Integrative approach to the therapeutic use of cannabis for orofacial pain

Abordagem integrativa do uso terapêutico da cannabis nas dores orofaciais

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ABSTRACT

BACKGROUND AND OBJECTIVES: Faced with the difficulty of treating chronic orofacial pain and seeking an approach that aims at the health and well-being of the patient in a broader way, cannabinoid therapy appears as an adjunct to pharmacological approaches.

CONTENTS: Cannabinoid therapy generates analgesia through the activation of the endocannabinoid system, as well as the use of palmitoylethanolamide (PEA), curcumin, grape seed extract, aromatherapy, acupuncture, laser therapy and the practice of physical exercise. In this way, these therapies allow a reduction in the use of analgesic drugs.

CONCLUSION: Cannabinoid therapy is part of this integrative approach and the combination of cannabinoids with other forms of activation of the endocannabinoid system contributes to a better therapeutic outcome and a better quality of life for countless patients suffering from chronic orofacial pain.

Keywords: Cannabidiol, Cannabis, Chronic pain, Endocannabinoids, Facial pain, Integrative dentistry.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Diante da dificuldade de tratamento das dores orofaciais crônicas e buscando uma abordagem que vise a saúde e o bem-estar do paciente de uma forma mais ampla, surge a terapia canabinoide como coadjuvante nas abordagens farmacológicas.

CONTEÚDO: A terapia canabinoide promove analgesia através da ativação do sistema endocanabinoide, assim como o uso da palmitoiletanolamida (PEA), curcumina, extrato de semente de uva, aromaterapia, acupuntura, laserterapia e a prática de exercício físico. Desta forma, essas terapias permitem redução do uso de fármacos analgésicos.

CONCLUSÃO: A terapia canabinoide faz parte dessa abordagem integrativa e a combinação dos canabinoides com outras formas de ativação do sistema endocanabinoide contribui para melhores resultados terapêuticos e melhor qualidade de vida para inúmeros pacientes que sofrem de dores orofaciais crônicas.

Descritores: Canabidiol, Cannabis, Dor crônica, Dor facial, Endocanabinoides, Odontologia integrativa.

INTRODUCTION

Pain is an unpleasant perception associated with the activation of the nociceptive pathway. The activation of the nociceptive pathway generates a nociception that corresponds to its sensory component, responsible for discriminating the intensity, location and duration of the nociceptive stimulus in the somatosensory cortex. On the other hand, the unpleasant perception corresponds to its emotional component, which involves the activation of several regions in the central nervous system involved in processing emotions.

Chronic pain (CP) is a much more complex experience than just pain that lasts longer than three months. It is often associated with maladaptive changes in the nervous system, as occurs in primary chronic pain, also called nociplastic pain. Pain is influenced by psychological, cognitive, behavioral, social, and neurophysiological factors[1,2].

Chronic orofacial pain, including temporomandibular disorders (TMD) and neuropathic pain, as well as chronic pain in general, present difficult treatment management. Among the possible causes of therapeutic failures are the exclusive focus on somatic complaints and neglect of psychosocial assessment, the variability of response to the same drug by different patients, the difficulty of its titration, its undesirable adverse effects (weight gain, decreased libido), and the need for the patient to change habits[3]. Recognizing the biopsychosocial model of CP, the need for a treatment with an integrative approach, seeking the health and

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HIGHLIGHTS
- Scientific evidence on the therapeutic use of cannabis in orofacial pain
- Integrative way of using phytocannabinoids in orofacial pain
- Different ways of activating the endocannabinoid system besides phytocannabinoids

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well-being of the patient with a view that goes beyond the somatic causes[4]. In this scenario, cannabinoids emerge as a possible therapeutic option.

CONTENTS

Getting to know cannabinoid therapy and the endocannabinoid system

The treatment of chronic pain, the most mentioned reason for the use of medical cannabis, as well as research using cannabis and phytocannabinoids, has grown exponentially in the last decade[5]. The introduction of cannabinoids in a compassionate manner in the control of orofacial pain has gained prominence in scientific studies that show its therapeutic potential in its control[6,7]. The most studied phytocannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), are already part of the therapeutic arsenal for treating orofacial pain, since, besides reducing pain, they promote well-being and improve patients' quality of life.

The role of the endocannabinoid system (ECS) is determinant in the modulation of pain and inflammation, besides the maintenance of a series of homeostatic and physiological functions[8], such as temperature, cognition, emotional processing, modulation of inflammatory and immunological responses[9]. It is composed of endocannabinoids, the cannabinoid receptors (CR) CB1 and CB2, and enzymes responsible for the synthesis and degradation of endocannabinoids, as already detailed in other articles.

The receptors, together with the endocannabinoids, act by modulating the levels and activity of most other neurotransmitters[10]. Endocannabinoids are neuromodulatory fatty acids produced on demand by phospholipid precursors and released by postsynaptic neurons in response to physiological and pathological stimuli. After their signaling function, endocannabinoids are enzymatically degraded[11]. There are three types of cannabinoids: endocannabinoids such as 2-arachidonoylglycerol (2-A) and anandamide (AEA), produced endogenously; phytocannabinoids, which come from cannabigerolic acid (CBGA) produced by the Cannabis sativa plant; and synthetic cannabinoids (molecules synthesized in a laboratory).

Cannabinoids act mainly on G-protein-coupled CRs, widely distributed throughout the body[12]. CB1 and CB2 cannabinoid receptors are expressed in several regions involved in the transmission and modulation of orofacial pain, such as in trigeminal ganglion neurons, including those that innervate the masseter muscle[13]. CB1 receptors are also found in the trigeminal spinal tract nucleus[14] and in areas involved in descending pain modulation pathways[15] and pain perception, such as the prefrontal cortex[16]. Thus, cannabinoids can modulate orofacial pain both peripherally by acting on peripheral and central trigeminal nociceptive fibers, as well as in regions involved in endogenous analgesia mechanisms, as well as in the perception of pain.

Cannabinoids can also act on other non-cannabinoid receptors, such as TRPV1, also expressed in the trigeminal ganglion[17], and GPR18 and GPR55, found in areas of the nervous system which are involved in pain modulation[18].

CBD and THC are considered the major phytocannabinoids. They come from the phytocannabinoid CBGA, which serves as a substrate for the synthesis of the major cannabinoids. The minor phytocannabinoids have been studied in several diseases. Among them, one can mention cannabigerol (CBG), cannabinol (CBN), tetrahydrocannabivarin (THCV), and cannabichromene (CBC), the third most abundant in the plant, second only to CBD and THC.

Terpenes and flavonoids are a class of compounds produced by cannabis, contributing to its aroma and pigmentation, respectively[19]. They have a wide range of biological and pharmacological activities. The main terpenes produced by cannabis are myrcene, caryophyllene, humulene, pinene, linalool, limonemene, and terpinolene. Myrcene is the most prevalent in the plant, it has antipsychotic, antioxidant, analgesic, anti-inflammatory, sedative, myorelaxant and anticancerous properties[20-23]. The most important is β-caryophyllene. It is the only terpene known to interact with the body's endocannabinoid system (it selectively binds to the CB2 receptor)[24].

Flavonoids are secondary polyphenolic metabolites. They are divided into four main groups: flavonoids isoflavonoids, neoflavonoids, and anthocyanins. There are about 20 different pharmacologically active flavonoids identified in cannabis[19], indicating the medicinal benefits of cannaflavins found exclusively in cannabis.

All the components of the cannabis plant (phytocannabinoids, terpenes, flavonoids) together exert superior therapeutic effect than any of its single compounds. This cooperation between the different components of the plant is called the "entourage effect," as proposed by chemist Raphael Mechoulam[25].

There are three presentations of CBD: the full spectrum - which has all the components of cannabis (phytocannabinoids, terpenes, and flavonoids), the broad spectrum - which is similar to the full spectrum except that it does not contain the THC molecule, and the isolated - which may be only the CBD or THC molecule. For pain modulation, full spectrum presentations are always chosen, due to the following advantages: the entourage effect, less risk of an inverted U-shaped effect curve, lower dose to reach the therapeutic target[26].

THC produces analgesic and antihyperalgesic effects[27]. Studies have confirmed that CBD reduces levels of pro-inflammatory cytokines, inhibits T-cell proliferation, induces T-cell apoptosis, and reduces migration and adhesion of immune cells. Most clinical studies for the treatment of refractory CP have typically used a 1:1 combination (THC:CBD) often taken orally and well tolerated. Combining THC with CBD ameliorates the deleterious and psychoactive effects of administering THC alone. CBD:THC formulations have been effective in reducing mean pain scores in CP patients with multiple sclerosis, in reducing neurophysical measures in response to noxious stimuli, and in reducing refractory CP[28].

CBG is also known as a partial agonist for the CB1 and CB2 receptors, in addition to inhibiting anandamide reuptake[22]. One study[23] showed high efficacy of CBG, as most patients reported that their conditions were "much improved." Moreover, 73.9% claimed superiority of CBG-predominant cannabis over conventional CP drugs.

There is a consensus to consider cannabis for the treatment of neuropathic pain, inflammatory pain, nociplastic pain, and mixed pain[29]. Prescribers must titrate and manage the dose scheme

to achieve the patient's treatment goals, which can be varied and therefore individualized. Because each individual's SEC is unique, dosing does not follow a standard and must be personalized. One should always start with a low dosage and gradually increase it until the therapeutic target is reached.

In a paper published with consensus recommendations on dosage and administration of phytocannabinoids to modulate CP, three types of protocols were proposed: the conservative, the standard, and the rapid. For each protocol, a titration to a maximum daily dose recommendation was followed. The clinician may consider moving a patient between protocols to individualize the patient's treatment. CBD and THC are dosed until a therapeutic response in modulating CP is achieved.

Although limited, scientific evidence suggests that cannabinoids reduce pain associated with temporomandibular dysfunction (TMD), neuropathic and oncologic pain, and improve the patients' quality of life.

In a preclinical study using the formalin test on the temporomandibular joint (TMJ)[30], it was observed that a cannabinoid agonist reduced pain, via activation of the CB1 receptor, as much as morphine and more than ketamine and the anti-inflammatory drug indomethacin[31]. In another preclinical study mimicking the symptoms of muscular TMD, application of delta-9-tetrahydrocannabinol (THC)[6], cannabidiol (CBD), cannabinol (CBN) and the combination of CBD/CBN (1:1)[13] to the masseter muscle reduced neural growth factor (NGF)-induced mechanical sensitization. The analgesic effect of THC was via CB receptors16 and the CBD/CBN combination induced a reduction in mechanical sensitization which lasted longer than that induced by each of these substances alone[13], which is in agreement with the entourage effect of cannabinoids.

These studies suggest that THC, CBD and CBN could peripherally reduce muscle TMD without central adverse effects, which was later confirmed in a randomized, double-blind, controlled clinical trial[32]. A full-spectrum cannabidiol cream on the masseter muscle of patients with muscular TMD achieved reduced pain, as assessed by means of the Visual Analog Scale (70.2% compared with 9.81% in the placebo group), and masseter muscle electromyographic activity (11% in the right and 12.6% in the left, compared with 0.23% in the right and 3.3% in the left masseter in the placebo group)[32]. Therefore, according to the study, peripheral application of cannabinoids could be an effective strategy for reducing pain of TMD muscles without adverse effects.

Cannabinoids represent a genuine therapeutic strategy in neuropathic orofacial pain[33]. Full-spectrum cannabidiol-enriched oil has been shown to reduce allodynia in the neuropathic orofacial pain model of infraorbital nerve constriction[34]. In the absence of persuasive evidence, a group of pain physicians, psychiatrists, scientists, and patient representatives concluded through a multicriteria decision analysis that cannabinoids have a better benefit-safety profile than other drugs used to control peripheral neuropathic pain, especially since they contribute more to quality of life and have a more favorable side effect profile than other drugs[35].

In a clinical case report, the use of nabiximol (CBD 25 mg/mL + THC 27 mg/mL) for day 30 days eliminated trigeminal neuralgia secondary to multiple sclerosis and refractory to other drugs[36].

With the purpose of seeking new therapeutic options against the use of opioids in orofacial pain, many cancer patients make autonomous use of *Cannabis sativa* for pain relief. In Canada, for example, 18% of patients reported the use of cannabis, and 46% used the plant for pain relief[37]. Another study achieved improved pain intensity via the Numerical Pain Scale and worse nausea and vomiting with the use of THC/CBD in the form of the drug Sativex compared to placebo, but no significant changes with THC administration alone or opioid reduction[38].

The use of nabiximols as an oromucosal spray has also been studied in the adjuvant therapy of patients with oncologic CP. Given the poor quality of life of cancer patients, scientific findings in meta-analysis justify the use of cannabinoids as a possibility of managing the adverse effects of nausea and vomiting from chemotherapy, also evidencing the therapeutic antiemetic efficacy of THC and dronabinol when compared to placebo and neuroleptics, in addition to reports in the improvement of appetite loss[39]. The synthetic cannabinoid also showed antiemetic properties, reducing the severity of nausea from 2.5 to 1.5 in the intervention group[40].

Regarding the association of orofacial pain with headache conditions, fibromyalgia, and emotional symptoms, one analysis has shown that from a sample of 145 patients treated with cannabis for three years, 60% of them reported a long-term reduction in headache frequency[41]. Another trial compared treatments between nabilone and ibuprofen, concluding that the former was more effective in reducing pain intensity and reducing painkiller use[42].

As for fibromyalgia, favorable signs were obtained in the parameters of the questionnaire applied to Israeli patients sampled and treated with medicinal cannabis, showing few adverse effects in this treatment[43]. Another observational, prospective study with patients from a medical cannabis clinic in Israel showed that gradually titrated cannabinoids appear to be a promising treatment, especially in situations where traditional pharmacological methods fail with low compliance rates[44].

A review of the literature conducted in 2020 observed that components of *Cannabis sativa*, especially CBD, also exert anxiolytic properties, thus proving an alternative for improving the quality of life of patients suffering from such comorbidity along with orofacial pain. However, although there are still no safety protocols that can structure the administration of cannabis in the treatment of anxiety disorders, the development of such evidence in further studies is important to support the possibility of therapeutic alternatives to benzodiazepines[45].

Integrative approach to cannabinoid therapy

The combination of different ways of activating the endocannabinoid system makes it possible to reduce the consumption of analgesics and improve the quality of life for patients with chronic orofacial pain. There are several natural ways to activate the endocannabinoid system, for example with the use of palmitoylethanolamide (PEA), curcumin, grape seed extract, aromatherapy, acupuncture, laser therapy, and physical exercise.

PEA is a fatty acid derivative produced in the body and is present in eggs, milk, peanuts, and soybeans with anti-inflammatory and

analgesic properties, among others. Its therapeutic effects involve the activation and desensitization of vanilloid receptor channels and transient receptor potential 1 (TRPV1), activation of peroxisome proliferator-activated receptor alpha (PPAR-α), of CR coupled to G protein 55 (GPR55) and G 119 (GPR119), and indirect activation of CR via inhibition of anandamide endocannabinoid (AEA) degradation[46].

In the TMJ, PEA was shown to be more effective than the anti-inflammatory drug ibuprofen in reducing pain and increasing mouth opening[47]. In cases of burning mouth syndrome, ultramicronized PEA was more effective than placebo[48] and, in a clinical case report, it promoted symptom improvement when combined with gabapentin[49]. The combination of PEA with cannabinoids potentiates the analgesic effect of cannabinoids[50], suggesting the possibility of using lower doses of cannabinoids.

Turmeric is the main source of the polyphenol curcumin, known for its analgesic and anti-inflammatory effect[51], including in some types of pain in the orofacial area[52]. Although it has a low bioavailability, the addition to piperine, the main active component of black pepper, it solves the problem. The peripheral analgesic effect of curcumin involves the activation of the endocannabinoid and opioid system[53]. It is possible that curcumin acts directly on opioid and cannabinoid receptors expressed on nociceptors, causing antinociception through the inhibition of neuronal excitability and/or increasing the release of endogenous endocannabinoids and opioids.

Grape seed extract contributes to the reduction of CP such as orofacial pain and migraine[54] due to its ability to activate the endocannabinoid system. Grape seed extract supplementation inhibits pain signaling in an experimental model of migraine via activation of central cannabinoid receptors[55]. However, more clinical studies are still needed to confirm the potential of grape seed extract in reducing chronic orofacial pain.

Aromatherapy has presented analgesic effects in migraine[56] and muscular TMD[57]. In practice, essential oils can be used topically while massaging the pain are and vaporized to be inhaled. One of the mechanisms involved in aromatherapy-induced pain reduction is the activation of the endocannabinoid system, as shown with the use of beta-carophyllene, which is a CB2 receptor agonist and a major component of *copaíba* oil[58], lavender essential oil[59] and *Cedrus atlantica* essential oil[60]. Thus, future studies may lead to the development of promising phytotherapic drugs for the treatment of conditions involving dysregulation of the endocannabinoid system, including orofacial pain.

Another way to activate the endocannabinoid system is through acupuncture. Acupuncture is an ancient Chinese treatment with numerous therapeutic benefits, including pain reduction[61]. There are mechanisms involving the activation of these endogenous analgesia systems[62], including the endocannabinoid system, as shown by both acupuncture[63] and electroacupuncture[64].

Scientific studies have reinforced the clinical recommendations for physical exercise since it prevents and reduces CP[65]. Physical exercise is a natural way of activating the endocannabinoid system as it increases endocannabinoid levels[66], which contributes to its hypoalgesic effect as shown in the orofacial neuropathic pain model of infraorbital nerve constriction[67].

CONCLUSION

Cannabinoids represent an important option for the control of chronic orofacial pain not only for their ability to reduce pain, but also to improve the quality of life of patients. Integrative treatment is undoubtedly the best way to go in the treatment of chronic pain in general, including orofacial pain.

Cannabinoid therapy is part of this integrative approach and the combination of cannabinoids with other forms of activation of the endocannabinoid system contributes to better therapeutic outcomes and improved quality of life for countless patients suffering from chronic orofacial pain. Considering that cannabinoids are relatively safe compared to other drugs used to control chronic orofacial pain, they should be included in the arsenal of the TMD and orofacial pain specialist as an effective adjunct treatment.

AUTHORS' CONTRIBUTIONS

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Conceptualization, Project Management, Methodology, Writing - Review and Editing, Supervision, Visualization
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