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The Journal of the Lebanese Dental Association **-JLDA-** is a multidisciplinary peer-reviewed journal published biannually (June and December) by the Lebanese Dental Association. JLDA has an ultimate aim of introducing and improving research in contemporary aspects of dental and craniofacial basic and clinical sciences. The **JLDA** publishes manuscripts on all aspects of dental medicine and surgery, including surgical dentistry, restorative and prosthetic dentistry, geriatric and pediatric dentistry, periodontology and implant dentistry, endodontics, esthetic and cosmetic dentistry, adhesive dentistry, orthodontics and dentofacial orthopedics, oral biology, oral and maxillofacial surgery, oral diagnosis/pathology/medicine, dental research, oral and maxillofacial radiology and imaging, public health dentistry, special care/needs dentistry, forensic odontology and dental mass disaster. Dentistry related fields are broadly defined and may include, for instance, facial growth/embryology, dental and orofacial genetics, orofacial anti-aging and esthetic medicine, dental and maxillofacial tissues engineering, medically compromised patients treated in dental practice, temporomandibular disorders and orofacial pains, sleep medicine in relation to dental practice, clinical trials of drugs relevant to dental/craniofacial practice, dental/oral histopathology, immunopathology and microbiology, dental anesthesiology, dental ergonomics, computer-assisted dentistry, aeronautic and veterinary dentistry.

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22 June 2003

Dear Dr Baba,

This is to acknowledge with thanks, the receipt of No. 1, Vol. 39, August 2001, No.1 & 2, vol. 40 March and August 2002 of the "Journal of Lebanese Dental Association - JLDA" which you have kindly sent to us.

I would like to congratulate you for publishing this Journal and have the pleasure of informing you that the Journal will be indexed in the Index Medicus for the WHO Eastern Mediterranean Region (IMEMR). We would appreciate your sending us all forthcoming issues, as soon as published.

The IMEMR has been compiled and published by the Eastern Mediterranean Regional Office since 1986. It aims to provide a comprehensive bibliographic control and indexing of all health and medical journals published in the Region. In addition to access to the Index, a document delivery service has also been activated which will enable any user to acquire a copy of any article listed in the Index. The IMEMR Current Contents Bulletin is issued quarterly. The contents of the Index Medicus are also available on the Internet and are updated regularly on: http://www.emro.who.int/HIS/VHSL/Imemr.htm.

Looking forward to our continued and fruitful co-operation.

Yours sincerely,

N. Al-Shorbaji

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JLDA
Journal of the Lebanese Dental Association

Guest Editorial

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Pain in the orofacial region can be a reaction to damaging or inflammatory processes in the mouth, jaws, and face or often idiopathic as in many cases of trigeminal neuralgia. The feeling of pain, despite its negative emotional impact, can have a positive value particularly when it warns about the existence of orofacial injuries or inflammations or helps guard against further damage resulting from such injuries.

However when pain becomes chronic, as in trigeminal neuralgia, temporomandibular joint disorders, or headaches, which can affect 10-15% of the population, its utility becomes highly doubted and its treatment more challenging. In fact, the "Tic douloureux" - a disorder related to the orofacial area - was among the foremost historical challenges leading to modern inquiries about the origin of chronic pain.

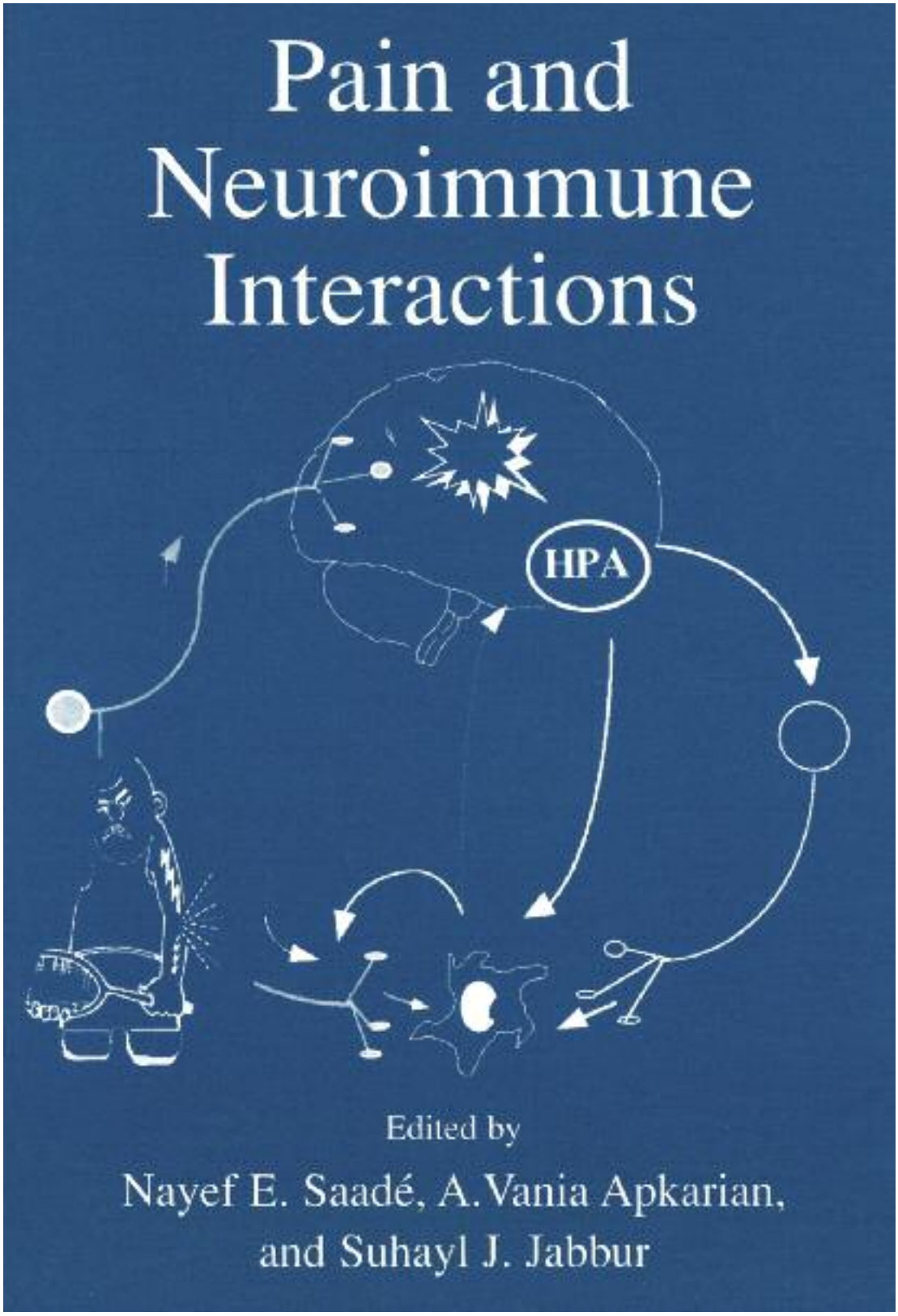
Emphasis on pains affecting orofacial area is related to the fact that this region can be considered as the most crowded and complex part of the body from organizational and functional points of view. As an illustration, the innervation of this area involves all 12 cranial nerves in addition to upper cervical spinal nerves and any damage or threat to it might impair one or more modalities of the special senses along with several vital functions. This assumption is supported by the fact that the most severe sequels of post-herpetic neuralgia are those observed following pathologies affecting one or more branches of trigeminal nerve. The importance of this area is further ascertained by heavy convergence of research interests and efforts from various medical, dental, and paramedical disciplines, focusing all on pain research and treatment.

The theme of Orofacial Pain has been adopted as the topic of the year October 2013 - October 2014 by the International Association of the Study of Pain (IASP) with the declared aim to "Encourage government leaders, research institutions, and other key decision-makers to support more research, ultimately producing more effective and accessible treatment methods and outcomes for those who suffer from orofacial pain". In line with this declaration, our local IASP chapter, the Lebanese Society for the Study of Pain (LSSP), organized a special symposium on orofacial pain that assembled specialists from neuroscience disciplines in medicine and dentistry at various research institutions in Lebanon. This special symposium provided a platform for the presentation and discussion of observations from clinical and research studies in the field.

Along the same line, the Journal of the Lebanese Dental Association is devoting a special issue on the topic of orofacial pain. The list of studies and the authors contributing to this issue reflect the diversity of specialists and the up-to-date approach of several hot topics in research and clinical practice.

As founding members of the LSSP, we are proud to see generations of practitioner-neuroscientists, from all walks of research and practice and from various Lebanese institutions, getting involved in searching for answer to some of the most challenging questions in the multiple fields of orofacial pain.

This JLDA special issue on orofacial pains is dedicated to Professors Nayef E. Saadé and Suhayl J. Jabbur for their unflagging support for neuroscience and pain research.



Editorial Comment

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The mouth, face, and jaws are the sites of some of the most common pains in the body, and some orofacial pains are unique to this region and can be excruciatingly painful (e.g. some types of toothaches; trigeminal neuralgia). Furthermore, epidemiological studies in many countries have shown that around 20% or more of the population suffer from acute orofacial pains such as that associated with an acute pulpitis, or from chronic orofacial pain states such as temporomandibular disorders and burning mouth syndrome (Lipton et al., 1993 --- Sessle, 2013). As a result, orofacial pain currently represents a huge socioeconomic burden on society, and changing demographics in most countries over the coming decades will likely result in an increased prevalence and burden of orofacial pain as a higher proportion of the population become middle-aged and elderly, the age range when chronic pain conditions are most prevalent. Even nowadays, the economic burden alone is staggering; for example, it has recently been estimated that the economic cost to the USA of orofacial pain is currently over $150 billion/year ! And then there is the social burden which is especially reflected in the devastating effects that orofacial pain can have on patients psychological and societal well-being. The orofacial region has special psychological and behavioural significance to all of us, whether we are healthy or not, because of its crucial roles in eating, drinking, speech, and facial expression of our feelings. Thus, if pain is occurring in orofacial region, and particularly if it is chronic and difficult to manage, it can have a major psychosocial impact on the patient suffering from it: this suffering may be reflected in depression or other psychological, emotional, and behavioural disruptions which are common accompaniments of pain states especially when they are chronic. It is little wonder then that a patient with an orofacial pain state that is chronic and associated with these complex but common psychosocial comorbidities, can represent a significant challenge to the clinician trying his/her best to diagnose and manage the condition effectively. While the dental profession has become very effective in treating most acute orofacial pains, chronic pain management is more problematic because of its complexity and multidimensional nature and the limited knowledge base and training that most dentists have gained about its management. Thus, to deal effectively with chronic as well as acute orofacial pain states, it is of utmost importance for dental clinicians to have a good understanding of their underlying mechanisms and of the recent developments of the know how in diagnosing and managing them.

Over the past 4 decades, there have been many new

or improved approaches for the diagnosis and management of orofacial pain states, and several papers in this JLDA special issue outline many of these. We also know much more about their mechanisms as a result of research studies in humans and animal models of orofacial pain, including those by Professors Suhayl Jabbur and Nayef Saadé who are quite appropriately being acknowledged and honoured in this JLDA special issue on orofacial pains.

New insights have been gained on biological, molecular, and genetic processes underlying chronic as well as acute orofacial pains: these include discoveries that tissue trauma can produce an increased excitability of nociceptive sensory nerve fibres that innervate orofacial tissues ("peripheral sensitisation") and of nerve cells in the brain that process or modulate pain-related signals that these nerve cells receive from nociceptive fibre inputs ("central sensitisation"). Central sensitisation has been shown to reflect a neuroplasticity of nociceptive pathways in the brain, emphasising that these pathways are not "hard-wired" but can undergo functional, even structural, neuroplastic changes as a result of damage to orofacial tissues and alterations to pain-modulatory pathways in patient's brain: studies of sensitisation phenomena have also revealed the involvement of several different chemical mediators as well as interactions with modulating factors of immune, endocrine and cardiovascular systems that have provided several novel targets for the development of new diagnostic or management approaches for pain. Furthermore, peripheral sensitisation and central sensitisation are now recognised as crucial elements in the development and maintenance of persistent pain states and can account for increased pain sensitivity that can occur as a result of an injury or inflammation of orofacial tissues.

Much more knowledge has also been gained on psychological and behavioural factors that can influence pain expression: this new knowledge has added support to the current view held by most pain experts that the diagnosis and management of a chronic pain patient need to be based on a biopsychosocial foundation given that pain, especially when chronic, is complex and multidimensional. This means that dentists need to be aware that they alone may not have all the knowledge and clinical skills required to provide comprehensive pain care for all chronic orofacial pain patients, and that consultation with pain expert clinicians and other health professionals such as psychologists and neurologists may be essential to provide optimal care.

To be sure, we still have much to learn more about orofacial pain, but with the new knowledge gained in recent decades as a basis and the expected advances over the coming years will assuredly result from research approaches encompassing fields such as bioengineering, biomarkers, bioinformatics, imaging, immunology, molecular biology, genetics, and neuropsychology: these advances hold out promise for new or improved clinical approaches that will help alleviate the pain and suffering of many patients experiencing chronic pain or help reduce the risk of patients developing a chronic orofacial pain state.

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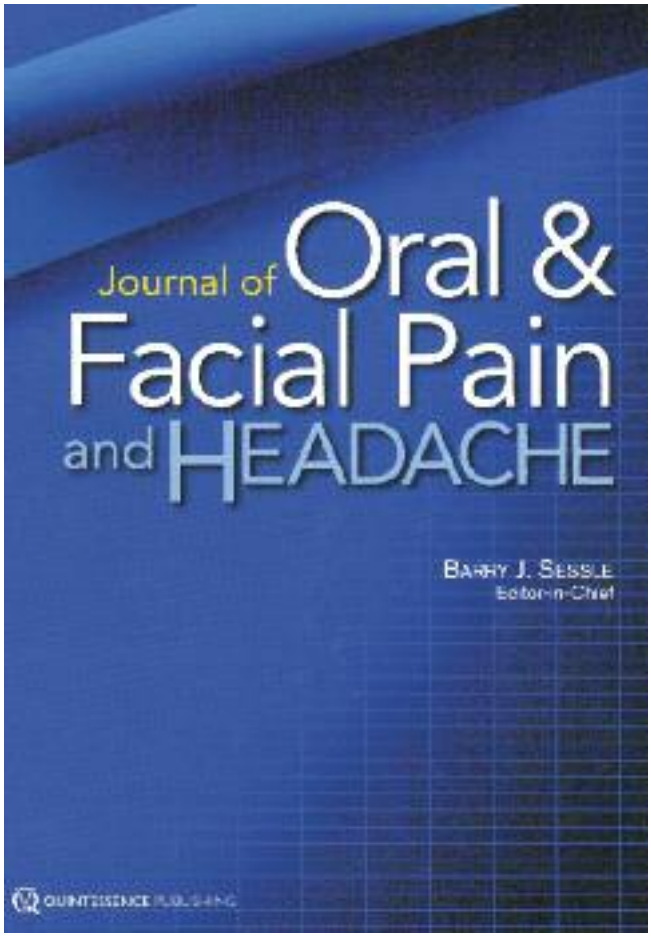

In Memorian

EMMANUEL TOMB (1958-2005),

Dentist, scholar, author, polymath, and dental educator

*Emmanuel (Asaad) Tomb, a **Lebanese French dentist**, earned the "Docteur en Chirurgie Dentaire" degree in 1986, after which he pursued postgraduate certificates in functional myotherapy, a university diploma in dental expertise (DU d'Expertise Bucco-Dentaire), another diploma in the legal-juridical compensation of body harm (DU d'études relatives à la réparation juridique du dommage corporel)and a Masters degree in Medical Biology.*

For many years, he worked, as Faculty, with the Paris 7 University Faculty of Dental Surgery (Garancière) where he was appointed Clinical Associate(Attaché de Consultation) in the Facial Pain and TMDs Clinic, and at the same time, he had his own private practice in Vittel(France)and collaborated, as Sworn Dental Expert, with the Nancy Court of Appeal, in France. And later, he also worked as Clinical Associate with the Pain's Evaluation and Treatment Center at Laennec Hospital in Paris, France.

*Dr. Tomb's career was marked by a combination of high academic achievement, both in teaching under and post-graduate students, and a highly regarded private and hospital consultant practice where his opinion and expertise were much in demand. He endeavored and published extensively in the fields of head and neck pain, and his topics of interest were migraine, cervical pain, and TMDs. Indeed, and among his academic exploits, he lectured with the International Headache Society-IHS-in Amsterdam, the International Academy of Legal Medicine -IALM- in Dublin, and the **European Federation of IASP (International Association for the Study of Pain) Chapters**, in Barcelone. He was also invited speaker in Beirut, Lebanon, where he addressed to Lebanese and Arab dentists, cervical and cranio-facial pains in seminars and workshops organized by the Lebanese Dental Association - LDA.*

*During his dental career, Dr. Tomb earned an international reputation in the field of Head and Neck Pains, especially after he published (with **Dr. Jean Thomas**, physician, and **Dr. Elisabeth Thomas**, pharmacist and biologist) a **textbook** on Migraine: this medical work was written in French and was titled **"LA MIGRAINE: LA COMPRENDRE ET LA GUERIR DEFINITIVEMENT"** (Migraine: understand it and cure it for good) and Dr. Tomb is often quoted in French dental and medical literatures as the **"VIRTUOSE DU TRAITEMENT DE LA MALOCCLUSION DENTAIRE"**.*

Nine years after his tragic death in February 2005, Tomb's contributions to pain science are now widely recognized in France and Europe.

On a personal standpoint, Dr. Tomb was always polite, without any malice or prejudices. He always had a ready and warm welcome and a big smile for his patients and colleagues alike. He seldom had a harsh word for anyone although he had an imposing way of maintaining discipline in his lectures and masterclasses. He was, indeed, a delightful colleague and was highly respected and appreciated by all his dental school and hospital confrères and consœurs. He was one of this early band of dental aspirants who obviously succeeded, where many others failed. Against many odds, he made it, making of himself a one of a kind dental professional.

Dr. Emmanuel (Asaad) Tomb was an inspirational teacher for his students. His dedication for his profession, his contributions to the science of head and neck pain, and his impact on his junior colleagues, made him ***a colorful figure in French and European dentistry****. During his career, he shaped and influenced countless number of general dentists in their approach to head and neck pains. Emmanuel made pain so indeniably interesting, attractive, and relevant to everyday dentistry. His outspoken language, honesty, sincerity, common-sense approach, ability to understand and analyse, and compelling logic, made him an outstanding and superlative communicator.*

I can say a lot and more about my old friend "Asaad", and when he crosses my mind (and this happens very often), i remember mostly his passion for life, pride, straight talking, political correctness, and razor-sharp logic. To me, "Asaad" was an unforgettable fighter for his happiness and the well-being of his patients. His guidance and friendship deeply enriched the lives of so many dentists. I consider him a pride for Lebanon, France, and Dentistry.

Since 2005, he is sorely and sadly missed, leaving a void that cannot be filled.

Dr. Tomb is survived by his daughter, Ambre, who lives in France.

Ziad Noujeim,
Editor-in-Chief, JLDA

Trigeminal Autonomic Cephalalgias -TACs-: a review of neuroimaging studies.

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Abstract

Trigeminal autonomic cephalalgias are a group of disabling and excruciating primary headache disorders, consisting of cluster headaches, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT). The attacks are strictly unilateral, presenting predominantly in the orbital, peri-orbital, and temporal regions, although pain may radiate to teeth and jaws. Pain is typically accompanied by prominent ipsilateral cranial autonomic symptoms. Ppathophysiology of these disorders is unknown and has therefore driven a number of studies using a variety of neuroimaging modalities in an attempt to unravel this. In this paper, we review the literature for neuroimaging studies that have been performed in these headache disorders and present their findings.

INTRODUCTION

Trigeminal Autonomic Cephalalgias (TACs) are a group of rare, short-lasting primary headache disorders with distinct features. According to the International Classification of Headache Disorders (ICHD), they include cluster headaches, paroxysmal hemicranias, hemicrania continua, and short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT). The characteristic features of this group are the presence of a strictly unilateral, often excruciating pain in orbital, periorbital or temporal regions, accompanied by marked cranial autonomic symptoms. These include ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, ptosis, myosis, eyelid edema, and/or facial sweating. Patients also usually complain of a sense of restlessness and/or agitation with the attacks.[1-3]

There is considerable overlap in the features of these disorders, with the individual temporal profile serving as distinguishing features. Duration and frequency of attacks vary between the disorders. Cluster headache usually lasts for 15-180 minutes with a frequency of attack ranging from one every other day to up to 8 attacks per day. As the name suggests, attacks usually come in 'clusters', ranging from days to weeks and exhibits a circadian and seasonal periodicity. Severity of each attack, usually described as thermal or punctate in character, has been reported to be worse than childbirth pain, hence it is sometimes also known as 'suicide headaches'. Alcohol and nitroglycerin have been known to be potent triggers for the headaches during a cluster period.[2,4,5]

On the other hand, paroxysmal hemicrania characteristically lasts 2-30 minutes with an attack frequency of usually more than 5 per day, but can be up to 40 attacks daily. Circadian periodicity is less prominent in this disorder. Attacks may be triggered by mechanical stimuli, such as head or neck movements. A striking feature of this headache is its dramatic and absolute response to therapeutic doses of indometacin[1,5], a NSAID commonly prescribed in premature labor, dysmenorrhea, headaches, Paget's disease of bone, rheumatoid arthritis, and osteoarthritis. On the other hand, SUNCT attacks are short lasting but has a higher frequency. Attacks are usually described as stabbing or pulsating in character, and last 5-240 seconds with a frequency ranging from 3-200 per day. It shares certain similarities with trigeminal neuralgia and diagnosis may often be confusing. In both disorders, attacks are short-lasting and may have cutaneous triggers. However, in

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SUNCT, cranial autonomic features (especially conjunctival injection and tearing) are prominent features and pain is often predominantly in the ophthalmic distribution of trigeminal nerve (V1). Moreover, patients with SUNCT are usually able to trigger an attack immediately following the previous one, thus do not have a refractory period.[1,5]

Hemicrania Continua (HC), described and coined in 1984 by Sjaastad and Spierings, features continuous head pain (continua) and unilaterality of head pain (hemicrania). Pain is moderate, rarely approaching a high intensity level, with nocturnal awakenings, but most patients are able to work.

Several theories have been put forward in an attempt to explain the pathophysiology behind this group of headaches. Cluster headache was initially thought to be a vascular headache originating from an inflammation within cavernous sinus. Resulting venous stasis causes pressure on trigeminal nerve and simultaneously activates intersecting parasympathetic and sympathetic nerves, eliciting pain and autonomic symptoms respectively.[2-5] Moreover, vasoconstrictive effect of sumatriptan, a 5-hydroxytryptamine (5-HT)* agonist, in aborting these attacks, further supported this hypothesis.[6,7] However, this theory could not explain circadian rhythmicity of attacks. Hence, it was superseded by the hypothalamic theory.

Circadian and seasonal periodicity of cluster headaches indicate a possible central involvement, with the human biological clock implicated as a potential site. This is situated in the suprachiasmatic nucleus within the hypothalamus, which is also responsible for regulating hormonal activities. This correlated with the findings of a significant decrease in plasma testosterone levels in male cluster headache patients. A reduced response to thyrotropin-releasing hormone further supported this hypothesis. Furthermore, a blunted nocturnal peak in melatonin**, a circadian system biomarker, has been found in patients with cluster headache.[4,6]

** 5-hydroxytryptamine or serotonin is a monoamine neurotransmitter primarily found in GI tract, patelet, and CNS. It is popularly thought to be a contributor to feelings of well-being and happiness.*

***Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that entertains circadin rhythms of several biological functions. It also protects nuclear and mitochondrial DNA and has a pervasive and antioxidant roles.*

This concept of a possible central involvement has led to much of the neuroimaging studies in this group of headaches, in an attempt to unravel the pathophysiological basis of these rare disorders. Much of the work done in this field has concentrated on cluster headaches, with few studies on paroxysmal hemicrania and SUNCT. However, due to their distinctive clinical phenotype, this group of disorders are assumed to have the same pathophysiological basis. This review aims to highlight the various methods used and the main findings of these studies.

NITROGLYCERIN: A RELIABLE TRIGGER?

The episodic nature of cluster headache makes it difficult to capture data on patients during spontaneous attacks, thus most neuroimaging studies to date have been performed on evoked attacks. The use of nitroglycerin (a potent vasodilator prescribed in angina pectoris and chronic heart failure) as a triggering agent has been studied by Ekbom[8] who deduced that attacks are inducible whilst patients are in their cluster period, with sensitivity being highest in the middle of a bout and gradually reducing towards the end. The onset of the attack ranges from 30-50 minutes following administration of nitroglycerin, and it is preceded by a fairly transient pulsation and pressure in temples and forehead. There is a refractory period of 6-8 hours following an attack and patients outside their cluster bout remain insensitive to provocation.

The first positron emission tomography (PET) study on cluster headache was performed by Hsieh and associates[9] in 1996, using butanol as the tracer for regional cerebral blood flow (rCBF). They studied four right-handed patients during their active cluster period, two with right-sided and two with left-sided attacks. The headaches were elicited within 18-35 minutes of administration of 1 mg sublingual nitroglycerin and successfully terminated following subcutaneous administration of sumatriptan (a synthetic drug of the triptan class, prescribed in migraine headaches). A 100 mm visual analogue scale (VAS) was used to enable patients to rate their headache intensity. Each patient underwent six scans: two at baseline (10 minutes apart), one following nitroglycerin administration, two following onset of cluster headaches (10 minutes apart)

and lastly following pain relief with sumatriptan. Authors reported that there was a preferential role of the right, non-dominant hemisphere, especially the anterior cingulate cortex, in the affective-cognitive processing of pain in these patients. The normal pain processing network was activated but there were no changes seen in the brainstem or diencephalon. Furthermore, they found a marked increase in activity in the cavernous sinus region, which suggested its possible role as the central generator of cluster headaches. However, this hypothesis is challenged following further studies, as discussed later.

May and co-workers[10] performed a similar study on 17 cluster headache patients. None of them were in their active cluster period, whilst eight who were in remission phase acted as controls. In this study, headaches were provoked by inhalation of 1.0-1.2 mg nitroglycerin, although one patient developed attacks spontaneously in the scanner. Each patient underwent 12 or 13 consecutive scans with VAS ratings. All patients reported similarity of the triggered attacks to their usual headaches. The cerebellum, bilateral anterior cingulate cortex, and insula, the contralateral posterior thalamus, ipsilateral basal ganglia, and cerebellum were found to be activated in these patients. However, unlike migraine, no brainstem activation was reported during the attacks.[11] A distinctive finding from this study was activation in the ipsilateral hypothalamic grey, which was not observed in the control group. This implies that this area is specifically activated only during a cluster headache attack, therefore providing substantial evidence of a possible hypothalamic involvement.[12-13] An increase signal in the cavernous sinus region of patients who were in their active cluster period was seen. No differences were noticed between the spontaneous and evoked attacks.

Sprenger and associates[14] also presented an incidental case of a spontaneous cluster attack in a patient whilst undergoing PET scanning to study the effects of deep brain stimulation. The areas activated were comparable to earlier studies done with nitroglycerin-induced cluster headaches. Hence, authors concluded it was unlikely that the use of nitroglycerin to trigger the attacks confounded the imaging data.

THE CAVERNOUS SINUS THEORY

Cluster headache has long been coined a vascular headache with the cavernous sinus being implicated as the focal generator of symptoms. Early studies looking at the cerebral blood flow of patients with cluster headaches reported inconsistent results, with some reporting an increase, some a decrease whilst others showed no changes in cortical blood flow.[15-17] Gawel and co-workers[18] studied 119 cluster headache patients using Gallium single-photon emission computed tomography (SPECT). Patients in active cluster period displayed a lesion on Gallium SPECT in the region of cavernous sinus, which fades as the patient moves out of cluster. On the contrary, no definite pathology was found in the cavernous sinus region in a magnetic resonance imaging (MRI) study of 14 cluster headache patients.[19] A repeat Gallium SPECT study done on 30 cluster headache patients and 7 "migraineurs" showed that marked activity within the parasellar region was not limited to cluster headaches only but was also seen in migraine[20]. Likewise, Schuh-Hofer and associates[21] found no evidence for an inflammatory process in the cavernous sinus of six cluster headache patients investigated using (99m)Tc-human serum albumin* and SPECT. These findings thus question the role of cavernous sinus as the pathophysiological focus in cluster headaches.

Despite consistent findings of significant activation within cavernous sinus region in PET studies, experimental pain studies have also reported similar findings. A PET study[22] performed observed the effects of cranial pain elicited by capsaicin (an active component of chili pepers prescribed, as analgesic, in topical ointments, nasal sprays, and dermal patches). Seven healthy subjects had a small amount of capsaicin injected to their forehead, in an attempt to elicit pain of the ophthalmic division of trigeminal nerve. Increased rCBF was observed bilaterally in the anterior insula, the ipsilateral anterior cingulate cortex, the contralateral thalamus, and bilaterally in the cerebellum as well as in the cavernous sinus.

Similar findings were reported by May and co-workers[23] who performed a magnetic resonance angiography (MRA) study in addition to the $H_2(15)O$ PET study above. Four volunteers had capsaicin subcutaneously administered to the forehead

** (99m) Tc-human serum albumin is the most commonly used radio-labeled colloid in Europe.*

to elicit pain. Patient who developed spontaneous cluster attack during the PET study was also included. A significant increase in blood flow was observed in ipsilateral internal carotid artery in all subjects. The fact that there is increased activity in cavernous sinus in experimental pain, during cluster attacks, and in "migraineurs" implies that this activation is not specific to cluster headaches. Vascular changes seen are thus more likely to be an epiphenomenon in response to trigeminal pain, rather than an initiator of attacks, hence dispelling the cavernous sinus hypothesis. Moreover, no activation of the hypothalamus was seen in the experimental pain study, further reinforcing its specificity to cluster headaches.

THE HYPOTHALAMIC HYPOTHESIS

In the wake of direct evidence found for a possible hypothalamic involvement, other neuroimaging modalities have been used to shed further light to this hypothesis. Morelli and associates[24] performed the first blood oxygen dependent level (BOLD) functional magnetic resonance imaging (fMRI) study on four patients with episodic cluster headaches. Patients had regular recurrence of their attacks, thus their scans were timed accordingly to allow spontaneous attacks to be captured. Significant activation in ipsilateral hypothalamic grey matter was observed.

May and co-workers[25] performed a voxel-based morphometric analysis on MRI and PET scans of 25 and 17 cluster headache patients respectively. A significant increase in grey matter density localised to inferior posterior hypothalamus was found bilaterally in these patients compared to controls. No difference was detected between patients with active headache and in the headache-free state, indicating that these changes are permanent.

Taking this into account, Lodi and associates[26] performed a proton magnetic resonance spectroscopy (1H-MRS) on 26 pain-free patients with cluster headache. Biochemical levels of N- acetylaspartate (NAA), creatine-phosphocreatine (Cr) and choline (Cho) were assessed. Level of NAA (a neuronal biomarker) was permanently reduced in the hypothalamus of these patients. Such abnormalities are usually identifiable in pathologies like stroke, degenerative disorders, and multiple sclerosis. Similar findings were reported from another proton magnetic resonance spectroscopy study of 47 episodic cluster headache patients. In addition to a reduction in NAA/Cr, a change in the Cho/Cr levels was also detected. These neurochemical changes were consistent with increased grey matter density and a hypothalamic dysfunction in patients with cluster headache, thus further strengthening the possible central role of the hypothalamus in this disorder.[27]

PAROXYSMAL HEMICRANIA (PH)

Seven patients with chronic paroxysmal hemicrania[28] who were completely pain-free on oral indometacin, underwent 11 to 13 radioactive PET scans. Medication was stopped 24-48 hours prior to scanning sessions. Scans were randomised in two states: patient in pain and off indometacin, and patient completely pain-free and off indometacin. All patients then underwent a further separate scan being completely pain-free after administration of 100 mg intramuscular indometacin. Activations in contralateral posterior hypothalamus and ventral midbrain, as well as the ipsilateral lentiform nucleus, anterior and posterior cingulate cortices, bilateral insulae, bilateral frontal cortices, contralateral temporal cortex, contralateral postcentral gyrus, precuneus, and contralateral cerebellum were identified during both the pain and interictal pain-free states. However, this was deactivated in the pain-free state following indometacin administration. The consistent hypothalamic activation observed in this study and those in cluster headaches highlight the related pathophysiological background of these syndromes and the potential role of this region in initiating the attacks (the activated subcortical structures may play a pivotal role in PH pathophysiology).

SHORT-LASTING UNILATERAL NEURALGIFORM HEADACHES WITH CONJUNCTIVAL INJECTION AND TEARING (SUNCT)

The first direct evidence for a hypothalamic dysfunction in SUNCT patients was reported by May and associates[29] who performed a BOLD fMRI. The patient developed 6 consecutive spontaneous attacks in the scanner, lasting from 36 to 96 seconds, with interattack intervals of 2 to 3.5 minutes. In contrast to

the pain-free state, ipsilateral hypothalamic activation was observed solely during attacks. This corresponded to the same area activated in cluster headaches.

Sprenger and co-workers[30] performed fMRI on a patient with a two year history of SUNCT. Interestingly, a vascular contact was detected on ipsilateral trigeminal nerve from structural MRI scans. Patient was able to self-trigger his attacks by touching his upper lip with the lower. Bilateral activation of hypothalamus was reported, as well as activation of the other pain processing areas of the brain. Patient subsequently had surgical decompression of his ipsilateral trigeminal nerve and was pain-free following this intervention. In a separate BOLD fMRI study, Sprenger and other co-workers[31] reported significant activation in the ipsilateral hypothalamic grey matter of a patient with atypical case of TAC.

Nine patients with primary SUNCT and one with symptomatic SUNCT secondary to a brainstem lesion were studied using BOLD fMRI scanning. Bilateral activation of hypothalamus was observed in five of the primary SUNCT cases, whilst two cases showed contralateral activation. Meanwhile, two patients had negative activation ipsilateral to the pain. Moreover, there was no hypothalamic activation in the patient with secondary SUNCT.[32] Authors also investigated two patients with SUNA (short lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms). This rare disorder is often thought to be a subset of SUNCT, due to its similar clinical phenotype, differing only in the amount of cranial autonomic involvement. In SUNA, patients may present with either conjunctival injection or tearing or any of the other cranial autonomic symptoms.[33]

DEEP BRAIN STIMULATION

Neuroimaging studies have provided considerable insight to the pivotal role of hypothalamus in the pathogenesis of TAC. This has brought about advancements in treatment modalities, namely deep brain stimulation (DBS), which has rendered intractable patients pain-free. PET studies performed on 10 cluster headache patients with implanted hypothalamic DBS electrodes found that stimulation induced activation and deactivation in cerebral areas normally involved in pain processing network and in acute cluster headache attacks. In particular, activation was reported in ipsilateral hypothalamic gray (the site of the stimulator tip), ipsilateral thalamus, somatosensory cortex, praecuneus, anterior cingulate cortex, and the ipsilateral trigeminal nucleus and ganglion. Deactivation was observed in the middle temporal gyrus, posterior cingulate cortex, and contralateral anterior insula. There was no evidence found for an antinociceptive effect or a pure inhibition of hypothalamic activity as the mode of action of DBS in cluster headache, thus suggesting the possibility of a yet unknown functional modulation of the neuronal pain-processing pathways.[34]

CONCLUSION

TACs are a group of primary headaches characterized by unilaterality of pain, short duration of symptoms, and associated ipsilateral cranial autonomic symptoms (Horner* syndrome, lacrimation, nasal congestion): There have been numerous studies using a multitude of neuroimaging modalities to help unravel pathogenesis of TAC. The majority have focused mainly on cluster headaches with few studies reported on paroxysmal hemicrania and SUNCT/SUNA. Despite our recent understanding of the hypothalamus as the primum movens structure in TAC, the exact pathways involved in the generation of resultant pain and cranial autonomic symptoms have yet to be identified. Exact mechanism explaining the variation in attack frequency and duration between cluster headaches, paroxysmal hemicrania, and SUNCT which are thought to share the same pathophysiological basis also remains a mystery. The discrepancy in hypothalamic activation visualised in the SUNCT/SUNA patients in the above studies also poses the question of how the strictly unilateral symptoms seen in these patients are exerted. Thus, although there has been much progress in our understanding of the pathophysiology of these disorders, there still remains much to be answered. Hence, further studies in this field are warranted to shed light on these issues.

** Horner syndrome (or Horner-Bernard syndrome or oculosympathetic palsy)= a combination of signs/symptoms caused by disruption of a nerve pathway from brain to face and eye, on one side of the body. Typically, it results in: decreased pupil size + drooping eyelid + decreased sweating on the affected side of the face.*

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Trigeminal Neuralgia - TN: diagnosis and management challenges.

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Abstract

Trigeminal Neuralgia (TN), also known as prosopalgia or "Fothergill's disease", or "suicide disease", was first described by Fehr and Locke at the end of the seventeenth century. Subsequently, Trousseau introduced the nomenclature "Epileptiform Neuralgia" based on a pathophysiological connotation, and in 1756, Nicholas André coined the term "Tic Douloureux". "Prosopalgia" was presented shortly thereafter by John Fothergill ("Fothergill's disease") to the Medical Society in London, England, in 1773. The diagnosis of this chronic neuropathic disorder is clinically based on a normal neurological examination in patients presenting with paroxysmal pain, usually intermittent and unilateral, in one (or more) of the trigeminal nerve branches. All tests show normal results, except in the symptomatic form of the disease.

In this paper, we review and discuss the clinical aspect of TN diagnosis and management.

INTRODUCTION

Patients presenting with TN consult a variety of clinicians, especially GPs, ENT specialists, maxillofacial surgeons, and dentists. The symptoms can occur spontaneously or may be triggered by local oral and maxillofacial causes such as touch, wind, chewing, and facial muscles movements. Therefore, a good diagnosis is essential to avoid unnecessary therapeutic interventions. Once the diagnosis is made and any symptomatic form of the condition rejected, management of TN is mainly medical. Only refractory form of the disease or patient intolerance to medical treatment will be subject to neurosurgical intervention.

Finally, the frequent identification of a vascular loop in contact with the Trigeminal Nerve leading to neurovascular conflict reduces the diagnosis frequency of "idiopathic" Trigeminal Neuralgia[5].

EPIDEMIOLOGY

Age of presentation is usually between 50 and 70 years, with some patients presenting at an age older than 70 not being uncommon. A younger age of onset should push the investigations towards an underlying tumoral or demyelinating pathology. Women to men ratio is 3:2. Incidence is 5 to 6 new cases per 100,000 per year[3,11,12]. Hereditary form of TN is rare.

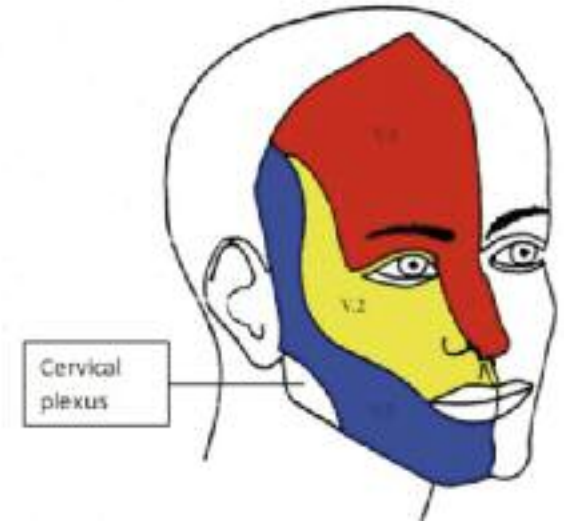

Fig. 1. Schematic drawing of trigeminal nerve territories: Ophtalmic (red), maxillary (yellow), mandibular (blue).

ANATOMY

The name "trigeminal" (literally, three twins) refers to the fact that 5th cranial nerve has 3 major divisions (ophtalmic, maxillary, and mandibular). Trigeminal nerve is a mixed (sensory and motor) cranial nerve responsible for tactition (pressure), thermoception (temperature), and nociception (pain). Its nuclei are

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located in the brainstem and upper cervical cord (spinal nucleus). It emerges from the Pons by two roots: the motor from pars minor and the sensory from pars major. The pars major is connected by a triangular plexus to the trigeminal ganglion (Gasserian ganglion) where the three peripheral branches of the nerve merge: ophthalmic (V1), maxillary (V2), and mandibular branches (V3: the only mixed branch, sensitive and motor). Each of these nerves contains sympathetic and parasympathetic fibers and they are responsible for temperature and touch sensitivity of ipsilateral facial skin, meninges, and teeth (Fig.1). Motor branch of V3 innervates masseter muscles, medial and pterygoid muscles, temporalis muscles, mylohyoid muscle, tensor (veli) palatini, and tensor tympani. Trigeminal nerve is involved in a number of reflexes (masseter, corneal) that are often examined by clinicians because of their clinical significance.

Gasserian ganglion (Fig. 2) is similar to spinal nerve ganglia. It contains all cell bodies of sensory fibers of the face. It is located at the anterior superior surface of the petrous apex. It is contained in the fibrous trigeminal cave (also known as Meckel's Cave or cavum trigeminale), a dural diverticulum in which cerebrospinal fluid surrounds the ganglion. This ganglion has a somatotopic organization: fibers coming from ophthalmic nerve are in a superior-medial position, those from maxillary nerve in middle position, and the ones from mandibular nerve in inferior-lateral position.

CLINICAL PRESENTATION

Diagnosis of essential TN is based on four elements: rapid onset of pain (electric discharge), unilateral topography strictly limited to the territory of trigeminal nerve, triggering circumstances with the presence of a trigger zone, and a normal neurological examination. Any unusual presentation must suggest a symptomatic origin (Table 1).

TN is a severe, stabbing pain to one side of the face: patients usually feel electric discharges, and sometimes pain is similar to burning sensation especially in chronic forms. Pain is paroxysmal, occurring in short bursts, lasting few seconds to few minutes. Apart from these bursts, patient is asymptomatic. The frequency of these bursts is highly variable; they tend to increase with the

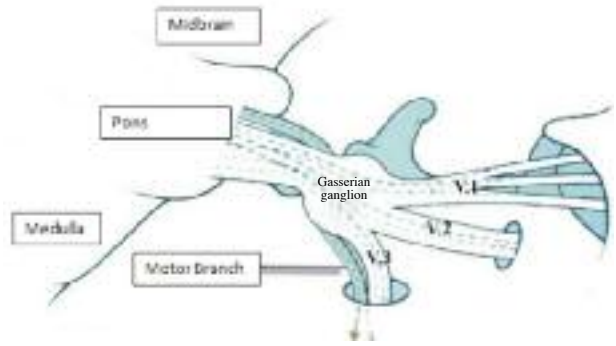

Fig. 2. Trigeminal nerve origin, Gasserian ganglion, and the 3 major divisions.

Trigeminal Neuralgia -TN-

	Typical	Atypical (TN2)
Localization	V1, V2 or V3	Unclear
Pain type	Electric discharge	Burns or other
Between attacks	No pain	Background pain
Vasomotor signs	Absent	May be present
Outbreak	Yes	No
Trigger zone	Yes	Rare
Carbamazepine response	+++–++	+

Table 1. Differences between typical and atypical forms of TN (Atypical TN is also referred to as “TN type 2).

progression of the disease and become continuous, leading to a very painful condition. Most often, the pain is described as intolerable by the patient, with a score of at least 5-6 over 10 on a Visual Analog Scale (VAS).

During a pain attack, facial muscles are tense, and sometimes clonic movements occur: ("Painful Tic"): indeed, pain may be so intense that patients wince unvoluntarily (hence the term “tic”).

Vasomotor phenomena (lacrimation, nasal discharge, ocular redness, and facial flushing) are rare, usually seen in chronic neuralgia and during severe attacks. Pain is unilateral, usually limited to one of the trigeminal nerve branches. Maxillary branch is the most commonly affected. Bilateral involvement, usually asynchronous, is observed in less than 2.5% of cases. Pain can be spontaneous, but is typically triggered by activities such as shaving, bathing, brushing teeth, feeding, speaking, and laughing.

There is usually no pain (or numbness) or facial

muscles dysfunction between attacks and although a flurry of attacks may last several weeks (or months), there are usually periods of months (sometimes years) that are pain-free.

Weight loss is sometimes observed when the patient tries to avoid triggering his pain. There is often a trigger point located in the painful trigeminal territory (upper gum, lip, ala of nose). Usually, a painless mechanical stimulus with low intensity (sneezing) is enough to trigger the attack, while electric or noxious stimuli have no activity.

Neurological examination is normal, except for the rare presence of a slight hypoesthesia in the painful area after an attack or in chronic forms of the disease. Presence of a neurological deficit should suggest a symptomatic neuralgia.

Response to Carbamazepine (an anticonvulsant and mood-stabilizing drug prescribed in epilepsy and bipolar disorder), especially early in the disease, is a key criterion in the diagnosis of essential TN[16]. Disease evolution is intermittent with spontaneous remission periods that can last several months. These periods become shorter and less spaced with disease progression. At the end, pain may become recurrent and chronic. Sometimes, symptom changes can be seen in chronic neuralgia: onset of a painful background, absence of the trigger area, burning pain, vasomotor signs.. etc...

DIAGNOSIS

TN is generally a disease of middle age or later life, and women are usually affected more than men. Most people feel the pain in their jaws, cheeks, or lips on one side of the face, and pain is often so severe that patients are afraid to talk, eat, or move during attacks. In TN, investigation tests are negative. They are usually prescribed in order to rule out symptomatic forms of TN, especially in young patients, and when clinical examination reveals associated neurological signs. MRI, thin cut CT-Scan, or contrast enhanced CT can reveal the cause of symptomatic neuralgia: demyelinating disease, Arnold-Chiari malformation (a brain malformation consisting of a downward displacement of cerebellar tonsils through foramen magnum), small posterior fossa tumor, or a skull base lesion compressing trigeminal nerve. The search for a vascular loop interfering with trigeminal nerve's root (Fig. 3) can be achieved using MRI or Magnetic Resonance Angiography (MRA). However, absence of an obvious loop on MRI does not rule out the presence of a neurovascular conflict. Similarly, the presence of a conflict can be observed in patients without neuralgia, where MRI is requested for another disease. In some patients, the neurovascular conflict is detected on the side contralateral to pain. This reflects the relative reliability of MRI and its limited value without clinical correlation.

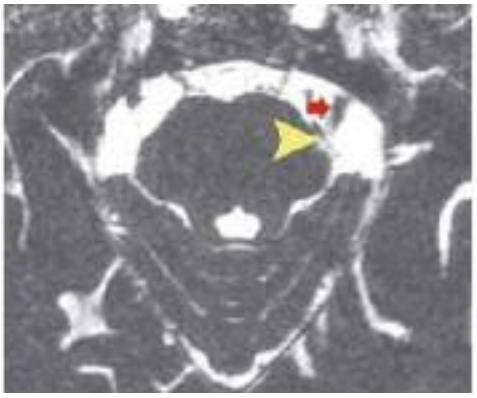

Fig. 3. Axial MRI image displaying a neurovascular conflict; Trigeminal nerve (red arrow), blood vessel (yellow arrow).

Differential Diagnosis

A number of differential diagnoses must be considered in patients presenting with facial pain suggestive of trigeminal neuralgia:

- Symptomatic TN: In most cases, clinical features are atypical. Any suspicion of symptomatic neuralgia should lead to diagnostic tests based on the clinical examination: brain MRI, thin cut CT-Scan, contrast enhanced CT, lumbar puncture, cerebral angiography, or evoked potentials. Etiology may be tumoral (cerebellopontine angle tumor, posterior fossa tumor...), inflammatory (Multiple Sclerosis*), infectious (Zona), a congenital malformation (Arnold Chiari with syringobulbia), traumatic, vascular, or post-radiotherapy…etc...

- Cluster headache: It differs from trigeminal neuralgia in the early age of onset, male predominance,

** Multiple Sclerosis -MS- (or disseminated sclerosis) is an inflammatory disease in which insulating covers of nerve cells in the brain and spinal cord are damaged (Jean-Martin Charcot, 1868).*

Only 2-4% of TN patients (usually younger) have evidence of MS (which may damage either trigeminal nerve or other parts of the brain).

presence of sympathetic component, a dazzling retro-orbital pain following the carotid territory, and specific duration and frequency of attacks.

- Other pain origins: ENT (sinusitis), eyes (glaucoma), dental pain, temporo-mandibular joint, muscular (temporal myalgia), arterial inflammatory disease (Horton's disease), psychogenic, and postherpetic neuralgia (after shingles) may cause similar symptoms if trigeminal nerve is damaged.

Management

The first line treatment of TN is pharmacological. Surgical treatment is proposed only after failure or decreased effectiveness of pharmacological treatment over time or patient drug intolerance. Note that, historically, neurosurgical treatment was used as first line therapy before the discovery of carbamazepine.

1- Pharmacological Treatment

Since its introduction in 1962 by Blom, Carbamazepine (Tegretol®) is the medical treatment of choice for TN: Dosage is gradually increased up to 1000 mg per day, and rarely up to 1200 to 1800 mg per day. Therapeutic response is rapid and satisfactory in 80% of patients, but over time, its effectiveness wears off in at least 50% of patients[5]. The immediate release form is preferable over the sustained-release form of the drug.

Response to treatment is an effective diagnostic test. In some cases, depletion of the analgesic effect over time may require a second or a third drug for control of breakthrough episodes, and may lead to the need of considering a neurosurgical treatment. However, there are no published studies directly comparing monotherapy with polytherapy[19]. Side-effects occurring early in the treatment usually fade with time and adverse reactions are rare[8].

Other drugs that are currently used as second-line treatment or in combination with Carbamazepine are Gabapentin[a] (Neurontin®) or oxcarbazepine (Trileptal®). Compared to the pharmacokinetics of older antiepileptic drugs such as Carbamazepine, these drugs, introduced in the early 1990s, have longer half-lives, permitting a once or twice-daily dosing. This reduced dose decreases potential for drug interactions, general hepatic enzyme induction, and facilitation of polypharmacy[9].

Oxcarbazepine is chemically related to Carbamazepine but follows a slightly different metabolic pathway which offers several clinical advantages. Unlike carbamazepine, oxcarbazepine is not metabolized to an epoxide metabolite, believed to cause toxic effect, and it evokes a lesser decrease in white blood cell count. Aplastic anemia and agranulocytosis that occur with carbamazepine may also occur but less frequently. The most common side-effects are dizziness, headaches, and gastrointestinal disturbances; however the most serious one is hyponatremia[7].

Little controlled data exists for the use of Oxcarbazepine, but trials on its efficacy has shown outcomes to be similar to that of Carbamazepine. The better tolerance of oxcarbazepine is considered to be an advantage, but due to the lack of control data and its higher cost, carbamazepine is still prescribed as first line treatment for TN[2].

Other medications have proved less effective, such as phenytoin[b] (Dilantin®, Di-HYDAN®), Clonazepam[c] (Rivotril®, Klonopin®) and Baclofen[d] (Lioresal®). WHO's class I to III analgesics (including opiates) are generally unsatisfactory in the treatment of Trigeminal Neuralgia.

2- Neurosurgical Treatment

In the eighteenth century, Gasserian ganglion excision was the first surgery proposed for the treatment of trigeminal neuralgia. Thereafter, several surgical techniques have been described; each has its advantages and disadvantages. Currently, there are three neurosurgical techniques for the treatment of TNs refractory to medical treatment:

- Percutaneous techniques: Percutaneous Radiofrequency Trigeminal Gangliolysis, Percutaneous Retrogasserian Glycerol Rhizotomy, and Percutaneous Balloon Microcompression.
- Microvascular decompression.
- Radiosurgery.

a: Gabapentin= anticonvulsant and analgesic drug, commonly prescribed in epilepsy and neuropathic pain arising from diabetic neuropathy, and post-herpetic neuralgia, and central neuropathic pain.

b: Phenytoin= hydantoin - derivative anticonvulsant prescribed primarily in complex partial seizures and generalized tonic-clonic seizures.

c: Clonazepam= benzodiazepine drug, having anxiolytic, anticonvulsant, muscle relaxant, sedative, and hypnotic properties.

d: Baclofen= derivative of GABA (Gamma-AminoButiric Acid), primarily used to treat spasticity, it is also used by compounding pharmacies in topical pain creams as a muscle relaxant.

2.1- Percutaneous techniques

The purpose of these techniques is to create a partial lesion in retrogasserian trigeminal nerve fibers so that the peripheral stimuli no longer trigger neuralgia.

These techniques are reserved for elderly patients with multiple sclerosis, and patients who refuse to undergo cranial surgery. Most patients are relieved from pain but with subsequent facial hypoesthesia. Facial sensory deficit is usually minimal and acceptable in most cases.

A- Percutaneous Radiofrequency Trigeminal Gangliolysis (PRTG)

This technique relies on the fact that theoretically, nociceptive fibers are more sensitive and preferably destroyed by temperatures between 60 and 80°C compared to fibers of touch and proprioception[15]. However, it is proven (experimentally) that all fibers are affected by heat, so that selectivity is only relative. This explains the accompanying tactile hypoesthesia, hypoalgesia, or analgesia after thermal lesion to trigeminal nerve.

Under general anesthesia (without intubation) and radiological control, an electrode is inserted through the cheek, lateral to the corner of the mouth (Hartel's path), passing through ipsilateral foramen ovale, into Meckel's cave to the Gasserian ganglion. The electrode is then positioned at the triangular plexus under radiological control (Figs. 4 and 5), in a retrogasserian position, somatotopically depending on the territory of pain[23]. Once the location of the electrode is considered optimal, radiofrequency lesion is performed. The intensity and duration of radiofrequency are adapted according to the touch hypoesthesia and analgesia obtained in the pain region, clinically assessed after discontinuation of anesthesia. Radiofrequency can be repeated several times during the same session in order to obtain the desired result[26].

A pain relief is obtained after this technique in more than 90% of cases. No recurrence is associated with permanent touch hypoesthesia, observed in 6-9% of cases. The long-term effectiveness is often correlated with the presence of inconvenient sensory disturbances (Anesthesia dolorosa*). Complications of this technique are rare: keratitis, painful anesthesia, masseter muscle paralysis, and exceptionally serious post-operative complications[24].

B- Percutaneous Retrogasserian Glycerol Rhizotomy (PRGR)

This technique consists of injecting glycerol (a sugar alcohol) into trigeminal cistern: under local analgesia, a trocar is introduced into the trigeminal cistern using a technique similar to the insertion of the radiofrequency electrode. A flow of cerebrospinal fluid then occurs, and the injection of non-neurotoxic water soluble contrast agent allows trigeminal cisternography to make sure that the tip of the trocar is in good position. After removal of the contrast agent, 0.2 to 0.4 ml of anhydrous glycerol is injected into the trigeminal cistern. The patient is requested to stay seated an additional two hours until the nerve is fully ablated, and to prevent the escape of glycerol into the posterior fossa[4, 17, 24].

Glycerol induces a reduction of afferent nerve influx that is usually responsible for triggering the attacks, by causing lipo-protidic membrane changes in nerve fibers. This challenging technique has not gained much popularity as the results are not always satisfactory, with a high rate of pain recurrence.

Complications of this technique are rare, and usual side-effects are transient (minor numbness of ipsilateral face and rash herpetiformis). Sensory loss is much less important than in radiofrequency[26].

C- Percutaneous Balloon Microcompression (PBM)

In this technique, the balloon of a Fogarty probe is inflated for few minutes in contact with trigeminal ganglion in Meckel's cave. It is implemented under general anesthesia, and the trocar is introduced into Meckel's cave by the same procedure as in the radiofrequency or glycerol injection. Complications reported include corneal anesthesia and jaw weakness[26]. Results published in the literature displayed success and recurrence rates substantially similar to those with radiofrequency, with fewer sensory deficits[19].

2.2- Microvascular decompression

This surgical technique is based on the presence of a neurovascular conflict in TN between trigeminal nerve and adjacent vessels (Figs. 6 and 7). This obviously calls

** Anesthesia dolorosa= burning, aching, or severe pain felt in an area (usually of the face) which is completely numb. It occurs after 1-4% of peripheral surgery for TN (It is one of the most dreaded complications of TN treatment and it presents with facial numbness, with pain in numb area).*

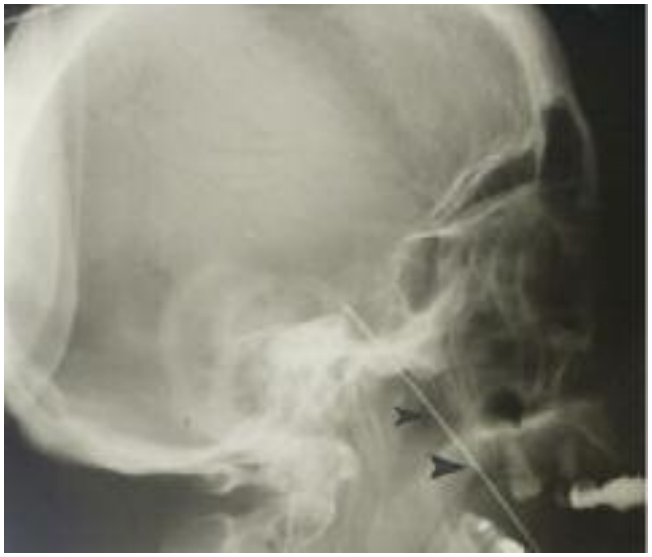

Fig. 4. Plain lateral skull X-ray displaying the position of the radiofrequency probe (2 black arrows).

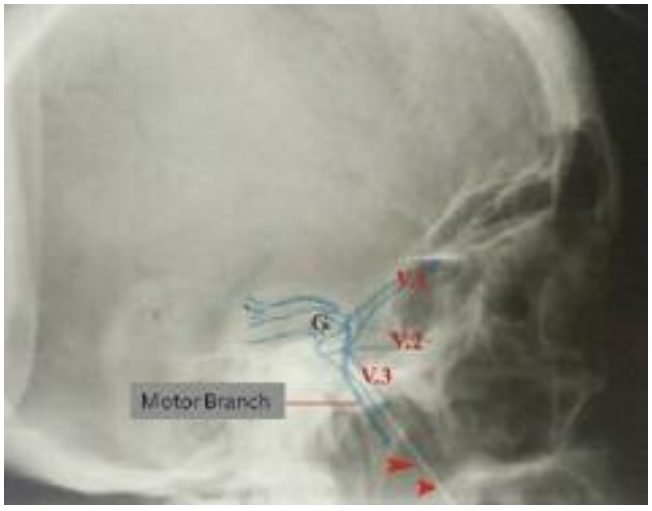

Fig. 5. Lateral Skull X-ray incidence displaying position of radiofrequency probe (two red arrows), theoretical projection of trigeminal ganglion (G) and branches of trigeminal nerve (V1, V2, V3).

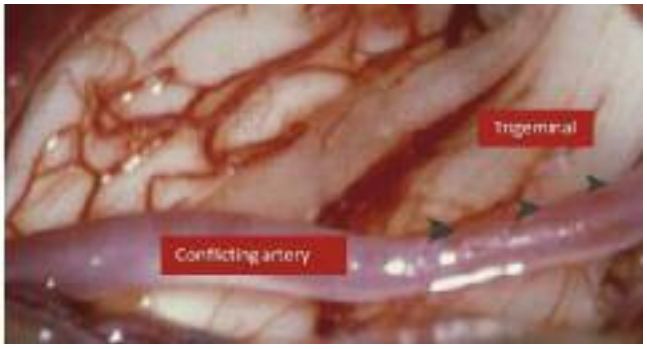

Fig. 6. Intraoperative picture displaying a neurovascular conflict (three arrows) between trigeminal nerve and superior cerebellar artery.

Fig. 7. This intraoperative image shows a neurovascular conflict between superior cerebellar artery (SCA) (red left) and trigeminal nerve (white).

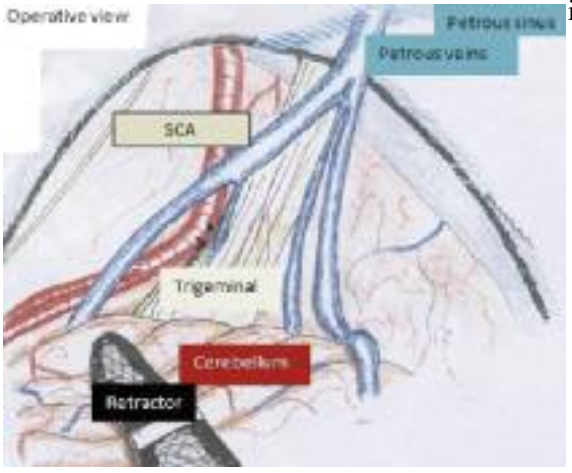

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Fig. 8. This diagram shows a neurovascular conflict (black arrows) between superior cerebellar artery and trigeminal nerve.

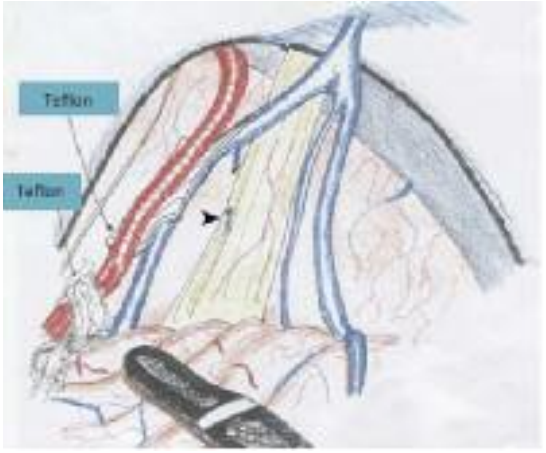

Fig. 9. This diagram shows the surgical release of the conflict (artery is kept away from nerve, using a piece of Teflon).

question the term “essential neuralgia” because there is an anatomical cause for this entity. Many arguments are in favor of this theory: the presence of a neurovascular conflict in more than 95% of cases of TN, high cure rates after surgically separating trigeminal nerve from conflicting vessel, and scarcity of this conflict in patients operated at the cerebellopontine angle for another pathology or for other facial pain etiologies (partial rhizotomy for cancer pain).

The conflict with trigeminal nerve occurs the most commonly with superior cerebellar artery, and less often with anterior inferior cerebellar artery. Sometimes, there are several conflicting vessels, including veins. Compression of trigeminal nerve by a vessel distorts the nerve with lesions of nerve fibers secondary to arterial pulsations, causing segmental demyelization with “bypasses” leading to pain.

Microvascular decompression for TN has been well described since the 1970s [14]. This surgical procedure is done under general anesthesia and lasts two hours on average. A 4 to 5 cm long skin incision is made behind the mastoid, with a craniotomy of 1.5 cm in diameter. Under the operating microscope, the trigeminal nerve is approached at the trigeminal cistern, and a dissection of the arachnoids is followed by a careful separation between the nerve and the conflicting artery. This separation is maintained using Teflon and / or Dacron to prevent subsequent compression (Figs. 8 and 9).

Advantage of this technique is in its conservative nature; it targets the "cause" of neuralgia and does not lead to sensory disorders observed in other techniques. This technique is indicated in patients with "physiological" young age, who present no contraindication for craniotomy under general anesthesia. There is no age limit, but surgery is preferred in patients less than 70-75 years of age. In addition, indication takes into account the skills of the neurosurgeon, especially in borderline cases, as well as the patient's personal choice between surgery and percutaneous techniques.

Results are very good, with total pain relief in more than 95% of cases, especially when the conflict is obvious. Recurrences are observed in 6-10% of cases. The most common complications are the usual surgical complications under general anesthesia, diplopia by nerve IV damage (Trochlear), ipsilateral hearing loss, temporary facial palsy, fistula of cerebrospinal fluid, and infection (meningitis)[1]. More serious

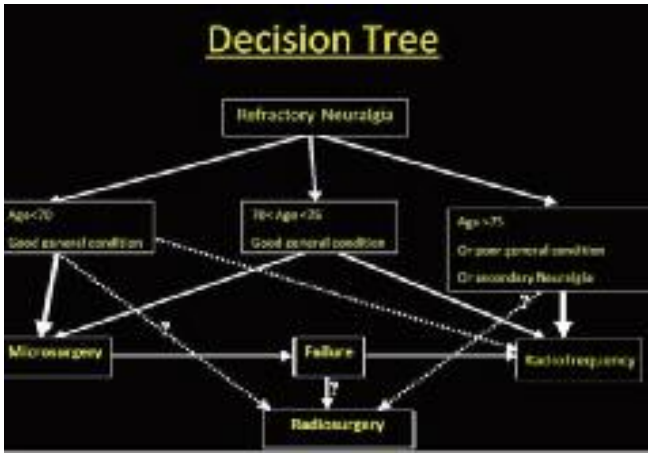

Fig. 10. Algorithm showing the most appropriate technique in patients with refractory TN.

complications are rare.

3- Stereotactic Radiosurgery - SRS (Gamma Knife® and Linac®)

SRS is a form of radiation therapy that focuses high-power energy on a limited (small) area of the body.

Gamma Knife® -GK- is a technique that was developed by Leksell, specifically for the treatment of TN. It has become more widely available since the early 2000s for the treatment of essential neuralgia[26]. It consists of delivering "focused" radiation therapy to the entry point of trigeminal nerve without the need for surgery[6,18]. It is the only non-invasive technique.

It is performed using a stereotactic frame installed temporarily on patient's head under local analgesia[26]. It takes place in a single session, delivering 75-90 Gy of radiation to the target to destroy specific components of the nerve[6,18]. The result is observed on average after 3-4 weeks following the procedure. It is recommended that patients who have a recurrence of pain following GK, or did not have a complete response can undergo a second radiosurgery using 50 to 70 Gy with a minimum elapsed period of 6 months[13].

Based on recent published series, this technique proved to be effective in two thirds of patients, with slight bothersome hypoesthesia correlated with its prognosis; sensory side effects are rare. Currently, it is indicated as second-line treatment after failure by pharmaceutical management and surgical decompression (including previous radiosurgical procedures). Patients who are shown to benefit most are patients following failure by pharmaceutical

management who have not yet received pharmaceutical interventions [10, 13]. Randomized controlled trials assessing more precisely its effectiveness and potential complications are essential to define its indications in the future.

Linac® is a newer stereotactic radiosurgery technique that uses a linear accelerator to create high-energy photons with a single source and a tightly focused beam. This technique rotates the radiation source relative to the patient during exposure, permitting a prescribed dose to be delivered to the target area while minimizing the dose to surrounding tissues. Theoretically, the smaller penumbra of the Linac®-based SRS should have an advantage over the Gamma Knife® for rates of success and reduced side-effects but no direct clinical comparisons have been completed[22].

4- Treatment choice

The treatment choice depends on several factors: patient's age, general condition, anesthetic consultation, desire of the patient and / or family, availability of neurosurgical techniques, and the neurosurgeon's preferences based on his/her experience. The algorithm displayed in figure 10 provides a general idea for the choice of treatment.

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** IRSA®= International RadioSurgery Association is an independent organization (dedicated, since 1995, to provide educational information and guidelines on stereotactic radiosurgery for brain tumors and brain disorders).*

Current guidelines for the diagnosis and management of TemporoMandibular Disorders (TMDs)

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Diplomate/American Board of Orofacial Pain

Abstract

TMDs are musculoskeletal disorders that can be detrimental to quality of life because of their chronicity and difficulty of management: they are not psychological or social disorders.

Counseling and reversible treatment modalities are first choice options. TMDs assessment, diagnostic subgroups, and management strategies are reviewed in this paper.

Musculoskeletal conditions affecting the jaw (TMD) are the major cause of acute non-odontogenic pain and the most common cause of chronic pain in the orofacial region.

TMDs are rare in children prior to puberty with the peak age around 35 to 45 years of age. Studies reporting the rates of ongoing presence of TMD pain range from 9% to 15% in women and 3% to 10% in men. Epidemiological studies reveal that females seek treatment more than males. Gender ratio varies between cross-sectional studies from anywhere from 6:1 to 2:1 female to male.[1, 2] Jaw disorders are similar to other musculoskeletal disorders, but currently little is known about the natural course of most jaw disorders and which signs and symptoms will progress to more serious conditions. As with other musculoskeletal disorders, jaw symptoms often wax and wane. Even though they are not life threatening, they can significantly affect the quality of life. [3, 4] They include masticatory muscle disorders (non-articular) and temporomandibular joint (articular) disorders. Internationally established pain classifications with operational diagnostic criteria for the various TMD conditions serve as useful guides. [5]

The American Academy of Orofacial Pain's classification of temporomandibular disorders includes a disparate group of nonarticular, masticatory muscle conditions and articular conditions that often have similar signs and symptoms.[6] Masticatory muscle disorders include myalgia, myofascial pain, myositis, myospasm or trismus, contracture, and neoplasia.[7, 8]

- Myalgia is characterized by regional or local dull, aching muscle pain that increases during function.
- Myofascial pain is characterized by localized tender sites or trigger points in the muscle, tendon, or fascia. Referral of pain to a distant site such as the teeth, ear, or head is present.
- Myositis is defined as a true inflammation of muscle usually due to direct trauma and/or infection.
- Myospasm or trismus is an acute muscle disorder characterized by a sudden, involuntary, tonic contraction (fasciculation) of a muscle. Acute pain is present at rest as well as during function, and function is significantly limited.
- Muscle contracture is a painless shortening of a muscle as a result of fibrosis or scarring of the supporting tendons, ligaments, and/or muscle fibers.
- Muscle neoplasia is defined as a new, abnormal, or uncontrolled malignant or benign growth of tissue within the muscle.

Articular disorders include developmental or acquired disorders, articular disc disorders, inflammatory-immune disorders, infection, osteoarthritis, condylar dislocation, ankylosis, and fracture.[9-10]

- Developmental disorders of mandibular condyle

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include agenesis, aplasia (faulty development), hypoplasia (incomplete or underdevelopment), and hyperplasia (non-neoplastic overdevelopment). Acquired disorders include benign (eg, osteoma, chondromas, synovial chondromatosis), malignant, or metastatic neoplasms.

• The most common TMJ* disc disorder is disc displacement with reduction, in which mandibular condyle moves into a more normal position with the displaced disc during translation, usually creating a joint sound at the time of the reduction (ie, clicking). Disc displacement without reduction (mandibular condyle fails to re-establish an improved anatomic relationship during movement), can be acute or chronic (over 3 months).

• Inflammation can occur in the synovium (synovitis) and/or capsule (capsulitis) as a result of local trauma, infection, or degeneration, or as a part of a systemic polyarthritic or collagen disease (rheumatoid arthritis, lupus, Reiter's syndrome).

• Osteoarthritis (OA), is a non-inflammatory degenerative condition of the joint characterized by deterioration and abrasion of articular tissue and concomitant remodeling of the underlying subchondral bone. Initially OA is an active degenerative process, but becomes stable within 18 to 48 months (natural history).

• Mandibular condyle subluxation or dislocation occurs when the condyle becomes positioned anterior and superior to the crest of articular eminence, usually during jaw opening, and is unable to return to a closed position. This condition is referred to as subluxation if the patient is able to self-manipulate his/her mandible back to a closed position. It is called open lock or dislocation if a health care provider has to reduce the anteriorly positioned mandibular condyle.

• Ankylosis can consist of either fibrous or bony adhesions that restrict mandibular condyle movement.

• Fracture of mandibular condyle usually results from direct trauma to mandible but can be iatrogenic or secondary to a pathologic process.

ASSESSMENT

It becomes a daunting task to correctly identify all of the possible sources of pain and/or dysfunction that might be the cause, the effect or be coincidental to a patient's complaints. Screening for jaw disorders (TMDs) is an essential part of all routine dental examinations. The need for the collection of additional records and diagnostic tests is based on the magnitude of the presenting complaints and the potential for the problem progressing physically or psychosocially. The diagnostic process is critical because an incorrect or omitted diagnosis is one of the most frequent causes of treatment failure. There is not a gold standard, such as biopsy with cancer, against which a diagnostic test can be easily compared for accuracy and reliability.[11,12] The best substitute is a comprehensive history, physical examination, and selective use of imaging for conditions affecting joint structures. *(See Addendum: AADR** TMD Policy Statement Revision).*

• Comprehensive history parallels the traditional medical history and review of systems, and consists of the chief complaint(s), history of the present illness(es), medical history, dental history, and personal history (social & family). It is important for the clinician not to get lost in multiple complaints, and thus, the history of the present illness should include a chronological history for each complaint.[3]

• Comprehensive physical examination consists of a general inspection of the head and neck, including a visual inspection and palpation; a comprehensive orthopedic evaluation of the TM joint, and cursory evaluation of the cervical spine; a masticatory and cervical muscle evaluation; cursory evaluation of the cranial nerves; and an intra-oral evaluation. It is important to note that many clinical signs are not measured reliably from both intra- and inter-operator standpoints.[6]

• The first, second and third cervical nerves innervate the angle of mandible, the region inferior to TMJ*, and parts of the ear, neck, and back of the head. Therefore, any irritation and/or dysfunction of these nerves can be associated with facial and mandibular pain. Also, convergence of noxious input from these upper cervical nerves with the trigeminal nerve can result in referred pain to the orofacial region.[13]

• Imaging of the TM joint and orofacial structures may be necessary to rule out structural disorders. They are ordered primarily when the clinical examination suggests some form of joint pathology or when there is

** TMJ= Temporo-Mandibular Joint.*

*** AADR= American Association for Dental Research.*

a suspicion of some other serious non-musculoskeletal pathology such as an infection or tumor.[14]

• A panoramic screening radiograph can provide helpful screening evidence of possible pathoses in the TMJ or other orofacial structures.

• Cone Beam Computed Tomography (CBCT) is the most accurate method for radiographically examining patients with suspected TM joint degenerative joint disease, bony abnormalities, i.e., developmental anomalies, trauma, or hard tissue neoplastic conditions of the TM joint.
(Radiation dosage is extremely low, approximating the dosage between a panoramic radiograph and full-mouth survey; approximately one/thirty-fifth of the dosage of a medical CT scan.[15, 16]*)*

• Magnetic resonance imaging (MRI) has diverse capabilities for examination of most cases of suspected TM joint soft tissue disorders and pathology, i.e., disc displacement, effusion, and tumors. However, for the routine study of jaw disorder patients, MRI is rarely indicated for non-surgical management primarily because the study does not usually change the treatment approach.

• A variety of additional diagnostic studies are available for use in selected cases to assist in confirming a physical diagnosis. Diagnostic tests may include laboratory tests (blood chemistries) for systemic arthritides, diagnostic injections for TM joint and masticatory muscle conditions, spray and stretch to determine if a soft-tissue trigger point is a source of pain, physical therapy evaluation to determine the appropriateness of rehabilitation, to evaluate the cervical spine as a source of orofacial pain and to perform a fibromyalgia screening to determine the scope of pain.[17]

• There are a number of adjunctive diagnostic devices marketed to diagnose jaw disorders (TMD), but recent published papers have questioned the sensitivity (percentage of correctly diagnosed patients) and reliability (percentage of correctly diagnosed normals) of these technical diagnostic "TMD" tests[18]. Many of the devices, including electromyography testing, jaw tracking, thermography, sonography and vibration analysis, lack research support and are subject to great biologic variability[19-26]. The risk of an incorrect diagnosis often based on over-interpretation of insignificant or normative physiological data can result in mistreatment or over-treatment of the patient and are not supported by the American Academy of Orofacial Pain, the Association of University-based Orofacial Pain Clinics, and the International and American Associations of Dental Research.

(There is insufficient evidence that vibration analysis of temporomandibular joint can diagnosis disc displacement with reduction more accurately than the use of stethoscope and palpation. Jaw tracking instrumentation that provides additional measurement data regarding mandibular movements, does not justify treatment of the occlusion for TMD patients. The "high-tech electronic devices" that record jaw relationships and jaw movement are often recording biologic variations with a misleading degree of diagnostic specificity resulting in a high number of false positive diagnoses, and unnecessary treatment. The interpretation that these data is often interpreted as supportive evidence that the occlusion needs to be altered from a TMD management standpoint is not in agreement with evidenced-based research.)

MANAGEMENT

The majority of patients with jaw disorders achieve good symptomatic relief with a medical model using noninvasive management[27,28]. Therefore, the scientific literature strongly supports that a special effort should be made to avoid aggressive, irreversible therapy for most temporomandibular disorders. Thus, based on the complications, risks and potential poor outcomes, surgery of the temporomandibular joint is only suggested in carefully selected cases. A multidisciplinary medical model that may include any combination of patient education and self-care, cognitive behavioral intervention, pharmacotherapy, physical therapy, and/or occlusal appliance (orthotic) therapy is endorsed for the management of TMD patients: Common goals are reduction of pain, reduction of adverse loading, improvement of mobility and function, and restoration of daily living activities. The emphasis should be on conservative therapy that facilitates musculoskeletal system's natural healing capacity[29,30]. Management requires the patient to assume responsibility for the physical and behavioral management of his/her own problem. *(See Addendum: AADR TMD Policy Statement Revision).* [31]

It is strongly recommended that use of the terms phase I and phase II in the treatment of TMDs be discontinued, as the terms imply that phase II inevitably follows phase I. The scientific literature does not support the need of two-phase treatment because definitive occlusal therapy is not required for effective treatment of TMD. There is no clear evidence that natural occlusal morphologic variation is a common cause of TMD[19, 32-35]. There is no evidence of a higher incidence of TMD with any type of malocclusion, and significant proportions of the population have occlusal discrepancies without any TMD pain or dysfunction. There are many testimonials and belief systems that claim that occlusion is the primary etiologic factor for jaw disorders (TMD), but scientifically a direct correlation is largely unproven[12, 36]. Fortunately, in most areas of medicine and dentistry, when significant research findings contradict a long-believed concept or assumption, it will eventually lead to the abandonment of that belief by both researchers and clinicians[37]. But as Dr. Charles Greene recently stated, "unfortunately, the TMD field seems to be one of those areas where such an orderly transition is very slow to make such a transition"[27]*.

• Patient Education and Self-Care

When the jaw disorder is mild, patient education and instructions in a self-care program may be all that is required. Self-care instructions should be diagnosis specific and goal oriented. These instructions typically include resting the masticatory system through soft diet, habit awareness, and modification. They may include the use of moist heat, ice, self-massage, and gentle range of motion exercises.

• Cognitive Behavioral Intervention

Simply making patients aware of their jaw habits is often enough to improve jaw relaxation skills, but changing persistent habits may require a structured program with a clinician trained in behavior modification strategies. Comprehensive stress management and counseling programs using a combination of EMG biofeedback, progressive relaxation, and self-directed changes in lifestyle appear to be more effective than any one behavioral treatment procedure in isolation.[38] Patients with long-standing pain or who have experienced multiple treatment failures require in-depth psychological evaluation and treatment by a mental health professional such as a psychologist or psychiatrist.[39]

• Pharmacotherapy

The indicated classes of pharmacologic agents include analgesics, non-steroidal anti-inflammatory drugs, corticosteroids, anxiolytics, muscle relaxants, and low-dose pain-dosing of antidepressants.[40] The non-opiate analgesics are effective for mild to moderate acute pain, whereas the opioid narcotics should only be used short term for controlling acute severe pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are effective analgesics, and are prescribed for painful articular inflammatory disorders. When NSAIDs are ineffective, oral or intra-articular injections of corticosteroids should be considered. The benzodiazepines are most commonly prescribed for their anti-anxiety effects, but have secondary muscle relaxation affects. Muscle relaxants, with the possible exception of Flexeril, derive their therapeutic action from their sedative effect only, but can be useful for masticatory muscle pain. The tricyclic antidepressants when used in low dosages (10mg.-75mg.) have been shown to work in the central nervous system improving the patient's pain regulation. They are prescribed for chronic pain patients who have neuropathic pain, persistent myofascial pain, and poor sleep. Early observations suggested that they, as well as Flexeril (= cyclobenzaprine, a muscle relaxant), may also reduce sleep bruxism.

• Physical Medicine

Physical therapy is well recognized as an effective, conservative approach for patients with jaw disorders. Physical therapy involves both a comprehensive head, neck and upper quarter orthopedic evaluation and a rehabilitation program designed to restore optimal masticatory and cervical functions. Treatment goals include pain control, optimizing joint biomechanics

** Also see Dr. Charles S. Green's article titled "Managing the care of patients with TMDs: a new guideline for care" and a revision of AADR's 1996 policy statement on TMDs, approved by AADR council in March 2010, and published in September 2010, in the Journal of the American Dental Association (JADA).*

and range of motion, restoring functional muscle strength and endurance, and restoring the ability to perform activities of daily living such as talking, chewing, yawning, and singing. Management begins with patient education and instructions in a structured self-care program. The next goal is to reduce pain as efficiently as possible, so patients can begin exercising their jaw, neck and upper quarter. Physical agents such as moist heat, cold packs, transcutaneous electrical nerve stimulators (TENS), iontophoresis, ultrasound, and vapocoolants, may be used as well.[41]

• Orthotic Therapy

Orthoses, also referred to as occlusal splints, orthopedic appliances, night guards, bite plates, or bruxism appliances, are commonly used in the management of jaw disorders[29,32,42]. Patients who report that their symptoms are clearly related to exaggerated jaw activity during sleep (sleep bruxism) may benefit from an orthosis worn at bedtime although some patients actually have increased symptoms with appliances worn at night[32]. Day-time bruxism and increased jaw tenseness can be modified by the patient and typically do not require an orthosis. There is new evidence that the amount of time of tooth contact during sleep is quite minimal (seconds to several minutes) and is far less sustained than awake bruxism.[43] There is great debate about the design and use of an orthosis for the greatest efficacy.[44-47] Recent outcome studies report that orthotic therapy is no more effective than other treatment modalities especially when two other treatments are utilized, especially when emphasizing patient education[46,48].

Newer guidelines strongly suggest that orthosis wear only occur during sleep and not the more historical concept of full-time wear. Risks associated with full-time wear include irreversible changes in mandibular posture often requiring complex occlusal treatment that would not otherwise be needed. The most recent studies show the orthosis design may not be a very critical factor as long as a template is placed between the teeth and that all the teeth on either the maxillary or mandibular arch are covered. Complete coverage of the teeth in the arch prevents tooth eruption and/or overload of a limited number of covered teeth creating tooth sensitivity or increased mobility such as with the use of a posterior tooth or anterior tooth contact only appliance. Anterior tooth contact only appliances (NTI) increase the loading in the TM joint, they are contraindicated for joint related diagnoses[28].

• Surgery

Temporomandibular surgery is the indicated treatment for a very small percentage of TMD patients. The most appropriate patients for surgery have localized structural articular disorders rather than global, diffuse pain conditions. Surgery is indicated for patients that require joint structural debridement and/or arthroplasty, such as for synovial chondromatosis, tumors, ankylosis, and displaced condylar fractures. Surgical management may vary from closed surgical procedures (arthrocentesis and arthroscopy) or open surgical procedures (arthrotomy) to subcondylar osteotomies (condylotomy)[49,50].

CHRONIC PAIN WITH ASSOCIATED COMORBIDTIES

The above temporomandibular disorder treatment modalities were presented regarding acute TMD disorders that are relatively short lived and not the more complex chronic TMD disorders that are usually present for many months or years. When pain becomes more persistent with associated neuroplasticity changes including peripheral and/or central nervous system sensitization, management dramatically changes[51-54]. The effects of these complex changes associated with an up-regulation in pain mechanisms typically result in allodynia (pain due to a stimulus which does not normally provoke pain) and hyperalgesia (an increased response to a stimulus which is normally painful). The chronic TMD pain patient develops an increase in anxiety, depression, and somatization (increased awareness of physical symptoms) psychometric levels that now require an interdisciplinary treatment approach or the normal acute TMD treatments described above will fail[39,55].

Lastly, many chronic TMD pain patients will have a number of comorbid or concurrent pain conditions, including but not limited to the following: headache, neck and shoulder pain, back pain, global muscle pain (fibromyalgia), irritable bowel syndrome, abdominal

pain, pelvic pain, and/or sleep depravation[56-59]. These very difficult, complex patients cannot be treated in isolation or the treatment will be far less successful. A multidisciplinary or interdisciplinary team of health providers is required in order to manage pain and return to the patient his/her reasonable functional daily living activities.

The management team can include pain specialists, anesthesiologists, neurologists and neurosurgeons, dentists and orofacial pain specialists, physical therapists, clinical psychologists, neuro-psychiatrists, nurses and other health care professionals trained to manage chronic pain. It is essential that the dentist recognize whom to treat and whom not to treat and when to refer to the appropriately trained health professionals.

ADDENDUM: AADR TMD Policy Statement Revision

AADR* recognizes that temporomandibular disorders (TMDs) encompass a group of musculoskeletal and neuromuscular conditions that involve temporomandibular joints (TMJs), masticatory muscles, and all associated tissues. Signs and symptoms associated with these disorders are diverse, and may include difficulties with chewing, speaking, and other orofacial functions. They also are frequently associated with acute or persistent pain, and the patients often suffer from other painful disorders (comorbidities). Chronic forms of TMD pain may lead to absence from or impairment of work or social interactions, resulting in an overall reduction in quality of life.

Based on the evidence from clinical trials as well as experimental and epidemiologic studies:

1. It is recommended that differential diagnosis of TMDs or related orofacial pain conditions should be based primarily on information obtained from patient's history, clinical examination, and when indicated, TMJ radiology or other imaging procedures. The choice of adjunctive diagnostic procedures should be based upon published, peer-reviewed data showing diagnostic efficacy and safety. However, the consensus of recent scientific literature about currently available technological diagnostic devices for TMDs is that except for various imaging modalities, none of them shows the sensitivity and specificity required to separate normal subjects from TMD patients or to distinguish among TMD subgroups. Currently, standard medical diagnostic or laboratory tests that are used for evaluating similar orthopedic, rheumatological and neurological disorders may also be utilized, when indicated, with TMD patients. In addition, various standardized and validated psychometric tests may be used to assess psychosocial dimensions of each patient's TMD problem.

2. It is strongly recommended that, unless there are specific and justifiable indications to the contrary, treatment of TMD patients initially should be based on the use of conservative, reversible, and evidence-based therapeutic modalities. Studies of the natural history of many TMDs suggest that they tend to improve or resolve over time. While no specific therapies have been proven to be uniformly effective, many of the conservative modalities have proven to be at least as effective in providing symptomatic relief as most forms of invasive treatment. Because those modalities do not produce irreversible changes, they present much less risk of producing harm. Professional treatment should be augmented with a home care program, in which patients are taught about their disorder and how to manage their symptoms.

(adopted 1996, revised 2010) [31]

* *AADR= American Association for Dental Research.*

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Anatomy and physiology of trigeminal networks conveying nociception: a review.

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Abstract

Trigeminal pain signaling system, like other sensory systems, employs specialized peripheral receptors to interact with its environment, with the goal to integrate information arising simultaneously from different sources. The purpose of this paper is to address some aspects of anatomical and functional organizations of trigeminal networks that convey nociceptive information. Peripheral polymodality, redundancy of representations of orofacial structures, pain pathways of trigeminal system, sensory transformation, and convergence are reviewed.

INTRODUCTION

A number of acute and chronic pain syndromes occur in the area innervated by the trigeminal nerve. Perhaps the main reasons to study the neurobiology of trigeminal pain lie in the fact that trigeminal neuralgia, idiopathic orofacial pain, cluster headache, temporomandibular disorders and migraine are specifically expressed in this region. Although little is known about their pathophysiological mechanisms, these chronic pain syndromes are among the most impairing and difficult to treat, leading to non-negligible expenses for health care services, loss of work-hours, and decreased productivity. A better understanding of the mechanisms of orofacial nociception will probably lead to the development of new treatment modalities for persistent orofacial pains.

Although modern neurobiological techniques have provided a better knowledge of nociceptive signal processing within the spinal cord, progress still remains to be made in order to elucidate the mechanisms underlying the processing of nociceptive information within the brainstem trigeminal complex. Anatomical and functional particularities of brainstem trigeminal sensory complex may also provide a better understanding of the processing of nociceptive information within spinal dorsal horn neuronal networks.

The trigeminal system represents an interesting model for the general study of pain since the somesthesic functions of oral cavity and the face are strongly represented. For instance, density of receptors on tongue or lips is higher than anywhere else in the body and orofacial thalamic and cortical maps are larger than those of the hand in humans. The purpose of this paper is to review some aspects of anatomical and functional organizations of trigeminal networks that convey nociceptive information.

INNERVATION OF OROFACIAL REGION

Orofacial region is supplied by trigeminal nerve and upper cervical nerves[(1)]. Trigeminal nerve emerges from brainstem at pontine level as two roots, a voluminous sensory root and a small motor root supplying masticatory muscles, tensor tympani, tensor (veli) palatini, anterior belly of digastric muscle, and mylohyoid muscle. Sensory root consists of 3 branches (Figs. 1 and 2):

- The ophthalmic branch (V1) that innervates skin of forehead, upper eyelid, cornea, meninges, and most of the nose. It is also responsible of innervation of a cutaneous territory including the front of temporal

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region, as well as a mucous territory containing nasal fossa, ethmoidal, and frontal sinuses.

- The maxillary branch (V2) exits the skull from anterior opening of foramen rotundum canal and emerges into upper pterygopalatine fossa. Maxillary nerve has the following branches: infra-orbital nerve (supplies lower eyelid, ala of the nose, upper lip, and skin of the cheek), superior alveolar nerve (innervates maxillary teeth, gums, and neighbouring parts of cheek's mucosa), pterygopalatine nerve (supplies the mucous membrane of hard and soft palates, uvula, tonsils, and mucous membranes of nose, maxillary sinuses, and nasal fossa).

- The mandibular branch (V3) exits the skull through foramen ovale and runs down into infratemporal fossa. It supplies the skin of temporal region, front of auricle (ear), external auditory canal, lower face, mucous membrane of anterior two-thirds of dorsal tongue, floor of the mouth, mandibular teeth, and temporomandibular joints.

- Other sensory innervation afferents contributing to head and neck, travel with upper cervical plexus (C2) (which supplies neck, posterior part of the skull, and angle of mandible) and Glossopharyngeal nerve (IX) (carries general sensory information from skin of external ear, internal surface of tympanic membrane, walls of upper pharynx and posterior one-third of the tongue).

FEATURES OF TRIGEMINAL NOCICEPTORS

Orofacial somatosensory information is processed by various types of fibers that can be classified according to their peripheral origin (cutaneous, muscular, articular, or visceral), conduction velocity, sensory modality, and neurochemical phenotype (expression of peptides). Nearly all primary afferents supplying orofacial tissues have their cell bodies in the trigeminal ganglion. Cell bodies with the largest diameters give rise to myelinated, rapidly conducting Aβ primary sensory fibers. Most, but not all[2], Aβ detect innocuous stimuli applied to skin, muscle and joints and thus do not contribute to pain. Indeed, stimulation of large fibers can reduce pain, as it occurs when you activate them by rubbing the irritated areas. By contrast, small- and medium- diameter cell bodies give rise to most of the nociceptors, "free endings nerves". Nociceptors are found in all orofacial tissues

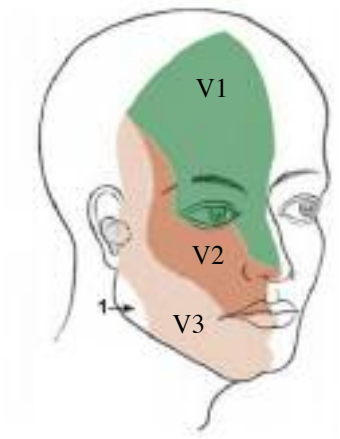

Fig. 1

Innervation of orofacial region (V1, V2, V3)
1. Upper cervical plexus (C2).

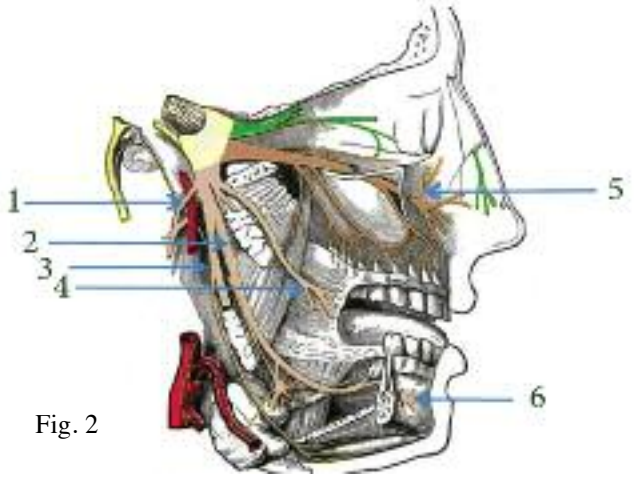

Fig. 2

1. Auriculotemporal nerve; 2. Lingual nerve;
3. Inferior alveolar nerve; 4. Buccal nerve;
5. Infraorbital nerve; 6. Mental nerve.
(from Wikipedia).

(skin, tooth pulp, periodontal, muscular, articular, and meningeal).

The primary function of a nociceptor is to detect damaging or potentially damaging environmental challenges to orofacial tissues. Some of the tissues in orofacial region (e.g. tooth pulp, periodontium, cornea) are unique to this part of the body and tissues such as dental pulp, cornea, and dura mater* lack appreciable innervation by large diameter afferent fibers and generally evoke nociception to natural stimuli[3].

* *Dura mater= the outermost and most fibrous of the 3 membranes (dura, arachnoid membrane, and pia mater) covering brain and spinal cord.*

There are two major classes of nociceptors[4]: the first includes medium diameter myelinated (Aδ) afferents that mediated acute, well-localized "first" or fast pain[5]. The second class includes small diameter unmyelinated (C) fibers that convey poorly localized, "second" or slow pain. Neuroanatomical and molecular characterizations have further subdivided C nociceptors into two major subtypes: one group contains neuropeptides, whereas the other group lacks peptides. All peptidergic primary afferents appears to contain Calcitonine Gene-Related Peptide (CGRP)[6]. Many of them also contain Substance P (SP), while a smaller portion contains somatostatin, and these two peptides are present in two non-overlapping populations[7]. They express the Transient Receptor Potential Vanilloide 1 (trpV1**) which is sensitive to temperatures higher than 43°C. Non-peptidergic C-fibers contain fluoride-resistant acid phosphatase activity (FRAP), binds the isolectin B4 (IB4)[8-10], and express adenosine triphosphate P2X3 receptor subunit, a member of the P2X family of ATP-gated ion channels[10].

C-fibers also differ anatomically in that they each terminate in distinct but overlapping regions of the superficial laminae of spinal trigeminal subnucleus caudalis (Sp5C). Peptide-containing neurons project to lamina I and outer lamina II[7], somatostatin afferents mainly project to outer lamina II[11,12], while IB4 and FRAP-positive neurons terminate predominantly in inner lamina II[13]. In the Sp5C, the P2X3-ir was observed in the inner portion of lamina II. In contrast, vanilloid receptors VR1 to which capsaicin binds with high affinity, are expressed both in these cells and in TrkA-expressing NGF-responsive neurons[14].

Another class of C fibers has recently been identified, the functional role of this class is not yet fully elucidated, but their neurophysiological response properties, fiber class, and slow conduction velocities preclude their role in any rapid mechanical discriminative or cognitive tactile tasks, and point to a more limbic function, particularly the emotional aspects of tactile perception[15,16].

Orofacial tissues are subject to frequent injury due to trauma, infection, or iatrogenic damage following surgery (e.g., tooth extraction) that can lead to peripheral sensitization. This phenomenon results from the production and release of chemical mediators from primary sensory terminal and non-neural cells in the environment. Some components of so-called "inflammatory soup" (potassium ions, hydrogen ions,

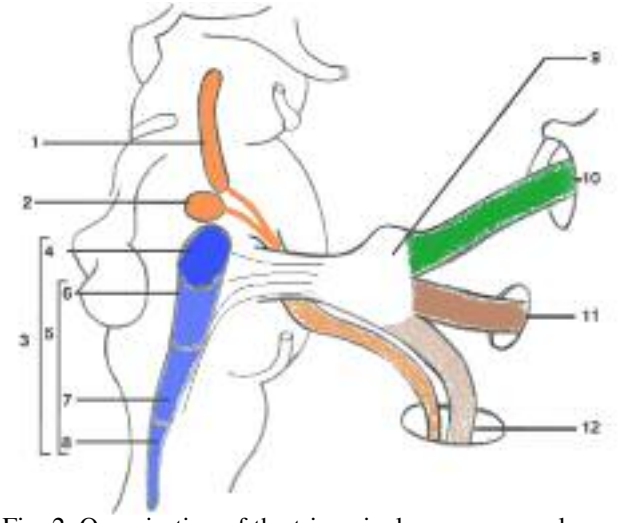

Fig. 2. Organisation of the trigeminal sensory complex
1:Mesenphalic nucleus; 2 : Motor nucleus; 3: Trigeminal Sensory Complex; 4: Principal Nucleus; 5: Spinal trigeminal nucleus; 6: Subnucleus Oralis (Sp5O);
7: Subnucleus Interpolaris (Sp5I); 8: Subnucleus Caudalis (Sp5C); 9: Trigeminal ganglion; 10: V1; 11: V2; 12: V3

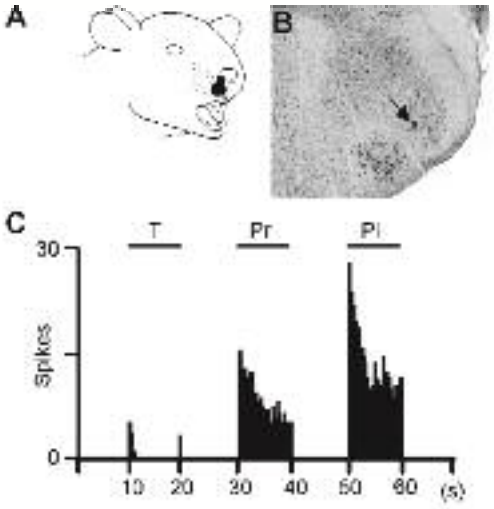

Fig. 3. Responses properties of a wide dynamic range (WDR) neuron to mechanical stimuli applied to its perinasal receptive field (A). (B) Microphotograph showing the histologically confirmed (arrow) recording locus of a WDR neuron. (C) Responses of a neuron to mechanical stimuli (T, touch; Pr, pressure; Pi, pinch).

*** trpV1 (also known as capsaicin receptor)= a protein that, in humans, is encoded by TRPV1 gene: functions of TRPV1 are detection and regulation of body temperature and sensation of scalding heat and pain.*

ATP, histamine) can alter neuronal excitability directly by interacting with ion channels on nociceptor surface whereas others (for example, bradykinin and NGF) bind to metabotropic receptors and mediate their effects through second-messenger signaling cascades[17]. Activation of nociceptors not only transmits afferent messages to trigeminal sensory complex, but also initiates the process of neurogenic inflammation. This is an efferent function of the nociceptor whereby release of neurotransmitters (notably substance P and CGRP) from peripheral terminal induces vasodilation and plasma extravasation, as well as activation of many non-neuronal cells, including mast cells and neutrophils. Moreover, electrical search stimuli have lead to the discovery of very high threshold or insensitive cutaneous nociceptors that were primarily activated by inflammation processes[18]. Many of these mechano-insensitive units respond to chemical stimulation and often become responsive to mechanical and thermal stimulation, when sensitized. However, similar silent nociceptors are not yet described in the orofacial cutaneous tissues.

The ion channel TRPV1 is considered to be a molecular integrator of different noxious stimuli such as heat, acids, and different endogenous pro-inflammatory substances. It was originally identified on the basis of its response to capsaicin, the powerful irritant vanilloid found in hot pepper. Studies also reported that inflammation promotes TRPV1 activity by increasing TRPV1 expression, release of endovanilloids, and decrease of pH and by enhanced temperature. Inhibition of TRPV1 was therefore hypothesized to reduce nociceptive activity, especially in inflammatory conditions[19]. Recently, the effects of a TRPV1 antagonist (AZD1386) were investigated in a clinical model of acute inflammatory pain (the third molar extraction model). Administration of AZD1386 resulted in a rapid analgesia with a relatively short duration of effect[19].

Local anesthetics are commonly used to abolish transmission of nociceptive information to central nervous system (CNS) by blocking voltage-gated sodium channels and thereby prevent the generation and propagation of action potentials. However, the administration of local anesthetics also produces numbness from block of low-threshold pressure and touch receptors, paralysis from block of motor axons,

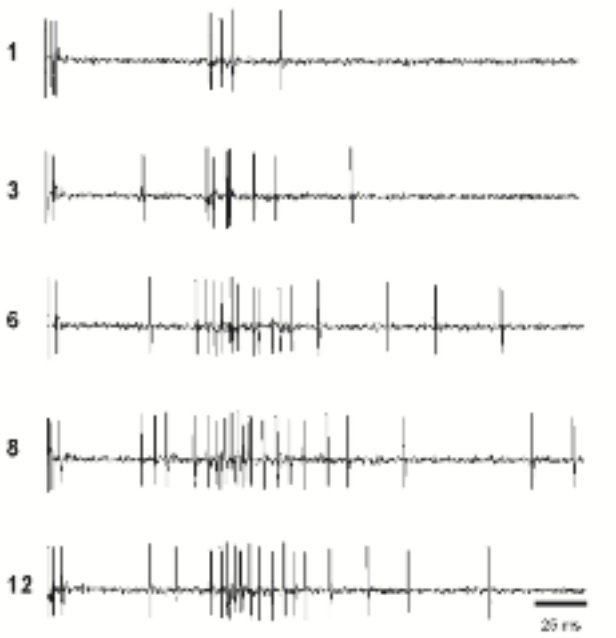

Fig. 4. Wind-up phenomenon. Consecutive single sweep recordings showing the evolution (from bottom to top) of the responses of a wide dynamic range (WDR) neuron following repetitive supramaximal percutaneous electrical stimulation applied to its receptive field.

and block of autonomic fibers. Selective block of pain signals might be possible either by targeting certain sodium channels that are present only in pain-sensing neurons[21] or by delivering sodium channel blockers selectively to nociceptive neurons. One strategy is to deliver a permanently charged sodium channel blocker such as QX-314 (N-ethyl-lidocaine) by entering through large-pore ion channels selectively expressed in nociceptive neurons[22]. The transient receptor potential vanilloid 1 (TRPV1) channel is a primary nociceptive transducer in nociceptive neurons, activated by noxious heat (>43°C), capsaicin, protons and endocannabinoids[23]. Chung and co-workers[24] demonstrated that pore of TRPV1 channels, when opened by the TRPV1 channel agonist capsaicin, might be large enough to deliver QX-314 or other large molecule selectively into nociceptive neurons. Binshtok and associates[22] demonstrated that QX-314, a charged membrane-impermeant lidocaine derivative, can be targeted selectively into nociceptors when co-administrated with capsaicin, resulting in selective blocking of sodium channels and inhibition of excitability of nociceptors.

Special features of trigeminal nerve and their clinical significance

The peripheral trigeminal nervous system has some characteristics which could explain certain particularities of orofacial pain conditions: 1) a resistance in the development ectopic activity after nerve injury[26] and 2) a hypersensibility to estrogens[27].

Complex regional pain syndrome (CRPS)* is a neuropathic pain condition with sympathetic involvement, often resulting from trauma or bone fracture to distal limbs[28]. The incidence of CRPS-like symptoms following trauma to craniofacial tissues is relatively low compared to injury of other tissues[29]. The exact reason for this observation is not certain. Spinal nerve injury induces sprouting of noradrenergic fibers into the dorsal root ganglia[30], whereas comparable injury to trigeminal nerve produces no such sprouting into the trigeminal ganglion[31,32]. Furthermore, cervical sympathectomy does not alter the development of ectopic discharge or increased mechanical sensitivity after inferior alveolar nerve transection[33].

In injured segmental nerves, many primary afferent neurons spontaneously generate impulses and develop hypersensitivity to a variety of physical, chemical and metabolic stimuli. The resulting ectopic discharge contributes to chronic paraesthesias and pain that often accompany nerve injury in humans[34]. However, while most amputees report chronic stump and/or phantom pain[35], phantom and chronic neuropathic pains are extremely rare after tooth extractions and root canal extirpations, even when multiple teeth are involved[36,37]. Using the teased fiber recording method, Tal and Devor[34] have compared pathophysiological properties of afferent axons injured in infraorbital nerve (ION) v/s sciatic nerve in rats. Both myelinated and unmyelinated axons ending in ION neuromas produced much less ongoing discharge than those ending in sciatic nerve neuromas. Similarly, mechanosensitivity and acute injury discharge in ION neuromas were minimal. These differences may be related to the different spectrum of neuropathic symptomatology associated with trigeminal nerve injury.

*** CRPS= 2 types recognized: Type 1 (corresponds to RSD: reflex sympathetic dystrophy) formerly termed Sudeck's atrophy - develops in distal extremities and causes poorly controllable pain, sensorimotor disorders, and serious trophic alterations. Type 2 (formerly called causalgia) refers to cases where a definable nerve lesion is present.*

Finally, trigeminal primary afferents seem particularly sensitive to estrogens. Estrogen can influence nociceptive sensory processing by regulating transcription of a variety of proteins, and neurotransmitter receptors[38]. Prevalence of most chronic craniofacial pain conditions is higher in women than men[39]. This is especially obvious for TMDs, migraine headache[39], and burning mouth syndrome[40].

Diogenes and associates[41] have demonstrated that expression of several genes in rat female trigeminal sensory neurons was regulated by estradiol. Prolactine (PRL) gene was found to be most upregulated (>40 fold) in TG neurons of OVX rats treated with estradiol replacement. Subsequent experiments showed the following: (i) PRL is present in sensory neurons in a releasable pool; (ii) and PRL-induced sensitization of capsaicin-evoked responses in vitro and in vivo is under control by estradiol; and (ii) PRL is able to increase the phosphorylation levels of TRPV1 in TG neurons. These findings propose that PRL could contribute to the development of certain pain disorders modulated by estrogen.

FEATURES OF TRIGEMINAL NOCICEPTIVE NEURONS

Somatosensory inputs from orofacial area are conveyed by the trigeminal nerve to the first central relay located within the trigeminal brainstem sensory nuclear complex (Fig.2). This complex can be subdivided into principal sensory and spinal trigeminal nuclei. The latter consists of three regions, which, from rostral to caudal, are the subnuclei oralis (Sp5O), interpolaris (Sp5I), and caudalis (Sp5C). The Sp5C, the largest subdivision of the spinal trigeminal nucleus, consists of an elongated laminated portion that merges without clear boundaries with the cervical dorsal horn, while the rostral Sp5C is displaced medially by the caudal tip of Sp5I to form a distinctive transition region. The ventral Sp5I/Sp5C transition region consists of rostral Sp5C with its fragmented laminar appearance, interstitial islands of neurons embedded in the trigeminal spinal tract, and a ventral crescent-shaped region of caudal Sp5I[42]. The dorsomedial aspect of the Sp5I/Sp5C transition region is an important integrative region for peri-oral and intra-oral sensory input.

Sp5C is generally considered as the main relay of

orofacial nociceptive information to brain's higher levels. However, several observations point to the involvement of the rostral spinal trigeminal nucleus in nociceptive mechanisms. For instance, a tractotomy performed just above the level of the Sp5C in humans does not produce complete orofacial and dental analgesia whereas more rostral lesions can interfere with intraoral pain[43,44]. Likewise, in cats, rats, and monkeys, a tractotomy does not completely abolish nociceptive behavioral, reflex responses, or cortical activity evoked by noxious orofacial stimulation[44-47]. Moreover, neurons in both Sp5O and Sp5I respond to noxious orofacial stimuli. Thus, spinal trigeminal subnuclei, as a whole, are involved in the processing of orofacial nociceptive information. As there are few data concerning properties of Sp5I neurons, we will focus our discussion on the characteristics of Sp5O and Sp5C neurons. However, it is possible that Sp5I shares several functional properties with Sp5O and Sp5C.

Classification and distribution of trigeminal nociceptive neurons (Fig. 3)

Two main types of nociceptive neurons have been identified in the spinal trigeminal nucleus: the first type, termed nociceptive-specific units (NS), respond only to noxious stimuli and are driven only from small-diameter slow-conducting (Aδ and C) nociceptive afferents. The second type, termed wide dynamic range (WDR) neurons (also labeled convergent or multireceptive neurons), respond to tactile as well as noxious stimuli and are driven by both large-diameter Aβ afferents and small-diameter afferents (Aδ and C-fibers).

Electrophysiological studies[48] have documented that nociceptive neurons (WDR and NS) are located in the three subdivisions of the spinal trigeminal nucleus. Nociceptive neurons did not appear to have any particular spatial grouping within the Sp5O and the Sp5I but were intermingled with non-nociceptive neurons[49-53]. In contrast, Sp5C nociceptive neurons are concentrated in the superficial (I/II) and deep (V/VI) laminae. Although there is no strict segregation of these two populations, it has been shown in several species that NS neurons are found mainly in the superficial dorsal horn (laminae I-II) whereas WDR neurons are located mainly in deep laminae (V-VI)[54-58].

Somatotopic organization and receptive fields of trigeminal nociceptive neurons

A somatotopic organization could be observed in the spinal trigeminal nucleus. The dorsal part of each subnucleus contains neurons with a receptive field in the orofacial region supplied by mandibular branch of trigeminal nerve. The ventral part contains neurons with an ophthalmic receptive field, and the area between the dorsal and ventral parts represents the maxillary region. Oral structures are usually represented medially[54,59-61]. However, in the caudal Sp5C, the topographic pattern of representation of the face and mouth shifts, with the intraoral and perioral regions represented in the rostral part of the subnucleus and more lateral regions of the face more caudally[62]. Intraoral and perioral regions are represented in all the subdivisions of spinal trigeminal nucleus.

Spinal trigeminal subnuclei receive cutaneous, mucosal and/or tooth pulp afferent inputs. Moreover, the Sp5C receives other types of peripheral inputs including cornea, TMJ, jaw muscles, cerebrovasculature or dura[63]. In addition, Sp5C can also be excited by other cranial nerve afferents (hypoglossal nerve or vagus) and by upper cervical nerve afferents[54,64]. In contrast to the widespread convergence from cutaneous and non-cutaneous inputs to Sp5C nociceptive neurons, Sp5O neurons respond chiefly to orofacial cutaneous/mucosa and/or tooth pulp stimuli. The narrow convergence of afferent inputs to the Sp5O suggests that this subnucleus plays a relevant role in the spatial detection of pain from intraoral and perioral superficial tissues. In contrast, the larger convergence of afferent inputs to the Sp5C suggests that it is involved in the spread and referral of pain frequently observed in several orofacial pain conditions such as TMJ disorders, toothaches, and headaches[63].

PROPERTIES OF TRIGEMINAL NOCICEPTIVE NEURONS

Responses to electrical stimulation

The response of Sp5O and Sp5C WDR neurons to electrical stimulation indicates that the whole spectrum of primary afferents can activate these neurons, ranging from large myelinated to unmyelinated fibers, while the trigeminal NS neurons are activated by Aδ and C-fibers[54,60,65]. The mean latencies of Aδ-fiber-evoked responses in Sp5O are generally shorter than those

reported in the Sp5C. For instance, the mean latency to tooth pulp stimulation in cat's Sp5O is significantly shorter than that for Sp5C neurons[66-68]. These findings suggest that Sp5O nociceptive neurons are involved in encoding the onset of nociceptive stimuli and that their activity allow to discriminate noxious from non-noxious stimuli. These phenomenon concern only nociceptive responses elicited by stimulation of Aδ-fibers supplying intraoral or perioral tissues. However, mean latencies of C-fiber-evoked responses in Sp5O are generally longer than those reported in Sp5C[69], suggesting that Sp5O WDR neurons receive C-fiber inputs indirectly, via Sp5C[70].

The Wind-up phenomenon (Fig.4), originally described in dorsal horn, consists in a progressive increase in C-fiber-evoked responses following repeated percutaneous electrical stimulation[71,72]. This was also observed for the long latency responses of Sp5O[50] and Sp5C[55,73] neurons. Wind-up occurs in the majority of WDR neurons located in the Sp5O and deeper laminae of the Sp5C, while NS neurons located in the superficial laminae of the Sp5C frequently exhibit no or little windup[73,74]. Recently, Coste and associates[75] stated that wind-up enhances the encoding of short-duration orofacial nociceptive stimuli intensity and allows detection of subthreshold nociceptive input. As a consequence, wind-up endows trigeminal WDR neurons with a greater ability to assess the intensity of nociceptive information. Wind-up thus may play a physiological role in trigeminal sensory processing, and enhanced wind-up may underlie the pathophysiology of several common chronic headache and facial pain conditions.

Responses to chemical stimulation (Fig. 3)

A substantial proportion of WDR and NS neurons in Sp5C respond to algesic chemical stimuli delivered to afferents supplying oral mucosa[76-78]. Most responsive units are located in superficial layers of dorsomedial Sp5C although a few lie also in the deeper laminae. Majority of Sp5C nociceptive neurons respond to a variety of irritant chemicals, some of which act at specific molecular receptors (e.g., capsaicin, histamine, serotonin, and nicotine), whereas others have nonspecific or unknown effects on nociceptor terminal membranes (mustard oil, piperine, NaCl, ethanol). Responses to the application of chemicals are not markedly affected by prior application of another chemical, except for capsaicin, piperine, and mustard oil, which often desensitize the tongue[76]. Responses to all chemicals increase in a dose related manner, suggesting that the trigeminal nociceptive neurons are capable to encode the intensity of chemical stimulation. In contrast, successive responses to repeated applications decrease significantly for nicotine, serotonin, capsaicin, and piperine[76].

Properties of deep tissue nociceptive neurons

One important feature of neurons in the spinal trigeminal nucleus is that almost all the neurons responsive to noxious stimulation of the deep tissues are located predominantly in the Sp5C. These neurons have widespread convergence from facial skin, tooth, oral mucosa, meninges, TMJ, and cranial muscles. Interestingly, TMJ, jaw muscles, and meninges are among orofacial tissues that have a specific representation at two distinct rostro-caudal levels in Sp5I/Sp5C and in Sp5C/C1[3].

A considerable proportion (~50 %) of Sp5C neurons can be also activated by noxious mechanical or chemical (e.g., hypertonic saline, bradykinin, glutamate) stimulation of TMJ or masticatory muscles afferents[52,79,80]. In addition, TMJ units can encode the concentration of pro-inflammatory chemicals[80]. Interestingly, persistent activation of TMJ tissues produced more robust and longer-lasting hyperexcitability of Sp5C neurons as compared with persistent cutaneous stimulation[81]. This may contribute to mechanism of persistent pain associated with orofacial deep tissues painful conditions.

Most of joint and muscle neurons have deep and cutaneous receptive fields[52,53]. A very small number has exclusively deep nociceptive fields[80]. It is also noteworthy that most of the neurons showing afferent convergence tend to have a larger cutaneous receptive field than those receiving only cutaneous afferent inputs[80]. The convergence of deep as well as cutaneous inputs onto the same neuron is considered to be an integral mechanism underlying the poor localization, spread and referral of pain[63]. Deep neurons could also play an important role in providing the necessary signals onto segmental circuits to

suppress unwanted reflexes and facilitate reflexes that enhance motor performance. Indeed, it has been shown that injection of hypertonic saline into muscle produces a predictable motor response[82]. This response, which is characterized by reduction of activity in agonist muscles and increased activity in antagonist muscles, acts to limit overall movement patterns and "protect" the injured muscle[52]. This phenomenon has been termed the pain adaptation response[83].

ASCENDING PATHWAYS

Ascending projection neurons in the trigeminal brainstem nuclear complex convey noxious information to various suprasegmental structures. Multiple ascending pathways originate from trigeminal subnuclei.

Superficial laminae neurons of the Sp5C project to several areas of the central nervous system, which are important for processing signals relevant for homeostasis*. They project to the ventrolateral medulla[84] and the nucleus of the solitary tract[85], two regions involved in cardio-respiratory regulation. The most dense projections from superficial laminae arise to the lateral parabrachial nucleus, an area that also participates in autonomic reactions[86-89]. Superficial laminae neurons of Sp5C also project to lateral and ventrolateral columns of periaqueductal gray[90,91], a region that contains different groups of neurons which when activated, elicit anti-nociceptive and well-defined cardio-vascular and defensive reactions such as decreases in blood pressure, hyporeactive immobility, avoidance behavior, and vocalization as well as general emotional state of fear and anxiety[92]. Sp5C-periaqueductal gray pathway could participate in feedback mechanisms involved in autonomic, aversive and anti-nociceptive responses to strong nociceptive stimulation. On the other hand, Sp5C establishes connections with the hypothalamus[93,94]. The participation of the trigeminohypothalamic pathway in autonomic, neuroendocrine, and emotional aspects of pain has been suggested.

Ascending projections from the deep laminae of Sp5C are similar to those from Sp5O. Major termination sites include superior colliculus[95-98], zona incerta[99-101], brainstem reticular areas[84,85], and anterior pretectal nucleus[102]. These regions are notably involved in motor reactions. Thus, deep laminae of Sp5C and Sp5O may participate the somatomotor integration.

Interestingly, both anatomical[103,104] and electrophysiological[63,105-108] studies have demonstrated that both superficial and deep laminae of Sp5C and Sp5O project to various thalamic structures, including ventral posterior medial nucleus (VPM) and posterior part of ventral medial nucleus (VMpo). Although these thalamic areas receive trigeminal projections directly or indirectly via brainstem reticular formation and mesencephalon and precisely encode different intensities of noxious stimuli, recordings in anaesthetized and awake monkeys have revealed important differences between these areas. A great number of neurons in parafascicular nuclei and VMpo are modality specific, showing either nociceptive or thermal responses. The receptive fields of VMpo cells in monkeys are restricted, whereas those from parafascicular cells are often very large. Both their borders and the magnitude of their evoked responses change with the monkey's behavioral state[109]. These features may indicate that parafascicular cells are better suited to behavioral reactions, thus strongly implicating these regions in the affective-emotional aspects of pain. This suggestion is supported by their cortical connectivity and by functional imaging studies. VMpo cells project to the mid/anterior insular cortex, an area that is activated by both innocuous and noxious thermal stimuli in humans and which has been implicated in the affective components of pain on the basis of its projections to various limbic structures such as the amygdala and perirhinal cortex. Parafascicular cells project to area 24 of the cingulate cortex, the activity of which appears to be more selectively modulated by noxious stimuli. In fact, this is a functionally heterogeneous area constituted by adjacent zones, which have been implicated in attentional, motor and autonomic reactions, which might allow it to elicit various behavioral reactions[110].

* *Homeostasis is the ability to maintain a constant internal environment in response to environmental changes. Nervous and endocrine systems control body homeostasis (homeostasis processes include temperature control, pH balance, water and electrolyte balance, blood pressure, and respiration).*

By contrast, in VPM, majority of neurons are WDR, have receptive fields, which are not modified by behavioral state and are smaller than those of spinal or trigeminal projecting neurons[109]. This suggests that VPM may subserve spatial discrimination. These regions project to the primary somatosensory cortex, and functional imaging studies have shown that noxious and innocuous stimuli similarly activate the contralateral primary somatosensory cortex, indicating a co-existence of pain and tactile representation in this area. Furthermore, single-unit recordings from a caudal ventral region of the thalamus in humans showed neurons that could be activated by noxious stimuli, and stimulation of this region induced thermal and/or painful sensations[111].

In conclusion, taken together, these data show that the fine encoding properties or the fact that thalamic neurons receive direct spinal and/or trigeminal inputs alone cannot account for the sensory-discriminative aspects of pain, since encoding is shared by all (thalamic and also lower CNS) regions implicated in pain processing. Moreover, the VPM, which are the best candidates for discrimination, can discharge with higher instantaneous frequency to innocuous than to noxious stimulation in awake monkeys. Thus it is likely that modulatory mechanisms and/or the concomitant activity of multiple neuronal populations could determine the final pain perception.

MODULATION OF TRIGEMINAL NOCICEPTION

Orofacial somatosensory inputs activate strong modulatory mechanisms implicating second order neurons, local interneurons, and descending modulatory pathways. These segmental and suprasegmental controls modulate nociceptive signals at different levels at the central trigeminal networks.

Afferent-induced modulation of trigeminal nociception

Several lines of evidence show that stimulation of peripheral afferents can modulate both neuronal and reflex responses at both metameric (segmental) or extra-metameric (plurisegmental) levels.

Modulation elicited by stimulation of non-nociceptive afferents

Activation of large diameter, myelinated peripheral fibers is able to inhibit firing of trigeminal neurons induced by noxious stimulation[112-115]. Such inhibitory effects are metameric in nature, but analogous effects can also be elicited by dorsal columns stimulation[116]. It was proposed that such stimulation triggers segmental inhibitory mechanisms via antidromic activation of large diameter peripheral fibers. Segmental inhibition has been proposed to explain the effectiveness of therapeutic procedures that employ weak intensity, high frequency percutaneous electrical nerve stimulation[117-119], vibratory stimulation[120] and also spinal cord stimulation[121]. These experimental data and their clinical counterpart arise directly from the predictions of the gate control theory[122] and underlie the important interactions between large and small diameter fibers at the level of the substantia gelatinosa.

Modulation elicited by stimulation of nociceptive afferents

Activity of trigeminal nociceptive neurons can also be strongly inhibited by activation of nociceptors. Such effects are not somatotopically organized since they are elicited by stimulation of any part of the body. They have been termed diffuse noxious inhibitory controls (DNIC)[123]. The principal feature of DNIC is that they inhibit the activity of all WDR neurons. Indeed, WDR neurons, whether recorded in the Sp5O[65,124,125] or in the Sp5C[57,126] are under the influence of DNIC. Similar inhibitions elicited by remote noxious stimuli were reported on the digastric reflex evoked by tooth pulp stimulation in cats[127,128] and rats[128,129]. However, comparing the strength of DNIC at trigeminal and lumbar levels shows that the inhibitions are more pronounced for trigeminal WDR neurons.

DNIC are subserved by a loop with the afferent and efferent pathways running within the ventrolateral quadrant and the dorsolateral funiculus of the spinal cord, respectively[130]. Nevertheless, that sectioning the spinal cord suppresses DNIC suggests that these controls also involve supraspinal areas[130]. Thus a region in the caudal medulla, the subnucleus reticularis dorsalis, was shown to be critically involved in DNIC[131]. More recently, we demonstrated that the

spinoparabrachial[124] and the hypothalamic dopaminergic descending pathways[125] contribute to the ascending and descending part, respectively, of the loop subserving DNIC.

Human studies conducted during the last years have demonstrated that several types of noxious conditioning stimuli including ischemia, thermal, electrical, and chemical, reduce the perception of orofacial pain[132-137]. Painful heterotopic conditioning stimuli also depress jaw[119,138] and blink reflexes[139], with stronger effects being observed with more intense conditioning stimuli. Based on these data, Cadden and Newton[140] suggested that alterations in these controls may explain why jaw inhibitory reflexes are often absent in patients with disorders such as craniomandibular dysfunction or tension headache[141,142]. Indeed, suppression of an inhibitory action on jaw closing motoneurons could, by increasing the use of these muscles, be a predisposing factor for myogenic pain experienced by such patients[119].

Descending modulation of trigeminal nociception

Electrical or chemical stimulation of various structures such as the cortex, periaqueductal gray[53,143,144], parabrachial area[145,146], anterior pretectal nucleus[145], nucleus raphe magnus[112,143,147,148] and locus coeruleus[149] inhibit the response of Sp5O and Sp5C neurons to tooth pulp stimulation. Furthermore, electrical stimulation of parabrachial area and nucleus raphe magnus modulate responses of Sp5C neurons to noxious stimulation of the skin, deep tissues and cornea[143,144]. Neuronal activity in Sp5C evoked by trigeminovascular nociceptive afferents is also modulated by activation or inhibition of periaqueductal gray[150,151]. However, stimulation of periaqueductal gray, nucleus raphe magnus, or locus coeruleus do not affect the input originating from cold nociceptors in orofacial regions[152-155]. More recently, it has been shown that electrical stimulation of secondary somatosensory cortex significantly reduced number of neurons expressing c-fos in the superficial layers of the Sp5C in response to formalin injected into the orofacial regions[156]. The stimulation of these structures can also suppress reflex and behavioral responses to noxious orofacial stimuli in awake, decerebrate, or anesthetized animals[156-159].

On the basis of anatomical and electrophysiological data, it is generally accepted that inhibitory effects induced by electrical stimulation of periaqueductal gray, parabrachial area, nucleus raphe magnus, and locus coeruleus, result from a direct action on trigeminal neurons[90,102,160-163]. Antinociceptive action of periaqueductal gray is also mediated through nucleus raphe magnus since direct periaqueductal gray-nucleus raphe magnus connections have been clearly demonstrated by anatomical investigations. Some of these projections to the spinal trigeminal nucleus have been shown to contain serotonin, norepinephrine, enkephalin, and cholecystokinin[60,161,163].

CONCLUSION

Our understanding of orofacial pain mechanisms has lately grown impressively. Trigeminal pain system, like other sensory systems, employs specialized peripheral receptors to interact with the environment, with the goal to integrate information arising simultaneously from different sources. Such information is conveyed to central structures using neural codes that change with regard to previous sensory experience and the interaction with other sensory systems. Pain signaling systems share some organizational principles, such as convergence and divergence, topographic projections, multiplicity of representation areas, and hierarchical organization.

This review illustrates several anatomical and functional particularities of trigeminal pain signaling system:

- **Peripheral polymodality:** Nociceptive neurons are polymodal since they are able to transduce a variety of strong stimuli such as heat, pressure, and chemicals into signals that are perceived as pain. Molecular biology studies have recently identified specific receptors and ions channels that allow us to perceive physical stimuli such as heat (TRPV1 receptor), cold (Transient receptor potential cation channel subfamily M member 8 (TRPM8)), and mechanical stimuli. These molecules are frequently expressed on the same nociceptor.
- **Redundancy:** One relevant feature of the trigeminal system is the redundancy of representations

of orofacial structures within the different brainstem nuclei. For instance, perioral cutaneous, oral mucosa and tooth pulp afferents project to all trigeminal subnuclei, while the cornea, TMJ and meninges are represented in two regions of the Sp5C, the Sp5I/Sp5C and Sp5C/upper cervical cord transition regions.

The trigeminal system also displays a functional redundancy since a single sensory modality may be processed within different subnuclei. This is clearly illustrated by dual integration of trigeminal nociceptive inputs, since in addition to Sp5C, Sp5O participates also in the processing of nociceptive information from orofacial regions. The functional significance of this redundancy remains to be established.

• **Multiplicity of pain pathways:** Anatomical, electrophysiological, and more recently, functional imaging studies, have shown that pain involves a number of structures in the brain. Such data reveal a multiplicity of ascending nociceptive pathways arising from laminae I and V of Sp5C as well as Sp5O. Several lines of evidence underline important differences in anatomical and functional organization of ascending nociceptive pathways. Such differences suggest different roles in the processing of nociceptive information. However, contribution of each of them to trigeminal pain processing remains obscure.

• **Sensory transformation:** Noxious inputs generated in peripheral tissues are conveyed through several relay structures before reaching cortical areas. These intermediate structures are under the influence of descending modulation arising from brainstem and cerebral cortex. It is obvious that noxious inputs undergo transformations at all central relay levels: such transformations probably provide the relevant codes necessary for eliciting different pain sensations and reactions.

• **Convergence:** there is a widespread convergence of inputs to trigeminal, thalamic, and cortical nociceptive neurons. In addition, a large fraction of such units respond to application of a variety of non-noxious and noxious stimuli, and to a variety of peripheral tissues. Such convergence is a common feature of many neurons in the CNS and suggests that individual cells can serve different functions at different times, depending on their patterns of activity.

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Acupuncture and Trigeminal Neuralgia pain.

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Trigeminal neuralgia (TN), also known as "tic douloureux" or "suicide disease", is a neuropathic disorder characterized by severe unilateral paroxysmal facial pain originating from trigeminal nerve.

It has been described as among the most painful conditions known to mankind and it is triggered by tactile irritation. Various drugs have been used to treat TN, among them anticonvulsants, centrally acting muscle relaxants, antidepressants, local anesthetic patches, and opiates. However, none of these drugs are free of side-effects.

Other TN therapies include invasive surgery such as microvascular decompression, percutaneous radiofrequency thermorhizotomy, and gamma knife radiosurgery. However, effectiveness decreases with time and the procedures are not free of complications.

Acupuncture is one of many therapeutic methods that are considered complementary to modern medicine. It is successfully used in the treatment of a wide range of neurological conditions such as trigeminal neuralgia, post-herpetic neuralgia, peripheral neuropathies, etc... This method of treatment was practiced in China around 2000 BC but became an integral part of modern medicine only lately. Acupuncture-induced analgesia is mediated by inhibition of pain transmission at spinal level and activation of central pain modulating centers. This neural modulation of acupuncture is considered a mode of peripheral sensory stimulation.[1,2]

In traditional Chinese medicine, acupuncture needles are inserted in specific points at specific meridians[3] and stimulation of these needles - either by hand, electrical devices, or moxibustion - stimulate supraspinal mechanisms (diffuse noxious inhibitory control-DNIC), inhibiting neurons of dorsal horn or trigeminal ganglion excited by pain.[2] Release of dynorphins, enkephalins, and other neuropeptides[4] play a major role in pain control. Modern neuroimaging methods (functional MRI and SPECT*) showed an increase in cerebral blood flow and cerebral oxygen supply, also in activation of subcortical and cortical centers[1] following acupuncture sessions.

In our clinic, we were successful in relieving at least sixty percent of TN pains. Almost all these patients were refractory to conventional medical therapy and they were still on anticonvulsants with or without antidepressants (Table 1).

Acupuncture treatment sessions were implemented three times per week (MWF), each session lasting twenty minutes. The treatment was spread over a period of one month, followed by one or two sessions per month depending on the case. In Table 1, local, distal, and ear acupuncture points were used.

Points stimulated were: GV 20, GB 14, ST 2,3,7,8, 36, 44, LI 4, LIV 3, CV24, ear sympathetic, and shenmen.

Variations in choosing the points depended on trigeminal branch involved.

Only one refractory nonresponsive case was referred to neurosurgery for invasive thermal ablation of the trigeminal branch nerve affected.

Over a period of fifteen years, eighty trigeminal neuralgia pain patients were referred to our clinic.

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* *SPECT= Single Photon Emission Computed Tomography*

They were all treated by acupuncture and followed-up for improvement using a visual analogue scale (VAS). Only one patient was referred to surgery for radiofrequency thermorhizotomy and the rest had at least sixty five percent improvement. Follow-up was implemented over a period of one year (Table 2). Unfortunately, control groups, adequate measure of outcome, statistical analysis, or long-term follow-up were inadequate due to lack of control randomized double-blinding.

In conclusion, acupuncture is an effective mode of treatment of TN pain, especially in refractory cases where conventional medical treatment is unable to provide satisfactory results or when unwanted side-effects overweighs benefits.

Patient	Age	Gender	Anticonvulsant	Antidepressant	Acupuncture	Surgery
1	65	M	Yes	Yes	Yes	No
2	54	F	Yes	Yes	Yes	No
3	71	F	Yes	No	Yes	No
4	68	F	Yes	Yes	Yes	No
5	60	F	Yes	No	Yes	No
6	72	F	Yes	Yes	Yes	No
7	43	M	Yes	Yes	Yes	Yes
8	58	M	Yes	Yes	Yes	No

Table 1

Patient	No of sessions	% pain relief (VAS)	Follow-up sessions	Reduced medications
1	18	65	4	Yes
2	16	70	2	Yes
3	22	65	4	Yes
4	18	65	4	Yes
5	18	75	2	Yes
6	16	70	2	Yes
8	20	70	2	Yes

Table 2

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Low-Level-LASER Therapy - LLLT - for the treatment of oral myofascial pain. A systematic review of the last thirteen years.

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Abstract

A systematic review of randomized clinical trials - RCTs - on Low-Level-LASER Therapy (LLLT) for the treatment of oral myofacial pain was conducted. Methods: we searched the literature (MEDLINE via PubMed, Cochrane CENTRAL and other sources) from 1999 to 2012 in order to identify RCTs on LLLT for myofacial pain. Two review authors (CR-B and SJ) compiled and evaluated the included studies. We analyzed 6 RCTs (n=223) on LLLT for myofacial pain. A high heterogeneity of applied dosages was observed. Conclusion: we found no evidence to support the use of LLLT for the treatment of myofascial pain. Dosage and regimen of administration are a major concern in future studies. We suggest the use of core outcomes in order to compare LASER therapy results with other short-term therapeutic strategies for myofacial pain.

Oral Myofacial pain (MP) is the most common diagnosis among the group of the temporomandibular disorder (TMD). The MP is characterized by chronic muscle pain or tenderness in masticatory muscles (group I of the RDC/TMD).

Etiology of TMD is still controversial. Currently, a multifactorial theory has received great support among the scientific community. This theory draws attention to the interaction of psychological, neuromuscular, and oral pathogenic factors.

Multiple possibilities have been proposed regarding the treatment of TMD. Currently, recognized standards of treatment for TMD prioritize reversible interventions over invasive ones. Analgesic effects of low-level LASER therapy have been tried for this condition.

While the LLLT has been positively evaluated for some muscular[1,2] and articular[3] conditions, contradictory reports did not discard the merely placebo effect of LLLT[4]. Some articles even appealed that LLLT has no effect at all in medical treatments[5]. Further discussions about the lack of standardization of doses and techniques attempt to explain these differences in clinical outcomes.

In a systematic review, many methodological deficiencies were found in studies of LLLT for lateral epicondylitis, however some evidence of the efficacy of LLLT on trigger points was supported[6]. It has been suggested that necessary irradiation dosage for clinical success depends on individual characteristics of the patients[1].

In another study, patients with myofascial pain syndrome showed clinical improvement after LLLT treatment compared to placebo LASER[7]. A combined therapy of stretching exercises and LLLT was reported more effective than only stretching exercises for the treatment of myofascial pain syndrome in a RCT including 62 patients[8]. In another RCT however, this combination did not result in any significant difference between groups[9]. As an adjuvant in whiplash treatment, one RCT reported no effect of LLLT[10]. In the oral area, Medeiros and associates reported an increase of bite strength in volunteers with masseter

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pain upon palpation after the application of laser therapy compared to placebo[11].

Many of the systematic reviews in LLLT reported difficulties to conclude judgments due to the poor quality of reports[12,13]

Currently, the mechanism of action of the low-level LASER on acupunctural points is unknown. Some authors support the theory that LLLT acts over inflammatory agents reducing prostaglandins or inhibiting cyclooxygenase-2 (COX-2)[14,15]. Alternatively, some theories suggested that action of LLLT is linked to the release of endogenous endorphins, or modifications in the conduction of nerve impulse at local level[16]. Other local effects have been suspected, for instance variations of microcirculation. In one study, however, no significant changes were observed in the microcirculation of irradiated zones[17]. No conclusive evidence exists until now.

This study is part of a series of systematic reviews aimed to evaluate the evidence regarding alternative treatments for TMD during the last thirteen years (1999-2012).

METHODS

Inclusion criteria:

Types of studies and participants

For this review were eligible only Randomized controlled clinical trials (RCTs) conducted in patients with oral myofacial pain (with or without concomitant arthrogenous diagnoses) published between 1999 and 2012. Quasi-randomized and non-randomized trials, observational studies, narrative reviews, commentaries and letters to editors were excluded.

Search strategy (Appendix 1):

1. Electronic searches

In order to identify potential relevant studies, we searched the databases MEDLINE via Pubmed (01.11.2012, app.1) and Cochrane CENTRAL (05.01.2013). Moreover, we conducted a computerized screening of the database and university catalogs via CITAVI software: GBV Gemeinsamer Bibliotheksverbund, BVB Bibliotheksverbund Bayern, Hessen HeBIS, Zürich Universität IDS, The British Library, Web of Science: BIOSIS Citation Index, WorldCat.

Keywords: an example of the electronic search strategy is available in Appendix 1. The same terms were used to search other databases.

Filters: the Publication dates filter was activated during the electronic search from 1999 to 2012. We applied the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity- maximizing version (2008 revision) PubMed format as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of The Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.2 updated March 2011.

Moreover, only three Languages were included: English, German, and Spanish.

2. Searching other resources

We conducted a handsearch of the Journal of Oral Rehabilitation, Cranio: the Journal of Craniomandibular Practice, and the Journal of Dental Research to identify relevant articles. Furthermore, the references of all relevant studies and existing reviews were screened for additional relevant publications.

Data processing and Analysis

All the potential relevant articles identified with the search strategy were tabulated and selected according to pre-defined selection criteria, first assessing the title and abstracts, and later in a second screening, using the full text version. All the full text versions were analyzed by one reviewer, and later verified by another review author. In case of discrepancy, evaluations were discussed, with the possibility to referral to a third review author.

The risk of bias of the randomized clinical trials was assessed using the Cochrane Collaboration's Tool for assessing risk of bias[18]. Additionally, we applied the Delphi list which emanated from a consensus of 33 international experts, in order to evaluate the quality of RCTs[19]. It consists of 9 items specified in table 1. We expected to analyze the evidence in two subunits namely laser acupuncture and LLLT.

RESULTS

The study flow diagram (Fig.1) shows the screening process according to recommendations of QUORUM/PRISMA20. RCTs were included, and studies were excluded (table 2).

Included studies (Table 3)

In spite of that, Carrasco and associates[33] defined myofascial pain syndrome as inclusion criterion, this condition was described as a unique localization of trigger points in masseter and temporalis. This description was compatible with our definition. Kulekcioglu and co-workers[35] distinguished in the sample 50% of myogenous TMD, and all other studies included myofacial pain according to the RDC/TMD.

Five studies compared LASER acupuncture with a placebo. Another study[38] contrasted LASER therapy and splint with different evaluation times (30 min after the last session). And a last one[34] evaluated LASER therapy v/s MENS*. All these RCTs measured outcomes at short-term.

Application of LASER varied in dosage and characteristics of the irradiation. Every research team indicated a regimen of two sessions weekly, apart from Kogawa and associates[34] who ran through three sessions a week and the study of Kulekcioglu[35] which did not specify the frequency.

Carrasco[33] tried 8 sessions of three different GaAlAs doses (25, 60, and 105 J/cm^2 at 780nm, 50, 60 and 70 mW); Kogawa[34] applied 10 sessions GaAlAs (4J output, 830-904nm wavelength, and 100mW power); Kulekcioglu[35] used 15 sessions GaAs 3J/cm^2 at 904nm 17mW; Moraes[36] applied 8 sessions GaAlAs 70J/cm^2 at 808nm 100mW; Öz[38] used 10 sessions 3J/cm^2 820nm 300mW; and Venezian[37] programmed 8 sessions GaAlAs780nm in two different doses (25J/cm^2 50mW, and 60J/cm^2 60mW).

LLLT was applied on trigger points or tender points (Carrasco-2009, Kulekcioglu-2003, Moraes-2012, Öz-2010, Venezian-2010).

Effects of intervention

Apparently, an important placebo effect influenced the results of the studies on LLLT vs. Placebo. No differences between laser acupuncture and placebo were found in the study by Carrasco[33]. Kulekcioglu[35] did not observe significant differences between LLLT and placebo groups for neither pain intensity nor joint sounds; however they reported a positive improvement of jaw motion. These results were not different between the subgroups of patients of myogenous and arthrogenous TMD.

Although EMG activity was not significantly different between LASER and placebo interventions in the study of Venezian[37], the betterment in the experimental group had longer effects.

Improvement of clinical parameters was reported for the laser group, and not for the placebo, however no analysis between groups was included in the study by Moraes[36].

In comparison to other treatment modalities, Kogawa[34] found a significant greater reduction of pain intensity for LLLT over MENS. Other outcomes were not dissimilar between groups.

The only study[38] evaluating clinical efficiency of LLLT v/s splint therapy showed pain relief and jaw motion measurements enhancement in both groups similarly after treatment. However, these results represented only immediate changes in clinical outcomes.

Quality of evidence: Risk of bias (fig. 2, table 4, fig. 3)

We registered a high heterogeneity in LASER application between studies. Most of these trials poorly described demographics of the participants and the randomization methods.

Included RCTs were mainly at unclear risk of bias. Despite the relatively simple design of study, blinding was not reported in all trials comparing LLLT with placebo LLLT (not active laser).

Moreover, Carrasco (2009) and Venezian (2010) defined more than one placebo group, virtually identical (they supposedly differ in doses, but the laser was inactive).

The general positive accomplishment of the Delphi list was 61.91%. RCTs with score 6 or higher were 57.14% of the included studies.

DISCUSSION

All the included studies applied different dosages from distinct characteristics of laser irradiation (wavelength and frequency). None but one of the included studies reported any advantage over placebo condition or a comparison group. Three studies found similar results for LLLT and placebo. Two trials did not conduct statistical analysis between these groups. Another study did not report differences between

**MENS= Microcurrent Electrical Neural Stimulation.*

LLLT and splint therapy at short-term. On the contrary, one study stated greater reduction of pain of LLLT in comparison with Microcurrent Electrical Neural Stimulation (MENS); nonetheless the therapeutic effect of MENS is unknown.

In a recently published RCT[39] (posterior to our search for literature), LLLT for treatment of myofacial pain was allegedly more efficient to produce pain relief and improvement of jaw opening when compared to placebo. However, sample of the study was limited and the time of follow-up was short.

LLLT to treat other chronic conditions remains controversial. In a systematic review[40] of LLLT for low-back pain, authors found small effects of this therapy applied alone, and no effect when combined with exercises.

In another systematic review[41] of LLLT for neck pain, authors avoided conclusive statements due to high heterogeneity and potential risk of bias of the studies. As mentioned above, methodological deficits on laser therapy reports were frequent. There is a large range of methodological topics which need to be improved, for instance the report of randomization methods and the allocation concealment.

Lack of consensus about LASER dosage and application sites is notable. Dose controversies are a common topic for LASER therapy, especially for LLLT[42]. Despite World Association for Laser Therapy published recommendations about treatment doses (WALT standards)[43], none of the included studies applied these recommendations. This fact makes the conduction of a meta-analysis of the published studies difficult. One systematic review of LLLT on joints concludes that appropriate energy dose of LASER can result in clinical improvements[44]. Studies of LLLT included in our review did not overcome placebo, none pre-established adequate ranges of energy doses.

We included only one study using LASER acupuncture. A comparison analysis between LASER therapies was not possible. Moreover, dissimilar reports of the outcomes were not comparable. For this reason it was not possible to conduct a meta-analysis.

We recognize several limitations in this review. We defined language and publication data as filters, a fact that reduced the extension of our findings. Most importantly, we did not use two parallel independent reviewers to screen potential articles. The extraction and evaluation of studies was supervised by our second author (SJ) who had access to the entire articles. As observed by the Cochrane Collaboration, this method may result in some errors during extraction of data[18]. However, we did not need any referral to a third author, due to the fact that we fully agreed on the evaluation process after discussion.

CONCLUSION

We did not find evidence to support the use of LLLT for the treatment of oral myofascial pain. We suggest for next investigations in oral myofascial pain to adopt core outcomes associated to the general research tendency on TMDs. Considering the short-term effect of LASER therapy, no psychological factors are expected to be modified, but clinical relevant aspects should be included, namely pain intensity, muscle tenderness upon palpation, and mouth opening. This may help to define an effective dose for treatment, in case there is a real clinical impact of LLLT not attributable to placebo effect in the treatment of TMDs.

Figure 1. Study flow diagram: LLLT for Myofascial Pain (1999-2012)

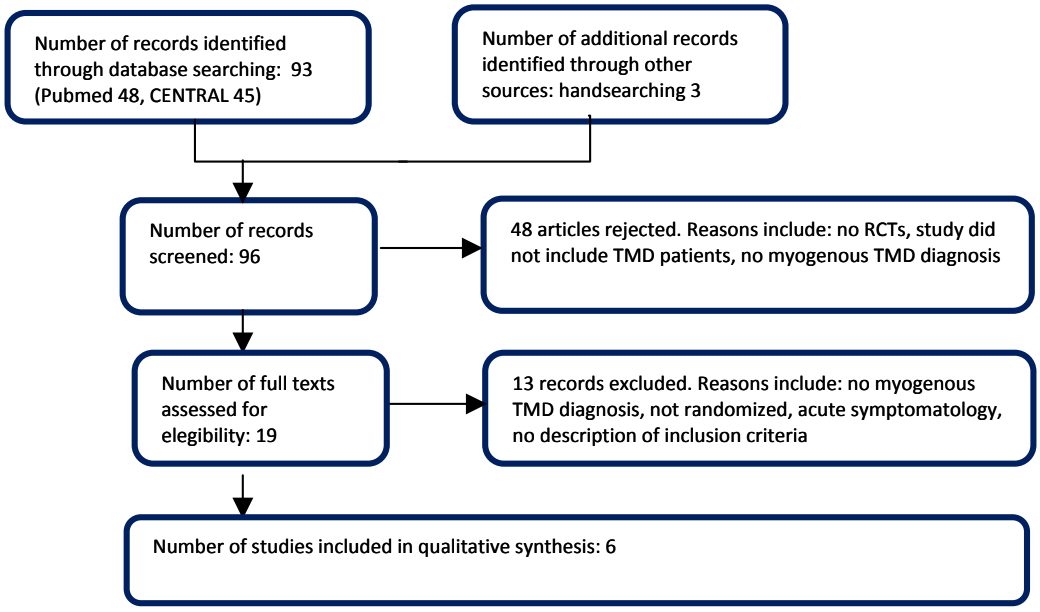
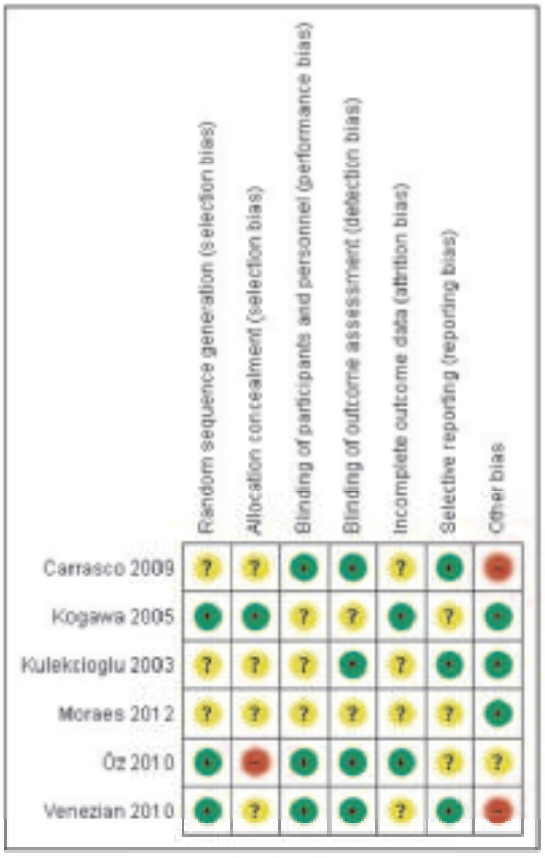
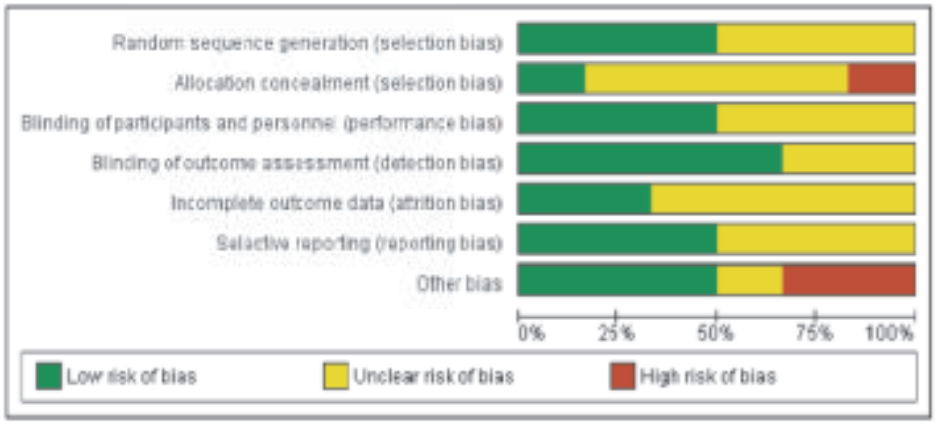


Figure 2. Collaboration's risk of bias* tool: summary of review author's judgements about each risk of bias item for each included study



* Bias is defined as any tendency or inclination which prevents unprejudiced consideration of a question

Figure 3. Risk of bias* graph: review author's judgements about each risk of bias item presented as percentages across all included studies



* Bias is defined as any tendency or inclination which prevents unprejudiced consideration of a question

Table 1. Delphi list to evaluate RCTs' quality
Treatment allocation
a. Was a method of randomization performed?
b. Was the treatment allocation concealed?
Were the groups similar at baseline regarding the most important prognostic indicators?
Were the eligibility criteria specified?
Was the outcome assessor blinded?
Was the care provider blinded?
Was the patient blinded?
Were point estimates and measures of variability presented for the primary outcome measures?
Did the analysis include an intention-to-treat analysis?

Table 2. Excluded studies

Study	Reason for exclusion
Carrasco 2008 [21]	No myogenous TMD patients
Cetiner 2006 [22]	Not randomized
Da Cunha 2008 [4]	No description of inclusion criteria
Emshoff 2008 [23]	No myogenous TMD patients
Fikácková 2007 [24]	Not randomized
Kato 2006 [25]	Not randomized
Katsoulis 2010 [26]	Laser acupuncture
Lassemi 2008 [27]	No description of inclusion criteria
Marini 2010 [28]	No myogenous TMD patients
Mazzetto 2007 [29]	No myogenous TMD patients
Mazzetto 2010 [30]	No myogenous TMD patients
Shirani 2009 [31]	No TMD (acute pain]
Venancio 2005 [32]	No myogenous TMD patients

Table 3. Included Studies

Author	Study design	Patient group	Intervention details	Outcome variables	Key findings
Carrasco 2009 [33]	Single center RCT, 6 parallel groups. Follow-up for 30 days	60 participants with complaint of myofacial pain presenting only one active trigger point in the anterior masseter and anterior temporal muscles Diagnosis of myofascial pain according to Travell, that is, for the presence of trigger points. Location: Brazil	Group A (n=10):LLLT at 25J/ cm^2 Group B (n=10):LLLT at 60J/ cm^2 Group C (n=10):LLLT at 105J/ cm^2 Group D (n=10):placebo LLLT at 25J/ cm^2 Group E (n=10):placebo LLLT at 60J/ cm^2 Group F (n=10):placebo LLLT at 105J/ cm^2 Continuous application of laser on trigger point twice a week for four weeks (GaAlAs, 780nm wavelength, continuous mode 50, 60 and 70 mW Twin Laser, MM Optics Ltda., Class IIIb laser product)	Pain intensity (VAS)	All groups showed a decrease of pain levels. No differences between groups were observed.
Kogawa 2005 [34]	Single center RCT, two parallel groups. Treatment for 3 weeks	19 participants with myofacial pain (RDC/TMD), and tenderness to palpation in the masseter or anterior temporalis: mean age= 26.4yrs.; 100%women Location: Brazil	Group A (n=9): LLLT (10 sessions Ga-Al-As 3 times a week [wavelength of 830 to 904nm, with an output of 4 joules per cm^2 and power of 100mW] (VR-KC-610 SOFT LASER – Dentoflex, São Paulo-SP, Brazil). Group B (n=10): Microcurrent Electrical Neural Stimulation (MENS) (10 sessions MENS 3 times a week [MIOSOFT MILLENNIUM MTC #17849 apparatus (DENTOFLEX, São Paulo – SP, Brazil)], application for 20 minutes, and the current frequency ranged from 40 to 160mA.	Pain intensity (VAS) Muscle tenderness upon palpation (according to RDC/TMD) Maximal jaw opening	Both groups exhibited improvements; however group A showed a significant greater reduction of pain compared to group B.
Kulekcioglu 2003 [35]	Single center RCT, two parallel groups. Follow-up for 1 month	35 participants with orofacial pain, TMJ sounds, limited mouth opening, or TMJ locking: mean age= 37.0 ±12.3 years (R=20-59); 80%women Location: Turkey	Group A (n=20): LLLT Elettronica Pagani1 Roland Serie CE Infrared-27 Laser Unit producing semi-conductive (diodic) GaAs wavelength904nm, output power17 mW, frequency1000 Hz, dosage3 J/ cm^2) (15 sessions of LLLT applied to the four most tender points selected during examination for 180sec + program consisting of range of motion exercises, stretching exercises and postural training) Group B (n=15): placebo (laser not turned on + program of range of motion exercises, stretching exercises and postural training)	Pain intensity (VAS) Number of tender points and joint sounds Maximal active and passive mouth opening, right and left lateral jaw motion (mm)	No differences were observed between arthrogenic and myogenic TMD patients. Both interventions reduced pain levels post-treatment, but they did not differ at follow-up. Jaw motion and tender points significantly changed more in group A.
Moraes 2012 [36]	Single center RCT, two parallel groups. Treatment 4 weeks, 30 days follow-up (FU)	21 participants with myofacial pain (RDC/TMD): mean age=27.76 (10.44); 90.48% women; 85.71% had high school degree Location: Brazil	Group A (n=14 [12]): LLLT (DMC Equipmentos®, São Carlos, SP, Brazil, GaAlAs, 660nm, 100mW, 70J/cm^2, continuous mode, applied at the trigger points of the anterior temporal and masseter muscles [previously noted in the clinical assessment]: five points were applied on each muscle, four forming a cross and one a central point) Group B (n=12 [9]): laser placebo	Pain intensity (VAS) PPT in anterior temporal and masseter muscles (kg/cm^2) Chewing test	Only the group A showed changes in the chewing test and PPT values at the end of the treatment, however only the effects on PPT in masseter muscle remained at FU. Both groups decreased pain intensity, but only group A persisted at FU. No statistical significant differences between groups were reported.
Venezian 2010 [37]	Single center RCT, four parallel groups. 1 month treatment, follow-up for 30	48 participants with myofacial pain (RDC/TMD): mean age=41.58 yrs;	8 sessions of GaAlAs Low Level Laser 780 nm. Infrared (Twin Laser, MM Optics LTDA, São Carlos, Brazil) was applied continuous and punctually within the upper, medium, and lower thirds of the masseter muscle (three points) and the anterior	EMG Pain to palpation (VAS)	At the end of the treatment most of the muscle sites upon palpation showed a decrease in pain intensity; however this effect remained mostly for muscle sites in active groups A and
Öz 2010 [38]	Single center RCT; two groups.	40 (out of 44) patients with myofacial pain (RDC/TMD): mean age=32.89; 85.0% women; mean years of education =10.08; mean months of pain duration =8.05 Location: Turkey	Group A (n=20): low-level laser therapy (Doris Diode Laser, CTL 1106MX;Warsaw, Poland) onto trigger points to 3J/cm^2 by applying 300-mW output power for 10 sec. from a 2-mm distance; 2 times per week for 10 sessions Group B (n=20): stabilization splint according to Okeson*, full time wearing for 3 months	Pain location. Pressure pain threshold (PPT) Functional examination according to RDC/TMD: Active and passive mouth opening, muscle tenderness to palpation	Both groups significantly improved in all outcomes, without showing any differences between groups. *Note:* The treatments did not have the same duration. The patients were evaluated 30 min. before the first session and 30 min. after the last session of the assigned intervention.

Appendix 1. Search strategy of Low-Level Laser Therapy for Myofacial Pain
MEDLINE via Pubmed. Database entry date: 01.11.2012
#1 Myofascial Pain Syndromes [MeSH]
#2 Craniomandibular Disorders [MeSH]
#3 Temporomandibular Joint Dysfunction Syndrome [MeSH]
#4 Temporomandibular Joint Disorders [MeSH]
#5 myofascial [tiab] AND pain [tiab] AND syndrom* [tiab]
#6 myofascial [tiab] AND trigger point [tiab] AND pain [tiab]
#7 craniomandibular [tiab] AND disorder* [tiab]
#8 craniomandibular disease* [tiab]
#9 temporomandibular joint dysfunction syndrome [tiab] OR myofascial pain dysfunction syndrome, temporomandibular joint [tiab]
#10 TMJ [tiab] AND syndrome [tiab]
#11 Costen* [tiab] AND syndrome [tiab]
#12 temporomandibular [tiab] AND joint [tiab] AND syndrome [tiab]
#13 temporomandibular [tiab] AND joint [tiab] AND disorder* [tiab]
#14 TMJ [tiab] AND disorder* [tiab]
#15 temporomandibular [tiab] AND disorder* [tiab]
#16 temporomandibular [tiab] AND joint [tiab] AND disease* [tiab]
#17 TMJ [tiab] AND disease* [tiab]
#18 craniofacial pain [tiab]OR masticatory muscle disorder [tiab] OR masticatory muscle pain [tiab] OR orofacial muscle pain [tiab] OR chronic muscle pain [tiab] OR myofacial pain [tiab]OR myogenous facial pain [tiab]OR myofunctional pain [tiab] OR orofacial myofunctional disorder* [tiab] OR myofunctional disorder [tiab]OR myoarthropat*[tiab]
#19 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 laser Therapy, Low-Level [MeSH]
#21 laser therap*[tiab] AND low-level [tiab]
#22 laser therap* [tiab] AND low level [tiab]
#23 laser [tiab] AND irradiation [tiab] AND low-power [tiab]
#24 laser [tiab] AND phototherap* [tiab]
#25 low-power [tiab] AND laser therap* [tiab]
#26 low power [tiab] AND laser therap* [tiab]
#27 LLLT [tiab] OR low-power laser irradiation [tiab] OR low power laser irradiation [tiab]
#28 laser [tiab] AND biostimulation [tiab]
#29 #20 OR #21 OR#22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#30 #19 AND #29
The above described search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); PubMed format as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of *The Cochrane Handbook for Systematic Reviews of Interventions,* Version 5.0.2 [updated March 2011].

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Low-Level LASER as supportive therapy of temporomandibular disorders -TMDs: a case report.

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Abstract

Objective: The aim of this report was to evaluate the effectiveness of Low-Level LASER Therapy -LLLT- in the treatment of a TMD.

Clinical Application: A patient complaining of TMD (myofascial pain, mainly in right and left masseter and temporal muscles) and mouth opening limitation, was treated with LLLT, for a period of one month. A Visual Analogue Scale (VAS) was used to evaluate pain level. An occlusal device therapy was used after treatment with LASER therapy.

Results: Patient was satisfied reporting a normal mouth opening and absence of pain in left and right temporal and masseter muscles.

Conclusion: LLLT was proposed as supportive therapy in combination with conventional occlusal device. Treatment protocol was effective in managing mouth opening limitation and TMJ muscles pain. Patient was put on a soft food diet during the treatment period.

INTRODUCTION

The term "Temporomandibular disorder" (TMD) is used to describe a large number of clinical signs and symptoms that affect muscles of mastication, temporomandibular joint (TMJ), and associated structures[1-3]. Orofacial pain is the most common complaint among individuals with TMD[1,4]. Other symptoms include limited mandibular movements, joint noises,[1,5,6] headache, dizziness, and ears ringing[7,8], affecting the quality of life of patients.

Low-level LASER therapy (LLLT) is a particular form of LASER medicine that uses low-level (low-power) LASERs (or light-emitting diodes) to alter cellular function. Other names for this therapy include soft LASER, cold LASER, biostimulation LASER, and LASER acupuncture. It produces photo-biochemical reactions that result in pain relief. Therapeutic effects of LLLT include modulation of inflammatory process and analgesia[9-12].

LLLT may reduce pain related to inflammation by decreasing levels of prostaglandin E2, interleukin 1-beta, tumor necrosis factor alpha, prostaglandine-endoperoxide synthase 2, oxydative stress, edema, and cellular influx of neutrophil granulocytes (Karu, 2008 and Bjordal et al., 2003 and 2006).

CASE REPORT

A 26 year-old female complaining of orofacial chronic pain (mainly in right and left masseters and temporal muscles), was referred to our private practice. After history taking and clinical examination, patient was diagnosed with a temporomandibular disorder condition combined with a mouth opening limitation (< 30mm). CT Scan radiographs excluded a disc displacement of TMJs (Fig. 1).

A visual analog scale was used before and after therapy to record pain level upon palpation of the left and right masseter, TMJs, lateral and medial pterygoids, and temporal muscles. This is a numeric rating scale that runs from 0 (absence of pain) to 10 (worst pain imaginable)[1,2]. The procedure was explained verbally to the patient and signed informed consent was obtained for the use of LLLT as supportive therapy.

The treatment using a LLLT diode LASER (Ezlase™, Biolase, USA) was performed twice per

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week over one month (total of 8 sessions). Patient was positioned with the Frankfurt plane parallel to the ground. The LASER handpiece was covered with disposable plastic wrap to avoid cross-contamination. The skin at the site to be irradiated was previously cleaned with 0.12% chlorhexidine digluconate solution. Both dentist (NAH) and patient used protective eye glasses.

The device has a wavelength of 940 nm, it was set to a power of 6 W, and a power pulse duration on continuous mode (manufacturer's recommendations). The LASER tip was placed on Temporalis, TMJ, and masseters (Fig. 2). The total exposure time will be 5 mins per side, resulting in a total energy density of 150J/cm2 per point. In regard to clinical application, LASER displays a conventional handpiece in contact with the skin and it covers an area of 4 cm^2 (Figs. 3,4)[13].

After 4 weeks, patient reported no pain (on VAS) and normal mouth opening (48 mm), and then an occlusal device was placed. Six-month follow-up reported no relapse of pain or discomfort.

DISCUSSION

5 to 15 percent of Americans experience pain associated with TMDs (women are more likely to experience such pain, compared to men), according to the National Institute of Dental and Craniofacial Research (part of the National Institutes of Health, Bethesda, Maryland, USA).

Different treatment options have been proposed (due to multifactorial etiology of TMDs) such as occlusal device therapy, LLLT, acupuncture, ultrasound, massage therapy, psychotherapy, and drug therapy[12,13]. LLLT is a low-cost, noninvasive form of treatment that offers pain relief, probably by reducing inflammatory response and blocking the effect of reactive oxygen species (ROS) and nuclear factor kappa B (NF-kB), both involved in the inflammatory process in muscles[14,15].

One of the most important fields of LLLT application is pain control, which is based on enhanced ATP synthesis in neurons. When ATP synthesis is reduced, a faint depolarization results, lowering the threshold of triggering and action potential. In contrast, enhanced ATP synthesis by LLLT leads to hyperpolarization and blockage of stimuli, thus decreasing induction of pain stimuli[16-18].

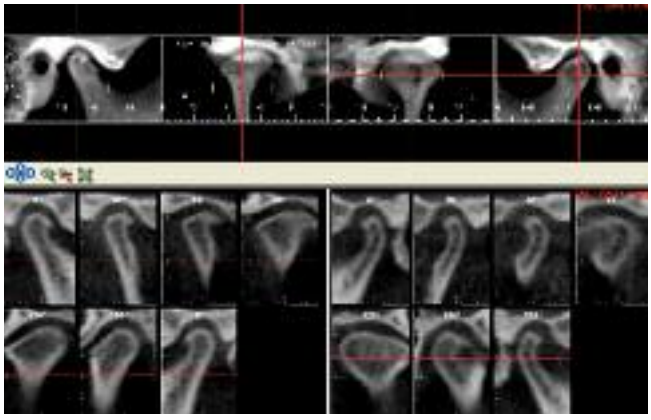

Fig. 1. CT of mandibular condyles (right and left).

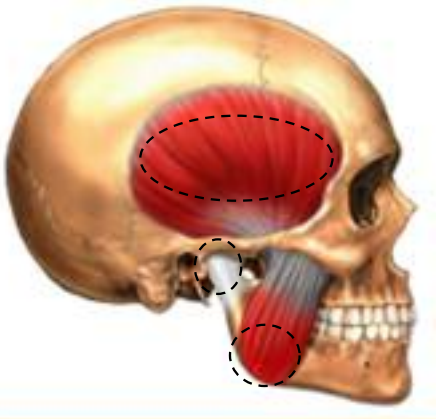

Fig. 2. Regions of LASER application.

Fig. 3. ezlase™940 handpiece.

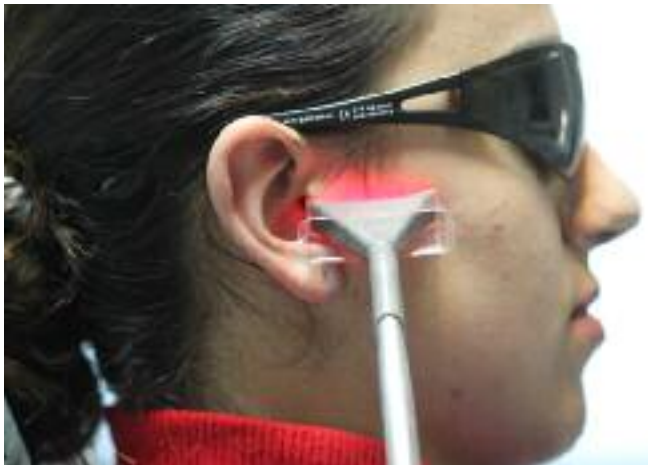

Fig. 4. LASER application on right TMJ.

Patient amelioration was observed during a month period according to VAS: before starting LLLT treatment sessions, pain on VAS was 8, after first week (the first 2 sessions) it was decreased to 7, then respectively second, third and fourth week to 5, 2 and 0. It is important to know that no drug was prescribed during the treatment period.

CONCLUSION

There is no consensus. yet, over ideal use of LLLT but many reports suggest its relative effectiveness in relieving short-term pain in rhumatoid arthritis (Brosseau et al., 2005), osteoarthritis (Jamtvedt et al., 2007), acute and chronic neck pain (Chow et al., 2009), and tendinopathy (Bjordal et al., 2008 and Tumilty et al., 2010). And within the limitation of this case report, the use of LLLT to reduce muscle pain in TMD patient showed a successful outcome. Further clinical studies should be designed to evaluate the effect of LLLT in TMD management and obtain a consensus regarding the best LLLT application protocol for pain relief in TMDs patients.

Last, but not least, if high-power LASERs ablate tissues, low-power LASERs may stimulate them, hence encouraging cells for better functions.

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Medication Overuse Facial Pain - MOFP: a case series and proposed diagnostic criteria.

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Abstract

Persistent idiopathic or chronic atypical facial pain (AFP) is a poorly defined syndrome. Patients with facial pain are often given this diagnosis after other causes had been excluded, It is therefore likely to encompass a variety of conditions. We present a case series of seven patients with facial pain of unknown cause, after clinical assessment and investigations. The common factor in this group of patients was overuse of large doses of strong analgesics or triptans. Medication withdrawal was associated with significant reduction in severity and frequency of facial pain. We propose the syndrome of Medication Overuse Facial Pain as a cause of atypical facial pain in some patients. This condition appears to be analogous to Medication Overuse Headache. Identification and medication withdrawal appear to be the key for managing these patients.

Conclusion: We have identified medication overuse as an important feature in some patients with atypical facial pain. A thorough history of medication overuse should be specifically taken, as withdrawal can lead to pain relief.

INTRODUCTION

Oro-facial pain is pain in structures predominantly innervated by the somatic portion of the trigeminal nerve namely the face, scalp, and mouth. It is often defined as pain which is experienced in the area below the meatal line, above the neck and up to the ear[(1)], thereby excluding headaches. Predominant oral causes of pain are dental with the majority being acute rather than chronic. There are a very wide range of causes for facial pain and these have been divided into three broad categories by Hapak[(3)] and associates: musculoligamentous, dentoalveolar, and neurological and vascular. This classification has been used in many epidemiological studies.

The incidence of chronic orofacial pain is comparable with other pain conditions in the body, accounting for between 20 to 25 % of chronic pain conditions[(4)]. In the study of Locker & Grushka[(6)], pain or discomfort in the jaws, oral mucosa, or face had been experienced by less than 10 % of the study population in the last four weeks. Bonica[(7)] estimated that five to seven million Americans suffer from chronic pain in the face and mouth, whereas Lipton and co-workers[(4)] estimated that between 25-45% are affected at some time of life. As mechanisms underlying these pains begin to be identified, more accurate classifications may come to be used.

The commonly accepted classifications of facial pain have been published by The International Headache Society (IHS), International Association for the Study of Pain (IASP), and the American Academy of Orofacial Pain (AAOP)[(14,15)]. Woda and associates[(22)] reported a recent cluster analysis in an attempt to streamline disorders that cause orofacial pain into aetiological categories: the neurovascular group included most ophthalmic division pain (headaches, giant cell arteritis) and also trigeminovascular headaches. The neuralgia group included trigeminal neuralgia (typical and atypical;), post-herpetic neuralgia (post-shingles pain which is 60% increased likelihood if the patient is over 50 years) and post-traumatic neuralgia (including iatrogenic nerve damage).

The idiopathic group included persistent idiopathic facial pain (previously known atypical facial pain and

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atypical odontalgia). This is a particularly difficult group of patients to treat: they often present with whole quadrants of teeth extraction and having undergone extensive restorative dental treatment with no pain relief.

Chronic oro-facial pain conditions represent a diagnostic challenge for any dental or medical practitioner. Patients are frequently misdiagnosed or attribute their pain to a prior event such as a dental procedure, ENT (Ear, Nose and Throat) causes, or facial trauma. Symptoms of depression and anxiety are prevalent in this population and compound the diagnostic conundrum. Treatment is less effective than in other pain syndromes.

Persistent idiopathic facial pain (atypical facial pain)

One category of chronic oro-facial pain which is especially difficult to manage is atypical facial pain (AFP). This term was used to denote a category of patients whose facial pain did not improve with neurosurgery. There is no precise definition of AFP in the 1984 IASP classification. The 2002 IHS classification used the term persistent idiopathic facial pain (PIFP) to denote a condition where "facial pain is present daily, persisting for most of the day, confined at onset to one side of the face that is deep and poorly localised". In these patients, there are no abnormalities on physical examination or investigations".

PIFP is reported to be more common in women. The area of pain does not follow any known neural pathway and tends to be present for months with frequent recurrences. Pain tends to be constant throughout the day and is often absent during sleep. Psychological factors are common. PIFP may coexist with other idiopathic pain syndromes in the mouth and face: atypical odontalgia, temporo-mandibular joint disorders, and oral dysaesthesia (Woda and Pionchon, 2001, Madland and Feinmann, 2002). AFP has been reported to respond to a multidisciplinary approach; addressing psychological factors and prescribing antidepressant drugs.

Medication overuse headache (MOH) and Facial pain

Medication overuse is increasingly recognised as an important cause of chronic headaches. MOH, also known as rebound headache (L. Kudrow, 1982) may evolve from migraine or tension type headache and is commonly associated with excessive and frequent use of both opioid and non-opioid analgesics as well as triptans. It has been estimated that between 1-2% of women in the developed countries have MOH. Medication withdrawal is the mainstay of treatment, although beneficial effects may not be apparent up to 2 months after cessation. In addition, it has been reported that usual medications used as prophylaxis for headaches are ineffective until withdrawal from the offending drug(s) have been successfully achieved.

Anatomical substrate for MOH is the ophthalmic division of trigeminal nerve. It is therefore likely that structures innervated by maxillary and mandibular divisions may also give rise to chronic pain secondary to medication overuse. We are not aware of any reports in published literature on overuse of medication in patients with orofacial pain, nor the effects of medication withdrawal in such patients.

We propose the concept of medication overuse facial pain (MOFP), a condition analogous to medication overuse headache (MOH). In this clinical study, we address a case series describing patients with oro-facial pain and excessive medication where pain relief was noticed following medication withdrawal.

METHODS

Over a period of 12 months (2008), patients with chronic facial pain with medication overuse were identified. Successful reduction in medication overuse associated with pain relieve was achieved in 7 patients and their details are outlined below. For all patients, a thorough pain and medical history was taken together with head and neck examination. All had undergone previous investigation with the majority having had an MRI scan of the head within 6 months of being seen in clinic. For those who did not have prior neuroimaging, this was performed. None of these patients had abnormalities on the scan that provided a cause for their facial pain. Patients were asked to verbally report their pain, at rest, on a scale ranging from 0 to 10 (0= no pain, 10= worst pain imaginable). Patients were then instructed to completely stop any conventional analgesics that were being taken. In patients where

medication withdrawal alone fail to reduce facial pain, patients were then started on or asked to continue with another form of medication; including tricyclic antidepressants (TCA), serotonin norepinephrine re-uptake inhibitors (SNRI), or anticonvulsants.

Patients were reviewed following cessation of conventional medication at a minimum of 4 weeks (range 4-18 weeks). Another verbal pain report assessment was attained and patients' medication use was again recorded at review to ascertain if patients had returned to their old regimen. Patients' general comments were also sought at review to clarify if any problems arose following cessation of the medication. Patients were then followed-up for a minimum of 3 months after their attempted cessation of analgesic consumption.

CASE 1

SH, 41 year old female

Initial presentation:

Patient presented to neurology department 5 months after onset of facial pain. She was initially treated with a course of antibiotics for suspected "sinusitis" (not demonstrated on CT), with only a short initial improvement in symptoms which recurred when antibiotics were discontinued. She sustained spontaneous exacerbations of sharp stabbing pain radiating from ear to jaw, superimposed on a constant burning cold pain "as if the face was frozen". The pain started on right cheek but spread bilaterally within weeks. She said she was able to sleep at night but woke every morning with increased tactile sensitivity of right cheek with stabbing pain in her teeth. Neurological examination was normal apart from subjective hyperalgesia of right face that did not correspond to any nerve distribution. A MRI scan of the head was reported to be normal.

Medication regimen:

Solpadol® (codeine phosphate 30mg/paracetamol 500mg) 4-6 tablets daily since June 2008 which gave her some pain relieve but did not completely alleviate her symptoms.

After careful explanation, she discontinued pain killers, was prescribed imipramine, a tricyclic antidepressant (10mg at night) and applied hot/cold packs to the face for pain relief.

On review:

She reported a gradual improvement over 4 weeks and was pain free 2 months after cessation of Solpadol®. After a further 2 months, she discontinued imipramine and remained pain free off all medications for a total of 3 months before she was discharged.

CASE2

AM, 39 year old female

Initial presentation

This patient presented to neurology outpatient clinic 5 months after onset of facial pain. The pain initially presented as a chronic daily headache as result of a whiplash injury to her neck. She then developed facial pain, predominantly on right side. She described daily shooting/stabbing pain present from waking and lasting all day. About 2-3 times a week, pain was perceived as bilateral. She had undergone 3 MRI scans of the head in last 2 years without an explanation for her facial pain.

Medication regimen

In an effort to alleviate a chronic daily headache, the patient was taking increasing doses of Codydramol® (Codeine tartrate 10mg/paracetamol 500mg), with the dose on consultation being 6-8 tablets/ day. Her family practitioner also prescribed amitriptyline, a tricyclic antidepressant (30mg at night) with partial alleviation of her headache.

After assessment and investigations, she was advised to discontinue Codydramol® and started on topiramate, an anticonvulsant drug.

On review:

Within 2 weeks of discontinuing codydramol, she became pain free. After a further 10 days without headaches or facial pain, she restarted taking codydramol. When last assessed, she was taking 4 tablets of codydramol a day and the facial pain was every other day. She was once again advised to stop taking codydramol and the dose of topiramate was increased to 75mg twice a day. She was referred to the pain clinic to consider having an occipital nerve block.

CASE 3

KC, 54 year old female

Initial presentation:

This patient was referred by otolaryngology

department with regards to a 2 year history of pain around the right eye, nose, and face. She described her pain as "deep and constant" with spontaneous exacerbations that last for over 2 hours. She also suffered from a long history of musculoskeletal back pain. MRI scan of the head and neck were reported to be normal.

Medication regimen:

In an effort to control facial and low back pain, patient was taking 2-8 tablets of Codydramol® every day for the past 2 years. She was also on venlafaxine, an antidepressant of the SNRI class (Serotonine-Norepinephrine reuptake inhibitor) (75mg a day). After clinical assessment, she was advised to discontinue Codydramol® but to remain on venlafaxine.

On review:

Over the next 5 months, constant pain abated and the frequency of exacerbations gradually reduced so that she only experienced 1 attack per week. She still consumed an average of 2 tablets of Codydramol® every week.

CASE 4

GA, 34 year old female

Initial presentation:

She presented with a 3 year history of right sided facial pain. Her symptoms started around left ear which rapidly spread to the right. She described a constant dull aching background pain with shooting and stabling exacerbations, lasting up to 90 minutes. The pain can be triggered off by loud noises or tactile stimuli to the face. She had a right trigeminal rhizotomy in the past with temporary pain relieve. She has had 2 previous CT and 2 MRI scans of the head in the last 3 years without any explanation for her facial pain. In particular, no vascular contact was seen along the course of the trigeminal nerves.

Medication regimen:

Patient was taking a cocktail of medications: Methadone, a synthetic opioid (60mg), Carbamazepine, an anticonvulsant and mood-stabilizing drug (200mg), Venlafaxine (75mg), Sevredol® (morphine, 80mg), Topiramate, an anticonvulsant (100mg daily). She admitted to consuming up to 30 tablets of Anadin® (Aspirin, 325mg/Caffeine*, 15mg) a day.

** Caffeine is a stimulant drug. In humans, it acts as a central nervous system stimulant, temporarily warding off drowsiness and restoring alertness. It is the world's most widely consumed psychoactive drug.*

Management:

The patient was admitted for medication withdrawal with a tapering course of prednisolone. She was discharged after one month with amitriptyline replacing methadone and cessation of Anadin®.

On review:

On 2 month follow-up, her continuous pain abated and she described a "generally clearer head". She still experienced episodic exacerbations.

At the sixth month follow-up, she managed to come off all medications and was pain free. She also announced the pleasant surprise that she was 12 weeks pregnant. She said that even the hyperacusis (= over-sensitivity to certain frequency and volume ranges of sound) has improved greatly and no longer troubled her.

CASE 5

EC, 54 year old female

Initial presentation

Four month history of pain in behind her eyes and tightness in her cheeks as well as episodic migraine attacks with nausea and vomiting up to 4 times a week. Previous brain MRI scan had shown non-specific white matter changes only.

Medication regimen:

She was taking Buprenorphine (a semi-synthetic mixed agonist-antagonist opioid receptor modulator), 200mcg, Zolmitriptan (a selective serotonin receptor agonist used for acute treatment of migraine attacks) 2.5mg up to 12 doses a month, Topiramate 50 mg, Imipramine 25mg, Melatonin (a hormone used to ease insomnia), 2mg on presentation.

Management:

The patient was advised to discontinue the buprenorphine and to take zolmitriptan no more than twice a weeek.

On review

On 8 month follow-up, she described that although she still experienced episodic migraines up to once a week, her constant pain had subsided and then disappeared.

CASE 6

AH, 57 year old female

Initial presentation

Eighteen month history of facial pain from left

corner of mouth to cheek and temple. Each episode lasted approximately 2-3 hours. Prior to her neurology consultation, episodes occured up to 25 times per month. She also suffered from migraine attacks consisting of right forehead pain with nausea 8-12 episodes a month. These episodes were distinct from her facial pain. She would usually take 1-2 doses of Zolmitriptan which is effective in alleviating her migraine but not facial pain. She was referred with a diagnosis of atypical trigeminal neuralgia.

Medication regimen

Zolmitriptan 5mg (12-24 tablets per month)

Management

Zolmitriptan was reduced to a maximum of 8 tablets per month

On Review

At 3 months following reduction in her medication, frequency of facial pain was reduced to less than once a week. She was also started on Amitriptyline in an effort to reduce frequency of migraine attacks.

CASE 7

HM, 47 year old female

Initial presentation

Over 20 year history of continuous facial pain with exacerbations every 4 years. Diagnosed as chronic sinusitis. Regular sinus drainage with no alleviation. Latest bout started 1 year ago with daily constant throbbing pain "as if face is in a clamp". Pain severity 8/10 on verbal analogue scale.

Medication Regime

Codydramol® (dihydrocodeine tartrate 10mg/ paracetamol 500mg), 6-8 tablets daily for the past 5 years.

Management

Codydramol® was discontinued and she was started on Topiramate, 25mg daily, and gradually increased to 50mg twice a day.

On Review

Complete pain relief within 6 weeks of discontinuing Codydramol®. At three months follow-up, remained pain free. Long-term aim to reduce and discontinue Topiramate.

RESULTS

The average duration of orofacial pain for this group of patients at initial consultation is 16 months, mean age was 46.57 year (range 34-57years). All patients were female.

Initial diagnoses in these patients included atypical trigeminal neuralgia, post-traumatic headache with facial pain, and persistent idiopathic facial pain.

All of these patients have taken analgesics or triptans in doses and frequencies known to be associated with medication overuse headache (MOH). The most common medication were opioids with patient GA consuming sevredol and methadone equivalent to over 500 mg of morphine daily. Other patients have consumed lower doses of opioids but were still taking medications at least 3 days a week. The majority (6/7) were taking opioids daily. Five out of the 7 patients were taking medication within the recommended daily dose, but at an excessive frequency (on a daily basis). Four of these patients excessively consumed medication available OTC. Three out of the 7 patients were taking an excessive combination of multiple drugs. Only one patient was taking an excessive daily dose of triptan. All patients experienced reduction in facial pain when they successfully reduced the dose and frequency of analgesic or triptan consumption. There was however a high risk of relapse with patients AM and KC continuing to consume opioids in spite of initial improvement in facial pain.

This case series demonstrates that a reduction in medication consumption was associated with significant pain reduction in all patients and complete pain resolution in three patients.

The majority of patients (5 out of 7) were thought to be on ineffective medication regimens, involving OTC medications, at initial consultation. Their medication regimens were subsequently changed by introducing an antidepressant medication and/ or complete cessation of the OTC. Only one patient was kept on the same medication regimen but was advised a reduced frequency (case 6).

DISCUSSION

This cohort* of patients demonstrates, for the first time, that medication withdrawal may be appropriate

** Cohort is a group of people who share a common characteristic or experience within a defined period. And a cohort study (or panel study) is a form of longitudinal study (a type of observational study) used in medicine and dentistry.*

for certain patients with chronic facial pain. Assessing medications consumption and withdrawal where appropriate is important in the management of patients with facial pain where there is no obvious cause. A failure to recognise and effectively deal with medication overuse may result in ongoing or even worsening symptoms. It may also lead to recognised side-effects for the patient.

Is this facial pain associated with migraine?

Migraine can be associated with facial pain. This commonly occurs during an attack and many parts of the body (including limb pain) have been reported. Migraine alone cannot be the explanation for our patients with facial pain. Some of our patients have not reported prior migraine headaches. More importantly, many of our patients with MOFP had persistent pain lasting months to years and managed to continue with their normal lives. One common feature of migraine is that during an attack, normal activities are curtailed. Therefore, migraine alone cannot be the explanation for facial pain experienced by this cohort of patients. Patients with migraine as well as MOFP (AH and EC) were able to differentiate between the 2 conditions. They have reported relieve of MOFP as distinct from the effects of medication reduction on their migraine.

What is the underlying diagnosis before patients develop MOFP?

These patients were referred with initial diagnoses of atypical trigeminal neuralgia, chronic sinusitis, or atypical facial pain. In patients with AFP, sinusitis was reported to be the most common extracranial "abnormality" seen on MRI scans (Ogutcen-Toller et. al., 2004). Whether this is a simple correlation or that sinusitis is the underlying pathology is controversial. Some authors have insisted that sinusitis rarely causes chronic facial pain (Jones, 2009). Where scans were performed for reasons unrelated to facial pain, it is not uncommon to see evidence of a fluid level, thickening of the mucosa, or polyps within sinuses. The evidence that "chronic sinusitis" is the cause of facial pain is sparse and in this cohort of patients, cannot be the explanation for chronic pain.

Diagnosis of atypical trigeminal neuralgia (atypical TN) however is more controversial. This term is commonly used in patients with trigeminal neuralgia but also constant pain between each bout of short "electric shock" sensation. Neurophysiological studies demonstrated enhancement of nociceptive transmission within the brainstem in patients with atypical TN as distinct from those with typical TN. For this reason, pharmacotherapy and surgery may be less efficient. The diagnosis of atypical TN may be correct in at least one of our patient (GA): she had undergone trigeminal rhizotomy with transient benefit. However, it is also clear that medication overuse contributed significantly to her facial pain and withdrawal of medications was associated with being pain free for over 4 months at last follow-up. This may prompt a re-evaluation of the diagnosis of atypical TN to exclude those with MOFP.

Triptans are also reported to be effective for treating acute TN. It would be interesting to study whether triptan overuse in patients with TN will also lead to the development of MOFP. Although our series of patients are too small to draw firm conclusions, it appears that regardless of the initial diagnosis, MOFP can evolve from any condition where there is excessive opioid or triptan consumption. Therefore, analogous to MOH, MOFP may evolve from whatever the initial cause of pain.

How long does MOFP take to develop?

Patients described above have been taking excessive amounts of analgesics and triptans for months. It is unclear how long a susceptible individual have to take medications before developing MOFP. The presumed period must be for many months. Once again, if MOFP is similar to MOH, someone will have to take medications for over 3 months. It is also unclear what characteristics predispose someone to develop MOFP. Just taking analgesics alone is insufficient (Anish Bahra paper on Rheumatology patients). Cephalophobia (or fear of having headaches) appears to be a prominent trait in MOH. It is likely that fear of facial pain drives the desire to take excessive amounts of analgesics or triptan which lead to the development of MOFP. All patients described in the present case series report were also women. The present sample is too small to make any definite conclusion but it would appear that women who are in

fear of face pain are at risk of developing MOFP if they have access to strong opioid analgesics and in one case, triptans.

How should patients with MOFP be managed?

Once characteristics that are likely to lead to MOFP are identified, strategies to prevent MOFP are obvious. Management of patients with undiagnosed and unexplained facial pain should not rely on just increasing doses of ever stronger analgesics. It is imperative to spend time listening to the patient, taking an exhaustive history, thorough examination, and an awareness of Up to Date assessment methods. Evaluating these patients requires time and patience and often a multidisciplinary team. Often this investment of one on one assessment will itself empower the patient to understand and cope with his/her pain. This will help to overcome the demand for ever stronger analgesics or more invasive therapies. The use of antidepressant drugs (especially tricyclics) in small doses as well as antiepileptics, early on, would appear to be a logical strategy. These medications have been shown to be effective for alleviating neuropathic pain. There is also some evidence that both amitriptyline and gabapentinoids may "pre-empt" pain. This will help reduce the risk of tachyphylaxis and patients habituating to ever stronger doses of opioids.

When MOFP has developed, management may be more difficult. For patients with MOH, it has been reported that one third of patients were not able to discontinue their consumption of analgesics. The anecdotal evidence in our clinical practice would support this. This case series described patients who have successfully reduced or stop their excessive analgesic consumption, which led to a reduction in facial pain. However, there are a number of patients initially identified who may fulfil the criteria of MOFP (presumed MOFP) who were unable to reduce frequency and dosage of taking opioids. We have not systematically followed them up but a number of them still experience facial pain when seen in outpatient clinic. It is therefore imperative to early identify and recognize the risk of MOFP in order to avoid the development of a condition where a substantial portion will not improve.

How common is MOFP and why was it not described previously?

It is simply impossible to estimate the prevalence of MOFP. This is the first time we are aware that this condition has been described. Many of our patients were referred from our ENT (otoloaryngology) or maxillofacial surgery colleagues with a presumptive diagnosis of "chronic sinusitis". Some patients have been seen in pain management clinics while others have been under the care of neurologists. Increasing the awareness of possible MOFP amongst these colleagues as well as those working in primary care will hopefully reduce the incidence of this condition. Overuse and over-prescription of opioids can lead to significant problems, especially when pain appears so severe and refractory to treatment. Consumption of maximum recommended dose of codeine or dihydrocodeine 60mg four times a day is equivalent of 25-30mg of morphine daily. It can be even more confusing when opioids are administered parenterally. The fentanyl 12 patch* for example delivers the equivalent of 45mg of morphine a day. For this reason, prescribers of opioids should familiarise themselves with the appropriate Up to Date guidelines.

The idea that medication overuse can lead to chronic headaches was recognised in the 1950's and 60's (Katsarava and Jensen, 2007). The International Headache Society (IHS), in its first classification of headaches, helped defining and giving better recognition to this condition. It is possible that MOFP was also described in the past but the possible aetiological role of medication overuse was not recognised. In our search of published literature, we did find the case report of a man with intractable left then right facial pain and no known diagnosis present for years. This patient was prescribed opioids in ever increasing doses to the extent of having intraventricular morphine 26mg on top of 400mg injected subcutaneously every day. He was admitted for opioid withdrawal with the addition of clonidine, (a sympatholic and centrally acting alpha 2 adrenergic agonist medication used to treat high blood pressure, anxiety disorders, migraine, and certain pain conditions). Substantial reduction in opioid administration was reported to be associated with

reduction in facial pain (Lorenz et. al., 2002). The description of this man's case is highly suggestive of MOFP. Pain relief was ascribed to intraventricular clonidine although there is no evidence that this drug is effective for alleviating facial pain. Even the use of clonidine orally as prophylaxis for migraine was not supported by results from large placebo controlled studies. It was more likely that opioid reduction rather than clonidine administration was responsible for pain relief in this man. It is likely that MOFP had existed but was not recognised.

What is the underlying pathophysiology of MOFP?

Pathogenesis of medication overuse headache remains unclear. Clinical and preclinical studies have demonstrated raised excitability of neurons in cerebral cortex and trigeminal system after medication overuse (Srikiatkhachorn et al., 2013 in: "J Chem Neuroanat" and "Headache")[40]. Theories included:

- Cortical hyperexcitability enhancing the development of cortical spreading depression, while increased excitability of trigeminal neurons may facilitate the process of peripheral and central sensitization. These changes may be secondary to the derangement of central, probably serotonin (5-HT)-, and perhaps endocannabinoid-dependent or other, modulating systems. Increased expression of excitatory cortical 5-HT2A receptors may increase the susceptibility to developing cortical spreading depression, similar to migraine aura.

- A reduction of diffuse noxious inhibitory controls may facilitate the process of central sensitization, activate the nociceptive facilitating system, or promote similar molecular mechanisms to those involved in kindling. Low 5-HT levels also increase expression and release of calcitonin gene-related peptide from trigeminal ganglion and sensitize trigeminal nociceptors.

Thus, derangement of central modulation of trigeminal system as a result of chronic medication use, may increase sensitivity to pain perception and foster or reinforce medication overuse headache and pain (Srikiatkhachorn et al., 2013).

CONCLUSION

Management of chronic orofacial pain is a significant challenge. In many patients, pain lasts for months and years. Current strategy for these patients is to prescribe increasingly potent analgesics together with invasive therapies in an effort to relieve pain. This case series of patients illustrate the failure of such an approach for treating some patients with chronic facial pain. The association of pain alleviation with analgesic withdrawal would suggest that these patients have medication overuse facial pain. This is a condition analogous to MOH and patients may respond to the same treatment strategies. Further studies are warranted to clarify how common this condition is and also for a better management of these patients.

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An evaluation of the effects of Platelet Rich Plasma -PRP- compared to Sodium Hyaluronate -SH- in the treatment of temporomandibular joint OsteoArthritis -OA-

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Abstract

The purpose of this study was to evaluate the efficacy and complications of (intra-articular) temporomandibular joint (TMJ) injections of 40 patients with TMJ osteoarthritis. Subjects were randomly divided into two groups, and patients received either one intra-articular injection of sodium hyaluronate (SH) or one intra-articular injection of platelet rich plasma (PRP). Effect of treatment was evaluated 10 days, 20 days, and 2 months after the initial injection and it was based on pain intensity and mandibular function. Both groups of patients had less pain intensity at the 20-days follow-up, and there was significantly less pain intensity in the group of patients receiving PRP, compared to sodium hyaluronate's one (P<0.05)) at the 2 months period. In both groups, mandibular vertical opening was similar at the two month period.

In conclusion, this study confirms that TMJ injection with PRP or sodium hyaluronate may reduce pain and improve function in patients with TMJ osteoarthritis. However, PRP injection was significantly more efficient in decreasing pain intensity after several months.

Tendons and ligaments connect muscles to bones, making it possible to perform all kinds of physical activities. Overuse or damage to tendons over a long period of time causes collagen fibers (that make up the tendons) to form small tears, a condition called Tendinosis[1]. Ligaments are composed of collagen fibers and hold bones together, they stabilize joints and control range of motion. Tendons and ligaments have poor blood supply, and they do not easily heal from damage caused by sprains, strains, and repetitive motion resulting in degenerative changes. At the level of temporomandibular joint (Fig. 1), impairment of the joint's sheath which is composed of damaged tendons and ligaments will result in joint's dislocation[13], thus activating an inflammatory and degenerative process[7].

Ostheoarthritis -OA- (known also as degenerative joint disease) is the most common form of chronic musculoskeletal disease which particularly affects aging population.

Patients with OA of TMJ who did not respond to conservative medical therapy (splint therapy, selected grinding, or physiotherapy) can be treated by arthrocentesis[2], which is associated with intra-articular injections of sodium hyaluronate (= the sodium salt of hyaluronic acid, a glycosaminoglycan - GAG - found in various connective, epithelial and neutral tissues) or corticosteroids. Results of both sodium hyaluronate and corticosteroid proved to be very effective in decreasing pain and improving mandibular function[4,6].

Recent studies supported postoperative injections of autologous blood in the TMJ[8], in patients with chronic recurrent dislocation as a simple, safe, and cost-effective technique: this therapy accelerates healing process after TMJ surgery (as substantiated by clinical and radiographic positive outcomes). Specifically, PRP enhances fibroblastic events involved in tissue healing including chemotaxis, proliferation of cells, proteosynthesis, reparation, extra-cellular matrix deposition, and remodeling of tissues[9].

Sodium Hyaluronate -SH- was first described in the 1970s by Rydell and Balazs and Helfet in the treatment of knee osteoarthritis. In this regard, Kopp and associates first reported in 1985[17] and 1987[18] the outcome of SH given after TMJ arthrocentesis.

PRP has been used in medicine and surgery since the 1970s (Sanchez-Gonzalez et al., 2012) and it is

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obtained from autologous blood: it is prepared by centrifuging autologous blood with anticoagulant such as sodium citrate, and this will separate blood in 3 layers in the test tube: 1-Platelet Poor Plasma -PPP-, 2-PRP, and 3-red blood cells (Sanchez-Gonzalez et al., 2012, and Prakash and Thakur, 2011).

The purpose of this study was to compare the efficacy of intra-articular injection with either SH or PRP for patients with osteoarthritis of TMJ.

MATERIALS AND METHODS

Two groups composed each of 20 patients having temporomandibular joint (TMJ) osteoarthritis were studied to compare the efficacy of intra-articular infiltration with either HA or PRP.

The following diagnostic criteria for patient selection were used: patients affected by a monolateral lesion with a history of chronic (for at least 4 months) pain or swelling of the TMJ and imaging findings of degenerative changes of the joint (radiographic or MRI findings of degenerative changes). The forty patients studied had a Visual Analogue Score (VAS) of 8 to 9[17].

Exclusion criteria were: age > 80 years; VAS < 8; systemic disorders such as uncontrolled diabetes, rheumatoid arthritis, hematological diseases (coagulopathy), severe cardiovascular diseases, infections, immunodepression, patients with anticoagulants or antiaggregants, use of NSAIDs during the 5 days before injection, and patients with platelet values < 100,000/mm^3.

Subjects were randomly divided, and patients received either one intra-articular injection of SH or one intra-articular injection of PRP. To prepare PRP[14], a small amount of blood was taken from the patient. Blood was then placed in a centrifuge that spins and automatically produces the PRP (volume of 2 cc), which is then injected directly into the center of the injury. The entire process to prepare PRP takes less than 15 minutes. The double centrifuging of blood increased the histological platelets concentration and growth factors at the site of injection up to 500%.

The sodium hyaluronate used (STRUCTOVIAL® Viscoelastic and isotonic gel for intra-articular injection, Pierre Fabre Santé Laboratories, Boulogne, France) has a low molecular weight with a volume of 2cc[16].

Ultrasound guidance was used to monitor and visualize the position of the needle for both groups. A single injection technique was used.

The effect of the treatment was evaluated 10 days, 20 days, and 2 months after the initial injection and was based on the following measurements: pain intensity using the Visual Analogue Scale (VAS)[15] and mandibular function (vertical mouth opening compared to the initial measurement).

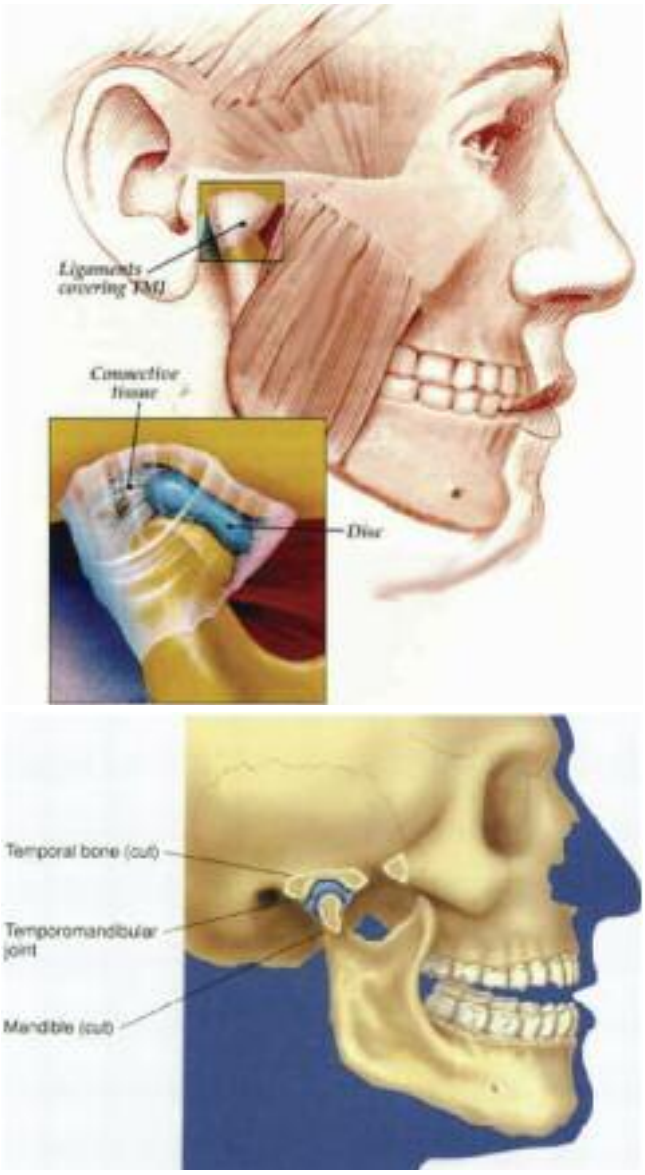

Fig. 1. Anatomy of tempomandibular joint (TMJ). (The disc holds TMJ, supported by the ligaments and connective tissues).

STATISTICAL ANALYSIS

All continuous data were expressed in terms of the mean and the standard deviation of the mean. One-way ANOVA[a] was performed to assess differences among groups when the Levene's test[b] for homogeneity of variances was not significant ($p<0.05$); the non-parametric Pearson's Chi square test[c] evaluated by

	Comparative demographics		
	PRP	SH	
N. of patients	20	20	
Age	50	52	N.S.
Sex	10M, 10 F	11 M, 9 F	N.S.
BMI	23	26	N.S.
Symptoms	2 months	2 months	N.S.
VAS	9	9	N.S.

Table 1. The two treatment groups are homogeneous for all evaluated parameters

Level of pain and swelling: comparison			
Pain		Swelling	
(n. of days x level 1–10)		(n. of days x level 1–10)	
PRP	SH	PRP	SH
16	8	11	7
PRP > SH		PRP = SH	

Table 2. PRP group showed a significantly higher post-injective pain reaction (p=0.031)

a One-way analysis of variance (ANOVA) is a test used to determine whether are any significant differences between the means of 2 or more independent (unrelated) groups.

b Levene's test is an inferential statistic used to assess the equality of variances for a variable calculated for 2 or more groups

c Pearson's Chi square test is a statistic applied to sets of categorical data to evaluate how likely it is that an observed difference between the sets arose by chance.

exact methods was performed to investigate the relationships between grouping variables. For all tests, $p<0.05$ was considered significant. Statistical Analysis was carried out by using the Statistical Package for the Social Sciences (SPSS) software version 15.0 (SPSS Inc., Chicago, USA).

RESULTS

The two groups used were found to be homogenous for the parameters evaluated (Table 1).

When comparing the two treatment modalities, significantly higher post-injective pain reaction was observed in the PRP group (Table 2). However, this reaction was self-limiting within a few days and did not compromise the overall outcome.

As for the pain intensity, there was a gradual decrease of pain in the first 20 days which not significant between the two groups (VAS decreased till 5). After two months, there was a significant decrease in pain for the PRP group as compared to the SH group ($P<0.05$) (Fig. 2). The VAS was below 3 for PRP group as compared to a linear VAS 5 for SH two months after injection.

Comparing both groups, vertical mouth opening was not significant during the two months period. Both groups had a maximum vertical opening of 2.5 cm significantly improving from the base line (Fig. 3).

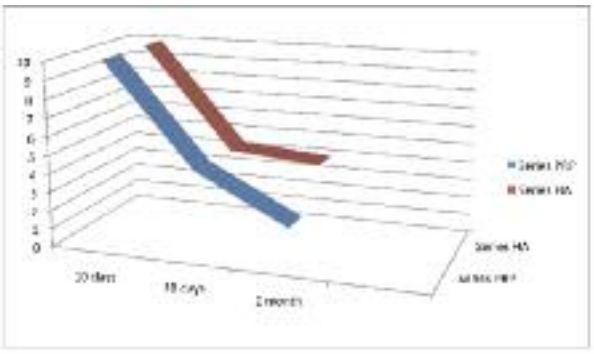

Fig. 2. Two series (PRP v/s SH) plotted for two months according to the VAS score (0 is minimum pain and 10 is maximum). PRP group has a significant VAS score with respect to SH group.

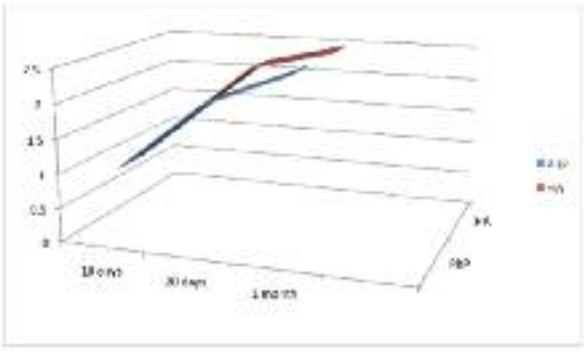

Fig. 3. Two series (PRP v/s SH) plotted for two month according to TMJ vertical opening in cm (0 cm is minimum and 2.5 cm is maximum). It is obvious that vertical opening is similar between the two groups reaching to 2.5 cm (not significant).

DISCUSSION

Many studies compared intra-articular injection of temporomandibular joint (TMJ) with either steroid[2,3,4,7,13,17,18] or sodium hyaluronate[2,3,4,13,17,18]. Both were proved to be effective in arthrosis of temporomandibular joint by decreasing pain intensity and improving joint function. Studies have also shown that cortisone injections may actually weaken tissue. Cortisone shots may provide a quick fix either by a temporary relief or a decrease of inflammation; Cortisone inhibits prostaglandin synthesis and decreases activity of collagenase and other enzymes that degrade articular cartilage[8]. Therefore, steroid injection can only be done for few times in any area because of this tissue weakening effect. Rationale for the use of corticosteroids[6,7,13,14,18,19] in temporomandibular joint therapy is doubtful because they do not generally provide long-term healing.

As for the SH injection, its long-term safety is still under study. Its effect is significant in osteoarthritis of the TMJ[3]. Hyaluronate acts as a lubricant[12], thus decreasing the friction between proximities of joints. This will decrease pain intensity and improve mobility.

Compared to the hyaloronate therapy, the mechanism of action of PRP differs completely. PRP acts directly on strengthening of TMJ by increasing thickness of tendons and ligaments holding this joint up to 40%[8].

Concentrated platelets (the body's repairment for damaged tissue) found in PRP contain huge reservoirs of bioactive proteins, including growth factors that are vital to initiate and accelerate tissue repair and regeneration[9]. These bioactive proteins initiate connective tissue healing, bone regeneration, and repair, promote development of new blood vessels, and stimulate wound healing process[10].

In this study, we compared the efficacy of the two injections (PRP v/s SH) in TMJ osteoarthritis, and the compared results (Fig. 2) were effective regarding pain scores and mandibular function, and according to our results, there was a great relation between the two groups with respect to pain intensity for the first 20 days; however, after a two month period, PRP group had an incremental increase in its regenerative effect and thus, an abrupt decrease in pain score with respect to SH group who has a steady linear effect and then an abrupt decrease. Gradual regenerative effects of PRP will generally provide long-term healing and thus a significant decrease in pain scores.

As for the mobility of the TMJ (Fig. 3), both injections had better results after 2 months. The similarity between the two groups may probably be time dependent. Knowing the slow regenerative effect of PRP may raise for us a four months period evaluation regarding the joint mobility the time needed for full histological activity.

Both groups did not show any complication during the 2 months period.

This study proved the efficacy and safety of clinical use of PRP in TMJ osteoarthritis.

CONCLUSION

It is time to shift for a safer way to treat osteoarthritis of TMJ? HA proved to be effective, but studies showed that autologous PRP[19] may have an outstanding therapeutic effect in treating TMJ osteoarthritis.

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Craniofacial Pain of Cardiac Origin (Angina / Acute Coronary Syndrome / Myocardial Infarction): a useful diagnostic tool for dentists.

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INTRODUCTION

Angina pectoris, or angina for short, is the term used when chest pain is thought to be attributable to myocardial ischemia. In patients with myocardial ischemia, chest pain is often, but not always, present. Myocardial ischemia can present itself with other symptoms such as shortness of breath or the pain can be located in other areas other than the chest.

PATHOPHYSIOLOGY OF MYOCARDIAL ISCHEMIA

Myocardial ischemia, and consequently angina, occur whenever myocardial oxygen demand exceeds oxygen supply.

MECHANISMS OF ANGINA

The mechanisms responsible for the sensation of angina are complex and not entirely understood. An important feature is that myocardial ischemia reduces the formation of adenosine triphosphate (ATP), resulting in a cascade of reactions leading to excretion of multiple chemical mediators. There is substantial evidence that primary mediator of angina is adenosine, via stimulation of the A1 adenosine receptor[2-5]. It is also possible that venodilation, as a response to ischemia, can activate these receptors. Nerve fibers travel along sympathetic afferent pathways from heart and enter sympathetic ganglia in lower cervical and upper thoracic spinal cord (C7-T4). Impulses are then transmitted via ascending spinothoracic pathways to medial and lateral thalamus and ultimately activate several areas of cerebral cortex[1].

Angina is a discomfort that is referred to the corresponding dermatomes that supply sympathetic afferent nerves to the same segments of the spinal cord as the heart (ie, C7-T4)[1]. Furthermore, stimulation of sensory receptors in different myocardial regions results in the transmission via the same neural pathway[5]. These characteristics account for two typical features of angina: It is often a diffuse discomfort felt in the chest, neck, mandible, and down the arm (typically the left); and most patients experience angina in the same distribution, regardless of which area of the myocardium is ischemic[5].

CLINICAL FEATURES

Initial presentation of myocardial ischemia with angina may be one of a stable pattern or an acute coronary syndrome/Myocardial infarction.

Most patients with myocardial ischemia will present with classic angina pectoris as the primary clinical manifestation. However, in some patients, myocardial ischemia may be silent or atypical.

• Quality

Angina is usually characterized more as a discomfort rather than pain. Terms frequently used by patients include squeezing, tightness, pressure, constriction, strangling, burning, heart burn, fullness in the chest, band-like sensation, knot in the center of the chest, lump in throat, ache, heavy weight on chest (elephant sitting on chest), like a bra too tight, and toothache (when there is radiation to mandible)[6]. In some cases, patient cannot qualify the nature of the discomfort, but places his or her hand fist in the center of the chest, known as the "Levine's sign[1]."

It is generally not described as sharp, dull-aching, knife-like, stabbing, or pins and needles-like pain.

• Location and radiation

As noted above, angina is a referred pain due to involvement of a neural reflex pathway via thoracic and cervical nerves. As a result, it is not felt in a specific spot, but is usually a diffuse discomfort that

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1. Levine's sign is a clenched fist held over chest to express ischemic chest pain.

may be difficult to localize.

Angina is referred to the corresponding dermatomes (C7-T4) that supply afferent nerves to the same segments of the spinal cord as the heart. Thus, angina often radiates to other parts of the body, including upper abdomen (epigastric), shoulders, arms (upper and forearm), wrist, fingers, neck, throat, mandible and mandibular teeth* (but not maxilla), and rarely to the back (specifically the interscapular region)[7,8]. Radiation to both arms is a stronger predictor of acute myocardial infarction (AMI)**. The location and radiation of angina are usually the same each time. Occasionally, location and radiation, but not quality, may be different after bypass surgery due to disruption of neural innervation of the heart.

In dental practice, it is important to be aware of an atypical presentation and location of angina, particularly when it presents as teeth or jaw pain. Early recognition is crucial for appropriate diagnosis and early treatment, and therefore better outcome/survival. I pulled out the following study[6] to support the above:

Craniofacial pain as the sole symptom of cardiac ischemia: a prospective multicenter study. *Kreiner M, Okeson JP, Michelis V, Lujambio M, Isberg A. J Am Dent Assoc. 2007;138(1):74-9.*

"BACKGROUND: Craniofacial pain can be the only symptom of cardiac ischemia. Failure to recognize its cardiac source can put the patient's life at risk. Authors conducted a study to reveal the prevalence of the distribution of and sex differences regarding craniofacial pain of cardiac origin.

METHODS: Authors prospectively selected consecutive patients (N = 186) who had had a verified cardiac ischemic episode. They studied location and distribution of craniofacial and intraoral pain in detail.

RESULTS: Craniofacial pain was the only complaint during the cardiac ischemic episode in 11 patients (6 percent), three of them had AMI. Another 60 patients (32 percent) reported craniofacial pain concomitant with pain in other regions. The most common craniofacial pain locations were throat, left mandible, right mandible, left temporomandibular joint/ear region and teeth. Craniofacial pain was preponderantly manifested in female subjects (P = .031) and was the dominating symptom in both sexes in the absence of chest pain.

CONCLUSIONS: Craniofacial pain commonly is induced by cardiac ischemia. This must be considered in differential diagnosis of toothache and orofacial pain.

CLINICAL IMPLICATIONS: Because patients who have AMI without chest pain run a higher risk of experiencing a missed diagnosis and death, the dentist's awareness of this symptomatology can be crucial for early diagnosis and timely treatment.

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** toothache referred from heart disease.*

*** AMI or heart attack (sudden chest pain behind sternum, shortness of breath, sweating, nausea, vomiting, anxiety...).*

Glossopharyngeal Neuralgia -GPN- secondary to ipsilateral compressive cerebellar mega-tonsil: a case report.

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Abstract

Glossopharyngeal Neuralgia -GPN- is a pain syndrome caused by irritation of the ninth cranial nerve. It is clinically and pathophysiologically comparable to trigeminal neuralgia -TN- with similar treatment options for both entities.

The clinical case we are addressing is a GPN secondary to an ipsilateral compressive cerebellar mega-tonsil, with no previous reports of the same etiology in the medical literature. Decompression without tonsillectomy was sufficient for pain relief.

INTRODUCTION

Glossopharyngeal neuralgia (GPN) is a condition in which there are repeated episodes of severe pain (lasting from few seconds to few minutes) in areas innervated by the 9th cranial nerve (glosso-pharyngeal nerve): nasopharynx, posterior one-third and base of the tongue, and tonsillar fossa. It is a pain syndrome clinically and pathophysiologically similar to trigeminal neuralgia (TN), but it is, by far, less common. The treatment strategy is similar for both entities: treatment initially consists of medical management with surgical options available for refractory cases. Among accepted surgeries, microvascular decompression is generally an effective treatment for TN and GPN because it is a nonablative procedure that addresses the underlying etiology of a neuro-vascular conflict[1, 2]. In contrast to TN, GPN is most commonly caused by a secondary etiology, such as infection or tumor[3].

CASE REPORT

A 59-year-old woman reported a 3-year history of left GPN characterized by paroxysmal pain attacks in left pharyngeal region, originating from mandible, base of the tongue, and pharynx, and irradiating to left ear. These pain attacks, triggered by speech chewing, first responded to Carbamazepine*, but were later resistant to this drug. The patient reported no episodes of syncope and neurological examination was normal. Brain magnetic resonance imaging (MRI) displayed a left cerebellar mega-tonsil (with a 3 mm herniation through foramen magnum) compressing brainstem and spinal cord (Figures 1 and 2). MRI failed to show a neurovascular conflict. Decompression of foramen magnum, mainly on the left side, with enlargement duroplasty was performed. Arachnoids were kept intact and tonsillectomy was avoided as well (Fig. 3).

RESULTS

Paroxysmal pain attacks disappeared immediately after surgery. One year after surgical operation, patient was totally free of symptoms. Control brain MRI displayed good decompression of occipito-cervical junction and absence of mass effect on brainstem (Figures 4 and 5).

DISCUSSION

GPN is an uncommon form of pain and represents 0.2 to 1.3% of the cases of facial pain[4]. Incidence of GPN is estimated to be 0.8/100.000 with a peak in patients aged 70 to 79 years. Left side is mostly affected, with a bilateral occurence in 2% of cases.

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** Carbamazepine (Tegretol®)= an anticonvulsant and mood-stabilizing drug used primarily in TN, epilepsy, bipolar disorder, phantom limb syndrome, and complex regional pain syndrome -CRPS-.*

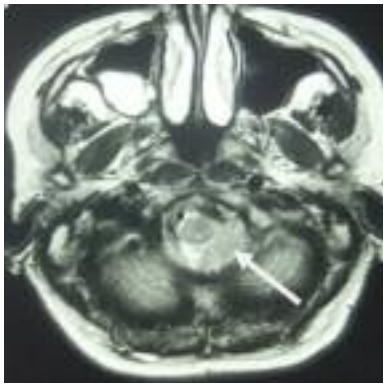

Fig. 1. Preoperative axial T2 weighted MRI showing left cerebellar mega-tonsil (white arrow).

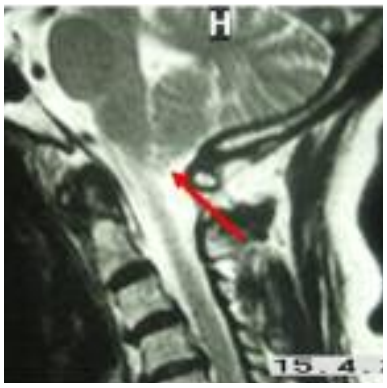

Fig. 2. Preoperative sagittal T2 weighted MRI showing left cerebellar tonsil herniation (red arrow).

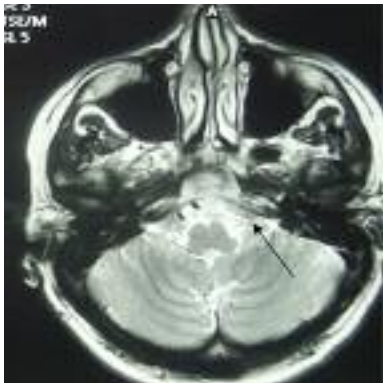

Fig. 3. Preoperative sagittal T2 weighted MRI showing compression of cranial nerve IX (black arrow).

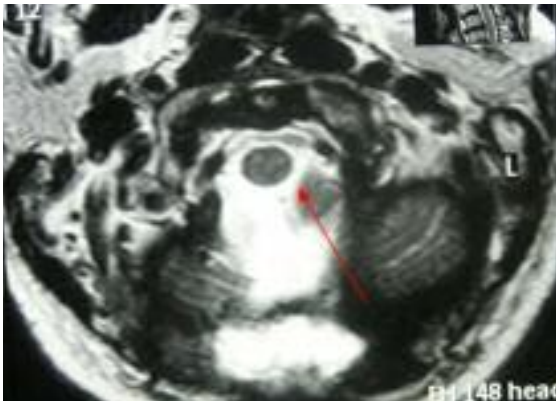

Fig. 1. Postoperative axial T2-weighted MRI. Note the absence of the mass effect (red arrow).

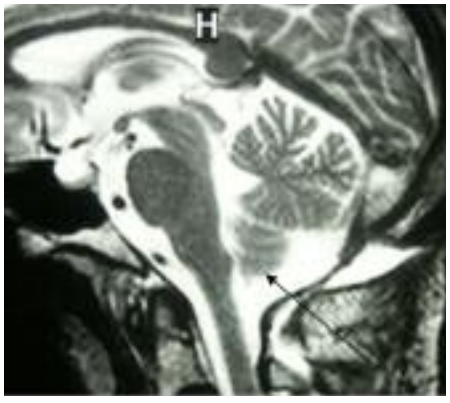

Fig. 2. Postoperative sagittal T2-weighted MRI showing the left cerebellar mega-tonsil (black arrow) with no more mass effect.

GPN is expressed as brief, but severe, attacks of pain that usually begins in the throat and radiates to neck, mandible, and external auditory canal, and this can be precipitated by swallowing or tongue protrusion (Wilson-Pauwels, Akesson, and Stewart, 1988), and sometimes, by chewing, coughing, laughing, speaking, sneezing, cold drinks, and clearing the throat. Pain occurs in episodes (few seconds to few minutes) and may be severe, and episodes occur several times per day and may awaken patients from sleep. Several pathogenic mechanisms may produce GPN. These may be idiopathic or secondary to cerebellopontine angle tumors, intracranial vascular compression, laryngeal and nasopharyngeal tumors with local invasion, parapharyngeal abscesses, trauma, multiple sclerosis**, Paget's disease*** or cranial base tumors, calcification of stylohyoid ligament, direct carotid punction, or dental extractions[5].

Literature review displayed two similar reported cases:

• A case[6] of unilateral GPN secondary to grade I Chiari malformation (bilateral) and a neurovascular conflict with the postero-inferior cerebellar artery, treated by ipsilateral tonsillectomy, vascular

*** Multiple Sclerosis -MS- = an inflammatory disease in which the insulating covers of nerve cells in brain and spinal cord are damaged.*

**** Paget's disease of bone= a chronic disorder that can result in enlarged and misshapen bones. It is caused by excessive breakdown and formation of bone, followed by disorganized bone remodelling.*

decompression of ninth cranial nerve, and enlargement duroplasty.

• A case[7] of unilateral glossopharyngeal neuralgia secondary to grade I Chiari**** malformation (one-sided), treated by ipsilateral tonsillectomy.

Both cases reported GNP associated with Chiari malformation, and both patients were submitted to tonsillectomy with enlargement duroplasty. In the case we are reporting here, patient presented with isolated unilateral cerebellar mega-tonsil without obvious neurovascular conflict, displayed on imaging. Decompression without tonsillectomy was sufficient for symptom relief and the arachnoids were kept intact. Thus, patient with GNP can have pain relief without the need to perform tonsil resection which we believe is a relatively more aggressive surgery than duroplasty alone. In addition, intact arachnoid are of utmost importance since this avoids post-operative fibrosis and cerebro-spinal fluid circulation drawbacks.

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**** *Arnold-Chiari malformation= brain malformation consisting of a downward displacement of cerebellar tonsils through foramen magnum.*

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Dental pulp pain: diagnostic implications.

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Abstract

Unlike other organs and tissues in human body, teeth display a distinctive and particular nociceptive mechanism. This has lead researchers during the last three decades to further investigate neurophysiology and pathophysiology of dental pulp pain.

Clinically, the type of dental pain should reflect the condition of tooth pulp. Adequate and successful dental treatment requires that the source of pain be detected and understood, however variability of pain experienced by patients may be confusing for patients and misleading for dentists. This review addresses dental pain experienced by patients, it helps dental clinicians to better understand dental pain conditions and establish an accurate diagnosis.

Tooth pulp consists of a densely innervated and vascularized tissue surrounded by a hard mineralized tissue. In normal healthy tooth, a hot or cold noxious stimulus does not usually elicit pain because of thermal insulating capacity (thermal diffusivity and conductivity) of the enamel. However under even mild inflammatory conditions, the low compliance of pulp chamber produces exaggerated pain.

Furthermore and unlike other tissues in human body, dentin responds by a painful sensation to a normal hot, cold, air-puff, or any type of stimulus[1]. This phenomenon suggests that teeth have a distinctive nociceptive mechanism by which they detect noxious stimuli in inflammatory conditions or when dentin is exposed[2].

Clinically, the type of dental pain should reflect the condition of the tooth pulp which orientates the dentist toward the treatment he should perform. Successful dental treatment requires that the source of pain be detected and understood. If the origin of pain is not found, inappropriate dental care may result. Variability of pain experienced by patients presents a challenge in terms of diagnostic methods. This review will help clinicians to understand the basic neurophysiology and pathophysiology of pulpal pain in order to explain pain condition and to establish a correct diagnosis.

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CLASSIFICATION

Pulpal pain arises from vital or non-vital pulps. Different attempts to classify pulpal pain according to the histologic characteristics of the pulp have failed. The most popular classification is based on clinical features to determine the vitality of pulp and its reparative capability[3].

- Dentin sensitivity
- Vital pulpal pain: reversible pulpitis
- Vital pulpal pain: irreversible pulpitis
- Non-vital pulpal pain

ETIOLOGY AND PATHOPHYSIOLOGY

Dental pain is the most common type of orofacial pain[(4)] and the most common oral pain is due to tooth pulp inflammation[5]. However, diagnosis of pain's origin is not always obvious. It could arise from non-dental sites and refer to adjacent teeth or in the contrary originate from teeth and irradiate to surrounding structures. The most appropriate treatment is the removal of the cause rather than addressing symptoms. Pains of pulpal origin are either related to dentin hypersensitivity or to reversible or irreversible pulpitis.

Etiology of dentinal sensitivity is the activation of nociceptors in dentin layer and exposure of dentinal tubules following enamel loss by mechanical erosion or attrition or by chemical agent such as acid erosion. Radicular dentin may be exposed as well by gingival

recession or traumatic teeth brushing. Three theories have been proposed to explain nerve activation: (1) neural theory, whereby nerve endings that penetrate dentinal tubules directly respond to external stimuli; (2) hydrodynamic theory, wherein fluid movements within the dentinal tubules are detected by nerve endings near the dentin; and (3) odontoblast transducer theory, where odontoblasts themselves may serve as pain transducers[2].

Etiology of pulp inflammation can be a direct exposure of pulp by caries, fractures, or accidental (iatrogenic) exposure. An indirect exposure through dentinal tubules can also occur. Other frequent causes are micro-trauma such as bruxism, heat, and vibration during teeth preparation with high- speed handpiece, dehydration of dentin, and chemical aggression during restorative procedures. The process of pulpal inflammation is related to the low compliance of pulp chamber which does not permit any expansion. When edema occurs, pressure increases, leading to damaging effects[6]. Inflammation of pulp may be aseptic as in traumatic exposure or by toxic effect on the pulp and indirect immune reactions that may be of the antigen-antibody cellular types[7].

CLINICAL CHARACTERISTICS

Pulpal pain is described as a deep somatic pain of visceral type. The hallmark of visceral pain is diffuseness and variability[6]. According to its origin, odontogenic pain may arise from sensitive dentin or from inflammatory pulp.

- Dentin sensitivity: is expressed as brief and sharp pain when exposed to a stimulus.
- Reversible pulpitis: is described by patients as a sharp pain provoked by osmotic or thermal stimuli that stop when stimulus is taken away. It is thus similar to dentin hypersensitivity. Pain may refer to other structures or teeth making sometimes the diagnosis uncertain.
- Irreversible pulpitis: is characteristically a deep, dull, aching sensation. Pain may be also throbbing or sharp, burning, or lancinating. Pain is normally lingering in response to thermal stimuli. Pain is often spontaneous, not necessary provoked by thermal stimuli but worsened by it.
- Non-vital pulpal pain: non-vital teeth are not normally painful and do not respond to cold or electric pulp testing, however they may be very sensitive to percussion if the inflammation has reached or crossed peri-apex.

DISCUSSION

Knowledge of factors associated with pulpal pain may provide important information for diagnosis and treatment. However, mechanisms of oral pain in general and dental pain specifically remained largely obscure until the last three decades, when advances in neurophysiology made such pain easier to understand and treat.

Animal model simulating acute human pulpitis in awake animals was described and validated by us[8,9,10,11]. The described model can serve as a useful tool for the study of tooth pulp reaction to various agents in in-vivo conditions. It permits the study of different reagents and variation of the levels of the various pro-inflammatory mediators and their modulation by treatment with anti-inflammatory drugs[11].

Despite the wide knowledge in the field, toothache is still confusing for dental practitioners. The challenge is to determine the source of pain, which tooth is the cause whenever pain is of dental origin, and the accurate diagnosis. This confusing issue is related to several points:

First of all, dental pain may spread to other structures; this is the case of pulpitis. Moreover, pain from other sites can be referred to the teeth.

The second problem we usually encounter is that successful treatment depends on accurate diagnosis in order to provide early and proper treatment. Early treatment is important for relief of primary symptoms, it prevents alteration of the immune system, prevents stress and alteration of the autonomic system and most important prevents alterations in the peripheral and central nervous system. Inadequate treatment may lead to persistent or to unnecessary or aggressive treatment. Pulpitis may be treated by extraction or by endodontic treatment, or better, by saving tooth vitality when possible. Pulp inflammation may be neurogenic or associated with bacterial endotoxins. It was demonstrated that pain control and healing depend on the origin of inflammation. In a study measuring the

effect of treatment with anti-inflammatory drugs after application of irritants on rat incisors and release of inflammatory mediators, dexamethasone antagonized the effects of endotoxin and capsaicin, while NSAIDs affected mainly the endotoxin-induced inflammation[11].

The third problem is related to classification. Most classifications mix clinical and histological terms resulting in misleading terminology and diagnosis. For example, in non-vital teeth, necrosis may be partial. Symptoms arising can be confusing, thus making diagnosis difficult, if not impossible.

Another example is irreversible pulpitis which is characteristically a deep, dull, aching sensation, but this kind of pain may be in some cases confusing. It could be also throbbing or sharp, burning or lancinating. This could be explained by neuroanatomic distribution of nerve fibers in the tooth. Even though A-delta fibers are more affected by a reduction of pulpal blood flow, compared to C-fibers, because A-delta fibers cannot function in case of anoxia[12-13], the arousal of the two components of pain, the first rapid and sharp and the second dull may explain this particular situation. In fact, characteristics of pain and the type of stimulus may indicate afferent fibre type involved in pain. Intradental A- and C-fiber groups are functionally different and can be activated separately by certain external stimuli.

A-fibers belong to myelinated axons and have a fast conduction speed (they evoke a rapid, sharp, lancinating pain reaction[14]) and low stimulation threshold. They are superficial (located in pulp and dentin junction) and are responsible for the sensitivity of dentine and thus for the mediation of the sharp pain induced by dentinal stimulation.

C-fibers are unmyelinated and have a low conduction velocity (they cause a slow, dull ,crawling pain[14]), a smaller diameter, and a higher excitation threshold. They are activated only if external stimuli reach the pulp and their activation may contribute to dull pain induced by intense thermal stimulation of tooth and to pain associated with pulpal inflammation. Thus, nociceptive response to different pulp testing methods is closely related to the type of nerve fiber involved in the test. A-delta fibers are stimulated in electric pulp testing[14]. On the contrary and because of their high threshold, C fibers need a stronger electric current to be stimulated[15]. For cold test and according to the hydrodynamic theory, outward movement of dentinal fluid (contraction of fluid) produces a stronger response in A-delta fibers compared to the inward movement of fluid caused by application of heat[16].

However, repeated application of cold will reduce displacement rate of fluids inside dentinal tubules, causing a less painful response from the pulp for a short time. This may explain why the cold test is sometimes refractory[14].

On the other hand, inflammation may remain in some conditions completely silent. In fact, many inflammatory periapical lesions are detected by chance with no history of previous pain. “Silent pulpitis” suggests that there may be a local antinociceptive mechanism that blocks transmission of stimuli in some circumstances[17].

A recent systematic review[18] about diagnostic accuracy of signs/symptoms and tests used to determine pulp’s condition in teeth affected by deep caries, trauma, or other types of injury failed to find evidence to assess the value of toothache or abnormal reaction to heat/cold stimulation for determining pulp’s condition.

The same applies to devices and methods for establishing pulp status. Electrical or thermal pulp testing may induce false positive or false negative response. It was assumed that vascular supply is more important to pulpal health than sensory supply[19]. Methods for measuring pulpal blood circulation were developed and tested but the overall result of these devices and methods does not guarantee reliable diagnosis for all pulpal conditions[18].

History of pain may be an interesting tool for dental pulp diagnosis. The type, intensity, duration, and aggravating factors of pain are not necessarily correlated with pulp’s condition. Preexisting condition of the pulp may modify inflammatory process, and therefore pain[20].

It was assumed that when pain is severe, or when mild to moderate pain is present with a previous history of dental pain, concerned tooth is in the irreversible pulpitis category. When clinical evidence indicates a mild to moderate pain with no previous occurrence, pulp is in the reversible pulpitis category[14].

Last, evidence has also showed that incidence of pain increases as pulp histopathosis worsens[14].

CONCLUSION

Dental pulp pain is a serious concern to both patient and dentist. Variability of clinical characteristics associated with pulpal pain remains a challenge in terms of diagnostic methods. Dental pain is a helpful tool to diagnose pulp condition or in contrary confusing and thus may mislead the dentist in his/her diagnostic search. Despite the huge amount of publications related to neurophysiology of tooth and pathophysiology of pain during the last three decades, several issues remain unsolved. According to Bender[14], 80% of patients with previous history of pain, display histopathologic evidence of chronic partial pulpitis with partial necrosis (endodontic or extraction indicated) and the other 20% manifest pulp histopathosis with slight inflammation to chronic partial pulpitis without necrosis (a treatable category).

This review aims to provide dentists with the basic clinical knowledge of pulpal pain and discuss some confusing clinical situations encountered during their daily practice. Further studies are warranted to further understand pulpal pain in order to implement new strategies and methods of dental pulp diagnosis.

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Practical pharmacological approach of orofacial pains: realities and clinical recommendations.

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Abstract

An analgesic (or pain killer) is a drug used to achieve analgesia (relief from pain): this drug can work either on peripheral or central nervous system. Analgesics are different from anesthetics which reversibly eliminate pain sensation.

When managing orofacial pains, analgesic choice is determined by the type of pain and its severity. The WHO "Pain Ladder" (or analgesic ladder) is a 3-step "ladder" for cancer pain in adults. It described the guidelines for the use of drugs in pain management: the general principle is to start with first step drugs(non-opioid), and then, to climb the ladder if pain is still present, and medications usually range from household (over-the-counter) drugs (acetaminophen and NSAIDs), to powerful opioids (morphine, buprenorphine, oxycodone).

For neuropathic orofacial pains, tricyclic antidepressants, class I antiarrythmics, and anticonvulsants remain the drugs of choice.

1. INTRODUCTION

General dentist and dental specialist treat patients with pain on a daily basis. Orofacial pain (perceived in the face and/or oral cavity) is caused by diseases or disorders of regional structures, dysfunction of the nervous system, or through referral from distant sources.

In addition to the diagnosis and treatment of acute dental pain and pathology, such as that which may arise from trauma, infection, orofacial pain dentist has the responsibility to diagnose and treat nonodontogenic orofacial pain. Inadequate knowledge of etiopathology of pain and neurobiological mechanisms underlying persistent pain can lead to inaccurate diagnoses and subsequent ineffective or harmful treatment. It's also the responsibility of orofacial pain dentist to assess the need for multidisciplinary pain management.

Complexity of the spectrum of orofacial pain disorders is compounded by close proximity of numerous anatomical structures, including eyes, nose, teeth, tongue, sinuses, ears, and temporo-mandibular joints. Diagnostic approach categorizes orofacial pain into four groups based on underlying pain mechanisms: musculoskeletal, neuropathic, neurovascular, and psychogenic pain.

2- CLASSIFICATION OF OROFACIAL PAINS

There were many attempts to classify orofacial pain, and the most updated classification was established by the American Academy of Orofacial Pain and it was based on the IHS* classification (Table 1).

Even though it can occur in different anatomical locations, management of chronic orofacial pain is usually applied in multidisciplinary pain clinics regardless of the origin of pain. Interdisciplinary therapies includes: education, counseling, medications,

Intracranial pain disorders	Neoplasm, aneurysm, abscess, hemorrhage, hematoma, edema.
Neurovascular disorders	Migraine, migraine variants, cluster headache, paroxysmal hemicrania, cranial arteritis, carotidynia, ocular-type headache.
Neurogenic disorders	Paroxysmal neuralgias (trigeminal, glossopharyngeal, nervus intermedius, superior laryngeal). Continuous pain disorders (de-afferentation, neuritis, postherpetic neuralgia, post-traumatic and postsurgical neuralgia). Sympathetically maintained pain.
Intraoral pain disorders	Dental pulp, periodontium, mucogingival tissues, tongue.
Temporo-mandibular disorders	Masticatory muscle, temporomandibular joint, associated structures.
Associated structures	Ears, eyes, nose, paranasal sinuses, throat, lymph nodes, salivary glands, neck.

Table 1. Differential Diagnosis of Orofacial Pain

** IHS= International Headache Society.*

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pain management techniques (acupuncture, nerve block..), psychological therapy, and physical therapy. Treatment goals usually focus on decreasing pain intensity and managing associated fear, anxiety, and depression.

3. DISCUSSION

Analgesics or pain killers are a group of drugs capable of reducing pain perception without causing loss of consciousness. Choices of the most efficient analgesics vary according to the type of pain, it's intensity, and its evolution with time, with frequent assessment of the efficacy of chosen therapy. An ideal analgesic doesn't exist yet, but the closest to the ideal is a drug that suppresses pain of all types and all severities without inhibiting other sensations or motor activity, it should be available in fast acting for immediate relief and in slow release forms. It shouldn't have toxic effect on other tissues, have no active metabolites, or can be easily antagonized. Opioids and the cyclooxygenase (COX) inhibitors are, so far, the closest to this ideal. Analgesics are prescribed in a step-up fashion, according to the intensity of the pain perception.

World Health Organization (WHO) has developed a three-step "ladder" for chronic pain relief in adults (Table 2).

3. 1- Level 1: non opioid analgesics (Table 3):

It consists of 3 major and widely prescribed analgesic drugs:

a) Paracetamol
b) Salicylates
c) NSAIDs

Non opioid analgesics are prescribed as a first line treatment for the management of pain, mainly for the treatment of mild to moderate pain. A wide variety of craniofacial disorders respond well to these drugs: Intracranial pain diorders, neurovascular disorders, migraine, tension and cluster headaches, neurogenic disorders, paroxysmal neuralgias, and as a first attempt, TMDs (Temporomandibular disorders).

a) Paracetamol (Panadol®, Panadol Joint®):

Paracetamol (or acetaminophen) is the analgesic of reference and the most prescribed. It's name came from chemical molecules used in it's compound. Harmon Northrop Morse (an American chemist) was the first to synthesize paracetamol in 1878, and it was first used in medicine in 1893. The extensive medical use of acetaminophen began in 1947.

Table 2

Level 1: non opioid analgesics - Paracetamol (acetaminophen) - Aspirin - NSAIDs	For mild to moderate pain
Level 2.A: mild opioids (pure agonists) - Codeine - Dextropropoxyphene - Tramadol	For intense pain or for a pain not controlled by a level 1 analgesic
Level 2.B: mixed opioids (agonists-antagonists) - Buprenorphine - Nalbuphine - Pentazocine	For very intense pain oe a pain not controlled by a level 2.A analgesic
Level 3: strong opioids (pure agonists) - morphine sulfate - Dextromoramide* - Fentanyl** - Pethidine***	For unbearable pain not controlled by a level 2.B analgesic

Table 3

** Dextromoramide (Palfium®, Dimorlin®): powerful opioid analgesic (approximately 3 times more potent than morphine, but shorter acting).*

*** Fentanyl (Sublimaze®, Duragesic®, Fentora®): synthetic opioid analgesic with rapid onset and short duration of action. It is also used as an anesthetic, in combination with a benzodiazepine. It is 50-100 times more potent than morphine.*

**** Pethidine or Meperidine (Demerol®, Dolosal®): synthetic opioid analgesic, delivered in tablets, syrup, or by IM, SC, IV injection.*

a.1- Pharmacokinetics:

Paracetamol exists in oral and in injectable forms. After oral administration, peak plasma concentrations are achieved in 30-60 minutes. It's mainly absorbed passively in jejunum and ileum, and it doesn't bound significantly to plasma proteins.

Paracetamol is mainly metabolised by hepatic microsomal enzymes to inactive metabolites: glucoronide (49%), sulphate (26%), and cysteine (3%). Less than 5% of paracetamol are excreted unchanged in urine and faeces (excrement).

Paracetamol plasma half-life is 2-3h after the usual doses.

a.2- Pharmacodynamics:

Paracetamol has a central analgesic and antipyretic effects, but it doesn't possess any anti-inflammatory actions. It's the first line drug in the management of mild to moderate pain. Exact mechanism by which it exerts its effects remains undefined (Fig. 1).

In adults, its effective posology is 1-1.5 g/24h divided regularly on a 4h period, the maximal acceptable dose is 3-4g/24 h.

Paracetamol metabolism is enhanced by anticonvulsants and oral contraceptive agents; also there is both a synergistic and an additive analgesic effect when given with opioids (Talacen®, Algo Cod®).

a.3- Paracetamol poisoning (Fig. 1):

The threshold dose in an adult has been estimated to be 10-15 g: at this dose there is a high risk of fulminant hepatitis causing life-threatening hepato-cellular insufficiency. This is due to accumulation of active metabolites associated with depletion of glutathione and covalent binding. Also, in very high doses, acute proximal tubular necrosis can occur.

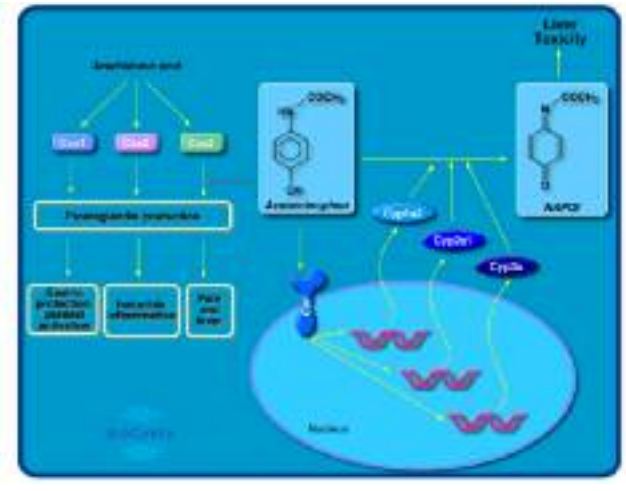


Fig. 1. Mechanism of action / toxicity of paracetamol.

Symptoms of paracetamol overdose include: diarrhea, increased sweating, nausea or vomiting, stomach cramps or pain, and swelling, pain, or tenderness in upper abdomen or stomach area.

Treatment must be instituted immediately in a medical center. N-Acetylcysteine -NAC- is the treatment of choice, it's a gluthation precursor given to prevent liver damage. It should be ideally given within 8-10 hours post ingestion of the toxic dose (guidelines of American College of Emergency Physicians).

Contra-indications to the use of paracetamol are exceptional and limited to the presence of a hepato-cellular insufficiency or a known allergy to paracetamol.

Adverse effects of paracetamol are also rare, limited mainly to an occasional skin rash, thrombopenia, unusual bleeding/bruising, tiredness/weakness, and tarry stools.

b) Non-Steroidal anti-inflammatory drugs (NSAIDs) (Table 4):

NSAIDs are the most prescribed medicines worldwide: they constitute a large heterogeneous class of drugs responsible for the most common and sometimes the most dangerous side-effects. NSAIDs contain numerous molecules that have some properties in common:

- They are weak acids, liposoluble, and bind highly with plasmatic proteins,
- They possess an anti-inflammatory effect,
- They are excellent analgesics and antipyretics as well.

Nonsteroidal Anti-inflammatory Analgesics

NSAID Agent	Maximum Daily Dose for Adults (mg)	Usual Dose (mg)	Dosing Interval (h)
Ibuprofen	2,400	400-800	6
Ketoprofen	300	25-50	6-8
Naproxen	1,500	250	6-8
Ketorolac	IV/IM: 120; oral: 40	IV/IM: 30; oral: 10	IV/IM: 6; oral: 4-6
Celecoxib	400	200	12

IM: intramuscular. NSAID: nonsteroidal anti-inflammatory drug.
Adapted from Reference 6.

Table 4

- They reduce nociception which is related to inflammation and inflammatory mediators whether from trauma, infection, or immune reactions.
- Their main side-effect is on the gastrointestinal tract.

b.1- Mode of action (Fig. 2):

All NSAIDs act by inhibiting prostaglandin synthesis by the injured tissue and this is due to the inhibition of cyclooxygenase enzymes (COX). There are 2 isomers for cyclooxygenase enzyme:

- COX-1* is called a constitutive enzyme because it's present in almost all tissues, mainly in gastric mucosa, platelets, and kidneys. It has a physiological role (as a regulatory enzyme). Thus, inhibition of COX-1 leads to inhibition of platelets aggregation, it also increases the risk of the development of a gastric ulcer and, to a lesser extent, a renal insufficiency.

- COX-2* enxyme (discovered by Professor Daniel L. Simmons) can be found physiologically in the brain, spinal cord, macula densa of the glomerulus, and intermittently, in the reproductive system, but its synthesis is mainly induced by inflammatory mediators such as interleukin 1 and tumor necrosing factor secondary to the occurrence of an inflammatory process. Thus, inhibition of COX-2 is the base for anti-inflammatory effect of NSAIDs.

Most of NSAIDs available on the market inhibit both COX-1 and COX-2, but some are more selective to COX-1, others more to COX-2 (they are called coxibs) (Table 5).

NSAIDs are mainly classified as: indolics, aryl-carboxylics, oxicams, pyrazols, and coxibs.

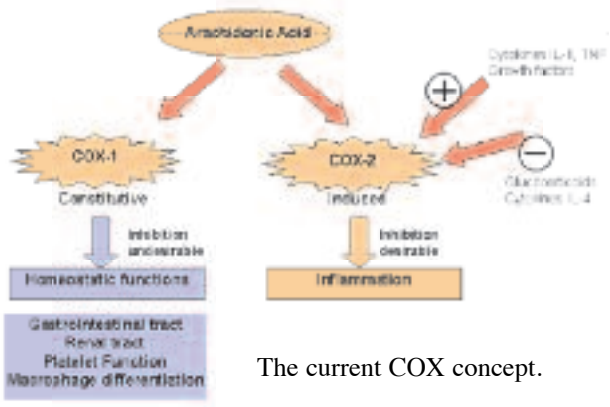
Coxibs (Celecoxib, Rofecoxib) are a relatively new drug class of NSAIDs, they inhibit specifically COX-2, and they have the same profile of action as other NSAIDs, but with less adverse effects (mainly on the gastrointestinal and on the coagulation systems). Rofecoxib (Vioxx®) was taken off the market in 2004 (because of significant increase of heart attacks and strokes) and Celecoxib (Celebrex®) received boxed warnings (because of 37% increase in incidence of nonfatal myocardial infraction and nonfatal stroke).

b.2- Contra-indications:

- Known allergy to any substance incorporated in the synthesis of NSAIDs
- Gastric or duodenal ulcer
- Severe renal, hepatic, or cardiac insufficiency
- During pregnancy mainly 3rd trimester, and during breast feeding
- Any bleeding disorder.
- Asthmatic patients.

b.3- Adverse effects (Fig. 3)*:*

All NSAIDs possess many adverse effects, most of



The current COX concept.

Fig. 2

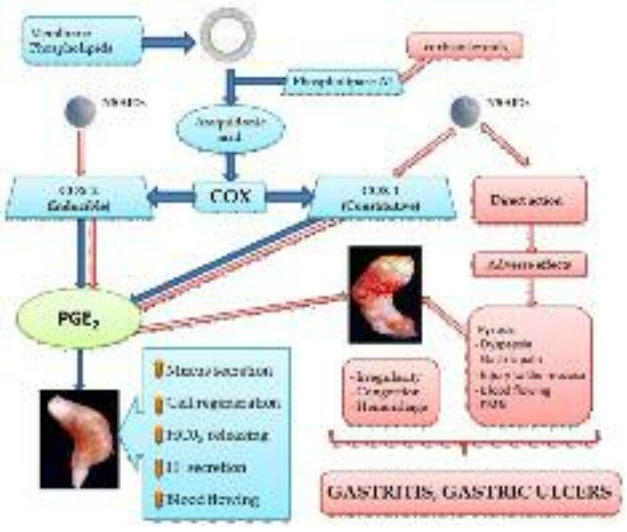


Fig. 3

More effective on COX-1	Similarly effective on both	More effective on COX-2
- Aspirin	- Diclofenac	- Celecoxib
- Indomethacin	- Naproxen	- Rofecoxib
- Ibuprofen	- Ketorolac	- Meloxicam
- Piroxicam	- Etodolac	

Table 5

COX-3 enzyme was discovered in 2002 (Botting, 2003 - Chadrasekharan et al., 2002) by Professor Daniel L. Simmons: it is the third most recently discovered COX isozyme. It has been found to be selectively inhibited by paracetamol, phenacetin, antipyrine, dipyrone, and some NSAIDs in rodent studies

them are thought to be due as a result of COX-1 inhibition, and they are dose-dependent.

a) Gastrointestinal tract:

Gastrointestinal disorders are the commonest of the adverse effects of NSAIDs, they include:

- Dyspepsia (10-30% of the patients).

- Gastrointestinal ulcers are observed in 15-25% of patients taking classical NSAIDs and 5% in patients taking coxibs. These ulcers occur mainly when NSAIDs are taken for 12 weeks at least, they are characteristically found on gastric big curve, and they can manifest directly by a gastric perforation or an upper GI bleed: these complications are mainly observed in: elderly patients (above 60 years), in patients who previously developed gastro-duodenal ulcer or upper GI hemorrhage, and if NSAIDs are used at very high doses or if salicylates were associated with anticoagulants. Piroxicam (Feldene®, Brexidol®, Dolonex®) is the most common NSAID implicated in causing GI bleeding, and Ibuprofen (Advil®, Brufen®, Motrin®, Nurofen®) is claimed to be the safest of conventional NSAIDs.

Patophysiology responsible for the occurrence of a GI ulcer is thought to be due to the uninhibited acid secretion, to the reduced mucus and bicarbonate secretion by gastric mucosa, and to the reduced mucosal blood flow (Fig. 3).

b) Renal:

NSAIDs exerts anti-diuretic, anti-natriuretic effect on kidneys, and inhibit renin* secretion, by inhibiting renal prostaglandin's synthesis. The most common renal side-effects are:

- Renal insufficiency with salt and water retention, (mainly in elderly patients, and in patients with severe hypovolemia, or in association with cardiac failure and liver cirrhosis).

- NSAIDs can rarely cause acute interstitial nephritis; evolution is favorable once the treatment is stopped.

- Hyperkalemia (blood elevated potassium - K^+), due to the indirect suppression of renin and aldosterone** secretion by NSAIDs. It's mainly observed with Indometacin.

c) Central nervous system:

Regular high doses of aspirin may cause damage to the 8th cranial nerve (vestibulocochlear), which will manifest by tinnitus (ringing of ears), vertigo, hypoacousia with acidosis, and respiratory depression. Aspirin overdose causes medullary stimulation and hyperventilation. In children less than 12 years, association of aspirin with viral infection can cause Reye's syndrome (a potentially fatal syndrome that displays a rash, vomiting, liver damage (= fatty liver), hypoglycemia, and serve encephalopathy).

d) Reproductive system:

Some NSAIDs are potentially teratogen mainly Celecoxib (Celebrex®). The prescription of NSAIDs is contra-indicated during the third trimester of pregnancy because it inhibits uterine contractions and prolongs labor, it also leads to premature closure of ductus arteriosus.

b.4- How to choose the compatible NSAID:

NSAIDs are a widely diffused class of drugs, they are usually used without a specific prescription which increases the risk of automedication and the occurrence of adverse effects. They possess the potential to reduce pain, especially late post-inflammatory pain, and are usually more effective for dental and orthopedic generated pain than are weak opioids (codeine, tramadol, dextropropoxyphene).

The choice of the best NSAID doesn't rely on the chemical nature of the molecule, or on the medical condition we are treating, or on the efficacy (cause till now, many studies showed that all NSAIDs possess almost the same efficacy), or on the dose or on the half- life of the molecules. Thus, the choice is mostly related to age with specific considerations to elderly patients (gastric tolerance). So when prescribing NSAIDs, dentists should avoid their association with ACE inhibitors***, diuretics (which increases the risk of renal insufficiency), anticoagulants (which increases hemorrhagic risk), also they should never associate two NSAID molecules, and it's mandatory to prescribe a gastric mucosal protector along with the NSAID (PPI- Proton Pump Inhibitor, i.e: Omeprazole, Pantoprazole, and Lansoprazole).

** Renin (or angiotensinogenase) is an enzyme that participates in the body's RAS (Renin-Angiotensin System) that mediates extracellular volume and arterial vasoconstriction. Thus, it regulates body's mean arterial blood pressure.*

*** Aldosterone is a steroid hormone produced by outer section of adrenal cortex of adrenal gland. It plays a central role in the regulation of blood pressure.*

**** ACE inhibitor= Angiotensin-Converting-Enzyme Inhibitor, a drug used for the treatment of hypertension and congestive heart failure (Captopril®, Ramipril®, Zofenopril®, Fosinopril®)*

Ibuprofen (Brufen®, Advil®, Motrin®, Nurofen®) is recommended as the first-line NSAID for simple analgesia, because it has the lowest incidence of adverse reactions. Diclofenac (Voltaren®, Arthrotec®) is popular because it is available in several formulations. Ketorolac (Toradol®, Apo-Ketorolac®) is the first choice for intravenous administration because of it's high lipid solubility. The selective COX-2 inhibitors have been shown to have similar analgesic efficacy as the one of conventional NSAIDs.

c) Salicylates:

The efficacy of Salicylates was reported by Stone in 1763. Aspirin was first synthesized in 1897 by Felix Hoffman, a chemist with the German company Bayer. Aspirin has been found to possess anti-inflammatory, antipyretic and analgesic effects. Its anti-inflammatory effect is apparent with high doses (between 3-5 g/24h) whereas at lower doses, it exerts its anti-aggregating role (100-500 mg/24/h). At high doses, it is associated with many adverse effects, most notably gastric toxicity (GI ulcers and stomach bleeding) and neurosensory effects (tinnitus or ears ringing).

3.2- Level 2.A : Weak or mild opioids (purs agonists) (Table 3):

The two most common used drugs are:

a) Codeine

b) Tramadol

They are indicated in the management of moderate pain, and in addition to non opioid analgesics if pain perception is not responsive to level 1 analgesics. For craniofacial pain disorders, they are indicated in intracranial pain, neurovascular disorders, neurogenic disorders, intraoral pain disorders, TMDs, cluster headache, carotidynia (tenderness of carotid artery, near bifurcation - Temple Fay, 1927), paroxysmal neuralgias during acute phase of pain, and neuritis.

a) Codeine (Solpadeine®, Co-codamol®, Algo Cod®, Codoliprane®):

Codeine (or 3-methylmorphine) is an weak opiate used for its analgesic, antitussive, antidiarrheal, anxiolytic, sedative, and hypnotic properties. It's mainly indicated for the relief of mild to moderate pain. Its action corresponds to the one tenth (1/10th) of that of morphine (that's why it's usually associated with another analgesic).

The usual adult dose of codeine is 15-60 mg every 4-6 hours, and for children 0.5 mg/kg every 4-6 hours as needed. The maximal 24h dose is 360 mg.

Pharmacokinetics and mechanism of action:

Codeine is a prodrug, itself inactive, but demethylated to the active morphine by the liver enzyme CYP2D6* to morphine. 70-80% of the dose undergoes glucuronidation to form codeine-6-glucuronide. 5-10% of the dose undergoes O-demethylation to morphine and 10% undergoes N-demethylation to form norcodeine. Morphine and norcodeine are further metabolized and undergo glucuronidation. The glucuronide metabolites of morphine are morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G). Both morphine and morphine-6-glucuronide are active and have analgesic activity. Norcodeine and M3G do not have any analgesic properties. There is no risk of pharmacodependance with codeine. Common side-effects of codeine include drowsiness, constipation, orthostatic hypotension, nausea, vomiting, and dry mouth.

b) Tramadol (Tramal®, Zaldiar®, Ultracet®, Tramacet®, Topalgic®):

Tramadol hydrochloride is an analgesic with central action, indicated in the treatment of moderate to severe pain. It is recommended for the management of pain in fibromyalgia, dental postoperative pain, cancer pain, and acute musculosketetal pain, and as an adjuvant to NSAID therapy in patients with osteoarthritis. It's prescribed at the dose of 100 mg for acute pain (every 4-6 h).

Pharmacodynamics and mechanism of action:

Its mode of action is not completely understood. Most common side-effects of Tramadol include dizziness, somnolence, constipation, diarrhea, vomiting, rash, and dry mouth.

3.3- Level 3: Strong opioids (Table 3):

Opioids have analgesic and central nervous system (CNS) depressant effects, as well as the potential to cause euphoria**. Morphine is the prototypical opioid. They are indicated in the treatment of intense pain, and if the strategies discussed above failed to relieve pain. For craniofacial pain disorders, strong opioids are indicated in intracranial disorders, neurovascular

** CYP2D6 is a member of the cytochrome P450 family enzymes involved in the metabolism of approximately 20% of drugs in clinical use.*

*** Euphoria= intense feelings of well-being, happiness, excitement, and joy.*

disorders, neurogenic disorders, TMDs, paroxysmal hemicrania, cranial arteritis, post-herpetic neuralgia, post-traumatic and post-surgical neuralgia.

a) Opioids receptors and mechanism of action (Table 5):

Opioids exert their analgesic effect through at least four groups of receptors: mu1, mu2, kappa, and delta, and probably other subpopulations as well. The distribution of these receptors throughout the body, along with their tissue densities within numerous organ systems, account for the global and varied effects of these drugs.

Opioids act at two sites (Fig. 4):

1. They reduce pain signal transmission by activation of pre-synaptic opioid receptors. This leads to reduced intracellular cAMP concentration, decreased calcium ion influx, and thus inhibits the release of excitatory neurotransmitters (glutamate, substance P).

2. At post-synaptic level, opioid-receptor binding evokes a hyperpolarisation of neuronal membrane which decreases probability of generation of an action potential.

Opioid's mechanism of action (Fig. 5)**:**

The most profound analgesic effects of opioids are mediated at the μ receptors. They induce intense analgesia, and a number of other effects such as bradycardia, sedation, euphoria, physical dependence, and respiratory depression. The effects of activation of neuronal mu receptors will depend on location of receptor, types of G proteins present in activated neural tissues, and frequency and duration of activation. Activation of mu receptors in the central nervous system will induce respiratory depression, analgesia, euphoria, and miosis (constriction of pupil). Stimulation of peripheral mu opioid receptors in smooth muscle of the bronchi and intestines, results in cough suppression and constipation.

Mu receptor activation can mediate a variety of G proteins. They are molecular intermediaries that initiate intracellular communication process and this will lead to secondary effects on messenger-generating enzymes (adenyl cyclase and phospholipase-C) Secondary messengers such as cyclic adenosine monophosphate (cAMP) are acutely decreased by opioid receptor activation.

b) Opioid's classification (Table 6)**:**

Nowadays, we distinguish natural opioids (such as morphine, codeine) from semisynthetic opioids (like hydromorphone, oxycodone, diacetylmorphine

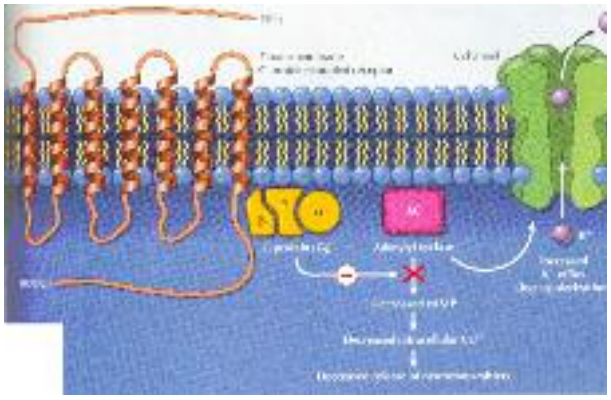


Fig. 4

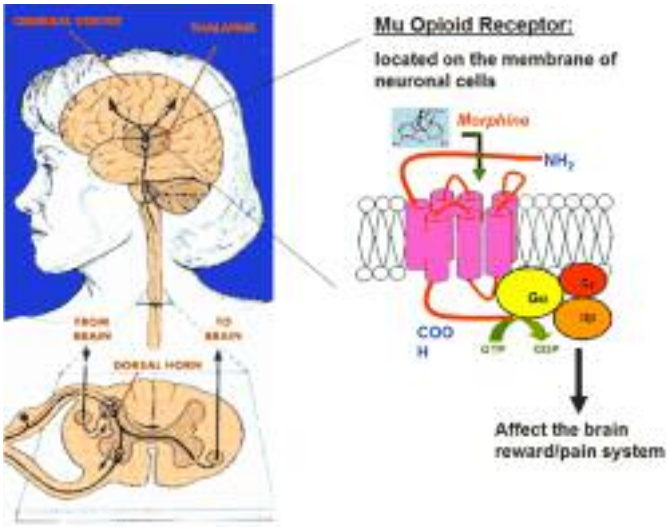


Fig. 5

OPIOID RECEPTORS	
Opioid Receptor Class	Effects
Mu_1	Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential
Mu_2	Respiratory depression, cardiovascular and gastrointestinal effects, miosis, urinary retention
Delta	Spinal analgesia, cardiovascular depression, decreased brain and myocardial oxygen demand
Kappa	Spinal analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system

Adapted from references 2 and 5.

Table 5

Opioid Alkaloids	Semisynthetic Opioids	Synthetic Opioids	Peptides
Morphine	Hydromorphone	Tramadol	Endorphin
Codeine	Oxycodone	Meperidine	Enkephalin
Papaverine	Naloxone	Fentanyl	
		Remifentanyl	

Table 6

([heroin]), and from fully synthetic opioids (such as nalbuphine, methadone, pentazocine*, fentanyl, sulfentanil, remifentanyl, alfentanyl). All these substances are classified as opioids including endogeneous opioids peptides such as endorphin, encephalin, and dynorphin which are short peptides released by the central nervous system under moments of severe pain or stress or both.

c) pharmacokinetics of opioids (Table 7) :

Oral: The majority of opioids are easily absorbed in gastrointestinal tract with an oral bioavailability of 35% (morphine) to 80% (oxycodone). However, they undergo an immediate first pass metabolism in the liver where glucuronic acid binding makes the drug inactive and ready for renal excretion. Exceptions are metabolites of morphine (they possess an analgesic effect and they are neurotoxic and can accumulate during renal impairment).

Intravenous/intramuscular/subcutaneous: While intravenous application of opioids gives immediate feedback about analgesic effect, intramuscular and subcutaneous routes have some delay (about 15-20 min) and should be prescribed on a fixed schedule to avoid large fluctuations in plasma concentrations. After parenteral administration, opioids are rapidly distributed within central nervous system, but this is followed by a second, slower phase of redistribution from fat and muscles into blood circulation with the possibility of re-occurrence of some opioid effects,

Sublingual/nasal: Only highly lipophilic substances such as fentanyl and buprenorphine (Temgesic® sublingual tablets, Suboxone®, and Subutex®) can be administered by these routes because they easily penetrate the mucosa and are absorbed by circulation.

Intrathecal/epidural: Opioids administered intrathecally or epidurally penetrate into central nervous system structures depending on their chemical properties: less ionized (i.e. more lipophilic, compounds such as sefentanyl, fentanyl, or alfentanil) penetrate much more easily (800 times) than more ionized (i.e. hydrophilic, compounds such as morphine). The effects of opioids within central nervous system are terminated by their redistribution into circulation and not by their metabolism, which is negligible.

d) Adverse effects of opioids are the following:

- Drowziness and dizziness
- Skin itching

Equianalgesic doses of different routes of administrations of opioids

Drug	Dose (mg)	Conversion Factor
Morphine, oral	30	1
Morphine, i.v., i.m., s.c.	10	0.3
Morphine, epidural	3	0.1
Morphine, intrathecal	0.3	0.01
Oxycodone, oral	20	1.5
Hydromorphone, oral	8	3.75
Methadone, oral	10	0.3
Tramadol, oral	150	0.2
Tramadol, i.v.	100	0.1
Meperidine, i.v.	75	0.13
Fentanyl, i.v.	0.1	100
Sufentanil, i.v.	0.01	1000
Buprenorphine, s.l.	0.3	100

Table 7

- Constipation, nausea, and vomiting
- Dry mouth
- Orthostatic hypotension
- Respiratory depression
- Opioid-induced hyperalgesia (after long-term use).

e) Clinical implications of opioids:

Opioids are widely prescribed because of their reliability, safety, multiple routes of administration, and ease of titration. Opioids can be used for all types of pain (ie, somatic, visceral, neuropathic). "Weak" and "strong" opioids are not inherently different in their ability to control pain, but are customarily used and dispensed in amounts appropriate for milder and stronger pain, respectively. "Weak" opioids (codeine, hydrocodone, oxycodone) are commonly prepared in combination with nonopioid analgesics (acetaminophen, aspirin, NSAIDs). Opioids are selected according to the route of administration and duration of action.

The “Ladder approach” (developed by the WHO) provides the administration of nonopioid medication (aspirin and paracetamol) (± adjuvants) first. This is followed by the use of mild opioids (eg, codeine) for mild to moderate pain, ± adjuvants, ± nonopioids. For pain that persists, strong opioids (eg, morphine) are prescribed, ± adjuvants, ± nonopioids. There is a great deal of interpatient variability. The answer to the question, "How much opioid is enough?" is whatever it takes to relieve the pain without producing intolerable side-effects.

Because there is (as opposed to most drugs used in medicine) no organ toxicity even at high doses and with long-term treatment, and because some important side-effects diminish with time, and other potential harmful

** Pentazocine (Fortral®, Sosegon®, Talwin®, Talacen®)*

side-effects can be avoided with correct use, opioids will probably remain the mainstay of pain management for most of patients for many years to come.

In summary, we addressed a practical pharmacological approach of orofacial pains, and in everyday practice, it seems obvious that combination of two molecules from different pharmacological classes gives the best results in the reduction of pain perception. For example, in dentistry, the most prescribed model is the combination of a weak opioid agonist such as codeine with a NSAID for the management of most orofacial pains.

4- CONCLUSION

Orofacial disorders consist of a wide variety of debilitating chronic reluctant diseases. The most common is temporo-mandibular joint (TMJ) and masticatory muscle disorders and surveys showed that approximately 7% (or 13 millions) Americans suffer from facial or jaw pain. These disorders are difficult to diagnose due to the proximity of multiple anatomical structures, and they are hard to manage because of the need of a strict daily regimen with the combination of appropriate medications. Management of patients with chronic pain is a true challenge, it often requires a multidisciplinary approach that includes dentist, physician, physical therapist, and psychologist / psychiatrist.

In orofacial neuropathic pain, conventional analgesics are inefficient and there is often benefit from class I antiarrhythmics (interfere with the Na+ channel = mexiletine), tricyclic antidepressants -TCAs- (amitriptyline, nortriptyline, desipramine, protriptyline, etc...), and anticonvulsants (Clonazepam, carbamazepine, oxcarbazepine, sodium valproate, phenytoin, gabapentin, pregabalin, etc...) that are not considered and classified as analgesics.

Drug therapy for chronic pain often involves simultaneous use of more than one drug. This takes advantage of the different mechanisms of action of different drugs. It may also allow the use of smaller doses and may reduce adverse effects. The most common example of this in dentistry is the combination of an opioid such as codeine with a NSAID.

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The Mylohyoid Nerve -MHN: clinical significance and implications for analgesia of mandibular teeth in restorative and surgical dentistry.

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Abstract

Inferior alveolar nerve block (IANB) is widely used in dental clinical practice for permanent mandibular teeth analgesia and impacted wisdom teeth surgery. Causes of dental analgesic failure should always be identified in order to ensure successful painfree dental treatment. Factors implicated in mandibular teeth analgesia failure include bifid inferior alveolar nerve, double/accessory mental foramen, exaggerated bone density, cross innervation of incisors, tissue inflammation, inactive anesthetic solution, and mylohyoid nerve accessory innervation. Mylohyoid Nerve-MHN-,a motor nerve to mylohyoid and digastric anterior belly muscles , is often implicated as a secondary(= additional) sensitive innervation of mandibular permanent teeth. It may escape analgesia in IANBs, and alternative local analgesia (MHN block) should be implemented to ensure total pain control of mandibular teeth.

INTRODUCTION

Mandibular division of trigeminal nerve (V3) consists of motor and sensory fibers. Motor division supplies muscles of mastication: masseter, temporal, pterygoid, mylohyoid, and anterior belly of digastric. Sensory portion of trigeminal supplies touch-pain-temperature to the face[7-9].

Immediately after exiting the skull through foramen ovale, mandibular nerve divides into anterior and posterior branches. Anterior branches are predominantly devoted to masticatory muscles. In contrast, posterior branches innervate structures involved in mastication, salivation, speech, and taste sensations – namely the lingual nerve, inferior alveolar nerve (IAN) and auriculotemporal nerve (ATN). Inferior alveolar nerve, and just before entering the mandibular foramen, gives off a small mylohyoid branch, the mylohyoid nerve -MHN-, that pierces sphenomandibular ligament and enters a shallow groove, the mylohyoid groove (MHG) on medial surface of mandible[9] (Fig. 1).

MHN, or nerve to mylohyoid, is a branch of the IAN, which arises above mandibular foramen. It originates at variable distances superior to mandibular foramen. Bennett and Townsend (2001) reported the average branching distance to be 13.4 mm while Wilson and co-workers (1984) reported an average branching distance of 14.7mm[5]. The nerve then passes downward and anteriorly within the mylohyoid groove on the medial surface of mandible (Fig. 2). The nerve courses anteriorly and parallel to mylohyoid muscle, giving branches that provide motor fibers to innervation to mylohyoid muscle on its infero-lateral superficial surface, also it supplies anterior belly of digastric muscle on its supero-medial deep surface[2,10]. MHN is primarily motor in nature, but it contains a sensory component to anterior and posterior mandibular teeth. It also supplies the chin and tip of the tongue in some individuals[2, 12].

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Mylohyoid groove -MHG- is a narrow 2-4 cm length and 1-3mm diameter groove located on medial aspect of mandibular ramus beginning at the lingula, just underneath inferior border of mandibular foramen (Fig. 1): It runs on the medial cortex of the ramus in an anterior - inferior fashion and it harbors MHN. It transmits the neurovascular bundle destinated to mylohyoid muscle.

IAN Block -IANB- is widely used in dental clinical practice for mandibular teeth analgesia. The terms mandibular block, inferior alveolar block,and pterygomandibular block (Chitre, 2006) are often considered synonymous. IANB has the highest failure rate of any dental injection, between 15 and 20% (Malamed, 1997). However, and in our everyday practice, failure rates for inferior alveolar nerve blocks proved to be around 5-10%: these analgesic failures can occur frequently even with experienced and skilled clinicians, and there are many reasons why this may occur (two major factors being poor operator technique and anatomical variations). A thorough knowledge of the anatomy of pterygomandibular space is essential for a successful administration of the IANB.

Communicating branches between IAN and Lingual Nerve -LN- are well described in the literature: these communications have been identified as a possible explanation for the inefficiency of mandibular teeth analgesia[3]. Many authors have outlined potential reasons for these failures in permanent mandibular molars, including accessory innervation from mylohyoid (nerve) and mental foramen.

The aim of this clinical comment is to revisit mylohyoid nerve and its practical clinical significance in dental practice.

DISCUSSION

Numerous techniques have been suggested to obtain adequate mandibular teeth analgesia. The direct approach remains one of the most commonly used. In addition to this conventional technique, other alternatives for anaesthetising the IAN include Gow-Gates and Akinosi-Vazirani approaches.

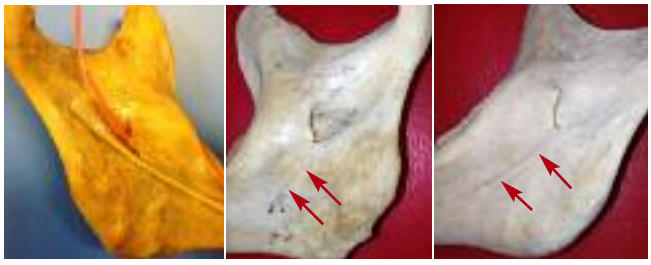

Fig. 1- Specimens of dry human mandibles showing the mylohoid groove-MHG (where mylo-hyoid nerve is located), immediately under lower aspect of mandibular foramen (red arrows indicate MHG).
(Courtesy of Ziad Noujeim, Laboratory of Human Oro-Facial Anatomy, Lebanese University School of Dentistry, Beirut, Lebanon).

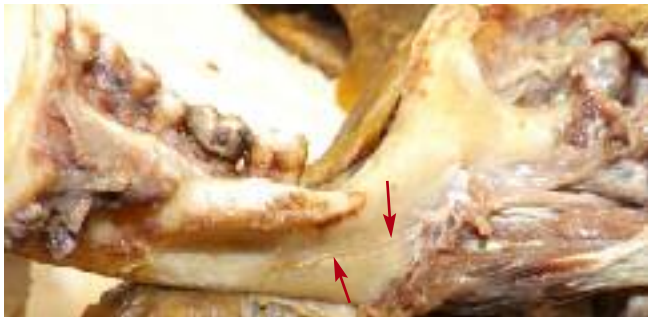

Fig. 2-Human mandible dissection displaying right MHN (red arrows) located in MHG (Notice right medial pterygoid muscle behind right MHN)
(Courtesy of Ziad Noujeim, Laboratory of Human Oro-Facial Anatomy, Lebanese University School of Dentistry, Beirut, Lebanon).

The direct IANB technique involves the pushing of an anesthetic needle into the pterygomandibular space by piercing buccinator muscle and progressing until mandibular ramus contact. The needle is then pulled back 2-3 mm following negative aspiration. The anasthetic solution is injected in the pterygomandibular space at a level just superior to the tip of the lingula mandibula and this anaesthetises the IAN before its entering at mandibular foramen level. The lingual nerve -LN- can be anaesthetised, as well, during IANB. Several intraoral landmarks are necessary to guide the clinician to administer an IANB: mouth should be widely open, and injection should be done lateraly to pterygomandibular raphe. The level at which the anesthetic needle should reache

the bone is indicated indicated by the maximum concavity of anterior border of mandibular ramus (coronoid notch).

Several factors are incriminated in locoregional analgesia failure of mandibular teeth, such as a bifid inferior alveolar nerve, bone density, inactivity of anesthetic product in presence of tissue inflammation, incorrect technique, MHN accessory innervation, inactive anesthetic solution, and cross innervation of incisors. Since the nerve to the mylohyoid has been shown to carry dental sensory fibers, a block of this nerve may be necessary to provide complete local analgesia of mandibular teeth. Administering MHN block in the lingual mucosa near the second premolar tooth, has been recommended (Roda and Blanton, 1994; Blanton and Jeske, 2003), and MHN may be blocked on the lingual aspect of the mandible between the first and second premolars (Sutton, 1974). This block may be administered on lingual mandible, as well, behind the distal root of the first molar (Sillanpää et al., 1988). The analgesic efficacy of the nerve to the mylohyoid may be due to the thin lingual mandibular cortex. Clarck and associates[15] found a higher success rate in posterior mandibular teeth analgesia by combining inferior alveolar nerve block and nerve to the mylohyoid block.

CONCLUSION

MHN is the only muscular branch of V3 posterior division (Woodburne and Burkel, 1988) and its role in mandibular teeth sensation remains a controversy. However, many authors reported the accessory innervation to pulps of anterior and posterior mandibular teeth (Frommer et al., 1972 --- Rood, 1976 --- Madeira et al., 1978 --- Wilson et al., 1984 --- Sillanpää et al., 1988 --- Clark et al., 1999).

Failure to achieve complete pulpal analgesia of mandibular teeth after an apparent successful IAN block remains a serious clinical problem in restorative and surgical dentistry. Consequently, it is advocated to block the MHN, in combination with IAN block, in order to possibly enhance pulpal analgesia of mandibular teeth.

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Pain in orthodontic treatment: etiology and management.

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Abstract

Orthodontic treatment is considered, by most patients, as a painful procedure. Studies have shown this reaction to have a major negative effect on orthodontic treatment and was reported to be an important reason for discontinuing treatment. Pain can be experienced during different orthodontic procedures like separator placement, banding, bonding, as well as archwire activation and debonding. This review attempts to highlight published literature regarding pain during different stages of orthodontic treatment, with an overview of current management strategies used to alleviate orthodontic pain.

BACKGROUND

Pain and orthodontic treatment can be perceived as the two faces for one coin, and this can be a reason to discourage orthodontic treatment for some future patients or reduce compliance for others undergoing treatment.[1-3] Orthodontic treatment requires applying forces on teeth, thereby generating different perceptions of pain in 91 to 95 % of patients, ranging from discomfort to severe pain.[4-8]

Surveys were performed to analyse the experience of orthodontic pain among patients and it was rated as a key deterrent to orthodontic therapy and a major reason for discontinuing treatment.[9-11] One survey rated pain as the greatest dislike during treatment and the fourth among major fears prior to orthodontic treatment.[12]

Different factors play a role in determining the intensity of pain such as age, gender, psychological status, types of appliances, and mechanical employed techniques.[13]

This disagreable sensation can be experienced during different procedures like separator placement, banding, bonding, as well as archwire activation and debonding. The main concern of orthodontists is to control, as much as possible, "this painful experience" to patients, which might reflect positively on the needed compliance and perseverance of those patients for a successful achievable result. The aim of this review is to highlight possible causes and management of discomfort and pain during and after orthodontic treatment.

MECHANISM OF ORTHODONTIC PAIN

Changes to teeth environment are crucial for orthodontic tooth movement. These changes include vascular alterations, recruitment of inflammatory mediators, and alveolar socket remodeling, and the assumption is that sources of that inflammatory pain during orthodontic treatment are from surrounding periodontal ligament. Collagen fibers of that latter are disrupted, some undergo compression, others tension, and necrosis will result, and the process of healing will start by formation of a blood clot and granulation tissue.[14] Granulation tissue will be later colonized by vascular and nervous components[15] and formation of new connective tissue will initiate.[16-18]

Several studies stated changes in circulation, tissue metabolism, and pulp vitality affected or compromised by applied orthodontic forces.[19-22] Thus another probable cause for orthodontic pain is the involvement of intradental nociceptive nerves where periodontal inflammatory reactions occur. These latter will spread to the pulp due to the release of some inflammatory

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mediators[23] (substance P-SP[a]-, histamine[b], enkephalin[c], dopamine[d], serotonin[e], prostaglandins[f]-PGs, and leukotrienes[g]) causing hyperalgesia[h]. The branching axons which innervate pulp and periodontal ligament, will undergo neurogenic inflammation resulting in pain sensation.[24-26]

In most of cases, no considerable damage to the teeth and their periodontium was noticed during orthodontic tooth movement. In general, pulpal side-effects are scarce but some may take place as altered pulpal respiration rate, internal root resorption, pulpal obliteration by secondary dentin, and pulpal necrosis.[27] Pulp ischaemia[28] is the transient factor that causes pain and discomfort during first days after orthodontic appliance adjustment. It results also from excessive forces applied with the overzealous wearing of intermaxillary elastics or excessively activated removable appliances.[29] This ischaemic pulpal pain will settle usually within a week if appropriate forces and mechanics are implemented. Death or necrosis of pulp was seldom reported during orthodontic treatment.[30] Besides, tooth sensitivity increases after light premature contacts ensuing from abnormal loading of teeth[31] which is common during the first phases of orthodontic treatment. These clinical symptoms will disappear progressively after elimination of interferences.

It is the responsibility of the orthodontist to recognize, as early as possible, any pulpal syndromes arising during orthodontic treatment and to treat them appropriately without delay.[32] Furthermore, teeth with severe periodontal injury are more vulnerable to pulpal reactions during orthodontic treatment, namely during intrusion and extrusion movements. [33]

REPORTED ORTHODONTIC CAUSES OF PAIN

Optimal forces in orthodontics are those forces able to move teeth most rapidly, with minimum discomfort to the patient and least damage to the teeth and their surrounding tissues.

Several authors advocated the use of light forces when moving teeth. It is thought that those forces produce more physiological effect, induce less pain, and minimize side-effects on different involved oral tissues.[34-38] Impingement on adjacent tissues by large forces was shown to cause greater periodontal compression, and thus, more pain.[39]

Other authors defended the use of heavy forces, especially for canines, justifying that higher forces per unit area increased the rate of biological response.[40-41]

On the other hand, some reports did not correlate level of applied force to discomfort experienced by patients after studying the relationship between initial tooth positions, applied force levels, and experienced pain and where no statistically significant correlation among the three parameters was found.[42]

SEPARATORS

Orthodontic separators are most often used by orthodontists to create spaces mesial and distal to the teeth, precisely posterior teeth, in order to fit the proper size of bands. They can be circular rubber bands or brass wires, spring type steel separators, and latex elastics. Placement of separators is known as a painful experience for almost all patients. Discomfort associated with orthodontic separation starts usually

a. SP= a neuropeptide that functions as a neurotransmitter and as a neuromodulator.

b. Histamine= a neurotransmitter (produced by basophils and mast cells) involved in the inflammatory response.

c. Enkephaline= a pentapeptide involved in regulating nociception in the body.

d. Dopamine= functions as a neurotransmitter in the brain (the brain includes several distinct dopamine systems).

e. Serotonin (5-HT)= a monoamine neurotransmitter primarily found in GI tract, platelets, and CNS. It has various functions, including regulation of mood, appetite and sleep, cognitive functions (memory, learning...), and it is thought to contribute to feelings of well-being and happiness.

f. PGs= a group of hormone-like lipid compounds that have a variety of strong physiological effects (regulating contraction and relaxation of vascular smooth muscle tissue, sensitization of spinal neurons to pain, inducing labor, regulating inflammation, etc...)

g. Leukotrienes= a family of eicosanoid inflammatory mediators produced in leucocytes, but also found in other immune cells. They use lipid signaling to convey information to either the cell producing them or neighboring cells, in order to regulate immune responses. Leukotriene production is usually accompanied by histamine and PGs, which also act as inflammatory mediators.

h. Hyperalgesia= an increased sensitivity to pain, which may be caused by damage to nociceptors or peripheral nerves (primary hyperalgesia is pain sensitivity occuring directly in damaged tissues, and secondary hyperalgesia is pain sensitivity occuring secondary in undamaged tissues).

four hours after placement of separators and the level of pain increases during the next following 24 hours.[13,43-46] An association was detected between pain intensity and crevicular fluid mediator levels: at 1 hour, an association was perceived between prostaglandin E2 (PGE2) levels and pain intensity while at day 1, pain intensity was associated to Interleukin-1ß (IL-1beta) levels.[4]

Intensity of pain and amount of separation were not similar with different types of separators. Both amount of separation and discomfort were found less with Kessling separators compared to elastomeric and brass wire separators.[47]

ARCHWIRE PLACEMENT AND ACTIVATION

One of major patients concern is the pain they are going to experience after the first appointment when placing the first orthodontic wire. Pain associated with initial archwire placement is experienced by majority of patients 4 hours after archwire placement, which will peak at 24 hours, and then decline.[6,13,48,49]

Orthodontic pain can vary, thereby it can be exacerbated in evenings and at nights, and usually lasts for 2 or 3 days and will gradually decrease in its intensity by fifth or sixth day. For some patients, it can be worse than pain experienced from tooth extraction.[5]

Some authors assessed orthodontic tooth pain at different time levels: after bracket placement (baseline), 1 hour after placement of initial archwires, 1 day after archwire placement, 1 week after archwire placement, and 1 month after archwire placement. Orthodontic patients experienced significant pain and discomfort 1 day after initial archwire placement.[50]

Studying of orthodontic pain was pushed to a level to compare various types of archwires in pain perception. No difference in intensity or duration of pain between different archwires was found.[49,51]

Other reports confirmed the prevalence of that pain at higher intensity in mandible than in maxilla[51], and in anterior teeth than in posterior ones. This was explained by differences in root surface area, increased involvement of anterior teeth during alignment, and more frequent involvement of anterior teeth in biting.[6,13,49]

ORTHOPEDIC SUTURAL EXPANSION

When craniofacial orthopaedics are indicated, high forces are usually applied. These forces are absorbed and transmitted to the craniofacial complex where a series of reactions, characterized by development of internal stress, will develop.[52,53]

One of the most adopted orthopedic forces in orthodontics is maxillary expansion, where heavy forces generated by a screw incorporated in an appliance will be applied on palate to split midpalatal suture. In an experimental expansion in rats, traumatic tears, exudates, death of fibroblasts, disruption of collagen fibers, and acute inflammation were observed. Inflammatory process resulted in a painful sensation, which is often expressed in the whole craniofacial region.[54]

Human reports in the literature confirmed that painful experience occurs after sagittal palatal expansion in children, and this occurs during initial phase and diminishes with time. [55-57]

EXTRA-ORAL APPLIANCES (HEAD GEAR AND FACEMASK)

Patients often experience discomfort after 24 hours of headgear wear and pain decreases significantly after 3 days of wear.[58] Another study[59] showed that 28 % of patients reported pain as the factor that prevented them from wearing their headgear. Pain caused by the use of protraction headgear (Facemask) was not of a muscular origin but part of the acute inflammatory reaction occurring in sutural regions.[60]

DEBONDING

Removal of braces is the moment that most of the patients wait for, but it is not accomplished without pain. Williams and Bishara[61] evaluated patient's discomfort at orthodontic bracket debonding and concluded that tooth mobility and force application were the two important influencing factors. They recommended that applying intrusive forces while debonding produce less pain in comparison with forces applied in other directions. They also suggested applying finger pressure or asking the patient to bite on a cotton roll to decrease pain. In another report, Rinchuse[62] suggested the use of an occlusal rim wax to minimize pain.

PERCEPTION OF PAIN

Psychological state is an important factor in pain perception following activation of an orthodontic

appliance. It has been reported that this pain is not directly related to the magnitude of force exerted but depends heavily on the psychological well-being of the individual.[63-66]

Orthodontic pain may also be related to gender. It is believed that females may be more sensitive to pain, while males can tolerate it better.[65] Other reports showed contradictory results where there was no differences between males and females in reporting pain sensation.[13]

The effect of age on pain perception was also investigated during orthodontic treatment. Several studies reported that adult subjects perceive more pain than young patients.[6,42] A study conducted during all phases of treatment such as separator placement, bonding, archwire placement, and activations, found that adolescents reported a higher level of pain than pre-adolescents and adults.[64]

CLASSIFICATION OF LOW-LEVEL ORTHODONTIC PAIN

Burstone[67] classified orthodontic pain in two ways:

A- Based on degree of pain perceived in response to amount of force application and it can be divided into three levels:

1. First level: patient is not aware of pain unless the orthodontist manipulates teeth to be moved by the appliance, e.g. using instruments such as a band pusher or force gauge.
2. Second level: pain or discomfort caused during clenching or heavy biting, usually occurs within the first week of appliance placement. Patient will be able to masticate food with this type of pain.
3. Third level: if this type of pain is perceived, patient might be unable to masticate food of normal consistency.

B- Based on time of onset, and it can be divided into two time frames:

1. Immediate: which is associated with sudden placement of heavy forces on tooth, e.g. hard figure of eight tie between central incisors to close a midline diastema.
2. Delayed: produced by variety of force values from light to heavy and representing hyperalgesia of periodontal membrane. This type of pain response decreases with time (i.e. pain reaction might start as third degree but becomes second or a first degree with time).

MANAGEMENT OF ORTHODONTIC PAIN

Chewing

Chewing gum or plastic wafer during first few hours of appliance activation are suggested to reduce pain as it will reduce ischemia and inflammation in periodontal ligament.[68] This will also temporarily displace teeth sufficiently and stimulation of vascular and lymphatic circulation would prevent the build-up of metabolic products, which are known to stimulate pain receptors.[69]

White[70] found that approximately 63% of patients reported less discomfort after chewing Aspergum® (a chewing gum containing 227mg of aspirin), after orthodontic activation. Hwang and co-workers[71] obtained the same results in 56 % of their patients after chewing Thera-Bite Wafers.

Low-Level LASER Therapy-LLLT

Low-level LASER (a form of LASER medicine that uses low-level/low-power LASERs or light-emitting diodes to alter cellular function) has been claimed to minimize orthodontic pain. The mechanism of LASER analgesia has been attributed to its anti-inflammatory effects.[72] Despite few reports that showed success in the reduction of orthodontic pain,[73,74] efficacy of low-level LASER therapy in reducing orthodontic pain was deemed discouraging and this type of phototherapy did not show immediate pain relief in orthodontic patients.[75]

Pain killers: anti- inflammatory versus pure analgesic drugs

Analgesics (pain killers) remain the main treatment modality to reduce orthodontic pain. A variety of drugs are suggested by practitioners but some are more efficient than others. Most of prescribed medications are painkillers and they can be classified into anti-inflammatory or pure analgesic drugs. Although all of them influence pain level perceived by patients, their effect is dissimilar on the rate of tooth movement. Nonsteroidal anti- inflammatory drugs (NSAIDs) are known to inhibit prostaglandins secretion, namely prostaglandine E2, an important inflammatory mediator essential for orthodontic tooth movement: PGE2 is responsible for initiation of osteoclastic activity essential for tooth movement, therefore a delay in orthodontic treatment is expected.

Ibuprofen, naproxen sodium, acetaminophen

(paracetamol), piroxicam, and aspirin are the most prescribed medications for pain alleviation. Acetaminophen is defined as a mild analgesic and not a nonsteroidal anti-inflammatory drug as all previous drugs already cited because it exhibits only weak anti-inflammatory activity. In a meta-analysis[76] comparing analgesic effect between ibuprofen and acetaminophen, there was no statistically significant difference between both drugs at any time point but ibuprofen had decreased pain at 2 hours and 6 hours after separators placement compared to placebo and not at 24 hours when pain peaks.

Preoperative medication was studied[77] with a goal of considerably decreasing perception of pain due to separators. No significant difference in pain was noticed after placement of separators between acetaminophen (650 mg) and ibuprofen (400 mg) taken 1 hour before separator placement, indicating an effective result of both analgesics. However, 20 mg of piroxicam administered 1 hour prior to separator placement were found more efficient in decreasing levels of pain than 400 mg of ibuprofen or placebo.[78] This significant decrease in pain was perceived at 2 hours, 6 hours, during nighttime, at 24 hours, and on the second and third days after separator placement.

Pre and postoperative medications were also advocated for a better control of pain resulting from separation of teeth. Positive results were reported with the use of 400 mg of ibuprofen 1 hour prior and 3 and 7 hours after separators placement.[79-82]

Differentiation between anti-inflammatory analgesic and purely analgesic drugs and the priority of the first ones in relieving pain after separators placement is of utmost significance in term of tooth movement. Anti-inflammatory analgesics inhibit prostaglandins secretion slowing down orthodontic tooth movement. Hence, it is important to limit as much as possible any interference with the inflammation response which is a normal tissue reaction in orthodontic tooth movement.

If bands are not used on molars but bondable tubes (no need for separators), patients will experience pain for the first time after insertion of the first wire. Studies reported that acetaminophen is the analgesic of choice in treating orthodontic pain without affecting orthodontic tooth movement.[83,84,86,87] Aspirin and ibuprofen had the same reduced effect on tooth movement while acetaminophen did not affect orthodontic tooth movement in rats and exhibited a statistically significant difference with the 2 above mentioned drugs[83]. In terms of pain, ibuprofen induces lower pain level during the first day after bonding compared to acetaminophen.[87]

CONCLUSION

Orthodontic pain is a major concern for parents, patients, and orthodontists. Studies have shown that it is the main negative factor to orthodontic treatment and an important reason for discontinuing treatment. It is important to inform patients about expected pain during different phases of treatment. When prescribing the analgesic of choice, appropriate drug should be selected. Thus, appropriate mechanotherapy and adequate pain management techniques should be well comprehended.

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Undertreatment of pain: is it acceptable?

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Awareness of pain and methods of treatment has become an up to date issue for both the person experiencing pain and the physicians responsible to treat this pain. This knowledge is readily available on internet, patient education brochures of pain societies and World Health Organization (WHO) laws.

Despite major advances in pain research and different modalities of treatment and pain relief drugs, millions of patients still suffer from undertreatment.

The aim of this introduction is not to explain and enumerate the different ways of pain treatment but rather to stress the issue of human right to pain relief. Accordingly, it is not acceptable anymore to tell the patient that he/she will be having pain either acute, postoperative, or chronic. Pain treatment has become a human right and the International Covenant on Economic, Social and Cultural Rights (ICESCR1) emphasizes the right "of everyone to the enjoyment of the highest attainable standard of physical and mental health". However, difficulty remains in the implementation of this right in different countries that signed this treaty, and the sanctions enforced on those who signed but do not comply. The major difficulty still hovers over the poor (developing) countries where resources are limited and medical aid lacks the strict necessary means to provide treatment facilities. Add to this, the strict laws for opioid analgesic prescriptions, lack of skilled personnel, and migration of physicians and other health care professionals to urban areas where better income provides better living.

Thus, the main taskforce to solve the issue of improper pain management should focus on pain education, providing facilities and resources for pain treatment and easier access to strong analgesics and opioids. This can be attained only by establishing pain clinics with group practice of physicians and health care providers interested in the topic and backed up by research in a university set up. WHO recommendations and each country's rules and regulations for release of opioid,and also other strong analgesics should be taken into consideration.

Lebanon is a leader country in its interest in programs for pain relief, treatment, and study. The Lebanese Ministry of Public Health has given permission for the establishment of a subspecialty in pain management**. There are two pain societies in Lebanon: the Lebanese Society for the Study of Pain released by the National Council for Scientific Research and the Lebanese Society for the treatment of Pain under the patronage of the Lebanese Order of Physicians (=Lebanese Medical Association).

At this stage, i cannot but stress the importance of the International Association for the Study of Pain - IASP- on pain research and treatment modalities and i would like to express my gratitude to IASP efforts that lead to the October 2010 Declaration of Montréal.

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** *Pain management (or Pain Medicine or Algiatry) is a branch of Medicine employing an interdisciplinary approach for easing the suffering of pain patients. Pain management team includes anesthesiologists, neurologists and neurosurgeons, dentists, clinical psychologists, psychiatrists, occupational therapists, physiotherapists, and nurses.*

"DECLARATION OF MONTRÉAL" Declaration that Access to Pain Management is a Fundamental Human Right

International Pain Summit (IPS) of the International Association for the Study of Pain (IASP)
Montréal, Canada, October 2010

We, as delegates to the International Pain Summit (IPS) of the International Association for the Study of Pain (IASP) (comprising IASP representatives from Chapters in 64 countries plus members in 130 countries, as well as members of the community), have given in-depth attention to the unrelieved pain in the world,

Finding that pain management is inadequate in most of the world because:

* There is inadequate access to treatment for acute pain caused by trauma, disease, and terminal illness and failure to recognize that chronic pain is a serious chronic health problem requiring access to management akin to other chronic diseases such as diabetes or chronic heart disease.
* There are major deficits in knowledge of health care professionals regarding the mechanisms and management of pain.
* Chronic pain with or without diagnosis is highly stigmatized.
* Most countries have no national policy at all or very inadequate policies regarding the management of pain as a health problem, including an inadequate level of research and education.
* Pain Medicine is not recognized as a distinct specialty with a unique body of knowledge and defined scope of practice founded on research and comprehensive training programs.
* The World Health Organization (WHO) estimates that 5 billion people live in countries with low or no access to controlled medicines and have no or insufficient access to treatment for moderate to severe pain.
* There are severe restrictions on the availability of opioids and other essential medications, critical to the management of pain.

And, recognizing the intrinsic dignity of all persons and that withholding of pain treatment is profoundly wrong, leading to unnecessary suffering which is harmful; we declare that the following human rights must be recognized throughout the world:

Article 1. The right of all people to have access to pain management without discrimination (Footnotes 1-4).

Article 2. The right of people in pain to acknowledgment of their pain and to be informed about how it can be assessed and managed (Footnote 5).

Article 3. The right of all people with pain to have access to appropriate assessment and treatment of the pain by adequately trained health care professionals (Footnotes 6-8).

In order to assure these rights, we recognize the following obligations:

* The obligation of governments and all health care institutions, within the scope of the legal limits of their authority and taking into account the health care resources reasonably available, to establish laws, policies, and systems that will help to promote, and will certainly not inhibit, the access of people in pain to fully adequate pain management. Failure to establish such laws, policies, and systems is unethical and a breach of the human rights of people harmed as a result.
* The obligation of all health care professionals in a treatment relationship with a patient, within the scope of the legal limits of their professional practice and taking into account the treatment resources reasonably available, to offer to a patient in pain the management that would be offered by a reasonably careful and competent health care professional in that field of practice. Failure to offer such management is a breach of the patient's human rights.

Note: *This Declaration has been prepared having due regard to current general circumstances and modes of health care delivery in the developed and developing world. Nevertheless, it is the responsibility of: governments, of those involved at every level of health care administration, and of health professionals to update the modes of implementation of the Articles of this Declaration as new frameworks for pain management are developed.*

FOOTNOTES

This includes, but is not limited to, discrimination on the basis of age, sex, gender, medical diagnosis, race or ethnicity, religion, culture, marital, civil or socioeconomic status, sexual orientation, and political or other opinion.

International Covenant on Economic, Social and Cultural Rights (ICESCR) (1966). The State parties of the ICESCR recognize "the right of everyone to the highest attainable standard of physical and mental health" (Art. 12), creating the "conditions which would assure to all medical service and medical attention in the event of sickness."

Universal Declaration of Human Rights (1948): Rights to Health (Article 25); Convention on the Rights of a Child (Article 24); Convention on the Elimination of All Forms of Discrimination Against Women (Article 12); Convention on the Elimination of All Forms of Racial Discrimination (Article 5(e) (iv)).

The Committee on Economic, Social and Cultural Rights. General Comment No.14, 22nd Session, April-May 2000 E/C 12/2000/4. "Core obligations" of all signatory nations included an obligation to ensure access to health facilities, goods, and services without discrimination, to provide essential drugs as defined by WHO, and to adopt and implement a national health strategy.

Committee on Economic, Social and Cultural Rights. General Comment No.14, 22nd Session, April-May 2000, E/C 12/2000/4, para. 12. General Comment No. 14 stated that health accessibility "includes the right to seek, receive and impart information and ideas concerning health issues."

Appropriate assessment includes recording the results of assessment (e.g., pain as the "5th vital sign," can focus attention on unrelieved pain, triggering appropriate treatment interventions and adjustments). Appropriate treatment includes access to pain medications, including opioids and other essential medications for pain, and best-practice interdisciplinary and integrative nonpharmacological therapies, with access to professionals skilled in the safe and effective use of these medicines and treatments and supported by health policies, legal frameworks, and procedures to assure such access and prevent inappropriate use. Given the lack of adequately trained health professionals, this will require providing educational programs regarding pain assessment and treatment in all of the health care professions and programs within the community for community care workers delivering pain care. It also includes establishment of programs in pain medicine for the education of specialist physicians in pain medicine and palliative medicine. Accreditation policies to assure appropriate standards of training and care should also be established.

Failure to provide access to pain management violates the United Nations 1961 Single Convention on Narcotic Drugs declaring the medical use of narcotic drugs indispensable for the relief of pain and mandating adequate provision of narcotic drugs for medical use.

The UN Universal Declaration of Human Rights (1948) (Article 5) states: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment…" Comment: Deliberately ignoring a patient's need for pain management or failing to call for specialized help if unable to achieve pain relief may represent a violation of Article 5.

The UN Special Rapporteur on the Right to Health and the UN Special Rapporteur on the question of torture and other cruel, inhuman, and degrading treatment stated: "The failure to ensure access to controlled medicines for the relief of pain and suffering threatens fundamental rights to health and to protection against cruel, inhuman and degrading treatment."

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Efficacy of Arthrocentesis on pain and mouth opening in the treatment of Temporomandibular Joint -TMJ- internal derangements: a 2-year retrospective clinical evaluation.

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Abstract

Objectives: *The objective of this study was to evaluate the efficacy of arthrocentesis on pain and mouth opening in the treatment of TMJ internal derangement (disc displacement without reduction).*

Methods: *Twenty-four patients were included in this study, knowing that they have TMJ derangement and treatment with TMJ arthrocentesis. The study was carried out in a dental specialized private clinic in Beirut, Lebanon, between February 2009 and June 2011.*

Results: *Twenty patients were selected. Arthrocentesis showed a significant reduction in pain and an increase in maximal mouth opening at the follow-up ($p<0.05$).*

Conclusion: *Within the limitations of this study, arthrocentesis proved to be an effective method in reducing pain and increasing maximum mouth opening (MMO) in patients with TMJ internal derangement.*

INTRODUCTION

Temporomandibular joints (TMJ) disorders are an ever increasingly encountered clinical condition. Internal derangement, defined as an abnormal relationship of the articular disc to the mandibular condyle, is cited as one of the most common disorders[1]. TMJ internal derangement features displacement of the intra-articular disc with resulting clicking and popping sounds.

In the past three decades, arthroscopic surgery of the TMJ has been introduced as an alternative minimally invasive procedure[2,3,22,23]. Later, TMJ arthrocentesis** was first described by Nitzan et al.[4] as a "relatively easy, minimally invasive, and highly efficient procedure" and is currently widely used in the treatment of various internal derangements as well as for diagnostic purposes[5]. Nowadays, it is the first surgical procedure used for a TMJ displaced disc. It is a minimally invasive procedure which reduces pain, joint sounds, and improves mouth opening. It works on the principle that it could loosen adherent disc, remove inflammatory content and pain-mediators allowing nutrient perfusion and thereby free sliding movement of the disc[6,7].

Several studies reported a high success rate for arthrocentesis in treating patients with pain and limitation of mouth opening resulting from closed lock of the TMJ[8-11].

The aim of this retrospective clinical study was to evaluate the efficacy of arthrocentesis on pain and mouth opening in the treatment of TMJ internal derangements.

MATERIALS AND METHODS

Twenty-four patients (8 men and 16 women) were included in this study. A review of patient's medical charts showed that they all had internal TMJ derangement and were treated with arthrocentesis. The patients were all treated between February 2008 and June 2011 at a specialized private clinic in Beirut (Lebanon). Inclusion criteria were the following:

- TMJ pain with mouth opening and/or chewing difficulty, and/or a positive MRI diagnosis of TMJ disc displacement without reduction (DD w/oR),
- a history of clicking with subsequent sudden onset of limited mouth opening with no clicking,

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** *also known as "joint aspiration".*

• No history of TMJ surgery, bilateral joint involvement, or serious systemic disease.

Patients with limited mouth opening caused by only masticatory muscle spasm, prior TMJ surgery, bilateral joint involvement, and serious systemic diseases were excluded from the study.

For a retrospective analysis, a questionnaire included dichotomous responses regarding the presence of symptoms and a visual analogue scale for pain[5]. Patients were asked to make an appointment for clinical examination. The same clinician (JBH) assessed the following parameters: age, gender, diagnosis, TMJ pain [using a visual analogue scale (VAS; 0= no pain and 10= worse unbearable pain)], and maximal mouth opening (MMO). Preoperative and postoperative measurements of these parameters were taken. Treatment plan began with an occlusal therapy as described by Nassif and co-workers[12] using an anterior deprogrammer device, later converted to a centric relation occlusal device and selective occlusal equilibration, if required.

Arthrocentesis was performed under local analgesia with 3% carbocaine and IV sedation. The procedure consisted in inserting two 18-gauge needles in the upper TMJ space and flushing of this space with 250ml of lactated Ringer's* solution (Fig. 1). Upon completion of the procedure, one needle was withdrawn and 5ml of sodium hyaluronate was injected in the upper joint space.

Non-steroidal anti-inflammatory drugs were prescribed along with muscle relaxants for 2 weeks and patients were advised to perform range of motion exercises on daily basis.

Follow-up of the patients ranged between 18 to 24 months.

The statistical analysis was done using paired t test for pain and Maximum Mouth Opening (MMO). Statistical significance was set to P=0.05.

RESULTS

Four patients were excluded from the study for failure to attend recall sessions. Eight men and 16 women patients (ages ranging between 18-47 years) remained in the study. The duration of chief complaints before consultation ranged between 1-2 years for all subjects. Chief complaint for most patients was pain (80%). A significant reduction in pain ($P<0.05$) as well as significant increase in maximal mouth opening ($P<0.05$) was noticed.

DISCUSSION

The management of temporomandibular disorders has always been a therapeutic challenge, mainly when pain is a major chief complaint[13]. The results of the present study showed a significant reduction in pain and significantly higher MMO in patients with TMJ internal derangement. These results are in accordance with the results reported by Fridrich and associates[14].

Success rates of arthrocentesis has been reported, in several studies[13,16,17], to vary from 70% to 90% from 6 months to 3 years follow-up in patients with TMJ closed lock.

Frost and Kendell[18] reported the effects of arthrocentesis in patients presenting acute closed lock, chronic closed lock, and chronic displaced disc with reduction, the results found were respectively excellent, good, and intermediate.

Studies[5,6,7,8,9,10,11,14,15,16,17,18,19,20,21] showed that arthrocentesis for the treatment of TMJ internal derangements offers favorable long-term stable results with regards to increasing maximal mouth opening and reducing TMJ pain and dysfunction, This is in accordance with the findings of our present study. Dimitroulis and co-workers[9] reported that treatment efficacy of arthrocentesis was the same compared with successful conventional non-surgical treatment and arthroscopic surgery as well.

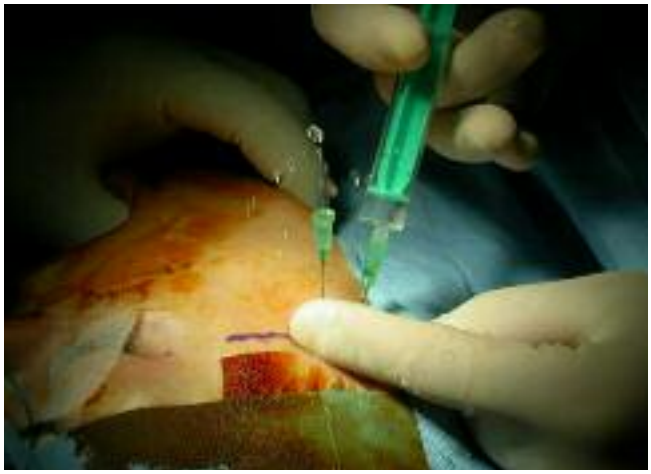

Fig. 1: Flushing ("lavage") of TMJ **(courtesy of Claude Lévy, MD, Paris, France).**

** Ringer's is a sterile solution of sodium chloride (6g/L), sodium lactate (3.1g/L), potassium chloride (0.3g/L), and calcium chloride (0.2g/L). Lactated Ringer's has an osmolarity of 273 mOsmol/L and a pH of 6.5.*

CONCLUSION

Arthrocentesis (Greek: arthros, joint + kentesis, puncture) is a clinical procedure (using a syringe) that aims to remove tissue breakdown products and reduce inflammation.

The mechanism of arthrocentesis in improving the clinical symptoms is still unclear: release of negative pressure on the disc, release of adhesions, and reduction in surface friction and viscosity of the synovial fluids are all suggested as possible reasons for TMJ improvement after arthrocentesis[5]. In particular, pain decrease after arthrocentesis was related to the reduction of inflammatory components and pain mediators in situ, allowing normal TMJ movements[18].

Our 2-year retrospective study suggests that TMJ arthrocentesis is a simple and safe procedure for patients with TMJ internal derangements: indeed, arthrocentesis improves mouth opening and decreases pain.

Future prospective clinical studies are warranted to validate the results of our study in the management of TMJ internal derangement.

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Botulinum Toxin injection for the management of orofacial pain conditions.

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Abstract

Botulinum toxin (Botox®) is an exotoxin produced from Clostridium botulinum. Its mode of action is to block the release of acetylcholine from the cholinergic nerve end plates, leading to inactivity of the innervated muscles. Botox® is best known for its beneficial role in facial rejuvenation. Recent literature has highlighted its application in multiple non-cosmetic medical head and neck conditions. This clinical note will review the current indications pertaining to the use of Botox® in managing different orofacial pain conditions.

INTRODUCTION

Botulinum toxin -BTX- is a protein and neurotoxin produced by Clostridium botulinum (a Gram+, rod-shaped, anaerobic spore-forming motile bacterium which produces 8 toxin serotypes: A, B, C, D, E, F, G, and H). Its mode of action is to block the release of acetylcholine from cholinergic nerve endings, causing muscle paralysis. Its effects are temporary and variable depending on the dose and frequency of administration. Botox's first medical use was to treat strabismus in 1980. In the early 2000, cosmetic effects of this neuromodulator were described. In 2002, the US Food and Drug Administration (FDA) approved the first cosmetic indication for Botox® (Botulinum Toxin type A)[1,2]. Currently, its cosmetic use includes on-label as well as off-label indications to treat facial wrinkles in upper and lower thirds of the face[2].

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Recently, the therapeutic indications of Botox® have expanded to include a wide range of medical and dental conditions. This has been aided by a greater understanding of its underlying physiology as well as improved efficacy and safety. This clinical note examines the various indications of Botox in treating non-cosmetic and painful conditions of orofacial region. Headache is a major indication for head and neck therapeutic use of Botox®[3]. Other head and neck indications include: blepharospasm (excessive blinking), strabismus (squints), cervical dystonia (spasmodic torticollis), and chronic migraine. Orofacial indications include: masticatory myalgia, trigeminal neuralgia, temporomandibular joint disorders, and bruxism.

Proper knowledge and clinical experience are required to increase patient safety. Botulinum toxin has a great safety profile. However, complications can occur. Common adverse events include inflammation, swelling, infection, pain at injection site, erythema, bruising, tenderness, bleeding, and redness. Headache and blepharoptosis can occur with Botox injections[4] as well. Additionally, local weakness may occur and it is usually related to improper dosage or injection technique[5]. Contraindications for Botox include a known hypersensitivity to the toxin, pregnant female patients, infection at the injection site, allergy to milk protein, and neuromuscular disorders[6,7].

MASTICATORY MYALGIA

Masticatory myalgia is due to chronic nociceptive irritation of the tendons and fascias of the facial muscles (masseter, temporalis, and medial pterygoid)[8,9]. Botox® has been shown to be effective in relieving pain associated with masticatory myalgia[10-12]. Indeed, Botox® results in atrophy of the affected incriminated muscles, leading to relieved tension and decreased pain. This results in decompression of afferent nociceptive neurons through reduction of substance P-mediated neurogenic inflammation[12,13]. Masticatory muscles of mastication are the primary target for neurotoxin injection. Figures 1 and 2 show the location for masseter injection. Figures 3 and 4 indicate neurotoxin injection for treating the temporalis muscle myalgia.

TRIGEMINAL NEURALGIA[13,15]

Trigeminal neuralgia (Tic douloureux) is a neuropathic disorder characterized by short episodes (few seconds to several minutes) of intense, electric shock-like facial pain. Botox® is useful for the management of patients with intractable and/or drug-refractory trigeminal neuralgia[14-16]. It results in a significant pain reduction in these patients[14-16]. Additionally, Botox® was found to be effective in combination with pharmacotherapy[14,17,18]. These patients are usually injected intradermally at the affected painful side. This can result in facial asymmetry, which usually resolves within 2-3 weeks post-injection[19].

TEMPOROMANDIBULAR JOINT DISORDERS

Botox has been effectively used in the management of temporomandibular joint disorders (TMDs). Multiple studies have showed control and decrease in pain in TMD patients treated with Botox®[8,10,12]. Muscles of mastication are usually targeted with botulinum toxin. This is especially helpful in preventing spasm of the lateral pterygoid muscle, which usually results in temporomandibular joint (TMJ) disc displacement anteriorly, resulting in chronic pain.

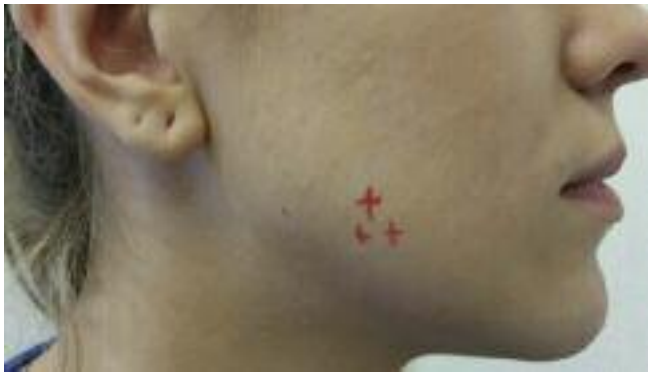

Fig. 1

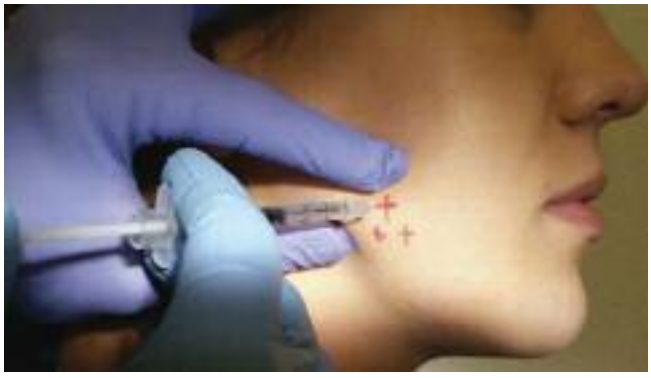

Fig. 2

Fig. 3

Fig. 4

BRUXISM

Bruxism is usually due to repetitive contraction of the masseter and temporalis muscles leading to teeth grinding[20]. Bruxism can ultimately result in TMD. Recent studies[9,10] has shown that Botox® resulted in reduction of myofascial pain in bruxers.

CONCLUSION

Botox® blocks nerve impulses that cause muscles to contract. This clinical note highlights the therapeutic role of BTX type A (Botox®, Dysport®, Xeomin®, Neuronox®) in a wide range of non-cosmetic painful conditions pertaining to dental patients. As its indications will continue to expand, dentists should be familiar and enough trained to implement these therapeutic treatment modalities.

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The Lebanese Society for the Study of Pain (LSSP)
In collaboration with

The Lebanese Society for the Treatment of Pain (SLTD)
Present

OROFACIAL PAIN: A MULTIDISCIPLINARY APPROACH

GLOBAL YEAR AGAINST OROFACIAL PAIN
OCTOBER 2013 – OCTOBER 2014
International Association for the Study of Pain

Friday December 6, 2013 (5:30 - 8:15 pm)

Amphitheater B
Campus of Medical Science – St Joseph University
Damascus road - Beirut – Lebanon

5h30 – 5h35: Welcome Word- President of LSSP
Joseph Maarrawi

5h35 – 5h45: Words of the deans of the Faculties of Medicine and Dentistry (USJ)
Roland Tomb & Nada Naaman

First session: Orofacial pain – Point of view of medico-surgical specialists
Moderators: Marie-Claire Antakly, Nayef Saadé, Nicole Naccache

5h45 – 6h00: Introduction and classification of orofacial pain
Hicham Abi Zeid

The Lebanese Society for the Study of Pain (LSSP) is a local chapter of the
International Association for the Study of Pain (IASP)
E-mail: lssp.council@gmail.com

6h00 – 6h15: Trigeminal neuralgia & cluster headache: Diagnosis & medical treatment
Salam Koussa

6h15 – 6h30: Psychologic dimension of orofacial pain
Sami Richa

6h30 –6h45: Radiofrequency & balloon technique in the management of trigeminal neuralgia
Elie Samaha

6h45 – 7h00: Radiosurgery & surgical techniques for orofacial pain
Ronald Moussa & Joseph Maarrawi

Second session: Orofacial pain – Point of view of dentists
Moderators: José Chidiac, Huda Huijer, Elie Al Chaer

7h00 – 7h15: Temporo-mandibular disorder in orofacial pain
José Johann Chidiac

7h15 – 7h30: Orofacial pain of dental origin
Hrant Kaloustian

7h30- 7h45: Atypical facial pain
Ziad Noujaim

7h45- 8h00: Round table about orofacial pain
Animated by Edgard Nehmé & Bechara Al Asmar

Third session: Sponsors corner
Moderator: Nabil Bitar

8h00- 8h15: Medications for orofacial pain

This activity is accredited for CME 3

The Lebanese Society for the Study of Pain (LSSP) is a local chapter of the
International Association for the Study of Pain (IASP)
E-mail: lssp.council@gmail.com

ABSTRACTS

1- Introduction and classification of orofacial pain

Hicham Abi Zeid

Head and face contain a large number of anatomical structures: the brain, eyes, nose, sinuses, teeth…. This density complicates diagnosis and treatment, added is the prominent psychological significance attributed to this region. Management of orofacial pain thus demands the services of clinicians from various specialties: dentists, pain specialists, neurologists, psychiatrists…
Complex referral patterns to adjacent structures are common in orofacial pain, and indeed, one man's headache is another man's facial pain. Thus, patient with orofacial pain may go from one specialist to the next in order to get help.
Chronic orofacial pain disorders are classified into three major clinical groups: Musculoskeletal conditions or temporomandibular disorders, orofacial neuropathies and neurovascular orofacial pain. Except for musculoskeletal pain, most are unique to the trigeminal system.

2- Trigeminal neuralgia & cluster headache: Diagnosis & medical treatment

Salam Koussa

Trigeminal autonomic cephalgias (TAC) are primary headaches with a common clinical phenotype consisting of trigeminal pain with autonomic signs, which may include lacrimation, rhinorrhoea and miosis. Cluster headache is the archetypal TAC, with severe pain and major autonomic activation. Neuroimaging, and careful physical and neurological evaluation, should be considered in all patients with TAC or TAC-like syndromes, particularly in those with atypical presentation.
Trigeminal neuralgia (TN), also known as tic douloureux, is a distinct facial pain syndrome that may become recurrent and chronic. It is characterized by unilateral pain following the distribution of cranial nerve V. International Headache Society criteria for TN are reviewed and atypical presentations are discussed.

3- Psychologic dimension of orofacial pain

Sami Richa

Somatoform disorders represent a part of psychiatric disorders with no justifying organic lesion. Among these disorders, chronic pain can occur anywhere in the body and especially in the orofacial area. Management is based in combined medical and psychotherapeutic support.

4- Radiofrequency & balloon technique in the management of trigeminal neuralgia

lie Samaha

Trigeminal neuralgia is the most common painful orofacial pain. It is often mistaken for a pain of dental origin. Pain relief was marked by the discovery of Carbamazepine. 75% of diagnosed

patients become resistant to oral medication; consequently, a more invasive therapy is needed. Percutaneous procedures (Injection of Glycerol, radiofrequency and balloon compression technique) are the mini-invasive way with immediate relieving effect. Adverse effects and recurrence rate of these techniques are relatively rare. Among all aggressive therapeutic approaches, the simplest techniques are percutaneous one, to be considered in the management of trigeminal neuralgia refractory to medical treatment.

5- Radiosurgery & surgical techniques for orofacial pain

Ronald Moussa & Joseph Maarrawi

Radiosurgery (Gamma Knife or LINAC) is a recently used technique for the treatment of essential neuralgia. It consists of delivering "focused" radiation therapy to the entry point of the trigeminal nerve without the need for surgery. It is performed using a stereotactic frame installed temporarily on the patient's head under local anesthesia. It takes place in a single session, the result is observed 3-4 weeks on average after the procedure. There are currently no sufficient data to judge its long-term effectiveness. Based on recent published series, this technique is effective in two thirds of patients, with slight hypoesthesia correlated positively with its prognosis. Sensory side effects are rare. Currently, it is indicated as second-line treatment after failure of surgical decompression. Randomized controlled trials assessing more precisely its effectiveness and potential complications are essential to define its indications in the future.

Microvascular decompression is a surgical technique based on the presence of a neurovascular conflict between the trigeminal nerve and adjacent vessels in trigeminal neuralgia. The compression of the trigeminal nerve by a vessel distorts the nerve with lesions of nerve fibers secondary to arterial pulsations, causing segmental demyelization with “bypasses” leading to pain. Microvascular decompression has been well described since the 1970s for patients with refractory pain. This surgical procedure is done under general anesthesia and consists of approaching the trigeminal nerve at the trigeminal cistern through a keyhole, with dissection of the arachnoids followed by a careful separation between the nerve and the conflicting artery. The advantage of this technique is its conservative aspect; it targets the "cause" of neuralgia and does not lead to sensory disorders observed with other less invasive techniques. This technique is indicated in patients with "physiological" young age, who present no contraindication for craniotomy under general anesthesia. The results are very good, with total pain relief in more than 95% of cases, especially when the conflict is obvious. Recurrences are observed in 6-10% of cases. Serious complications are rare.

6- Temporo-mandibular disorder in orofacial pain

José Johann hidiac

Temporomandibular disorders (TMD) have a multifactorial etiology. They are therefore difficult to diagnose and treat. This presentation is about what is related to TMD and what is not: Starting from the relationship between the ear, the neck, the migraines and TMD, in acute and chronic situations. A guide to medical practitioners and to medical personnel is described as well.

7- Orofacial pain of dental origin

Hran Kalous ian

Oral, facial and cervico-cephalic pain is often intricate. This presentation will focus specifically on the pain of dental origin by pulpal and periodontal inflammation that can cause this tangle.

8- Atypical facial pain

Ziad Noujaim

In 1982, Joseph Marbach reported probably the first description of neuropathic oro-facial pain by John Hunter over 200 years ago. A problem for dental practitioners in diagnosing neuropathic pain has been the use of various terms ascribed by different investigators over the years .Originally, the condition was described as "Atypical Odontalgia"-AO-in response to its "atypical" nature ,and this term was subsequently listed in the Taxonomy of Chronic Pain Syndromes by the IASP, in 1994. Other terms have included "Idiopathic Odontalgia", "Neurovascular Odontalgia", "Phantom Tooth Pain"-PTP, and "Neuropathic Oro-Facial Pain". Patients affected with "Atypical Facial Pain"-AFP- may present to the endodontist with a persistent severe pain ,yet there are no clearly identifiable clinical or radiographic abnormalities: this specific neuropathic pain was first described as a painful and unusual condition that occurs in the dento-alveolar structures and oral mucosa (Rees and Harris,1979),with patients reporting pain that was moderate to severe in intensity, and with a pattern of referral that may cross the anatomical midline of maxilla and/or mandible. In clinical practice, AFP presents as a syndrome featuring oral paresthesia or persistent pain following procedures such pulp extirpation, routine inferior alveolar nerve block, oral peripheral nerve trauma, teeth extractions, apicoectomy, periodontal surgery, and exenteration of maxillary sinus contents. The purpose of our short presentation is to revisit this unusual, unclear, and troublesome pain syndrome and address the current state of knowledge that will enable dentists to understand, diagnose and manage this unique kind of pain. It is essential for dentists and endodontists to gain and apply the knowledge of neuroplasticity of the nervous system associated with oro-facial neuropathic pain, and this will allow them to adopt a crucial role for patients sustaining neuropathic oro-facial pain, in order to achieve a successful outcome.

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