Effects of pre and postoperative dexamethasone for control of pain, swelling and trismus after third molar surgery: a randomized, triple-blind clinical trial

Abstract
The aim of the present study was to establish the effects of pre- and postoperative administration of dexamethasone for upper and lower third molar surgery. A randomized, triple-blind clinical trial with a split-mouth design was conducted with a sample composed of 30 patients. Participants were divided in two groups: Group A (one dose of dexamethasone 12 hours after surgery) and Group B (one dose of placebo 12 hours after surgery). All patients received single dose of dexamethasone (8mg) and nimesulide (100mg) per oral route, one hour before surgery. The outcome variables were: pain, total number of analgesics taken, interval between analgesics, swelling and trismus. Those parameters were evaluated in different timepoints. Quantitative data were subjected to the Kolmogorov-Smirnov normality test and compared by means of the paired t-test and ANOVA. Group A showed less selling and trismus 48h after surgery (p=0.167), but no statistical significant different were found. On assessment of postoperative pain 16 hours after surgery, the scores were higher in Group B (placebo) (p=0.031). One additional dose of dexamethasone administered in the postoperative period decreased the pain score and caused reductions in the facial swelling measurement and trismus.

Keywords: corticosteroids, third molar surgery, dexamethasone, swelling, pain, trismus

Introduction
Inflammation is crucial for the body’s defense as concerns tissue lesions, such as those associated with surgical interventions. This process includes release of inflammatory mediators that result in vasodilation, increased vascular permeability, protein extravasation and other tissue phenomena at the cellular level, which can cause swelling, pain, increased temperature, erythema and loss of function.1

Reduction of postoperative discomfort after third molar removal is of interest for all oral and maxillofacial surgeons and their patients. Many techniques are employed to reduce the Pain, swelling and trismus of third molar removal. Various drugs have been considered in the attempt to reduce the postoperative inflammatory response associated with lower third molar removal, with many published studies.2,3

In 1965, Lingenerg employed dexamethasone, a synthetic adrenocortical steroid, to control swelling and reduce mouth opening limitation and pain after oral surgery. From that time onward, use of synthetic steroids in oral surgery became increasingly more popular as a function of their beneficial effects for the reduction of post-inflammatory signs and symptoms.2,3

Several studies have investigated the influence of systemic steroids administered before or after third molar removal with satisfactory results.4-7 Dexamethasone has been used for many years in oral surgery due to its powerful mechanism of action and long half-life.8 Although several protocols have been suggested for the use of steroids in third molar surgery, there is not yet a consensus in this regard9,10.

Steroids act at the early stage of inflammation, suppressing the production of vasoactive substances, such as prostaglandins and leukotrienes, thus reducing fluid transudation and resulting swelling and the synthesis of several cytokines involved in inflammation and pain.9,10 While steroids might contribute to the control of pain, they must be used in combination with some analgesic with clinically significant effect.9 The occurrence of adverse effects of steroids depends on the dose and duration of use. Prolonged use might delay tissue repair and increase susceptibility to infection; in turn, side effects are rare in treatments consisting of one single dose or a short course, as is frequently the case in oral surgery.9

The aim of the present study was to assess the effects of pre- and postoperative administration of dexamethasone for control of postoperative pain, swelling and trismus following the removal of impacted third molars.

Materials and methods
Study design
The present study consisted of a randomized, triple-blind clinical trial with a split-mouth design. The study was approved by the Unichristus human research ethics committee and complied with the
CONSORT (Consolidated Standards of Reporting Trials) statement. All patients signed an informed consent form before inclusion in the study.

Sample size calculation

Based on the study by Barbalho et al., which found that pain scores four hours after lower third molar removal were lower among patients who received dexamethasone and nimesulide (1.02±0.92) compared with the ones given dexamethasone alone (2.00±1.50), the number of patients to compose a representative sample considering split-mouth design, 80% power and 95% confidence was estimated at 26. To compensate for probable losses, the sample was increased by 15%, resulting in a total of 30 patients.

Sample selection and randomization

Thirty healthy individuals aged 18 to 22 years old were selected to participate in the study, which was conducted at the Unichristus oral surgery clinic. Inclusion criteria were: orthodontic indication of bilateral upper and lower third molar removal with similar surgical difficulty between both sides according to the Pell and Gregory classification following clinical and tomographic assessment. Exclusion criteria were as follows: the use of anti-inflammatory or analgesic drugs different from the tested ones within 15 days from the onset of the study, hypersensitivity to the drugs or other substances employed in the study and pregnancy or breastfeeding and severe pain regardless possible alveolitis.

To ensure that the patients, principal investigator, surgeon and statistician were blind to the drugs administered at each surgical procedure, the tablets (placebo or steroid) were of the same size and color. The tablets were kept in similar envelopes, encoded as A or B by specialized staff. The code was broken only after the end of data collection and analysis. Randomization was performed by an investigator not directly involved in the assessment of patients or surgical procedures through the use of sequential sealed envelopes.

The envelopes were randomly distributed (Microsoft Excel RAND function); each envelope contained specifications for the combination (established by the lottery method) of drugs to be administered after surgery (dexamethasone or placebo, 12 hours after surgery) and mouth side (right or left). In each case, the investigator opened the envelope and informed the principal investigator and the surgeon as to which side of the mouth was the target and administered the drugs to patients 12 hours after surgery. The second surgical procedure was performed on the contralateral side 30 days after the first procedure. Thus, patients, surgeon and principal investigator—charged with the assessment of swelling and trismus—remained blind as to the drug allocated to each surgical procedure.

Surgical procedures and drugs

One hour before surgery, all patients received a single dose of dexamethasone (8mg) and nimesulide (100mg) per oral route. Patients were subjected to two surgical removals, always in the afternoon, performed by the same surgeon. Before surgery, the patients received extra-oral antisepsis with 10% povidone-iodine (PVP-I) in alcohol solution. Local anesthesia was performed using 4% articaine and epinephrine 1:100,000, two cartridges applied to the lower and one cartridge to the upper molars; a standardized technique was performed in all surgical procedures.

For the lower molars, an incision was first performed on the alveolar crest at the distal-to-mesial direction to reach the distolingual area of the second molar. Next, an intrasulcular incision was performed around the second molar until the interdental papilla between the second and first molar. All of the patients were subjected to a relaxing incision on the mesial area of the second molar. Osteotomy and ostectomy were performed to expose the amelocemental junction, followed by tooth sectioning as needed. The tooth was removed using a Potts elevator, followed by careful curettage, bone smoothing and cleansing of the surgical cavity through abundant irrigation with saline solution. The flap was replaced, an X suture was performed on the distal of the second molar and another suture on the relaxing incision. Silk 4-0 sutures were used. For the upper molars, following anesthesia, an incision was performed on the alveolar crest in the distal-to-mesial direction on the second molar, followed by an intrasulcular incision around the second molar until the interdental papilla between the second and first molar. The tooth was removed using a Potts elevator, followed by careful curettage, bone smoothing and cleansing of the surgical cavity through abundant irrigation with saline solution. Flap repositioning was performed as in the case of the lower molars.

Postoperative control

Following all surgical procedures, the patients were given orientations on routine postoperative care. They were also instructed to take one tablet of dipyrone (500mg), only if it was needed (pain intensity over 3 on a visual analog scale (VAS)). Dipyrone was selected since there is no anti-inflammatory effect; there is a well-known analgesic action, moreover, because it is a drug often used by the local population. The patients did not use antibiotics because of the protocol used in the institution.

Clinical parameters

Following each surgical procedure, the patients were asked to indicate the intensity of pain on a 10-point scale. To facilitate the patients’ understanding, the scale had various colors and faces depicting various expressions. Pain was assessed in different timepoints: 30 min, 2h, 4h, 8h, 16h and 48h after surgery. The patients were also instructed to record the number of rescue medications taken until postoperative day 7.

Swelling was assessed using a tape measure. Three measurements were performed in each patient for three reference points:

A. Tragus / external angle of the eye (Tragus–EA).
B. Tragus / lateral angle of the mouth (Tragus-LA).
C. External angle of the eye/gonion (EA-Go).
D. Measurements were performed before surgery (baseline), 48 hours, 72 hours and 7 days after surgery. Swelling progression was assessed by subtracting the value obtained at each postoperative time-point (addition of the three postoperative measurements) from the baseline total.

Mouth opening limitation (trismus) was assessed by measuring the maximum mouth opening between the left maxillary and mandibular central incisors with a simple caliper. Measurements were performed before surgery (baseline) and 48 hours, 72 hours and 7 days after surgery. Mouth opening was defined as the difference in measurements before surgery and at each postoperative time-point. Swelling and trismus were assessed by the same trained and calibrated examiner. Calibration was performed based on measurements performed on 30 volunteers on two different occasions with a 3-day interval.
Statistical analysis

Quantitative data were subjected to the Kolmogorov-Smirnov normality test, expressed as the means and standard deviations and compared by means of the paired t-test or repeated measures ANOVA followed by the Bonferroni post-test (parametric data) or the Wilcoxon or Friedman test followed by Dunn’s post-test (non-parametric data). Categorical data are expressed as absolute frequencies and were analyzed by means of McNemar’s test.

All of the analyses were performed with the software Statistical Package for the Social Sciences (SPSS) version 17.0 for Windows (IBM Corp., Armonk, NY, USA), with 95% confidence.

Results

Sample characterization

A total of 30 patients were included in the present clinical trial, consisting of 25 females (83%) and 5 males (17%), with average age of 20±2 years old. Thirty patients were divided into two groups, as shown in the CONSORT flowchart in Figure 1.

Surgical difficulty did not exhibit a significant difference between the groups. Surgery duration (p=0.510), total number of used anesthetic cartridges (p=0.102), bone removal frequency (p=1.000), tooth sectioning (p=1.000) and Pell and Gregory classifications (p=1.000) did not exhibit significant differences between the groups. No side effects or postoperative bleeding occurred in any group (p=1.000) (Table 1).

Swelling

The Tragus-EA and Tragus-LA measurement showed a significant increase in the dexamethasone group and Placebo group starting 48 hours after surgery and then presented a significant reduction until reaching the baseline values 72 hours after surgery (Table 2).

The EA-Go measurement exhibited significant increases starting 48 hours after surgery in both groups, and significant reductions were observed 72 hours after surgery in the dexamethasone group and on day 7 in the placebo group (Table 2).

There were no significant differences in the cumulative effects of swelling relative to the EA-Tragus (p=0.235) and EA-Go (p=0.925) measurements between the groups. However, the dexamethasone group showed a shorter EA-Go measurement compared with group B when the cumulative effect along the assessment time-points was considered (p<0.001) (Table 2).

Table 1 Characteristics of the removed third molars

|                        | Group A      | Group B      | p-Value |
|------------------------|--------------|--------------|---------|
| Surgical difficulty    |              |              |         |
| Surgery duration       | 19.32±3.09   | 19.22±3.14   | 0.510*  |
| Cartridge number       | 3.07±0.45    | 2.93±0.37    | 0.102*  |
| Bone removal (+/-)*    | 22/8         | 22/8         | 1.000*  |
| Tooth sectioning (+/-)*| 10/20        | 10/20        | 1.000*  |
| Pell and Gregory (1/2/3)*| 11/19/0   | 11/19/0      | 1.000*  |
| Pell and Gregory (A/B/C)*| 17/13/0  | 17/13/0      | 1.000*  |
| Side effects (+/-)     | 0/60         | 0/60         | 1.000*  |
| Postoperative bleeding (+/-) | 0/60   | 0/60         | 1.000*  |

*p<0.05, Wilcoxon test (mean±SD); p<0.05, McNemar’s test (+/-). *Mandibular teeth

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Table 2 Comparison of swelling between protocols – Group A (dexamethasone) and Group B (placebo) – at different postoperative time points

| Group      | 0 hours | 48 hours | 72 hours | 7 days | p-Value | Cumulative effect (0 hours-7 days) |
|------------|---------|----------|----------|--------|---------|-----------------------------------|
| Tragus-EA  |         |          |          |        |         |                                   |
| Group A    | 78.03±4.65 | 78.33±4.73 | 78.67±4.51 | 78.03±4.65 | 0.459ª | 78.39±0.42                       |
| Group B    | 77.53±4.21 | 78.40±4.17 | 78.10±4.31 | 77.53±4.21 | 0.559ª | 77.89±0.38                       |
| p-Value    | <0.001   | <0.001   | <0.001   | 0.459ª  |         |                                   |
| Cumulative effect (0 hours-7 days) | 78.39±0.42 | 77.89±0.38 | 0.235ª  |         |         |                                   |

| Tragus-LA  |         |          |          |        |         |                                   |
| Group A    | 107.60±6.04 | 110.27±6.38 | 110.30±6.35 | 107.67±5.96 | <0.001 | 109.0±0.57                        |
| Group B    | 107.80±5.55 | 109.70±6.02 | 109.63±6.18 | 107.83±5.63 | <0.001 | 108.7±0.53                        |
| p-Value    | <0.001   | <0.001   | <0.001   | <0.001  |         |                                   |
| Cumulative effect (0 hours-7 days) | 109.0±0.57 | 108.7±0.53 | 0.925ª  |         |         |                                   |

| EA-Go      |         |          |          |        |         |                                   |
| Group A    | 99.40±6.23 | 101.97±5.70 | 101.57±6.12 | 99.43±6.24 | <0.001 | 100.6±0.56                        |
| Group B    | 99.47±6.27 | 102.60±5.96 | 102.30±5.94 | 99.57±6.18 | <0.001 | 108.7±0.53                        |
| p-Value    | <0.001   | <0.001   | <0.001   | <0.001  |         |                                   |
| Cumulative effect (0 hours-7 days) | 100.6±0.56 | 108.7±0.53 | <0.001ª |         |         |                                   |

*p<0.05 versus 0 hours; **p<0.05 versus 48 hours; †p<0.05, paired t-test; ‡p<0.05, repeated measures ANOVA/Bonferroni (mean±SD)

**Trismus**

The peak of trismus occurred 48 hours after surgery in both groups and showed significant reductions starting 72 hours after surgery in the dexamethasone group and on day 7 in the placebo group. There were no differences in the cumulative effects of trismus along the assessment time-points between the groups (p=0.167) (Table 3).

**Pain**

Neither the dexamethasone group (p=0.062) nor the placebo group (p=0.850) exhibited a significant peak of pain 48 hours after surgery. However, 16 hours after surgery, the pain score was higher in the placebo group (p=0.031). The cumulative effect of pain along the assessment time-points was significantly higher in the placebo group compared with the dexamethasone group (p=0.001).

There were no significant differences in either the number of days of rescue medication use (p=0.920) or the time to first rescue medication (p=0.809). However, rescue medication intake (dipyrone, 100%) was lower in the dexamethasone group (p=0.038) (Table 4).

Table 3 Comparison of trismus between protocols – Group A (dexamethasone) and Group B (placebo) – at different postoperative time points

|          | Group A       | Group B       | p-Value |
|----------|---------------|---------------|---------|
| Trismus  |               |               |         |
| 0 hours  | 52.53±5.35    | 52.50±5.30    | 0.326ª  |
| 48 hours | 39.30±10.89ª  | 37.57±10.99ª  | 0.366ª  |

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Table 4 Comparison of pain score, number and amount of rescue medication between protocols – Group A (dexamethasone) and Group B (placebo) – at different postoperative time points

|                      | Group A       | Group B       | p-Value       |
|----------------------|---------------|---------------|---------------|
| **Trismus**          |               |               |               |
| 72 hours             | 43.10±9.88†   | 40.70±9.91†   | 0.202ª        |
| 7 days               | 51.80±5.51†   | 51.43±5.51†   | 0.532ª        |
| **p-Value**          | <0.001ª       | <0.001ª       |               |
| **Cumulative effect (0 hours-7 days)** | 46.68±0.91†   | 45.55±0.96†   | 0.167ª        |

*p<0.05 versus 0 hours; †p<0.05 versus 48 hours;
ªp<0.05, paired t-test, †p<0.05, repeated measures ANOVA/Bonferroni (mean±SD)

Discussion

Steroids such as dexamethasone and methylprednisolone have been widely used in dentoalveolar surgery due to their almost pure glucocorticoid effects with practically no mineralocorticoid effect and little adverse effect on leukocyte chemotaxis.15,16 Dexamethasone has been used by oral surgeons since 1965 in the attempt to reduce postoperative pain and trismus.17

In 1993, Baxendale18 observed that dexamethasone ought to block all of the inflammatory response aspects, thus reducing swelling and trismus and, consequently, pain. Favorable clinical impressions led to the broad use of this drug, but formal confirmation of its efficacy through controlled trials was still lacking. Control of postoperative inflammation and its associated symptoms demands adequate anti-inflammatory treatment. The mechanism of action of steroids includes inhibition of enzyme phospholipase A2 (PLA2), which decreases the release of arachidonic acid from the cells at the inflammation site. As a result, the synthesis of prostaglandins and leukotrienes is reduced, with a consequent decrease of neutrophil accumulation, which at least partially accounts for the greater power of steroids by comparison to nonsteroidal anti-inflammatory drugs (NSAIDs).19

Preventive analgesia via administration of different classes of analgesic and anti-inflammatory agents, such as dexamethasone, ibuprofen, diclofenac, acetaminophen, codeine, acetoclofenac, ketorolac and tramadol, has been widely investigated to develop pharmacological protocols likely to reduce postoperative pain.20,21 Other approaches for control of oral surgery pain include maximization of drug levels at their site of action and minimization of systemic adverse effects, along with the use of combinations of various drugs or routes of administration for one and the same drug.21 Independently from the approach selected, the protocol used ought to be standardized before assessment of therapeutic efficacy. The surgical technique and staff ought to be the same in all procedures, and patients need to be carefully selected to ensure homogeneity in the magnitude of surgical

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inflammatory efficacy, steroid doses should be administered over a

of pain and swelling when placebo was used. To maintain their anti-

occurred in the present study since patients exhibited higher levels

surgery, they do not exhibit effects 24 hours later

Every 8 hours for 3 days). Better outcomes in terms of pain, swelling

3 days), while another group was given diclofenac sodium (50mg
taken from the site of dental extraction 2 to 3 hours after surgery.

for third molar surgery detected higher COX-2 mRNA levels in tissues

to 3 hours after surgery when placebo was administered instead of
dexamethasone. Similarly, some studies that employed microdialysis
for third molar surgery detected higher COX-2 mRNA levels in tissues
taken from the site of dental extraction 2 to 3 hours after surgery.
The same authors also found that dexamethasone was ineffectual to reduce the prostaglandin levels at the injury site, especially when compared with NSAIDs.

NSAIDs considerably reduce prostaglandin levels, which suggests that steroids do not sufficiently suppress prostaglandins to reduce the sensitization of peripheral nociceptors at the wound site. The inefficacy of steroids to reduce pain might derive from the fact that these drugs inhibit beta-endorphin release by the anterior pituitary. Beta-endorphin is known to be a powerful endogenous analgesic and is present in the peripheral circulation. In addition, changes in the circulating beta-endorphin levels have an effect on postoperative pain after oral surgery. This fact is in contrast to the results of the present study; analysis of the clinical parameters showed that patients exhibited lower rescue medication use across the full study period, and lower pain levels after postoperative administration of the drug, 16 hours after surgery.

Lima and colleagues performed a study with 30 participants, in which patients received 8mg of dexamethasone (every 8 hours for 3 days), while another group was given diclofenac sodium (50mg every 8 hours for 3 days). Better outcomes in terms of pain, swelling and trismus were found in the group given dexamethasone in the postoperative period. These authors believe that one intravenous dose of dexamethasone administered in the immediate preoperative period is highly beneficial for the control of swelling and trismus in the early postoperative period. Nevertheless, when steroids are administered in one single dose in the preoperative period for oral surgery, they do not exhibit effects 24 hours later. This phenomenon occurred in the present study since patients exhibited higher levels of pain and swelling when placebo was used. To maintain their anti-inflammatory efficacy, steroid doses should be administered over a longer time, which disagrees with previous studies in which the number of analgesics taken seems to have been influenced by steroid administration. In a systematic review with meta-analysis, Markiewicz et al. asserted that steroids do not play a major role in pain relief but are only beneficial to reduce pain and swelling.

Several studies demonstrated the efficacy of dexamethasone to reduce trismus after lower third molar surgery, when used in a preemptive manner. In the present study, the results showed reduction of postoperative trismus on postoperative day 2. In the study conducted by Lima et al., dexamethasone had better results than diclofenac sodium. In the present study, the group of patients who received an extra dose of dexamethasone exhibited discrete reductions in trismus; this finding might be due to lower pain levels, with consequent lesser discomfort upon opening the mouth (p>0.05).

Several studies point to improvements in trismus when dexamethasone is used in a preemptive manner. The difference between the groups, more evident on postoperative day 2, might be accounted for by the biological half-life of the drug since dexamethasone is considered to be a long-acting steroid (36-54 hours). For this reason, an additional dose might promote higher drug concentrations.

In order to minimize possible bias, we choose to use the split-mouth clinical trial, introduced in 1968 by Ramfjord and co-authors. This methodology is extensive used to study third molars extraction. Patients were submitted to same surgical procedures protocol in both sides. No difference were observed between groups regarding surgical difficulty and degree of impaction (Table 1).

Ramfjord et al. introduced the ‘split-mouth’ clinical trial in 1968 when they compared the efficacy of two types of periodontal therapy by randomizing the treatment methods to half of each subject’s dentition divided by the mid-sagittal plane between the central incisor teeth. Nas cirurgias de terceiros molares deste modelo de estudo é amplamente utilizado como observado na literatura. Based on the results obtained, one might infer that an additional dose of dexamethasone in the postoperative period reduces pain, swelling and trismus. This drug might be used more easily and decrease post-operative discomfort, resulting in less harm to patients as a function of the reduction of the numbers of analgesics used and in the shortest possible time.

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Conflicts of interest
The authors declare that there are no conflicts of interest.

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