechanical stimulation tests can confuse some individuals because they may require a long explanation and repeated testing. Third, QST on painful areas are difficult to perform and may have to be explained very carefully to the subjects before examination. Finally, although we suggested pinprick as a similar QST to be performed in a clinical setting, this test was not evaluated in this study, and further studies must be done to indicate the pinprick for IT and AO discrimination.

We conclude that some QST methods might aid in the differential diagnosis of AO and IT with strong accuracy, and some QST methods may be used as complementary diagnostic tests. To date, the most accurate QST methods to use for differential diagnosis between subjects with AO and IT are the MDT test, the pain detection threshold test, and dynamic mechanical allodynia.

Acknowledgments

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The authors deny any conflicts of interest related to this study.

References

1. Campbell RL, Parks KW, Dodds RN. Chronic facial pain associated with endodontic therapy. Oral Surg Oral Med Oral Pathol 1990;69:287–90.
2. Vickers ER, Cousins MJ, Walker S, Chisholm K. Analysis of 50 patients with atypical odontalgia. A preliminary report on pharmacological procedures for diagnosis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:24–32.
3. Matwychuk MJ. Diagnostic challenges of neuropathic tooth pain. J Can Dent Assoc 2004;70:542–6.
4. Melis M, Secci S. Diagnosis and treatment of atypical odontalgia: a review of the literature and two case reports. J Contemp Dent Pract 2007;8:81–9.
5. Marbach JJ. Is phantom tooth pain a deafferentation (neuropathic) syndrome? Part I: evidence derived from pathophysiology and treatment. Oral Surg Oral Med Oral Pathol 1993;75:95–105.
6. Vena DA, Collie D, Wu H, et al. Prevalence of persistent pain 3 to 5 years post primary root canal therapy and its impact on oral health-related quality of life: PEARL Network findings. J Endod 2014;40:1917–21.
7. Khan AA, Maixner W, Lim PF. Persistent pain after endodontic therapy. J Am Dent Assoc 2014;145:270–2.
8. Nixdorf DR, Drangsholt MT, Ettlin DA, et al. Classifying orofacial pains: a new proposal of taxonomy based on ontology. J Oral Rehabil 2012;39:161–9.
9. List T, Leijon G, Svensson P. Somatosensory abnormalities in atypical odontalgia: a case-control study. Pain 2008;139:333–41.
10. Okeson JP. *Bell's Orofacial Pains*, 6th ed. Chicago: Quintessence; 2005.
11. Graff-Radford SB, Solberg WK. Atypical odontalgia. J Craniomandib Disord 1992;6:260–5.
12. Baad-Hansen L. Atypical odontalgia - pathophysiology and clinical management. J Oral Rehabil 2008;35:1–11.
13. Tarce M, Barbieri C, Sardella A. Atypical odontalgia: an up-to-date view. Minerva Stomatol 2013;62:163–81.
14. Pigg M, Svensson P, Drangsholt M, List T. Seven-year follow-up of patients diagnosed with atypical odontalgia: a prospective study. J Orofac Pain 2013;27:151–64.

ANNEX H

Email de Submissão Clinical Oral Implants Research (ARTICLE 2)

Somatic, Visceral and Neuropathic Pain Present Different Somatosensory Profiles

De: coir@zmk.unibe.ch
Assunto: Clinical Oral Implants Research - Manuscript ID COIR-Nov-15-OR-5183
Data: 13 de novembro de 2015 14:48
Para: andreporporatti@yahoo.com.br
Cc: brigitte.baur@zmk.unibe.ch

13-Nov-2015

Dear Dr. Porporatti:

Your manuscript entitled "SOMATIC, VISCERAL AND NEUROPATHIC PAIN PRESENT DIFFERENT SOMATOSENSORY PROFILES." has been successfully submitted online and is presently being given full consideration for publication in Clinical Oral Implants Research.

Your manuscript ID is COIR-Nov-15-OR-5183.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://mc.manuscriptcentral.com/coir and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc.manuscriptcentral.com/coir.

Thank you for submitting your manuscript to Clinical Oral Implants Research.

Sincerely,
Clinical Oral Implants Research Editorial Office

Appendixes

APPENDIX A

Ficha de Pesquisa

FICHA DE PESQUISA

Examinador: André Luís Porporatti
Data do exame:_____/_____/_____ **GRUPO:** _____ **Número do Sujeito da Pesquisa:** _____
Nome do Sujeito da Pesquisa: _____
Data de Nascimento: _____ /_____ /_____ **Idade:**_____
Cidade: _____ **Telefone: (**____**)** _____
Email: _____
Gênero: (**)M** **(** **)F**

Escala de análise visual

Indique a média da sua intensidade de dor neste momento, marcando com uma linha vertical a escala abaixo. A extremidade esquerda indica **ausência total de dor** e a extremidade direita **indica a pior dor imaginável**.

BASELINE (EAV 1)

_____

sem dor pior dor imaginável

DURANTE O PROCEDIMENTO (EAV 2)

_____

sem dor pior dor imaginável

APÓS 01 HORA DO TÉRMINO DO PROCEDIMENTO (EAV 03)

_____

sem dor pior dor imaginável

APÓS 02 HORAS DO TÉRMINO DO PROCEDIMENTO (EAV 04)

_____

sem dor pior dor imaginável

APÓS 03 HORAS DO TÉRMINO DO PROCEDIMENTO (EAV 05)

_____

sem dor pior dor imaginável

APÓS 04 HORAS DO TÉRMINO DO PROCEDIMENTO (EAV 06)

_____

sem dor pior dor imaginável

APÓS 05 HORAS DO TÉRMINO DO PROCEDIMENTO (EAV 07)

_____

sem dor pior dor imaginável

01 DIA APÓS O PROCEDIMENTO (EAV 08)

_____

sem dor pior dor imaginável

01 SEMANA APÓS CIRURGIA (EAV 09)

_____

sem dor pior dor imaginável

01 MÊS APÓS CIRURGIA (EAV 10)

_____

sem dor pior dor imaginável

03 MESES APÓS CIRURGIA (EAV 11)

_____

sem dor pior dor imaginável

	MDT	PDT	PDT EAV
BASELINE			
1 MÊS APÓS PROCEDIMENTO			
3 MESES APÓS PROCEDIMENTO			

DMA1

BASELINE

sem dor _____ pior dor imaginável

1 MÊS APÓS PROCEDIMENTO

sem dor _____ pior dor imaginável

3 MESES APÓS PROCEDIMENTO

sem dor _____ pior dor imaginável

WUR	0s	10s	20s	30s
BASELINE				
1 MÊS APÓS PROCEDIMENTO				
3 MESES APÓS PROCEDIMENTO				

CPM	0s	10s	20s	30s
BASELINE				
1 MÊS APÓS PROCEDIMENTO				
3 MESES APÓS PROCEDIMENTO				

NEUROMETER CPT	2000Hz (Aβ)	250Hz (Aδ)	5Hz (C)
BASELINE			
1 MÊS APÓS PROCEDIMENTO			
3 MESES APÓS PROCEDIMENTO			

APPENDIX B

TCLE – Termo de Consentimento Livre e Esclarecido

Universidade de São Paulo
Faculdade de Odontologia de Bauru

Departamento de Prótese

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

O(a) senhor(a) está sendo convidado(a) a participar da pesquisa: Avaliação Comparativa dos Mecanismos Somatossensoriais Envolvidos na Gênese das Dores Orofaciais de Origem Somática, Visceral e Neuropática. Neste estudo o(a) senhor(a) será solicitado(a) a responder um questionário sobre alguns sintomas relacionados à dor que você tem apresentado, além de ser examinado para avaliar a intensidade dessa dor, a condição de seus músculos da face e de sua articulação. Os questionários têm duração de 20 minutos. Além disso, o(a) senhor(a) será solicitado(a) a realizar alguns testes para avaliar a sua sensibilidade na região em que sente a dor dentro da boca. Os testes realizados são testes mecânicos de ligeira pressão, utilizando fios de nylon e eletrodos de mensuração elétrica. Caso o(a) senhor(a) não relate dor, os testes serão realizado em uma região intraoral aleatória, em gengiva, em região próxima ao dente.

O(a) senhor(a) não terá qualquer custo com os exames ou procedimentos realizados, e há risco mínimo quanto à realização dos exames, que podem envolver algum desconforto ou sensação de formigamento na região avaliada, garantido de indenização diante de eventuais danos decorrentes da pesquisa. As avaliações não produzirão qualquer tipo de dano físico, moral ou material pra os(as) senhores(as). As informações fornecidas serão mantidas confidenciais, respeitando sua privacidade. Os resultados obtidos serão analisados e publicados em meios de informação científicos, sem a sua identificação, de qualquer forma.

É importante que você esteja consciente de que a participação neste estudo é completamente voluntária e de que você pode recusar-se a participar ou sair do estudo a qualquer momento sem penalidades. A recusa em participar ou a saída do estudo não influenciarão seus cuidados nesta instituição.

Você receberá uma cópia deste termo onde consta o telefone e o endereço do pesquisador principal, podendo tirar suas dúvidas sobre o projeto e sua participação, agora ou a qualquer momento. Caso você tenha mais perguntas sobre o estudo, por favor, ligue para André Luís Porporatti no telefone (14) 98115-2914, pós-graduando em Ciências Odontológicas Aplicadas da Faculdade de Odontologia de Bauru, Universidade de São Paulo, localizada na rua Al. Octávio Pinheiro Brisola, 9-75 (CEP 17012-901 - Bauru - SP), ou envie suas perguntas pelo email: andreporporatti@usp.br. Qualquer reclamação quanto à elaboração desta pesquisa, você pode procurar atendimento no Comitê de Ética em Pesquisa da Faculdade de Odontologia de Bauru (CEP-FOB), localizado à Alameda Dr. Octávio Pinheiro Brisolla, 9-75, Vila Universitária, ou pelo telefone (14)3235-8356, e e-mail: cep@fob.usp.br.

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Universidade de São Paulo
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Departamento de Prótese

Pelo presente instrumento que atende às exigências legais, o Sr. (a) _____, portador da cédula de identidade _____, após leitura minuciosa das informações constantes neste TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO, devidamente explicada pelos profissionais em seus mínimos detalhes, ciente dos serviços e procedimentos aos quais será submetido, não restando quaisquer dúvidas a respeito do lido e explicado, firma seu CONSENTIMENTO LIVRE E ESCLARECIDO concordando em participar da pesquisa proposta. Fica claro que o sujeito da pesquisa, pode a qualquer momento retirar seu CONSENTIMENTO LIVRE E ESCLARECIDO e deixar de participar desta pesquisa e ciente de que todas as informações prestadas tornar-se-ão confidenciais e guardadas por força de sigilo profissional (Art. 9o do Código de Ética Odontológica). Por fim, como pesquisador(a) responsável pela pesquisa, comprometo-me a cumprir todas as exigências contidas no item IV.3 da resolução do CNS/MS n. 466 de dezembro de 2012, publicada em 13 de junho de 2013.

Por estarmos de acordo com o presente termo o firmamos em duas vias (uma via para o sujeito da pesquisa e outra para o pesquisador) que serão rubricadas em todas as suas páginas e assinadas ao seu término.

Bauru, SP, _____ de _____ de _____.

_____ _____

Assinatura do Sujeito da Pesquisa Assinatura do Pesquisador: André Luís Porporatti

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