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Analgesic treatment in acute pain of odontogenic origin

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ABSTRACT

Pain is one of the main reason that compels patients to visit dentists. Poorly managed pain following treatment in the dental office can lead to patients lack of trust in the dentist, postponing or even avoiding dental treatments.
The physiopathology of pain is a complex process involving both the central nervous system and the peripheral nervous system, so the use of analgesics with different modes of action can lead to improved, faster and longer-lasting pain relief.
This article provides an overview of the mode of action, effectiveness and results obtained from studies in the literature related to the combination of ibuprofen and paracetamol in a single tablet.

Keywords: analgesic, paracetamol, ibuprofen

INTRODUCTION

It is well known that in dentistry, the reason patients get into the dental practice is often dental pain. The control of pain and associated inflammation is absolutely necessary to provide comfort to the patient during the treatment.

Dental and orofacial pain is always associated with subjective and objective clinical signs, which lead to the establishment of a diagnosis of certainty and the approach to therapeutic behavior, which can include, when necessary, an antibiotic medication associated with the anti-inflammatory and analgesic one.

Among the subjective signs, pain is the most common complaint. The quantification of pain in medical practice is "a tricky business": a difficult matter and difficult to obtain. It is, to the same extent, a particularly important aspect because it appears frequently in dental practice [1]. The weight derives from the fact that two aspects intervene in the description of the pain:

- the sensory component (perception of the painful sensation), which can be more easily expressed by parameters such as: location of pain, intensity, its spatial and temporal characteristics;
- the affective (emotional) component, which is given by the interpretation of the painful stimulus and which is extremely subject to countless variables: gender, age, previous painful experiences, level of education, behavioral patter, etc.

Pain in the oro-maxillofacial sphere has multiple causes, and the first important element in its management is the precise identification of the etiological factors. It can be the consequence of a pathological process or an untreated condition or it can appear as a consequence of a therapeutic medical intervention. The most common pains are those caused by pulpal and periapical inflammation or following surgical interventios such as: tooth extraction, removal of tumor formations, interventions after dentoalveolar or maxillar trauma, or the insertion of dental implants. Also, pain is frequently present after surgical periodontal therapy and is directly proportional to the the magnitude of tissue injury. The pathological mechanisms of pain and inflammation are different and their knowledge is essen-

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tial for a successful result. Thus, when it comes to dental surgery, an extremely important aspect arises, the purpose of the anti-inflammatory and analgesic medication being both to reduce the trauma of the tissues that have been traumatized, but most important to control the host's immunological defense phenomena that can affect the outcome, respectively reducing the risk of rejection of an inserted graft [2].

Another type of odontogenic pain that appeared with the large-scale use of composite resins as the material of choice for the loss of hard substance due to carious and non-carious etiology, is post-operative sensitivity/pain, which appears after a resin composite restoration is placed. This kind of painful sensitivity is not produced by inflammatory dental pulp phenomena. It is caused by the dentin directly exposed to stimuli from the external environment or by the microleakage between dentin and composite resin. Dentinal pain is triggered by the fluid movements within open dentinal tubules to the pulp where the A delta nerve fibers are activated [3]

In contrast, in the pulp inflammation process, neuropeptides intervene, with the role of neurotransmitters and neuromodulators: substance P, calcitonin gene related peptide (CGRP), neurokinin A.

In periapical inflammatory processes, which frequently trigger painful exacerbations, the immunological reactions are complex and include:

- an immediate immune response, which includes vasodilatation, increased vascular permeability and which is mediated by endogenous mediators (neuropeptides, prostaglandins, kinins);
- non-specific immune response, which includes the migration of macrophages, polymorphonuclear leukocytes(PMN), along with the appearance of substances with a role in bone resorption (cytokine). [4]

Pain following surgical dentomaxillary interventions, where tissue damage occurs, includes complex, immunological, hematological and metabolic mechanisms. The phenomena are triggered by the release of biomolecules damage-associated molecular patterns (DAMPs), which induce and control the inflammatory response.

Taking into account all these aspects, respectively the clinical situation, etiology, character and intensity of the pain in the oro-maxillo-facial sphere, the association of paracetamol and ibuprofen proved to be the most successful in the current practice for the management of subjective clinical signs.

Management of postoperative pain and inflammation is a critical component of patient care and is important in the most efficient use of medical resources [5].

Patients usually associate dental treatments with pain. As it was stated before, the pain has both a physiological and a psychological component so that the patients become more difficult to treat and consequently do not follow the indications given by the doctors. Odontogenic pain refers to pain initiated in the teeth or periodontal tissues, in the oral mucosa, jaw or mandible [6].

The standard model in the pharmaceutical industry for evaluating the effectiveness of analgesics against “everyday” pain is the use of randomized, double-blind clinical trials after third molar extraction [7].

Ibuprofen/paracetamol indications

Whether it is recommended for the relief of fever, muscle pain, joint pain, menstrual pain, toothache, as well as in the case of dental surgical procedures, from inserting implants to tooth extractions, after endodontic treatment, paracetamol and ibuprofen are the most indicated over-the-counter drugs for pain management.

Paracetamol (acetaminophen)

Also known as acetaminophen, it is classified as a general non-opioid analgesic used for mild to moderate pain, with a rapid analgesic and antipyretic effect. Although the mechanism of action is uncertain [8], it is considered to be a weak inhibitor of prostaglandin synthesis, so unlike non-steroidal anti-inflammatory drugs (NSAIDs) it has little anti-inflammatory action. It is generally safe for acute pain, although very large, single doses have been associated with hepatotoxicity [9].

Paracetamol 1000mg has been shown to be an effective treatment compared to placebo for extractions of impacted molars and other oral surgeries such as difficult extractions, alveolotomies, multiple extractions, biopsies, apical resections and gingival curettages [10].

A meta-analysis examining the effectiveness of acetaminophen 1000mg demonstrated that maximum effectiveness is recorded up to 4 hours after administration [11].

Paracetamol has proven to be an analgesic indicated for low-intensity pain, but its relatively low effect has limited its use as monotherapy in moderate or increased postoperative pain [12].

Ibuprofen

Ibuprofen belongs to the class of non-steroidal anti-inflammatory drugs (NSAIDs) and has the effect of inhibiting cyclooxygenase enzymes (COX-1 and COX-2) and the subsequent synthesis of prostaglandins and other related products at the peripheral level in damaged tissues [13]. This leads to a reduced sensitivity of the terminal branches of nociceptive nerves to mediators such as bradykinin, in addition to the fact that it inhibits the migration of activated leukocytes to the inflamed regions [14]. The antipyretic activity of ibuprofen is caused by

the central inhibition of prostaglandins at the level of the hypothalamus [15].

It has been shown that at doses of 400mg ibuprofen and 1000mg paracetamol, these being the most used doses in clinical practice, ibuprofen is superior to paracetamol in treating pain after a wisdom tooth extraction [16].

Ibuprofen and paracetamol combination analgesic therapy

The goal of combining analgesics with different mechanisms of action is to use lower doses of each drug component, thus improving analgesia and limiting the occurrence of adverse effects [12]. This can be achieved by simultaneously targeting different pain pathways [17] and increasing the area of action by combining a fast-acting, short-acting pain reliever (acetaminophen) for milder and slow-onset pain with a longer-acting pain reliever for more intense pain. Also, when used together, lower doses can be administered through the cumulative effect [18,19].

According to a study on patients with moderate to severe pain, including after wisdom tooth extraction, those who received ibuprofen and paracetamol together showed improved relief compared to patients who received ibuprofen or paracetamol alone [20]. These data support other studies that demonstrated the increased effectiveness of the combined administration of ibuprofen and paracetamol, especially in the treatment of postoperative pain [21-25].

As can be seen in Figure 1, the conclusions of a study emphasize those presented above by saying that a tablet containing 200mg paracetamol/500mg ibuprofen or 1000mg paracetamol/400mg ibuprofen has significantly more effective effects in relieving pain compared to the individual administration of each medicine with the same dose [26].

The association ibuprofen 400mg/paracetamol 1000mg related to:

- placebo was more effective throughout the 8-hour period;
- ibuprofen 400 mg more effective between 30-120 minutes and again at 240 minutes;
- paracetamol 1000mg more effective after 90 minutes;

The association of ibuprofen 200 mg/ paracetamol 500 mg compared to:

- placebo was more effective throughout the 8-hour period;
- ibuprofen 200 mg more effective throughout the period less than 480 min;
- ibuprofen 400 mg more effective between 15-120 minutes
- paracetamol 500 mg more effective for the entire duration of 8 hours;
- paracetamol 1000 mg more effective at 15 minutes and between 60 and 480 minutes [25].

Pharmacokinetics

Administered together, having different modes of action and similar therapeutic effects, ibuprofen

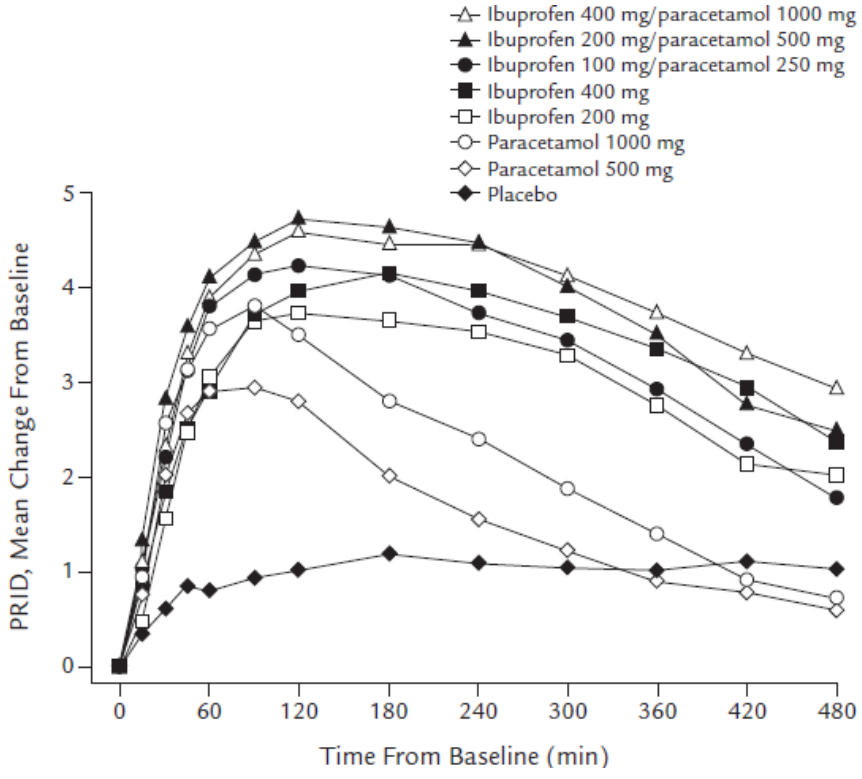

FIGURE 1. Mean changes in pain relief scores from baseline during the first 8 hours after surgical extraction of impacted molars [26]

and paracetamol can have increased effect in achieving improved analgesia compared to individual administration. Thus, the existence of a single tablet containing the ibuprofen/paracetamol combination in fixed doses offers an increased degree of compliance and comfort for patients, but limits the possibility of adjusting the dose according to needs.

A small study on the pharmacokinetic properties of co-administered ibuprofen and paracetamol found no significant change in the pharmacokinetic parameters of the two drugs [27]. The rate and volume of absorption of ibuprofen and paracetamol from the same tablet were considered bioequivalent to those of individual administration, however, the absorption rate of paracetamol was faster in the case of the tablet containing the two associated drugs compared to monotherapy administration [28].

Peak serum levels occur within 1 to 2 hours of administration for ibuprofen and between 30 minutes and 2 hours for paracetamol [29]. In the case of combining the two in a single tablet, the average plasma concentrations of ibuprofen and paracetamol were recorded faster and were higher compared to individual administration [28]. A clear relationship was observed between the plasma concentrations of ibuprofen [30] and paracetamol [31-33] and the degree of pain relief.

The absorption of the two was significantly delayed when the fixed-dose tablet containing both paracetamol and ibuprofen was administered postprandial compared to administration on an empty stomach [28].

No significant changes in hematological and biochemical parameters were observed and no clinically conclusive safety issues were identified during the administration of the tablet containing the two associated drugs [28].

Safety and possible side effects

According to a study [34], the most common adverse reactions in order of occurrence were: nausea (26.7%), vomiting (19.5%), headache (14.9%), dizziness (9.9%).

The same study claims that the prevalence of the need for the treatment of side effects was much lower in the case of administration of one or two tablets containing ibuprofen and paracetamol (24.9% and 18.5%) compared to the administration of two ibuprofen/codeine tablets (34,9%), paracetamol/codeine (39.8%) or placebo (38.2%).

The adverse reaction reporting rates were 5.8% in the case of administration of a single tablet and 4.8% in the case of administration of two tablets.

The administration of the combination of ibuprofen and paracetamol is contraindicated in patients with a history of hypersensitivity to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs), gastric ulcer, coagulation defects, severe renal, hepatic or cardiac insufficiency and in patients who have concomitant treatment with other drugs that contain paracetamol, aspirin or non-steroidal anti-inflammatory drugs (NSAIDs).

Drug interactions

The possible drug interactions between the tablet containing ibuprofen and associated paracetamol and other medicinal products can be found in Table 1 [15].

TABLE 1.

Drug	Possible interaction
Antihypertensives	Decreases antihypertensive efficacy
Antiplatelet agents	Increase the risk of gastrointestinal bleeding
Chloramphenicol	Increase plasma chloramphenicol concentration
Corticosteroids	Increase the risk of gastrointestinal bleeding
Cyclosporin	Increase the risk of nephrotoxicity
Diuretics	Diuretic effect decreases
Metoclopramide	Increase the absorption of paracetamol
Lithium	Decrease the elimination of lithium
Methotrexate	Decrease the elimination of methotrexate
Quinolones	The risk of convulsions increases
Selective serotonin reuptake inhibitors	Increase the risk of gastrointestinal bleeding
Tacrolimus	Increase the risk of nephrotoxicity
Warfarina, anticoagulants	Increase the anticoagulant effect

CONCLUSIONS

Firstly, the existence of a single tablet containing both active substances, ibuprofen, respectively acetaminophen, increases the degree of compliance of patients for the prescribed treatments, with a decrease of overdose. We are talking about a single tablet administration which combines two different mechanism for pain control, thus offering an increased patient comfort and reducing recovery time after dental treatments.

Secondly, the findings of the countless studies cited above support an increased effectiveness of this tablet in treating pain compared to monotherapy treatments with paracetamol and/or ibuprofen, with a faster and also longer-lasting effect. Also combining two different modes of action against pain in one drug results in a wide range of action, efficient in severe pain even at lower doses.

Finally, an extremely large number of scientific and clinical studies has found no evidence that the administration of ibuprofen and paracetamol in a single tablet has more side effects than separate administration of these drugs.

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