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Effects of co-administered dexamethasone and nimesulide on pain, swelling, and trismus following third molar surgery: a randomized, triple-blind, controlled clinical trial

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Abstract. This study aimed to determine the effect of the co-administration of dexamethasone 8 mg and nimesulide 100 mg given 1 h before mandibular third molar surgery. A prospective, randomized, triple-blind, split-mouth clinical trial was developed at the study institution in Pernambuco, Brazil. A pilot study was first performed (95% confidence interval, 80% test power, and 5% error), and a sample of 40 patients aged between 18 and 40 years was selected. The patients were randomized and divided into two groups: dexamethasone + placebo and dexamethasone + nimesulide. The following parameters were evaluated: pain (visual analogue scale), total number of rescue analgesics taken, time taken to first rescue analgesic consumption, oedema, trismus, and patient satisfaction. The paired *t*-test and the Wilcoxon test were used to compare means. Statistically significant differences were found between the groups in pain values at 2, 4, and 12 h postoperative, and in the total number of rescue analgesics and time taken to first rescue analgesic ingestion ($P < 0.05$), with results in favour of dexamethasone + nimesulide administration. Oedema and trismus were similar in the two treatment groups and decreased over time postoperatively. The co-administration of dexamethasone and nimesulide reduces pain intensity and the need for rescue medication after third molar surgery.

Key words: third molar; pain; oedema; trismus; anti-inflammatory agents.

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Pain, swelling, and trismus are complications resulting from the inflammatory processes that often occur after third molar surgery. These complications may compromise quality of life and thus impair the patient's ability to perform their daily activities.[1,2] The pre-emptive administration of non-steroidal anti-inflammatory drugs (NSAIDs) and anti-inflammatory steroids is recommended for the purpose of minimizing the inflammatory response.[2,3]

Corticosteroids act by increasing lipocortin synthesis. Lipocortin inhibits phospholipase A2 and consequently the formation of arachidonic acid from the phospholipids that originate in cell membranes. This action results in a decreased production of inflammatory mediators such as leukotrienes, prostacyclins, prostaglandins, and thromboxane A2.[4] The diverse effects of corticosteroids depend on the dosage and duration of administration. Prolonged use can delay healing and increase susceptibility to infection. These adverse effects are rare in therapies using a single short duration dose.[5]

The corticosteroid dexamethasone has an effective anti-inflammatory mechanism of action and a prolonged half life. The literature reports several protocols for the administration of dexamethasone in third molar surgery.[6] A recent study by Alcântara et al. showed an oral dose of 8 mg dexamethasone to be more effective than 40 mg methylprednisolone in minimizing swelling and trismus, but no statistical difference was found with respect to pain.[7]

NSAIDs have a therapeutic effect through cyclooxygenase (COX); they also inhibit the production of prostaglandins that interact synergistically with other inflammatory mediators promoting inflammatory reactions and hyperalgesia.[8] Nimesulide is a selective COX-2 inhibitor that has analgesic, anti-pyretic, and anti-inflammatory properties. When compared to conventional NSAIDs, it is well-tolerated and causes fewer adverse gastrointestinal effects. Nimesulide does not promote blood disorders or significant coagulation effects when administered at a daily dose of 200 mg. More than 200 clinical studies including approximately 90,000 patients have shown nimesulide to be effective in the treatment of inflammatory conditions and acute pain. This drug has a rapid analgesic effect onset (15 min) and is, therefore, a viable option when rapid pain relief is necessary.[9,10]

The pre-emptive co-administration of NSAIDs and corticosteroids in oral surgery has been employed in order to prevent and minimize postoperative sequelae. The synergy of the different mechanisms of action of these drugs may have greater benefits with regard to pain, swelling, and trismus, as compared to their isolated administration.[11] The combination of a prolonged half-life corticosteroid (dexamethasone) and a fast-acting anti-inflammatory analgesic (nimesulide) represents an ideal therapy for the reduction of postoperative pain, swelling, and trismus. However, there is a lack of published studies evaluating the efficacy of the pre-emptive oral administration of 8 mg dexamethasone associated with 100 mg nimesulide.

The aim of this study was to compare the postoperative effects (pain, swelling, trismus, and overall evaluation) of the pre-emptive use of oral dexamethasone 8 mg co-administered with oral nimesulide 100 mg in third molar surgery.

Materials and methods

Study design and sample

A randomized, triple-blind, split-mouth design clinical trial was performed in the oral and maxillofacial surgery department of a university dental school in Pernambuco State, Brazil. The study was approved by the human research ethics committee of the study institution and was performed between January and September 2014.

The researchers followed the requirements for the performance of clinical trials based on the Consolidated Standards of Reporting Trials (CONSORT) statement. After reading an informed consent agreement form, all patients agreed to participate and signed the document. Forty patients aged 18–40 years were selected for the study and underwent the removal of two mandibular third molars, which had to be symmetrically positioned.

The following inclusion criteria were applied: ASA 1 status (American Society of Anesthesiology classification; a healthy patient with no systemic disease and not on continuous medication); similar root formation characteristics, position, and degree of impaction for both mandibular third molars; absence of pericoronitis during the last 30 days; no signs of inflammation. Exclusion criteria encompassed patients who refused to participate after reading the informed consent form, those who were allergic to any of the drugs used in the study, smokers, pregnant or breast-feeding women, and patients on medication that could interact with the drugs in the study. Patients who did not attend the second surgery, proved intolerant to the drug regimen, or were unable to follow the study protocol were also excluded, as were those whose surgical time exceeded 40 min and those who presented a postoperative infection.

A preoperative clinical form was completed after careful clinical examination. The following information was collected: age, sex, oral condition, general condition, blood count, platelet count, international normalized ratio (INR), and fasting glycaemia. Panoramic radiography was used to determine tooth position according to the Pell and Gregory classification, as well as root formation characteristics and the degree of impaction. The two surgeries were performed in two separate clinical sessions with a 3-week interval.[2,12] The drugs were administered 1 h before surgery: dexamethasone + placebo (group A), or dexamethasone + nimesulide (group B).

The use of antibiotics prior to surgery was not recommended. Patients were given 500 mg dipyrone as a rescue analgesic,[13,14] one capsule orally every 6 h, or when they felt discomfort corresponding to a score of 3 on the visual analogue scale (VAS) for pain.[15] Chlorhexidine-based mouthwash (0.12%) was also prescribed, for use three times a day for 7 days, starting 24 h after surgery.

Pilot study and sample size determination

Ten patients were selected to undergo 20 third molar removal surgeries in order to determine the sample size for the study. The following parameters were used: 95% confidence interval, 80% test power, and 5% error. The variable 'pain' showed a mean difference between groups of 0.57 with a standard deviation of 1.26. On the basis of these values, a minimum sample size of 40 patients was calculated to be required.

Blinding

Patients eligible to participate in the study were invited into a room by an assistant investigator (S.Q.A), where envelopes containing details of the treatment allocation were opened. These envelopes were sealed, opaque, sequentially numbered, and contained the combination of drugs to be administered and the side to be operated on. Once the envelope was open, the assistant researcher entered this information on a standardized spreadsheet. Subsequently, the assistant informed the principal researcher (J.C.B) and surgeon (R.J.H) of the side to be operated on and provided the drugs for each patient 1 h

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