Pain control with dexamethasone, etoricoxib or ibuprofen associated with arginine in impacted third molar surgery

Analgesia pós-operatória em exodontias de terceiros molares mandibulares inclusos: estudo comparativo com dexametasona, etoricoxibe e ibuprofeno associado à arginina

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ABSTRACT

Objective
The aim of this study was to perform a comparative evaluation of postoperative analgesia associated with ibuprofen arginine, etoricoxib and dexamethasone in bilateral extractions of mandibular third molars.

Methods
TFourty two volunteers (12 men and 30 women), took part in this randomized, blinded, parallel, clinical trial and were divided into 4 groups: group 1, who received 600mg of ibuprofen and 555mg of arginine, G2, treated with 90 mg etoricoxib, G3, receiving 8 mg dexamethasone and G4, treated with a placebo, administered orally 90 minutes prior to surgery. Pain intensity was assessed using a 101 point numerical scale (101P) and a 4-point verbal scale (VRS) after 2, 4, 6, 8, 12, 24, 36 and 48 hours. For the statistical analysis of the data,the Kruskal-Wallis test was employed (p≤0.05).

Results
The results showed that volunteers in G4 exhibitedmore pain than the other groups, at 4 and 12 hours. The G3 showed higher pain intensity than G2 at 2 hours via the VRS and at 6 hours with the 101P, and in comparison with G1 after 4 and 6 hours with the 101P. There was a statistical difference between G4 and G3 and between G4 and G2 when comparingthe consumption of pain relievers.

Conclusion
Conclusion: It was concluded that all the drugs evaluated promoted postoperative analgesia when compared to the placebo. The analgesic consumption is lower when employing etoricoxib or dexamethasone. This work filed inthe Clinical Trials Registerunder no.U1111-1129-1722.

***Indexing terms**: Anti-inflammatory agents. Molar third. Tooth extraction.*

RESUMO

Objetivo
Avaliar, de forma comparativa, a analgesia pós-operatória com o ibuprofeno associado à arginina, etoricoxibe e dexametasona, em exodontias bilaterais de terceiros molares inferiores inclusos.

Métodos
Tomaram parte deste estudo clínico randomizado, paralelo e cego 42 voluntários (12 homens e 30 mulheres), que foram divididos em 4 grupos: grupo 1, que receberam 600mg de ibuprofeno e 555 mg de arginina; grupo 2, tratados com 90 mg de etoricoxibe; grupo 3, que receberam 8 mg de dexametasona e o grupo 4, tratados com placebo, administrados por via oral, 90 minutos antes da cirurgia. A intensidade da dor foi avaliada por meio de uma escala numérica de 101 pontos (101P) e de uma escala verbal de 4 pontos (VRS), após 2, 4, 6, 8, 12, 24, 36 e 48 horas. Na análise estatística dos dados foi empregado o teste de Kruskall-Wallis (p≤ 0,05).

Resultados
Os resultados mostraram que os voluntários do grupo 4 acusaram maior intensidade de dor do que os demais grupos, nos períodos de 4 e 12 horas. O grupo 3 apresentou maior intensidade de dor do que grupo 2 no tempo de 2 horas pela escala verbal de 4 pontos e após 6 horas pela escala numérica de 101 pontos, e em relação ao grupo 1 após 4 e 6 horas pela escala numérica de 101 pontos. Houve diferença estatística entre grupo 4 e grupo 3, e entre grupo 4 e grupo 2 na comparação do consumo de analgésicos de resgate.

Conclusão
Concluiu-se que todos os fármacos avaliados promoveram analgesia pós-operatória se comparados ao placebo. O consumo de analgésicos é menor quando se emprega o etoricoxibe ou a dexametasona. Registro de Ensaios Clínicos: U1111-1129-1722.

Termo de indexação: Anti-inflamatórios. Dente serotino. Extração dentária.

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INTRODUCTION

Extractions of impacted mandibular third molars generally cause patients discomfort, making it difficult for them to cope with their normal routines. The postoperative phase is characterized by signs and symptoms such as pain, edema, restricted opening of the mouth and potential loss of function, due to the inflammatory response to the surgery[1]. This inflammatory response, however, is often excessive, more accentuated than is required for the tissue repair process.

Pain, edema and the control of anxiety in patients are probably the biggest concerns for the dental surgeon when planning the extraction of impacted mandibular third molars[2]. It is necessary, therefore, for the professional to establish a medication protocol to minimize these concerns[3].

Preemptive analgesia is one concept that has aroused a lot of interest recently, and is the subject of research studies in the fields of medicine and dentistry. It is defined as an analgesic regimen which begins before the noxious stimulus, with the aim of preventing hyperalgesia,and the consequent stimulus which amplifies the pain. It differs from the regimen of preventive analgesia, when the analgesic medication is introduced after tissue trauma resulting from surgery, though prior to the commencement of the painful sensation, after the effects of the local anesthetic have worn off[4].

In a randomized, double-blind, placebo-controlled study of 498 patients submitted to third molar surgery, the pure form of ibuprofen (200 mg or 400 mg) was compared to ibuprofen (200 mg or 400 mg) combined with arginine, and it was demonstrated that the ibuprofen/arginine combination provided a faster analgesic effect (28 minutes for 200 mg and 29 minutes for 400mg) when compared with ibuprofen by itself (52 minutes with 200mg and 44 minutes with 400mg)[5].

In a separate clinical study, using the model of a bilateral extraction of impacted mandibular third molars, on 50 patients, it was concluded that an8mg dose of dexamethasone, administered 2 hours prior to the surgical procedure, significantly reduces postoperative pain and edema, when compared to the placebo group[6].

Dexamethasone is quite widely used to minimize pain, and principally edema, after third molar extractions. Despite this, researchers have suggested further studies using Prostaglandin-endoperoxide synthase-2 (COX-2) selective inhibitors for oral surgery[7-8]. A number of authors have stated that corticosteroids should be used for extractions that require osteotomy or in procedures that cause considerable tissue trauma, as for the majority of patients, oral medication is convenient, economical and a safe way of administering this medication[9].

Etoricoxib is a COX-2 selective inhibitor anti-inflammatory drug which has been shown to be effective in treating pain, having a rapid response and prolonged effect. When comparing etoricoxib doses of 60mg, 120mg, 180mg and 240mg, the conclusion was reached that the lowest dose for obtaining maximum effectiveness in the control of post-extraction pain was 120mg[10]. Other authors compared the use of a pre-operative120 mg dose of etoricoxib prior to the extraction of mandibular third molars and a 4mg dose of dexamethasone. These authors found that both are effective in controlling postoperative pain and that there was no statistical difference between the two groups[11].

Researchers have pointed out that in single-dose situations, the COX-2 selective inhibitors demonstrated a longer duration of analgesic action when compared to ibuprofen[12].

In yet another trial which compared the effectiveness of celecoxib and dexamethasone in the prevention and control of postoperative pain in periodontal surgery, the authors recommend further studies on the subject, employing the model of the bilateral extraction of impacted mandibular thirdmolars[13].

In the literature, different medication protocol scan be found for controlling pain and edema after the extraction of impacted mandibular third molars[1,10-14-16], however there is still no consensus on the topic. So the present study proposed to test if anti-inflammatory drugs of different groups (one corticosteroid, one COX-2 selective non-steroidal anti-inflammatory drug and one non-selective combined with arginine), promote postoperative analgesia with this type of surgery.

METHODS

In this randomized, parallel and blind clinical study, a total of 42 volunteers was selected from both sexes (12 men and 30 women), aged between 18 and 43, who were cared for in the dental clinic at the integrated faculties of the Campos Gerais Higher Education Center (CESCAGE), referred for the removal of impacted mandibular third molars, after anamnesis, physical examination and X-ray. The stratification was carried out according to the position

of the third molar using the Pell & Gregory[17] and Winter[18] classifications.

The exclusion criteria were as follows: chronic use of painkillers, anti-inflammatory, anticoagulant orantiplatelet drugs during the previous 6 months, pregnant or lactating women, or those who presented with an existing clinical condition of pericoronitis, diabetes mellitus, a history of gastritis orgastrointestinal ulcers, high blood pressure, renal alterations or allergy to any of the drugs used in the study.

The patients were divided into 4 groups (G): G1 (n=10) which received 600 mg of ibuprofen together with 555mg of arginine, G2 (n=9) which received 90 mg of etoricoxib, G3 (n=10) which received 8 mg of dexamethasone and G4 which received a placebo (n=13), all of which were administered orally 90 minutes before surgery. The intensity of postoperative pain was evaluated using a numeric scale of 101 points (101P) and a separate 4-point verbal scale (VRS), at 2, 4, 6, 8, 12, 24, 36 and 48 hours after the procedure.

The drugs were removed from their original commercial packaging and were packed in similar packages, but called: A, B, C and D. After selecting the volunteers, they received an identification number. In order to preserve anonymity, a second researcher delivered the packs to the research study subjects and monitored the correct use of the medication.

A solution of mepivacaine 2% with epinephrine 1:100.000 (mean = 3.53; standard deviation = +2.47) was used for the local anesthetic. After extraction, all patients received 750 mg tablets of the pain reliever paracetamol, to be taken every 6 hours in the event of pain, and the patient was to mark on the record card the times that it was necessary to use them.

A pain-scale card (VRS and 101P) was handed out to the volunteers on the day of the surgery and this was returned at the next checkup for the removal of sutures and preservation. For the 4-point verbal scale, the patient was instructed to mark a number between 0 and 100 to indicate how intense the pain was at that moment, 0 signifying no pain and 100 equating to intolerable pain. On the verbal scale, the patient noted how he was feeling at that point in time (no pain, slight pain, moderate pain or severe pain). The data were processed statistically using the Kruskall-Wallis and Mann Whitney tests was set at 5% ($p<0.05$).

This study was approved by the Ethics in Research Committee at the State University of Ponta Grossa (Record no. 16272/09).

RESULTS

The data obtained using the 101 point scale (Figure1) show that the volunteers in all the groups reported some intensity of pain, at all the points in time evaluated. Four hours after extraction, there was a statistically significant difference in relation to the placebo group (G4=60.3) when compared to the other groups (G1=13; G2=18.8; G3=35). In the six-hour period there was a statistically significant difference between G2 (13.3) and G3 (36.5) and between G1 (8.0) and G3 (36.5). As far as the period of 12 hours was concerned, there was a statistically significant difference between G4 (24.2) and G2(3.3) and between G4 (24.2) and G1(9.2).

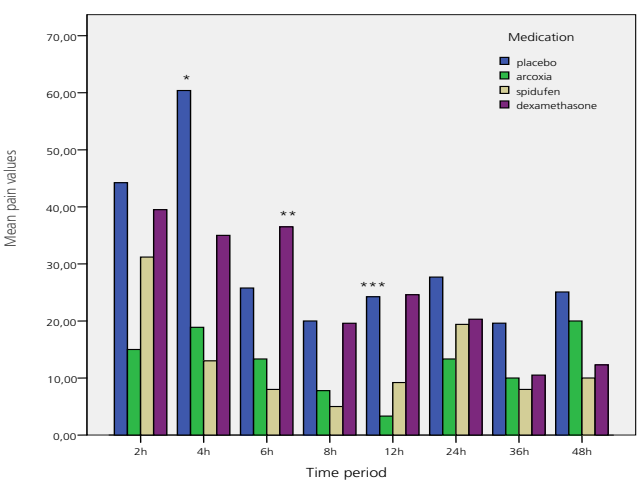

Figure 1. Mean of pain values noted on the 101 pointscale, by time interval.
NB* Statistically significant in relation to the other groups; ** Statistically significant between dexamethasone and Arcoxia and between dexamethasone and Spidufen; *** Statistically significant between placebo and Arcoxia and between placebo and Spidufen.

Figure 2 shows the mean value of the volunteers' pain when the 4-point verbal scale was used. Two hours after extraction, there was found to be a statistically significant difference between G2 (2.0) and G4 (3.0) and between G2 (2.0) and G3 (2.8). At 4 hours there was a statistically significant difference between G4 (3.5) in relation to the other groups (G1=1.6; G2=2.1; G3=2.4). At12 hours, a statistically significant difference was found between G4 (2.0) and G2(1.1) and between G4 (2.0) and G1(1.5).

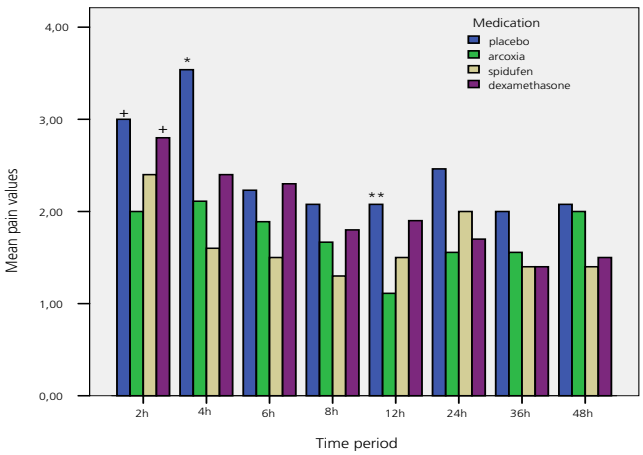

Figure 2. Mean of pain values noted on the 4-point verbal scale, by time interval. NB* Statistically significant in relation to the other groups; ** Statistically significant between placebo and Arcoxia and between placebo and Spidufen; + Statistically significant between Arcoxia and placebo and between Arcoxia and dexamethasone.

In Figure 3, the mean value of the pain relievers can be seen for each group, in which a statistically significant difference was observed between G4 (3.7) and G2(1.5) and between G4 (3.7) and G3(1.9).

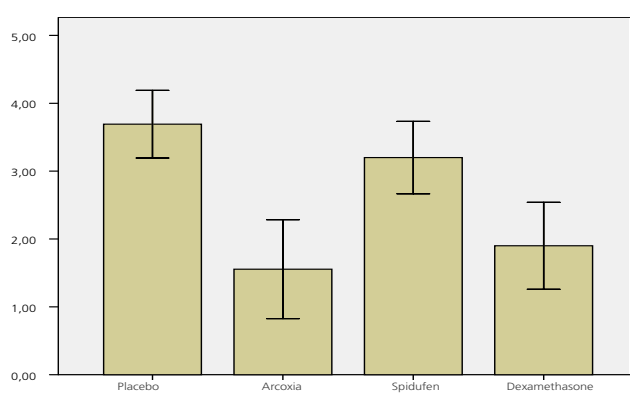

Figure 3. Mean value of pain relievers for each group. NB* Statistically significant between placebo and Arcoxia and between placebo and dexamethasone.

DISCUSSION

The anti-inflammatory drug etoricoxib (Arcoxia) is a COX-2 selective inhibitor which is effective in the treatment of pain, having a fast response and a prolonged effect. It has already been demonstrated that the dose which provides maximum efficiency in controlling postoperative pain in oral surgery is 120mg[10].

Ibuprofen with arginine is more effective as an analgesic when compared to ibuprofen by itself[5]. For this reason, and because ibuprofen is considered to be a safe drug, which serves as the gold standard when comparing with other anti-inflammatory drugs, including the COX-2 selective inhibitors[5], it was decided, in the present study, to use ibuprofen combined with arginine.

Researchers have noted that the COX-2 selective inhibitors were clearly better than Ibuprofen, and in single-dose situations, COX-2 selective inhibitors demonstrated a longer period of analgesic action when compared to ibuprofen[12].

It should be stressed that none of the studies[1-2,5-6,8-12] compared etoricoxib with ibuprofen. As etoricoxib does not alter bleeding time, it has the big advantage of being administered in just one daily dose and not causing gastrointestinal alterations, apart from the fact that it still has not been widely studied.

As for the present study, no statistical difference was found when comparing treatments with etoricoxib or ibuprofen. Therefore, these drugs had similar patterns in terms of the promotion of preemptive analgesia. So our results agree to another study[19] conducted in 2011 where they compared etoricoxib, 90 mg and 120mg, with ibuprofen 600 mg; these authors concluded that there was no difference between these 3 groups, and that all are effective in controlling pain after the extraction of impacted third molars.

Many studies have already shown that preemptive analgesia with a placebo is lower than that observed when compared to anti-inflammatory drugs in controlling pain after extraction of mandibular third molars[1,3,5,6,8,20]. These studies are consistent with the results of the present study where the placebo also obtained results lower than the other protocols applied, with both scales and at the different points in time post-surgery.

Researchers concluded that the use of (two 6mg) doses of dexamethasone reduces post-surgical pain, spasm and edema in the third molars[20]. Other authors concluded that there was no statistically significant difference between a single 8mg dose of intramuscular dexamethasone and a single oral dose of 8mg dexamethasone[21]. In a another study[22] conducted using similar methodology, there was found to be no difference between the groups that used different routes of administration (oral and intramuscular) for dexamethasone 8mg. It should be stressed that dexamethasone is a low-cost drug, thereby facilitating its

use in the various social strata and has the advantage of having only a small mineral ocorticoid effect[12].

Taking into consideration the abovementioned studies, the present study used dexamethasone orally due to ease of administration and to it being readily accepted by the patients. However, at 6 hours following extraction, using the 101 point numerical scale, the groups etoricoxib and ibuprofen combined with arginine had better pain control than the dexamethasone group. Two hours after extraction, when using the 4-pointverbalscale, it was found that etoricoxib presented better results than dexamethasone and the placebo. These results diverge from those obtained in another study[11] where the researchers found no statistical differences between the group that was medicated with etoricoxib and the dexamethasone group.

Some authors[20] have shown a reduced postoperative use of analgesics in patients who made preoperative use of dexamethasone in third molar surgery, when compared to the placebo. The present study confirms this study, since a statistically significant difference was found between G4 and G2 and between G4 and G3 with the consumption of pain relievers. Another study showed that patients subjected to the extraction of third molars who used dexamethasone co-administered with ibuprofen, used less pain relieving medication in comparison with individuals who used ibuprofen by itself or a placebo[23].

The use of ibuprofen in preemptive analgesia was compared to the use of the same medication as a preventive analgesia. The results showed that there was no statistical difference between the two methods of administration of ibuprofen in controlling pain and edema after the extraction of mandibular thirdmolars[24].

CONCLUSION

It may be concluded that the anti-inflammatory drugs tested promote greater analgesia in the first four hours after surgery, compared to the placebo, and the consumption of analgesics (pain relievers) is lower when using etoricoxib or dexamethasone.

Collaborators

AH LISBOA took part in the development of the study protocol, performed the collection and analysis of data, helped with the interpretation of results and the composition of the article. GL PILATTI took part in the development of the study protocol, conducted the statistical part of the study, helped with the interpretation of the results and the composition of the article.

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