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OROFACIAL PAIN AND TRADITIONAL CHINESE MEDICINE:

Integrated Clinical Approach of Acupuncture with other Traditional and Innovative Methods for the Management of Pain in Dysfunctional and Orthodontic Patients

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Non giudicare sbagliato ciò che non conosci, prendi l'occasione per comprendere.

(Pablo Picasso)

Sé stesso è anche l'altro; l'altro è anche sé stesso.

(Zhuāngzǐ 莊子)

Alla commistione dei saperi

ABSTRACT

Background: Orofacial pain (OP) is a frequent form of pain perceived in the face and/or oral cavity. It may be caused by diseases of regional structures or dysfunction of the nervous system, and it also may be induced by several dental procedures. Pain related to temporomandibular disorders (TMD) is one of the most common OP conditions, usually affecting adult population, determined by several organic and/or functional causes and characterized by a significant and complex symptomatology. Orthodontic pain is defined as OP induced by orthodontic tooth movement, and is therefore more likely afflicting paediatric population. Compared to OP related to TMD, orthodontic pain is characterized by a less intense symptomatology; it is equally commonly encountered in dentists' clinical practice, but usually more underestimated. Acupuncture (AT) is a versatile therapeutic tool, and for this reason it is applied in various medical areas, including dentistry. Although many physiological and neurological mechanisms are still unknown, its clinical efficacy in pain therapy is widely proven. However, AT application in OP field is still lacking, and some of AT techniques and methods of points stimulation, currently used in acupuncturists practice, are completely missing in the west scientific literature. Furthermore, there is no evidence concerning the application of technologic devices, such as electrostimulation or vibration therapy, in the stimulation of acupoints for the treatment of pain in the oral and craniofacial area.

Aims: The general aim of this doctoral thesis was to deepen the knowledge about the use of AT as pain management tool in OP field, investigating both the clinical efficacy of different AT techniques, including innovative technological ones, and molecular mechanisms underlying AT. The primary focus was TMD-related pain, the secondary one was orthodontic pain. ***Study I*** investigated the effects of different AT techniques in patients affected by TMD-related pain of mixed origin, including traditional and modern technologic methods of acupoint stimulation. ***Study II*** focused on the use of microsystems techniques (ear AT, abdominal AT) in TMD patients and patients affected by OP induced by fixed orthodontic appliances. ***Study III*** focused on molecular and neurological mechanisms underlying AT, investigating the salivary proteic response to ear AT in TMD myalgia patients.

Methods and Results: ***Study I*** involved the application of different acupuncture methods and the use of devices for electrostimulation and vibrational therapy for treating OP in TMD patients. Two clinical studies were conducted, a prospective randomized clinical study that included TMD patients with pain of mixed origin and compared the clinical application of three different acupuncture methods (somatic AT, electroacupuncture, AT+ cupping), and a randomised double-blind placebo-controlled preliminary study, that analysed the effectiveness of at-home local vibration therapy for the management of TMD-related myofascial pain. From both studies significant improvements resulted in all types of pain treated after all the treatments applied. No significant differences were noted in the improvement of TMDs related-pain according to the different acupuncture techniques. ***Study II*** involved the application of two acupuncture microsystems therapy, abdomen and ear, respectively on treatment-resistant TMD patients and on orthodontic patients. Two different clinical studies were conducted on these different clusters of patients. All the treatments yielded to interesting results, mainly of improvement, for all the different kinds of OP treated. ***Study III*** was a pilot study and was conducted in collaboration with the Karolinska Institute of Stockholm during the period of international mobility. It consisted in the application of a protocol of ear acupuncture for the duration of 1 week, and the collection of two saliva samples before and after the treatment, on both healthy persons and patients affected by TMD myalgia. The samples were then analysed, looking for eventual differences in saliva Glutamate and Substance P fluctuation. According to the different groups analysed (real acupuncture, sham acupuncture, control group), some differences in the protein's concentration were found, but with no significant results.

All the clinical studies conducted (Study I and II), due to the COVID-19 pandemic and the relative difficulties in applying the therapy in the hospital facilities, didn't reached the planned sample size, anyway they leaded to interesting results about the possibilities of acupuncture methods in the management of different kinds of OP.

Conclusions: The three studies that form this doctoral thesis suggest that acupuncture could be a versatile and effective tool in OP field. The different methods of acupuncture applied, on both dysfunctional and orthodontic patients, lead to a general improvement of orofacial pain. Further studies are needed to confirm these clinical results and to better understand the molecular mechanisms underlying the effects of acupuncture in orofacial pain field.

LIST OF SCIENTIFIC PAPERS

I. Longitudinal epidemiological analysis of three decades of TMD populations
E. Serritella, P. Di Giacomo, C. Vompi, G. Falisi, C. Di Paolo
Dental Cadmos. 2020 Jan 22; 88(8):527-536

II. Evaluation of Vision in Gnathological and Orthodontic Patients with Temporomandibular Disorders: A Prospective Experimental Observational Cohort Study.
C. Vompi, **E. Serritella**, G. Galluccio, S. Pistella, A. Segnalini, L. Giannelli, C. Di Paolo
Journal of International Society of Preventive and Community Dentistry. 2020 Aug 6;10(4):481-490

III. Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment: A Randomised, Double-Blind, Placebo-Controlled Preliminary Study
E. Serritella, G. Scialanca, P. Di Giacomo, C. Di Paolo
Pain Research and Management. 2020 Dec 5; 2020:6705307

IV. Comparison of the effectiveness of three different acupuncture methods for TMD-related pain: a prospective randomized clinical study
E. Serritella, G. Galluccio, A. Impellizzeri, P. Di Giacomo, C. Di Paolo
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V. Perceived Pain during Rapid Maxillary Expansion (RME): Trends, Anatomical Distinctions, and Age and Gender Correlations
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Pain Research and Management. 2021 Jul 14; 2021:7396466

VI. Auriculotherapy used to manage Orthodontic Pain: a Randomized Controlled Pilot Study
E. Serritella, A. Impellizzeri, A. Liguori, G. Galluccio
Dental Press Journal of Orthodontics. 2021 Dec 17;26(6): e2119381

LIST OF ABBREVIATIONS

AA	Auricular Acupuncture
AbdA	Abdominal Acupuncture
AT	Acupuncture
AurT	Auriculotherapy
BDNF	Brain Derived Neurotrophic Factor
BPI	Brief Pain Inventory
CAM	Complementary Alternative Medicine
CT	Cupping therapy
DC/TMD	Diagnostic Criteria for Temporomandibular Disorders
EA	Electroacupuncture
FPS-R	Wong–Baker Faces Pain Rating Scale
GT	Glutamate
IASP	International Association for the Study of Pain
JFLS	Jaw Functional Limitation Scale
LVT	Local Vibration Therapy
NCM	Non-Conventional Medicines
NGF	Nerve Growth Factor
NRS	Numeric Rating Scale
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OBC	Oral Behaviour Checklist
OHIP	Oral Health Impact Profile
OP	Orofacial Pain
PGI-I	Patients' Global Impression of Improvement
PHQ	Patient Health Questionnaire
PSS	Perceived Stress Scale
SP	Substance P
TCM	Traditional Chinese Medicine
TMD	Temporomandibular Disorders
TMJ	Temporomandibular Joint
VAS	Visual Analogue Scale
VNS	Verbal Numeric Scale

CONTENTS

INTRODUCTION

Pain is an individual and subjective sensation, hard to be described by patients and harder to be defined by clinicians and scholars. The latest definition by the IASP (International Association for the Study of Pain) if of "*An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage*". (Raja et al., 2020)

This definition is also expanded upon by the addition of six key Notes:

- *Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors*
- *Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons*
- *Through their life experiences, individuals learn the concept of pain*
- *A person's report of an experience as pain should be respected*
- *Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being*
- *Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain*

This new and comprehensive definition of pain reflects all the complexity of this particular sensation/symptom, especially in multifactorial diagnosis, such as *Orofacial Pain* (OP).

At the same time, it emphasises the need to treat pain through the most varied weapons, which determine not only the reduction/elimination of the symptom but also focus on those emotional and biopsychosocial components that are influencing the onset, modulation and chronicization of the pain itself, greatly affecting the well-being and quality of life of the individual.

Patients affected by OP and temporomandibular disorders/dysfunction (TMD) come to seek help, but sometimes the conventional therapies (splint, drugs, physiotherapy) used for pain relief are not enough for a complete remission of symptomatology. Patients wearing orthodontic appliances experience a certain degree of pain, that is often taken for granted and underestimated by clinicians, as it is considered minor.

The idea underlying this scientific thesis arose from all these reflections, by an orofacial pain and orthodontics specialist and expert acupuncturist, in a specialistic university hospital where dysfunctional and orthodontic patients are daily treated.

Acupuncture therapy presents peculiar indication for pain, especially when related to complex and chronic pathologies, but despite the growing interest showed in the past two decades from both patients and clinicians, it still represents a field full of question to be responded to, especially in areas like dentistry.

The hope for this doctoral thesis is to bring new knowledge about the use of acupuncture for the treatment of orofacial pain, through the analysis of several methods and techniques, encouraging the use of this particular and versatile tool in the management of such complex and multifactorial kind of pain.

PAIN PERCEPTION

Nociception is the sensory process that provides the signals that lead to pain. This process occurs through nociceptors, specialized peripheral sensory neurons that are activated by physical or potential harmful stimuli. The nociceptors mediate the signals from the activated receptor in the periphery through afferent fibres that transmit the signals to the brain via the spinal cord. The pain perception occurs when the signals are interpreted by central areas of the brain. [130] The ability to perceive pain is extremely essential and may be the strongest drive to survival. Typically, pain is classified from a temporal perspective as acute and chronic, but it can also be categorized based on its aetiology as nociceptive, neuropathic, nociplastic, or idiopathic. [75,130]

Acute pain is an important warning signal that indicates a threat to the body and aims to protect the body by activating reflexes that lead to withdrawal or immobilization of body parts. The pain is provoked by a specific disease or damage to tissue and typically has a sudden onset and limited duration [75,130] During their life, most people experience acute pain, for example, headache, back pain, burns, toothache, or post-surgical pain. Usually, acute pain resolves with the healing of its underlying cause. In some cases, the pain persists beyond the expected normal healing time or arises without any history of disease or damage (e.g., chronic pain). [134] Unlike acute pain, *chronic pain* lacks a protective value or obvious function for survival. Usually, pain is regarded as chronic when it lasts or recurs for more than three months. Compared to acute pain, chronic pain is poorly understood and is more complex. [134] In chronic pain, the nervous system is not hardwired, which implies that the exact same noxious stimulus each time elicits a different nervous system response. *Melzack and Wall* (1965) suggest that repeated stimulation of nociceptors results in a progressive accumulation of electrical response in the CNS, winding up the CNS and eventually intensifying activity in secondary nerve fibres. This phenomenon, called *wind-up* or *central sensitization*, is responsible for pain continuing long after expected recovery time for an injury. [93]

Patients suffering from *chronic pain* may not show the behaviours associated with acute pain. Chronic pain can affect physiological systems such as immunological, endocrine, autonomic, and motoric functions. Other problems usually accompany the pain, such as fatigue, sleep disturbance, mood changes, and cognitive functions. Together, these factors can lead to social isolation and impaired quality of life. [134] In addition to suffering, the annual cost to society related to chronic pain is relatively high, including health care service, loss of work, decreased productivity, and disability compensation. [14] In the United States, the costs associated with chronic pain are estimated to be approximately 560-635 billion dollar/year and exceed the costs estimated for public health disease such as cardiovascular disease, cancer, and diabetes. [39] In Europe, these costs run approximately into 300 billion euro/year [101]; in Italy socioeconomic costs and national healthcare conditions associated with chronic pain are 36.4 billion euro/ year, equivalent to 2.3% of GDP (Gross Domestic Product). [2] A recent population-based survey shows that between 20-35% of the adult population suffer from chronic pain. [13,14,25] The spread in

prevalence between studies may reflect differences in definition of chronic pain, pain intensity, and selection of subjects. Nevertheless, the most common sites for pain are back, joints, head, and neck. [13]

Orofacial pain

Orofacial pain (OP) includes, by definition, pain that originates from oral structures accompanied by facial pain. [28] The facial area includes the region demarcated as below the orbitomeatal line, above the neck, and anterior to the ears. However, the craniofacial region has a high density of anatomic structures, and pain often radiates from one area to the other. For this reason, patients with OP may seek help from a number of specialists. [6] The prevalence of OP is around 17% to 26%, out of which 7% to 11% is chronic. [60, 87-89,117]

Orofacial pain usually starts as acute pain, however, if not treated, this pain develops into chronic pain. Chronic pain in the orofacial region is most commonly due to TMD. [117] These pain conditions present a recurrent, persistent, or disabling pattern because of the particular complex anatomy of the orofacial area and difficulties in the diagnostics and management of chronic pain. OP conditions are often associated with psychosocial co morbidities such as anxiety, depression, and somatization. [38,117,124]

There are currently four main pain classification systems relevant to orofacial pain conditions: the International Association for the Study of Pain (IASP), International Classification of Headache Disorders (ICHD), the American Academy of Orofacial Pain (AAOP) and the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD). [7,52,113,117] Of the four, the DC/TMD is the most biopsychosocial system, with the remaining three focusing more on the biomedical aspects. Despite ongoing attempts, an accepted overarching classification of OP is still a work in progress. [112] There is an urgent need for a robust classification system for OP, and the newly published International Classification of Orofacial Pain (ICOP), [59] a document that is aligned with the International Classification of Diseases (11th revision) and the International Classification of Headache Disorders (3rd edition) [52] tried to satisfy this need. ICOP aims to create an instrument that will improve research as well as clinical management of OP and increase collaboration between professionals working on pain in the orofacial area.

An overview of the new ICOP classification is presented in Table 1.

Table 1: Summary of ICOP-I classification [59]

ICOP code	Diagnosis
1	***Orofacial pain attributed to disorders of dentoalveolar and anatomically related structures***
1.1	Dental pain
1.1.1	Pulpal pain
1.1.2	Periodontal pain
1.1.3	Gingival pain
1.2	Oral mucosal, salivary gland and jaw bone pains
1.2.1	Oral mucosal pain
1.2.2	Salivary gland pain
1.2.3	Jaw bone pain
2	***Myofascial orofacial pain***
2.1	Primary myofascial orofacial pain
2.1.1	Acute primary myofascial orofacial pain
2.1.2	Chronic primary myofascial orofacial pain
2.2	Secondary myofascial orofacial pain
3	***Temporomandibular joint (TMJ) pain***
3.1	Primary temporomandibular joint pain
3.1.1	Acute primary temporomandibular joint pain
3.1.2	Chronic primary temporomandibular joint pain
3.2	Secondary temporomandibular joint pain
3.2.1	Temporomandibular joint pain attributed to arthritis
3.2.2	Temporomandibular joint pain attributed to disc displacement
3.2.3	Temporomandibular joint pain attributed to degenerative joint disease
3.2.4	Temporomandibular joint pain attributed to subluxation
4	***Orofacial pain attributed to lesion or disease of the cranial nerves***
4.1	Pain attributed to lesion or disease of the trigeminal nerve
4.1.1	Trigeminal neuralgia
4.1.2	Other trigeminal neuropathic pain
4.2	Pain attributed to lesion or disease of the glossopharyngeal nerve
4.2.1	Glossopharyngeal neuralgia
4.2.2	Glossopharyngeal neuropathic pain
5	***Orofacial pains resembling presentations of primary headaches***
5.1	Orofacial migraine
5.2	Tension-type orofacial pain

5.3	Trigeminal autonomic orofacial pain
5.4	Neurovascular orofacial pain
6	***Idiopathic orofacial pain***
6.1	Burning mouth syndrome (BMS)
6.2	Persistent idiopathic facial pain (PIFP)
6.3	Persistent idiopathic dentoalveolar pain
6.4	Constant unilateral facial pain with additional attacks (CUFPA)
7	***Psychosocial assessment of patients with orofacial pain***

TMD pain

Temporomandibular Disorders (TMD) is a group of related conditions in the masticatory muscles, temporomandibular joint, and associated surrounding structures (e.g., ligaments and connective tissues). [117] These disorders are characterized by a triad of clinical features involving muscle and/or joint pain, limited jaw movements, joint noises, and alteration in the mandibular movements. [35,110]

In 2014, the International Research Diagnostic Criteria for Temporomandibular Dysfunction Consortium Network published an updated classification structure for TMD: *Diagnostic Criteria for TMD (DC/TMD).* The new criteria aimed to improve the sensibility and specificity of the previous RDC/TMD through improvement of Axis I and Axis II, which can be used not only in research but also in clinical settings. [117] Axis I contain an effective screener for detecting any pain related TMD and effective diagnostic criteria for discriminating between the most common pain-related TMD with a sensitivity 20.86 and a specificity 20.98. In addition, Axis I also exhibit a strong inter-examiner reliability for pain-related TMD with a kappa 20.85. The axis II protocol includes both a screening and a self-assessment instrument. The screening instruments assess pain intensity, disability related to pain, psychological distress, limitations in jaw function, parafunctional behaviours, and a pain drawing to assess the location of pain. The self-assessment instruments assess in more detail limitations in jaw function, anxiety, psychological distress, and presence of comorbid pain conditions. [117]

TMD cause a great deal of suffering in the community and is a widespread problem in clinical practices. It affects 10-15% of the adult population with an incidence rate between 2-4% and TMD myalgia seems to be the most frequent diagnosed TMD pain condition with a frequency of 42%. [35,80,120] Several studies have demonstrated a rather low prevalence of TMD in childhood. However, TMD becomes more prevalent during adolescence and early adulthood and appears to peak during midlife and to decrease in the elderly. [35,60] Women are more susceptible to TMD. According to epidemiological studies, two of every three patients with TMD signs are female. [60,120] TMD represent the most common OP diagnosis, and in

particular myalgia/myofascial pain, though patients also often complain about restricted mouth opening capacity and chewing difficulties. [33] These difficulties are described in terms of dysfunction limiting daily life activities. [8,23,96] Such coexisting dysfunction is something that chronic orofacial pain shares with many other types of chronic pain. It has been reported that TMD-related pain is one of the most common forms of musculoskeletal pain. [90,99] Widespread pain has been associated with painful TMD and lack of treatment response, and subjects with a chronic pain condition quite commonly experience comorbid chronic pain conditions. [102] It has been suggested that also TMD may be part of a broader generalized pain condition. [43] *Sipilä et al.* (2005) presented that subjects with facial pain were more likely to report pain and have more muscular tenderness in other areas of the body. [129] Individuals with painful TMD also seem to be more sensitive to experimental pain stimuli, with lower thermal and ischemic pain threshold values as well as lower tolerance values than non-TMD subjects. [43,68]

The ICOP-I Classification reports a main distinction in pain related to TMD, between *Myofascial orofacial pain* and *Temporomandibular joint (TMJ) pain.* [59] The classification and characteristics of the different diagnosis of OP related to TMD are presented in Table 2.

Table 2: TMD pain diagnosis according to ICOP-I classification

ICOP code	Diagnosis
2	***Myofascial orofacial pain***
2.1	Primary myofascial orofacial pain
2.1.1	Acute primary myofascial orofacial pain
2.1.2	Chronic primary myofascial orofacial pain
2.1.2.1	Chronic infrequent primary myofascial orofacial pain
2.1.2.2	Chronic frequent primary myofascial orofacial pain
2.1.2.2.1	Chronic frequent primary myofascial orofacial pain without pain referral
2.1.2.2.2	Chronic frequent primary myofascial orofacial pain with pain referral
2.1.2.3	Chronic highly frequent primary myofascial orofacial pain
2.1.2.3.1	Chronic highly frequent primary myofascial orofacial pain without pain referral
2.1.2.3.2	Chronic persistent primary myofascial orofacial pain with pain referral
2.2	Secondary myofascial orofacial pain
2.2.1	Myofascial orofacial pain attributed to tendonitis
2.2.2	Myofascial orofacial pain attributed to myositis
2.2.3	Myofascial orofacial pain attributed to muscle spasm
3	***Temporomandibular joint (TMJ) pain***
3.1	Primary temporomandibular joint pain
3.1.1	Acute primary temporomandibular joint pain
3.1.2	Chronic primary temporomandibular joint pain

3.1.2.1	Chronic infrequent primary temporomandibular joint pain
3.1.2.2	Chronic frequent primary temporomandibular joint pain
3.1.2.2.1	Chronic frequent primary temporomandibular joint pain without pain referral
3.1.2.2.2	Chronic frequent primary temporomandibular joint pain with pain referral
3.1.2.3	Chronic highly frequent primary temporomandibular joint pain
3.1.2.3.1	Chronic highly frequent primary temporomandibular joint pain without pain referral
3.1.2.3.2	Chronic highly frequent primary temporomandibular joint pain with pain referral
3.2	Secondary temporomandibular joint pain
3.2.1	Temporomandibular joint pain attributed to arthritis
3.2.1.1	Temporomandibular joint pain attributed to non-systemic arthritis
3.2.1.2	Temporomandibular joint pain attributed to systemic arthritis
3.2.2	Temporomandibular joint pain attributed to disc displacement
3.2.2.1	Temporomandibular joint pain attributed to disc displacement with reduction
3.2.2.1.1	Temporomandibular joint pain attributed to disc displacement with reduction, with intermittent locking
3.2.2.2	Temporomandibular joint pain attributed to disc displacement without reduction
3.2.3	Temporomandibular joint pain attributed to degenerative joint disease
3.2.4	Temporomandibular joint pain attributed to subluxation

Orthodontic Pain

Orthodontic therapies, like most dental procedures, cause emotional stress to the patient and are often associated with pain that at times may even be intense. [69] Often the discomfort experienced is described as a feeling of pressure, tension, or soreness in the teeth, in other cases as actual pain. [109] It has been shown that there are important variations depending on factors such as age, gender, individual pain threshold, intensity of applied force, emotional state and/or stress, cultural differences, and previous experience of pain. [70,81,109]

Orthodontic pain is an inflammatory pain that is initiated by orthodontic force-induced vascular occlusion followed by a cascade of inflammatory responses, including vascular changes, the recruitment of inflammatory and immune cells, and the release of neurogenic and pro-inflammatory mediators. Ultimately, endogenous analgesic mechanisms check the inflammatory response and the sensation of pain subsides. The orthodontic pain signal, once received by periodontal sensory endings, reaches the sensory cortex for pain perception through three-order neurons: the trigeminal neuron at the trigeminal ganglia, the trigeminal nucleus caudalis at the medulla oblongata and the ventroposterior nucleus at the thalamus. Many brain areas participate in the emotion, cognition and memory of orthodontic pain,

including the insular cortex, amygdala, hippocampus, locus coeruleus and hypothalamus. [19,77,81,98] Figure 1 shows the mechanisms underlying orthodontic pain. (*Long et al., 2016*)

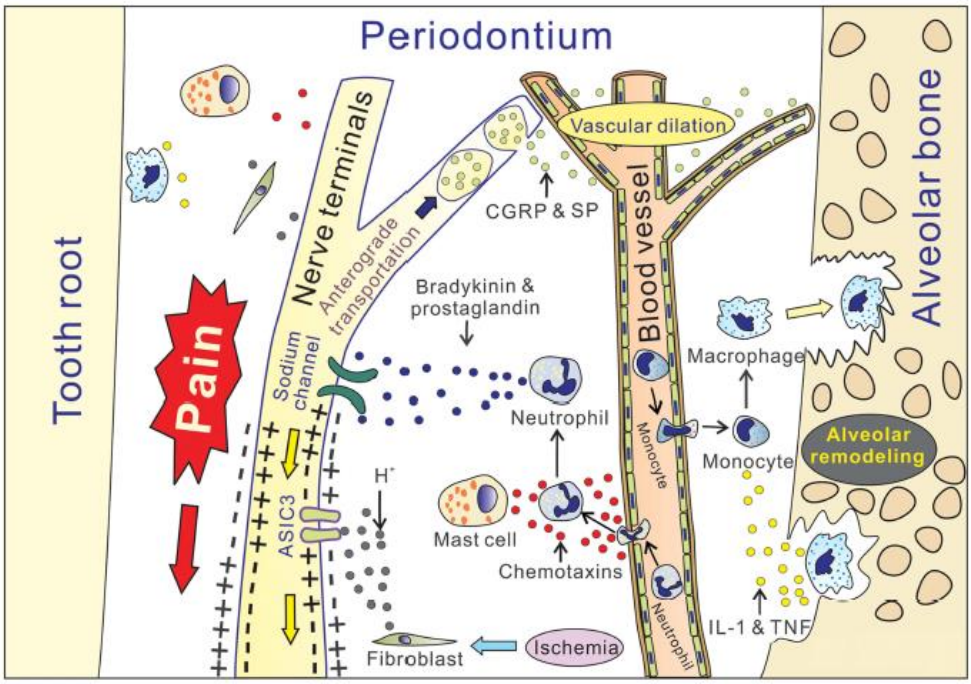

Figure 1. The mechanisms underlying orthodontic pain. The dental root (left) moves in the direction of force towards the alveolar bone (right) with the periodontium between them. Upon vascular compression and local ischaemia, periodontal cells, mainly fibroblasts, undergo anaerobic respiration and cause local acidosis. The proton ion (H+) binds to ASIC3 receptors on sensory endings to generate pain. As local ischaemia progresses, mast cells and fibroblasts release various chemotaxins to recruit leucocytes, for example, neutrophils and monocytes. These leucocytes release abundant inflammatory mediators (for example, bradykinin and prostaglandin) and cytokines (for example, IL-1 and TNF). Bradykinin and prostaglandin bind to sensory endings to generate painful sensations. The released cytokines amplify local inflammation and stimulate monocyte-derived macrophages to participate in alveolar bone remodelling. Moreover, via anterograde transportation, sensory endings release various neurogenic mediators (for example, CGRP and SP) to dilate local blood vessels and enhance local inflammation, amplifying local painful sensation and alveolar remodelling. CGRP, calcitonin gene-related peptide; IL, interleukin; SP, substance P; TNF, tumour necrosis factor. [Long et al. 2016]

Orthodontic pain may be perceived during all orthodontic procedures, such as placement of space separators, activation of arches, application of orthopedic forces and debonding, but several studies have shown that *fixed orthodontic appliances* cause the most intense pain, also compared to the removable or functional ones. [70,109]

Orthodontic pain is a major concern for parents, patients, and clinicians. Studies have reported this reaction to be a major deterrent to orthodontic treatment and an important reason for discontinuing treatment. [70,109] Nevertheless, it is surprising how this important area, both in clinical practice and in scientific research, is almost ignored, as evidenced by the scarcity of publications on the subject. [70,109] In the ICOP classification, orthodontic pain can be related to *Periodontal pain attributed to traumatically induced periodontal inflammation* (*1.1.2.1.1)* [59], but the lack of a specific category within this classification, concerning the application of orthodontic forces, reflects this point.

Orofacial pain management

Due to the wide variety of clinical manifestations of OP, its treatment involves different therapeutic methods, mainly drugs, and splint therapy for TMD-related pain.

Concerning *TMD pain*, currently, there is a lack of consensus regarding the most efficacious treatment approach, precisely because of the multifactorial nature of TMD. [146] Pharmacological and occlusal therapy are generally considered the elective and most effective therapy for patients affected by TMD. [144,146] The most commonly used medications are myorelaxants, nonsteroidal anti-inflammatory drugs (NSAIDs), analgesics, tricyclic antidepressants, benzodiazepines and corticosteroids. [144] Occlusal devices represent a treatment method in line with the current literature indications that recommend a conservative, careful and personalized therapeutic approach towards the TMD. [133] Occlusal appliances may be used for occlusal stabilization, for the treatment of pain related to TMD, or for the prevention of dentition wear, and are used in a vast majority of patients to restore the static and dynamic symmetry of the stomatognathic system. Occlusal splints, when selected on the basis of the diagnosis and the type of patient, and correctly managed, can represent an elective method for the recovery of the TMJ functions and the relief of the consequent pain symptomatology, determining valid and stable results over time. [72, 133,144]

But besides these conventional therapies, due to the wide variety of clinical manifestations of TMDs related pain, its treatment involves usually different therapeutic methods, such as surgical therapy, physical therapy, low-level laser therapy (LLLT), transcutaneous electrical nerve stimulation (TENS), ultrasound, vibrational therapy, psychological support and, increasingly in recent times, acupuncture. [73,123,144]

Concerning *orthodontic pain* management, different methods have been studied, including the use of anaesthetics, analgesics, the application of low-level laser therapy to the periodontal tissues, Transcutaneous Electrical Nerve Stimulation (TENS), and vibratory stimulation of the periodontal ligament. [78,81,92,125,142] All these methods have been partially successful in achieving pain relief. However, the use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) is the preferred method of pain control which is related to fixed orthodontic appliances. [125] Many NSAIDs like ibuprofen, aspirin and acetaminophen have been shown to produce significant reductions in the dental pain, by taking up randomized, double-blind placebo-controlled clinical trials. [4,12,76,104] However, their effects on tooth movement are controversial (NSAIDs resulted to interfere with collagenase activity and procollagen synthesis, which results in impeded periodontal remodelling), and their side-effects should be identified before prescribing these medications in routine clinical practice. [81] Furthermore, while these therapeutic strategies have proven useful in the management of pain during treatment, orthodontists generally do not prioritize pain management; the lack of standardized and efficacy-proven pain protocols reflects this point.

TRADITIONAL CHINESE MEDICINE & ACUPUNCTURE

Traditional Chinese Medicine (TCM), compendium of the experience of the Chinese working masses in the battle against disease for thousands of years, is invaluable for its rich store of practical knowledge and constitutes a complete and integrated theoretical system, defined since ancient times. (III-IV sec. a.C.)
For TCM, the organism is an integrated functional system in which apparatuses, organs, tissues and functional activities are closely related to each other in a relationship of cooperation and interconnection that translates into a relationship of mutual promotion and mutual inhibition for the maintenance of the dynamic balance essential to the continuity of life. [85]

Acupuncture and moxibustion, one of the major branches of TCM, are important procedures used to prevent and treat disease through the insertion of needles or the application of heat, with burning moxa wool, to specific points on the body (acupoints).

The use of unconventional therapeutic protocols, as alternative or support to conventional medical methods, is a much-discussed issue in literature. [85,107,151] Among the *Non-Conventional Medicines (NCM), TCM* is certainly the most widespread in the world, as well as the only one to remain intact in the principles up to now and, therefore, the best systematized. In particular *Acupuncture (AT)*, a versatile therapeutic tool, and therefore applied in different medical areas, including dentistry. [45,107,115] Sure enough, thanks to its action on all the body regulatory systems, acupuncture has a therapeutic effect on a wide range of pathologies, both acute and chronic: gastrointestinal, cardiological or pneumological diseases, dermatological or allergic manifestations, osteoarticular and rheumatological pathologies, neurological and psychiatric problems. [95]

Despite the various fields of action, analgesia is certainly the therapeutic application that has always aroused the greatest interest in the international medical community, favouring the integration of AT with conventional therapies. [95,143,150]
Acupuncture for analgesic purposes is especially investigated, often to understand more deeply its mechanisms of action. Although many physiological and neurological mechanisms are still unknown, acupuncture therapeutic efficacy in pain therapy is well established. [73,147] In dentistry, the most investigated field is certainly cranial-cervico-mandibular pain, where acupuncture was effective in numerous studies; in relation to orthodontic pain, moreover, there is evidence regarding the effectiveness of somatic acupuncture. [10,44,58,135,146]

Acupuncture in orofacial pain management

The field of dentistry has a long history of using *Complementary and Alternative Medicine (CAM)* and nonpharmacological approaches for the relief of orofacial pain. The first such CAM procedure in dentistry was probably hypnosis, which was first reported in 1837 by *Oudet*, a French dentist, who used hypnoanesthesia for a dental extraction. [114] Today, many dentists use techniques to distract patients and reduce anxiety during acute painful dental procedures, and a number of CAM procedures are used for patients experiencing chronic orofacial pain, including TMD-related pain. [114] Among these procedures TCM, and particularly acupuncture, are undoubtedly the most studied methods with proven clinical efficacy in OP field.

In many clinical studies, acupuncture has been proven an effective form of pain management, particularly pain of musculoskeletal origin, in TMD patients. [146] An interesting recent review by *Wu et al.* (2017), compared the clinical effectiveness of AT therapy in TMD patients through the meta-analysis of published results. The results indicate that acupuncture therapy penetrating the skin has greater effectiveness and reduces the pain degree to a greater extent, especially myofascial pain symptoms, compared with both sham nonpenetrating acupuncture and sham laser therapy. [146]

Acupuncture comprises a wide range of treatment techniques, methods of points stimulation, and devices. [18] There are several clinical studies that investigate AT effectiveness for OP related to TMD, through the use of different traditional and modern AT methods, including microsystem and laser stimulation. [34,106,128,153] While only a few studies have investigated acupuncture to treat orthodontic pain and none of them study the application or effectiveness of technique different from the traditional body acupuncture. [10,135]

The principal AT techniques/methods of point stimulation currently used in acupuncture practice, and with strong indication for the treatment of pain in cranio-facial area, are described as follows.

Body Acupuncture

Body or somatic acupuncture represents the classic and most common stimulation method of acupuncture, and the most frequently mentioned for the treatment of pain. It involves the insertion of needles into the selected acupoints, which are manually stimulated by the operator. This technique is actually the most investigated in orofacial pain field, followed by laser-acupuncture, and different microsystem acupuncture methods, such as ear, scalp, mouth and fingers. [34,106,121,128,153] *Zotelli et al.* verified the effectiveness of body acupuncture in the treatment of pain of muscular and mixed origin in patients with TMD, showing an improvement of pain in the treated patients. [153] A review by *Fernandes et al.* evaluated the effectiveness of various body and laser acupuncture treatments for

temporomandibular disorder myofascial pain, showing that both the techniques can be effective in relieving patients' signs and symptoms. [34]

There are only two evidences about the application of body acupuncture for the treatment of orthodontic pain. To manage post-adjustment orthodontic pain, *Vachiramon and Wang* proposed the use of just one acupoint, *Hegu* (LI4), stimulated by needles or simple acupressure. [135] *Boleta-Ceranto et al.* analyzed patients' pain levels during the second quarter of fixed orthodontic therapy; they applied a treatment of somatic acupuncture, and found a statistically significant reduction in pain level indexes both for men and women when acupuncture therapy was performed before the orthodontic adjustment. [10]

Cupping Therapy (CT)

Cupping therapy belongs to belongs to TCM and represents one of the most ancient methods of point stimulation. It consists in using one of several kinds of cups (bamboo cups, glasses or earthen cups) placing them on the desired acupoints or sore spots on patients' skin, producing hyperemia or hemostasis, which results in a therapeutic effect. [22] The majority of systematic reviews and RCTs to date suggest a favourable effect of cupping for pain, especially tension headache and musculoskeletal pain. [1,17] The negative pressure applied to the skin during the cupping procedure has been proven to induce muscle relaxation, changes in local tissue structures and in blood circulation, reducing significantly peripheral and local P substance and inflammation, and resulting in pain reduction. [152]

This method resulted effective for treating several pain conditions, especially when combined with other treatments, but its use in orofacial pain field is poorly documented. [1,17,48] A single study by *Han et al*. analyzed the effect of acupuncture combined to medicated cupping therapy, reporting this method as effective in treating orofacial pain related to TMD. [48]

Microsystems Acupuncture

Over time Traditional Chinese Medicine (TCM) has been supplemented and amplified and several other approaches of acupuncture, beside the classical traditional ones, have been developed. One of these approaches is *microsystem acupuncture*. [53,127] It has been suggested that systematic point patterns are found on circumscribed parts of the body—for example, the auricle, the scalp, the oral cavity and other areas. [41] Beside physiological mechanisms proposed for traditional acupuncture, microsystems have been reported to have a greater influence on the vegetative nervous system. [148]

Simma et al. (2009), observed a reduction of pain intensity in TMD using a combination of microsystem acupuncture points including oral, auricular and scalp acupuncture points. [127] *Peixoto et al.* reported that scalp acupuncture was effective in TMD patients in terms of pain intensity, as well as occlusal splints

and manual therapy, reducing it in the short term. [106] In 2009 a German article described the use of microsystems in the field of otorhinolaryngology, 14 highlighting the system in the oral mucosa (mouth microsystem). A previous study investigated the effects of auricular and oral acupuncture on pain relief in TMD. [127] However, larger trials have not been published so far. [128] The ear is probably the most widely known and applied microsystem. [53] It was seen that ear acupuncture has synergistic action on conventional occlusal splint treatment, resulting effective in the reduction of TMD related-pain in the short term. [37] Concerning orthodontic pain, there are no evidences about the efficacy of microsystem acupuncture application so far.

Abdominal Acupuncture

Abdominal acupuncture is particular and relatively new microsystem technique, which was set up in the last 30 years in China by Prof. Bo Zhi Yun, director of Bo's Abdominal Acupuncture Centre of Beijing. [9] Nowadays, it is effectively used in treatment of various disorders, especially pain and neurological disorders [82,118]; however, there is no evidence about the effectiveness of abdominal acupuncture on orofacial pain and TMD related symptoms. The abdominal acupuncture has an important characteristic: needles, after their insertion into the acupoints, are not manipulated. This technique, while avoiding needle stimulation, is an easy-to-be-standardized repeatable method, as required by research methodology.

Auricular Acupuncture

Auricular or Ear Acupuncture (AA) is a particular treatment system based on normalizing the body's pain and dysfunction through stimulation of points on the ear. The different auricular areas have distinct influence on autonomic functions and it has been shown that auricular acupuncture plays a role in vagal activity of autonomic functions of cardiovascular, respiratory, and gastrointestinal systems. [100,137,148] This technique resulted effective in treating various types of pain, both acute and chronic. [21,61,137,148]

This method includes the so-called *Auriculotherapy (AurT)*, that involves the application of *Vaccaria seeds* to specific auricular acupoints, instead of the insertion of needles, and therefore offering the additional advantage of being well-received by patients, including paediatric subjects. [122,137]

A recent review from *Vieira* et al. has shown ear acupuncture to have a positive effect when paired with conventional treatments of chronic and acute pain. [137] *Iunes et al.* investigated the efficacy of Auriculotherapy in a group of TMJ dysfunctional patients, demonstrating it to be significantly effective in reducing pain in the temporal and TMJ areas. [61] A meta-analysis from *Yeh et al.* establishes that ear acupuncture provides significant pain relief when compared to a sham or control group. [148]

Application of innovative technologies in acupuncture

Historically, stimulation of skin at specific acupoints might have been performed with stones or bones; currently, traditional acupuncture is performed by inserting a metal filiform needle into the skin at an acupoint, and electric currents can be passed between needles (electroacupuncture). More recently, acupuncture practitioners have begun to use nonthermal, low-intensity laser irradiation to stimulate acupoints (laser acupuncture). [73,147,149]

Electroacupuncture

Electroacupuncture is a form of acupuncture extensively studied for its analgesia effects. [15,71,79] This technique involves electrical stimulation of needles, and its growing use in pain management is supported by scientific research demonstrating differential modulation of endogenous opioids by electrical stimulation of varying frequencies. [15] Few studies investigated the effects of electroacupuncture on TMD related-pain; though has been proven to provide significant analgesia, its role in the management of orofacial pain has not been fully established. [15,71]

Laseracupuncture

In addition to traditional acupuncture, performed with the insertion of needles into acupoints, laser acupuncture may also be useful in the treatment of TMD since the low-intensity laser is considered a tool capable of bringing significant benefits in the treatment of many maxillofacial disorders.[105] According to *Hotta et al.*, laser acupuncture may be beneficial in the control of TMD patients' pain, constituting an alternative therapy in the treatment of this dysfunction.[55] *Huang et al.* showed that approximately 85% of patients with TMD treated with LA presented a 63% reduction of pain after treatment.[58] Laser acupuncture may be the preferred acupuncture modality for specific patient populations, such as geriatric and paediatric patients, because it is non-invasive, pain-free, and possibly associated with fewer adverse effects.[56]

Vibrations

One of the most recently proposed physical therapy treatments is vibration therapy. Local vibration therapy produces vibrations that reach up to 6 centimetres of tissue depth; it is used to regulate muscle tone, relieve localized pain, and stimulate an increase in blood and lymphatic circulation. [5,29,40] This therapy is most frequently applied in the treatment of chronic pathologies affecting the muscles, tendons, and joints. Several studies evaluating the impact of vibration therapy on skeletal muscles and joints have

highlighted its effectiveness for increasing joint mobility and decreasing pain [20,40,83], but analysis of its potential for the craniofacial region is still lacking. Only two studies have addressed the application of this therapy to TMD and both demonstrate its effectiveness for muscle pain relief. [49,116]

Several methods may be used to stimulate acupuncture points, including vibration. However, there is no evidence of the application of the vibratory stimulus on acupoints for treating orofacial pain. A single study by Weber *et al.* (2015) investigated the clinical effects of the combined application of music and vibration on acupoints, for the treatment of chronic pain in patients affected by fibromyalgia. The obtained results exhibited a beneficial effect for the short-term treatment of fibromyalgia symptoms, but also suggested a quite remarkable placebo effect. [141]

AIMS

General Aim

The general aim of this doctoral thesis was to deepen the knowledge about the use of Acupuncture in Orofacial Pain field, focusing primary on TMD-related pain, and secondary on orthodontic pain.

Through a corollary of studies, we tried to outline the possible therapeutic contribution of acupuncture in the management of orofacial pain, a field in which it has strong indications and has already produced numerous results of clinical efficacy. [114,146] The clinical application of acupuncture is characterized by an extreme variety of diagnostic/therapeutic schemes, techniques and methods of point stimulation but, especially in a such heterogeneous field as OP, still presents many gaps of specific indications, and suffers from the complete lack of applications of some techniques already proven effective in other areas of musculoskeletal and chronic pain and currently used in acupuncturists practice. [18,34,135,146]

For this reason, some acupuncture techniques that have never yet been investigated, at least in Western literature, were applied, such as traditional cupping, abdominal acupuncture and electroacupuncture in the dysfunctional patient, and auriculotherapy for treating pain related to fixed multibrackets appliances.

In order to provide specific therapeutic indications and deepen the mechanisms underlying this particular therapeutic tool, acupuncture has been explored in terms of clinical efficacy and biomolecular effects, through the use of different acupoint patterns and stimulation methods, including the most traditional and the most modern technological ones, on different types of patients.

Specific Objectives

1. To investigate and compare the effects of different acupuncture techniques and methods, including the use of innovative technological instruments for acupoint stimulation, i.e. *electrostimulation* and *vibration*, in patients affected by pain of TMD origin. (***Study I***)

2. To explore the use and analyse the effects of "microsystem acupuncture" techniques, i.e. *Ear* and *Abdomen* microsystems, in the management of orofacial pain connected to TMD and to the use of fixed orthodontic appliances. (***Study II***)

3. To investigate molecular and neurological mechanisms underlying acupuncture stimulation, studying the salivary proteic response to ear acupuncture in healthy subjects and patients affected by TMD Myalgia. (***Study III***)

METHODOLOGY

This thesis includes three studies. Two of these were clinical studies that included patients affected by pain of TMD (***Study I-II***) and orthodontic origin (***Study II***) that were conducted at Sapienza University of Rome, Department of Oral and Maxillofacial Sciences, Divisions of Clinical Gnathology and Orthodontics. The other is a preliminary experimental molecular study (***Study III***) including both healthy subjects and subjects affected by myalgia, and was conducted at Karolinska Institutet of Stockholm, Department of Dental Medicine, Division of Oral Diagnostics and Rehabilitation, during the candidate's international mobility period.

Beside the four main clinical studies involving therapeutic procedures that are described as follows (***Study I-1***, ***Study I-2, Study II-1, Study II-2***), this doctoral project also comprises three epidemiological and observational studies (Papers I, II and V) concerning the analysis of some epidemiological and pain-related characteristics of different population of dysfunctional and orthodontic patients. These studies were all conducted during the Ph.D. period and are corollary studies of this doctoral thesis, for this reason the relative published papers are entirely reported in this thesis but they are not explained in details in the following sections. (see Papers I, II and V) All the studies that comprise this doctoral thesis are decribed and summarised in Table 3.

The methods, the selection of participants and the therapies applied, were all approved by the Institutional Ethical Review Board in Italy (93/17- 0001385, 53/18–0000711, 47/19-0001155) and the Swedish Ethical Review Authority (2021-00427, 2021-03-24).

All participants received careful information regarding the aims and procedures of the studies and signed an informed consent form prior to participate. All the study protocols followed good clinical practice and the guidelines according to the Declaration of Helsinki. [144] The patient enrolment and interventions process followed the CONSORT (Consolidated Standards of Reporting Trials) and the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) criteria. [3,30]

Study I

Study I represent the major study of this thesis, focusing on the application of different acupuncture techniques, both traditional and technological ones, for the treatment of TMD-related pain.

Study I-1: ***Comparison of the effectiveness of three different acupuncture methods for temporomandibular disorders-related pain***

This is a randomized clinical study that aimed to compare the effectiveness of three acupuncture methods for TMD related-pain. Four different locations of pain were considered: temporomandibular joint (TMJ)

pain, muscle pain, headache and neck pain. Sixty patients were assigned randomly to one of three treatment groups (20 patients in each): *Group BA* received body acupuncture, *Group EA* received electroacupuncture, and *Group CA* received acupuncture + cupping. The groups were compared in terms of pain (verbal numeric scale, VNS), pain-related disability (Brief Inventory Pain, BPI), and impression of the treatment's effectiveness (Patients' Global Impression of Improvement Scale, PGI-I). These were recorded before (T0), after 8 sessions of acupuncture treatment (T1), and after 4 weeks of follow-up after treatment (T2). The between-group and within-group differences in the data were analyzed statistically.

Study I-2: ***Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment***

This is a randomised, double-blind, placebo-controlled preliminary study, that analyses the effectiveness of at-home local vibration therapy (LVT) for the management of TMDs-related myofascial pain.
Fifty-four TMD patients were randomly subdivided into two groups. The study group (AG) received 1 week of at-home LVT treatment with the NOVAFON Pro Sk2/2: 50/100Hz, bilaterally applied to the pain area for 16 minutes daily. The placebo group (IG) followed the same protocol using inactive devices. Temporomandibular joint pain (TMJ), muscular pain (MM), and headache (HA) were assessed. Pain was evaluated using the visual analogue scale (VAS) before (T0) and after therapy (T1).

Since there were no evidences regarding the application of such innovative vibratory device (NOVAFON Pro Sk2/2) for the treatment of TMD-pain, we decided to conduct this preliminary study first, that involved the application of the device on painful facial areas, and not on acupuncture points. (Paper III) The second step of this study, involving a new clinical protocol concerning the application of LVT on a specific acupuncture scheme, was stopped in February 2020 due to the COVID-19 pandemic. Patients' enrolment started again in October 2021 after the candidate mobility period, but there aren't enough data to be discussed in this thesis.

Study II

Study II-1: ***Abdominal acupuncture in patients with subacute and chronic TMD pain not responding to conventional therapy***

This is a retrospective observational study in general practice that evaluated the effects of abdominal acupuncture (AbdA) on maximum mouth opening (MMO) and orofacial pain intensity (VNS) in patients with subacute and chronic TMD-related pain non-responding to conventional treatments, and affected or not by systemic pain conditions.

A population of twenty-eight patients was treated 2 times per week for 4 weeks with AbdA. A 0-100 verbal numeric scale (VNS) was used to measure the pain intensity at temporomandibular, muscular and facial

level, at the beginning (T0) and at the end (T1) of AbdA therapy. The Brief Pain Inventory (BPI) was used to assess pain and pain interference with common activity and quality of life of patients, at T0 and T1.

Study II -2: *Auriculotherapy used to manage Orthodontic Pain*

This is a randomized, controlled pilot study that evaluates the analgesic effects of Auriculotherapy (AurT) during the first 3 months of fixed orthodontic treatment.

Thirty-six patients were selected and randomly allocated to two homogeneous groups, Study Group (SG) and Control Group (CG), depending on the application / non-application of AurT. Patients rated their pain scores monthly on the 0 to 10 visual analogue scales (VAS) at the time of bonding (T0) and again at two appliance adjustments (T1 and T2). At each of these treatment phases, VAS was applied in 6 different time moments: immediately before, immediately after, after 4 hours, after 8 hours, after 24 hours, and after 72h hours.

Study III

This study consists of two separate studies that were conducted between March 1 and August 31, 2021 at the Department of Dental Medicine, Karolinska Institutet (KI), Huddinge Sweden, during the candidate's international mobility period. The first study (Study III-1) is a randomized case-control study encompassing 30 healthy, pain-free participants and the second study (Study III-2) is an exploratory non-blinded observation study encompassing 10 patients with TMD myalgia.

Study III-1

A population of 30 healthy subjects was randomly allocated into 3 groups of 10 subjects each: *Group SG* received auricular acupuncture, *Group ShG* received auricular sham acupuncture (placebo), and *Group CG* received no therapy (control). A saliva collection was performed in order to evaluate pain perception-related protein fluctuations; in particular the proteins analyzed were: Glutamate (GT), Nerve Growth Factor (NGF), Brain-derived Nerve Growth Factor (BDNF) and Substance P (SP). This procedure, in patients of all groups (SG, ShG and CG), was performed at two time points: T0, which corresponds to the start of therapy (baseline), and T1, which corresponds to the end of therapy (1 week after T0).

Study III-2

This is a pilot on which 10 patients affected by TMD myalgia were treated with auricular acupuncture in the same manner as the SG above. Saliva was collected before and after treatment, i.e. at T0 and T1, and the same protein analysis was performed. At T0 and T1, facial pain variation was also assessed through the 0-10 VAS scale.

Table 3: Summary of the different studies included in the doctoral project and their principal characteristics

		Type of Study	Patients (n)	Age (mean)	Diagnosis	Treatment
Study I						
	Longitudinal epidemiological analysis of three decades of TMD populations	Preliminary Study	387	35.37	TMD (DC/TMD, Axis I and II)	
	Evaluation of Vision in Gnathological and Orthodontic Patients with Temporomandibular Disorders: A Prospective Experimental Observational Cohort Study.	Preliminary Study	100	32.63	TMD (DC/TMD, Axis I)	
	*Comparison of the effectiveness of three different acupuncture methods for TMD-related pain: a prospective randomized clinical study (**Study I-1**)*	Clinical Study	60	44.9	Arthralgia, Myalgia, Disc Displacement With Reduction	Somatic Acupuncture, Electroacupuncture, Cupping
	*Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment: A Randomised, Double-Blind, Placebo-Controlled Preliminary Study (**Study I-2**)*	Preliminary Clinical Study	54	40.7	Chronic local myalgia (ICD-9 729.1)	Vibrations
Study II						
	Perceived Pain during Rapid Maxillary Expansion (RME): Trends, Anatomical Distinctions, and Age and Gender Correlations	Preliminary Study	96	10.11	Maxillary arch contraction with mono/bilateral cross-bite	RME
	*Abdominal acupuncture in patients with subacute and chronic TMD pain not responding to conventional therapy (**Study II-1**)*	Clinical Study			TMD (DC/TMD, Axis I)	Abdominal Acupuncture
	*Auriculotherapy used to manage Orthodontic Pain: a Randomized Controlled Pilot Study (**Study II-2**)*	Clinical Study	36	19.5	Malocclusion of I, II or III class	Fixed orthodontic therapy Auriculotherapy with Vaccaria seeds
Study III						
	Salivary proteic response to acupuncture for Temporomandibular Disorders (ACUPROTMD): a pilot project	Preliminary Study	40		Myalgia (n=10)	Auriculotherapy with thumbtack needles

Participants

Patients were recruited by means of specialistic personnel or an advertisement distributed among TMD patients and orthodontic patients referred to the specialist clinic for orofacial pain and jaw function at the Department of Oral and Maxillofacial Sciences at the Sapienza University of Rome, Italy (Study I-II) and at the University Dental Clinic at the Karolinska Institute of Stockholm, Sweden (Study III).

The studies (Study I-1 /I-2, Study II-1/II-2 and Study III) thus initially included 268 patients, of whom 218 patients in total, 165 women and 53 men, completed the studies. 50 individuals in total dropped-out, 37 during Study I, 11 during Study II and 2 during Study III. The demographic distribution of the patients is presented in Table 4.

The healthy pain-free participants were recruited by advertisement from students and staff at the University Dental Clinic at Karolinska Institute, Huddinge, Sweden (Study III). The healthy pain-free participants included in the studies numbered 30 individuals in total, 20 women and 10 men. 2 pain-free participants dropped-out during Study III. The demographic distribution of the healthy participants is also presented in Table 4.

Different individuals were included in the different studies, mainly adults but also paediatric subjects (Study II). The following table lays out the characteristics of the whole sample with regard to demographic data, pathology, and type of acupuncture therapy performed. (Table 4)

Table 4: demographic data, pathology, and type of acupuncture therapy performed in Study I-III

	Patients (n)	**Gender (n)**		**Age (mean)**	**Diagnosis**	**AT Method**
Study I		**F**	**M**			
Study I-1	60	50	10	44.9	Arthralgia, Myalgia, Disc Displacement With Reduction	Body Acupuncture, Electroacupuncture, Cupping
Study I-2	54	43	11	40.7	Chronic local myalgia (ICD-9 729.1)	Vibrations on local muscle points
Study II						
Study II-1	28	24	4	49.3	TMD pain (ICD-9 729.1; ICD-9 524.62; ICD-9 339.89; ICD-9 524.63)	Abdominal Acupuncture
Study II-2	36	22	14	19.5	Malocclusion (class I, II, III)	Auriculotherapy with Vaccaria seeds
Study III	40	26	14			
Study III-1	30	20	10	31.3	Healthy subjects	Auriculotherapy with thumbtack needles
Study III-2	10	6	4	35.2	Myalgia (ICD-9 729.1)	Auriculotherapy with thumbtack needles

Inclusion and exclusion of participants

For *patients*, the general inclusion criteria were as follows:

1. Aged over 18 years *(**Study I-II-III***) and under the age of 14 (***Study II***)
2. Women and men *(**Study I-II-III***)
3. A diagnosis of TMD pain (ICD-9 729.1; ICD-9 524.62; ICD-9 339.89; ICD-9 524.63) greater than or equal to 3 on the Numeric Verbal Scale (NVS), according to the diagnostic criteria for temporomandibular disorders (DC/TMD) [117] (***Study I-II***)
4. A frequency of TMD pain greater than or equal to 1 time/week and a pain duration of at least 3 months (***Study I-II***)
5. A diagnosis of local myalgia or myofascial pain or myofascial pain with referred pain in the masseter muscle, with or without temporal myalgia, according to DC/TMD [117] (***Study III***)
6. Patients undergoing a conventional fixed multibracket orthodontic therapy, applied to one or both dental arches, and patients undergoing to rapid maxillary expansion therapy (RME) (***Study II***)

For *patients*, the general exclusion criteria were as follows:

1. A diagnosis of Disc Displacement without Reduction joint disorders (ICD-9 524.63) and/or Degenerative Joint Diseases (ICD-9 715.18) according to DC/TMD [117] (***Study I-II-III***)
2. Patients receiving ongoing gnathological treatment (***Study I-II-III***)
3. General chronic pain conditions or systemic inflammatory diseases such as fibromyalgia, rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis (***Study I-II-III***)
4. Chronic and/or current use of analgesic medication or other drugs that can affect the pain experience (e.g. anxiolytic drugs) (***Study I-II-III)***
5. Pregnancy or lactation (***Study I-II-III)***
6. Severe psychiatric disease diagnosed by psychiatrist (e.g., schizophrenia, bipolar disorder) (***Study I-II-III)***
7. Allergy to any of substances such as needles and/or orthodontic appliance used in the studies. (***Study I-II-III)***

Additional criteria for exclusion from ***Study I (Study I-2)*** included:

8. Presence of open wounds/eczema on the skin or the skin membranes involved in the treatment
9. Diagnosis of arteriosclerosis, thrombosis, cardiac arrhythmias, or use of pacemaker
10. Diagnosis of epilepsy
11. Use of brain stimulators or presence of metal implants
12. Presence of tumour lesions

For *healthy participants* (**Study III**) the inclusion criteria were as follows:

1. Aged over 18 years
2. No known significant health problems

For *healthy participants* (**Study III**) the exclusion criteria were as follows:

1. Current acute or chronic pain
2. Systemic inflammatory disease (e.g., rheumatoid arthritis)
3. Neuromuscular disease (e.g., dystonia)
4. Severe psychiatric disease diagnosed by psychiatrist (e.g., schizophrenia, bipolar disorder)
5. Pregnancy or lactation
6. Current analgesic medication or other drugs that can affect the pain experience (e.g. anxiolytic drugs)

Clinical examination

All participants were clinically examined, extra- and intra-orally prior to inclusion. All examinations in all three studies were performed by trained examiners, specialists in orofacial pain (***Study I-II-III***) and orthodontics (**Study II**) using standardised protocols. [117] Diagnoses and eligibility were established according to the International Classification of Orofacial Pain (ICOP). [59] Based on this classification, for TMD-diagnoses associated with pain the Diagnostic Criteria of Temporomandibular Disorders (DC/TMD – Axis I) [117], an improved version of the previous Research Diagnostic Criteria of TMD (RDC/TMD) [31], was adopted.

The DC/TMD includes:

- **Axis I** - A screening tool for detecting pain-related TMD physical signs symptoms with a sensitivity of>=0.86 and a specificity of>=0.98
- **Axis II** - A screening and a self-assessment instrument for assessing psychological, behavioural, and disability factors, as well as co-morbid pain conditions
- An additional **Axis III** - This is proposed and yet to be established; it is currently undergoing development through active research. However, Axis III hopes to offer a tool for assessing biomarkers and risk factors for orofacial pain [132]

Questionnaires

The participants were asked to complete several questionnaires, that varied across the three studies. Overall, validated and reliable questionnaires were used as instruments to assess multiple subjective variables regarding pain, oral and general health, jaw function, various psychosocial aspects, the interference of pain with the patients' general activity and quality of life, and the patients' impression on the received therapies. Several of these instruments are included in Axis I and II of DC/TMD [117], and the ones adopted from this selection were:

- the *Oral Behaviour Checklist (OBC)*, used to better determine the presence of parafunctional behaviors (**Study I-II-III**)
- the *Jaw Functional Limitation Scale* (JFLS-8), used for the overall assessment of functional limitation of the masticatory system (**Study III**)
- the *Patient Health Questionnaire (PHQ-4)*, used to assess symptoms of depression (**Study III**)

The other validated questionnaires adopted were the following:

- the *Perceived Stress Scale-4*, used to assess subjectively perceived stress [97] (**Study III**)
- the *Oral Health Impact Profile (OHIP)*, used to assess how the respondent's oral health is subjectively perceived by patients [119] (**Study III**)
- the *Brief Pain Inventory (BPI)*, used to assess severity of chronic pain and related disability in daily activities and quality of life [11] (**Study I-II**)
- the *Patients' Global Impression of Improvement (PGI-I) Scale*, used to assess the impression of the treatment's effectiveness [117] (**Study I-II**)

Pain assessment

Orofacial pain intensities, in all three studies, were assessed through validated pain scales, used as a tool of pain self-assessment. [46]

For *TMD pain assessment* the pain scales used were as follows:

- The 0-100 **Verbal Numeric Scale (VNS)**, is a commonly used self-report measure of pain intensity in adult populations. The interaction is verbal, using no materials or equipment, to measure pain self-assessment, with 0 indicating "no pain" and 100 "the worst imaginable pain"

- The 0-100 **Visual Analogue Scale (VAS)**, the scale is represented as a straight line, with 0 indicating "no pain" and 100 "the worst imaginable pain." The patient is asked to mark his pain

level on the line between the two endpoints. The distance between 'no pain at all' and the mark then defines the subject's pain

For *Orthodontic pain assessment* the pain scales used were as follows:

- the **Visual Analogue Scale (VAS)**, the scale is represented as a straight line of 10 cm between two poles: "no pain" (0) and "maximum pain" (10)
- the **Numeric Rating Scale (NRS),** in this scale patients are asked to circle/mark the number between 0 and 10, 0 and 20 or 0 and 100 that fits best to their pain intensity. Zero usually represents "no pain at all" whereas the upper limit represents "the worst pain ever possible"
- the **Wong–Baker Faces Pain Rating Scale (FPS-R),** is a self-report pain measure with strong validity and reliability in 4- to 17-year-olds. The scale shows a series of faces ranging from a happy face at 0, or "no hurt", to a crying face at 10, which represents "hurts like the worst pain imaginable". Based on the faces and written descriptions, the patient choose the face that best describes their level of pain

Acupuncture treatments

The studies carried out in this doctoral thesis involved the use of several acupuncture techniques and method of point stimulation, described as follows.

In all the AT procedures, regardless of the technique used, the needles were inserted after asepsis of the skin with 70% alcohol at the needle penetration site. The needles were all disposable and sterilized, individually packed (TEWA, ASIA-MED GMBH & CO. KG), of the following sizes: 0.25x25 mm, 0.30x30mm, 0.30x40mm. The depth of needle penetration varied considering the anatomical differences of the application sites in each patient.

***Body or somatic acupuncture* (*Study I*)**

This procedure involved the insertion of needles into the selected acupoints, which were manually stimulated by the operator. The needle was manipulated clockwise and counterclockwise to achieve the proper feel of the needling with acupuncture called "Deqi". The acupuncture points used were: ST6 (Jiache), ST7 (Xiaguan), GB20 (Fengchi), BL10 (Tiazhu), LI4 (Hegu), ST36 (Zusanli), SP6 (Sanyinjiao) and LR3 (Taichong). The anatomical location of all the acupoints used is presented in the following figure. (Fig. 2)

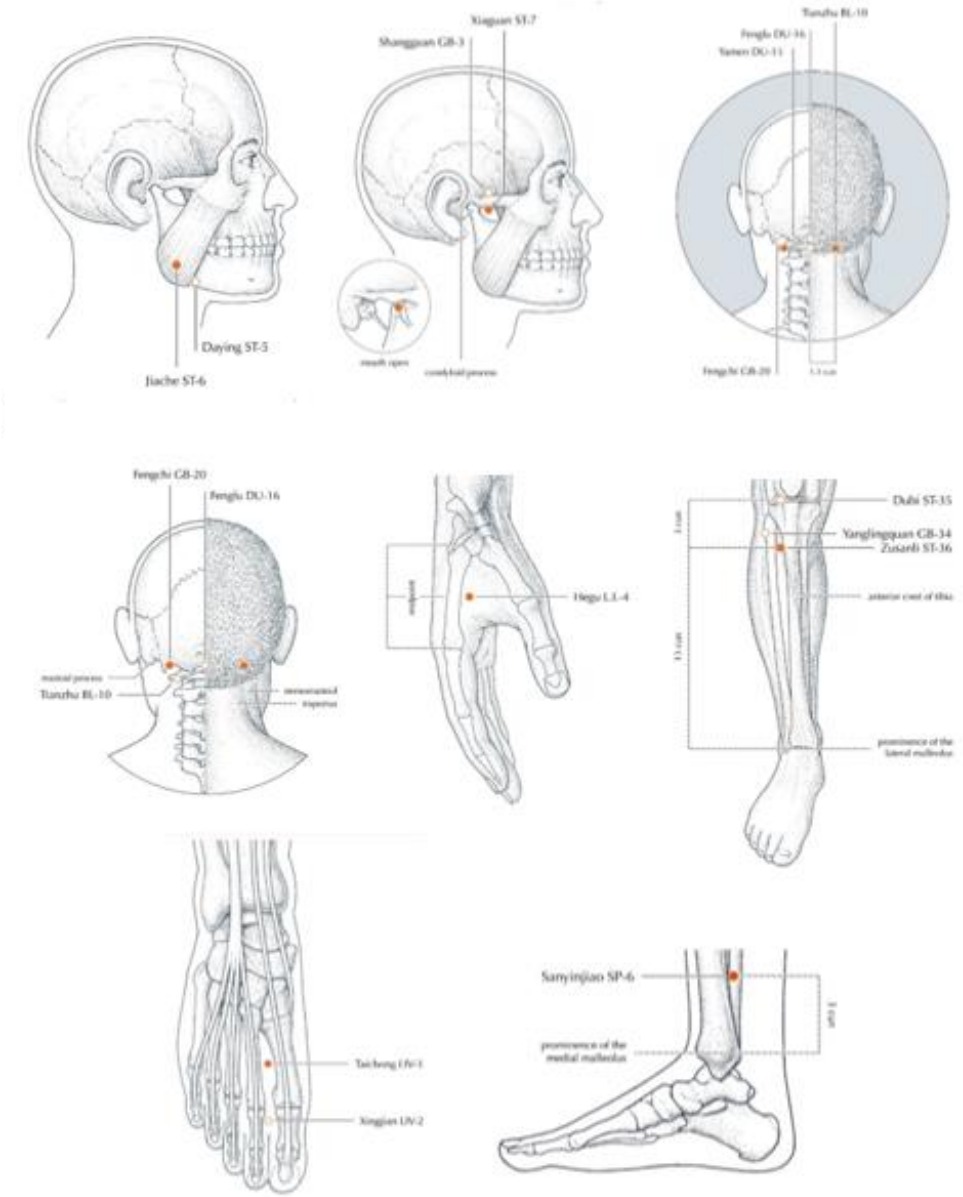

Figure 2. Acupoints selected for the application of different acupoints stimulation in Study I

Cupping therapy (*Study I*)

In Study I, cupping was used in combination with body acupuncture: at the end of the body acupuncture session, the cupping was carried out with sterile glass cups (Mayfair Medical Supplies Ltd, Kowloon, Hong Kong), size 3 cm, at the affected side, in correspondence of the acupoints ST6 and ST7. According to the classical method of "retained cupping", the practitioner used the flaming heating power to achieve

suction; the glass cups were retained for about 1-2 minutes and then were detached. The cupping procedure was carried out repeatedly for 10 min. The applied CT therapy is showed in Figure 3.

Figure 3. A) Traditional cupping flaming procedure before the application; Application of cups at the selected acupoints ST7 (B) and ST6 (C) to a study patient

Abdominal acupuncture (*Study II*)

The acupuncture points used in this study were according to the Bo's Method of Abdominal Acupuncture [9,82,118]: CV 12 (Zhongwan), CV10 (Xiawan), CV6 (Qihai), CV4 (Guanyuan), ST24 (Huaroumen) bilaterally, EX - Ab1 (Shangfengshi) bilaterally, KI17 (Shangqu), KI19 (Yindu). According to the same method, the depth of needle penetration was "standard depth" for all selected point, except for KI19 ("superficial depth"). The needles were not manipulated; they remained in place for 30 minutes and were then removed. The patients were treated 2 times per week for 4 weeks.

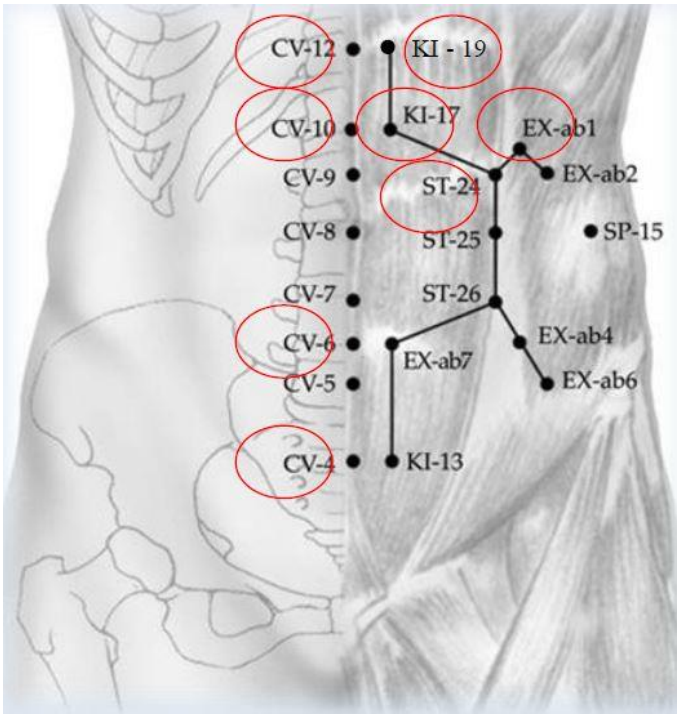

Figure 4. *The miraculous tortoise*: Bo's abdominal acupuncture scheme and selected acupoint

Auricular or ear acupuncture (*Study II-III*)

In ***Study II and III***, both the most popular methods of auricular point stimulation were used: *vaccaria seed* and *thumbtack needle*, for treating respectively patient affected by orthodontic pain (Study II-2), and patients with TMD myalgia and healthy volunteers (Study III).

The same procedure was applied to both clinical studies, as follows:

The treatment was performed on a single auricle. At the start of therapy, the side for auriculotherapy application was selected. Side selection was based on the personal sensitivity on the ear palpation (the most sensitive side is chosen). Treatment begun after the ear surface was cleaned with a cotton wool pad soaked in 70% ethyl alcohol and then dried. An *auriculotherapy speculum* was used to identify sensitive or reactive points, through palpation of the ear surface. Once a reactive or sensitive area was located, the speculum was pressed deeper so as to leave a mark on the skin corresponding to the point to be treated. A *Vaccaria seed* or a *thumbtack needle* was applied immediately afterwards and fixed to the skin with a bandage. This procedure was repeated for all the points to be treated. The auricular patches, with the inserted needle/seed remained in place for 7 days after the application and then were removed by the same acupuncturist; the points where the needles were placed were pressed repeatedly by the participants, for the duration of the 7 days. The correct stimulation technique was taught to all participants, and were confirmed that patients had correctly carried it out at the end of the treatment.

Figure 5 shows the distribution of auricular acupoints on different ear charts. Figure 6 present the auricular points used according to the different studies and the needle/vaccaria seed application procedure.

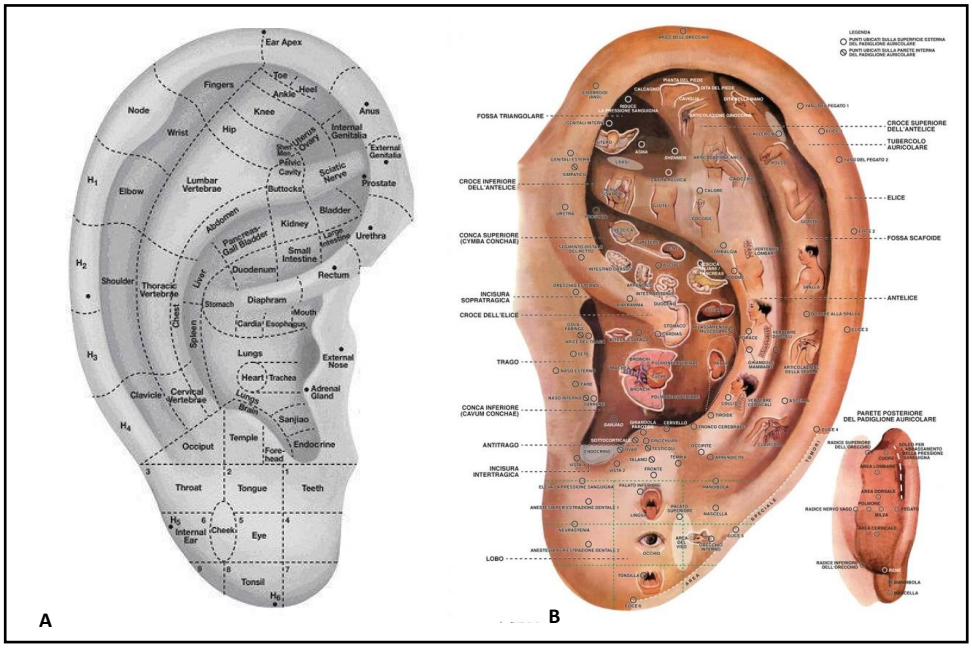

Figure 5. Illustration of TCM distribution on the auricular pavilion of: A) anatomical body areas; B) acupoint locations

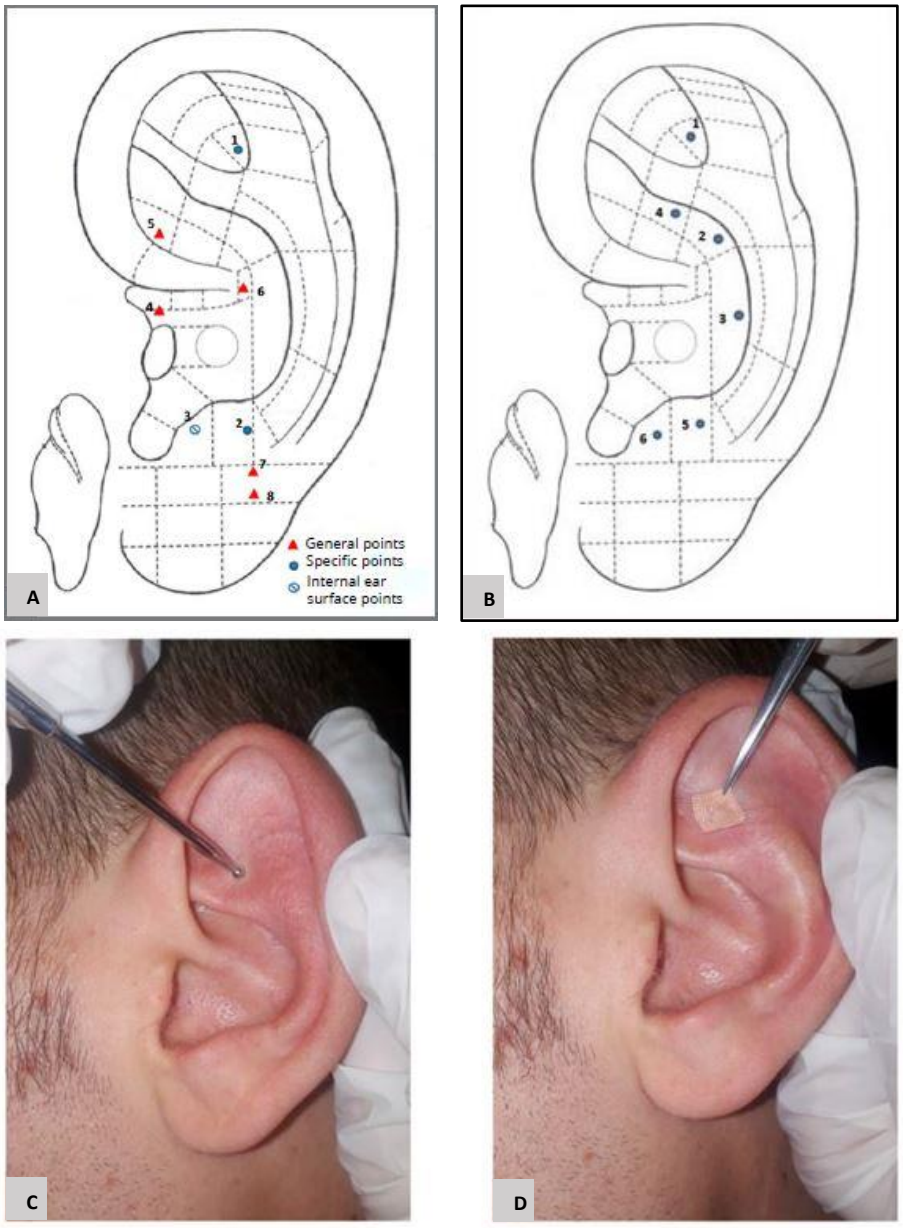

Figure 6. A) Map of auricular points used in Study II-2: (1) Shenmen; (2) Occiput; (3) Subcortex; (4) Mouth; (5) Large Intestine; (6) Stomach; (7) Lower jaw; (8) Upper jaw. B) Map of auricular points used in Study III: (1) Shenmen; (2) Liver; (3) Spleen; (4) Gallbladder; (5) Occiput; (6) Temple. Example of C) sensitive points research and D) *Vaccaria* seed/thumbtack needle application

Innovative technology applications

Electroacupuncture (Study I)

In electroacupuncture (EA), needles are inserted by hand but then attached to a device that generates electrical current that cause stimulation of the needles at the desired frequency, intensity, and pulse duration of the electric current. [71,149] The acupuncture points selected with this technique were the same acupoints used with body acupuncture, as well as the needle penetration procedure and timing, and the needle's size and characteristics. In this study, an electrical apparatus (Hwato SDZ-II, Suzhou Medical Appliance Factory) producing a dense-dispersed wave with a frequency of 1/100Hz was connected to the needles with alligator clips to stimulate pairs of needles inserted at ST36- SP6 and LI4-GB20. The fixed current intensity was uniformly 0.2 mA. (Figure 7)

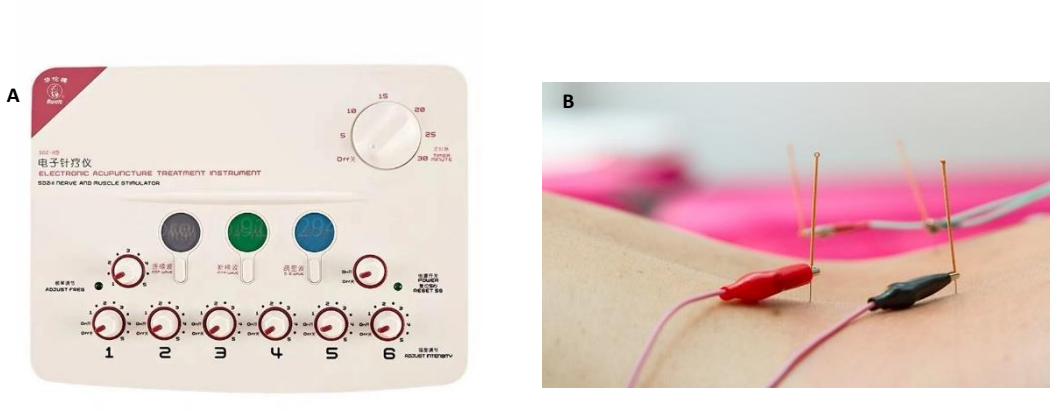

Figure 7. SDZ-II electrical apparatus (A) and example of the application of EA to needles through alligator clips (B)

Vibrations (Study I)

Patients were treated with both active, functioning devices and with placebo devices identical to the functioning ones but therapeutically inactive. The therapeutic protocol involved 7 applications of vibration therapy: the first and last applications were performed by a specially trained operator at the Clinical Gnathology Department; the remaining 5 were carried out at home by the patient.

A single operator carried out the distribution of the devices and provided patient instruction on correct methods of use; all patients were given the same instructions for home use following the indications provided by the manufacturer. Patients used the active or placebo device for 5 days for 16 minutes a day. The device used was the NOVAFON Pro Sk2/2 (NOVAFON GmbH, Weinstadt). The device and the application points used are presented in Figure 8.

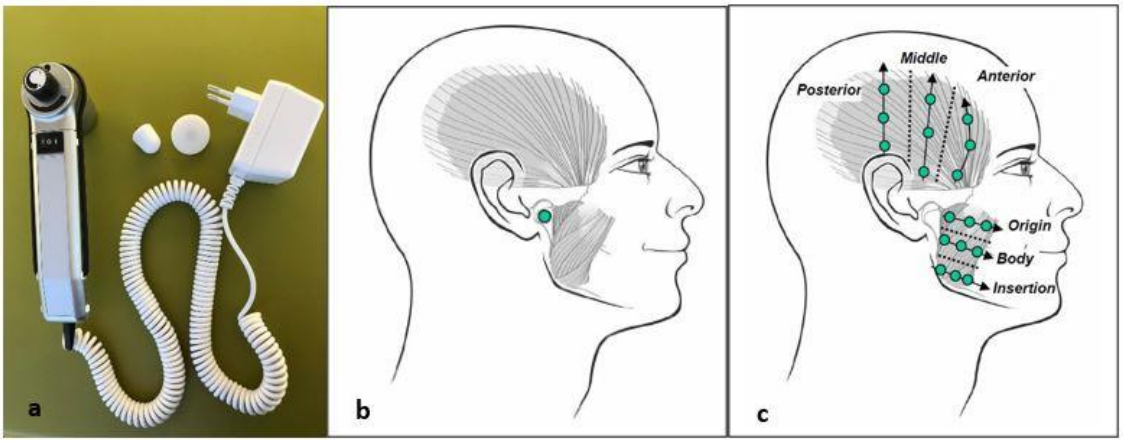

Figure 8. NOVAFON Pro Sk2/2 (a); application points used at the (b) temporomandibular joint; (c) masseter muscle and temporalis muscle

Saliva sampling and Biochemical analysis

This procedure was conducted in Study III, twice in each subject participating the study, i.e. before (T0) and after (T1) the application of the ear acupuncture therapy.

Through a standardized protocol, 5 ml of salivary fluid were collected and analyzed at T0 and T1. Stimulated whole saliva was collected in the morning using a standardized protocol, described previously by *Jasim et al*. (2020). [62,63] In order to prevent any contamination from other sources, the participants were asked to rinse their mouth with water before saliva collection. Saliva was stimulated with paraffin gum (Orion Diagnostica, Esbo, Finland). After 60 s of chewing, the participants were asked to swallow the saliva present in the mouth and then started to chew and expectorate the saliva into polypropylene tubes, until 5 mL of whole stimulated saliva was collected. Once collected, the saliva samples were immediately centrifuged at 2500_ g for 15 min to separate the supernatant from cell pellet and debris. The supernatant was then aliquoted and stored at -80 °C until analysis.

The samples were analyzed blinded with a multiplex panel for pain and inflammatory markers of interest: *Glutamate* (GT), *Nerve Growth Factor* (NGF), *Brain-derived Nerve Growth Factor* (BDNF) and *Substance P* (SP). The analyses were done at the Painomics laboratory in Linköping, Sweden. The concentration of glutamate in saliva was determined as described previously by *Jasim et al.* [62] Briefly, 50 µl of the sample was centrifuged at 4 °C for 5 min at 12000 x g. The supernatant was collected, and 5 µl was immediately analysed using an ISCUSS Analyser (CMA Microdialysis, Solna, Sweden). The detection limit was 1.0 to 150 µmol/L. Saliva samples were thawed on the day of analysis, blinded and randomly analysed for NGF (the active form βNGF was measured) and BDNF using multiplex electrochemiluminescence assay panel from Meso Scale Discovery (MSD, Rockville, MD, USA) according to the manufacturer's protocol. Data were collected and analysed using MESO QUICKPLEX SQ 120 instrument (Meso Scale Diagnostics (MSD), Rockville, MD, USA) equipped with DISCOVERY WORKBENCH® data analysis software (MSD, Rockville, MD,

USA). The limits of detection (LOD) were 0.036 pg/ml for NGF and 0.373 pg/ml for BDNF. For detection of GT and SP the enzyme-linked immunosorbent assay kit (ADI-900-018), and for 5-HT the colorimetric competitive enzyme immunoassay kit (ADI-900-175) from Enzo Life Sciences (Farmingdale, NY, USA) were used. The LOD for SP was 8.04 pg/ml and for 5-HT 0.293 ng/ml. Both kits were used according to the manufacturer instructions using 96 well plate. The plates were analyzed using a spectrophotometer (CLARIOstar®, BMG Labtech, Ortenberg, Germany).

Statistical Analyses

Descriptive analyses and the Chi-square test were used analyze and to compare the patient characteristics in all three studies (**Study I-III**). Normality of data distributions was checked in all three studies (**Study I-III**) using the Shapiro-Wilk test.

To assess whether there were significant differences in the pain levels before and after treatments, the student's *t*-test was performed in **Study I-2**, **Study II** and **Study III-2.** To analyze the differences in protein fluctuation in all groups in **Study III**, the paired *t*-test was used for normal data, and the Wilcoxon signed-rank test was used for not normal data.

Concerning the assessment of continuous and normal distributed variables, within the study groups, with regard to changes in all variables, parametric analysis of variance (ANOVA) was used, with Bonferroni-corrected post hoc tests applied for multiple comparisons. (**Study I-1**) Friedman test was used to test changes over three time intervals in the same group, and the comparisons of two time intervals were performed with the Wilcoxon signed-rank test. (**Study I-1**)

Data analysis was performed with SPSS (version 23) statistical processing software for Study I, and SAS software for Studies II-III. For all tests, the level of significance was set at $P<0.05$. Descriptive data were presented in mean and standard deviation (SD) or median and interquartile range (IQR) format, depending on the nature of the variables and normality of the data.

RESULTS

Study I

Study I-1: ***Comparison of the effectiveness of three different acupuncture methods for temporomandibular disorders-related pain***

Figure 9 shows the quantitative results related to pain (VNS scale), subdivided by the four types of pain analyzed: TMJ pain, muscle pain, headache and neck pain. These results show that in in each acupuncture treatment group analyzed (BA, EA and CA) pain presents average lower values after the treatments (T1) and at the follow-up visits (T2), compared to T0. (Fig. 9)

After the treatments (T1) and during the subsequent follow-up visit (T2), no significant differences were observed between the groups (all $P > 0.05$). Within-group analyses showed significant improvements in pain VNS values at T1 and T2 compared to baseline values (T0) in all study groups (all $P < 0.05$), except for TMJ pain in EA group, and muscle pain in BA group. Wilcoxon signed-rank test, for the comparison of baseline (T0) and after treatment (T1) scores and follow-up (T2) scores, resulted significant in all study groups, for all the types of pain considered (all $P < 0.05$) and particularly significant for headache (all $P < 0.001$) and neck pain ($P < 0.001$ in EA and CA groups). The results of this analysis and the exact P-values are shown in Table 2 in Paper IV.

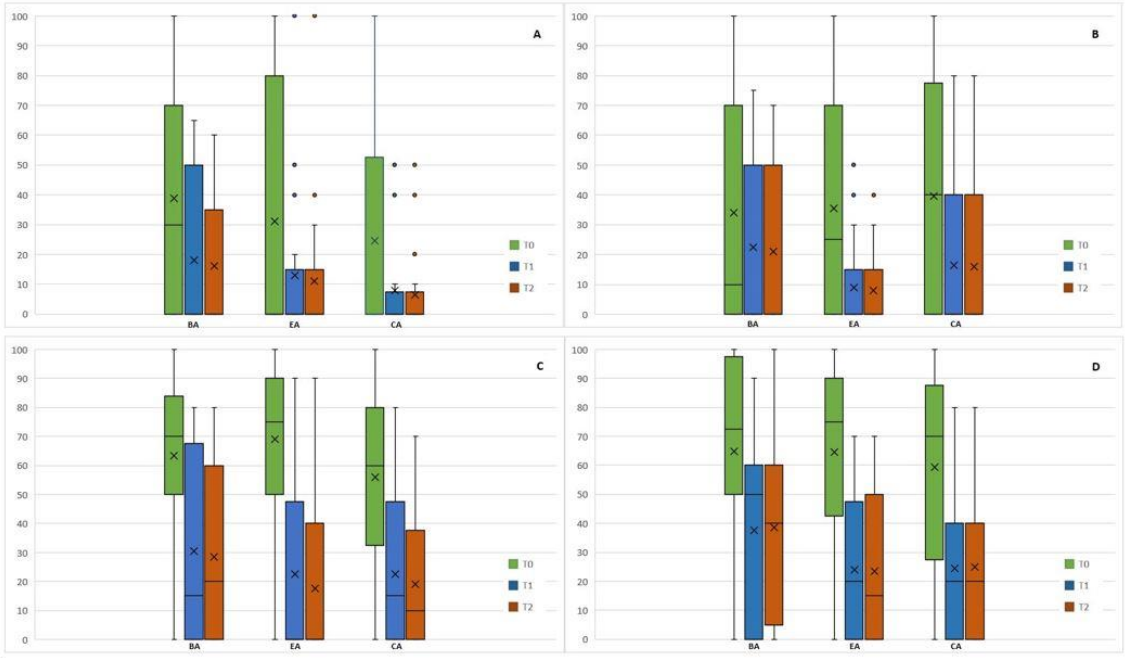

Figure 7. Pain distribution between BA, EA and CA at T0, T1 and T2: (A) TMJ pain; (B) muscle pain; (C) headache; (D) neck pain. BA=body acupuncture; EA= electroacupuncture; CA: acupuncture + cupping

Concerning the evaluation of the pain related interference in patient's common activities and quality of life, after the treatments (T1) and during the subsequent follow-up visit (T2), no significant differences

were observed between the groups (all P > 0.05), except for the variable mood (P= 0.015). Interference values were significantly higher in groups BA and CA than in group EA for the variables “mood” and “relations with other people” after the treatment (T1) and at follow-up visit (T2). Within-group analyses showed significant improvements in interference values at T1 and T2 compared to baseline values (T0) in all study groups (all P < 0.05), except for the variable “walking ability”. Wilcoxon signed-rank test, for the comparison of baseline (T0) and after treatment (T1) scores and follow-up (T2) scores, resulted significant in all study groups, for all the variables considered (all P < 0.05), except for the variable “walking ability”. It resulted particularly significant for the variables “general activity”, “mood” and “sleep” (P < 0.001) in EA and CA groups. The results of this analysis and the exact P-values are shown in Table 3 of Paper IV.

Study I-2: ***Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment***

Results for the group that carried out the therapy with active devices (AG) show a decrease between T0 and T1 in average values of all types of pain considered, with a statistically significant difference for TMJ pain, muscle pain and headache. Results for the group that performed the therapy with inactive devices (GI) show a decrease in average values of muscular pain and an increase in the average values of TMJ pain and headache. (Figure 10)

In comparing data between the start (T0) and end of therapy (T1), the student’s t-test was not significant for TMJ pain and muscular pain. The student’s t-test analysis of the decrease in relative average pain values between patients who performed active and inactive therapy at T1 did not show significant results for TMJ pain, muscular pain, or headache (P> 0.05). The results of this analysis and the exact P-values are shown in Table 2 of Paper III

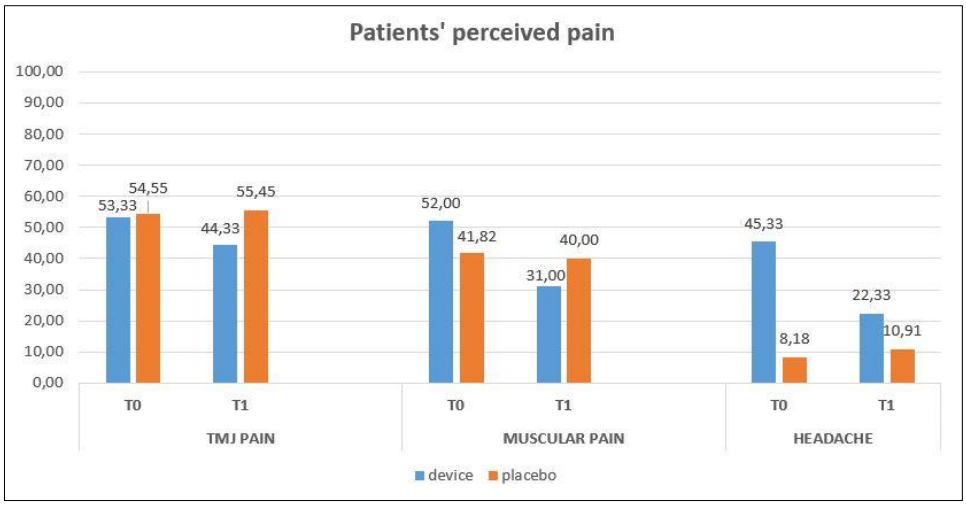

Figure 10. Average values of perceived pain in AG and IG at T0 and T1, according to VAS

Study II

Study II-1: ***Abdominal acupuncture in patients with subacute and chronic TMD pain not responding to conventional therapy***

The application of Abdominal acupuncture (AbdA) therapy resulted in a general improvement in MMO and patients' orofacial pain perception. (Table 6, Figure 11-13)

The difference in MMO and the improvement in pain perception, according to both VNS and BPI, at T0 and T1, resulted statistically significant for all the considered variables (all $p < 0.05$). (Table 6)

Table 5 shows the participants demographic and clinical characteristics. Table 6 shows the exact results from data analysis. Figures 9-11 show the distribution of patients OP pain and interference of pain perceptions, at T0 and T1, according to VNS (Fig.11) and BPI (Fig. 12-13) scales.

Table 5. Patients' demographic and clinical baseline characteristics of the participants

No.	Gender	Age	Diagnosis			Side	MMO[b] (mm)	Pain duration (month)	Systemic disease	Past treatment
			Arthralgia	Myalgia	DDWR[a]					
1	F	49			×	B	39	5		PT, ST
2	F	65	×			R	39	4		ST
3	F	52	×	×	×	B	36	144	FM, UCTD	D, PT, ST
4	F	46	×	×		L	42	18		D, PT, ST
5	F	54	×		×	B	41	84	FM	D, PT, ST
6	F	49		×		B	40	60	FM, PsA	D, PT, ST
7	F	57		×		B	42	120	FM, UCTD	D, PT, ST
8	F	44	×			B	44	24		D, PT, ST
9	F	63	×			R	39	48	OP	D, ST
10	F	73	×	×	×	L	40	18	RA	D, PT, ST
11	F	61	×			B	41	6	OP	D, ST
12	F	45		×		R	42	18		PT, ST
13	F	27		×		B	34	42		D, PT, ST
14	M	28		×		B	43	12		PT, ST
15	F	48		×		B	40	4		D, ST
16	M	53	×			B	43	36		D, PT, ST
17	F	56	×	×		L	38	96	FM	D, PT, ST
18	F	37		×		B	37	24		PT, ST
19	F	62	×	×		B	49	84	RA	D, PT, ST
20	M	55	×			B	43	30		D, PT, ST
21	F	48	×	×	×	R	35	60		D, PT, ST
22	F	61		×		B	38	120		D, PT, ST
23	M	32		×		B	39	7		PT, ST
24	F	18		×		B	38	24		ST
25	F	45	×		×	L	36	18		D, PT, ST
26	F	60		×		B	42	144	FM	D, ST
27	F	52	×			L	40	60		D, PT, ST
28	F	42	×		×	B	42	4		ST

[a] DDWR= disc displacement with reduction
[b] MMO= maximum mouth opening
D= drugs; FM= fibromyalgia; OP= osteoporosis; PsA= psoriatic arthritis; PT= physical therapy; RA= rheumatoid arthritis; ST= splint therapy; UCTD= Undifferentiated Connective Tissue Disease

Table 6. Effect of abdominal acupuncture on treatment-resistant TMD

Variable	**BEFORE TREATMENT**	**AFTER TREATMENT**	**Z**	**P value**
Pain (VNS)				
TMJ PAIN	34.64 ± 39.11	7.50 ± 15.54	-3.408	0.0006
MUSCLE PAIN	37.5 ± 4.88	14.28 ± 23.32	-3.296	0.0009
HEADACHE	62.14 ± 33.81	22.50 ± 27.16	-4.197	<0.0001
NECK PAIN	64.46 ± 35.68	28.21 ± 26.39	-4.197	<0.0001
MMO	40.07 ± 3.13	41.82 ± 2.52	-3.724	0.0002
Brief Pain Inventory (BPI)				
Pain (VAS)				
1	6.43 ± 2.20	3.46 ± 2.22	-4.372	<0.0001
2	3.21 ± 2.29	1.11 ± 1.42	-3.602	0.0003
3	5.21 ± 1.83	2.32 ± 1.87	-4.493	<0.0001
4	4.78 ± 2.68	1.36 ± 1.61	-4.2378	<0.0001
Pain interference (VAS)				
General activity	4.03 ± 2.38	1.89 ± 2.02	-4.107	<0.0001
Mood	5.68 ± 2.88	2.68 ± 2.11	-4.197	<0.0001
Walking ability	1.89 ± 2.79	0.89 ± 1.69	-2.665	**0.0084**
Normal work	3.64 ± 2.69	1.61 ± 1.90	-3.919	0.0001
Relations with other people	3.11 ± 2.30	1.93 ± 2.29	-3.296	0.0009
Sleep	4.71 ± 2.76	3.00 ± 2.71	-3.621	0.0003
Enjoyment of life	3.28 ± 2.55	1.82 ± 1.90	-3.621	0.0003

1= WORST pain in the last 24h; 2= MINIMUM pain in the last 24h; 3= AVERAGE pain in the last 24h; 4= pain value IN THIS MOMENT

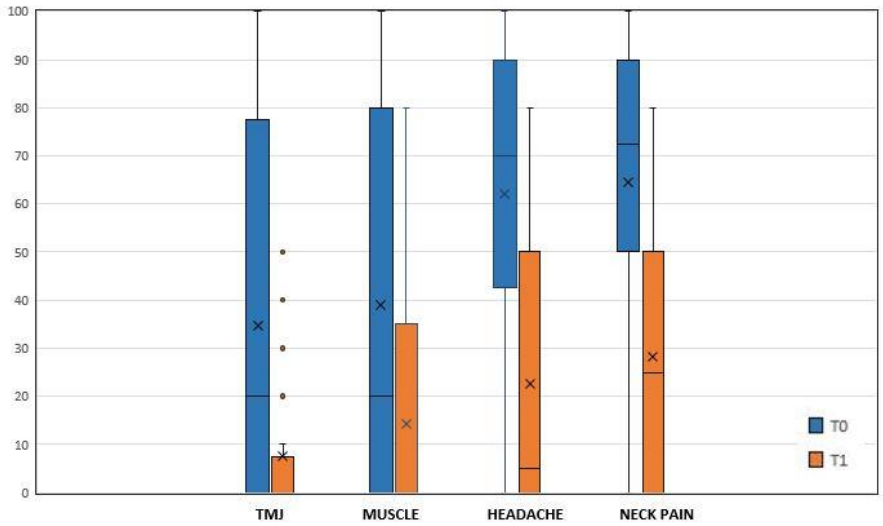

Figure 11. Patients Orofacial Pain distribution at T0 and T1, according to different locations: TMJ, Masticatory muscle, Head and Neck

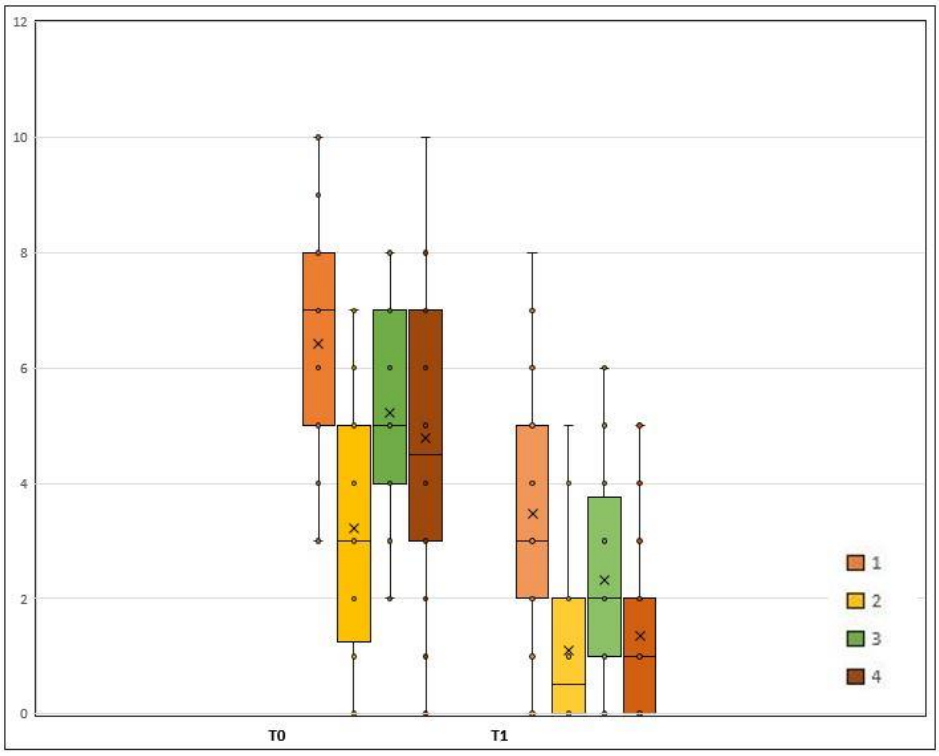

Figure 12. Orofacial pain distribution at T0 and T1, according to BPI
1= WORST pain in the last 24h; 2= MINIMUM pain in the last 24h; 3= AVERAGE pain in the last 24h; 4= pain value IN THIS MOMENT

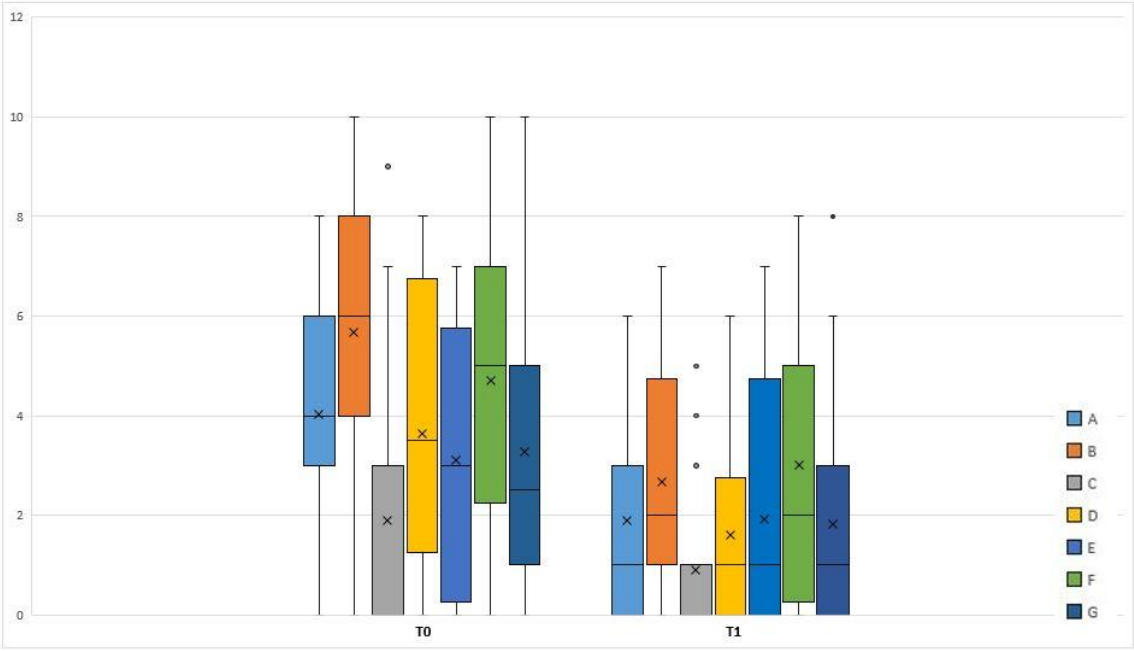

Figure 13. Pain interference distribution at T0 and T1, according to BPI
A= General activity; B= Mood; C= Walking ability; D=Normal work; E= Relations with other people; F= Sleep; G= Enjoyment of life

Study II -2: *Auriculotherapy used to manage Orthodontic Pain*

Patients undergoing Auriculotherapy (SG) during orthodontic treatment report lower pain values than patients not receiving treatment (CG). These values are on average lower for all the time periods analyzed (T0, T1, T2). Patients treated with AurT report lower pain levels than non-treated patients, regardless of their gender. The values reported by male patients are on average higher than those reported by female patients for all the time periods considered, with the exception of the moment "immediately before" for CG patients (see Tab.2 and Fig.3 of Paper VI). The values reported by male patients are higher on average than those reported by females for all the time intervals considered, with the exception of the moments "immediately after" for SG patients and "immediately before" and “after 72 hours” for CG patients. (Tab.2 and Fig.3b of Paper VI)

Figure 14 shows the quantitative results related to pain (VAS scale), subdivided by the time interval analyzed: T0 (start of therapy), T1 (first adjustment), and T2 (second adjustment) respectively. These results indicate that for both the SG and CG pain appeared immediately after the bonding/adjustments and tended to increase in the following hours, reaching the highest values after 24 hours. CG patients on average assigned pain values greater than those of the SG for all the time intervals considered. (Fig. 14) (Paper VI)

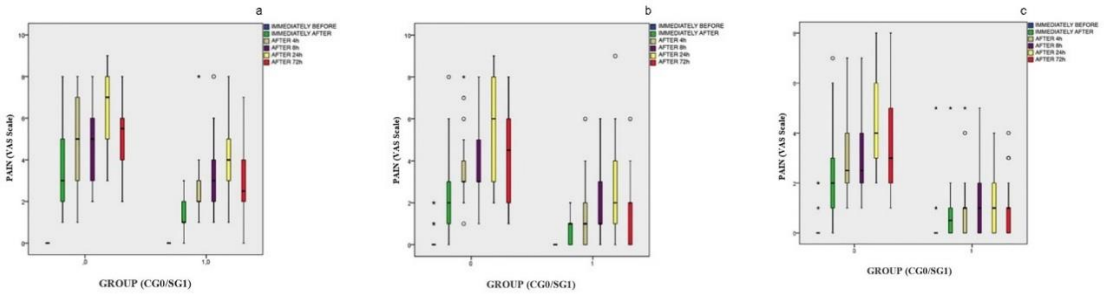

Figure 14. Pain distribution between the SG and CG at: **(A)** the beginning of therapy (T0); **(B)** the first adjustment (T1); **(C)** the second adjustment (T2)

The *student's t-test* was significant in the comparative analysis of pain between the SG and CG for almost all time moments considered at both the start of therapy and the following two adjustments (t0, t1 and t2). (Tab.3 of Paper VI) The *Chi-square test* did not show significant differences in pain perception for any of the following parameters: age, gender, malocclusion, or treated dental arch ($p>0.05$). The only exception was TM "after 24 h" in t0, where *gender* was found significant ($p= 0.042$). (Paper VI)

Study III: *Salivary proteic response to acupuncture for Temporomandibular Disorders (ACUPROTMD)*

The general characteristics of the entire study population are presented in Table 7.

Biochemical analysis resulted in a high number of missing values for the NGF and BDNF that did not allow for consistent statistical analyses; therefore, only results related to the analysis of the GT and SP are reported below.

The exact concentration of Glutamate and Substance P of the entire study population, before and after the AurT treatment (T0 and T1), is presented in the following table. (Tab. 7)

Table 7: Concentration of Glutamate (GT) and Substance P in Study III-1 and Study III-2 population at T0 and T1 (N=40)

	Glutamate (µM)		**SP (pg/ml)**	
	T0	**T1**	**T0**	**T1**
Study III-1				
SG	78	30	34.75	37.93
	25	27	14.87	12.19
	5	9	22.75	32.61
	14	7	50.38	49.46
	22	7	41.15	34.80
	22	13	34.05	18.71
	6	6	89.76	26.99

	4	3	27.80	37.38
	8	24	12.52	<< std range
	8	6	4.99	25.56
ShG	14	8	>> std range	32.14
	6	11	45.23	34.48
	10	11	40.98	49.03
	20	14	6.29	11.74
	6	4	27.75	35.73
	23	53	7.06	24.87
	55	42	37.71	13.10
	35	30	91.13	101.12
	15	14	9.48	32.03
	13	21	11.70	23.70
CG	11	18	14.15	17.94
	3	5	38.77	8.67
	40	17	8.62	54.59
	11	8	41.84	10.78
	7	16	<< std range	<< std range
	29	27	23.80	40.19
	31	32	17.94	18.34
	4	16	32.45	57.95
	15	15	>> std range	>> std range
	20	8	82.29	126.68
Study III-2				
	25	39	59.13	51.5
	6	4	59.13	>> std range
	15	3	<< std range	29.64
	21	18	36.49	16.83
	28	12	<< std range	11.98
	15	38	49.58	94.98
	17	17	18.39	27.65
	8	29	28.56	25.71
	17	20	18.25	45.12
	11	17	61.99	36.83

The saliva concentration of both the biomarkers analysed (GT and SP) resulted different between T0 and T1, for all the groups of Study III. The basic statistics of GT and SP, evaluated at T0 and T1, are shown as follows, presented with respect to the entire population and to Study III-1 and Study III-2. (Table 8-9)

In ***Study III-1***, GT concentration resulted decreased at the end of AurT therapy (T1) compared to the baseline (T0) in groups SG and CG, and increased in group ShG. (Table 8) SP concentration resulted decreased at T1 compared to T0 in groups SG and ShG, and increased in group CG. (Table 9)

In ***Study III-2***, both GT and SP concentrations resulted increased at T1 compared to the baseline (T0). (Table 8-9)

Table 8: Glutamate (GT) basic statistical analysis

	Study III		***Study III-1***						***Study III-2***	
Glutamate(μM)	**Tot T0**	**Tot T1**	**SGT0**	**SG T1**	**ShG T0**	**ShG T1**	**CG T0**	**CG T1**	**T0**	**T1**
count	40	40	10	10	10	10	10	10	10	10
mean	18.07	17.47	19.2	13.2	19.7	20.8	17.1	16.2	16.3	19.7
std	14.67	11.96	22.09	9.95	15,13	15.99	12.56	8.38	7.01	12.45
min	3	3	4	3	6	4	3	5	6	3
25%	8	8	6.5	6.25	10.75	11	8	9.75	12	13.25
50%	15	15.5	11	8	14.5	14	13	16	16	17.5
75%	22.25	24.75	22	21.25	22.25	27.75	26.75	17.75	20	26.75
max	78	53	78	30	55	53	40	32	28	39

Table 9: Substance P (SP) basic statistical analysis

	Study III		***Study III-1***						***Study III-2***	
SP (pg/ml)	**Tot T0**	**Tot T1**	**SGT0**	**SG T1**	**ShG T0**	**ShG T1**	**CG T0**	**CG T1**	**T0**	**T1**
count	37	37	10	10	9	9	9	9	9	9
mean	31.67	35.04	33.30	28.54	30.82	36.20	29.96	38.32	32.438	37.80
std	22.92	26.07	24.17	12.42	27.37	26.96	23.07	38.29	20.43	24.83
min	4.99	8.67	4.99	9.76	6.29	11.74	8.63	8.67	9.76	11.99
25%	12.52	17.94	16.84	20.42	9.48	23.71	14.15	10.78	18.26	25.71
50%	27.80	29.64	30.92	29.80	27.75	32.03	23.80	18.35	28.56	29.64
75%	41.15	40.18	39.55	36.74	40.98	35.73	38.77	54.59	49.58	45.12
max	91.13	126.68	89.76	49.46	91.13	101.13	82.30	126.68	61.99	94.98

The paired t-test for the comparison of the difference in the concentration at T0 and T1 resulted not statistically significant (p>0.05), for both GT and SP, in all study groups analysed. The exact P-values are reported in Table 10.

Table 10: Student t-test results for GT and SP difference values between TO and T1

	test statistics	***P-value***
Glutamate (GT)		
Study III-1		
SG	0.88	0.37
ShG	0.30	0.75
CG	0.28	0.79
Study III-2	-0.83	0.43
Substance P (SP)		
Study III-1		
SG	-0.21	0.82
ShG	-1.11	0.30
CG	-0.90	0.40
Study III-2	-0.71	0.50

In **Study III-2**, the patients' pain perception resulted decreased from the baseline (T0) to the end of therapy (T1), with a statistically significant difference (p=0.00043).

Patient's pain perception at T0 and T1, and the pain trend during the 7 days of therapy are showed respectively in Figure 15 and Figure 16.

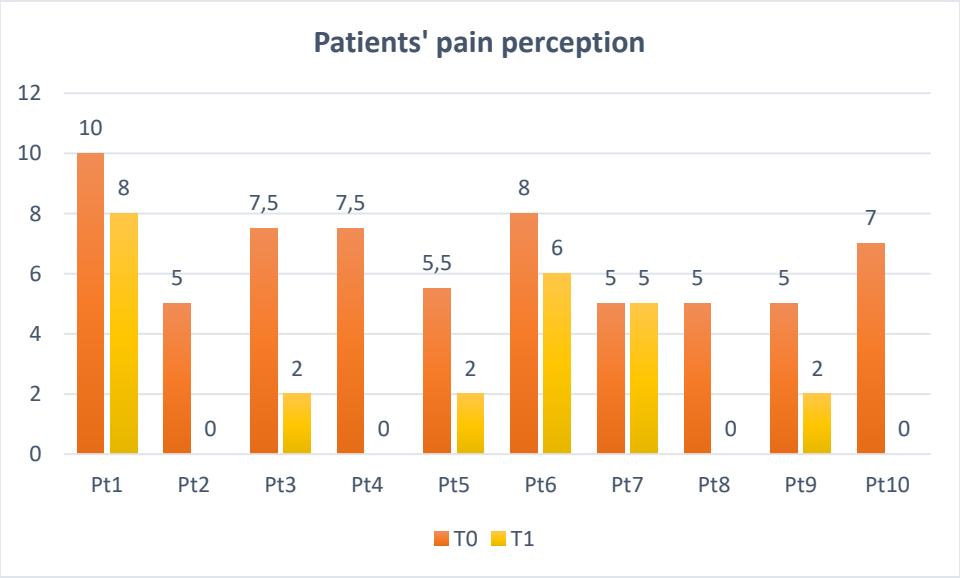

Figure 15. Pain values of Study III-2 patients at T0 and T1 (VAS)

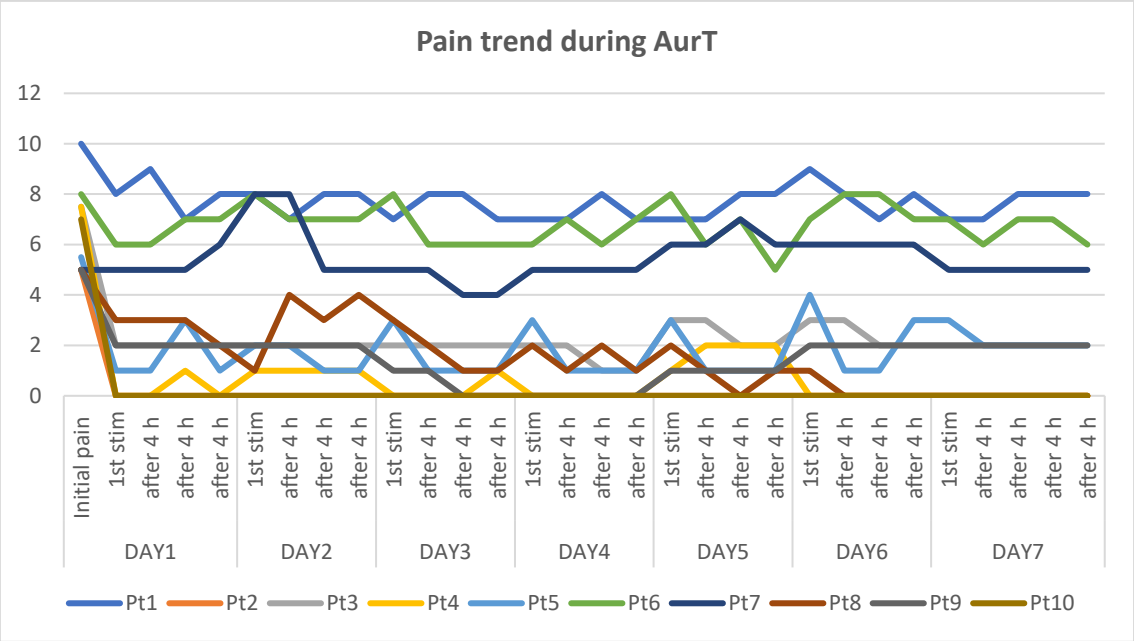

Figure 14. Pain trend during 7 days of AurT therapy in patients of Study III-2 (VAS)

Questionnaire results

The scores of the questionnaires used for overall assessment of patients in all three studies (Study I-III) are presented in the following table. (Tab.11)

Table 11: Questionnaire scores for overall assessment used in Study I-III (*mean ± SD)*

Variable	Study I-1		p- value	Study II-1		p-value	Study III
	T0	T1		T0	T1		
OBC	43.53 ± 12.81	37.00 ± 14.58	0.014	45.43 ±13.85	37.68 ±13.99	0.021	5.67± 3.67
JFLS							0.61 ±1.19
PHQ							2.61 ± 2.08
PPS							4.14 ± 3.09
OHIP							2.31 ± 2.30

OBC=Oral Behaviour Checklist; OHIP=Oral Health Impact Profile; JFLS=*Jaw Functional Limitation Scale; PHQ=Patient Health Questionnaire; PSS=Perceived Stress Scale*

The scores of the Brief Pain Inventory (BPI), used to assess severity of pain and related disability in daily activities and quality of life in Study I-1 and Study II-1 are respectively reported in Table 3 of Paper IV and in Table 6 of this manuscript.

The scores of the *Patients' Global Impression of Improvement (PGI-I) Scale*, used to assess the impression of the treatment's effectiveness, are reported in Table 4 of paper IV (Study I-1), in Figure 5 of Paper III (Study I-2) and in the following figure for Study II-1. (Figure 15)

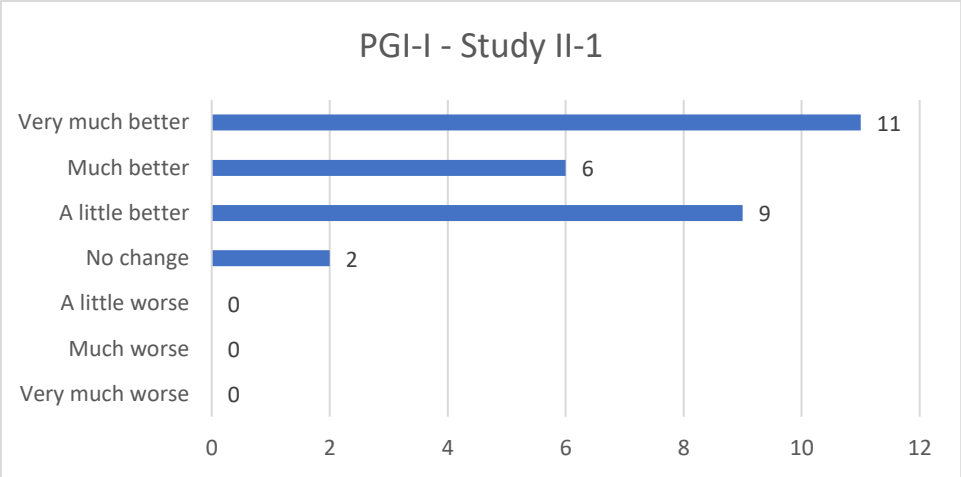

Figure 15. Patients' impression of the effectiveness of AbdA treatment, according to the PGI-I Scale

DISCUSSION

Study I

This study investigated and compared the effectiveness of different acupuncture (AT) techniques and methods of acupoint stimulation, including innovative technologies applications, in the treatment of the main types of TMD-related pain: TMJ pain, masticatory muscle pain, headache, and neck pain.

For the first time, *Study I-1* analysed and compared the effects of three methods on AT stimulation (*body acupuncture, electroacupuncture* and *acupuncture + cupping*) on the perception of pain and on the interference determined by pain on several common activities and aspects influencing the quality of life of patients affected by pain related to TMD. Based on the results, all the analysed treatment methods yielded significantly improved outcomes regarding all types of pain considered compared to baseline, reinforcing the evidence that acupuncture is an effective treatment in patients suffering from pain with TMD origin. [34,44, 58,146,153] Furthermore, the impact of pain on all considered activities and quality of life aspects was found to be significantly decreased after the AT treatment and in the short-term follow-up in all three study groups, except for the aspect of "walking ability." (Paper IV- Table 2-3)

The previous studies that investigated the clinical effects of different acupuncture techniques on TMD-related pain mostly focused on pain of muscular origin, reporting in general effective results in the improvement of several clinical features. [34,58,153] Only few studies investigated pain of essentially joint origin (TMJ pain) or the main comorbidities related to TMD (headache and neck pain), which were instead equally investigated in this study. [44,146]

In *Study I-1*, no statistically significant differences emerged between the different AT methods applied, suggesting that there is no specific guidance in selecting one of these methods (BA, EA, CA) based on the TMD-related pain to be treated and thus the referral diagnosis. This may be explained by the fact that, in the three study groups, different methods of needle stimulation were applied to the same acupuncture points (acupoints) in order to evaluate any differences based only on the type of needle stimulation, not on the treatment principle or scheme. However, despite the lack of evidence of statistical significance, several differences among the results obtained in the different study groups can be highlighted, depending on the type of pain treated. (Paper IV- Table 2)

The therapeutic efficacy of ***body acupuncture (BA)****,* the most frequently mentioned AT method for the treatment of orofacial pain, is mostly reported on TMD pain of muscular origin. [34,146,153] However, in *Study I-1*, masticatory muscle pain was the only type of pain that did not exhibit a statistically significant decrease when comparing the patient's average values both after treatment (T1) and at the subsequent follow-up visit (T2). (Paper IV- Table 2) Furthermore, patients of the BA group reported statistically significantly lower average values of TMJ pain overall, compared with patients of the CA group and especially those of the EA group. Only one previous study by *Corcos and Brandwein (1976)* focused on the

effects of body acupuncture treatment for pain related to the temporomandibular joint in 46 patients affected by rheumatoid arthritis and osteoarthritis. This study also pointed out the value of the body acupuncture method in improving TMJ pain. [24]

The addition of ***cupping therapy*** **(CT)** to body acupuncture was found to be the most effective treatment method in the management of muscle pain. This evidence is consistent with the majority of systematic reviews and RCTs to date which suggest a favourable effect of cupping for pain, especially tension headache and musculoskeletal pain. [22] The negative pressure applied to the skin during the cupping procedure has been proven to induce muscle relaxation and changes in local tissue structures and in blood circulation, significantly reducing peripheral and local P substance and inflammation and thus resulting in pain reduction. [22] *Han* et al. (2015) compared the therapeutic effect of medicated cupping and acupuncture combined with medicated cupping in 120 TMD patients, reporting a significant improvement of TMDs' signs and symptoms in both groups after a treatment course of 10 days. [48] In line with the present study, the authors suggested that the combination of the two treatments leads to superior clinical outcomes, compared to the use of single medicated cupping therapy. However, it is difficult to make a comprehensive comparison with the results obtained in this study, since the authors did not specify the type of pain treated or the TMD diagnosis of these patients; moreover, the cupping therapy procedure involved the addition of medicinal herbal substances.
To our knowledge, *Study I-1* is the first study to analyse the effects of the classic technique of dry retention cupping combined with acupuncture on the most common types of pain associated with TMD. Given the positive results obtained, the need for further studies becomes evident to deepen and better define the therapeutic potential of this ancient medical practice in relieving pain related to TMD.

Concerning the use of innovative technological methods of point stimulation, interesting results emerged from both *Study I-1* and *Study I-2*, that involved respectively the application of two innovative technological instruments poorly investigated in the actual scientific literature: electrostimulation and vibration.
Electroacupuncture (EA) is considered a particularly effective method of AT for the treatment of persistent tissue and nerve injuries, chronic pain, and visceral pain, as addressed by several research studies conducted within the last decade. [71,79,149] *Zhang et al.* (2014) suggested that the electroacupuncture mechanism of action in relieving pain is the result of activation or inhibition of various bioactive chemicals in peripheral, spinal, and supraspinal pathways. [149] Despite its popularity in pain management, few studies investigated the clinical effects of EA on TMD-related pain. A literature search by *Kuo* et al. yielded to nine publications from Chinese practitioners concerning the use of EA for treating TMD symptoms, and all of them reported analgesic efficacy in the treatment of pain, especially of muscular origin. [71] However, the authors highlighted the inconsistency in most of these studies,

accentuating the need for more well-designed and long-term studies in this research area. The results obtained in *Study I-1* agree with these few lines of evidence, pointing out that this method was particularly effective in reducing pain of muscle origin, as well as headache and neck pain.

A peculiar and interesting result is that EA was found to be effective in improving the influence of pain on the patient's quality of sleep and mood, with a statistically significant difference compared to BA and CT. (Paper IV-Table 3) These results are consistent with the evidence defining EA as an effective therapeutic intervention for patients with anxiety, depression, and primary insomnia, capable of improving patients' life and sleep quality without serious adverse effects. [47,74]

Possible weaknesses of *Study I-1* were the sample size and the duration of the acupuncture treatment. Acupuncture comprises several acupoint stimulation methods, treatment patterns, and timing, allowing the application of individualized therapies. Due to its versatility and special effectiveness in multifactorial diseases, acupuncture is particularly suitable for the treatment of TMD-related pain, which in turn is characterized by a very complex and varied symptomatology. For these reasons, despite the positive results obtained, the patient sample size examined is still too limited to present reliable results regarding the comparison of the effectiveness of three different acupuncture methods in reducing TMD-related symptoms. Furthermore, these results correspond to a single course of 4 weeks of therapy. Due to the tendency of TMD to become chronic, a prolonged course evaluation with additional long-term follow-up is necessary.

For the first time, *Study I-2* involved the use of **vibrations** directly at the level of the joint area and masticatory muscles (masseter and temporalis), through the application of a novel vibration device (NOVAFON Pro Sk2/2), in order to evaluate the effectiveness of local vibration therapy for reducing TMD-related joint/muscular pain and headache. The subjects of the group who underwent active local vibration therapy reported a significant decrease in average values of TMJ pain, muscular pain, and headache. (Paper III-Table 2) Furthermore, there were no significant decreases in average pain values for patients in the study group that received placebo therapy with inactive devices; these patients reported an increase in TMJ pain and headache that was statistically significant for the latter with respect to the initial pain level. The choice to use vibratory stimulation in dysfunctional patients was based on evidence from previous studies showing the effectiveness of vibration therapy in reducing chronic musculoskeletal pain and in delaying the onset of muscular pain. [20,86] Several studies have shown that vibratory stimulus is capable of exciting afferents in both the Pacinian corpuscles and in the receptors of the skin, periodontium, muscle spindles, and tendon organs. [83,84,103] Moreover, from the gate control theory, we know that these sensory afferents can interact with the pain transmission pathways at the spinal level, causing modulation in response to the pain sensation. [83,84,93] All these mechanisms may contribute to the symptoms decrease observed in dysfunctional patients undergoing vibratory therapy in *Study I-2*.

Study I-2 did not involve the stimulation of acupoints but was applied directly on facial tender points, according to DC/TMD. [117] It was indeed intended as a preliminary study to test the efficacy of such

novel vibratory device never used before, and therefore with no data of reliability in the current literature at the moment of the study onset. Unfortunately, the study planned to follow, which involved the application of the same device but this time on an acupoint scheme, was interrupted due to the COVID-19 pandemic, which prevented the recruitment of patients to our university hospital for several months in the year 2020.

Study II

This study explored the use of two microsystem acupuncture techniques, the *abdominal acupuncture (AbdA)* and the *auriculotherapy (AurT),* in the management of chronic and non-responder TMD pain and orthodontic pain in patients with fixed multibrackets appliances, respectively.
Both *AbdA* and *AurT* were for the first time applied to their corresponding patient populations, and the results of applying of these particular AT methods leaded to an improvement in both types of pain treated.

The use of the abdomen and abdominal points as microsystem is quite recent, thanks to the development of the abdominal acupuncture system codified about 30 years ago by the Chinese physician *Bo Zhiyun*. [9] The scientific literature is still paying little attention to AbdA, but some primary indications about its application are still present, and essentially include the treatment of pain and neurological disorders. [42,118] A recent metanalysis of Chinese studies (*Su et al., 2021*) showed that this AT method is effective in treating post-stroke depression [130], and a randomized single-blind trial indicated that short-term AbdA was more effective than pharmacological treatment for relieving insomnia in a group of Chinese women. [138] Concerning pain treatment, *Marchetti* et al. (2021) presented a case report about the major efficacy of AbdA compared to somatic acupuncture for treating the *complex regional pain syndrome* (CRPS) in a 13-year-old girl with CRPS of the upper limb. [91] A randomized controlled trial by *Ho et al.* (2017) provided evidence regarding the clinical efficacy of abdominal acupuncture for neck pain. [54] *Huang et al*. (2008) reported that Bo's abdominal acupuncture has a good curative effect in patients with chronic fatigue syndrome, especially on lassitude, anorexia, insomnia, amnesia, diarrhoea, and general pain. [57] Finally, investigating the mechanism underlying acupuncture for pain treatment *Valeriani et al*. (2021) founded AbdA to be effective in the reduction in laser-evoked potential (LEP) amplitude and laser-pain rating. The exact mechanism of this analgesic effect is still not known, but the authors supposed that could be mediated by a segmental spinal mechanism. [135]

In *Study II-1*, the application of ***abdominal acupuncture (AbdA)*** to a population of dysfunctional patients characterized by subacute/chronic TMD pain non-responding to conventional gnathological therapy, resulted in a statistically significant decreasing of pain, and pain-related disability in common activities and quality of life, for all the variables considered except for the aspect of “walking ability.”(Table 6) These results are consistent with various clinical studies that support the abdominal acupuncture technique for

the treatment of other kinds of musculoskeletal disorders such as cervical spondylosis, prolapse of lumbar intervertebral disc, knee osteoarthritis and shoulder periarthritis. [54,91,140]

Despite evidence of clinical efficacy of AbdA on dysfunctional non-responder patients, *Study I-1* is a retrospective study on a population of subjects not homogeneous concerning the presence or absence of painful systemic diseases, and this is a limitation. The promising results obtained, however, lay the basis for a randomized controlled clinical trial with placebo group, to confirm the effectiveness of AbdA and to better explore the therapeutic possibilities of a microsystem method currently little investigated but with strong indications in clinical acupuncture practice, especially for chronic pain.

Study II-2 was carried out by applying a particular ear acupuncture (AA) method: ***auriculotherapy (AurT)***, which involves the application of *Vaccaria seeds* to specific auricular acupoints. This technique, unlike other acupuncture methods, does not involve the insertion of needles and therefore offers the additional advantage of being well-received by patients, including paediatric subjects. Moreover, it resulted effective in treating various types of pain, both acute and chronic. [61,137,148] *Iunes* et al. investigated the efficacy of auriculotherapy in a group of TMJ dysfunctional patients, demonstrating auriculotherapy to be significantly effective in reducing pain in the temporal and TMJ areas. [61] A meta-analysis from *Yeh et al*. established that auriculotherapy provides significant pain relief when compared to a sham or control group. [148] This evidence of the efficacy of auriculotherapy in pain management supports the application of AurT in orthodontic pain management.

Only a few studies have investigated acupuncture to treat orthodontic pain and none of them studied the application or effectiveness of auriculotherapy. *Jia* et al. studied the clinical efficacy of transcutaneous electrical acupoint stimulation (TEAS) for orthodontic toothaches through the use of three acupoints: *Juliao* (ST3), *Jiachengjiang* (Extra), and the auricular point *Ya* (LO1). [65] In this study, the pain scores of the TEAS group were lower than those in the two control groups. An animal study by the same authors showed satisfactory results regarding the therapeutic and preventive effects of TEAS on rabbits with orthodontic toothaches. [66] To manage post-adjustment orthodontic pain, *Vachiramon and Wang* proposed the use of just one acupoint, *Hegu* (LI4), stimulated by needles or simple acupressure. [135] Finally, *Boleta* et al. analyzed patients' pain levels during the second quarter of fixed orthodontic therapy. They applied a treatment of somatic acupuncture, using two acupoints, *Hegu* (LI4) and *Jiache* (ST6), and found a statistically significant reduction in pain level indexes, both for men and women, when acupuncture therapy was performed before the orthodontic adjustment. [10] These studies highlight the effectiveness of acupuncture in the treatment of pain during fixed orthodontic therapy; the results obtained from the application of AurT in this study confirm such findings.

In *Study II-2*, from the moment of the application of orthodontic force, the study group undergoing AurT perceived lower pain values than the control group, both at the beginning of therapy (T0) and in the two consecutive months of treatment (T1 and T2). The results show this difference in perceived pain for all the time moments considered (immediately before, immediately after, after 4h, after 8h, after 24h, and

after 72h), with a statistically significant difference between average values of perceived pain for most time moments considered. (Paper VI - Table 3)

In this study, except for orthodontic pain other factors were not evaluated, and this can be considered a limitation of the research, since personal and psychological factors can affect the perception of pain. Ideally, sham auriculotherapy (a bandage fixed on the same acupoints, but without the use of *Vaccaria* seeds) should also have been applied in this study. However, this preliminary research aimed to evaluate the potential efficacy of auriculotherapy in the management of orthodontic pain, despite the lack of evidence of its previous use in this specific area; it was therefore considered appropriate to proceed without the sham group. Further studies should aim to improve upon this point by addressing such factors.

Study III

This study explored the molecular basis underlying acupuncture, analysing the salivary response to *auricular acupuncture* (*AurT*) stimulation with thumbtack needles in a group of healthy subjects, and comparing it with those of a placebo group (sham AA) and a control group not subjected to any treatment. (Study III-1) The same biomolecular analyses were carried out on a pilot group of patients affected by TMD myalgia and subjected to the same AurT protocol, with the aim of explore if this technique can be an effective acupuncture method in TMD myalgia patients, through a better understanding of its neuromodulation effects. (Study III-2)

Auricular Acupuncture **(AA)** is a particular treatment system based on normalizing the body's pain and dysfunction through stimulation of points on the ear. [100,148] The different auricular areas have distinct influence on autonomic functions and it has been shown that AA plays a role in vagal activity of autonomic functions of cardiovascular, respiratory, and gastrointestinal systems. [16,51] Mechanism studies suggested that afferent projections from especially the auricular branch of the vagus nerve (ABVN) and the auriculotemporal branch of the trigeminal nerve, form the anatomical basis for the nervous regulation of AA. [16,51,108] Furthermore, several studies showed that the stimulation of the acupoints determines a variation of gene and protein expression in the treatment of neuropathic pain and various nerve pathologies. [26,64,139] *Dawidson* et al. (1998) investigated the effect of acupuncture on salivary secretion by measuring the release of neuropeptides in saliva under the influence of sensory stimulation. Their results showed significant increases in the release of calcitonin gene-related peptid (CGRP), neuropeptide Y (NPY), and vasoactive intestinal peptide (VIP) both during and after acupuncture stimulation, especially in connection with electroacupuncture. [27]

Proteomics, defined as the systematic analysis of the proteins expressed by an organism following a certain stimulus, has become an important tool for better understanding the pathophysiological mechanisms underlying painful pathologies. [63] In recent years, multiplex panels have been developed

which allows for analyses of several molecular markers at the same time. This has become an important tool for better understanding of the pathophysiological mechanisms underlying different pathologies. Studies concerning the proteomic analysis of saliva of subjects suffering from myalgia and myofascial pain have shown an overexpression of various proteins involved in metabolic processes, in the immune response and in the stress response, some of which (PGK1, GAPDH, sAA, CRISP3, FABP) have been proposed as candidates to objectify pain assessment in these patients. [62,63] However, these studies highlight the lack of a significant correlation between the expression of these proteins and the clinical characteristics of myalgia.

The present is the first study that evaluate the release of protein markers in saliva in response to auricular acupuncture in healthy subjects and TMD patients suffering from related pain, such as TMD myalgia.
The results obtained in *Study III* showed no significant differences in the fluctuation of Glutamate (GT) and Substance P (SP), between the baseline (T0) and the end of the AA treatment (T1), for all the study groups that underwent the AA treatment protocol or not (control group). (Tab.7) However, some differences can be noticed in the concentration of GT and SP, before and after AA, between the different groups. (Tab.8-9)
It has been seen that both glutamate and substance P appear to increase with noxious stimulations and after tissue and/or nerve injuries, and a previous study by *Jasim et al.* showed that patients with myalgia have on average a higher salivary concentration of GT and SP than healthy subjects [62]; however, the results obtained in this study do not appear to be consistent with this evidence. (Tab.7)
Very few studies investigated the fluctuation of these two markers in relation with acupuncture treatments, and none of them used salivary fluid as tool of detection. [50,67,94]

Concerning **substance P *(SP)***, *Karatay* et al. founded conflicting evidence with the results of the present study, reporting lower serum levels of SP after a real acupuncture treatment in a group of fibromyalgia patients, compared with the group subjected to sham acupuncture. [67] SP resulted decreased after AT treatment, and compared to a sham group, also in a study by *Mohammed et al.*, that investigated SP fluctuation in patients with knee osteoarthritis subjected to laser-acupuncture. [94] In the present study, SP resulted decreased in the groups of healthy subjects that underwent to the AA treatment, both real (SG) and sham (ShG); however, in the group of subjects with pathology (TMD myalgia) of Study III-2, the values of SP resulted increased after the acupuncture treatment. (Tab.9)

A single MRI study by *Harris* et al., investigated the relationship between changing levels of **glutamate (GT)** within the insula and changes in multiple pain domains in patients with fibromyalgia (FM). [50] From this study resulted an increase of GT levels within the insula after AT treatment, related to a decrease of multiple pain domains in patients with FM after the AT treatment. The results of this study are in line with those of the present Study III-2, since the patients with TMD myalgia treated with AA referred a significant

improvement in pain perception after the treatment, and the GT values of this group resulted increased, also if with a not significant statistical difference. (Tab.8)

The evidence of not statistical significance in the results of *Study III* may be due to the short duration of the AurT treatment, i.e. 1 week, while in clinical practice a course of acupuncture treatment lasts 3-4 weeks on average. However, given the characteristic efficacy of the ear microsystem for treating pain in a very short time, also confirmed in this study by the results obtained in the sample of patients suffering from myalgia (Fig.15-16), the brief timing of treatment was chosen precisely to verify a possible correspondence on a molecular basis of this widespread clinical evidence. Another possible limitation could be related to other factors not considered in this study and that can influence the levels of GT and SP in the salivary fluid. *Shimada* et al. suggested a possible influence of digested monosodium glutamate (MSG) on the daily levels of GT in plasma and saliva; in this study the peak glutamate concentration in the dialysate samples was observed 1 h after administration of MSG. [126] All *Study III* participants were asked not to consume food or beverages for at least 1 hour before salivary sampling, therefore this is a factor that may have affected GT results. Furthermore, being a preliminary study, the samples analysed were very small (10 subjects/each), and this is another factor that may have influenced the results, given the extreme individual variability of the composition of the salivary proteome.

However, given the different and nonlinear trend of salivary values of GT to SP depending on the application of real (SG), sham AA (ShG), or no therapy at all (CG), and the contrast of this trend between a healthy (SG) and a pathologic population underwent the same treatment (Study III-2) (Tab.8-9), further studies should be carried out involving the application of AA for longer times, in order to verify the obtain results, and explore better the possible molecular mechanisms underlying acupuncture treatments.

CONCLUSIONS

The three studies forming this doctoral thesis suggest that:

1. Acupuncture is effective in reducing pain of TMD origin, regardless of the acupuncture technique or method of points stimulation used, including innovative technologic instruments such electrostimulation and vibration (***Study I***)
2. The "microsystems techniques" of abdominal acupuncture and auriculotherapy can be both effectively used for the management of orofacial pain connected respectively to TMD and to the use of fixed orthodontic appliances (***Study II***)
3. There is no significant correlation between the salivary proteic response and the application of ear acupuncture in both healthy subjects and patients affected by TMD Myalgia (***Study III***)

Acupuncture is an effective, safe and versatile tool for orofacial pain treatment. However, the extremely various possibilities of application, treatment patterns and stimulation methods represent a big challenge for the scientific systematization and for the development of specific protocols or therapeutic indications. Further studies are needed to fill these lacks, and to deepen the neurophysiological mechanisms that may determine the clinical efficacy of acupuncture for treating pain, especially in a complex area such as the craniofacial district.

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I

Analisi epidemiologica longitudinale di tre decadi di popolazioni affette da DTM

Longitudinal epidemiological analysis of three decades of TMD populations

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RIASSUNTO

OBIETTIVI

L'obiettivo di questo studio è di confrontare i dati epidemiologici di pazienti disfunzionali – afferenti presso il Servizio di gnatologia clinica dell'Azienda ospedaliera universitaria Policlinico Umberto I-Sapienza Università di Roma – in maniera longitudinale, ossia attraverso uno studio di coorte, al fine di evidenziare i caratteri salienti dei Disordini temporomandibolari (DTM) e dei pazienti che ne sono affetti, e valutare l'evoluzione nel tempo di tali caratteristiche.

MATERIALI E METODI

È stata selezionata una popolazione omogenea di 387 pazienti disfunzionali, appartenenti a tre diversi decenni, scelti in modo randomizzato dalle cartelle cliniche presenti in archivio, in cui erano presenti tutti i loro dati anagrafici, anamnestici e clinici. Tutti i pazienti selezionati sono stati divisi in tre gruppi omogenei di 129 pazienti: GI (1990-1993), GII (2000-2003) e GIII (2010-2013). Di tutti i dati clinico-anamnestici è stata effettuata un'analisi statistica descrittiva.

RISULTATI

Il sesso femminile (F) è di gran lunga più interessato allo sviluppo di DTM, anche se nei gruppi di studio di epoche più recenti si evince una tendenza all'aumento dell'incidenza a carico del sesso maschile (M): in GI i pazienti di sesso M e F risultano, rispettivamente, il 14,84% e l'85,16%; in GII sono il 15,50% contro l'84,50%; in GIII risultano, rispettivamente, il 20,16% e il 79,84%. La fascia di età più colpita, in tutti e tre i gruppi, è quella compresa tra i 16 e i 40 anni: l'80% in GI, il 68,26% in GII e il 62,02% in GIII. Tuttavia, le fasce più alte di età, ossia dai 41 ai 70 anni, mostrano un progressivo aumento di incidenza, a partire dagli anni Novanta (GI) a oggi (GIII): 17,27% in GI; 30,16% in GII; 37,20% in GIII.
I DTM più frequenti sono le patologie articolari (GI: 85%; GII: 54,3%; GIII: 51,2%). La dislocazione riducibile del disco è presente nel 44,89% di GI, nel 40,31% di GII e nel 34,11% di GIII. La dislocazione non riducibile del disco è presente nel 40,15% di GI, nel 13,96% di GII e nel 17,06% di GIII. GIII mostra un aumento dell'incidenza di patologie muscolari (37,2%) rispetto alle precedenti decadi (GI: 10,2%; GII: 35,6%). Le parafunzioni sono un dato di notevole incidenza in tutti i gruppi di studio, in particolar modo nel gruppo GIII. Il serramento è presente nel 17,05% di GI, nel 30,23% di GII e nel 62,8% di GIII. Il bruxismo è presente nel 14,96% di GI, nell'11,63% di GII e nel 35,66% di GIII. Il dolore articolare

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è il sintomo con maggior incidenza in tutti i gruppi analizzati, essendo riferito dal 74,42% di GI, dal 79,07% di GII e dal 69,77% di GIII. Tale sintomo, sia esso presente a destra, a sinistra o bilateralmente, viene riferito per lo più come moderato/forte dai pazienti di GI, GII e GIII, e non mostra discrepanze degne di nota tra le diverse epoche. La cefalea è un sintomo riferito per lo più come bilaterale, ed è la comorbidità più rappresentata in tutti e tre i gruppi: 45,74% in GI, 57,36% in GII, 66,67% in GIII. La cervicalgia si manifesta per lo più bilateralmente ed è riferita da una percentuale maggiore di pazienti di GIII (61,24%) rispetto a GII (41,87%).

CONCLUSIONI

Il paziente affetto da DTM, rispetto al passato, è mediamente meno giovane e afflitto da patologie dolorose e tendenti alla cronicizzazione che manifestano associazione con varie comorbidità, come la cefalea e la cervicalgia. Questo profilo rende il paziente disfunzionale più complesso da esaminare e pone quindi lo specialista di fronte alla necessità di formarsi in modo adeguato per poter avere una valida competenza diagnostica e terapeutica.

SIGNIFICATO CLINICO

Le differenti caratteristiche assunte dal paziente disfunzionale devono essere tenute presenti nella pratica clinica.

PAROLE CHIAVE

- DTM
- ATM
- Disordini temporomandibolari
- Epidemiologia
- Studi longitudinali

ABSTRACT

OBJECTIVES

This study aims to compare the epidemiological data of three cohorts of dysfunctional patients attending to the Clinical Gnathology Service of Policlinico Umberto I University Hospital - Sapienza University of Rome, in order to highlight the salient characteristics of Temporomandibular disorders (TMD) and patients who are affected, and understand their evolution over time.

MATERIALS AND METHODS

A homogeneous population of 387 dysfunctional patients, belonging to three different decades, consecutively extracted from the medical records in the archive, which contained all their personal, anamnestic and clinical data, was selected. All patients were divided into three homogeneous groups of 129 subjects: GI (1990-1993), GII (2000-2003) and GIII (2010-2013). A descriptive statistical analysis of all the clinical and anamnestic data was performed.

RESULTS

The female gender (F) is far more interested in the development of TMD, although the study groups of more recent times shows an increasing trend in the incidence on the male one (M): in GI, the patients of M and F sex are respectively 14.84% and 85.16%; in GII are 15.50% and 84.50%; in GIII are 20.16% and 79.84%. Regarding the age, in all three groups the most affected range is between 16 and 40 years: 80% in GI, the 68.26% in GII and the 62.02% in GIII. However, the highest age groups, from 41 to 70 years and over, shows a progressive increase in incidence, from the 90s (GI) to today (GIII): the 17.27% in GI; the 30,16% in GII; the 37.20% in GIII. The most frequent TMDs are the joint diseases (GI: 85%; GII: 54.3%; GIII: 51.2%). The disc displacement with reduction (DDWR) is present in the 44.89% of GI patients, the 40.31% of GII, and the 34.11% of GIII. The disc displacement without reduction (DDWoR) is present in the 40.15% of GI patients, the 13.96% of GII, and in the 17.06% of GIII. GIII shows an increased incidence of muscular pathologies (37.2%) compared to previous decades (GI: 10.2%; GII: 35.6%). The parafunctions are a datum of remarkable incidence in all the study groups, especially in GIII. Clenching is present in the 17.05% of GI, in the 30.23% of GII, and in the 62.8% of GIII. Bruxism is present in the 14.96% of GI, in the 11.63% of GII, and in the 35.66% of GIII. Joint pain is the symptom with higher incidence in all analyzed groups, being reported by the 74.42% of GI, the 79.07% of GII and the 69.77% of GIII. This symptom, whether present on the right, on the left or bilaterally, is mostly referred as moderate/severe by patients of GI, GII and GIII, and shows no remarkable discrepancies between the different decades. Headache is a symptom mostly referred as bilateral, and is the comorbidity most reported all three groups: 45.74% in GI, 57.36% in GII, and 66.67% in GIII. Neck pain occurs mostly bilaterally and is reported by a higher percentage of GIII patients (61.24%), compared to GII (41.87%).

CONCLUSIONS

The TMD patient, compared to the past, is on average less young and afflicted by painful and chronic diseases, almost constantly accompanied by painful symptoms associated with the purely articular or muscular one, such as headache and neck pain. These features make the dysfunctional patient more complex to be examined, so the specialist need to train properly in order to have a valid diagnostic and therapeutic expertise.

CLINICAL SIGNIFICANCE

The dysfunctional patient has changed over time several characteristics that must be considered in clinical practice.

KEY WORDS

- TMD
- TMJ
- Temporomandibular joint disorders
- Epidemiology
- Longitudinal studies

1. INTRODUZIONE

I Disordini temporomandibolari (DTM) sono largamente diffusi nella popolazione; essi sono caratterizzati da un complesso corteo di segni e sintomi, costituiti prevalentemente da dolore muscolare e/o articolare, rumori articolari, limitazioni funzionali e rappresentano una delle principali forme di algie muscolo-scheletriche della regione cranio-cervicale[1]. Lo stato attuale delle conoscenze sui DTM non consente di focalizzarne l'eziologia che viene definita multifattoriale e determinata da un'interazione di elementi strutturali, comportamentali, psicologici, sociali, ambientali e genetici[2].

Gli studi epidemiologici di popolazione sui DTM mostrano alcuni aspetti comuni tra i quali i più noti sono: la prevalenza del genere femminile[3-5], la maggiore insorgenza nella fascia di età 25-40 anni, la tendenza di questi disturbi a diminuire con il progredire dell'età[3,5,6], la loro associazione con le parafunzioni[5,7-9]. Rimane invece non chiara la correlazione con fattori occlusali come la perdita di elementi dentari e la presenza di specifiche malocclusioni[10-13]. Da qualche anno si è resa più evidente l'influenza che hanno su tali disturbi stati di stress o ansia, la presenza di disagio sociale e/o psichico[12,14-16], le parafunzioni[11,17-19].

La maggior parte delle analisi presenti in letteratura tende a inquadrare la popolazione in modo verticale, scremando campioni di popolazione più o meno ampi in un periodo specifico e limitato di tempo come una ricerca eseguita dalla nostra scuola e pubblicata nel 2013. Avendo a disposizione un ampio archivio di pazienti disfunzionali iniziato negli anni Ottanta, si è deciso di studiare la popolazione in senso orizzontale analizzando tre coorti di pazienti disfunzionali, appartenenti a tre differenti decadi confrontando i dati per comprenderne l'evoluzione nel tempo.

Data la grande mole di dati ottenuti si è ritenuto di suddividere lo studio in due parti: una descrittiva e una statistico/associativa. Il presente articolo, rappresenta la prima parte, e consiste nella caratterizzazione epidemiologica definita attraverso l'analisi quantitativa dei dati dei tre campioni esaminati e selezionati tra coloro che, negli ultimi trent'anni, sono giunti all'osservazione del Servizio di gnatologia clinica del DAI testa-collo dell'Azienda ospedaliera universitaria Policlinico Umberto I della Sapienza Università di Roma.

2. MATERIALI E METODI

È stata valutata una popolazione omogenea di pazienti, rivoltasi consecutivamente presso il Servizio di gnatologia clinica sopra indicato, selezionata dalle cartelle cliniche presenti nell'archivio. Questo studio è stato approvato dal Comitato Etico Istituzionale dell'Università Sapienza di Roma (N. 53/2018 - 0000711), ed è stato realizzato in accordo con gli standard etici stabiliti nella Dichiarazione di Helsinki del 1964.

Si è deciso di selezionare pazienti di decenni diversi. Volendo effettuare un'analisi comparativa, si è ritenuto opportuno considerare fasce che partissero con l'inizio di ogni decennio. Le prime cartelle relative all'attività clinica del nostro reparto sono datate 1983, anno non classificabile come inizio decennio, pertanto la campionatura è iniziata dai primi tre anni della decade successiva 1990-1993. Partendo da questa, sono state poi costruite le altre fasce della stessa ampiezza e della stessa distanza temporale 2000-2003 e 2010-2013.

Negli anni Novanta i pazienti venivano registrati con una cartella clinica completa solo se erano sottoposti a una terapia, pertanto la serie consecutiva di cartelle considerata valida nei primi tre anni di quella decade è stata di 129 pazienti. Allo scopo di mantenere costante il numero di pazienti presi in esame, anche nelle altre fasce sono stati raccolti dati per 129 pazienti, omogeneamente distribuiti nei tre anni di ogni fascia.

Il solo criterio di inclusione è stato l'essere un paziente affetto da DTM, secondo le linee guida di riferimento DC/TMD, mentre non avere una cartella clinica completa è stato l'unico criterio di esclusione applicato. Nelle fasce 2000-2003 e 2010-2013, sulla base di tali criteri, sono state escluse rispettivamente due e tre cartelle.

L'analisi è stata effettuata, quindi, su un totale di 387 pazienti, divisi in tre gruppi di studio:

- *Gruppo I (GI)*, 129 pazienti, appartenenti al periodo 1990-1993, di cui 20 di sesso maschile e 109 di sesso femminile, con un'età media di 29,64 anni;
- *Gruppo II (GII)*, 129 pazienti, appartenenti al periodo 2000-2003, di cui 20 di sesso maschile e 109 di sesso femminile, con un'età media di 34,98 anni;
- *Gruppo III (GIII)*, 129 pazienti, appartenenti al periodo 2010-2013, di cui 26 di sesso maschile e 103 di sesso femminile, con un'età media di 41,49 anni.

I dati sono presentati secondo la sequenza diagnostica della cartella clinica, come qui di seguito presentato.

Aspetti anagrafico-anamnestici

1. *Sesso* (maschi/femmine).
2. *Età* (valore assoluto).
3. *Professione*: in base a quanto riferito dai pazienti, questi sono stati inseriti in una delle seguenti categorie: intellettivo/scientifica, tecnici/operatori,

impiegati, operatori non specializzati, casalinghe, studenti, pensionati, disoccupati, altro. Questo dato è presente in cartella solo per i gruppi GII e GIII.

4. *Stato civile*: sono state considerate quattro categorie: celibe/nubile, sposato/a, divorziato/a, vedovo/a. Questo dato è presente in cartella solo per i gruppi GII e GIII.

Aspetti clinico-semeiologici

1. *Sintomatologia*: algia (ATM/muscolare), cefalea e cervicalgia. Le sensazioni algiche dei pazienti sono state arbitrariamente suddivise in quattro categorie in base al valore da essi conferitegli in termini di scala VAS: lieve (0-30); medio (30-50); forte (50-70); molto forte (>70). La cervicalgia è un dato presente in cartella solo per i gruppi GII e GIII.
2. *Parametri clinici*: LAB (limitazione apertura della bocca) e rumori (click, crepito, altro).
3. *Parametri occlusali*: classe dentale (I, II, III); denti mancanti nel settore posteriore destro (dx) e sinistro (sn) (in base a quanto riportato in cartella questo dato è stato inserito in uno dei seguenti range: 0, 1-2, 3-4, 5-8); denti mancanti nel settore anteriore, dato inserito in uno dei seguenti range: 0, 1-2, 3-6, >6; perdita di altezza verticale posteriore; guida incisiva ripida; faccette di usura. Di questi ultimi tre dati è stata considerata la presenza/assenza.
4. *Diagnosi*: lussazione, dislocazione riducibile del disco, dislocazione irriducibile del disco, artrosi, mialgia locale e mialgia diffusa. Di tutte le patologie considerate se ne è valutata la presenza a livello dell'articolazione destra (dx), sinistra (sn) o bilaterale.

   Negli anni Novanta non vi era una classificazione univoca dei DTM, ma vi era della letteratura a riguardo. Su questa base gli autori hanno stilato la suddetta classificazione, che è molto simile a quelle che sono state standardizzate in seguito (RDC/TMD - DC/TMD). Dato che si riferisce al primo campione in ordine temporale (GI), si è scelto di utilizzarla anche per i campioni successivi (GII e GIII).
5. *Parafunzioni*: bruxismo e serramento (riportato dal paziente e/o reperto clinico).

È stata effettuata la seguente analisi statistica descrittiva: ogni carattere è stato analizzato, per ogni fascia di anni, in tabelle di distribuzione di frequenza al fine di osservarne l'evoluzione nel corso del tempo. Per quanto riguarda i caratteri quantitativi, sono stati calcolati deviazione standard, media, mediana, minimo e massimo.

Si è scelto, inoltre, di valutare la distanza temporale tra l'insorgenza dei DTM e la prima osservazione clinica (mesi) dei pazienti considerati e l'affluenza dei pazienti, in tutte e tre le fasce temporali considerate, attraverso la seguente formula:

Incremento = (n. pazienti anni 00-03/10-13) - n. pazienti anni 90-93 / n. pazienti anni 90-93) * 100.

3. RISULTATI

Di tutti i risultati ottenuti vengono di seguito riportati solo quelli più significativi, anche in virtù delle evidenze espresse dai dati epidemiologici attuali presenti in letteratura.

Aspetti anagrafico-anamnestici

Il sesso prevalente è quello femminile, in tutte le fasce temporali considerate. Dal Novanta in poi, però, si è notato un aumento dell'incidenza del sesso maschile, soprattutto per quanto riguarda GIII, in cui si è manifestato un aumento di 6 punti percentuali rispetto a GI **(grafico 1)**.

L'età media dei pazienti disfunzionali è in aumento nel corso del tempo, passando da 29,64 in GI a 41,49 in GIII. Le fasce di età che risultano in aumento crescente nel tempo sono state dalla "41-50" in poi. Le fasce di popolazione più anziana ("61-70" e "70+") risultano poco o per niente interessate in GI e GII, mentre in GIII aumentano di tre punti percentuali **(grafico 2)**.

Aspetti clinico-semeiologici

Sintomatologia

Il dolore (algia ATM/muscolare) è stato un sintomo molto frequente in tutti i pazienti considerati. Esso viene riferito in GI dal 74,42% (96 pazienti) del campione; in GII

1

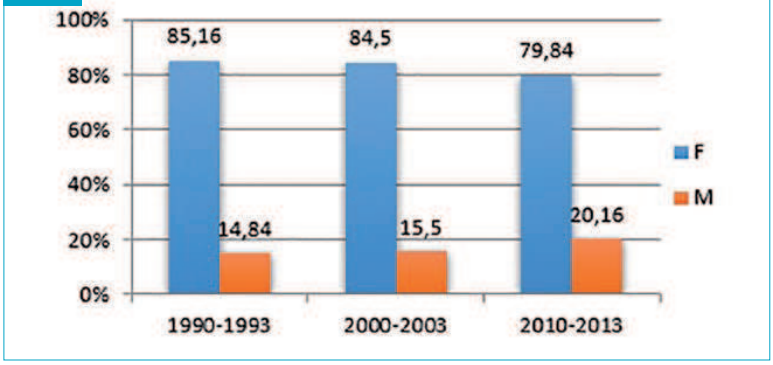

Grafico 1 Distribuzione del sesso in GI, GII e GIII

dal 79,07% (102 pazienti); in GIII dal 69,77% (90 pazienti) **(grafico 3)**.

Il dolore, da tutti e tre i gruppi di studio, viene riferito per lo più come moderato/forte (GI: 81,9% - 106 pazienti; GII: 75,6% - 97 pazienti; GIII: 62,3% - 80 pazienti), meno frequentemente viene invece riferito come lieve o grave (GI: 18,04% - 23 pazienti; GII: 24,3% - 31 pazienti; GIII: 37,7% - 48 pazienti).

Non si notano grandi discrepanze nella distribuzione delle diverse categorie, se non un lieve aumento dei pazienti che riferiscono il dolore come grave nell'ultimo decennio (GIII: 40,97% - 53 pazienti) rispetto al primo (GI: 10,32% - 13 pazienti).

L'intensità del sintomo cefalea ha mostrato una distribuzione abbastanza omogenea tra i vari gruppi, come si nota nel **grafico 4**. Rispetto agli altri due gruppi, in GIII si è notata una percentuale maggiore di pazienti che riferiscono la cefalea come grave. La cervicalgia risulta complessivamente riferita da una percentuale maggiore di pazienti di GIII, rispetto a GII **(grafico 4)**.

Parametri clinici

La presenza di rumori tende a diminuire progressivamente tra i gruppi. Tra tutti, il

2

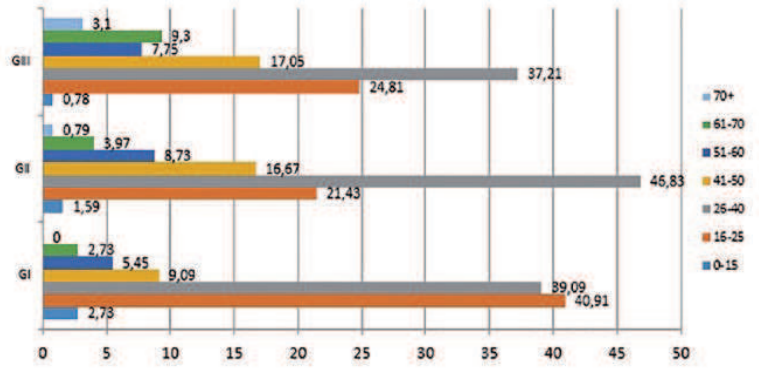

Grafico 2 Distribuzione dell'età in GI, GII e GIII

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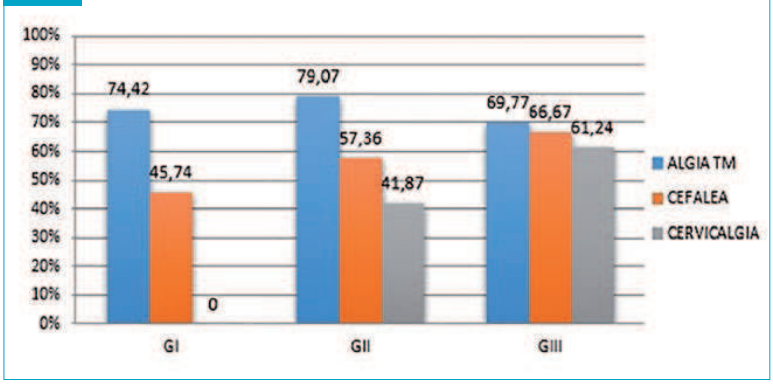

Grafico 3 Incidenza dei sintomi in GI, GII e GIII

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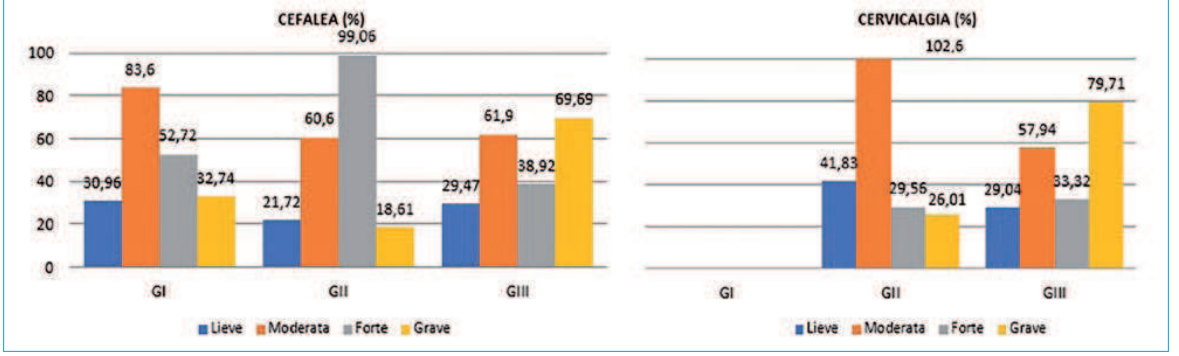

Grafico 4 Intensità dei sintomi cefalea e cervicalgia in GI, GII e GIII

click è stato quello che si è manifestato più frequentemente, in tutti i gruppi di studio: GI (63 pazienti: 49,61% del campione), GII (50 pazienti: 38,76% del campione), GIII (44 pazienti: 34,11% del campione).
La limitazione della massima apertura della bocca è un dato che si è presentato con un trend in diminuzione **(grafico 5)**.

Parametri occlusali

Di tutti i parametri occlusali esaminati il dato più rilevante e costante è stato una mancanza di elementi dentali nei settori latero-posteriori. Il parametro è risultato presente in più del 50% di ogni gruppo analizzato. GIII mostra la percentuale minore di soggetti che presentano denti mancanti su una o entrambe le arcate, pari al 59,69% (77 pazienti) del campione, mentre in GII rappresentano l'82,95% (107 pazienti) e in GI il 75,62% (93 pazienti) del campione.

Diagnosi

La lussazione di mandibola è risultata essere una patologia poco frequente in tutti e tre i gruppi. Mentre in GI e GII affligge una piccola parte della popolazione oggetto di studio, in GIII risulta quasi del tutto assente.
La dislocazione riducibile del disco è stata abbastanza frequente in tutti e tre i gruppi, colpendo complessivamente il 44,89% di GI (57 pazienti), il 40,31% di GII (52 pazienti) e il 34,11% di GIII.
La dislocazione non riducibile del disco non è risultata molto frequente in tutti i gruppi, in particolar modo in GII (18 pazienti: 13,96% del campione) e GIII (22 pazienti: 17,06% del campione), mentre in GI ha interessato il 40,15% del campione (51 pazienti).
La mialgia locale è risultata interessare una parte della popolazione di tutti i gruppi considerati, rispettivamente nel 7,88% (10 pazienti) in GI, nel 16,28% (21 pazienti) in GII e nel 24,03% (31 pazienti) in GIII.
La mialgia diffusa è stata poco rappresentata in tutti i gruppi con una lieve maggior presenza nei pazienti di GII e GIII. In GI si è presentata nel 2,36% (3 pazienti), nel 19,39% (25 pazienti) in GII e nel 13,18% (17 pazienti) in GIII.
Considerate nel loro complesso, le patologie di ordine neuro-muscolare hanno evidenziato un andamento similare nei tre gruppi analizzati, risultando presenti nel 10,24% (13 pazienti) di GI, nel 35,67% (46 pazienti) di GII e nel 37,21% (48 pazienti) di GIII **(grafico 6)**.

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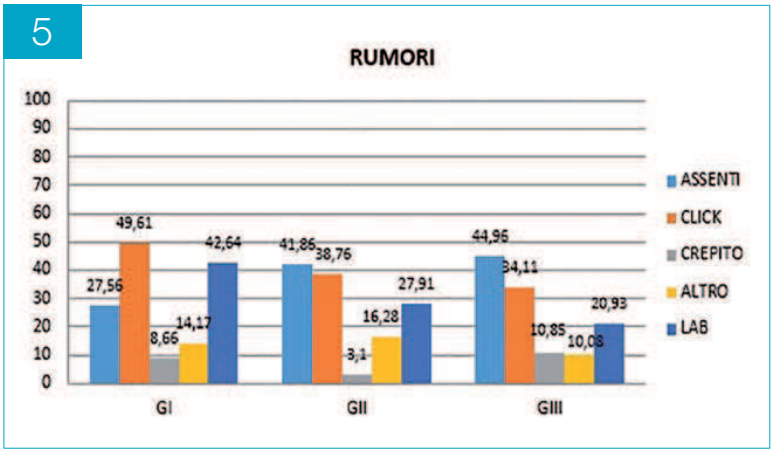

Grafico 5 Distribuzione dei parametri clinici considerati in GI, GII e GIII

Parafunzioni

Per quanto riguarda le parafunzioni, sia il digrignamento che il serramento sono considerevolmente più presenti in GIII rispetto agli altri due gruppi. Il serramento, infatti, è presente nel 17,05% di GI (22

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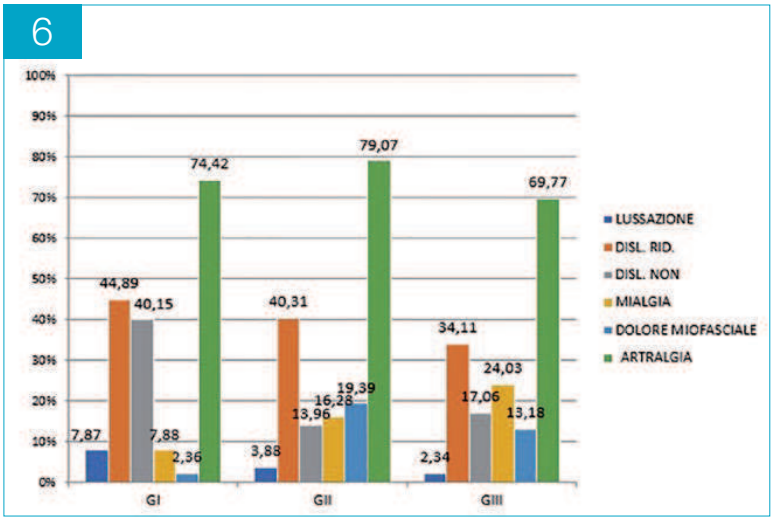

Grafico 6 Distribuzione delle patologie articolari e muscolari in GI, GII e GIII

pazienti), nel 30,23% di GII (39 pazienti) e nel 62,8% di GIII (81 pazienti). Il digrignamento è presente nel 14,9% di GI (19 pazienti), nell'11,63% di GII (15 pazienti) e nel 35,66% di GIII (46 pazienti). Considerate complessivamente, le parafunzioni risultano molto rappresentate in tutti e tre i gruppi analizzati: 31,95% (41 pazienti) in GI, 41,86% (54 pazienti) in GII e 98,46% (127 pazienti) in GIII.

Distanza temporale insorgenza DTM/prima osservazione clinica e affluenza

La distanza temporale media tra l'insorgenza dei DTM e la prima osservazione clinica, in tutti e tre i gruppi di studio, è stata di 22 mesi. In GI (1990-1993) il tempo medio è stato 10 mesi, in GII (2000-2003) è stato di 22 mesi e in GIII (2010-2013) di 34 mesi.

Nelle tre fasce temporali considerate si è registrato un deciso incremento dell'affluenza: 810,85% in GII e 940,31% in GIII. Da un punto di vista prettamente statistico, è stato ritenuto opportuno evidenziare quelle discrepanze tra le stesse modalità del medesimo carattere, in archi temporali differenti, che in termini di differenze percentuali superassero una data soglia. Tale soglia è stata fissata al 20%, ritenuto un valore ragionevolmente rappresentativo di una consistente discrepanza. I risultati significativi sono riportati in **tab. I**.

4. DISCUSSIONE

Per effettuare un confronto tra i dati ottenuti e l'attuale stato dell'arte è stato preso come riferimento uno studio recente di Köhler[20], nonché uno dei pochi che può essere assimilabile alla presente ricerca in quanto analizza coorti di pazienti affetti da DTM con un'analisi longitudinale nel tempo. Tale studio prende in considerazione le caratteristiche di una popolazione svedese di 130 soggetti a decennio, per tre decenni consecutivi, dal 1983 al 2003. I risultati ottenuti mostrano tendenze simili per quanto riguarda la sintomatologia dolorosa e le parafunzioni. Da questo studio, infatti, si evince che i sintomi più frequentemente associati a DTM sono click articolare, cefalea ricorrente e affaticamento mandibolare. La prevalenza dei suddetti sintomi, inoltre, vede un incremento dal 1983 al 2003. Nel 2003 la prevalenza di cefalea ricorrente in pazienti appartenenti a giovane fascia di età (20 anni) vede un netto incremento (1983: 8%; 1993: 7,5%; 2003: 13%) così come il bruxismo (1983: 14%; 1993: 18%; 2003: 23%).

Un dato da sottolineare è stato un iniziale cambiamento del trend che riguarda il sesso prevalente. In GI, infatti, i pazienti di sesso maschile e femminile sono, rispettivamente, il 14,84% (20 pazienti M) e l'85,16% (109 pazienti F); in GII sono il 15,50% (20 pazienti M) contro l'84,50% (109 pazienti F); in GIII risultano rispettivamente il 20,16% (26 pazienti M) e il 79,84% (103 pazienti F). Questi dati paiono in accordo con quanto affermato diffusamente in letteratura[3-5], cioè che il sesso femminile è di gran lunga più interessato allo sviluppo di DTM rispetto a quello maschile. Dai risultati ottenuti nei gruppi di studio sembra emergere una lieve tendenza all'aumento dell'incidenza nel sesso maschile come mostra la letteratura più recente **(grafico 1)**.

Per quanto riguarda l'età, i risultati ottenuti mostrano che in tutti e tre i gruppi la fascia più colpita è quella compresa tra i 16 e i 40 anni: in GI questi pazienti rappresentano l'80% (88 pazienti) del cam-

Tab. I Discrepanze percentuali significative per archi temporali diversi

Parametro	Archi temporali	Discrepanza (%)
Dolore, bilaterale	1990-1993 e 2010-2013	21,70%
Cefalea, assente	1990-1993 e 2010-2013	20,93%
Cefalea sinistra, 51-70 (forte)	2000-2003 e 2010-2013	26,55%
Cefalea sinistra, 71-100 (grave)	2000-2003 e 2010-2013	26,83%
Cefalea sinistra, 71-100 (grave)	1990-1993 e 2010-2013	20,29%
Cefalea destra, 51-70 (forte)	1990-1993 e 2000-2003	27,10%
Cefalea destra, 51-70 (forte)	2000-2003 e 2010-2013	33,58%
Cefalea destra, 71-100 (grave)	2000-2003 e 2010-2013	24,24%
Cervicalgia, bilaterale	2000-2003 e 2010-2013	23,25%
Cervicalgia sinistra, 21-50 (moderata)	2000-2003 e 2010- 2013	28,81%
Cervicalgia sinistra, 71-100 (grave)	2000-2003 e 2010- 2013	26,19%
Cervicalgia destra, 71-100 (grave)	2000-2003 e 2010- 2013	27,50%
LAB	1990-1993 e 2010-2013	21,70%
Denti mancanti nel settore posteriore, nessuno	2000-2003 e 2010-2013	23,25%
Dislocazione irriducibile del disco, assente	1990-1993 e 2010-2013	23,10%
Bruxismo	2000-2003 e 2010-2013	24,03%
Bruxismo	1990-1993 e 2010-2013	20,69%

pione, in GII rappresentano il 68,26% (86 pazienti) e in GIII il 62,02% (80 pazienti). Ciò è in linea con quanto si evince in letteratura riguardo all'età di maggiore incidenza di questi disturbi[3,5,6], che si attesta, anche secondo Köhler, nella fascia 40-50 anni. Va però rimarcata la notevole discrepanza presente nei dati tra gli anni Novanta (GI) e oggi (GIII). Questa difformità si manifesta con un aumento significativo di incidenza a carico dell'età che va dai 41 agli oltre 70 anni. In GI, infatti, tale fascia rappresenta il 17,27% (19 pazienti) del campione, in GII rappresenta il 30,16% (38 pazienti) e in GIII il 37,20% (48 pazienti) **(grafico 2)**.

Per ciò che riguarda i parametri clinici, il rumore articolare tipo click risulta il più frequente sintomo riportato in tutti i gruppi considerati, dato che è in linea anche con i risultati ottenuti da Köhler, in tutte e tre le fasce temporali analizzate. Tra i parametri occlusali la mancanza di elementi posteriori è un dato significativamente presente nel campione esaminato; esso è presente in più del 50% di ogni gruppo analizzato benché con un trend in diminuzione tra GI e GIII. Nello studio di Köhler non è presente nello specifico il dato relativo alla mancanza di elementi dentari, né vengono valutati altri parametri occlusali.

Il dolore (algia ATM/muscolare) risulta essere molto frequente in tutti i gruppi analizzati, essendo riferito dal 74,42% (96 pazienti) di GI, dal 79,07% (102 pazienti) di GII e dal 69,77% (90 pazienti) di GIII. Tale sintomo, sia esso presente mono o bilateralmente, viene riferito per lo più come moderato/forte dai pazienti di GI, GII e GIII, e non mostra discrepanze degne di nota tra le diverse epoche. In GIII è stata rilevata un'incidenza maggiore di pazienti che riferiscono il dolore ATM come grave. In questo gruppo, infatti, è ritenuto grave dal 40,97% (24 pazienti), mentre in GI dal 10,32% (8 pazienti) e in GII solo dal 5,3% (14 pazienti). Questi dati risultano in controtendenza rispetto allo studio di Köhler, in cui il dolore facciale/articolare è un sintomo riportato più frequentemente solo dai soggetti molto giovani (10 anni di età) nell'anno 2003 (4%) rispetto agli anni 1993 e 1983 (1%), e risulta in generale un dato poco frequente e con una differenza non significativa tra i tre periodi considerati.

La cefalea è un sintomo riferito per lo più come bilaterale, ed è anch'essa riportata da un numero consistente di pazienti di tutti e tre i gruppi: dal 45,74% (59 pazienti) di GI, dal 57,36% (74 pazienti) di GII e dal 66,67% (86 pazienti) di GIII. Per quanto concerne l'intensità di dolore con cui viene riferita, gli autori hanno riscontrato che in GIII vi è un aumento percentuale abbastanza significativo di pazienti che la riferiscono come grave, rispetto ai decenni precedenti. Questi rappresentano, infatti, il 69,6% (52 pazienti) del campione; in GI questi pazienti rappresentavano il 32,74% (18 pazienti) del campione e in GII il 18,61 (12 pazienti) **(grafico 4)**. Nello studio svedese questo sintomo risulta abbastanza frequente nei campioni analizzati e pare altresì aumentare progressivamente nel tempo: 13% nel 2003, 8% nel 1993 e 7,5% nel 1983. A differenza del nostro campione, però, tale sintomo è riferito in maniera significativa da fasce di età molto giovani (dai 10 ai 20 anni).

La cervicalgia si manifesta per lo più bilateralmente ed è riferita da una percentuale maggiore di pazienti di GIII (79 pazienti: 61,24% del campione), rispetto a GII (54 pazienti: 41,87%). In GIII, inoltre, viene riferita grave da un numero superiore di pazienti (55 pazienti: 79,71%) rispetto a GII (11 pazienti: 26,01%) **(grafico 4)**.

Tra tutte le diagnosi evidenziate, riferite all'Asse I secondo la classificazione DC/TMD, le più frequenti in tutti e tre i gruppi sono i disordini articolari, con una lieve flessione di incidenza nella fascia temporale più recente. La dislocazione riducibile del disco è risultata presente nel 44,89% (57 pazienti) di GI, nel 40,31% (52 pazienti) di GII e nel 34,11% (44 pazienti) di GIII. La dislocazione non riducibile del disco è risultata presente nel 40,15% (51 pazienti) di GI, nel 13,96% (18 pazienti) di GII e nel 17,06% (22 pazienti) di GIII. In GIII si è riscontrato un aumento dell'incidenza delle patologie muscolari (mialgia locale e mialgia diffusa), che complessivamente risultano abbastanza rappresentate in tutti i gruppi analizzati **(grafico 6)**.

Le parafunzioni sono risultate essere un dato di notevole rilevanza in tutti i gruppi di studio con un netto incremento nel gruppo GIII. Questo progressivo aumento delle parafunzioni è in linea con i risultati dello studio svedese, in cui si riscontra un simile graduale incremento percentuale nel tempo: 14% nel 1983, 18% nel 1993 e 23% nel 2003.

È stato, inoltre, effettuato un confronto con uno studio epidemiologico precedentemente condotto e pubblicato nel 2013 sulla stessa popolazione, ma analizzata verticalmente, che ha coinvolto un campione di 2375 pazienti disfunzionali afferenti tra il 1983 e il 2006. Alcuni dati, come è plausibile attendersi, risultano essere in linea con il presente lavoro[11]. Tra i tanti si ritiene opportuno sottolineare l'alto numero di pazienti che presentava mancanza di elementi dentali posteriori: nello specifico l'86,1% dell'intero campione aveva un'assenza da 1 a 8 elementi nei settori latero-posteriori. Il sintomo più rappresentato è stato anche qui il dolore, sia articolare che muscolare, riferito rispettivamente dal 60% e dal 30% dei pazienti analizzati. Altro dato similare riguarda l'alta percentuale di pazienti che riferivano cefalea, per lo

più bilaterale, che si attestava al 46%. Anche in questo studio, inoltre, le patologie articolari risultavano le maggiormente evidenziate, in particolar modo la dislocazione riducibile del disco (53,2%), e si poneva l'accento sull'incremento delle parafunzioni, che nel complesso erano presenti nel 37,8% dei pazienti analizzati.

Tornando ai dati attuali, un risultato di notevole interesse è stato quello relativo all'incremento di affluenza evidenziato negli anni; infatti, rispetto al periodo 1990-1993, nel periodo 2000-2003 si è avuto un incremento di pazienti dell'810,85% che è arrivato al 940,31% per il periodo 2010-2013. Ciò può essere dovuto a più fattori dei quali è difficile differenziare il peso relativo quali: un aumento dell'informazione mediatica su questi argomenti con conseguente accresciuto interesse verso un servizio specializzato alla diagnosi e alla cura di tali patologie, la presenza di struttura dedicata nel contesto di una delle più grandi Aziende ospedaliere universitarie in Italia, un reale aumento dell'incidenza dei DTM. Qualunque sia il motivo principale che ha determinato questo dato, è comunque importante sottolinearlo in quanto particolarmente significativo e soprattutto confermato dalla costante e continua crescita di affluenza che si è manifestata dal 2014 a oggi.

Per quanto riguardo lo studio della distanza temporale tra l'insorgenza dei DTM e la prima osservazione clinica, il tempo medio riportato, in tutti e tre i gruppi di studio, è stato di 22 mesi. In GI (1990-1993) il tempo medio è stato 10 mesi, che tende progressivamente a crescere fino a diventare una media di 34 mesi in GIII (2010-2013). Non è stato possibile evidenziare le ragioni di tale dato; si può però osservare che esso coincide con la diminuzione dell'osservazione di sintomatologie acute che in genere motivano i pazienti a ricercare subito un trattamento. Un'altra ragione può essere legata al maggiore impegno nella vita e nel lavoro che caratterizza gli anni più recenti rispetto al passato, e che porta probabilmente i pazienti a sottostimare queste patologie, così come periodi di difficoltà economica che allontanano i pazienti dall'osservazione clinica. Questo potrebbe anche spiegare la grande incidenza di co-morbità presenti in GIII e l'aumento di gravità della sintomatologia dolorosa a tutti i livelli. Questi dati concordano con studi di popolazione dell'ADA (American Dental Association) che evidenziano quanto un intervento precoce sui DTM sia un metodo anche economicamente vantaggioso, e invita i medici a considerare un tale approccio nello sviluppo di piani di trattamento per questi pazienti che una volta diventati cronici risultano più difficili da trattare[21].

5. CONCLUSIONI

Questo studio da un lato conferma alcune evidenze già presenti in letteratura, per esempio la maggiore incidenza dei DTM a carico del sesso femminile e la rilevanza delle parafunzioni; dall'altro evidenzia un netto incremento di affluenza di soggetti richiedenti cure, e ciò mette in luce come negli anni sia migliorata la conoscenza e l'attenzione della popolazione nei confronti dei disturbi che affliggono l'ATM e il distretto cranio-cervico-mandibolare oltre che l'affinamento del personale medico specialistico nella costante applicazione di sistematiche diagnostiche validate. Differenze emerse dall'analisi della letteratura sono state, in particolare, il dato relativo all'assenza di elementi dei settori latero-posteriori e quello dell'età. Quest'ultimo, soprattutto, evidenzia un trend con un progressivo aumento, negli anni più recenti, di pazienti con un'età media maggiore di 50 anni e una relativa diminuzione della fascia di età inferiore.

Alla luce di queste osservazioni è possibile delineare che il paziente disfunzionale abbia avuto delle evoluzioni nel tempo: prima era un soggetto giovane o giovane adulto con sintomi per lo più a carico dell'ATM, oggi è un paziente mediamente adulto, tardo adulto o giovane anziano, afflitto per lo più da patologie dolorose e tendenti alla cronicizzazione che manifestano associazioni con varie comorbidità: le più frequenti sono risultate altre patologie dolorose di ampio spettro epidemiologico come la cefalea e la cervicalgia. Questo profilo rende in genere il paziente più complesso da esaminare e pone quindi lo specialista di fronte alla necessità di formarsi in modo adeguato per poter avere una valida competenza diagnostica e terapeutica.

In ultimo, si vuole segnalare come particolarmente negativo il dato della frequente cronicità della patologia temporomandibolare evidenziata nel corrente decennio che sembra essere dovuta alla sempre maggiore distanza temporale che intercorre tra l'insorgenza del quadro sintomatologico e l'osservazione clinica. Alla luce dei trend emersi da quest'analisi longitudinale, gli autori auspicano che possano essere progettati protocolli nazionali mirati al controllo di queste patologie per favorire forme di prevenzione a tutti i livelli cominciando dai soggetti di età giovane e pediatrica per evitare questa sfavorevole tendenza. ■

CONFLITTO DI INTERESSI
Gli autori dichiarano di non avere alcun conflitto di interessi.

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II

Original Article

Evaluation of Vision in Gnathological and Orthodontic Patients with Temporomandibular Disorders: A Prospective Experimental Observational Cohort Study

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ABSTRACT

Objectives: Temporomandibular disorders (TMDs), orthodontic diseases, and vision dysfunctions seem to be strictly related. The purpose of this study was to prove the relationship, to evaluate the prevalence and the distribution of vision defects in dysfunctional and orthodontic patients, and to establish the type of the relationship. **Materials and Methods:** A total of 100 patients with TMDs were selected and studied through epidemiological analyses of the following factors: gnathological parameters (temporomandibular joint pathologies according to Diagnostic Criteria for Temporomandibular Disorders); occlusal and skeletal parameters (overjet, overbite, dental class, transversal discrepancies, and mandibular asymmetry); and orthoptic parameters (refractive defects and oculomotor diseases). A prospective experimental observational cohort study was conducted. A comparison with the average frequency of vision defects of the Italian population was performed. The prevalence of vision defects was evaluated. All gnathological and orthodontic parameters were associated with the orthoptic ones. A descriptive and statistical analysis of the data was carried out with the Statistical Package for the Social Sciences software; *z* test ($P < 0.05$), frequency analysis (frequency >50%), chi-square test, and Student's *t* test ($P < 0.05$) were performed. The scientific consistency was evaluated by using the scientific criteria of Bradford Hill. **Results:** The comparison with the Italian population showed a higher frequency of refractive defects in the study sample ($P < 0.001$). The most frequent vision defects were phorias (92%) and tropia (3%). The increased frequency of ocular convergence reduction in the presence of disc displacement with reduction was significant ($n = 28$; 60%; $P < 0.05$). In the presence of asymmetry, low frequencies of astigmatism ($n = 18$; 30%) were observed compared to its absence ($n = 22$; 54%) ($P < 0.05$) and high frequencies of motor ocular deviations ($n = 59$; 100%) were observed compared to its absence ($n = 36$; 88%) ($P < 0.05$). In the presence of headache, low frequencies of emmetropia ($n = 13$; 22%) and higher frequencies of hyperopia ($n = 18$; 30%) were observed ($P < 0.05$). Two of five scientific criteria of Bradford Hill were met. **Conclusion:** It seems to emerge a possible positive relationship between

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TMD and vision defects. In particular, the most interesting associations were found between functional or skeletal orthognathic alterations and oculomotor dysfunctions. However, it was not possible to establish the type of relationship.

Keywords: *Malocclusion, orthodontics, temporomandibular disorders, vision defects, vision dysfunctions*

Introduction

Common comorbidities such as balance alterations, cervical problems, tinnitus, orofacial pain, headache, and emotional disorders are widely discussed in literature. Little interest has been shown, however, in the relationship between temporomandibular disorders (TMDs) and vision disorders, although both are very widespread in the Italian population.[1-3] The two systems, stomatognathic and oculomotor, represent the main exteroceptors of the head–neck district, capable of influencing the balance and behavior of patients.[4] The correlation between the two systems is expressed through three types of connection: anatomical through craniofacial sutures;[5,6] neurological through a connection between the encephalic nuclei such as the vestibular, trigeminal, oculomotor, and accessory nuclei;[4,7-11] and functional through the muscle chains.[12,13] Only recent studies, even if not very specific and controversial, have introduced a possible connection between the two systems. Some scientific researches have correlated vision defects, such as astigmatism, hyperopia, myopia, and strabismus, with orthodontic alterations such as first-, second-, and third-class malocclusions and crossbite.[14-20] Monaco *et al.*[21,22] in two studies of 2003 and 2005 have shown that mandibular deviation and myofascial pain lead to a reduction in ocular convergence, whereas Cuccia and Caradonna[23] have shown that binocular vision is reduced in patients with temporomandibular joint disc disorders. There are no studies on many samples that can establish the report with scientific certainty. The correlation between each individual TMD and each individual vision defect is not specified. No scientifically validated classification systems have ever been used to identify the various TMDs. The type of relationship between the two entities (comorbidities and cause–effect) is not yet absolutely clear. The low quality of the works, their heterogeneity, and the difficulty of making valid comparisons require great caution in considering these connections scientifically sustainable, both in diagnostic phase and in therapeutic phase. To verify the existing report more clearly, an experimental study was carried out with the following four objectives:

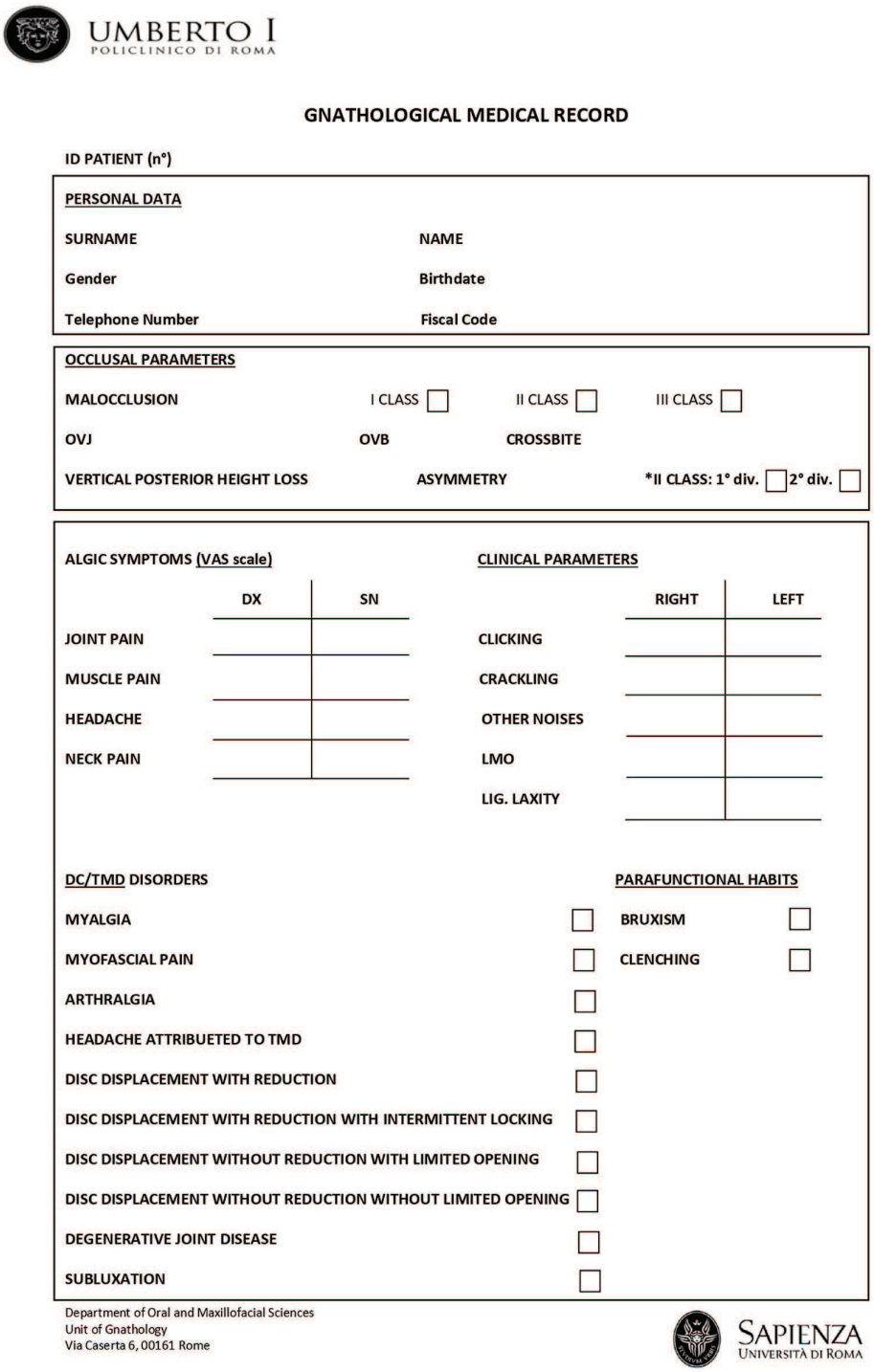
1. To verify an epidemiological relationship between TMDs and vision defects
2. To assess the prevalence of vision defects in gnathological and orthodontic patients
3. To analyze the distribution of vision diseases in dysfunctional and orthodontic patients
4. To describe the type of relationship between orthognathic and orthoptic diseases

Materials and Methods

A consecutive series of 334 patients from the Units of Gnathology and Orthodontics, Department of Head and Neck, Umberto I Hospital, Sapienza University of Rome, Rome, Italy, was selected from December 2017 to June 2018. Specifically, 231 patients were selected from the Unit of Gnathology and 103 patients from the Unit of Orthodontics. All patients were screened for TMDs by the same calibrated personnel according to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) of Axis I. A prospective experimental observational cohort study was conducted. All patients had been previously informed about the study, including its aims and the potential risks, and they were given an informed consent form. The study was approved by the Institutional Ethics Committee of Sapienza University of Rome (Approval no. 12/2018 – 0000106). The sample was selected at two levels of evaluation: (1) gnathological one (first assessment) and (2) orthoptic one (second assessment) [Figure 1].

First assessment

All 334 patients were analyzed through a complete gnathological specialist examination by the same calibrated personnel by using a specific medical record, developed in accordance with the hospital system. Subsequently, a first clinical form, developed specifically for the study, was filled in with the most relevant data for the experimental study [Figure 2]. All patients with at least one TMD according to the Axis I of DC/TMD classification were included in the study. Instead, patients showing dentoskeletal malformations with asymmetry superior to 4 mm, complete removable dentures, fixed prosthesis on more than two lateral-posterior dental elements, absence of more than lateral-posterior dental elements, systemic diseases, and patients who had already



UMBERTO I
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GNATHOLOGICAL MEDICAL RECORD

ID PATIENT (n°)

PERSONAL DATA

SURNAME	NAME
Gender	Birthdate
Telephone Number	Fiscal Code

OCCLUSAL PARAMETERS

MALOCCLUSION I CLASS ☐ II CLASS ☐ III CLASS ☐

OVJ OVB CROSSBITE

VERTICAL POSTERIOR HEIGHT LOSS ASYMMETRY *II CLASS: 1° div. ☐ 2° div. ☐

ALGIC SYMPTOMS (VAS scale)

	DX	SN
JOINT PAIN		
MUSCLE PAIN		
HEADACHE		
NECK PAIN		

CLINICAL PARAMETERS

	RIGHT	LEFT
CLICKING		
CRACKLING		
OTHER NOISES		
LMO		
LIG. LAXITY		

DC/TMD DISORDERS

- MYALGIA ☐
- MYOFASCIAL PAIN ☐
- ARTHRALGIA ☐
- HEADACHE ATTRIBUETED TO TMD ☐
- DISC DISPLACEMENT WITH REDUCTION ☐
- DISC DISPLACEMENT WITH REDUCTION WITH INTERMITTENT LOCKING ☐
- DISC DISPLACEMENT WITHOUT REDUCTION WITH LIMITED OPENING ☐
- DISC DISPLACEMENT WITHOUT REDUCTION WITHOUT LIMITED OPENING ☐
- DEGENERATIVE JOINT DISEASE ☐
- SUBLUXATION ☐

PARAFUNCTIONAL HABITS

- BRUXISM ☐
- CLENCHING ☐

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SAPIENZA
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Figure 1: Flowchart of the study

undergone gnathological or orthodontic treatments were excluded. The variables considered were as follows: personal data; occlusal parameters such as malocclusions (presence or absence), overjet and overbite (increased or decreased), and posterior vertical height loss (presence or absence); skeletal parameters such as mandibular asymmetry (presence or absence on radiography); pain symptoms such as arthralgia, myalgia, neck pain, and headache (scale); and gnathological clinical parameters such as clicking, crackling, other noises, limited mouth opening (LMO), and ligamentous laxity (presence or absence). International DC/TMD such as myalgia, myofascial pain, arthralgia, headache due to TMD, disc displacement with reduction (DDR), DDR

with intermittent locking, disc displacement without reduction (DDNR) with limited opening, DDNR without limited opening, degenerative joint disease, and subluxation (presence or absence) were used for the formulation of the diagnosis.[24] The first assessment population comprised 123 patients.

Second assessment

The 123 patients previously selected were sent to the visual postural center of the same polyclinic. All patients underwent a second evaluation according to orthoptic exclusion criteria such as the presence of eye diseases, ocular trauma, patients who had already undergone ophthalmic surgery, alterations of ocular mobility, and binocular collaboration. As a result, 23 patients were excluded. Therefore, the study sample comprised a total of 100 patients. Among them, 25 were men (25%) and 75 were women (75%), with an average age of 32.63 years (standard deviation = 15.37; range, 10–68 years). The recruited sample was examined by the same calibrated personnel through orthoptic evaluation tests: visual acuity test, evaluation test of ocular alignment (cover test [CT], corneal bright reflex test, or Hirschberg test), ocular motility, convergence test, and Lang test [Figure 2].[2,25,26] A second clinical form, developed specifically for the study, was filled in with the orthoptic data [Figure 3].

Statistical analysis

A descriptive and statistical analysis was then carried out using the Statistical Package for the Social Sciences software (IBM: Armonk, New York, US). To verify the first objective, a z test was performed, significant when $P < 0.05$; to clarify the second objective, a frequency analysis of vision defects was conducted, significant when the variable considered occurs in more than 50% of the sample; to clarify the third objective, an association between variables with a chi-square test and a difference between averages with a parametric Student's t-test were performed, both significant when $P < 0.05$; and to clarify the fourth objective, the scientific criteria of Bradford Hill were used.

Results

A large amount of data emerged from the analysis. Consequently, only the results that were most statistically significant and clinically interesting were reported. The results were listed according to the four objectives.

Objective 1

As regards vision problems, myopia occurred in 38% of the sample and 31% of the population; astigmatism in 40% of the sample and 24% of the population; hyperopia in 22% of the sample and 25% of the population; and strabismus in 4% of the sample and 3% of the population ($P < 0.001$) [Figure 4].

Objective 2

The most frequent vision defect in the sample was oculomotor dysfunctions. In particular, of 100 patients, 92% had phoria, 3% had tropia, and 5% had orthophoria [Figure 5].

Objective 3

One of the most important associations was found between DDR and ocular convergence. Of 53 patients without DDR, 34 (64%) had normal convergence and 19 (36%) had decreased convergence, whereas of 47 patients with DDR, 19 (40%) had normal convergence and 28 (60%) had decreased convergence ($P < 0.05$) [Figure 6].

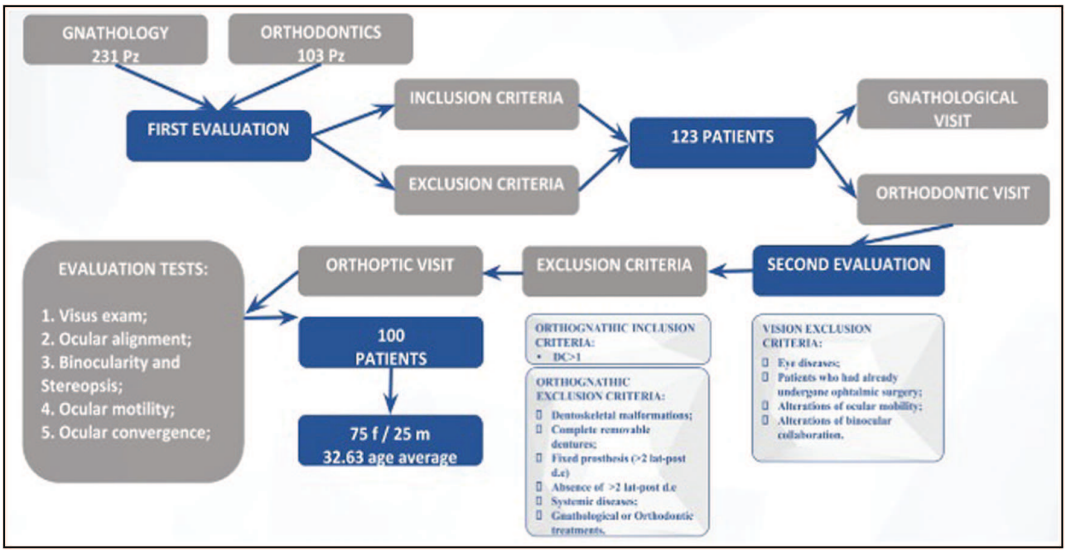

Figure 2: Gnathological medical record

ORTHOPTIC MEDICAL RECORD

DATE

SURNAME NAME

AGE TELEPHONE NUMBER

MEDICAL HISTORY

AUTOREF RIGHT EYE LEFT EYE

LAF in use RIGHT EYE LEFT EYE

VISUS (without correction)

(with correction)

CORNEAL BRIGHT REFLEX TEST

Near Far

CT

OCULAR MOTILITY: Hyperfunction

Hypofunction

CONVERGENCE TEST:

LANG TEST:

ABNORMAL HEAD POSITION:

Figure 3: Orthoptic medical record

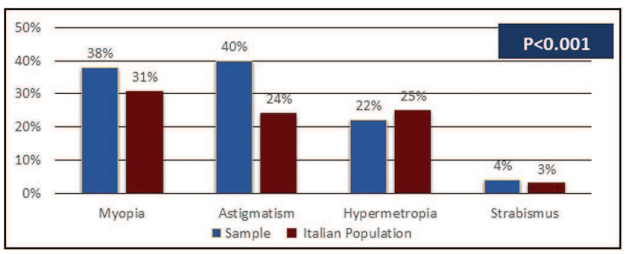

Figure 4: Comparison of frequencies of vision alterations between the sample and the Italian population

Another important association was found between asymmetry and astigmatism. Of 41 patients without asymmetry, astigmatism was absent in 19 (46%) and present in 22 (54%). Of 59 patients with asymmetry, astigmatism was absent in 41 (70%) and present in 18 (30%) ($P < 0.05$) [Table 1].

In addition, asymmetry was found statistically associated with oculomotor deviations. In particular, of 59 patients with asymmetry, 56 (95%) had phoria, 3 (5%) had tropia,

and 0 (0%) had orthophoria. Of 41 patients without asymmetry, 36 (88%) had phoria, 0 (0%) had tropia, and 5 (12%) had orthophoria ($P < 0.01$) [Figure 7].

Finally, a significant association was found between headache and emmetropia. Of 40 patients without headache, emmetropia was absent in 23 (58%) and present in 17 (42%), whereas of 60 patients with headache, emmetropia was absent in 47 (78%) and present in 13 (22%) ($P < 0.05$) [Table 2].

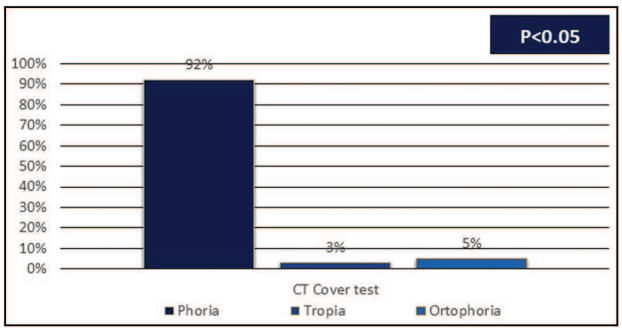

Figure 5: Prevalence of heterophorias in the sample

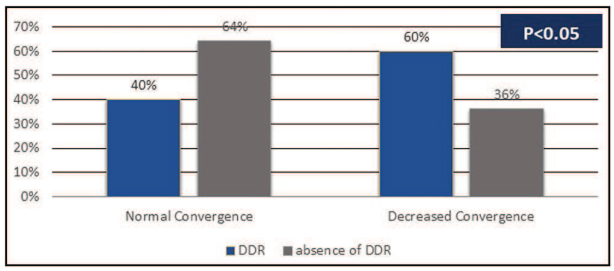

Figure 6: Association between disc displacement with reduction and convergence

Headache was also found significantly associated with hyperopia. Of 40 patients without headache, hyperopia was absent in 36 (90%) and present in 4 (10%). However, of 60 patients with headache, hyperopia was absent in 42 (70%) and present in 18 (30%) ($P < 0.05$) [Table 3]. The difference between the average values of gnathological algic symptoms and the ones of astigmatism, resulted statically significant.

The average values of arthralgia were equal to 1.9 when astigmatism was absent and equal to 2.1 when it was present. The average values of myalgia were equal to 1.36 when astigmatism was absent and equal to 2.1 when it was present. The average values of headache were equal to 1.93 when astigmatism was absent and equal to 2.65 when it was present. The average values of neck pain were equal to 2.17 when astigmatism was absent and equal to 2.33 when it was present ($P < 0.05$) [Table 4].

The results of associations between vision defects and the others DC/TMDs were not reported because of the low number of patients affected by. No associations between the subluxation and vision defects resulted statistically and/or clinically important to be shown.

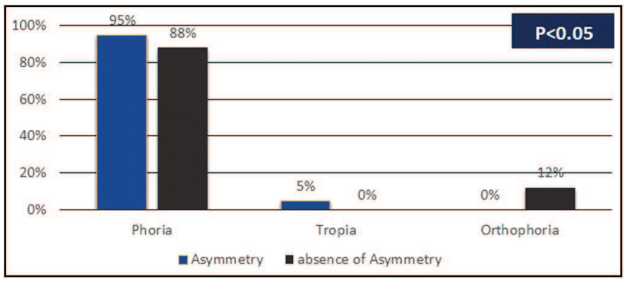

Figure 7: Association between asymmetry and oculomotor deviations

Table 1: Association between asymmetry and astigmatism. (a) Contingency table; (b) Chi-squared test

a. Contingency table			Asymmetry		Total
			Absence	Presence	
Astigmatism	Absence	Count	19	41	60
		Stand. residues	-1.2	1.0	
	Presence	Count	22	18	40
		Stand. residues	1.5	-1.2	
Total		Count	41	59	100

b. Chi-squared test	Value	df	Asymp. sig. (2 sides)	Exact sig. (2 sides)	Exact sig. (1 sides)
Pearson Chi-squared	5.938[a]	1	.015		
Continuity correction[b]	4.965	1	.026		
Likelihood ratio	5.940	1	.015		
Fisher exact test				.021	.013
Linear-linear association	5.878	1	.015		
Number of valid cases	100				

[a]0 cells (,0%) have an expected count of less than 5. The minimum expected count is 16,16

[b]Calculated only for a table 2 × 2

Table 2: Association between headache and emmetropia. (a) Contingency table; (b) Chi-squared test

a. Contingency table			Headache		Total
			Absence	Presence	
Emmetropia	Absence	Count	23	47	70
		Stand. residues	-.9	.8	
	Presence	Count	17	13	30
		Stand. residues	1.4	-1.2	
Total		Count	40	60	100

b. Chi-squared test	Value	df	Asymp. sig. (2 sides)	Exact sig. (2 sides)	Exact sig. (1 side)
Pearson Chi-squared	4.728[a]	1	.030		
Continuity correction[b]	3.808	1	.051		
Likelihood ratio	4.681	1	.030		
Fisher exact test				.044	.026
Linear-linear association	4.680	1	.031		
Number of valid cases	100				

[a]0 cells (,0%) have an expected count of less than 5. The minimum expected count is 12,12

[b]Calculated only for a table 2 × 2

Table 3: Association between headache and hyperopia. (a) Contingency table; (b) Chi-squared test

a. Contingency table			Headache		Total
			Absence	Presence	
Hyperopia	Absence	Count	36	42	78
		Stand. residues	.9	-.7	
	Presence	Count	4	18	22
		Stand. residues	-1.6	1.4	
Total		Count	40	60	100

b. Chi-squared test	Value	df	Asymp. sig. (2 sides)	Exact sig. (2 sides)	Exact sig. (1 side)
Pearson Chi-squared	5.801[a]	1	.016		
Continuity correction[b]	4.675	1	.031		
Likelihood ratio	6.292	1	.012		
Fisher exact test				.025	.013
Linear-linear association	5.742	1	.017		
Number of valid cases	100				

[a]0 cells (,0%) have an expected count of less than 5. The minimum expected count is 8,89

[b]Calculated only for a table 2 × 2

Among the nonsignificant associations, although clinically important and widely discussed in the literature, the association between dental class and refractive defects has to be highlighted.

Of 45 patients with Class I malocclusion, 16 (36%) had myopia, 17 (38%) emmetropia, 7 (16%) hyperopia, and 17 (40%) astigmatism. Of 44 patients with Class II malocclusion, 15 (34%) had myopia, 10 (23%) emmetropia, 14 (32%) hyperopia, and 17 (39%) astigmatism. Of 11 patients with Class III malocclusion, 8 (73%) had myopia, 3 (27%) emmetropia, 1 (9%) hyperopia, 6 (56%), and astigmatism ($P > 0.05$) [Figure 8].

Objective 4

The consistency and the coherence criteria were verified. The strength, the specificity, and the temporal sequence criteria were not verified.

Discussion

Compared to the reference values of Italian population, most of the frequency values of vision defects were found to be higher in the study sample: myopia increased from 31% to 38%; astigmatism increased from 24% to 40%; hyperopia decreased from 25% to 22%; and strabismus increased from 3% to 4%.[2,3] The incidence rates of the same defects were also confirmed in other studies.[27] Considering that frequencies of most of the vision defects increased in the study sample, a positive relationship between the two systems can be confirmed. The most frequent vision dysfunction evaluated with the CT was oculomotor deviation. The most frequent vision dysfunction evaluated with the CT was oculomotor deviation: in particular, phoria or latent strabismus (92%), tropia or manifest strabismus (3%). Therefore, only 5% of the whole sample had

Table 4: Differences between the average values of gnathological algic symptoms and astigmatism. (a) Group statistics; (b) contingency table

a. Group statistics	Emmetropia	*n*	Average	Std. deviation	Std. error average
Arthralgia	Presence	30	2.07	1.484	.271
	Absence	69	1.94	1.740	.209
Myalgia	Presence	30	1.67	1.729	.316
	Absence	69	1.65	1.713	.206
Headache	Presence	30	1.67	1.709	.312
	Absence	69	2.46	1.668	.201
Neck pain	Presence	30	2.57	1.612	.294
	Absence	69	2.09	1.687	.203

b. Contingency table		*t* Test for equality of averages		
		Sig. (2-tailed)	Difference between averages	Difference standard error
Arthralgia	Take equal variances	.733	.125	.365
	Don't take equal variances	.717	.125	.342
Myalgia	Take equal variances	.969	.014	.376
	Don't take equal variances	.969	.014	.377
Headache	Take equal variances	.032	-.797	.367
	Don't take equal variances	.036	-.797	.371
Neck pain	Take equal variances	.191	.480	.364
	Don't take equal variances	.185	.480	.358

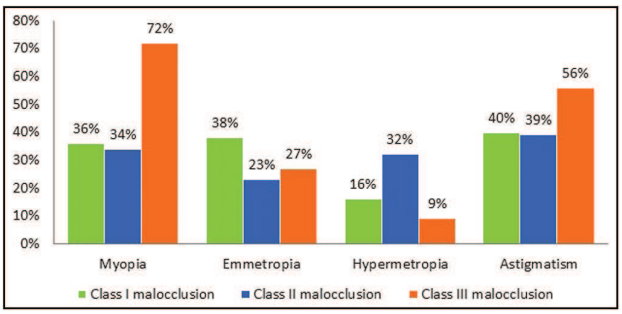

Figure 8: Association between dental class and refractive defects

orthophoria. A first very interesting significant association, as it adds a value to the hypothesis already present in the literature, is the association of the clicking and the DDR with ocular convergence.[22] In this study, the convergence deficit was found in 60% of patients with DDR. Also, in the reference study, the convergence deficit occurred more frequently in patients with DDR (22%) than in healthy controls (19%), but not significantly. Tissue inflammation and algic symptoms, due to progressive modification of joint structures, could affect the response at oculomotor level and could lead to hypersensitivity, induced by central sensitization, temporal sum, and activation of glial cells.[28] It can be postulated that the alteration of binocular motility may be due to a dysfunction at the level of the upper colliculus, center of visual, and somesthetic and proprioceptive afferences, involved in motor postural and gaze control.[23] One might think that the continuous intra-articular nociceptive stimulus could reduce the activation mechanism of the motoneurons of the extrinsic eye muscle and thus alter the maintenance of proper eye convergence.

Mandibular asymmetry was also found to be significantly associated with astigmatism. The frequencies of astigmatism were found to be lower in patients with asymmetry (30%) than in those without asymmetry (54%). The observed data did not coincide with the expected data. One could, in fact, think that an alteration at the osteobasal level could be associated with an asymmetry at the corneal level. But the astigmatism is an anatomical vision defect that it is difficult to be influenced by neurofunctional and muscular mechanisms. Another important association was found between asymmetry and oculomotor deviations evaluated with CT. The frequency of orthophoria was found to be higher in patients without asymmetry (12%) compared to those with asymmetry (0%). Therefore, it could be stated that in the presence of asymmetry, the risk of motor eye deviations increases.

One of the orthodontic and gnathological variables most frequently associated with vision defects was headache. It was observed that in patients with headache (59%), the presence of emmetropia was very low (22%) and the absence of it was very high (78%). Therefore, most of the patients with headache had a refractive defect, especially hyperopia. It occurred more frequently when headache was present (30%) as compared to when it was absent (10%). Another important correlation was found between average values of gnathological symptoms

and astigmatism. All average values of gnathological symptoms (arthralgia, myalgia, headache, and neck pain) were found to be increased when astigmatism was present as compared to when it was absent. In particular, the average value of headache increased from 1.93 to 2.65. Although from a gnathological point of view the headache could create a visual dysfunction, from an orthoptic point of view the headache is a consequence of vision dysfunctions. In fact, it is a very frequent symptom in vision defects due to the physical effort of the subject to improve vision.[29] It is also true that headache has been diagnosed by anamnesis as a pain symptom present at least twice a week but has not been evaluated by the neurologist. This limit prevents the nosological classification of the type of headache and the definition of the influence between it and the oculomotor alterations.

In the literature, several studies showed a correlation between vision defects and malocclusion. In this study, none of these associations were significant. In the largest study, taken in consideration as a reference, a higher frequency of hyperopia (59%) and astigmatism (50%) was found in Class I malocclusions, and a higher frequency of myopia (50%) in Class II malocclusions. In this study, hyperopia was found to be more frequent in Class II malocclusions (32%), whereas astigmatism (56%) and myopia (72%) were found to be higher in class III malocclusions.[16] The difference between the two studies lies in the size of the sample, which is 1326 in the reference study and 100 in this study, and in the type of malocclusion considered, skeletal in the first study and dental in the second one. The results obtained in the study may be due to the consideration of the dental class. It was not possible to define the type of relationship between TMDs and vision diseases. The consistency criterion was satisfied; the strength one could not be met because this study only analyzed a group of subjects exposed to the hypothetical risk (dysfunctional patients) and not a group of subjects not exposed (healthy). However, the study sample was compared with the Italian population, and it was found that the study sample was out of norm. The specificity criterion is not met if we consider each TMD (DC/TMD), whereas it can be defined positively if we consider temporomandibular disturbances as anomalies capable of disturbing biological functions. The temporality criterion cannot be applied because the time of the onset of the temporomandibular disorder with respect to the vision defect has not been detected. The criterion of coherence seems to be satisfied as the association is biologically plausible, given the numerous anatomical, neurological, and functional biological correlations between the stomatognathic apparatus and the oculomotor system.

Conclusion

A statistically and clinically significant relationship between some orthoptic and gnathological variables seemed to exist. Frequencies of many vision defects, such as oculomotor dysfunctions and most of refractive defects, seemed to be high in patients with TMDs. The most interesting associations were found between functional or skeletal orthodontics and gnathological alterations and oculomotor disorders. The type of relationship or the direction of influence between the two entities could not be established. Further studies by enlarging the sample should be conducted in the future to define the relationship. Patients with these types of vision defects should be included in a diagnostic multidisciplinary protocol. Although there is a positive significant association between the two anomalies, no orthodontic treatment is currently justified to correct an oculomotor alteration and vice versa.

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Conflicts of interest

There are no conflicts of interest.

Authors contributions

C.V., E.S.; performed experiments, analysed data and co-wrote the paper. S. P., A.S.; contributed to sample preparation. L. G.; contributed to the interpretation of the results. C. D. P., G.G.; devised the project, the main conceptual ideas and proof outline. Each group of authors analyzed the results, according to their specialty, all participated in the discussion and actively contributed to the drafting, CDP carried out the overall and definitive revision of the manuscript.

Ethical policy and institutional review board statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Approval no. 12/2018 – 0000106) and with the Helsinki declaration (1964) and its later amendments or comparable ethical standards.

Patient declaration of consent

Informed consent was obtained from all individual participants included in the study.

Data availability statement

The data that support the findings of this study are available from the corresponding author, [C.V.], upon reasonable request.

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Review Article

Local Vibratory Stimulation for Temporomandibular Disorder Myofascial Pain Treatment: A Randomised, Double-Blind, Placebo-Controlled Preliminary Study

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Several methods are currently used to manage pain related to temporomandibular disorder (TMD). Vibratory stimulation is applied as a pain treatment for several musculoskeletal disorders, but it has not yet been studied in-depth for TMD symptoms. The aim of this study is to analyse the effectiveness of at-home local vibration therapy (LVT) for the management of TMDs-related myofascial pain. *Methods*. Fifty-four TMD patients (43 F, 11 M) with an average age of 40.7 (age range: 29–54 yr.) were randomly subdivided into two groups. The study group (AG) received 1 week of at-home LVT treatment with the NOVAFON Pro Sk2/2 : 50/100 Hz, bilaterally applied to the pain area for 16 minutes daily. The placebo group (IG) followed the same protocol using inactive devices. Temporomandibular joint pain (TMJ), muscular pain (MM), and headache (HA) were assessed. Pain was evaluated using the visual analogue scale (VAS) before (T0) and after therapy (T1). Statistical analysis and Student's *t*-tests were applied (statistical significance for $P < 0.05$). *Results*. AG patients reported decreased average values for all types of pain considered between T0 and T1, with a statistically significant difference for TMJ pain ($P < 0.05$), MM pain, and HA ($P < 0.001$). IG patients reported a no statistically significant decrease in the average values of MM pain and an increase in the average values of TMJ pain and HA. *Conclusion*. The study supports the use of local vibration therapy in the control of TMD-related TMJ pain, local muscular pain, and headache.

1. Introduction

Temporomandibular disorders (TMD) comprise a large number of pathologies related to the masticatory muscles and/or temporomandibular joint (TMJ) and constitute a part of the musculoskeletal disorder group [1]. Current indications for treatment of these conditions follow a conservative approach that includes information, reassurance, control of functional excesses, physiotherapy rehabilitation, application of physical therapies, administration of drugs, and intraoral devices [1–3]. Like other musculoskeletal disorders, TMD has been treated in recent years with various physical therapy methods, in cases with different types of TMD pain (pain-related, intraarticular, degenerative groups). TENS (transcutaneous nerve electrical stimulation) and low-level laser therapy (LLLT) are among the most utilized treatment procedures [4–6].

One of the most recently proposed physical therapy treatments is local vibration therapy. Local vibration therapy produces vibrations that reach up to 6 centimetres of tissue depth; it is used to regulate muscle tone, relieve localized pain, and stimulate an increase in blood and lymphatic circulation [7–9]. This therapy is most frequently applied in the treatment of chronic pathologies affecting the muscles, tendons, and joints. Several studies evaluating the impact of local vibration therapy on skeletal muscles and joints have highlighted its effectiveness for increasing joint mobility and decreasing pain [10, 11], but analysis of its potential for the temporomandibular region is still lacking. Only two studies have addressed the application of this therapy to TMD and

both demonstrate its effectiveness for muscle pain relief [12, 13].

The aim of this study is to evaluate the effectiveness and efficiency of local vibration therapy in the treatment of craniomandibular pain by comparing the application of an active vibratory device with the application of an inactive placebo device on two samples of dysfunctional patients.

2. Materials and Methods

A randomized, double-blind, placebo-controlled clinical study was conducted at the Clinical Gnathology Unit of the Department of Oral and Maxillofacial Sciences at the "Sapienza" University of Rome. The study was approved by the Institutional Ethics Committee (N. 93/2017-0001385); all patients signed an informed consent document before participating in the study.

2.1. Participants. The patient enrollment process followed the CONSORT (Consolidated Standards of Reporting Trials) criteria (Figure 1).

During the period of February 2018–July 2019, 317 subjects under observation in our department were assessed for eligibility. All patients were screened for temporomandibular disorders (TMD) by specialists in the field using the DC/TMD diagnostic criteria [14]. Criteria for inclusion in the study were as follows: (1) diagnosis of chronic local myalgia (ICD-9 729.1) with average reported pain greater than or equal to 3 on the numeric verbal scale (NVS); (2) availability to participate in the study; and (3) current residence in Rome or the surrounding province. Patients meeting the following exclusion criteria were excluded from the study: (1) diagnosed with widespread pain; (2) diagnosis of joint disorders (ICD-9 524.63; ICD-9 715.18; and ICD-9 830.0); and (3) receiving ongoing gnathological treatment. Following manufacturer indications for the therapeutic device, additional exclusion criteria were also applied: (1) presence of open wounds/eczema on the skin or the skin membranes involved in the treatment; (2) diagnosis of arteriosclerosis, thrombosis, cardiac arrhythmias, or use of a pacemaker; (3) diagnosis of epilepsy; (4) use of brain stimulators or presence of metal implants; (5) presence of tumour lesions; and (6) pregnant women.

256 patients were excluded according to these criteria. The resulting study sample consisted of 61 patients, 16 male (26.2%) and 45 female (73.8%), with an average age of 38.39 years (range 29–54 years).

2.2. Interventions. The study involved the administration to all patients of a local vibration device (NOVAFON Pro (Sk2)) for professional/home mixed use. Patients were treated with both active, functioning devices and placebo devices identical to the functioning ones but therapeutically inactive. The therapeutic protocol involved 7 applications of vibration therapy: the first and last applications were performed by a specially trained operator (G.S.) at the clinical gnathology department; the remaining 5 were carried out at home by the patient.

A single operator (G.S.), blinded to the diagnosis and symptoms of patients, carried out the distribution of the devices and provided patient instruction on correct methods of use; all patients were given the same instructions for home use following the indications provided by the manufacturer. Patients used the active or placebo device for 5 days for 16 minutes a day.

The symptoms evaluated for all patients were joint pain, muscular pain (masticatory muscle pain), and headache (attributed to TMD). Each type of pain was measured at the following times:

(i) T0 : before treatment

(ii) T1 : after the last application (7 days after T0)

The 0–100 visual analogue scale (VAS) was used to measure pain self-assessment, with 0 indicating "no pain" and 100 "the worst imaginable pain."

At the end of treatment (T1), all patients were given a questionnaire regarding their impression of the treatment's effectiveness: Patients' Global Impression of Improvement (PGI-I) Scale (Figure 2).

In order to perform a comparative data analysis of the active and inactive devices, all participants were subsequently divided into two groups: a study group (AG) that received active devices and a placebo group (IG) that received inactive devices.

The primary outcome of the study was to evaluate the change in perceived pain levels after one week of local vibration therapy in the group that received active devices (AG) and in the group that received placebo devices (IG).

2.3. Local Vibration Device and Application Procedure. The device used was the NOVAFON Pro Sk2/2 (NOVAFON GmbH, Weinstadt).

This direct current electromedical device consists of a switch with two levels to adjust the intensity of the vibration produced (50/100 Hz); a handpiece to modify the power of the vibration; spherical and disc-shaped extra oral heads (means of stimulating the skin and mucous membranes); and an extension clamp (Figure 3(a)).

Two different application modalities were applied on both sides of the face to the masseter (deep and superficial) and temporal (anterior, middle, and posterior) muscles and to the TMJ [1], for a total of 16 minutes per day (Figures 3(b) and 3(c)):

(1) Use of the disc head on button 2 (50 Hz) for 4 minutes/side. The device was used with moderate pressure and rotational movements along the masseter and temporal muscles. The disc surface allows for greater dispersion of vibratory stimulation, with the aim of relaxing the musculature.

(2) Use of the spherical head on button 1 (100 Hz) for 4 minutes/side. The device was used with moderate pressure and punctual movements localized on patients' most painful areas along the masseter and temporal muscles and temporomandibular joint. The spherical surface concentrates vibratory stimulation

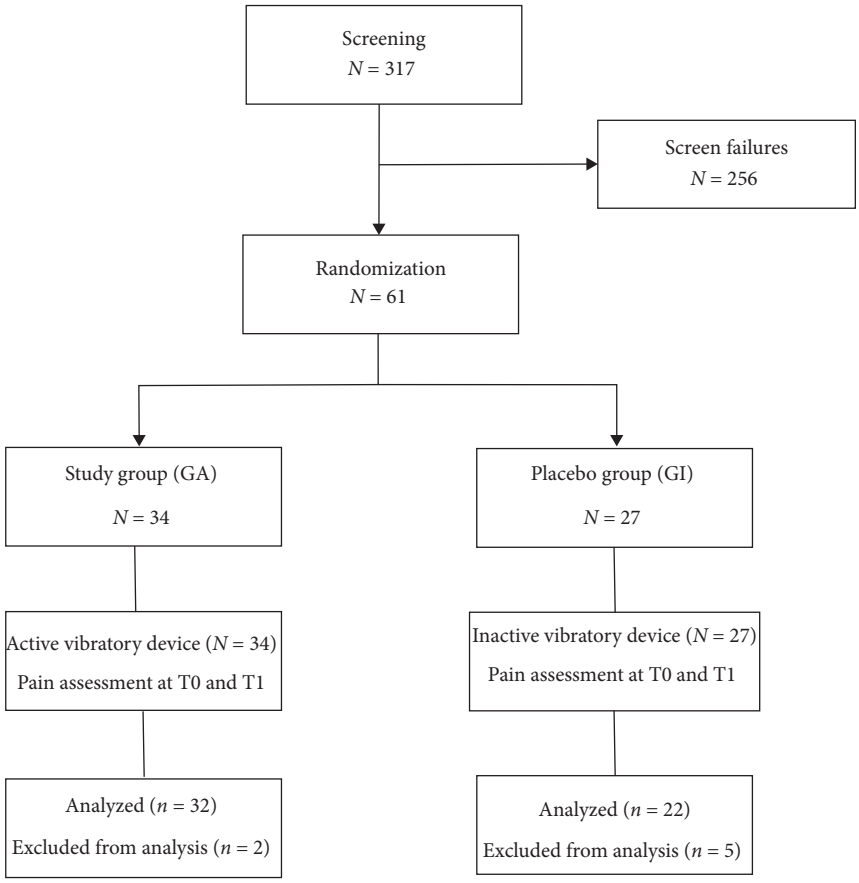


Figure 1: CONSORT flow diagram of patient enrollment and interventions.

Patients' Global Impression of Improvement (PGI-I) Scale

Check the box that best describes how your pain condition is now, compared with how it was before you had the local vibration treatment:

- ☐ Very much better
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

Figure 2: PGI-I Scale used to evaluate patients' impression of improvement.

on a smaller surface, with the aim of resolving muscle contractures and reducing myalgia.

2.4. Sample Size Estimation and Randomization. Since there were no data available from other clinical studies about the application of this kind of vibratory stimulation for TMD-related pain, patients were recruited using convenience sampling.

All local vibration devices (active and inactive) were randomly assigned to the study population using a random number generator (Research Randomizer©).

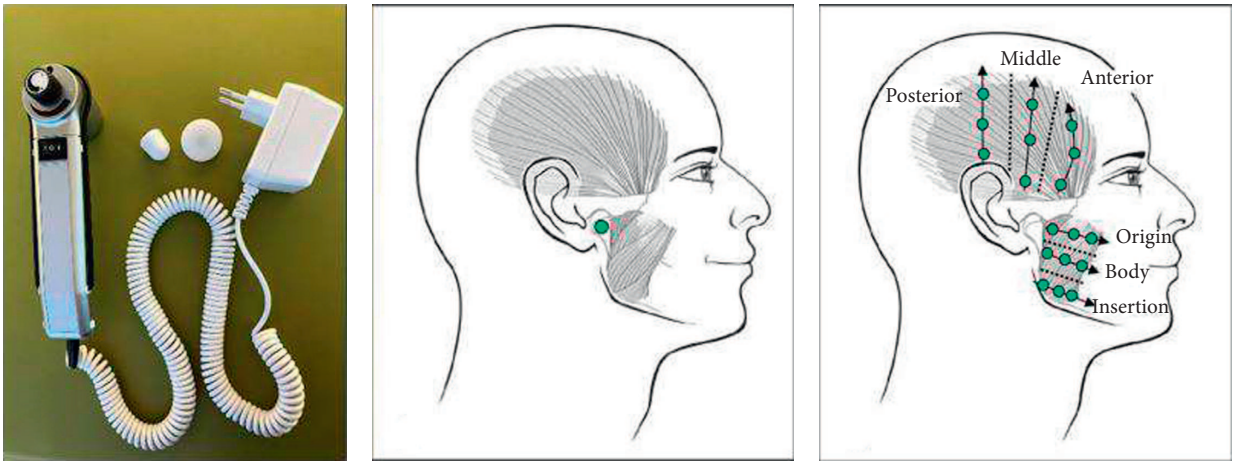
We used a total of 10 devices received from the manufacturer, 5 active and 5 inactive. These devices were delivered to patients by a single operator (G.S.); 34 active and 27 inactive devices were assigned over the course of the study. The devices showed the same exterior and functional characteristics. Neither the patients nor the operator knew which devices were active.

2.5. Statistical Analysis. Data analysis was performed with SPSS (version 23) statistical processing software. To assess whether there were significant differences in the pain levels (joint pain, muscular pain, and headache) of AG and IG patients at T0 and T1, a paired samples t-test was performed (statistical significance for $P < 0.05$).

3. Results

From the expected sample of 61 suitable patients, 7 were excluded for not carrying out the therapy according to the planned treatment modalities (Figure 1).

The resulting study sample therefore consisted of 54 patients; the characteristics of all study subjects are shown in Table 1.



(a) (b) (c)

Figure 3: NOVAFON Pro Sk2/2 (a); application points used at the (b) temporomandibular joint; (c) masseter muscle and temporalis muscle.

Table 1: Characteristics of the study population.

Variable	Study group (AG), $N = 32$	Placebo group (IG), $N = 22$	Total, $N = 54$
Gender, no. (%)			
Female	24 (75.0)	19 (86.4)	43 (79.6)
Male	8 (25.0)	3 (13.6)	11 (20.4)
Age, mean (SD)	39.8 (9.9)	41.1 (9.9)	40.7 (9.9)

We found no significant differences comparing male and female subjects. Results for the group that carried out the therapy with active devices (AG) show a decrease between T0 and T1 in average values of all types of pain considered, with a statistically significant difference for TMJ pain, muscle pain, and headache. Results for the group that performed the therapy with inactive devices (IG) show a decrease in average values of muscular pain and an increase in the average values of TMJ pain and headache. In comparing data between the start (T0) and end of therapy (T1), Student's *t*-test was not significant for TMJ pain and muscular pain (Table 2 and Figure 4).

3.1. Device-Placebo Comparison. The Student's *t*-test analysis of the decrease in relative average pain values between patients who performed active and inactive therapy at T1 did not show significant results for TMJ pain, muscular pain, or headache ($P > 0.05$).

3.2. Treatment Effectiveness (PGI-I). The results of patients' self-evaluations of treatment effectiveness using the PGI-I Scale are shown in Figure 5.

4. Discussion

This is the first study involving application of a local vibration device directly at the level of the joint area and masticatory muscles (masseter and temporalis) in order to evaluate the effectiveness of local vibration therapy for reducing TMD-related joint/muscular pain and headache.

The subjects of the group who underwent active local vibration therapy (AG) reported a significant decrease in average values of TMJ pain, muscular pain, and headache. Furthermore, there were no significant decreases in average pain values for patients in the study group that received placebo therapy with inactive devices (IG); these patients reported an increase in TMJ pain and headache that was statistically significant for the latter with respect to the initial pain level.

The choice to use vibratory stimulation in dysfunctional patients was based on evidence from previous studies showing the effectiveness of local vibration therapy in reducing chronic musculoskeletal pain and in delaying the onset of muscular pain [10, 11]. Several studies have shown that vibratory stimulus is capable of exciting afferents in both the Pacinian corpuscles and in the receptors of the skin, periodontium, muscle spindles, and tendon organs [15–17]. Moreover, from the gate control theory, we know that these sensory afferents can interact with the pain transmission pathways at the spinal level, causing modulation in response to the pain sensation [15, 18, 19]. All these mechanisms may contribute to the symptoms decrease observed in dysfunctional patients undergoing vibratory therapy in this study.

The pain symptomatology afflicting temporomandibular disorder patients is very complex and often invalidating, and it demonstrates a tendency to become chronic when there is no timely therapeutic intervention. There are several therapeutic strategies for relieving TMD-related pain, but only two studies evaluated the possible application of vibratory

Table 2: Average values of perceived pain in AG and IG.

	Study group-AG mean (SD)			Placebo group-IG mean (SD)		
Pain (VAS)	T0	T1	*P* value	T0	T1	*P* value
TMJ	53.33 (6.17)	44.33 (7.37)	0.0053*	54.54 (21.15)	55.45 (20.18)	(NS)
Muscular	52.00 (26.70)	31.00 (21.75)	7.0223*E*−06**	41.82 (22.28)	40.00 (19.49)	(NS)
Headache	45.33 (29.88)	22.33 (24.31)	1.3521*E*−05**	8.18 (14.01)	10.91 (18.68)	0.0407*

*$P < 0.05$ and **$P < 0.001$ in the difference T0–T1.

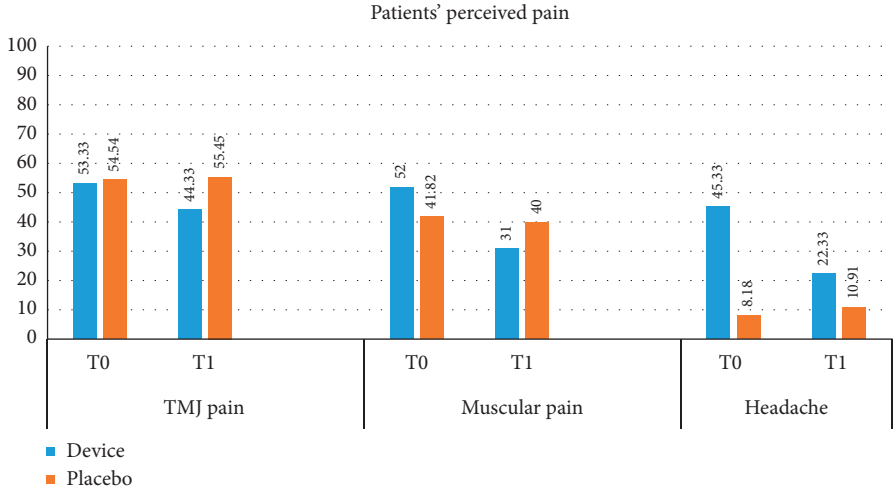


Figure 4: Average values of perceived pain in AG and IG at T0 and T1, according to VAS.

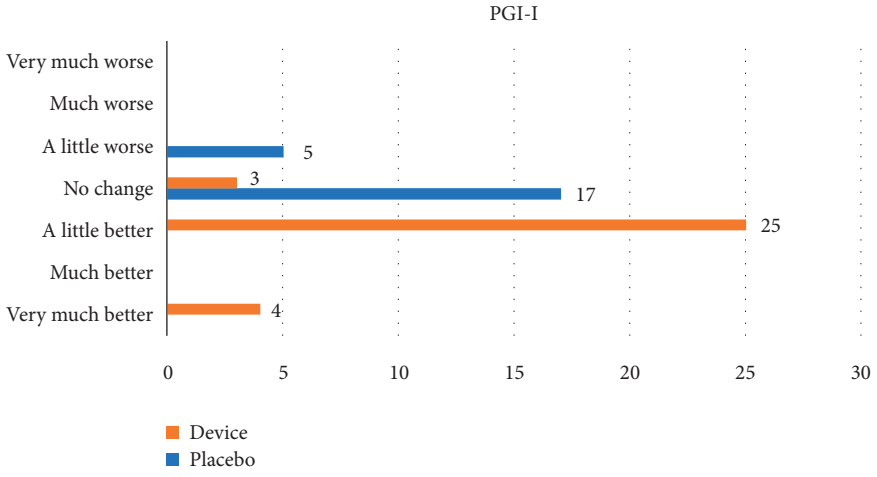


Figure 5: Patients' impression of the effectiveness of treatment according to the PGI-I Scale.

stimulation, and both report results in line with those obtained by our research.

Roy et al. [12] investigated the effect of vibrotactile therapy on resolution of chronic temporomandibular pain for a sample of 17 patients through the use of a stimulator that emitted vibrations of 20 Hz and 100 Hz. The results show the validity of this therapy in relieving TMD-associated pain, with a greater effectiveness at 100 Hz than 20 Hz for reducing muscular pain. Hara et al. [13] examined the analgesic efficacy of vibratory stimulation of an occlusal splint for a sample of 10 patients. The results highlighted significant variations in pain values on the VAS scale and on palpation, indicating the efficacy of the device in resolving TMD-related muscular pain.

In light of this evidence, the type of the device we used is particularly versatile, since it allows for daily home use for short periods and the possibility of extraoral application near the location of the pain. Patients who underwent therapy with an active device mostly reported an improvement in their pain condition and had no notable difficulty in following the home prescription. The extraoral application of the therapy also presents the additional advantage of being able to be applied in concomitance with the conventional therapy of occlusal splints, for patients

needing mechanical support. Our study results reinforce the evidence that local vibration therapy is most effective for muscular and tension pain, such as local myalgia and headache. Our results regarding decrease in TMJ pain, however, also suggest that this therapy is able to resolve strictly articular problems. From this perspective, local vibration therapy could be a valuable addition to complement other conservative therapies.

This study also presents several limitations. First, despite the positive results obtained, the patient sample examined is still too limited to represent reliable and significant results regarding the efficacy of NOVAFON Pro Sk2/2 in reducing TMD-related symptoms. We see evidence of this limitation in the statistical nonsignificance, despite the encouraging clinical decrease of symptoms, of the compared average pain values between AG and IG at the end of therapy (T1) (with significance threshold set at 5%). Having noticed values close to the aforementioned significance threshold and in light of the limited sample size, the same test was carried out with an increased significance threshold of 10%. The results obtained from the second test show a significant difference regarding TMJ pain and headache with a P value of 0.08 and 0.06, respectively. To address this limitation and obtain more reliable results, the study sample is currently being expanded.

Second, the results obtained correspond to a single week of therapy, while prolonged evaluation, extending beyond the completion of therapy (follow-up), is necessary. Finally, pain assessment in this study was limited to patient self-assessment, but the importance of using multiple methods of pain assessment, given the complexity of changes this symptom can undergo during experimental procedures, has been well documented [20, 21].

5. Conclusion

Local vibration therapy is a valid support tool in the control of TMD-related familiar muscular pain. The extraoral application method is versatile, easy to apply, and integrates well with other conservative therapies; it is also useful for increasing patient compliance with other rehabilitation treatments. Moreover, this therapy offers the advantage of being performed at home by the patient, in different therapeutic moments, allowing the clinician greater possibility for treatment individualization.

Further studies are needed, however, to confirm the results obtained with larger samples and to include the short/long-term follow-up.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Research Article

Comparison of the Effectiveness of Three Different Acupuncture Methods for TMD-Related Pain: A Randomized Clinical Study

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Purpose. This study aimed to compare the effectiveness of three acupuncture methods for temporomandibular disorders-(TMDs-) related pain. *Materials and Methods.* Different locations of pain, according to DC/TMD clinical assessment, were considered: temporomandibular joint (TMJ), masticatory muscles, head, and neck. Sixty patients were assigned randomly to one of three treatment groups (20 patients in each): group BA received body acupuncture, group EA received electroacupuncture, and group CA received acupuncture + cupping. The groups were compared in terms of pain (verbal numeric scale), pain-related disability (Brief Inventory Pain, BPI), and impression of the treatment's effectiveness (Patients' Global Impression of Improvement Scale, PGI-I). These were recorded before sessions of acupuncture treatment (T0), after 8 sessions of acupuncture treatment (T1), and after 4 weeks of follow-up after treatment (T2). The between-group and within-group differences in the data were analyzed statistically. The baseline characteristics were similar in all groups ($p > 0.05$). *Results.* Significant improvements were noted in all types of pain compared to baseline values in all groups (all $p < 0.05$). No significant differences were noted in the improvement of TMDs-related pain according to the different acupuncture techniques (all $p > 0.05$). All acupuncture methods used resulted to be significantly effective in improving the pain-related interference in the patient's common activities and quality of life. EA resulted to be significantly more effective than BA and CA in improving the interference of pain with patients' mood ($p = 0.015$) and quality of sleep ($p = 0.014$). *Conclusion.* BA, EA, and CA are all effective acupuncture methods in reducing pain and pain interference with common activities and quality of life in patients affected by TMD.

1. Introduction

Temporomandibular disorders (TMDs) are considered as one of the major causes of orofacial pain [1]. Pain related to TMDs is typically reported in the chewing muscles, preauricular area, or the temporomandibular joint (TMJ) [1, 2]. Often, many patients do not show localized pain but a more complex symptomatology, including headache, cervical pain, atypical facial pain, and head and neck muscle hypersensitivity [3, 4]. The presence of these symptoms may worsen the quality of life of patients and interfere with their emotional and social lives [5]. Due to the wide variety of clinical manifestations of TMDs-related pain, its treatment involves different therapeutic methods, such as splint therapy, medication, surgical therapy, physical therapy, low-level laser therapy (LLLT), transcutaneous electrical nerve stimulation (TENS), ultrasound, vibrational therapy, psychological support, and, increasingly in recent times, acupuncture [6–8].

Although many of acupuncture's physiological and neurological mechanisms are still unknown, the efficacy of acupuncture for pain therapy has been well established [9, 10]. In many clinical studies, acupuncture has been proven to be an effective form of pain management, particularly pain of musculoskeletal origin, including TMDs [9, 11–14]. Acupuncture comprises a wide range of treatment techniques, methods of point stimulation, and devices [15]. *Body acupuncture* is the most common type of

acupuncture treatment; it involves the insertion of needles into the selected acupoints, which are manually stimulated by the operator until the achievement of the proper feel of the needling with acupuncture called "Deqi." This method is actually the most investigated in the orofacial pain field, followed by laser acupuncture, as well as different microsystem acupuncture methods, such as ear, scalp, mouth, and fingers [16–20]. *Electroacupuncture* is a form of acupuncture extensively studied for its analgesic effects [21–23]. This technique involves electrical stimulation of needles, and its growing use in pain management is supported by scientific research demonstrating the differential modulation of endogenous opioids by electrical stimulation of varying frequencies [23]. Few studies investigated the effects of electroacupuncture on TMDs-related pain; although it has been proven to provide significant analgesia, its role in the management of TMDs has not been fully established [22, 23]. *Cupping therapy* belongs to traditional Chinese medicine (TCM), dating back at least 2,000 years. It consists in using one of several kinds of cups (bamboo cups, glasses, or earthen cups) placing them on the desired acupoints or sore spots on patients' skin, producing hyperemia or hemostasis, which results in a therapeutic effect [24]. This method resulted to be effective for treating several pain conditions, especially when combined with other treatments, but its use in the orofacial pain field is poorly documented [24, 25]. A single study by Choi et al. [24] analyzed the effect of acupuncture combined with medicated cupping therapy, reporting this method as effective in treating pain related to TMDs.

Although many studies have assessed the significant effects of different types of acupuncture treatment on TMD-related pain, the conclusions are inconsistent. In particular, due to the lack of direct comparison of different methods of treatment, it is not conducive to the choice of clinical application and the implementation of the best treatment. Therefore, the aim of this clinical study was to evaluate and compare the effectiveness of three different methods of acupuncture treatment (body acupuncture, electroacupuncture, and acupuncture + cupping) in alleviating pain and their interference in common activities and quality of life of patients affected by temporomandibular disorders.

2. Materials and Methods

This clinical study was conducted at the Clinical Gnathology Unit of the Department of Oral and Maxillofacial Sciences at the "Sapienza" University of Rome. The study was approved by the Institutional Ethics Committee (N.47/19/0001155); all patients signed an informed consent document before participating in the study.

During the period of February 2019–March 2021, 466 subjects under observation in our department were assessed for eligibility. All patients were screened for temporomandibular disorder (TMD) by specialists in the field and calibrated in using the DC/TMD diagnostic criteria [1]. Criteria for inclusion in the study were as follows: (1) diagnosis of at least one of the following kinds of pain at the craniocervicomandibular level, according to the DC/TMD clinical assessment procedure for the differentiation of pain location in the craniofacial area [1]: TMJ pain, masticatory muscle pain, headache, and neck pain; (2) diagnosis of at least one of the following TMDs (according to Axis I of DC/TMD classification): Myalgia (ICD-9 729.1), Arthralgia (ICD-9 524.62), Headache Attributed to TMD (ICD-9 339.89, ICD-9 784.0), and Disc Displacement with Reduction (ICD-9 524.63); (3) familiar pain intensity greater than or equal to 30 on the verbal numeric scale (VNS); (4) frequency of familiar pain greater than or equal to 1 time/week; and (5) availability to participate in the study. Patients meeting the following exclusion criteria were excluded from the study: (1) diagnosed with widespread pain; (2) chronic use of analgesic medications; (3) diagnosis of Disc Displacement without Reduction Joint disorders (ICD-9 524.63) and/or Degenerative Joint Diseases (ICD-9 715.18); and (4) receiving ongoing gnathological treatment.

2.1. Randomisation and Allocation Concealment. Since there were no data available from other clinical studies about the comparison of different acupuncture methods for the treatment of TMD-related pain, patients were recruited using convenience sampling. The patients who met the inclusion criteria were assigned randomly to three different acupuncture treatment groups. An independent investigator used a random number generator (Research Randomizer©) to allocate participants into each group by block randomisation in a 1 : 1 : 1 ratio. The results of random allocation were sealed, such that they cannot be seen from outside, stored, and managed at the Clinical Gnathology Unit. Before treatment, a random envelope was opened in front of the enrolled participant by the treatment provider. The random allocation numbers assigned to each group were recorded in an electronic chart, and no changes were allowed after allocation.

2.2. Blinding. Given the characteristics of the treatments, this study does not allow the participant or treatment provider to be blinded to their group; thus we used a single-blinded design, where only the assessors were blinded. Participants were assessed away from the acupuncture treatment area by investigators who did not participate in treatment procedures and were blinded to the treatment group. The statistician was not involved in randomisation and analyzed the data without having access to information about allocation.

2.3. Acupuncture Treatment Groups. The treatment protocol was developed according to the treatment methods used in traditional Chinese medicine (TCM) [14, 15], with the selection of application points based on TCM principles and previous studies [16, 18, 22, 25].

2.3.1. Body Acupuncture (BA Group). Patients assigned to the first group were treated with body acupuncture (BA). The acupuncture points used were ST6 (Jiache), ST7 (Xiaguan), GB20 (Fengchi), BL10 (Tianzhu), LI4 (Hegu), ST36

(Zusanli), SP6 (Sanyinjiao), and LR3 (Taichong). After asepsis of the skin with 70% alcohol at the needle penetration site, the needles were inserted bilaterally. The needles were disposable and sterilized, individually packed, with size of 0.25×25 mm (TEWA, asia-med GmbH, Pullach, Bavaria, Germany). The depth of needle penetration varied considering the anatomical differences of the application sites in each patient. The needle was manipulated clockwise and counterclockwise to achieve the proper feel of needling with acupuncture called "Deqi."

2.3.2. Electroacupuncture (EA Group). Patients assigned to the second group were treated with electroacupuncture (EA). The acupuncture points used in this group were the same acupoints selected in the BA Group, as well as the needle penetration procedure and timing, and the needle's size and characteristics. In the EA group, an electrical apparatus (Hwato SDZ-II, Suzhou Medical Appliance Factory, Suzhou, Jiangsu, China) producing a dense-dispersed wave with a frequency of 1/100 Hz was connected to the needles with alligator clips to stimulate pairs of needles inserted at ST36-SP6 and LI4-GB20. The fixed current intensity was uniformly 0.2 mA.

2.3.3. Acupuncture + Cupping (CA Group). Patients assigned to the third group were treated with acupuncture combined with cupping therapy (CA). The acupuncture points used in this group were the same acupoints selected in BA and EA groups, as well as the needle penetration procedure and timing, and the needle's size and characteristics. In the CA group, at the end of the body acupuncture session, the cupping was carried out with sterile glass cups (Mayfair Medical Supplies Ltd., Kowloon, Hong Kong, China), with size of 3 cm, at the affected side, in correspondence to the acupoints ST6 and ST7. According to the classical method of "retained cupping," the practitioner used the flaming heating power to achieve suction; the glass cups were retained for about 1-2 minutes and then were detached. The cupping procedure was carried out repeatedly for 10 min.

In all groups (BA, EA, and CA), the needles remained in place for 30 minutes and were then removed. The therapies consist of 8 sessions, administered over 4 weeks, twice a week. The needles were inserted by the same licensed acupuncturist and specialist in orofacial pain with 7-year experience (E. S.) in all treatment groups.

2.4. Outcome Measures and Data Analysis. The symptoms evaluated for all patients were the following: temporomandibular joint (TMJ) pain, masticatory muscle pain, headache, and neck pain. Each type of pain was measured at the following times:

(i) T0: Baseline, before acupuncture treatment

(ii) T1: End of treatment, 4 weeks after T0 (after the last acupuncture session)

(iii) T2: Short-term follow-up, 4 weeks after T1

The 0–100 verbal numeric scale (VNS) was used to measure pain self-assessment, with 0 indicating "no pain" and 100 "the worst imaginable pain."

At the same times (T0, T1, and T2), all patients completed the following questionnaires, in order to evaluate the general pain-related disability and the impression of the treatment's effectiveness: Brief Inventory Pain (BPI) and Patients' Global Impression of Improvement (PGI-I) Scale [1].

The primary outcome of interest was the pain level and its variation over T0, T1, and T2 in all groups. The secondary outcomes were general pain-related disability (BPI) and the patient's impression of the treatment's effectiveness (PGI-I).

Data analysis was performed with SPSS (version 23) statistical processing software. Descriptive analyses and the Chi-square test were used to compare the patient characteristics. One-way ANOVA on ranks (Kruskal-Wallis test) was used to test differences at the same time interval between groups. Bonferroni-corrected post hoc tests were used for multiple comparisons. Friedman test was used to test changes over three time intervals in the same group. Comparisons of two time intervals were performed with the Wilcoxon signed-rank test. The level of significance was set at $p < 0.05$.

3. Results

376 patients were excluded according to the inclusion/exclusion criteria. The resulting study sample consisted of 90 patients, 28 males (31.1%) and 62 females (68.9%), with an average age of 46.93 years. The patient enrollment and intervention process followed the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) criteria and is shown in Figure 1.

From the expected sample of 90 suitable patients, 30 were excluded from the analysis for discontinued intervention, mainly due to the impossibility in providing acupuncture treatments caused by COVID-19 pandemic in the period of March–November 2020 (Figure 1).

The resulting study sample therefore consisted of 60 patients (20 patients in each group). The baseline characteristics of the study groups, including age and gender, are shown in Table 1. There were no differences between the groups in terms of baseline characteristics ($p > 0.05$) (Table 1).

No significant adverse effects were seen with respect to the procedure itself. A total of two adverse events were recorded: 12 in the EA group (4 needling pain after treatment and 8 hematomas), 10 in the BA group (3 needling pain after treatment and 7 hematomas), and 11 hematomas in the CA group. These adverse events could remit spontaneously within 1 week. No other side effects or complications were evident and all patients tolerated the treatment well.

3.1. Evaluation of Pain Scores. The baseline pain VNS scores in the three groups were comparable for all different pains considered (all $p > 0.05$) (Table 1).

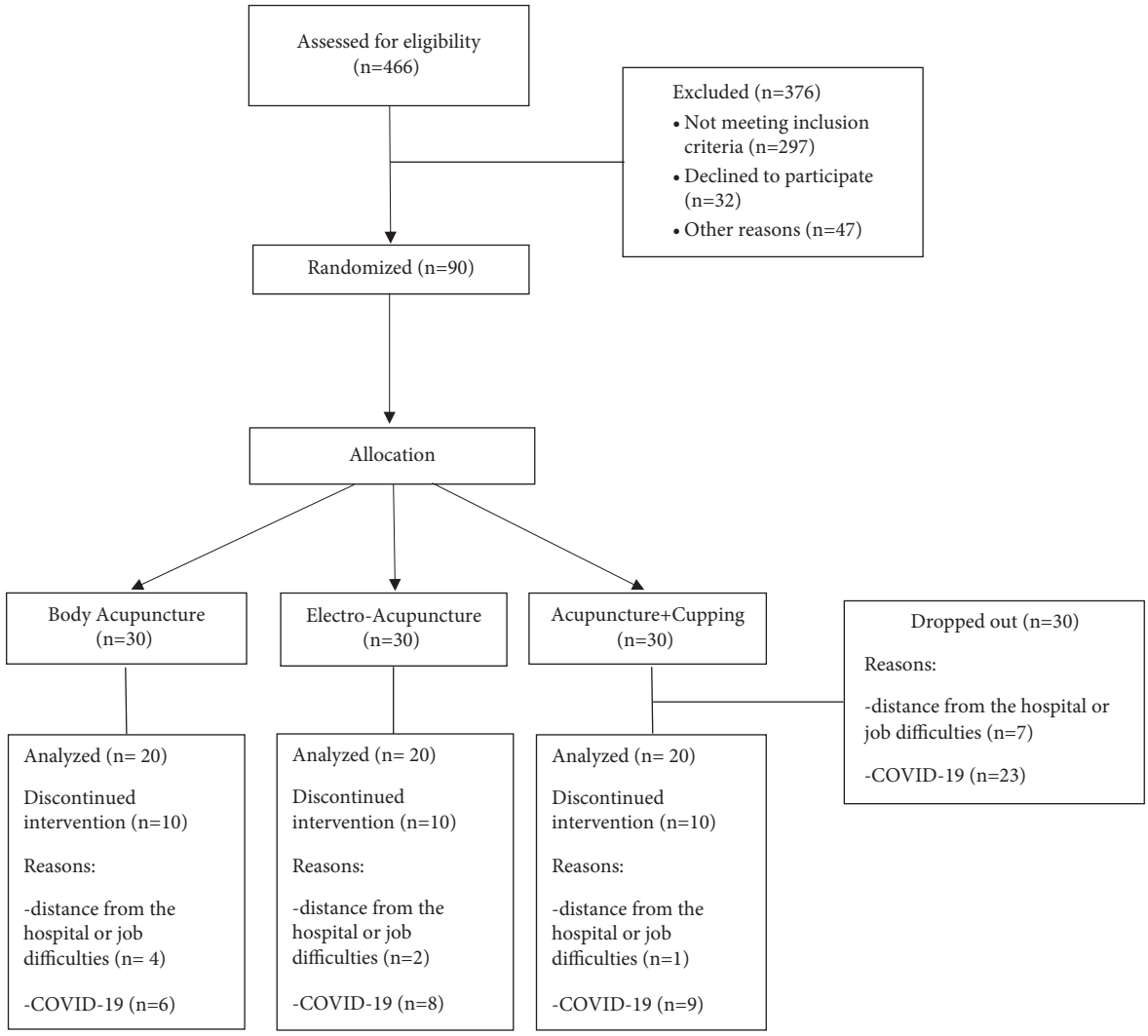

Figure 1: Flow diagram of patient enrollment and interventions.

After the treatments (T1) and during the subsequent follow-up visit (T2), no significant differences were observed between the groups (all $p > 0.05$).

Figure 2 shows the quantitative results related to pain (VNS scale), subdivided by the four types of pain analyzed (TMJ pain, masticatory muscle pain, headache, and neck pain). These results show that, in each acupuncture treatment group analyzed (BA, EA, and CA), pain shows average lower values after the treatment (T1) and at the follow-up visits (T2), compared to T0 (Figure 2).

Within-group analyses showed significant improvements in pain VNS values at T1 and T2 compared to baseline values (T0) in all study groups (all $p < 0.05$), except for TMJ pain in EA group and muscle pain in BA group (Table 2).

Wilcoxon signed-rank test for the comparison of baseline (T0) and after treatment (T1) scores and follow-up (T2) scores resulted to be significant in all study groups for all types of pain considered (all $p < 0.05$) and particularly significant for headache (all $p < 0.001$) and neck pain ($p < 0.001$ in EA and CA groups). The results of this analysis and the exact p values are shown in Table 2.

3.2. Evaluation of Pain-Related Disability (BPI). Concerning the evaluation of the pain-related interference in the patient's common activities and quality of life after the treatment (T1) and during the subsequent follow-up visit (T2), no significant differences were observed between the groups (all $p > 0.05$), except for the variable mood ($p = 0.015$). Interference values were significantly higher in BA and CA groups than in EA group for the variables "mood" and "relations with other people" after the treatment (T1) and at follow-up visit (T2) (Table 3).

Within-group analyses showed significant improvements in interference values at T1 and T2 compared to baseline values (T0) in all study groups (all $p < 0.05$), except for the variable "walking ability" (Table 3).

Wilcoxon signed-rank test for the comparison of baseline (T0) and after treatment (T1) scores and follow-up (T2) scores resulted to be significant in all study groups for all variables considered (all $p < 0.05$), except for the variable "walking ability." It resulted to be particularly significant for the variables "general activity," "mood," and "sleep"

Table 1: Baseline characteristics of the participants.

Characteristics		Groups			*p* value
		BA group ($n = 20$)	EA group ($n = 20$)	CA group ($n = 20$)	
Age, years, mean (SD)		48.25 (15.7)	38.50 (13.67)	48.05 (14.06)	0.0609*
Initial pain (VNS), mean (SD)	TMJ	38.75 (38.45)	31.00 (42.66)	24.5 (33.95)	0.5076*
	Masticatory muscle	34.00 (37.79)	33.50 (38.45)	39.5 (38.72)	0.8960*
	Head	63.25 (31.13)	69.00 (25.73)	56.00 (32.83)	0.3966*
	Neck	64.75 (33.54)	64.5 (36.77)	59.25 (33.65)	0.8522*
Gender, number (%)	Female	17 (85)	16 (80)	17 (85)	0.8869**
	Male	3 (15)	4 (20)	3 (15)	
TMD diagnosis, number (%)	Arthralgia	6 (30)	3 (15)	7 (35)	0.4181**
	Myalgia	13 (65)	13 (65)	8 (40)	
	DDWR[a]	3 (15)	6 (30)	5 (25)	
Side, number (%)	Right	3 (15)	2 (10)	1 (5)	0.5362**
	Left	3 (15)	1 (5)	1(5)	
	Both	14 (70)	17 (85)	18 (90)	

BA group, body acupuncture treatment; EA group, electroacupuncture treatment; CA group, acupuncture + cupping treatment. [a]Disc Displacement with Reduction. *p value for the comparison of the age and pain distributions among groups (one-way ANOVA). **p value for the comparison of the gender, diagnosis, and side distributions among groups (Chi-square test).

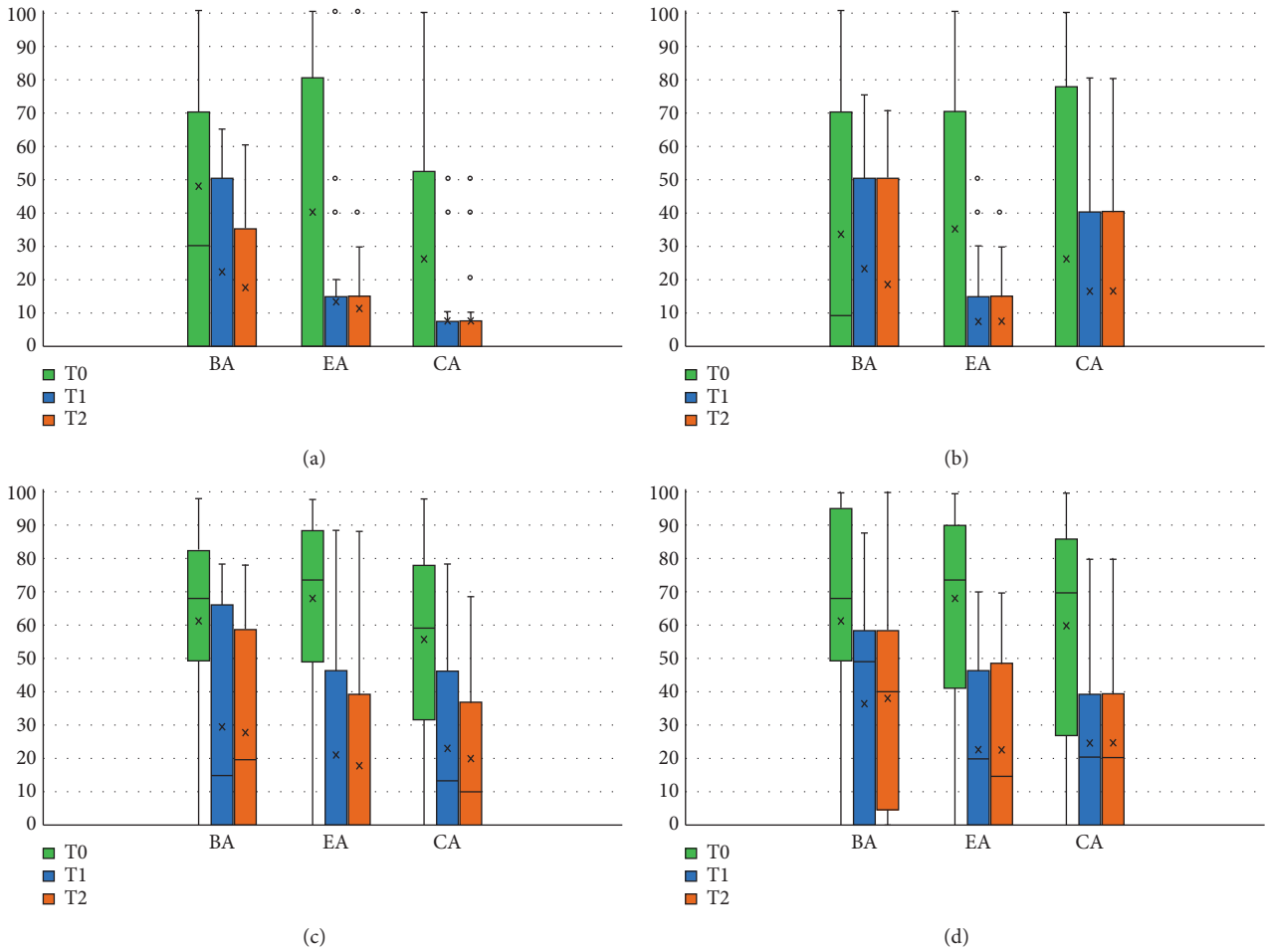

Figure 2: Pain distribution between BA, EA, and CA at T0, T1, AND T2: (a) TMJ pain; (b) muscle pain; (c) headache; (d) neck pain.

Table 2: Comparisons of pain scores (VNS) within groups after acupuncture treatments (T1) and follow-up visit (T2) ($n = 20$ in each group); mean ± SD values.

Group	T0	T1	T2	P_T	$P_{0\text{-}1}$	$P_{0\text{-}2}$
TMJ pain						
BA group	38.75 ± 38.45	18.00 ± 24.46	16.00 ± 22.57	**0.004**	**0.002**	**0.002**
EA group	31.00 ± 42.66	13.00 ± 26.77	11.00 ± 24.47	0.247	**0.035**	**0.035**
CA group	24.50 ± 33.96	8.00 ± 17.04	6.50 ± 14.24	**0.047**	**0.008**	**0.009**
Masticatory muscle pain						
BA group	34.00 ± 37.79	22.50 ± 28.40	21.00 ± 27.51	0.118	**0.022**	**0.014**
EA group	35.50 ± 38.45	9.00 ± 16.83	8.00 ± 14.72	**0.047**	**0.009**	**0.009**
CA group	39.50 ± 38.73	16.50 ± 25.19	16.00 ± 24.58	**0.004**	**0.002**	**0.002**
Headache						
BA group	63.25 ± 31.13	30.50 ± 32.84	28.50 ± 31.00	**≤0.001**	**≤0.001**	**≤0.001**
EA group	69.00 ± 25.73	22.50 ± 28.45	17.50 ± 26.73	**≤0.001**	**≤0.001**	**≤0.001**
CA group	56.00 ± 32.83	22.50 ± 25.31	19.00 ± 22.92	**≤0.001**	**≤0.001**	**≤0.001**
Neck pain						
BA group	64.75 ± 33.54	37.50 ± 31.44	38.50 ± 32.00	**0.003**	**0.002**	**0.004**
EA group	64.50 ± 36.77	24.00 ± 25.42	23.50 ± 25.19	**≤0.001**	**≤0.001**	**≤0.001**
CA group	59.25 ± 33.65	24.50 ± 25.02	25.00 ± 24.39	**≤0.001**	**≤0.001**	**≤0.001**

VNS, verbal numeric scale; SD, standard deviation. BA group, body acupuncture; EA group, electroacupuncture; CA group, acupuncture + cupping. P_T, p value for the within-group comparison (Friedman test); $P_{0\text{-}1}$, p value for the comparison of baseline (T0) and after 4 weeks (T1) scores (Wilcoxon signed-rank test); $P_{0\text{-}2}$, p value for the comparison of baseline (T0) and after 8 weeks (T2) scores (Wilcoxon signed-rank test).

($p < 0.001$) in EA and CA groups. The results of this analysis and the exact p values are shown in Table 3.

3.3. Treatment Effectiveness (PGI-I). The results of patients' self-evaluation of treatment effectiveness using the PGI-I Scale are shown in Table 4.

4. Discussion

The present study compared the effectiveness of body acupuncture, electroacupuncture, and a combination of body acupuncture with cupping therapy in the treatment of the main types of TMD-related pain: TMJ pain, masticatory muscle pain, headache, and neck pain. Based on the results, all three treatment methods yielded significantly improved outcomes regarding all types of pain considered compared to baseline, reinforcing the evidence that acupuncture is an effective treatment in patients suffering from pain with TMD origin. No significant differences emerged from the between-group analysis, suggesting that there is no specific guidance in selecting one of these three methods based on the TMD-related pain to be treated and thus the referral diagnosis. These results may be explained by the fact that, in the three study groups, different methods of needle stimulation were applied to the same acupuncture points (acupoints) in order to evaluate any differences based only on the type of needle stimulation, not on the treatment principle or scheme. In light of the TCM principle of "treating with the least effort," using the classical somatic acupuncture stimulation alone can be effective in improving the pain symptoms of the dysfunctional patient. Moreover, body acupuncture does not require any accessory tool/instrument unlike the other two methods used, resulting to be the most easily accessible and the most favorable in terms of cost/benefit. However, despite the lack of evidence of statistical significance, several differences can be highlighted among the results obtained in the three study groups, depending on the type of pain treated.

Body acupuncture represents the classic and most common stimulation method of acupuncture and the most frequently mentioned for the treatment of orofacial pain. It involves the insertion of needles into the selected acupoints, which are manually stimulated by the operator. *Zotelli* et al. [17] verified the effectiveness of body acupuncture in the treatment of pain of muscular and mixed origin in patients with TMD, showing an improvement of pain in the treated patients. A review by *Fernandez et al.* [16] evaluated the effectiveness of various body and laser acupuncture treatments for temporomandibular disorder myofascial pain, showing that both of these techniques can be effective in relieving patients' signs and symptoms. These findings are consistent with those of the present study, since the patients belonging to the BA group reported a remarkable decrease of all types of pain analyzed. Although the therapeutic efficacy of body acupuncture is mostly reported on muscle pain, in this study, it was the only type of pain that did not exhibit a statistically significant decrease when comparing the patient's average values both after treatment (T1) and at the subsequent follow-up visit (T2) ($P_T = 0.118$). Furthermore, patients of the BA group reported statistically significantly lower average values of TMJ pain ($P_T = 0.004$) overall, compared with patients of the CA group ($P_T = 0.047$) and especially those of the EA group ($P_T = 0.247$). Only one previous study by *Corcos and Brandwein (1976)* focused on the effects of body acupuncture treatment for pain related to the temporomandibular joint in 46 patients affected by rheumatoid arthritis and osteoarthritis. This study also pointed out the value of the body acupuncture method in improving TMJ pain [26]. The other two study groups (CA group and EA group) were characterized by the use of the same therapeutic scheme and procedure as the BA group but

Table 3: Comparisons of the results of the BPI questionnaire between and within groups *after acupuncture treatments (T1) and at follow-up visit (T2) (n = 20 in each group)*; mean ± SD values.

Group	T0	T1	T2	P_T	P_{0-1}	P_{0-2}
A. General activity						
BA group	4.45 ± 3.53	2.30 ± 2.66	2.40 ± 2.72	**0.002**	**0.002**	**0.002**
EA group	4.25 ± 2.99	2.00 ± 2.69	1.75 ± 2.40	**≤0.001**	**≤0.001**	**≤0.001**
CA group	4.45 ± 2.11	2.35 ± 2.18	2.45 ± 2.37	**≤0.001**	**≤0.001**	**≤0.001**
p^*	0.954	0.678	0.529			
P_{1-2}	0.785	0.587	0.469			
P_{1-3}	0.870	0.782	0.803			
P_{2-3}	0.838	0.374	0.249			
B. Mood						
BA group	6.25 ± 3.07	3.40 ± 2.94	3.25 ± 2.65	**≤0.001**	**≤0.001**	**≤0.001**
EA group	5.30 ± 2.96	2.05 ± 2.33	1.75 ± 1.94	**≤0.001**	**≤0.001**	**≤0.001**
CA group	6.25 ± 2.29	3.30 ± 2.25	3.35 ± 2.32	**≤0.001**	**≤0.001**	**≤0.001**
p^*	0.561	**0.015**	0.059			
P_{1-2}	0.279	**0.023**	0.074			
P_{1-3}	0.623	0.830	0.816			
P_{2-3}	0.576	**0.007**	**0.022**			
C. Walking ability						
BA group	3.05 ± 3.68	1.40 ± 2.66	1.45 ± 2.78	0.089	0.175	0.196
EA group	1.45 ± 2.50	0.60 ± 1.14	0.60 ± 1.14	0.549	0.491	0.491
CA group	2.30 ± 2.87	1.20 ± 1.85	1.20 ± 1.85	0.091	0.252	0.252
p^*	0.337	0.675	0.675			
P_{1-2}	0.156	0.582	0.582			
P_{1-3}	0.671	0.922	0.922			
P_{2-3}	0.276	0.340	0.340			
D. Normal work						
BA group	4.10 ± 3.51	2.30 ± 3.06	2.35 ± 3.12	**0.011**	**0.003**	**0.004**
EA group	3.60 ± 3.22	1.75 ± 2.47	1.65 ± 2.28	**0.011**	**0.004**	**0.002**
CA group	4.00 ± 2.83	2.00 ± 2.27	2.30 ± 2.41	**≤0.001**	**≤0.001**	**0.003**
p^*	0.154	0.875	0.582			
P_{1-2}	0.097	0.677	0.589			
P_{1-3}	0.097	0.988	0.673			
P_{2-3}	1	0.641	0.284			
E. Relations with other people						
BA group	3.95 ± 3.17	2.15 ± 2.60	2.30 ± 2.77	**0.023**	**0.005**	**0.005**
EA group	2.60 ± 2.76	1.05 ± 1.67	1.10 ± 1.55	**0.048**	**0.007**	**0.008**
CA group	3.70 ± 2.30	2.60 ± 2.54	2.70 ± 2.72	**0.010**	**0.003**	**0.006**
p^*	0.266	0.092	0.186			
P_{1-2}	0.193	0.239	0.390			
P_{1-3}	0.753	0.364	0.443			
P_{2-3}	0.132	**0.026**	0.053			
F. Sleep						
BA group	4.80 ± 3.30	2.95 ± 2.84	3.10 ± 2.83	**≤0.001**	**≤0.001**	**≤0.001**
EA group	4.50 ± 3.47	0.95 ± 1.05	1.75 ± 1.77	**≤0.001**	**≤0.001**	**≤0.001**
CA group	5.05 ± 3.14	3.65 ± 3.12	3.95 ± 3.05	**0.023**	**0.004**	**0.017**
p^*	0.874	**0.014**	0.062			
P_{1-2}	0.775	**0.024**	0.155			
P_{1-3}	0.796	0.484	0.317			
P_{2-3}	0.614	**0.007**	**0.022**			
G. Enjoyment of life						
BA group	5.05 ± 3.89	3.35 ± 3.98	3.35 ± 3.98	**0.047**	**0.015**	**0.015**
EA group	3.05 ± 3.27	1.35 ± 2.50	1.40 ± 2.54	**0.023**	**0.005**	**0.005**
CA group	3.65 ± 3.12	2.30 ± 2.49	2.40 ± 2.68	**≤0.001**	**≤0.001**	**≤0.001**
p^*	0.222	0.210	0.224			
P_{1-2}	0.101	0.142	0.147			
P_{1-3}	0.281	0.757	0.790			
P_{2-3}	0.419	0.107	0.118			

VNS, verbal numeric scale; SD, standard deviation. BA group, body acupuncture; EA group, electroacupuncture; CA group, acupuncture + cupping. p^*, p value for the comparison among groups (one-way ANOVA on ranks); P_{1-2}, p value for multiple comparisons of BA group and EA group (Bonferroni-corrected post hoc test); P_{1-3}, p value for multiple comparisons of BA group and CA group (Bonferroni-corrected post hoc test); P_{2-3}, p value for multiple comparisons of EA group and CA group (Bonferroni-corrected post hoc test). P_T, p value for the within-group comparison (Friedman test); P_{0-1}, p value for the comparison of baseline (T0) and after 4 weeks (T1) scores (Wilcoxon signed-rank test); P_{0-2}, p value for the comparison of baseline (T0) and after 8 weeks (T2) scores (Wilcoxon signed-rank test).

Table 4: Patients' impression of the effectiveness of treatment of the entire study population, according to the PGI-I scale, *after acupuncture treatments (T1) and at follow-up visit (T2) (n = 60)*; Pt *n* (%).

Patients' impression of the treatment	T1	T2
Very much worse	0 (0%)	0 (0%)
Much worse	0 (0%)	0 (0%)
A little worse	0 (0%)	0 (0%)
No change	9 (15%)	11 (18.3%)
A little better	16 (26.7%)	16 (26.7%)
Much better	17 (28.3%)	16 (26.7%)
Very much better	18 (30%)	17 (28.3%)

adding a "supplemental" stimulation to the selected acupoints. From the results obtained, this addition seems to determine a greater effectiveness in the treatment of pain and especially for headache and neck pain (all $p < 0.001$). Furthermore, both patients belonging to the EA and CA groups reported more significant results compared to patients treated with body acupuncture alone for all types of pain considered, except for TMJ pain.

The addition of *cupping therapy* to body acupuncture was found to be the most effective treatment method in the management of muscle pain. This evidence is consistent with the majority of systematic reviews and RCTs to date which suggest a favorable effect of cupping for pain, especially tension headache and musculoskeletal pain [24]. The negative pressure applied to the skin during the cupping procedure has been proven to induce muscle relaxation and changes in local tissue structures and in blood circulation, significantly reducing peripheral and local P substance and inflammation and thus resulting in pain reduction [24]. *Han* et al. [25] compared the therapeutic effect of medicated cupping and acupuncture combined with medicated cupping in 120 TMD patients, reporting a significant improvement of TMDs' signs and symptoms in both groups after a treatment course of 10 days ($p < 0.01$). In line with the present study, the authors suggested that the combination of the two treatments leads to superior clinical outcomes, compared to the use of single medicated cupping therapy. However, it is difficult to make a comprehensive comparison with the results obtained in this research. The authors did not specify the type of pain treated or the TMD diagnosis of these patients; moreover, the cupping therapy procedure involved the addition of medicinal herbal substances.

To our knowledge, this is the first study to analyze the effects of the classic technique of dry retention cupping combined with acupuncture on the most common types of pain associated with TMD. Given the positive results obtained, the need for further studies becomes evident to deepen and better define the therapeutic potential of this ancient medical practice in relieving pain related to TMD.

Electroacupuncture is considered a particularly effective method of acupuncture for the treatment of persistent tissue and nerve injuries, chronic pain, and visceral pain, as addressed by several research studies conducted within the last decade [21, 22, 27]. Zhang et al. [27] suggested that the electroacupuncture mechanism of action in relieving pain is the result of activation or inhibition of various bioactive chemicals in peripheral, spinal, and supraspinal pathways. Despite its popularity in pain management, few studies investigated the clinical effects of electroacupuncture on TMD-related pain. A literature search by *Kuo* et al. [22] yielded to nine publications from Chinese practitioners concerning the use of electroacupuncture for treating TMD symptoms, and all of them reported analgesic efficacy in the treatment of pain, especially of muscular origin. However, the authors highlighted the inconsistency in most of these studies, accentuating the need for more well-designed and long-term studies in this research area. The results obtained in the present study agree with these few lines of evidence, pointing out that this method was particularly effective in reducing pain of muscle origin, as well as headache and neck pain.

While evaluating the effectiveness of treatment methods for TMD, the psychological and emotional status of the patients, as well as their functioning in daily activities, should also be considered. Numerous studies highlighted the association between pain and some social, emotional, and psychological features influencing the quality of life of people affected by TMD [28–30]. Moreover, a particular interest is shown to deepen the correlations between TMD-related pain and quality of sleep and insomnia. When compared to pain-free controls, TMD patients exhibited poorer sleep quality and were mainly categorized as poor sleepers [31, 32]. In addition, poorer sleep quality has been associated with coexisting headaches, body pain, clenching habit, and reduced mouth opening [33]. Connections between mood disorders and TMD were also investigated. Several studies reported high prevalence of symptoms such as anxiety, hostility, anger, paranoid ideation, and especially depression in patients affected by TMD, in particular of muscular origin [34–36]. The presence of depressive symptoms in TMD patients was reported to be related to the presence of a painful condition [36]; the onset or the exacerbation of sufferance and pain in these patients could be generated and perpetuated by the presence of such psychological aspects [34]. In the present study, the impact of pain on all considered activities and quality of life aspects was found to be significantly decreased after the acupuncture treatment and in the short-term follow-up in all three study groups, except for the aspect of "walking ability." In particular, electroacupuncture was found to be effective in improving the influence of pain on the patient's quality of sleep and mood, with a statistically significant difference compared to body acupuncture and acupuncture combined with cupping. These results are consistent with the evidence defining EA as an effective therapeutic intervention for patients with anxiety, depression, and primary insomnia, capable of improving patients' life and sleep quality without serious adverse effects [37–41]. A multidisciplinary therapeutic approach is needed to address all factors, including sleep and mood alterations, which modulate pain experience. The results of this study indicate that acupuncture, especially electroacupuncture, rehabilitated the patients' ability to perform daily work activities, sleep quality, and emotional and social aspects, rapidly and effectively, up to 1 month after treatment.

Strengths of the present study include the randomized allocation of participants to the treatment groups, the follow-up recording, the differentiation of four types of TMD-related pain recorded, the evaluation of the participants' disability in common activities and quality of life by means of a validated questionnaire, and the evaluation of different methods of stimulation of acupoints using the same therapeutic scheme. Possible weaknesses of the study were the sample size and the duration of the acupuncture treatment. Acupuncture comprises several acupoint stimulation methods, treatment patterns, and timing, allowing the application of individualized therapies. Due to its versatility and special effectiveness in multifactorial diseases, acupuncture is particularly suitable for the treatment of TMD-related pain, which in turn is characterized by a very complex and varied symptomatology. For these reasons, despite the positive results obtained, we think that the patient sample size examined is too limited to present reliable results regarding the comparison of the effectiveness of three different acupuncture methods in reducing TMD-related symptoms. Furthermore, our results correspond to a single course of 4 weeks of therapy. Due to the tendency of TMD to become chronic, a prolonged course evaluation with additional long-term follow-up is necessary.

5. Conclusions

(i) Body acupuncture, electroacupuncture, and acupuncture combined with cupping therapy are all effective methods in reducing pain and pain interference with common activities and quality of life in patients affected by TMD.

(ii) For the first time, the classical method of retained cupping is reported to be effective in the management of TMD-related pain, when combined with body acupuncture.

(iii) Electroacupuncture reduces the interference of pain in patients' mood and sleep quality more effectively than body acupuncture alone or combination with cupping therapy.

(iv) Further studies are needed to confirm the results obtained and to better define the eligibility of one of these methods in improving the complex symptomatology connected with TMD.

Data Availability

All the data are contained and described within the manuscript. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors report no conflicts of interest in this work.

Supplementary Materials

Table 4: STRICTA 2010 checklist of information to include when reporting interventions in a clinical trial of acupuncture (Expansion of Item 5 from CONSORT 2010 checklist). Table 5: CONSORT 2010 checklist with the Nonpharmacological Trials Extension to CONSORT (with STRICTA 2010 extending CONSORT Item 5 for acupuncture trials). (*Supplementary Materials*)

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Research Article

Perceived Pain during Rapid Maxillary Expansion (RME): Trends, Anatomical Distinctions, and Age and Gender Correlations

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Objectives. To investigate pain trends and characteristics of different facial districts in patients undergoing rapid maxillary expansion (RME) and its possible correlations with age and gender. *Materials and Methods*. 85 subjects (45 males and 40 females) undergoing RME were selected and analyzed during first two weeks of treatment. Patients rated daily two types of pain perception: the general perceived pain (GPP), i.e., the pain overall perceived in the face, and the local perceived pain (LPP), i.e., the pain perceived locally in the following anatomical areas: anterior palate (APA), posterior palate (PPA), nasal (NA), joint (JA), and zygomatic (ZA). Patients were provided the Numeric Rating Scale (NRS) and Wong–Baker Faces Pain Rating Scale (FPS) to correctly assess their GPP and LPP. Pearson correlation coefficient and analysis of variance (ANOVA) were, respectively, used to define the linear relationship between all the variables considered and to verify whether the response variables (gender and age) were significantly different ($\alpha < 0.05$). *Results*. Sample's mean age was 10.11 years. Average pain values of GPP and LPP progressively rise from day 1 to days 2-3 (pain peak) and tended to decrease until day 14, with a linear decrease for GPP and a not linear decrease for LPP. PPA and APA resulted the most painful areas, followed, respectively, by JA, ZA, and NA. Statistically significant differences resulted in average pain values according to patients' age and gender, both in GPP and LPP. *Conclusion*. RME causes perception of pain in several maxillofacial areas. Pain reported during RME resulted positively correlated with age and gender of patients.

1. Introduction

Fear of suffering is often a major deterrent against beginning an orthodontic treatment and is the primary cause of discontinuity and lack of compliance in patients undergoing long-term procedures [1]. Pain and discomfort occur during all types of orthodontic procedures, such as separator placement, archwire placement and activations, application of orthopedic forces, and debonding. Patients wearing fixed appliances reported higher values for intensities of pressure, tension, pain, and teeth sensitivity when compared with patients wearing removable appliances [2]. The greatest levels of discomfort and pain were reported by patients undergoing fixed orthodontic therapies and orthopedic therapies [1, 2]. The active phase of palatal expansion is variable in length, generally lasting 10–14 days, with patients reporting pain mainly during the first days of device activation [1, 2]. Despite the importance of this factor in clinical practice, orthodontic pain is rarely scientifically investigated, especially with regards to common fixed orthodontic therapies, such as rapid maxillary expansion (RME) [3, 4]. Variable amounts of orthopedic force are generated in RME of median palatal sutures. This force is absorbed and propagated in the three planes of the craniofacial complex through tissue displacement and remodeling mechanisms that exert pressure on the bones surrounding the maxilla via cranial and circummaxillary sutures [3, 4]. Analyzing stress and force distribution during RME on craniofacial

structures, Jafari et al. have observed a high level of stress dissemination to all circummaxillary sutures and important bone displacements, not only in the anterior and posterior palate but also in nasal and zygomatic bones [5]. Moreover, with respect to growing age, it has been demonstrated that RME is capable of modifying the condyle-fossa relationship and of affecting the joint area [6].

Several clinical studies have investigated pain related to RME, mostly comparing the use of different activation protocols (2 turns/die vs. 1 turn/die) or of different types of appliances [7, 8]. However, there has been little study of the perception of pain in craniofacial districts other than those that are most heavily loaded, i.e., the palate and upper teeth. The single study (Önçağ et al.) that has examined RME-related pain perception in 5 craniofacial areas (palatal, dental, malar, frontal, and temporal) reported increased pain perception in the dental and palatal areas compared to the others and a significant statistical difference in average pain for all the anatomical districts considered [9].

The aim of this study is to analyze pain trends and characteristics and the possible correlations with age and gender variables, during the first 14 days of RME therapy, observing patient perceived pain not only in the palatal area but also in the nasal, joint, and zygomatic areas.

2. Materials and Methods

A consecutive series of patients under the age of 14 undergoing RME therapy in the Orthodontics Department of the Sapienza University Hospital of Rome were asked to participate in the study, from March 1st to December 27th 2019, a total of 96 patients. The contraction of the maxillary arch and the presence of a mono or bilateral cross-bite were criteria for inclusion. Intellectual disability, metabolic/chronic disease, current use of pain medication, previous orthodontic treatment, or failure to give informed consent by each patient's parents were criteria for exclusion. This study was approved by the Institutional Ethics Committee (N.53/18–0000711), and informed consent was obtained from each patient's parents.

All patients underwent expansion therapy of the upper jaw using a rapid palatal expander (RPE) that was attached to bands on the first maxillary molars with traditional hyrax screws (A0620 SS, manufactured by Leone S.p.A, Florence, Italy). The RPE appliance activation protocol, which lasted 14 days, required 2 activations per day: 1 in the morning and 1 in the evening.

The participants were asked to avoid analgesic medication throughout the activation period; those who took medication of this type during the period of therapy were later excluded from the study.

At the time of positioning of the palate expansion appliance, parents were instructed about the methods and activation times of the appliance. All patients received a pain assessment card and were instructed how to correctly fill out the form, which was then returned once completed. Participants were asked to indicate their pain perception at the end of each day, precisely 30–60 minutes after the second daily activation, for all 14 days of treatment. To minimize participant dropout, patient's parents were asked to set an alarm clock and check the proper compilation of the pain assessment card every day.

Both of the scientifically recognized scales for pain assessment [10, 11], the Numeric Rating Scale (NRS) and the Wong–Baker Faces Pain Rating Scale (FPS), were used; the former was used to evaluate the general pain perceived during the day and the latter to evaluate pain perceived in specific anatomical areas.

General perceived pain (GPP): overall perceived pain during the day. The pain self-assessment scale used was the Numeric Rating Scale (NRS) (Figure 1(a)).

Local perceived pain (LPP): pain perceived during the day related to a specific anatomical zone. The areas considered were the anterior palate area (APA), posterior palate area (PPA), joint area (JA), nasal area (NA), and zygomatic area (ZA) (Figure 1(b)).

The areas were also represented graphically on the card with numbers to facilitate the evaluation (Figure 1(c)). The pain self-assessment scale used was the Wong–Baker Faces Pain Rating Scale (FPS).

2.1. Statistical Analysis. All data obtained were examined using SAS software (version 9.4). Statistical analysis identified several different indicators (mean, median, standard deviation, max and min), which were used to construct a line plot graph to represent the distribution. The Shapiro–Wilk test was used to test the normality assumption of data. A Pearson correlation coefficient was used to define the linear relationship between all the variables considered. Analysis of variance (ANOVA) was used to verify whether the response variables (gender and age) were significantly different. The threshold for statistical significance was set at $\alpha < 0.05$.

3. Results

A total of 96 patients participated in the study. However, 7 subjects were excluded because of incomplete data, and 4 subjects were excluded because they took pain medication during treatment. Thus, the final number of study participants was 85 patients: 45 males and 40 females. The age range was 7–14 years, with a median age of 10.11 years (Table 1).

All patients (100%, $n = 85$) reported general pain (NRS) during the 14 days of the study and in all the anatomical areas examined (FPS). The mean pain range for GPP was from 2.58 (day 14) to 6.17 (day 2), using the NRS scale. The mean pain range for LPP was from 0.23 (ZA_day 11) to 4.82 (PPA_day 2), using the FPS scale.

3.1. General Perceived Pain (GPP). Figure 2 shows the trend and quality of perceived pain, according to the NRS scale. Males reported higher average pain values (5.02_NRS) than females (2.58_NRS) for each day of treatment (Figure 2(b)). On day 2, the highest pain values were reported by both male (6.89_NRS) and female (5.37_NRS) patients.

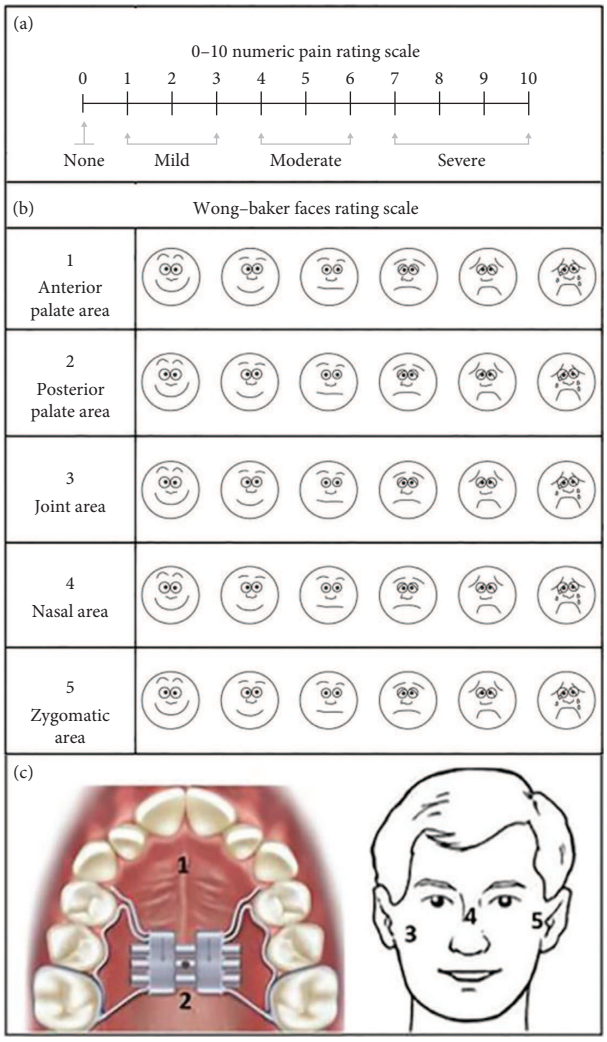

Figure 1: Pain scales used for daily evaluation. (a) NRS. (b) Wong–Baker FPS. (c) Picture used to facilitate patients' identification of anatomical areas.

Table 1: Basic characteristics of the participants and average pain values (FPS) in the different anatomical areas analyzed in the first 2 weeks of treatment.

Characteristics	Subjects		
	Male	Female	Total
Age, years, mean (SD)	10.89 (1.93)	9.25 (1.73)	10.11 (2.00)
Gender, number (%)	45 (53%)	40 (47%)	85 (100%)
Pain values (FPS), mean (SD)			
Anterior palate area (APA)	1.41 (0.27)	2.75 (1.39)	2.04 (0.73)
Posterior palate area (PPA)	1.70 (0.98)	3.43 (1.34)	2.51 (1.11)
Joint area (JA)	1.67 (1.22)	1.64 (0.54)	1.65 (0.82)
Nasal area (NA)	1.30 (0.32)	1.67 (0.66)	1.10 (0.37)
Zygomatic area (ZA)	0.94 (0.33)	1.29 (1.05)	1.19 (0.57)

An age-related analysis reveals differences in pain perception between all ages under investigation. Results for each age group are listed in the decreasing order of average pain values during the 14 days of study (NRS): "13 y" (average = 5.57; 5 Pt.), "12 y" (average = 5.28; 15 Pt.), "11 y" (average = 4.96; 10 Pt.), "14 y" (average = 4.57; 5 Pt.), "10 y" (average = 4.05; 15 Pt.), "9 y" (average = 3.31; 15 Pt.), "7 y" (average = 2.46; 10 Pt.), and "8 y" (average = 1.96; 10 Pt).

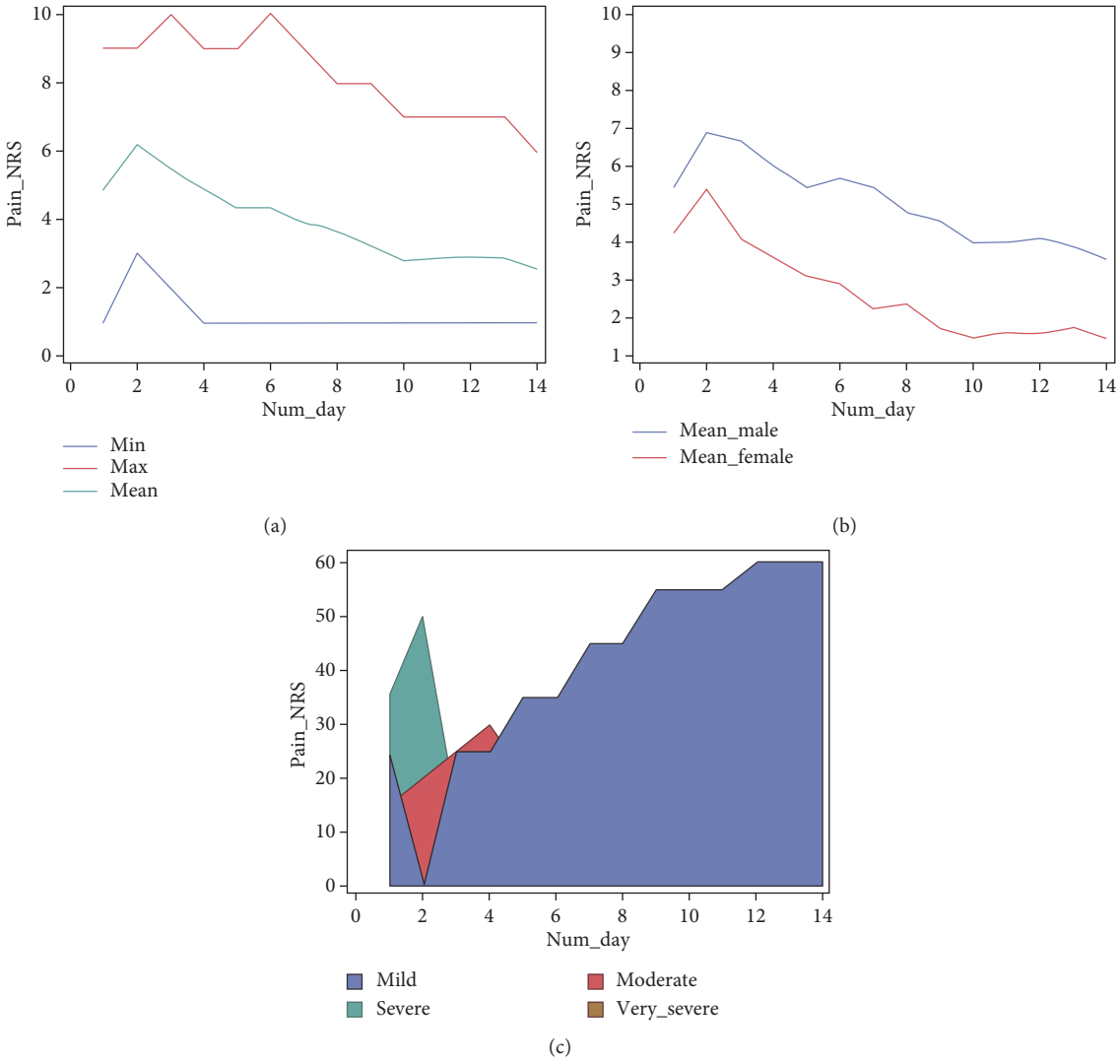

Figure 2: Pain related to RME in the first 2 weeks of treatment according to the NRS scale. (a) Pain values over time in all patients and (b) in male and female patients. (c) Qualitative perception over time in all patients.

The ANOVA t-test supports "gender" and "age" as statistically significant variables ($\alpha < 0.05$).

3.2. Local Perceived Pain (LPP). Figure 3 shows the pain trend in each analyzed area, according to the FPS scale. All the averages by the area are listed in Table 1. Females reported higher pain values than males for every considered area except for JA (Table 1, Figures 3(b) and 3(c)). On days 2 and 3, the highest pain values were reported by both male and female patients, differently according to the anatomical area analyzed. Day 2 resulted the pain peak day for the areas APA (F = 5.25_FPS/M = 1.55_FPS) and PPA (F = 6.25_FPS/M = 3.55_FPS). Day 3 resulted the pain peak day for the areas NA (F = 3.00_FPS/M = 1.33_FPS) and ZA (F = 3.00_FPS/M = 1.11_FPS). Concerning the area JA, day 3 resulted the pain peak day for females (3.00_FPS) and day 2 for males (4.44_FPS).

There were differences in the pain perception of patients of different ages in each of the areas analyzed. Results are listed in Table 2 in a decreasing order, from the age reporting the most pain to the one reporting the least pain during the 14 days of therapy.

The pain trend was not linear across the areas examined, so the "Pearson correlation coefficient" was applied to evaluate whether any linear correlation existed among the different variables. In terms of pain increase, positive linear correlations were found among peak days and several of the following days ($\rho > 0.7$). In particular, there was a strong relationship of dependence among peak days 2 and 3 and days 6 and 8, for all investigated anatomical districts ($0.72 < \rho < 0.94$) (Table 3). It, therefore, was decided to examine these four days more closely. The results of this analysis are listed in Table 4 under Supplementary Materials Section, organized according to gender and age.

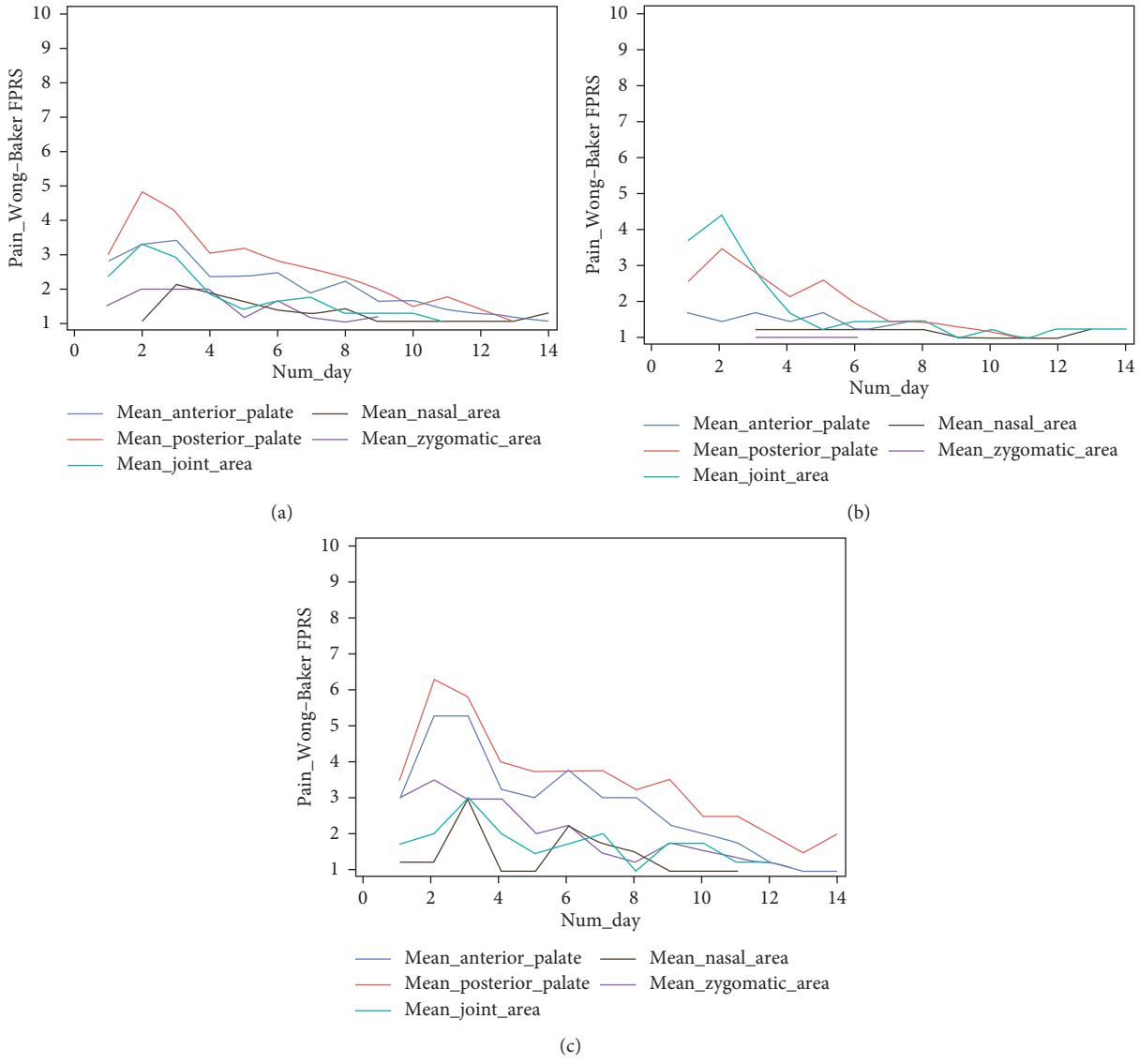

Figure 3: Pain related to RME in the first 2 weeks of treatment according to the Wong–Baker Scale in the different districts analyzed (a) and according to gender: male (b) and female (c).

The ANOVA t-test demonstrated significant differences between the "gender" and "age" variables ($\alpha < 0.05$), except for in JA, where gender was not significant.

Supplementary data related to the ANOVA test analysis of both GPP and LPP are listed in Table 5 under Supplementary Materials Section.

4. Discussion

Clinical studies have demonstrated pain related to RME as a frequent symptom, reported by 66, 12–99% of patients [12, 13]. These data are confirmed by the present study, in which 100% of subjects undergoing RME ($n = 85$) reported pain throughout the entire active phase of therapy (NRS) and in all the examined anatomical districts (FPS).

Analysis of general perceived pain (GPP) indicates pain was greatest during the first 6 days of activation, with a maximum peak at day 2 (NRS: 6, 18) and tended to decrease gradually in the following days; these findings concur with the current literature [7, 13, 14]. However, the quality of RME-related pain reported in our study is not consistent with those of previous studies. Indeed, though GPP pain levels were mostly described as mild throughout the treatment period, they were referred to as moderate or strong by the majority of our participants during the first days of activation. Needleman et al. [7] also reported high pain levels, especially after the first 6 screw turns; during this period, 69% of patients, moreover, had to take pain medication. Geçgelen Cesur and Aksoy [12] indicated moderate pain levels during the initial 7 days of therapy. Two other studies demonstrate pain presence throughout the entire therapy, but with very low reported values [14, 15].

However, our local perceived pain (LPP) analysis resulted in average pain levels inferior to the NRS, with FPS

Table 2: Average pain values (FPS) in the different anatomical areas analyzed in the first 2 weeks of treatment, according to patient age.

Anterior palate (APA)		Posterior palate (PPA)		Joint area (JA)		Nasal area (NA)		Zygomatic area (ZA)	
Average pain*	Patient age	Average pain*	Patient age	Average pain*	Patient age	Average pain*	Patient age	Average pain*	Patient age
3.14 ± 1.70	13	4.36 ± 2.06	8	4.57 ± 1.55	8	4.00 ± 2.22	14	3.68 ± 2.08	14
2.78 ± 1.76	8	3.57 ± 1.70	7	2.48 ± 1.42	9	1.48 ± 0.98	10	1.82 ± 1.31	9
2.64 ± 0.84	7	3.14 ± 1.87	13	1.78 ± 0.58	7	1.44 ± 1.01	11	1.48 ± 1.01	8
2.52 ± 1.69	10	2.48 ± 1.58	10	1.71 ± 1.25	12	1.09 ± 0.49	12	1.33 ± 0.83	10
2.14 ± 0.99	12	2.48 ± 1.53	12	1.14 ± 1.87	14	1.00 ± 1.27	9	1.18 ± 0.66	12
1.21 ± 0.89	11	1.78 ± 0.80	11	0.71 ± 1.81	11	0.43 ± 0.75	7	0.30 ± 0.75	11
1.14 ± 0.89	9	1.43 ± 2.11	9	0.095 ± 0.24	10	0.14 ± 0.53	8	0.01 ± 0.53	7
0.86 ± 1.87	14	1.00 ± 2.04	14	0.00 ± 0.00	13	0.00 ± 0.00	13	0.00 ± 0.00	13

*Mean ± standard deviation.

Table 3: Linear correlations among peak days 2 and 3 and days 6 and 8, for all investigated anatomical districts, according to Pearson correlation coefficient.

—	ρ*	P value**
Anterior palate (APA)		
Day 2_day 6	0.73	<0.0001
Day 2_day 8	0.72	<0.0001
Day 3_day 6	0.83	<0.0001
Day 3_day 8	0.79	<0.0001
Posterior palate (PPA)		
Day 2_day 6	0.74	<0.0001
Day 2_day 8	0.85	<0.0001
Day 3_day 6	0.79	<0.0001
Day 3_day 8	0.72	<0.0001
Joint area (JA)		
Day 2_day 6	0.73	<0.0001
Day 2_day 8	0.77	<0.0001
Day 3_day 6	0.83	<0.0001
Day 3_day 8	0.78	<0.0001
Nasal area (NA)		
Day 2_day 6	0.72	<0.0001
Day 2_day 8	0.74	<0.0001
Day 3_day 6	0.94	<0.0001
Day 3_day 8	0.76	<0.0001
Zygomatic area (ZA)		
Day 2_day 6	0.85	<0.0001
Day 2_day 8	0.76	<0.0001
Day 3_day 6	0.83	<0.0001
Day 3_day 8	0.81	<0.0001

*ρ, Pearson correlation coefficient; positive linear correlation for $0.72 < \rho < 0.94$. **P value <0.0001.

ranging from 1.10 to 2.51. Even painful days (days 2, 3, 6, and 8) resulted in mild discomfort according to this analysis; furthermore, we saw great variability between the anatomical districts examined. These outcomes, together with the conflicting evidence in the existing literature, draw attention to the difficulties surrounding subjective pain evaluation even using validated scales as well as to the necessity of further investigating how other variables (gender, age, psychological factors, and hormonal factors) contribute to pain evaluation and extreme individual variability.

In this regard, interesting gender-related and age-related results were found by this study, including a statistically significant difference between male and female pain perception. While males reported higher pain values than females for GPP (NRS), this evidence was contradicted by their reporting of LPP (FPS). Females, in fact, reported higher LPP (FPS) pain values in all considered facial districts, except the joint area (JA), which is also the only area showing no statistical significance.

Though several clinical studies of RME-related pain have not identified significant gender differences [7, 8, 13], others similarly demonstrate females experiencing significantly more pain than males [14, 15]. Variability in pain perception based on sex and gender has been long debated. Genetic, molecular, physiological, and psychosocial factors contribute to differences in processing pain and pain perception in men and women. In particular, women's threshold for pain is greater, more varied, and more variable than for men.[16]. In a study including children and adolescents, Allen et al. [17] noticed important sex differences in the cortisol-pain relationship. Increase in cortisol was positively associated with greater pain tolerance in males and greater pain sensitivity in females. A literature review by Berkley et al. [16] highlighted the importance of gender in pain perception and inflammation, underlining the influence of hormonal modulation on nociception through factors such as estradiol, menstrual cycle, or the sex-related effects of NSAIDs and ASICs. These findings validate the existence of a gender-related difference in pain perception during RME, though increased sensitivity in females only occurred in LPP.

Our age-related analysis also pointed to significant variations in evaluations of both GPP and LPP. Though studies of pain and its correlation with age and aging show increased perception of discomfort with age, research on the prevalence of pain in children and adolescents displays inconsistent findings, and it is difficult to reach general conclusions concerning pain prevalence and characteristics in this particular population group [18]. Haraldstad et al. [19] reported that pain increases with age, with girls between 16 and 18 reporting the highest discomfort. A study by Blankenburg et al. [20], of perception of different nociceptive stimuli, including pressor and mechanical stimulation, found that children are more sensitive to most painful stimuli than adolescents and also noted that growth-related changes during puberty seem to influence pain perception. At the craniomaxillofacial level, these different pain

perceptions may be explained by tissue and morphological differences in bones structures related to age changes. During craniofacial growth, sutures represent secondary growth centers that respond to mechanical stress with various structural effects: sutural interdigitation becomes more complex with increase in age. Median palatal sutures respond to RME with a greater expansion rate at the age of 8 than in patients who are 12, 13, or 14 years old [2]. In this study, GPP results support the evidence in the literature, with greater reported pain as age increases: patients aged 7-8 reported inferior pain values than older patients; the values reported by patients aged 12-13 were especially high. However, our LPP results show great variability among examined districts as well as highest pain values in patients aged 8 (mean = 2.66) and 14 (mean = 2.14). The lowest values were reported by patients aged 11 (mean = 1.09) and 13 (mean = 1.26).

The differences emerging from comparison of the two analyses may be due to the use of different scales, NRS and FPS, and reflect the findings of previous studies that have also used both [10, 11].

There were also interesting trends our LPP findings on pain location and timing. As expected, the posterior and anterior palate areas resulted in the highest pain values. It is interesting to note that the nasal area, the closest anatomical area and the one experiencing the greatest changes after RME, was the district in which the lowest average pain level was reported. However, some pain was reported for every examined district. Jafari et al. observed the deep anatomical effects of RME appliances, reporting the highest stress levels in the areas of the maxillary bone, zygomatic process, external walls of the orbit, frontozygomatic suture, and the frontal process of maxilla [5]. Interestingly, these areas of high-stress distribution coincide with some of the most painful anatomical districts of this study. These findings are suggestive of the role of circummaxillary sutures in modulating orthodontic pain perception, as a constraint on the transmission of the expansion forces to the other neighbouring anatomical districts.

As with the GPP findings, using the NRS scale, reported LPP pain was greater in the first day of the activation of the appliance, unlike the GPP findings; however, there is no clear linearity in the decrease of LPP pain over time. Various increases in pain values, different for each examined area, were noticed from day 3 to day 14. The pain values reported on days 6 and 8, in particular, were strongly correlated with the peak days, in all the areas considered ($\rho > 0.7$). Some studies on cranial sutures undergoing mechanical stress could explain this pain "reactivation" over time. Cleall et al. [21] reported the presence of highly vascularized connective tissue with moderate chronical inflammation response inside the sutural bone of monkeys undergoing RME after 14 days of treatment. Investigating histological changes in the mean palatine suture in patients undergoing RME, Caprioglio et al. [22] later reported the presence of a highly vascularized and coagulum-rich central osteoid matrix, especially on day 7 of activation. A recent murine study by Wu et al. [23] describes a particular arrangement and orientation of new bone formation in expanding sutures, with the largest volumetric increase on day 7 of expansion. Finally, an interesting investigation by Che et al. [24] on the role of the nonneural cholinergic system in bone remodeling after RME shows increasing values of ACh and an increasing RANK/OPG ratio after 1, 3, and 7 days of expansion. The presence of pronounced bone remodeling phenomena, such as ACh, seems to align with the results about pain development obtained in our study, which indicate days 6 and 8 as the most related to average pain peak days (days 2 and 3). These inflammation processes involve increased molecular expression that we know to be involved in pain modulation.

Despite the interesting results obtained, this study presents some limitations. The patient sample examined is too limited to represent reliable results regarding the characteristics of RME-related pain, especially in connection with patients' age and gender. Furthermore, the pain assessment was limited to patient self-assessment, but the importance of using multiple methods of pain assessment, given the complexity of changes that this symptom can undergo during experimental procedures, especially in a children's population, needs to be emphasized.

5. Conclusions

(i) RME therapy caused pain in the entire study population at the palate, joint, zygomatic, and nasal areas

(ii) Age and gender were positively correlated with overall pain perception and with pain perception in every single area analyzed except the joint area

(iii) In all examined facial areas, perceived pain trends do not decrease linearly; further studies are needed to deeply analyze if bone remodeling and inflammation processes during RME might modulate pain perception over time.

Data Availability

The data used to support the findings of this study are included within the article and the datasets are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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Supplementary Materials

Table 4: Pain levels in the different anatomical areas analyzed on days 2, 3, 6, and 8 (FPS). *Mean ± standard deviation. Table 5: ANOVA procedure supplementary data of NRS and FPS scales analysis, according to age and gender response variables. (*Supplementary Materials*)

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VI

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Auriculotherapy used to manage orthodontic pain: a randomized controlled pilot study

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ABSTRACT

Introduction: Several methods are commonly used to decrease orthodontic pain, but versatile tools and standardized protocols are still lacking.

Objective: In response to the need for alternatives to conventional analgesic methods, this study evaluates the analgesic effects of auriculotherapy (AT) during the first three months of fixed orthodontic treatment.

Methods: A sample of 36 subjects was selected, with patients randomly allocated into two homogeneous groups, Study Group (SG) and Control Group (CG), depending on the application/non-application of AT. Patients rated their pain scores monthly from 0 to 10, on visual analogue scales (VAS) at the time of bonding (T_0) and again at two appliance adjustments (T_1 and T_2). At each of these treatment phases, VAS was applied in six different time moments (TM): immediately before, immediately after, after 4 hours, after 8 hours, after 24 hours, and after 72h hours. Descriptive statistical analysis, a Student's t-test, and a Chi-square test were applied to the collected data (statistical significance for $p < 0.05$).

Results: SG patients reported lower pain levels than CG patients, both at T_0, T_1 and T_2. Moreover, average pain intensity values were lower in the SG for all TM analyzed, with the *t*-test significant ($p < 0.05$) for most TMs.

Conclusion: AT was effective in the pain treatment of patients with fixed orthodontic appliances. Further studies are needed with a sham control group to confirm the validity of these results.

Keywords: Pain. Fixed orthodontic appliance. Auriculotherapy. Acupuncture.

RESUMO

Introdução: Vários métodos são comumente usados para diminuir a dor proveniente do tratamento ortodôntico, mas ainda faltam ferramentas versáteis e com protocolos padronizados.

Objetivo: Em resposta à necessidade de alternativas aos métodos analgésicos convencionais, o presente estudo avalia os efeitos analgésicos da auriculoterapia (AT) durante os primeiros três meses de tratamento ortodôntico com aparelhos fixos.

Métodos: Foi selecionada uma amostra de 36 indivíduos, e os pacientes foram alocados aleatoriamente em dois grupos homogêneos: Grupo Experimental (GE) e Grupo Controle (GC), com aplicação / não aplicação da AT, respectivamente. Os pacientes registraram seus escores de dor de 0 a 10, mensalmente, em escalas visuais analógicas (EVA) logo após a colagem do aparelho (T_0) e novamente em duas consultas de manutenção do aparelho (T_1 e T_2). Em cada uma dessas fases do tratamento, a EVA foi aplicada em seis momentos diferentes (MT): antes, imediatamente após, após 4 horas, após 8 horas, após 24 horas e após 72 horas. Uma análise estatística descritiva, o teste *t* de Student e o teste do Qui-quadrado foram aplicados aos dados coletados (significância estatística para $p < 0,05$).

Resultados: Os pacientes do GE relataram níveis de dor mais baixos do que os pacientes do GC, tanto em T_0 quanto em T_1 e T_2. Além disso, os valores médios de intensidade da dor foram menores no GE em todos os MTs analisados, com o teste *t* significativo ($p < 0,05$) para a maioria das MTs.

Conclusão: A AT foi eficaz no tratamento da dor em pacientes com aparelhos ortodônticos fixos. Mais estudos são necessários, com um grupo de controle placebo, para comprovar a validade desses resultados.

Palavras-chave: Dor. Aparelho ortodôntico fixo. Auriculoterapia. Acupuntura.

INTRODUCTION

Orthodontic therapies, like most dental procedures, cause emotional stress to the patient and are often associated with pain that at times may even be intense.[1] Orthodontic pain may be perceived during all orthodontic procedures, but several studies have shown that fixed orthodontic appliances cause more intense pain than removable or functional ones.[2,3] Different methods for orthodontic pain management have been studied, including the use of pharmacological and mechanical therapies, laser therapies, and behavioral strategies.[4,5] While these therapeutic strategies have proven useful in the management of pain during treatment, orthodontists generally do not prioritize pain management; the lack of standardized and efficacy-proven pain protocols reflects this point.

The use of unconventional therapeutic protocols as alternatives to support conventional medical methods is much-discussed in medical and scientific literature.[6] Among Non-Conventional Medicines (NCM), Traditional Chinese Medicine (TCM) is the most widespread globally, as well as the most systematic, since it is organized around several key principles that have been preserved for centuries. Acupuncture, one of its main branches, is a versatile therapeutic tool that has been applied in various medical areas,

including Dentistry.[7,8] Several studies indicate that acupuncture could supplement conventional dental treatment methods, in particular for treatment of dental anxiety, gag reflex, temporomandibular dysfunction, facial/neck pain, and headache.[9,10] Acupuncture for analgesic purposes is of particular interest. Although many of acupuncture's physiological and neurological mechanisms are still unknown, the efficacy of therapeutic acupuncture for pain therapy has been well established.[11,12] While several studies support the use of acupuncture for the management of dental pain,[13,14] the most investigated field for the use of acupuncture in pain management is facial and cranial-cervico-mandibular pain.[15,16] Conversely, acupuncture has not been extensively studied for the treatment of orthodontic pain, though there is some evidence of the effectiveness of somatic acupuncture in this area.[17,18]

On the basis of this preliminary scientific evidence, it was decided to undertake an experimental study to evaluate the severity and evolution of pain in the early stages of fixed orthodontic therapy and to verify the efficacy of analgesic acupuncture in patients undergoing these kinds of therapies. The study was carried out by applying an acupuncture method not yet studied in the management of orthodontic pain: auriculotherapy (AT), which involves the application of *Vaccaria* seeds to specific auricular acupoints. Compared to other acupuncture

methods involving the insertion of needles at the cutaneous level, auriculotherapy offers the additional advantage of being well-received by pediatric subjects. The study results demonstrate this technique to be an effective treatment for a variety of types of pain, both acute and chronic.[19,20]

This research aimed to analyze the efficacy of auriculotherapy in the control of pain associated with the use of fixed orthodontic appliances, and to propose a therapeutic protocol effective for reducing orthodontic pain.

MATERIAL AND METHODS

A consecutive series of eligible patients was selected from a university hospital ward, with no discrimination with regards to gender or age, between May 2018 and May 2019. All patients included in the study were undergoing a conventional fixed multibracket orthodontic therapy, applied to one or both dental arches. Patients with intellectual disabilities, chronic and/or metabolic diseases, as well as those undergoing analgesic drug therapy or who had already begun or previously undergone orthodontic treatment, were excluded. All patients were informed about the study, including its aims and the potential risks, and signed an informed consent form in advance. The study was approved by the Institutional Ethics Committee, Department of Oral and Maxillofacial Sciences, Sapienza University, Rome, Italy (#53/2018 – 0000711).

Selected patients were randomly allocated into two groups, depending on the application/non-application of auriculotherapy during the first three months of orthodontic treatment:

» Study Group (SG): auriculotherapy.
» Control Group (CG): no auriculotherapy.

During the session for placement of the fixed orthodontic appliances, a *pain assessment card* was distributed to all participants, which was then returned to the medical staff, once fully completed.

All participants were asked to indicate their pain perception in the oral cavity and the maxillofacial region during the initial period of orthodontic treatment, at the following three time intervals:

» Start of therapy (T_0): time at which the bonding of one or both dental arches occurred.
» First adjustment (T_1): one month after T_0. Time at which the orthodontic appliance was adjusted, by changing the archwire of one or both dental arches.
» Second adjustment (T_2): one month after t1. Time at which the orthodontic appliance was adjusted, by changing the archwire of one or both dental arches.

A Visual Analogue Scale (VAS) was used as a tool of pain self-assessment. The scale is represented as a straight line of 10 cm between two poles: "no pain" (0) and "maximum pain" (10). Study participants were instructed to indicate the value of pain experienced during all three times intervals by plotting a mark on the scale. Patients' pain sensations were arbitrarily divided into five categories, based on the value given on the VAS scale: no pain (0), mild (1-3), medium (3-5), severe (5-7), very severe (> 7).

Both at the beginning of therapy and in the following two adjustments (T_0, T_1 and T_2), the VAS scale was used to quantify the sensation of pain immediately before, immediately after, after 4 hours, after 8 hours, after 24 hours, and after 72 hours. Each patient therefore completed six pain assessments at each of the above-mentioned time intervals (T_0, T_1 and T_2) during the first three months of therapy.

In addition to the values related to pain perception, epidemiological data were collected, as well as data on the pathology and type of therapy performed: age, gender (male, female), malocclusion (Class I, Class II, Class III), and dental arch treated (upper, lower, both).

AURICULOTHERAPY TREATMENT PROTOCOL

A treatment protocol was developed according to the standardized auriculotherapy treatment methods used in traditional Chinese medicine (TCM), with the selection of application points based on TCM principles.[21] We used both specific pain points (Shenmen, Subcortex, Occiput) and points defined as general that pertained to the topographic location of the pain sensation (Mouth, Large Intestine and Lower Jaw for the lower arch, Stomach and Upper Jaw for the upper arch) (Fig 1A). The protocol was elaborated and defined in collaboration with the Paracelso Institute of Rome (Moral Institution of the Ministry of Health m.d. 15 April 1996; China-Italy Center of Traditional Chinese Medicine) and was performed by an experienced acupuncturist licensed in TCM.

PROCEDURE

The treatment was performed on a single auricle at each time interval. At the beginning of orthodontic therapy (T_0), the side for auriculotherapy application was selected. Side selection was based on the patient's gender, with application on the right side for females and left side for males. The sides treated were then alternated at the following two adjustments (T_1 and T_2).

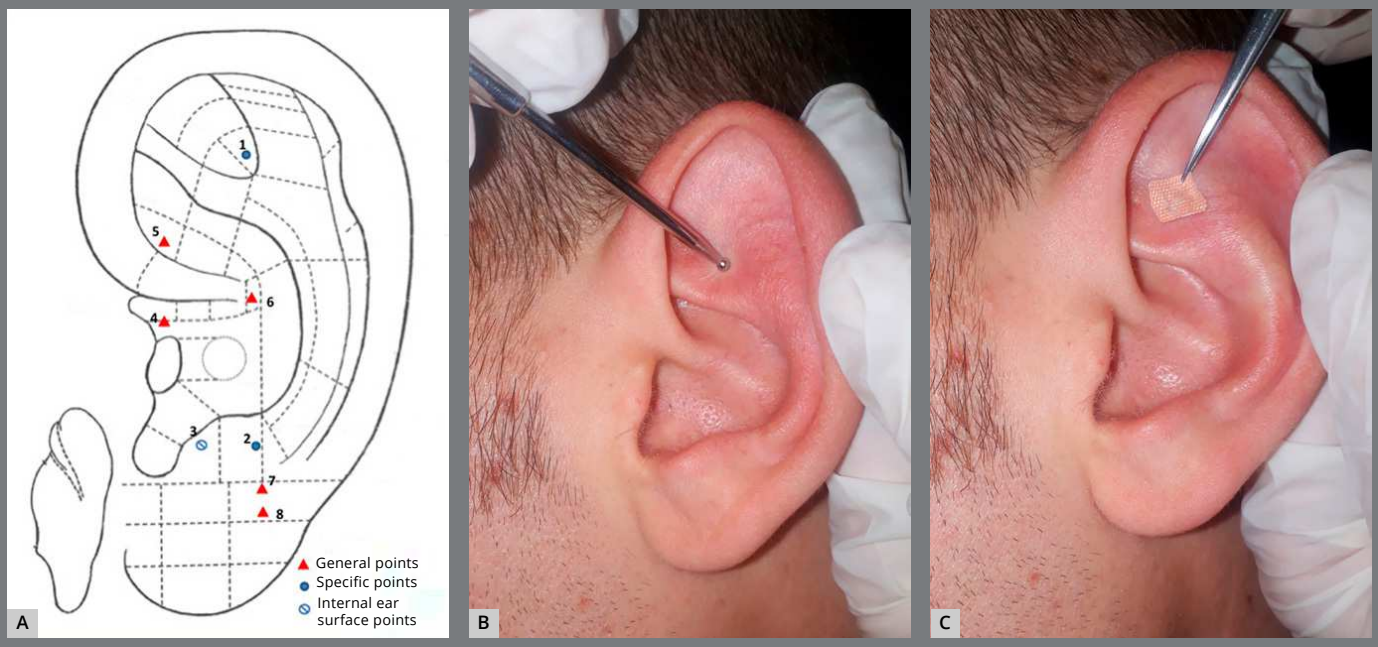

Figure 1: A) Map of auricular points used: (1) Shenmen; (2) Occiput; (3) Subcortex; (4) Mouth; (5) Large Intestine; (6) Stomach; (7) Lower jaw; (8) Upper jaw. Example of (**B)** sensitive points research and of (**C)** *Vaccaria* seed application.

Treatment began after the ear surface was cleaned with a cotton wool pad soaked in ethyl alcohol and then dried. Three points for pain control were selected: the "Mouth" point and the points relating to the dental arch on which the fixed orthodontic appliance was applied. When both dental arches were bonded at the same time, all protocol points were selected. An auriculotherapy speculum was used to identify sensitive or reactive points, through palpation of the ear surface. Once a reactive or sensitive area was located, the speculum was pressed deeper so as to leave a mark on the skin corresponding to the point to be treated. A *Vaccaria* seed was applied immediately afterwards and fixed to the skin with a bandage (Fig.1B, 1C).

This procedure was repeated for all the points to be treated. The auriculotherapy procedure started within 5 minutes of the end of the clinical bonding procedures (T_0) and the following adjustments (T_1 and T_2). The *Vaccaria* seeds remained in place for three days after each application, and then were removed by the patient; the points where the seeds were placed were subjected to intermittent pressure for about one minute, 3 to 5 times a day, for the duration of the three days. This technique was taught to all participants, and it was confirmed that patients had correctly carried it out at each time interval. The alternate ear was treated in the same way after the subsequent adjustments.

Since data regarding the application of auriculotherapy in orthodontic pain was not available from other clinical studies, patients were recruited using convenience sampling.

All patients were randomly assigned to the control (CG) or study group (SG) at a rate of 1:1 allocation. The randomization was performed using a multiplicative congruential generator of pseudo-randomized numbers (Lehmer RNG). Patients were enrolled sequentially, based on the order produced by the generator. To increase the accuracy of the study, randomization continued until we reached the same number of patients in both groups; the final sample size was made up of 36 subjects (18 in each treatment group).

Given the characteristics of the treatment, participants and investigators were not blinded to treatment allocation. The statistician was not involved in the randomization process and analyzed data without assess to information about allocation.

The primary outcome of interest was the pain level and its variation over the three time intervals (T_0, T_1 and T_2) in both groups, for all the time moments analyzed. The secondary outcome was pain level distribution according to the epidemiological data (age, gender, malocclusion, and treated dental arch).

STATISTICAL ANALYSIS

All obtained data were examined using SAS software. Descriptive statistical analysis involved calculation of the following quantitative characteristics: standard deviation, mean, median, minimum, and maximum. This analysis was carried out for both epidemiological characteristics: those related to the therapy and those concerning pain intensity and its trends over time. Performance of a Student's *t*-test allowed for identification of significant differences between the average pain levels of the study group and the control group; a Chi-square test was performed to determine significant differences between the average pain levels according to gender, age, malocclusion, and treated dental arch *(*statistical significance for $p < 0.05$*).*

RESULTS

The study sample was comprised of 36 Caucasian subjects, 14 male and 22 female, with a mean age of 19.5 years (range: 13-54 years) (Fig 2). Table 1 presents the characteristics of the whole sample with regard to demographic data, pathology, and type of therapy performed.

Table 1: Participants' epidemiological data.

	Study group (SG)	Control group (CG)	TOTAL (SG + CG)
Age			
MEAN ± S.D.	20.89 ± 6.67	18.05 ± 10.10	19.47 ± 8.48
Gender			
MALE (n, %)	8 (44.4%)	6 (33.3%)	14 (38.9%)
FEMALE (n, %)	10 (55.6%)	12 (66.7%)	22 (61.1%)
Malocclusion			
Class I	8	4	12
Class II	7	10	17
Class III	3	4	7
Treated dental arch			
Upper	14	14	28
Lower	4	4	8
Both	0	0	0

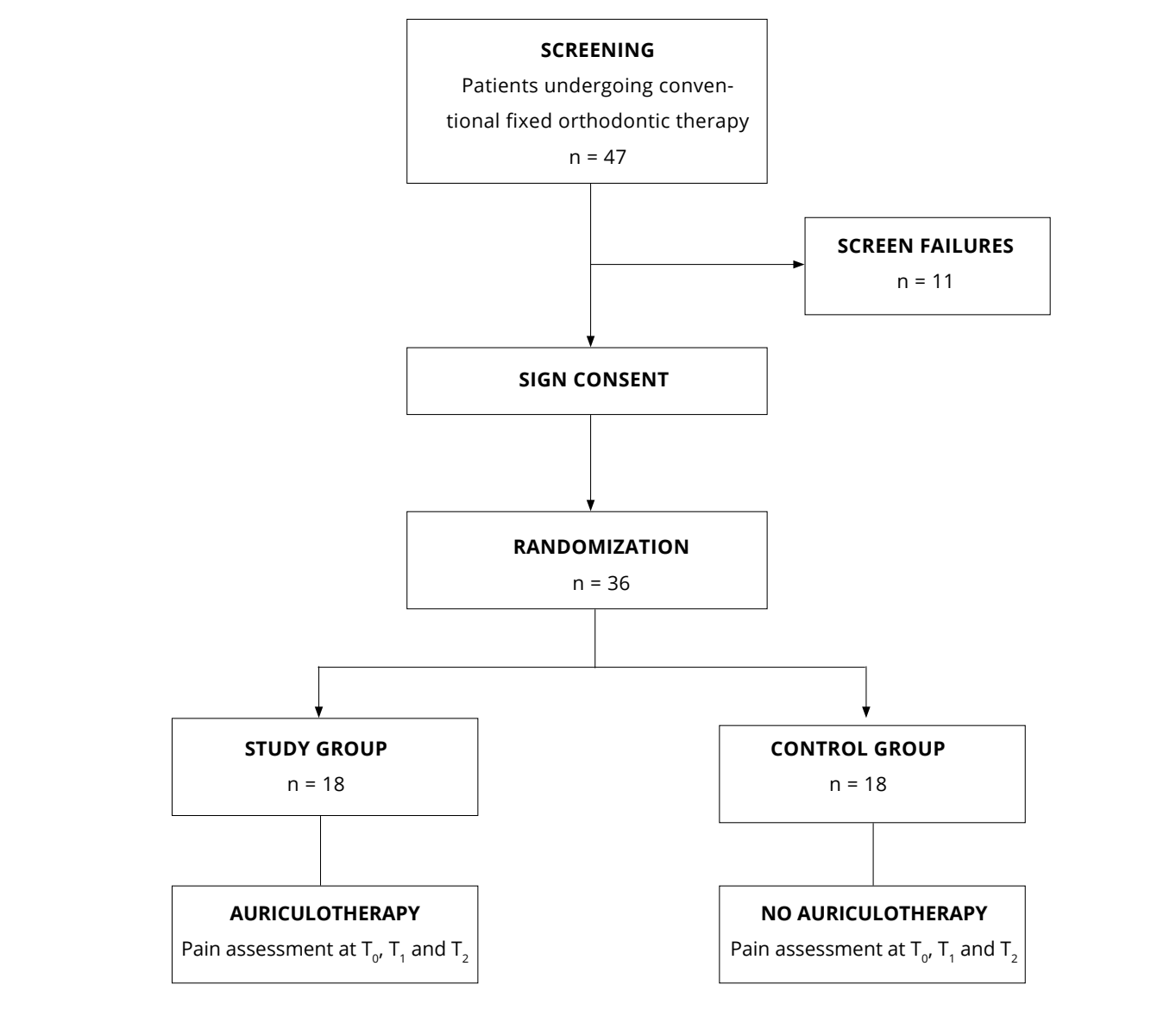

Figure 2: Flow chart of patient enrollment and interventions.

SG patients reported lower pain values than CG patients. These values were lower, on average, for all the time intervals analyzed (T_0, T_1 and T_2). Figure 3 shows the quantitative pain results (VAS scale) in terms of mean values of pain perception for both groups (SG and CG) across all three time intervals analyzed (T_0, T_1 and T_2), with indication of whether or not patients underwent auriculotherapy treatment (Fig 3A), and divided according to the gender (M and F) of the patients (Fig 3B).

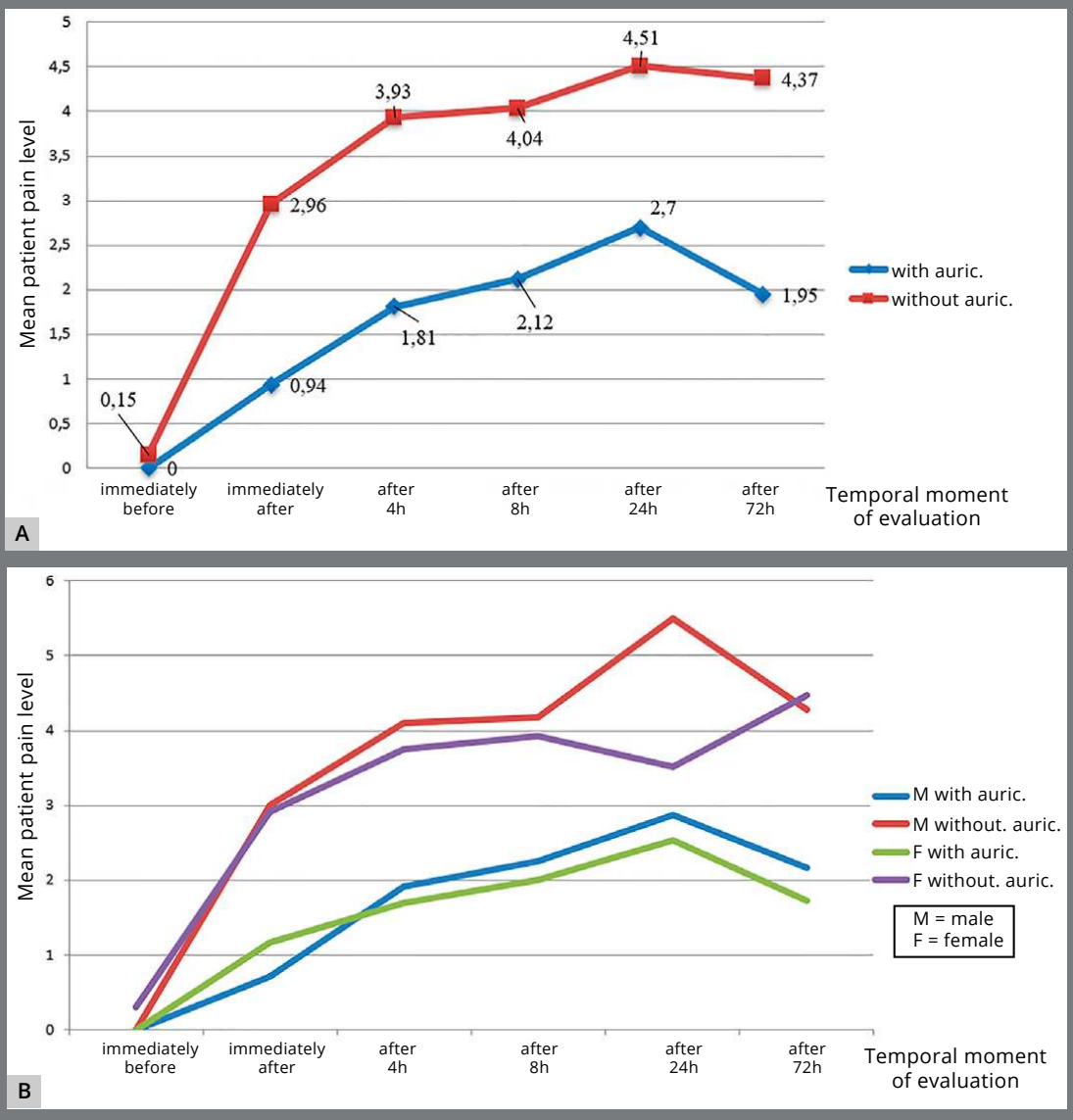

Figure 3: Mean pain levels over time in patients with and without auriculotherapy **(A)**, and based on patient's gender **(B)**.

The values reported by male patients were higher, on average, than those reported by females for all the time intervals considered, with the exception of the moments "immediately after" for SG patients and "immediately before" and "after 72 hours" for CG patients (Table 2 and Fig 3B).

Table 2: Average pain levels over time based on patient's gender (mean values for the three time intervals considered: T_0, T_1 and T_2).

SG - WITH AURICULOTHERAPY (mean ± S.D.)						
Gender	Immediately before	Immediately after	After 4h	After 8h	After 24h	After 72h
M	0	0.71 ± 0.69	1.92 ± 1.84	2.25 ± 2.00	2.87 ± 2.4	2.17 ± 2.10
F	0	1.17 ± 1.08	1.70 ± 1.53	2.00 ± 1.62	2.53 ± 2.09	1.73 ± 1.70
CG - WITHOUT AURICULOTHERAPY (mean ± S.D.)						
Gender	Immediately before	Immediately after	After 4h	After 8h	After 24h	After 72h
M	0	3.00 ± 2.30	4.11 ± 1.84	4.17 ± 2.06	5.50 ± 2.20	4.28 ± 1.77
F	0.30 ± 0.67	2.92 ± 2.29	3.75 ± 2.09	3.92 ± 1.96	3.52 ± 2.42	4.47 ± 2.11

Figure 4 shows the quantitative results related to pain (VAS scale), subdivided by the time interval analyzed: T_0 (start of therapy), T_1 (first adjustment), and T_2 (second adjustment). These results indicate that for both the SG and CG groups, pain appeared immediately after the bonding/adjustments, and tended to increase in the following hours, reaching the highest values after 24 hours. CG patients on average assigned pain values greater than those of the SG for all the time intervals considered (Fig 4).

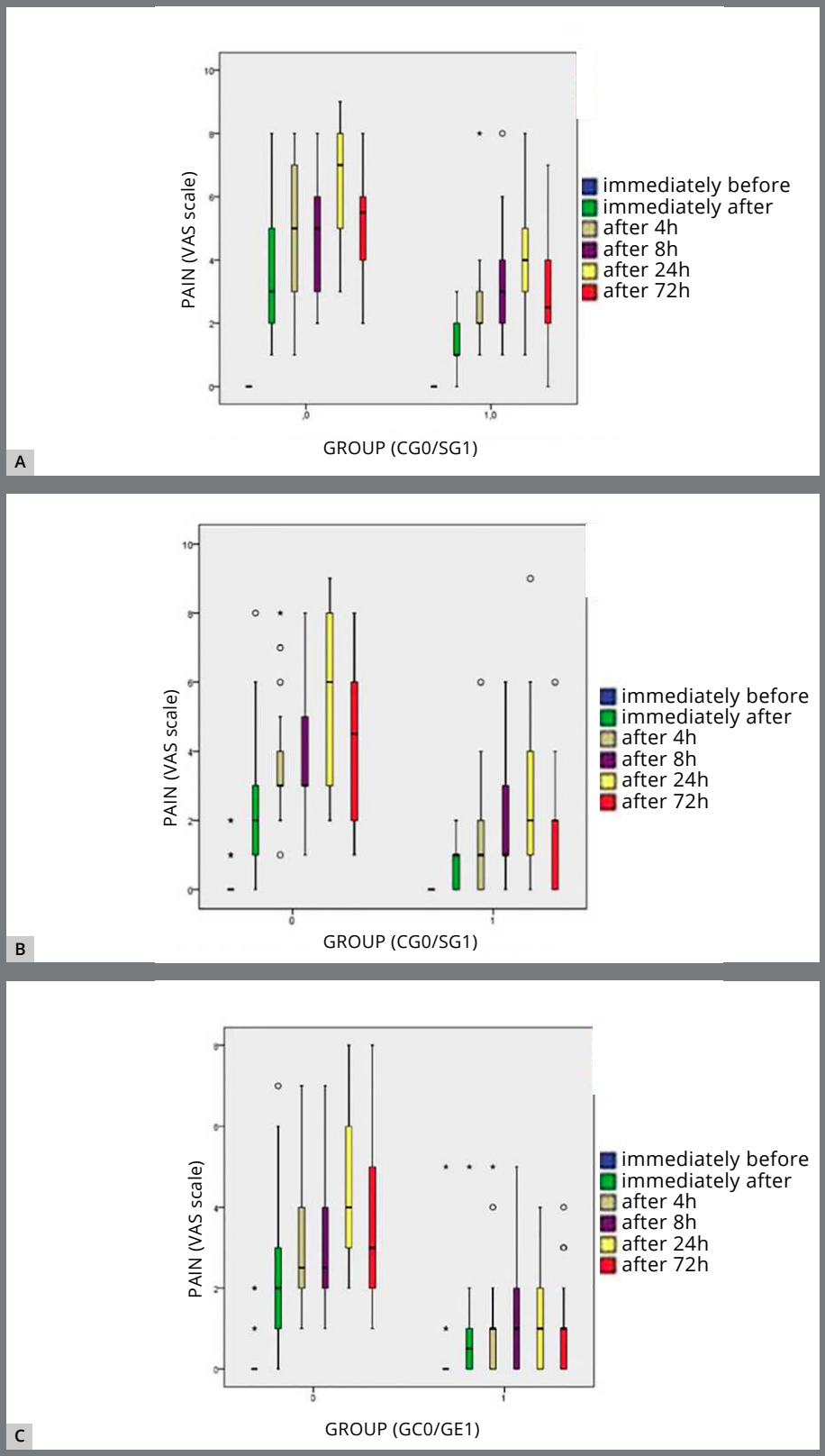

Figure 4: Pain distribution between the SG and CG at: **(A)** the beginning of therapy (T_0); **(B)** the first adjustment (T_1); **(C)** the second adjustment (T_2).

Table 3 shows the pain severity for both groups in the three therapeutic intervals considered (T_0, T_1 and T_2), divided for each time moment analyzed: immediately before, immediately after, after 4h, after 8h, after 24h, and after 72h.

The Student's *t*-test was significant in the comparative analysis of pain between the SG and CG for almost all time moments considered, at both the start of therapy and the following two adjustments (T_0, T_1 and T_2) (Table 3).

The Chi-square test did not show significant differences in pain perception for any of the following parameters: age, gender, malocclusion, or treated dental arch ($p > 0.05$). The only exception was TM "after 24 h" in T_0, where gender was found to be significant ($p = 0.042$).

Table 3: Pain severity in the SG and CG groups, in the three time intervals considered (T_0, T_1 and T_2), divided by time moment.

	AURICULOTHERAPY (SG) Patients: n (%)					NO AURICULOTHERAPY (CG) Patients: n (%)				
Immediately before										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0*	18 (100)	0	0	0	0	18 (100)	0	0	0	0
T_1*	18 (100)	0	0	0	0	14 (77.8)	4 (22.2)	0	0	0
T_2	16 (88.9)	1 (5.5)	1 (5.5)	0	0	15 (83.3)	3 (16.7)	0	0	0
Immediately after										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0**	2 (11.11)	15 (83.3)	1 (5.5)	0	0	0	7 (38.9)	7 (38.9)	1 (5.5)	3 (16.7)
T_1*	7 (38.9)	11 (61.1)	0	0	0	1 (5.5)	9 (50)	5 (27.8)	2 (11.11)	1 (5.5)
T_2	9 (50)	8 (44.4)	1 (5.5)	0	0	2 (11.11)	10 (55.5)	3 (16.7)	3 (16.7)	0
After 4h										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0*	0	10 (55.5)	7 (38.9)	0	1 (5.5)	0	2 (11.11)	9 (50)	5 (27.8)	2 (11.11)
T_1*	5 (27.8)	9 (50)	3 (16.7)	1 (5.5)	0	0	4 (22.2)	11 (61.1)	2 (11.11)	1 (5.5)
T_2*	8 (44.4)	8 (44.4)	2 (11.11)	0	0	0	9 (50)	6 (33.3)	3 (16.7)	0
After 8h										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0	0	8 (44.4)	8 (44.4)	1 (5.5)	1 (5.5)	0	1 (5.5)	9 (50)	6 (33.3)	2 (11.11)
T_1*	4 (22.2)	9 (50)	4 (22.2)	1 (5.5)	0	0	4 (22.2)	11 (61.1)	1 (5.5)	2 (11.11)
T_2*	5 (27.8)	11 (61.1)	2 (11.11)	0	0	0	9 (50)	6 (33.3)	3 (16.7)	0
After 24h										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0**	0	4 (22.2)	11 (61.1)	1 (5.5)	2 (11.11)	0	0	5 (27.8)	5 (27.8)	8 (44.4)
T_1*	4 (22.2)	6 (33.3)	6 (33.3)	1 (5.5)	1 (5.5)	0	3 (16.7)	5 (27.8)	3 (16.7)	7 (38.9)
T_2**	5 (27.8)	10 (55.5)	3 (16.7)	0	0	0	3 (16.7)	9 (50)	3 (16.7)	3 (16.7)
After 72h										
	No pain	**Mild**	**Medium**	**Severe**	**Very severe**	**No pain**	**Mild**	**Medium**	**Severe**	**Very severe**
T_0*	1 (5.5)	8 (44.4)	6 (33.3)	3 (16.7)	0	0	1 (5.5)	8 (44.4)	7 (38.9)	2 (11.11)
T_1**	6 (33.3)	8 (44.4)	3 (16.7)	1 (5.5)	0	0	5 (27.8)	8 (44.4)	3 (16.7)	2 (11.11)
T_0**	8 (44.4)	7 (38.9)	3 (16.7)	0	0	0	7 (38.9)	8 (44.4)	2 (11.11)	1 (5.5)

* $P < 0.05$, ** $P < 0.01$ for pain values differences between SG and CG.

DISCUSSION

Pain is a frequent result of dental procedures, including orthodontic treatments, and is characterized by extreme individual variability. Studies analyzing the evolution of pain in patients with fixed orthodontic appliance show that orthodontic pain arises after application of orthodontic force, with a spike after 12-24 hours and a progressive decrease in the following hours, and can persist for 5-7 days after the force application.[3,22,23] The results of this study confirm that evidence: pain occurs, on average, immediately after orthodontic appliance adjustment and progressively increases in the following hours; patients belonging to both study groups indicated higher pain values in the period "after 24h", and these values decreased in the next time interval analyzed.

A non-linear relationship has been established among pain perception in response to orthodontic force and age, gender, and psychological state. Though several studies have reported that adult patients perceive more pain than younger patients, it is difficult to generalize conclusions concerning age-related pain prevalence and characteristics in Orthodontics, especially due to the different therapeutic approaches performed on patients of different ages.[23] Our analysis also found no significant age-related pain variation in either the SG or CG groups.

Differences in pain perception according to sex and gender have long been debated. Genetic, molecular, physiological, and psychosocial factors contribute to pain elaboration and influence pain perception in separate ways in men and women. Females have a greater prevalence of many clinical pain conditions, and it is believed that they are more sensitive to pain than males.[24] However, conflicting results regarding male and female pain perception during fixed appliance treatment have emerged. Some studies show no gender differences in reported orthodontic pain with respect to pain threshold.[23] Only two studies have found that girls report more discomfort/pain and ulceration than boys during fixed orthodontic treatment.[3,25] In this study, male patients seemed to experience more pain, on average, than female patients, but gender was still not found to be a significant factor in determining the onset and intensity of pain.

Other factors were not evaluated in this study, and this can be considered a limitation of the research, since personal and psychological factors can affect the perception of pain. Ideally, sham auriculotherapy (a bandage fixed on the same acupoints, but without the use of *Vaccaria* seeds) should also have been applied in this study. However, this preliminary research aimed to evaluate the potential efficacy of auriculotherapy in the management of orthodontic pain, despite

the lack of evidence of its previous use in this specific area; it was therefore considered appropriate to proceed without the sham group. Further studies should aim to improve upon this point by addressing such factors.

The study was carried out by applying a particular acupuncture method: auriculotherapy (AT), which involves the application of *Vaccaria seeds* to specific auricular acupoints. This technique, unlike other acupuncture methods, does not involve the insertion of needles and therefore offers the additional advantage of being well-received by patients, including pediatric subjects. Moreover, it was effective in treating various types of pain, both acute and chronic.[19,20,26] A recent review from Vieira et al.[26] has shown auriculotherapy to have a positive effect when paired with conventional treatments of chronic and acute pain. Iunes et al.[19] investigated the efficacy of auriculotherapy in a group of TMJ dysfunctional patients, demonstrating auriculotherapy to be significantly effective in reducing pain in the temporal and TMJ areas. A meta-analysis from Yeh et al.[20] established that auriculotherapy provides significant pain relief when compared to a sham or control group. It has also been demonstrated that auricular acupressure is more effective than auricular acupuncture.[20] This evidence of the efficacy of auriculotherapy in pain management supports the application of AT in orthodontic pain management.

Considering the high number of patients reporting discomfort or pain during orthodontic therapies, several analgesic methods have been studied. Most existing studies propose the administration of non-steroidal anti-inflammatory drugs (NSAIDs), which are effective in reducing pain, but may limit the extent of dental movement during therapy.[2,4,27] Satisfying results in pain reduction have been found in studies concerning Low-level laser therapy (LLLT), although its use is poorly documented.[7,28] Only a few studies have investigated acupuncture to treat orthodontic pain and none of them studied the application or effectiveness of auriculotherapy. Jia et al.[29] studied the clinical efficacy of transcutaneous electrical acupoint stimulation (TEAS) for orthodontic toothaches through the use of three acupoints: *Juliao* (ST3), *Jiachengjiang* (Extra), and the auricular point *Ya* (LO1). In this study, the pain scores of the TEAS group were lower than those in the two control groups. An animal study by the same authors showed satisfactory results regarding the therapeutic and preventive effects of TEAS on rabbits with orthodontic toothaches.[17] To manage post-adjustment orthodontic pain, Vachiramon and Wang[30] proposed the use of just one acupoint, *Hegu* (LI4), stimulated by needles or simple acupressure. Finally, Boleta et al.[18] analyzed patients' pain levels during the second quarter of fixed orthodontic therapy. They applied a treatment of somatic acupuncture, using two acupoints, *Hegu* (LI 4) and *Jiache* (ST 6), and

found a statistically significant reduction in pain level indexes, both for men and women, when acupuncture therapy was performed before the orthodontic adjustment.

These studies highlight the effectiveness of acupuncture in the treatment of pain during fixed orthodontic therapy; the results obtained from the application of auriculotherapy in this study confirm such findings. From the moment of the application of orthodontic force, the study group undergoing auriculotherapy perceived lower pain values than the control group, both at the beginning of therapy (T_0) and in the two consecutive months of treatment (T_1 and T_2). The results show this difference in perceived pain for all the time moments considered (immediately before, immediately after, after 4h, after 8h, after 24h, and after 72h), with a statistically significant difference between average values of perceived pain for most time moments considered (Table 3).

The therapeutic auriculotherapy protocol proposed in this study is versatile, easy to apply, minimally invasive, and low-cost. Acupuncture procedures, including auriculotherapy, do not produce side effects and can be safely applied by qualified acupuncturists. This is an important feature, especially given the extreme heterogeneity of orthodontic patients, high percentage of pediatric subjects, and growing demand from patients to limit the use of medication.

CONCLUSION

Auriculotherapy seems to be effective in pain management for patients undergoing fixed orthodontic treatment. Despite the limitations of this study, we can consider auriculotherapy a valid analgesic alternative in the treatment of orthodontic pain. Further studies must be conducted to confirm the results obtained.

AUTHORS CONTRIBUTIONS

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Conception or design of the study:

ES, GG.

Data acquisition, analysis or interpretation:

ES, AI, AL, GG

Writing the article:

ES.

Critical revision of the article:

ES, AI, AL, GG.

Final approval of the article:

ES, AI, AL, GG.

Overall responsibility:

GG.

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