Comparative analysis of preemptive analgesic effect of dexamethasone and diclofenac following third molar surgery

José Leonardo Simone
Waldyr Antonio Jorge
Anna Carolina Ratto Tempestini Horliana
Talita Girio Canaval
Isabel Peixoto Tortamano

Department of Stomatology, Discipline of Integrated Clinical Dentistry, School of Dentistry, Univ de São Paulo - USP, São Paulo, SP, Brazil.

Abstract: The objective of the study was to compare the analgesic effectiveness of dexamethasone and diclofenac sodium administered preemptively after surgical removal of third molars. Forty-four ASA (American Society of Anesthesiologists) I patients (19 men, 35 women; 16–28 years old) randomly and double-blindly received diclofenac sodium (50 mg) or dexamethasone (8 mg) or placebo 1 h before surgery. Intensity of pain, measured with a visual analog scale (VAS), was the variable studied at different postoperative times (1 h, 2 h, 3 h, 6 h, 8 h, 12 h, 48 h, 4 d and 7 d). The total amount of rescue medication (TARM) ingested (paracetamol) was another variable of the study. The Kruskal-Wallis statistical test was used. A p value of $< .05$ was adopted to reject the null hypothesis. The dexamethasone group showed lower pain intensity ($p < .05$) than the diclofenac sodium and placebo groups ($p < .05$). No difference in TARM was observed among the groups ($p < .05$). Preemptively administered, dexamethasone was effective in controlling postoperative pain.

Descriptors: Surgery, Oral; Pain; Randomized Controlled Trial; Pain, Postoperative.

Introduction

Preemptive analgesia, also called preoperative analgesia, has been studied ever since the beginning of the 20th century as a way of reducing or preventing the production of mediators responsible for nervous stimulation. It is characterized as an antinociceptive treatment for the prevention of central changes induced by afferent sensitization due to tissue injury caused by surgical procedures. The preemptive analgesia concept was based on a series of successful experimental trials performed with animals, which showed central nervous system plasticity and post-nociceptive sensitization.[1] Preemptive analgesia is defined as an antinociceptive treatment used to prevent central changes that amplify postoperative pain. Because preemptive analgesia reduces the processing of central sensorial changes, it is ideal to reduce the incidence of pain resulting from post-surgery hyperalgesia. Preemptive analgesia is a pathophysiological phenomenon desirable to prevent the processing of sensorial changes. However, controversy remains about whether preemptive versus conventional analgesic intervention is more effective to control postoperative pain.[2-5] It is known that tissue injury leads to the release of chemical mediators, including histamine, serotonin, kinins, and prostaglandins,

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Corresponding Author:
José Leonardo Simone
E-mail: *jlsimone@usp.br*

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directly related to the inception and evolution of algic and inflammatory processes. Inflammatory response is intrinsic to the tissue repairing process. However, its influence can be negative when the response is too intense. Therefore, inflammatory response intensity should be kept under control in certain clinical situations to promote quicker healing with less discomfort to the patient.

Postoperative pain due to surgical removal of third molars causes much discomfort to the patient. Therefore, it should be minimized as much as possible by adequate surgical techniques and analgesic and anti-inflammatory drugs.[6] Anti-inflammatory drugs with peripheral analgesic action are divided into steroidal (SAID), so called for being analogous to hormones produced by the adrenal glands, and non-steroidal anti-inflammatory drugs (NSAID), which include many drugs that inhibit cyclooxygenase enzyme activity. Both of these groups of drugs act by inhibiting the same chain reactions that degrade phospholipids released by cell membranes injured by surgical trauma, leading to the production of important pro-inflammatory mediators.[7] When the levels of these mediators were compared after ingestion of SAID and NSAID and placebo, it was observed that both of these anti-inflammatory drugs reduce the levels of prostaglandin E_2, and are effective in controlling inflammation and postoperative pain.[8] For these reasons, researchers have been focusing on alternatives to prevent postoperative pain, by testing different medications and routes of administration.[9-11] With this in mind, the purpose of this study was to assess the analgesic efficiency of dexamethasone (8 mg) and diclofenac sodium (50 mg) comparatively in patients submitted to third molar removal, according to a visual analog scale (VAS), by counting the amount of analgesics ingested in the preoperative period.

Methodology

This randomized, double-blind, parallel, placebo-controlled study was approved by the local ethics committee (# 124/2009), and is also in compliance with the Helsinki Declaration. All participants included in this study signed a free and informed consent form and underwent surgery during sessions that were part of the Oral and Maxillofacial Surgery and Trauma specialization course at the Foundation for the Scientific and Technological Development of Dentistry (*Fundação para o Desenvolvimento Científico e Tecnológico da Odontologia* - FUNDECTO). All patients [n = 54; both genders; 16–28 years old; ASA (American Society of Anesthesiologists) I] were indicated for extraction of unerupted or partially erupted third molars. Patients allergic to medications used in the study, with a history of pericoronitis, local or systemic infection and hepatotoxicity, as well as smokers, pregnant or lactating women, or patients who took analgesics or anti-inflammatory drugs within one week before surgery were excluded. One hour before surgery, the patients randomly (1:1:1) and double-blindly received single oral doses of diclofenac sodium (50 mg), dexamethasone (8 mg)[12] or placebo. The randomization was calculated using the Microsoft Excel program by a volunteer not participating in the experiments or the statistical analysis. The drugs were prepared in the Buenos Ayres Pharmacy (São Paulo, Brazil). Medications were packed in amber envelopes and letter-coded for later identification. All procedures, medications and surgical techniques were applied identically on both sides of the mouth. The primary outcome variable (postoperative pain) was measured by VAS-based pain scores assigned to the postoperative periods (1 h, 2 h, 3 h, 6 h, 8 h, 12 h, 24 h, and 48 h, 4 d and 7 d) and registered on a specific form. In the event of severe pain, patients were advised to use medication, such as rescue analgesics (paracetamol, 500 mg, single dose, 1000 mg; 1 dose = 2 tablets), and were instructed to take 2 tablets (1 g) every 6 hours for pain relief, but only if necessary (maximum daily dose = 4 mg/day); the medication was provided to the patient. This routine was registered on a postoperative clinical record, which was provided to the patient. The total amount of rescue medication (paracetamol) was the second outcome variable. All assessments of interventions to participants were performed by the same researcher, who was blinded to the medications used (F.L.D).

Regarding statistical analysis, the non-parametric Kruskal-Wallis test for one-factor analysis of

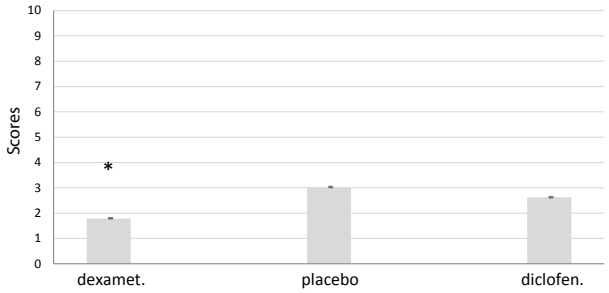

Figure 1 - Mean of pain scores for each medication administered during the entire evaluation period (*$p_{[KW]}$ = .0003; significant statistical difference).

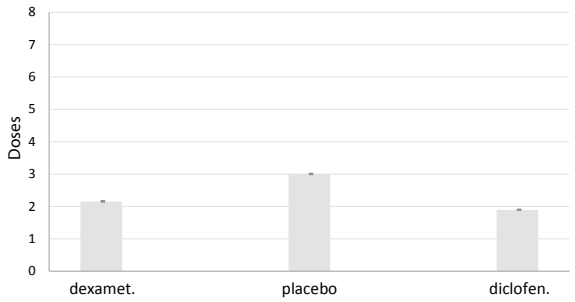

Figure 3 - Mean of rescue medication doses for each medication used during the entire evaluation period ($p_{[KW]}$ = .6005; non-significant statistical difference).

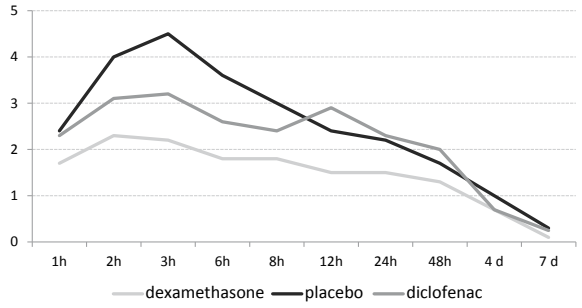

Figure 2 - Mean and standard deviation (SD) of pain scores for each time point evaluated (1 h, 2 h, 3 h, 6 h, 8 h, 12 h, 24 h, 48 h, 4 d and 7 d) according to the medication used (non-significant statistical difference in the times analyzed).

Table 1 - Description of the sample.

Medications	*n*	Men	Women	Mean age ± SD
Dexamethasone	20	6	14	-
Placebo	14	4	10	-
Diclofenac	20	9	11	-
Total	54	19	35	22 ± 3.6

n: number of subjects. SD: standard deviation.

Table 2 - Mean and standard deviation (SD) of medication doses of paracetamol used in each group during the total postoperative period assessed.

Medications	Mean	SD (±)
Dexamethasone	2.1	3.4
Placebo	3.0	4.0
Diclofenac	1.7	2.7

variance (SPSS 8.0 for Windows, 1997; SPSS Inc., Chicago, USA) was used to assess the primary and the secondary outcome variable. A p value < .05 was used to reject the null hypothesis. Results were expressed as mean ± standard deviation (SD). The desired sample size of a minimum of 17 patients was based on the results of our pilot study and was calculated to provide 90% effective representation (α = 0.05).

Results

Demographic data, gender and mean age of the sample of patients (*n*) studied in each group, may be found in Table 1.

Five patients were excluded because they did not follow the protocol strictly, and seven, because of the excessive duration of the surgery on one side of their mouth. This left a total of 54 patients who were analyzed to assess the primary and secondary outcomes under study. The mean values of the pain scores for each medication administered during the entire period evaluated are shown in Figure 1. Pain intensity reported in the post-operatory periods (1 h, 2 h, 3 h, 6 h, 8 h, 12 h, 24 h, 48 h, 4 d and 7 d) is shown in Figure 2. The mean value of pain scores for each medication (dexamethasone, diclofenac and placebo) was calculated and statistically analyzed as a function of time. No significant statistical difference was found in the times analyzed. The mean value of the rescue medication doses for each medication administered during the entire period evaluated is shown in Figure 3 and Table 2. Multiple comparisons (Dunn method) were made and no difference between mean values of the pain scores

was observed when using dexamethasone and placebo ($p < .05$) and dexamethasone and diclofenac ($p < .05$).

Discussion

The mechanism of action of analgesic and anti-inflammatory drugs seems to be well understood. Both steroidal and non-steroidal analgesic drugs act by inhibiting the same chain reactions that degrade phospholipids of injured cell membranes, responsible for the algic and inflammatory response.[13-15] Insofar as pain and inflammation are consequences of the release of chemical mediators produced after tissue trauma, it would be reasonable to conclude that preemptive medication contributes to lowering the concentration of these mediators in tissue, considering that the presence of the drug in the blood stream inhibits their initial production. As a result, the lower the tissue concentration of these mediators, the weaker the algic and inflammatory response. For these reasons, the preemptive approach has became widely discussed.[1-3,5,11,16-19] However, results of some studies are controversial.[2-5]

When the preemptive analgesic effectiveness of dexamethasone (SAID) and diclofenac (NSAID) are compared through the mean pain scores during the first 72 h, it can be observed that the group treated with dexamethasone showed the lowest values on the analog pain scale (1.7), followed by the groups treated with diclofenac (2.6) and placebo, which obtained the highest mean value (3.0) among the groups. Differences between these mean values are statistically significant when dexamethasone and placebo ($p < .05$) is compared with dexamethasone and diclofenac ($p < .05$) (Figure 1). These results show that dexamethasone was more effective in controlling pain during the period studied. The better performance of dexamethasone compared with diclofenac can be attributed to the mechanism of action of these drugs. Dexamethasone prevents hyperalgesia through phospholipase A_2 and inducible cyclooxygenase inhibition.[20] Diclofenac acts directly on ongoing inflammatory hypersensitization. These analgesics restore the nociceptor by stimulating the arginine/NO/cGMP/K(ATP) channel pathway.[20]

Evolution of postoperative pain over time (7 days) for the three groups showed that the highest mean pain scores were registered 3 h after the end of surgery in the placebo and diclofenac groups. The dexamethasone group showed the highest mean pain score in the 2nd hour after surgery, but with values very similar to those observed in the 3rd hour. The longitudinal evolution of postoperative pain was similar in the three groups during the entire evaluation period. However, the values for the placebo group were significantly higher than those for the dexamethasone and diclofenac groups. Evolution of postoperative pain during the evaluation period showed that the pain levels for the three groups were very similar in the 1st hour after surgery. This finding could be explained by a remaining anesthetic effect. In this study, the algic peak was obtained in the 2nd or 3rd hour after surgery. Two factors must be considered to explain this behavior:

1. end of the anesthetic effect, and
2. higher nociceptive sensitivity due to the short time elapsed after surgical trauma, which leads to a higher concentration of chemical mediators responsible for local nervous sensitization.

During our evaluation period, the evolution of postoperative pain proved similar to that found in the literature.[17] However, some authors[13] reported an algic peak around the 5th hour after surgery. This could be explained by the action of the anesthetic agent used to perform the nerve blockage. The mean time of action of lidocaine (2%) with epinephrine (1:100,000), used in this study, and of mepivacaine are lower than that of articaine.[13] Therefore, extending the anesthetic effect was a determinant in shifting the algic peak, as observed in this study.

A comparison between the quantities of rescue medication (paracetamol) consumed by the groups shows that consumption of paracetamol by the placebo group was greater than its consumption by the other groups during the entire evaluation period. A comparison between the dexamethasone and diclofenac groups showed very similar evolution, with slightly higher values for the dexamethasone group. Although no difference between the groups was observed, the highest consumption of rescue medica-

tion by the placebo group indicates that higher levels of pain occurred in this group (Figure 1). The experimental models observed in the literature[21-23] have methodological differences, mainly regarding the drugs administered. The authors studying these models used a combination of steroidal and non-steroidal drugs, and compared their effectiveness with the drugs administered singly. Conversely, the analgesic effectiveness of steroidal and non-steroidal drugs administered singly was compared in the present study. According to the literature, associations are more effective in controlling pain before surgery. Although higher effectiveness has been reported with associations, statistical differences have been non-significant.

Conclusion

Preoperative dexamethasone (8 mg, orally) administered separately is effective in controlling postoperative pain.

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