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REVIEW ARTICLE

Neuralgia inducing cavitational osteonecrosis*

Neuralgia induzida por cavitação osteonecrótica

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SUMMARY

BACKGROUND AND OBJECTIVES: To review neuralgia inducing cavitational osteonecrosis (NICO), its differential diagnosis with regard to major facial pains as well as its management.

CONTENTS: NICO is a disease with numerous causes, such as trauma, infections, use of local anesthetics with vasoconstrictors which decrease blood ‡ow inside the bone, direct or indirect application of heavy metals and steroids after oral surgeries, use of nicotine and coagulation problems. The diagnosis is based on the clinical history associated to pain quality, duration and in general ineffective therapeutic response to different neuromodulators. Complementary exams are standard periapical X-rays of the area to be investigated, panoramic X-rays and CT, which may show or not unilocular radiolucent foci. Scintigraphy normally shows an area of increased uptake. Treatment may be clinical with anticoagulants, anabolic steroids or local antibiotic injection; or surgical promoting local bleeding by osteotomy or ostectomy, depending on NICO level and extension.

CONCLUSION: The search for new drugs less detrimental for bone tissues and more information to dentists about NICO may help decreasing its incidence by establishing an earlier diagnosis, thus making different management techniques more effective.

Keywords: Clinical treatment, Neuralgia inducing cavitational osteonecrosis, Neuropathic pain, Orofacial pain, Surgical treatment.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Realizar uma revisão sobre a neuralgia induzida por cavitação osteonecrótica (NICO) seu diagnóstico diferencial em relação às principais dores bucofaciais, bem como o seu tratamento.

CONTEÚDO: A neuralgia pela NICO é uma doença que tem inúmeras causas, como trauma, infecções, o emprego de anestésicos locais com vasoconstritores que diminuem o ‡uxo sanguíneo no interior do osso, a aplicação direta e/ou indireta de metais pesados, de corticosteroides, pós-cirurgias bucais, o uso de nicotina e problemas de coagulação. O diagnóstico baseia-se na história clínica associada à qualidade da dor, duração, resposta terapêutica normalmente ineficaz ao uso de diferentes neuromoduladores. Emprega-se, como exames complementares, radiografla periapical padrão da área a ser investigada, radiografla panorâmica, tomografla computadorizada que podem demonstrar, ou não, focos radiolúcidos uniloculares. O exame cintilográfico apresenta normalmente área de hipercaptação. O tratamento pode ser clínico conservador utilizando anticoagulantes, esteroides anabolizantes, injeções de antibióticos no local, ou cirúrgico, promovendo o sangramento local por osteotomia ou ostectomia, dependendo do grau e extensão da NICO.

CONCLUSÃO: A pesquisa de novos medicamentos, menos prejudiciais aos tecidos ósseos, e maior informação aos cirurgiões-dentista sobre a NICO podem ajudar a diminuir sua incidência, estabelecendo o diagnóstico mais precocemente e consequente-

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mente tornando mais eficaz as diferentes formas de tratamento.
Descritores: Dor neuropática, Dor orofacial, Neuralgia induzida por cavitação osteonecrótica, Tratamento cirúrgico, Tratamento clínico.

INTRODUCTION

Neuralgia inducing cavitational osteonecrosis (NICO) is a disease characterized by cavitary lesions in the mandible and/or jawbone, very often not radiologically detectable[1,2]. It may be caused by trauma, such as dental extraction, endodontics and secondary alveolar hemorrhage, or even by an infectious process[3-5].

NICO has been pointed as frequent cause of face neuralgias involving the trigeminal territory. It is a severe, piercing pain like an electric shock, of short duration which does not wake up the patient and some times is continuous[3,4,6-9]. It affects more females than males and may partially or totally disappear after anesthetic block of the painful area. At neurological evaluation, cranial pairs are normal[10]. Such bone radiolucent areas may be detected or not[1,2] through periapical or panoramic X-rays, CTs and MRI[1], but the golden standard is bone scintigraphy[11].

Due to lack of knowledge of health professionals it is called atypical facial pain. In fact, it is an ischemic necrosis of the alveolar bone. Current studies describe ischemic alveolar bone marrow coagulation disorders as the cause for NICO, which may also be the result of thrombosis with or without hypoflbrinolysis, which would obstruct vascular spaces impairing blood ‡ow in the region[12-14]. So, it could be treated with anticoagulants or anabolic steroids[15-18].

Other therapeutic options would be regional osteotomy and curettage of the painful area, or osteotomy associated to local application of absorbable gelatine sponge associated to tetracycline, with tetracycline and cephalexin, or clindamicine with gentamicine[1-4,9]. Treatment is decided in a case-by-case basis, depends on professional's experience, on previous treatments, on the extension of the involved area and on patient's general status. If the choice is surgery, removed bone should be sent for pathologic exam.

For such, and aiming at flnding adequate and relevant studies, the following terms were combined: aseptic necrosis of bone, ischemic necrosis, avascular osteonecrosis, osteonecrosis of jaw, neuralgia inducing cavitional, osteonecrosis, jawbone cavities.

The following databases were queried: BBO,Cochrane, LILACS and Medline in the period from 1970 to 2011, supplemented by manual query of journals and chapters of books. This query was limited to studies in humans written in Portuguese and English.

GENERAL NICO CHARACTERISTICS

NICO is a sequela of the action of several local factors which impair vascularization of the affected bone region[1]. It was deflned as a neurogenic pain syndrome caused by decreased bone vascularization with consequent tissue necrosis and formation of bone cavities difflcult to see by imaging exams[1,2]. Together with bone marrow edema and regional ischemic osteoporosis, ischemic necrosis may lead to the development of NICO. This is one of the commonest human bone diseases, but only recently it has been evaluated as a head and neck disease[2].

Bone tissue necrosis and formation of cavities were justifled 31 years ago by the continuity of chronic infectious processes triggered after tooth extraction in alveolar processes both of jawbone and mandible[3,4]. Professionals hardly associated facial pains to neuralgias or to bone origin, classifying pains with no dental origin as psychogenic. Studies in this area have advanced and some authors[3] have found association between patients suffering of facial pain and bone lesions of infectious origin, which may be caused by nonspecifIc aerobic or specifIc anaerobic bacteria.

The first series of studies reporting asymptomatic cavitary bone lesions difficult to diagnose by conventional methods was published in 1976[5]. In 1926, the neurosurgeon Wilfred Harris presented an etiologic theory where a chronic, low-intensity maxillomandibular bone infection surrounding some trigeminal branches could cause constant orofacial pain. This infection would cause neural degeneration or demyelination generating an anomalous nervous impulse pattern and, as a consequence, an abnormal pain[1]. Over the years, with the advance of imaging diagnosis processes and the study and detection of genetic changes, one may also include as a cause of NICO the decreased bone marrow blood flow causing bone cavities. All of this was also associated to genetic mutations which would predispose patients to thrombophilia and hypofibrinolysis[13,14].

Initially, NICO etiopathogenesis was considered infectious with lesions caused by microorganisms in alveolar bone lesions region and consequent osteomyelitis and bone necrosis[5]. With the advance of

diagnostic studies and disease identifIcation, some authors[1,9] have suggested two major theories for NICO etiopathogenesis: one is infectious, considering bacteria as major disease-causing agents; the other is ischemic which has as its major cause bone tissue infarction due to lack of blood irrigation.

DEVELOPMENT MECHANISM AND ETIOLOGY

NICO development mechanism is still being studied[1], however NICO triggering factor would be a local trauma associated to pathological process triggering factors being flve of them already described: the flrst suggests that patients may have some local or systemic immunodeflciency which impairs local infection elimination. The second would be the presence of speciflc pathogenic bacteria stimulating, during the in‡ammatory process, tissue necrosis, thus impairing vascularization leading to infarction and necrosis. The third mechanism suggests that the lack of tissue vascularization leads to hypoxia or bone marrow infarction generating less resistance to pathogens and making odontogenic infections easier. The fourth hypothesis supposes a lack of neutrophils and / or macrophages, which would lead to decreased chemotaxis and phagocytosis, promoting infections installation and propagation. The flfth and last mechanism would be the lack or decrease of bone growth factors mandatory for new bone formation, as well as a change in tissue pH decreasing osteoinducing potential[1].

In addition to etiological factors, NICO has worsening and hereditary factors associated to the disease. Researchers[13,15,16] have concluded that patients with such neuralgia have differences in coagulation factors which are common as hereditary forms of thrombophilia and hypoflbrinolisis, also related to risk factos such as femoral head osteonecrosis. Seventy-one percent of NICO cases are caused by alcohol abuse, trauma, prednisone, estrogen, pregnancy, sickle cell anemia, lupus erythematosus and use of chemotherapy for malignant neoplasias. Smoking and atherosclerosis are less commonly associated[19].

Seldom associated to this disease are osteomielytis and inanition[16]. Bisphosphonates are also to be added to these risk factors[20]. These drugs act by decreasing bone reabsorption, especially by inhibiting recruitment and inducing osteoclasts apoptosis. In addition to decreased osteoclast activity there is inhibition of growth factors and other bone matrix factors release. Its use has been associated to NICO, especially in patients submitted to tooth extractions[20,21]. The best way to prevent bone necrosis problems in dental procedures is an adequate oral exam and the treatment of all dental needs of the patient, especially removing infection foci, before starting bisphosphonates therapy[22].

The risk for osteonecrosis with this drug increases with time of use, even more if associated to steroids. When there is the need for invasive procedure, such as oral surgeries, and patient is under some oral bisphosphonate for osteoporosis, the recommendation is to withdraw the drug three months before and three months after the procedure. This approach is based on studies reporting oscillations of osteoclasts function during the period of drug administration, which improve in cases of osteonecrosis[22]. Also to prevent osteonecrosis during the use of bisphosphonates, it is recommended that patients avoid smoking and alcohol[23].

According to recent coagulation studies which describe ischemic alveolar bone marrow changes as cause of cavitation after tooth extraction, it is proposed that jawbone osteonecrosis could be result of thrombosis with or without hypoflbrinolysis, which would obstruct vascular spaces, impairing blood ‡ow to the region. In this situation, intramedullary pressure would be decreased producing hypoxia and cell death[13,14,24]. Toxins, immunoglobulins and in‡ammatory mediators released in necrotic or ischemic regions would stimulate nervous terminations which would produce neurogenic pain[9].

INCIDENCE

NICO incidence by gender is of four females for one male. This number takes into account medical records and research of such entity in groups of patients. Female predominance may reach 80% and is explained by two reasons: more personal care of females as compared to males and because they look for help more often due to the use of hormones as replacement therapy or the use of contraceptives. The use of female hormones by females with hereditary hypercoagulation disorders increases the risk for venous thrombosis and tissue infarction. With regard to age, females above 65 years of age have a higher risk for developing NICO than the remaining population, however the highest incidence is seen in middle-aged people between 35 and 55 years of age[1,2].

NATURE OF PAIN

NICO pain is still not totally explained and falls into the infectious theory which is still controversial be-

cause it may mask its real cause. Another explanation suggests that pain may be caused by bone ‡uid exchanges resulting from ischemia and from in‡ammation mediators, more than nervous lesions. Vessels and nerves may be affected by increased pressure and ischemic thrombosis allowing the development of nervous injury[1,13].

Major symptom of this disease is a severe pain in the face or in the alveolar bone[3,4,25], in trigeminal nerve distribution sites, being piercing, paroxysmal and may be continuous in some cases. More affected regions are tooth extraction sites both in the mandible and jawbone, and may also be bilateral[7,8]. In general, it is not possible to see mucosal changes or some other type of oral manifestation at clinical evaluation. In a study[8] with 2023 patients, 48% reported pain in the region of the third lower molars, which has been described as in shock and paroxysmal, being it totally or partially controlled with anesthetic block of the affected region. Some patients also presented diplopia, nasal congestion, balance changes and face dysesthesia, in addition to pain[4].

DIAGNOSIS

To adequately diagnose NICO, it is necessary, in addition to clinical information, to use additional exams. Studies[3,19] have proposed the following diagnostic criteria: pain in the alveolar bone in regions innervated by the trigeminal nerve and temporary pain relief when the region is submitted to anesthetic block.

NICO also interferes with quality of life and may be easily mistaken for other neuropathic and / or deep somatic musculoskeletal and visceral diseases[4,8,9,25-29].

IMAGING EXAMS

Conventional exams, such as periapical and panoramic X-rays, sometimes are not enough for an accurate NICO diagnosis.

Chronic bone diseases caused by lack of blood ‡ow are difficult to see in imaging exams leading to a high false-negative rate. In alveolar bone marrow disease, up to half the cancellous bone may be destroyed without signiflcant radiographic changes which would only be detected by an experienced eye and a thorough X-rays analysis[1,11,12]. Studies[1,2] have published NICO radiographic flndings reporting the presence of light and discrete radiolucent areas, like soap bubbles, and the presence of radiopaque areas in the shape of cotton. It is possible to radiographically observe the lack of normal bone tissue healing, with the presence of lamina dura close to the alveolus, in the regions corresponding to the zones were teeth had been extracted.

These same authors also reported[1,2] that ischemic osteonecrosis is difflcult to see in conventional X-rays, however when present it appears as a radiolucent area and there may be a weak oval central sclerosis surrounded by a thick radiolucent circle which is also surrounded by a thick sclerotic ring however poorly distinct, being also described as “bull’s eye lesion”.

Bone scintigraphy using technetium 99 is the golden standard for bone marrow ischemia diagnosis. This technique is still being used although being expensive and needing intravenous contrast injection, in addition to resulting in 30% of false-negatives[1,11,12].

HISTOLOGICAL EXAM

The histopathology of ischemic osteonecrosis is directly related to its duration and to the intensity of blood flow decrease in the medullary bone. Characteristics of bone marrow edema include dilated and sinusoidal medullary capillaries, serous exudate around blood vessels, presence of adipocytes, delicate fiber bundles (ischemic myelofibrosis) between fat cells, areas of dense fibrosis and a slight dispersion of chronic inflammatory cells in myelofibrosis regions. Trabecular bones in general remain viable, however inactive, thin and largely spaced. It is possible to find focal areas of medullary hemorrhage or microinfarctions, considered by some as pathognomonic signals of osteonecrosis.

When there is necrotic bone tissue, there is also the lack of osteocytes foci. One may also flnd stained globular calcifled necrotic debris masses which may also be darkened. The heat generated by rotary tools may also generate necrotic debris similar to those caused by ischemia, however these are more peripheral in tissue fragments, which allows for their differentiation[1,2,9].

TREATMENT

Treatment is based on clinical and imaging exams. Surgery is performed with complete resection of the bone tissue corresponding to the painful zone, using bone marrow curettage and placing in the site a sponge impregnated with antibiotics[1-4]. It is also possible to use local infiltration with tetracycline alone or com-

bined with cephalexin with 90% improvement which may last from two months to nine years[3].
Other authors[30] have studied the effects of warfarin, an anticoagulant, in 10 patients with NICO and thrombophilia and the use of stanozolol, an anabolic steroid, in 20 patients with osteopathy and hypoflbrinolysis. Results have shown that both warfarin and stanozolol may be used to treat osteopathies, NICO and hypoflbrinolysis, however these drugs have relieved pain in just 5% of cases.

DISCUSSION

Current dentistry is improving a lot the biocompatibility of materials used in procedures, however, several still cause bone tissue lesions[31]. Materials such as heavy metals, lead and phosphorus, products used for disinfections of root canals for endodontic treatments, use of anesthetics with vasoconstrictor and local application of steroids, associated to old age and hereditary factors related to thrombophilia and hypoflbrinolysis[13,141,18,22] are major NICO causes, in addition to surgery-related infections[1-4]. This disease has a silent onset causing pain and discomfort only at an advanced stage of bone commitment[3,4],. Added to these factors, NICO is also difflcult to diagnose because most of the times it is not diagnosed with conventional X-rays[1,11,12], needing more accurate exams such as scintigraphy[11]. NICO must be differentiated from trigeminal, glossopharyngeal and superior laryngeal nerve neuralgias, from atypical toothache, Eagle's syndrome, Ernest's syndrome and temporomandibular dysfunction. Table 1 describes differences and similarities between NICO and other bucofacial pains[25-63].
Trigeminjal neuralgia is the most frequent facial neuralgia, presenting as a piercing pain in electric shock, limited to regions innervated by the flfth cranial nerve. It normally affects individuals between 50 and 70 years of age, with mean age of 50 years and mostly females. Pain attack is sudden, triggered by a tactile stimulation in points known as triggering points. Pain may last from seconds to minutes, may occur many times a day without motor changes in the affected area. Neuromodulators signiflcantly improve pain in the beginning, and there may be pain latency periods. There are cases where pain returns without apparent reasons[25-29,32-35].
Glossopharyngeal neuralgia is similar to trigeminal neuralgia being differentiated by the anatomic site. It occurs between 15 and 85 years of age, with mean age of 50 years. It is an episodic, unilateral pain like an electric shock, piercing and severe. Attacks are short, from 30 to 60 seconds, and may be repeated for some hours. Pain trigger seems to be swallowing, yawning, speech, chewing or touching the tonsil with some tool. In general, the site of more severe pain referred by patients is below the mandible angle and triggering points may be located close to the external acoustic meatus[27,32,36,37].
Superior laryngeal nerve neuralgia manifests as acute, unilateral, short duration, electric shock pain located in the lateral pharyngeal area, submandibular area and infra-auricular or auricular area. There is no predilection for gender or age. It may be triggered by swallowing, shouts, head rotation and blowing the nose. Triggering zones of this disease are located in the hypothyroid region and in the lateral pharyngeal region. Laboratory and imaging exams do not show changes, thus poorly contributing for the diagnosis. Clinical pain characteristics, its duration and nature, associated to anesthetic blocks and the use of neuromodulators help diagnosis and treatment[32,38-41].
Atypical toothache is a persistent pain in the maxillofacial region which does not follow the diagnostic criteria for any other orofacial pain and does not have an identifiable cause. It affects especially females, with mean age of 40 years, but may also occur during adolescence. Pain may be located in a small area of the face or extend to associated areas, such as temporal and cervical regions[27,28,32]. Pain is described as deep, diffuse, continuous and persistent and may present sensation of burning or pressure. Pain may be started by an invasive dental treatment or surgery[42-44].
Eagle's syndrome is a disease affecting styloid processes, which are extensions of the temporal bone with length varying from 15 to 30 millimeters. Such bone gives origin to stylopharyngeal, styloglossus and stylo-hioid muscles. The disease is manifested due to the elongation of the styloid process generating electric shock pain or stabbing pain in the cervical pharyngeal region irradiating to the mastoid region and worsened during swallowing. It affects more females between 30 to 50 years of age. Patients report sensation of foreign body in the throat with pain at head rotation, in the shoulders and headache. Tonsillar fossa palpapation worsens pain. The diagnosis may be conflrmed by anesthetic infiltration of the tonsillar fossa which temporarily relieves pain while the effects of the anesthetic persist, and by X-rays showing the styloid process with more than 30 mm length[45-53].

Table 1. Differences and similarities between NICO and other bucofacial pains

	NICO	Trigeminal neuralgia	Glossopharyngeal neuralgia	Superior laryngeal nerve neuralgia	Atypical toothache	Eagle's syndrome	TMD	Ernest's syndrome
Pain location	Region innervated by the trigeminal nerve.	Areas innervated by the trigeminal nerve.	Áreas innervated by the glossopharyngeal nerve.	Lateral region of pharynx, submandibular, infra-auricular and auricular regions	Close to the region of upper molars and premolars	Cervical region, pharynx and mastoid	Pre-auricular, masseter, occipital and temporal regions	Lower auricular, temporal and posterior teeth regions
Age	40-50 years	50-70 years	15-85 years	--	40 years and also adolescence	30-50 years	20-80 years	Varied
Gender	F>M	F>M	-	M=F	F>M	F>M	F>M	-
Quality of pain	Electric shock, pulsatile and piercing.	Electric shock or burning	Electric shock or burning	Electric shock	Constant, diffuse and in pressure	Electric shock and / or stabbing	Electric shock, pressure, pulsatile, continuous, Constant, or all	Pulsatile
Duration	1 to 2 seconds / constant	Few seconds to minutes	30 to 60 seconds and may repeat for some hours	May last for minutes	From short episodes to constant.	According to stimulation.	According to severity	According to severity
Frequency of pain	1 day to constant	Several times a day	Several times a day	Several times a day	Varied	Varies according to stimulation	Varied	Varied
Stimulation	No	Slight touch on the face,	Yawning, swallowing	/swallowing, shouts, head rotation	Varied	Swallowing, tonsil palpation and head rotation.	Stomatognathic system functions	Palpation of stylomandibular ligament and mandibular protrusion

Ernest's syndrome is caused by the in‡ammation of the stylomandibular ligament. This condition is caused by trauma in the mandibular region, skull or face. Mandibular osteotomies where distraction and mobility are promoted may also be causes. Diagnosis is based on clinical history, clinical evaluation with palpation of the stylomandibular ligament insertion by extraoral access, and anesthetic block may be used in the insertion of such ligament which will conflrm such syndrome because pain disappears and returns after anesthetic recovery. Diagnosis is then clinical since radiographically such disease is not detected. It is an in‡ammation without ligament calciflcation[54,55].

Temporomandibular dysfunction is a set of conditions associated to stomathognatic system abnormalities which trigger not only joint dysfunction but also of adjacent tissues, including facial and cervical muscles. It affects individuals of different ages, from 20 to 80 years of age, especially females. Clinical characteristics and most common symptoms are electric shock localized pain and / or in pressure in the TMJ with the function, articular noise(s) during mouth opening and closing, or both, deviation or mandibular de‡ection and mouth opening limitation. It may also present as continuous, constant and diffuse facial pain which worsens with mandibular movement and /or palpation of masticatory and cervical muscles, earache, headache and cervical pain. All these characteristics may be associated to parafunctional habits deleterious for joint and dental tissues, such as bruxism, nail biting and history of trauma or mandibular fracture[61]. Imaging exams may help the diagnosis. Transcranial and cephalometric X-rays and CTs are commonly used, however the golden standard for the diagnosis of intra-articular diseases is MRI[27,32,56-58].

CONCLUSION

NICO is caused by trauma, dental surgical procedures, by the direct action of drugs daily used

by dentists, by pathogenic agents acting on the bone tissue, and by genetic character, especially related to blood coagulation problems such as thrombophilia and hypoflbrinolysis. The search for new drugs less detrimental for bone tissues and more information to dentists about NICO may help decreasing its incidence by establishing an earlier diagnosis, thus making different management techniques more effective.

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