

Systematic Review and Meta-Analysis Oral Surgery

Efficacy of corticosteroids versus placebo in impacted third molar surgery: systematic review and meta-analysis of randomized controlled trials

**R. de A. C. Almeida,
C. A. A. Lemos, S. L. D. de Moraes,
E. P. Pellizzer, B. C. Vasconcelos**
Department of Oral and Maxillofacial Surgery,
University of Pernambuco – School of
Dentistry (UPE/FOP), Tabatinga,
Camaragibe, Brazil

R. de A. C. Almeida, C. A. A. Lemos, S. L. D. de Moraes, E. P. Pellizzer, B. C. Vasconcelos: Efficacy of corticosteroids versus placebo in impacted third molar surgery: systematic review and meta-analysis of randomized controlled trials. Int. J. Oral Maxillofac. Surg. 2019; 48: 118–131. © 2018 International Association of Oral and Maxillofacial Surgeons. Published by Elsevier Ltd. All rights reserved.

Abstract. The aim of this systematic review was to identify randomized, placebo-controlled clinical trials investigating the effectiveness of corticosteroids in the control of pain, oedema, and trismus following third molar surgery, and to analyse the effects of the type of drug administered and the time and route of drug administration on the outcomes of interest. Searches were performed in the PubMed, Scopus, and Cochrane Library databases. This review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The search identified 1223 studies. After assessing eligibility based on the inclusion and exclusion criteria, 17 studies were selected for the qualitative analysis (a total of 730 patients aged 15–45 years). Ten studies were included in the meta-analysis, which was performed using Review Manager software. The corticosteroids were effective in controlling pain ($P = 0.002$; mean difference -17.38 , 95% confidence interval -24.81 to -9.95) and trismus ($P < 0.00001$; mean difference 6.10 , 95% confidence interval 3.42 to 8.77). With the exception of the submucosal route, the route of administration did not appear to affect the outcomes. The administration of a corticosteroid in the preoperative phase was superior to its use in the postoperative phase for the control of trismus.

Key words: third molar extraction; corticosteroid; oedema; trismus; pain; meta-analysis.

Accepted for publication 30 May 2018
Available online 23 June 2018

Third molar surgery is commonly performed by the oral and maxillofacial surgeon and poses varying degrees of difficulty depending on the location, depth, and angle of the

tooth, bone density, etc.^{1,2}. The postoperative phase is often associated with pain, oedema, and trismus, clinically represented by moderate to severe inflammatory signs

and symptoms that can have a significant impact on the quality of life of the patient^{3,4}.

Both steroidal and non-steroidal anti-inflammatory drugs are widely used to

control pain and inflammation⁵. Corticosteroids limit inflammation and oedema by inhibiting vascular dilation, as well as by reducing the transudation of fluids, the formation of oedema, cellular exudates, and the deposition of fibrin around the inflamed area. The mechanisms responsible for these effects include the inhibition of leukocyte chemotaxis to the inflamed area and the suppression of the production of numerous inflammatory mediators^{6,7}.

The corticosteroids used to control the undesirable inflammatory effects associated with the surgical removal of impacted third molars include dexamethasone and betamethasone (which are long-lasting drugs), prednisone, prednisolone, methylprednisolone, and triamcinolone (which have an intermediate duration), and hydrocortisone (which is a short-duration drug). These medications are administered either orally or parenterally (intravenous, intramuscular, or submucosal) in the preoperative or postoperative phases.

The literature is rich in randomized clinical trials that have attempted to demonstrate the beneficial effects of corticosteroids with regard to the extraction of impacted mandibular third molars. However, the variety of methods, doses, administration routes, and administration times used has hampered the decision-making process in clinical practice. Indeed, the best drug, dose, route of administration, and time of administration for corticosteroids need to be standardized in light of better evidence. Thus, the aim of the present study was to perform a systematic review of the literature to determine the efficacy of corticosteroids used as medicinal therapy for patients undergoing third molar surgery, testing the alternative hypothesis that these drugs are effective in the control of postoperative pain, oedema, and trismus.

Materials and methods

Protocol and registration

This systematic review was conducted in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁸. The methods used are registered in the International Prospective Register of Systematic Reviews (PROSPERO) under protocol number CRD42017064363.

PICO question

The PICO question of this study was “Are corticosteroids effective at controlling pain, oedema, and trismus following the

surgical removal of impacted third molars?”

Eligibility criteria

The following were the inclusion criteria: patients of any age submitted to the extraction of one or more impacted mandibular third molars; studies that compared the use of any type of corticosteroid to a control group given a placebo drug; studies that investigated pain, oedema, and/or trismus (with no restrictions on how these outcomes were measured); and randomized controlled clinical trials published in English with no restriction regarding the year of publication.

The following were the exclusion criteria: failure to provide information on the dose, administration route, or time of administration; comparison between corticosteroids and other drugs without the use of a placebo group; articles published in languages other than English; randomized clinical trials without a placebo control group, cohort studies, case-control studies, case reports, case-series reports, and laboratory studies; and studies for which the full text could not be obtained.

Search strategy

Two reviewers (R.A. and C.L.) performed independent searches of the PubMed/MEDLINE, Scopus, and Cochrane Library databases for articles published up to April 2017. Key words were selected for the search strategies in the three databases. The search strategy is provided in the **Supplementary Material** (File 1). Hand searches of the main journals in the field of oral and maxillofacial surgery and trauma were also performed: *International Journal of Oral and Maxillofacial Surgery*; *Journal of Oral and Maxillofacial Surgery*; *British Journal of Oral and Maxillofacial Surgery*; and *Journal of Cranio-Maxillo-Facial Surgery*.

The article selection process was conducted in two steps: (1) reading of the title and abstract; and (2) full-text analysis. Two reviewers (R.A. and C.L.) performed blinded, independent analyses based on the eligibility criteria. Divergences of opinion regarding the inclusion or exclusion of a study were settled by consensus, with the involvement of a third reviewer (B.V.) when necessary. Data were extracted from the articles selected following the full-text analysis, and all articles were evaluated with regard to the risk of bias. Contact was made with the authors of six of the selected articles for complementary information to enable the meta-

analysis. However, only two positive responses were received.

Data extraction

One reviewer (R.A.) performed the data extraction and another (C.L.) checked the information through the tabulation of demographic characteristics and data on the study populations, interventions, and outcomes of interest (pain, oedema, and trismus).

Risk of bias and quality of the included studies

The risk of bias was determined based on the appraisal criteria of the Cochrane Collaboration tool for assessing randomized clinical trials. The articles were analyzed for selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome evaluation), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other bias (other threat related to origin bias).

Summary measures

The meta-analysis was based on inverse variance methods for continuous outcomes. Pain and trismus were the outcomes evaluated by the mean difference (MD) and corresponding 95% confidence interval (CI). The MD was considered significant when $P < 0.05$. Review Manager 5.3 software program (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) was used for the meta-analysis. The fixed-effects model was employed when the P -value related to heterogeneity was greater than 0.10, and the random-effects model was used when the P -value was less than 0.10⁹.

Additional analyses

The kappa test was used for the evaluation of inter-examiner agreement during the study selection process after the reading of the titles and abstracts for the pre-selection of articles to be submitted to full-text analysis¹⁰. Sub-group analyses were performed for the drug employed, time of administration (preoperative or postoperative), and route of administration with regard to the outcomes of interest (pain, oedema, and trismus).

Results

The electronic search led to the retrieval of 1223 articles from the databases employed: 364 from PubMed/MEDLINE, 722 from Scopus, and 137 from the Cochrane Library. After the removal of duplicates and reading of the titles and abstracts, 65 articles were selected for full-text analysis, 48 of which were excluded for not meeting the eligibility criteria. Thus, 17 articles were included in the present systematic review^{11–27}. Figure 1 displays the flowchart of the article selection process. The reasons for exclusion of the 48 articles not meeting the eligibility criteria are given in the **Supplementary Material** (File 2)^{28–75}. Inter-examiner agreement was calculated (kappa coefficient) after the pre-selection of the articles based on the reading of the titles and abstracts for each database: $\kappa = 0.91$ for PubMed/MEDLINE, $\kappa = 0.93$ for Scopus, and $\kappa = 0.94$ for Cochrane. The kappa values demonstrated a high level of agreement between the reviewers¹⁰.

The 17 studies selected included a total of 730 patients aged 15 to 45 years. It was

possible to quantify the number of male ($n = 314$) and female ($n = 346$) subjects in 15 of the studies; two of the studies did not offer a distinction of the sex of the patients^{11,12}. With regard to the corticosteroids administered to the study groups, long-duration drugs were used in 11 studies, nine of which employed dexamethasone^{13–21} and two betamethasone^{22,23}. Medium-duration corticosteroids were used in six studies, five of which employed methylprednisolone^{11,12,24–26} and one prednisolone²⁷. In all studies, the placebo group was given either glucose pills (oral administration) or saline solution (submucosal, intramuscular, intravenous, intra-alveolar, or pterygomandibular space). Table 1 displays the qualitative data for the studies analyzed.

Pain was evaluated using a visual analogue scale (VAS) in 15 studies and the number of rescue pills in one study²⁴. Oedema was evaluated based on craniometric points for soft tissues as the reference in 11 studies (employing different techniques), ultrasound in two studies (one of which also employed computed tomography), a VAS in two studies, and using a five-point Likert

scale in one study. Postoperative trismus was evaluated based on the inter-incisal distance during mouth opening in 13 studies, a VAS in one study, and a five-point Likert scale in one study.

Pain control

In the analysis of the results of the articles included in the present review, 13 studies demonstrated a positive effect of corticosteroid use in comparison to placebo use with regard to postoperative pain^{11–14,16,19–22,24–27}, and three studies found no difference^{15,17,23}. The studies by Boonsiriset et al.²⁰ and Chopra et al.²² demonstrated no difference in the evaluation performed at 7 days following surgery. In the study by Mojsa et al.²¹, results similar to the placebo were found when the corticosteroid was administered in the preoperative period.

Regarding the use of rescue painkillers, 12 studies employed analgesics. Although the number of pills taken was greater in the placebo group, the difference was only statistically significant in five studies^{14,19–21,25}.

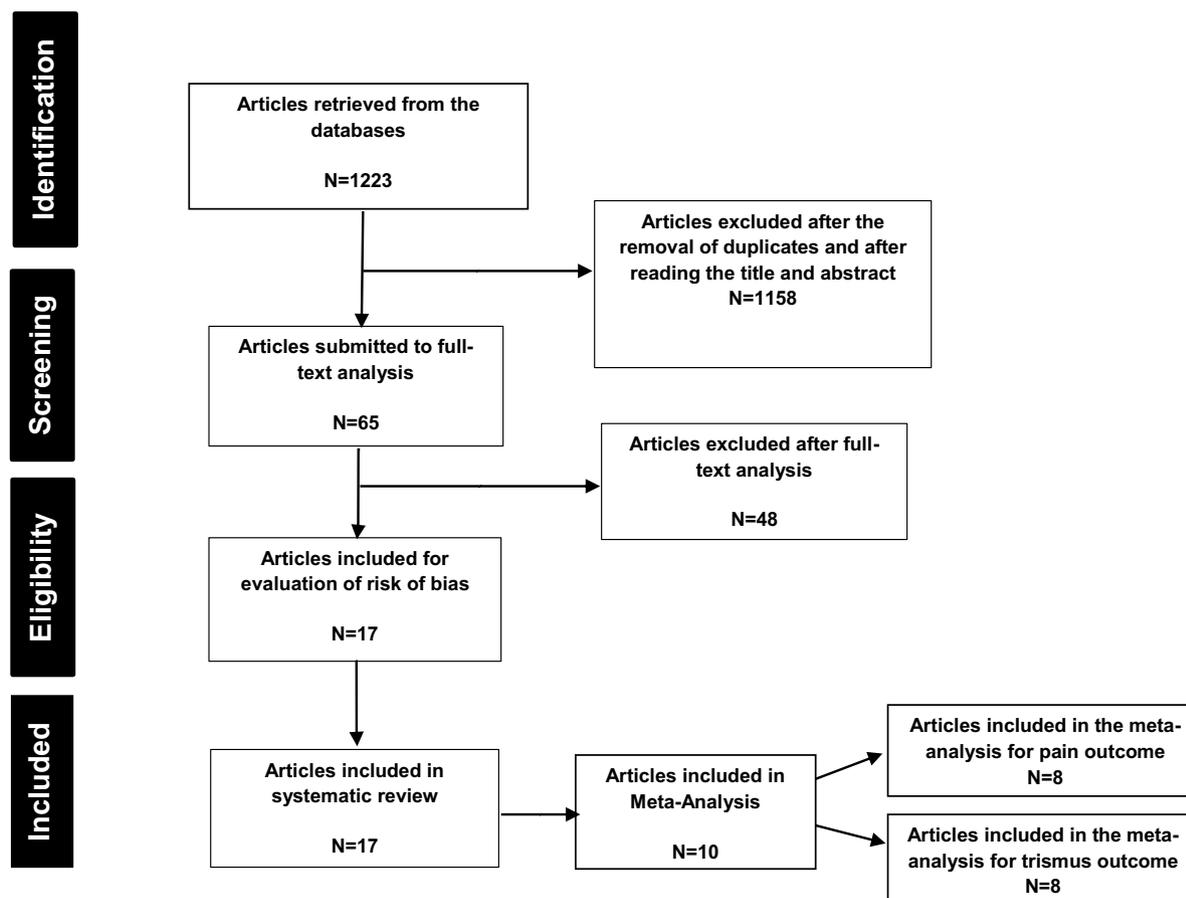


Fig. 1. Flow diagram of the search strategy.

Table 1. Characteristics of the studies included in the review.

Authors and year	Study design	Number of patients	Groups	Sex Age (years)	Intervention drug (dose) Route of administration Timing of administration	Rescue analgesic	Outcomes assessed	Effect of corticosteroid	
								First assessment ^a	Day 7
Simone et al., 2013 ^{16,b}	RCT	34	DX: 20 PLA: 14	10 M, 24 F 22 ± 3.6 years	Dexamethasone 8 mg Oral route Preoperative	Paracetamol 1 g	Pain	Positive	Positive
Bortoluzzi et al., 2013 ^{15,b}	RCT	26	DX: 14 PLA: 12	5 M, 21 F Mean 22 years	Dexamethasone 8 mg Oral route Preoperative	Acetaminophen 750 mg	Pain Swelling Trismus	None None None	– – –
Al-Dajani, 2017 ¹⁹	RCT	32	DX: 32 PLA: 32	18 M, 14 F NR	Dexamethasone 0.1 mg/kg Intramuscular route Preoperative	Ibuprofen 400 mg every 6 h	Pain Swelling Trismus	Positive Positive Positive	Positive Positive Positive
Klongnoi et al., 2012 ¹⁴	RCT	20	DX: 20 PLA: 20	6 M, 14 F 19–32 years (Mean 21 years)	Dexamethasone 8 mg Intramuscular route Preoperative	Paracetamol 1 g every 4 or 6 h	Pain Swelling Trismus	Positive Positive None	Positive None None
Dereci et al., 2016 ¹⁸	RCT	20	DX: 20 PLA: 20	9 M, 11 F 15–32 years (Mean 21 years)	Dexamethasone 8 mg Intramuscular route Postoperative	–	Swelling	Positive	–
Mojsa et al., 2017 ²¹	RCT	90	DX1: 30 DX2: 30 PLA: 30	32 M, 58 F 18–42 years (Mean 23.5 years)	Dexamethasone 4 mg Submucosal route Pre- and postoperative	Paracetamol 500 mg	Pain ^c Swelling Trismus	DX preop.: None DX postop.: Positive Positive	– – Positive
Deo, 2016 ¹⁷	RCT	30	DX: 19 PLA: 11	19 M, 11 F 20–41 years	Dexamethasone 8 mg Submucosal route Preoperative	Ibuprofen 400 mg	Pain Swelling Trismus	None Positive Positive	None None None
Boonsiriseth et al., 2017 ²⁰	RCT	31	DX: 31 PLA: 31	11 M, 20 F 16–32 years (Mean 22 years)	Dexamethasone 8 mg Pterygomandibular space route Preoperative	Acetaminophen 500 mg	Pain Swelling Trismus	Positive Positive Positive ^d	None Positive None
Pappalardo et al., 2007 ¹³	RCT	100	DX1: 20 DX2: 20 DX3: 20 DX4: 20 PLA: 20	52 M, 48 F 26.45 ± 4.2 years	DX1: Dexamethasone 10 mg Intra-alveolar route Postoperative DX2: Dexamethasone 10 mg Submucosal route Intraoperative DX3: Dexamethasone 4 mg Intravenous route Intraoperative DX4: Dexamethasone 8 mg Intramuscular route Intraoperative	–	Pain Swelling Trismus	Positive ^d Positive ^d Positive ^d	Positive ^d Positive ^d Positive ^d
Chopra et al., 2009 ^{22,b}	RCT	60	BT: 30 PLA: 30	36 M, 24 F 18–45 years (Mean 28.05 years)	Betamethasone 0.5 mg Oral route Postoperative every 8 h for 3 days	Tramadol 100 mg	Pain Swelling Trismus	Positive Positive Positive	None None –
Marques et al., 2014 ²³	RCT	25	BT: 25 PLA: 25	13 M, 12 F 23.44 ± 5.14 years	Betamethasone 12 mg Submucosal route Postoperative	Metamizole 575 mg every 8 h	Pain Swelling Trismus	None None None	– None None

Table 1 (Continued)

Authors and year	Study design	Number of patients	Groups	Sex Age (years)	Intervention drug (dose) Route of administration Timing of administration	Rescue analgesic	Outcomes assessed	Effect of corticosteroid	
								First assessment ^a	Day 7
Acham et al., 2013 ²⁵	RCT	16	MPD: 16 PLA: 16	6 M, 10 F 23.9 ± 3.3 years	Methylprednisolone 40, 60, or 80 mg Oral route Preoperative	Ibuprofen 400 mg	Pain Swelling Trismus	Positive Positive Positive	Positive Positive None
Prashar et al., 2016 ^{12,b}	RCT	30	MPD: 15 PLA: 15	NR 18–40 years (Mean 25.6 years)	Methylprednisolone 8 mg Oral route Postoperative every 8 h for 3 days	–	Pain Swelling Trismus	Positive Positive Positive	Positive Positive Positive
Christensen et al., 2013 ²⁶	RCT	126	MPD1: 31 MPD2: 34 MPD3: 30 PLA: 31	69 M, 57 F 25.0 ± 4.7 years	Methylprednisolone 32 mg Oral route Preoperative + 16 mg every 12 h for 1 day	–	Pain Swelling Trismus	Positive Positive Positive	Positive Positive Positive
Esen et al., 1999 ²⁴	RCT	20	MPD: 20 PLA: 20	9 M, 11 F 19–25 years (21.6 ± 0.43 years)	Methylprednisolone 125 mg Intravenous route Preoperative	Acetaminophen 500 mg	Pain Swelling Trismus Pain	Positive Positive Positive Positive	– None None –
Ilhan et al., 2014 ^{11,b}	RCT	40	MPD: 20 PLA: 20	NR 19–40 years	Methylprednisolone 80 mg Intravenous route Preoperative	–	Swelling Trismus	Positive Positive	– –
Buyukkurt et al., 2006 ^{27,b}	RCT	30	PD: 15 PLA: 15	19 M, 11 F 18–36 years	Prednisolone 25 mg Intramuscular route Postoperative	Acetaminophen 500 mg, every 6 h	Pain Swelling Trismus	Positive (7 h postop.) Positive None	– None None

BT, betamethasone; DX, dexamethasone; MPD, methylprednisolone; NR, not reported; PD, prednisolone; PLA, placebo; RCT, randomized controlled trial.

^aFirst assessment: 24 hours for pain; 48–72 hours for swelling/trismus.

^bOnly data referring to the study groups of interest and the placebo group were extracted.

^cThe 'pain' outcome was evaluated only for 24 hours.

^dPositive effect of corticosteroids when administered intravenously, intramuscularly, and intra-alveolar.

Eight studies were included in the meta-analysis of the pain outcome. The VAS (0–100 scale) was the assessment tool and evaluations at 1 and 7 days postoperative were considered. At 24 hours after surgery, the use of a corticosteroid (independent of the drug administered) was favourable to the control of pain; this result was statistically significant ($P = 0.002$; MD -17.38 , 95% CI -24.81 to -9.95) (Fig. 2A). At 7 days, a favourable difference in comparison to the placebo was only found for methylprednisolone ($P < 0.0001$; MD -9.57 , 95% CI -14.33 to -4.82) (Fig. 2B).

Independent of the time of administration (preoperative or postoperative), the corticosteroids demonstrated significantly better results in comparison to the placebo at 24 hours postoperative (Fig. 3A) ($P < 0.00001$; MD -17.51 , 95% CI -24.96 to -10.07). At 7 days postoperative, however, the corticosteroids only demonstrated a significantly better performance than the placebo when administered in the postoperative period ($P = 0.0005$; MD -8.93 , 95% CI -13.94 to -3.92) (Fig. 3B).

Independent of the route of administration, the corticosteroids demonstrated significantly better results in comparison to the placebo at 24 hours ($P < 0.00001$; MD -17.51 , 95% CI -24.96 to -10.07). At 7 days, however, only oral administration had a significantly better performance in comparison to the placebo ($P < 0.0001$; MD -9.57 , 95% CI -14.33 to -4.82) (Fig. 4).

Trismus

Eleven studies demonstrated a positive effect of corticosteroids in comparison to placebo use in the evaluation of trismus^{11–13,17,19–22,24–26}, whereas no difference was found in four studies^{14,15,23,27}. Furthermore, four studies found no difference between the groups at the day 7 evaluation^{17,20,24,25}.

Eight studies performed evaluations of trismus based on inter-incisal distance during mouth opening at 48 hours, 72 hours, and at 7 days after surgery. The evaluations performed at 48–72 hours, which is when greater oedema and trismus is expected, were considered the first evaluation in an effort to incorporate a greater number of studies in the meta-analysis.

A significant difference favouring the corticosteroids was found with regard to inter-incisal distance at 48–72 hours after surgery ($P < 0.00001$; MD 6.10, 95% CI 3.42 to 8.77) and at the day 7 evaluation ($P < 0.00001$; MD 2.51, 95% CI 1.74 to 3.28). Considering the type of corticosteroid, a single study analyzing the effect of beta-

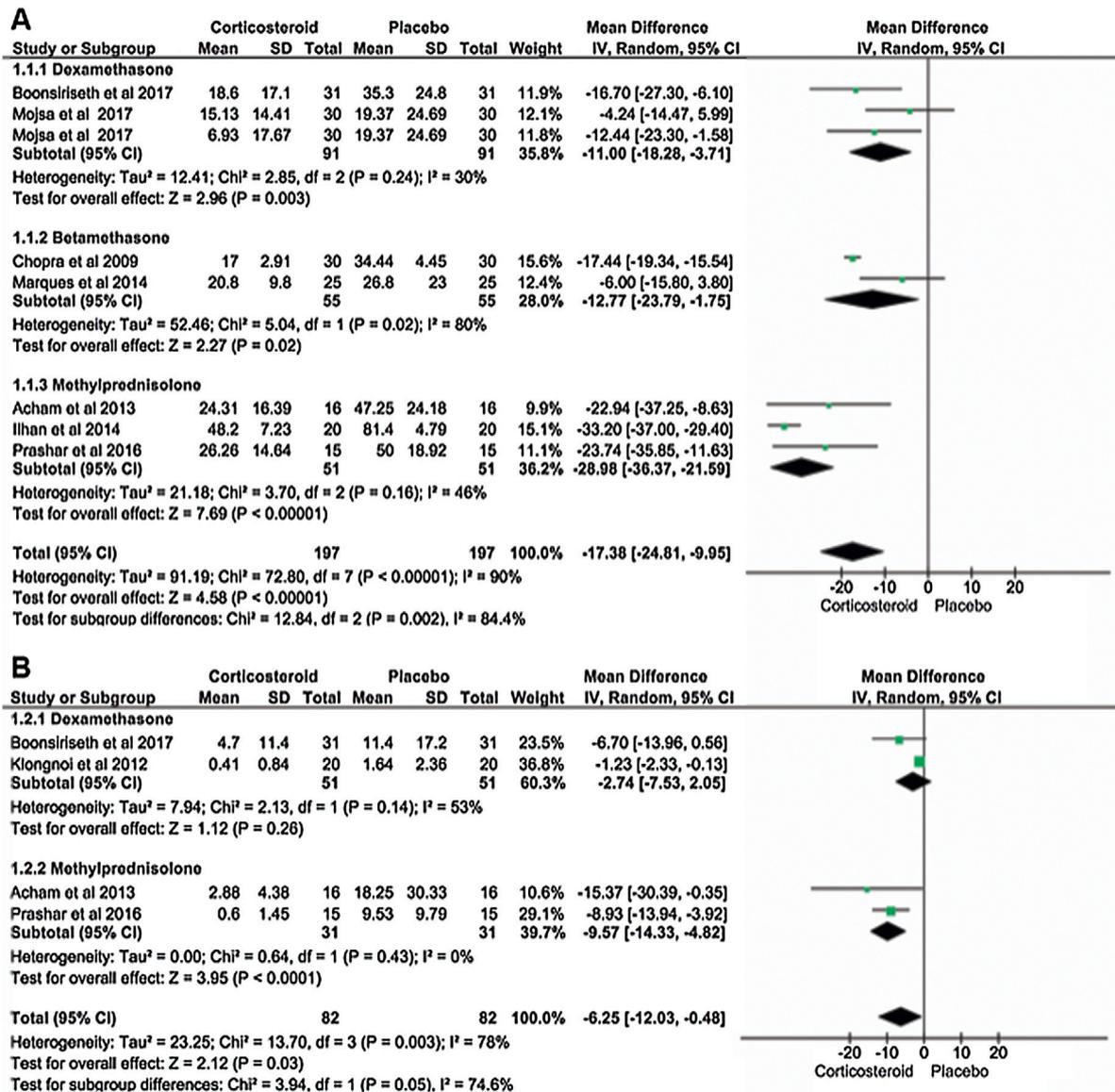


Fig. 2. Evaluation of pain according to the drug administered: (A) at 24 hours; (B) at 7 days.

methasone found no difference in comparison to the placebo at 48–72 hours ($P = 0.31$; MD 3.10, 95% CI -2.90 to 9.10) or at 7 days ($P = 0.59$; MD 1.20, 95% CI -3.12 to 5.52) (Fig. 5).

In the comparison of the time of administration, preoperative administration of the corticosteroids performed better in comparison to the placebo at 48–72 hours ($P < 0.0001$; MD 5.58, 95% CI 2.96 to 8.20), whereas no difference was found when the corticosteroids were administered in the postoperative period ($P = 0.08$; MD 6.35, 95% CI -0.76 to 13.45) (Fig. 6A). At 7 days, the corticosteroids performed better than the placebo independent of the time of administration ($P < 0.00001$; MD 2.51, 95% CI 1.74 to 3.28) (Fig. 6B).

With regard to the route of administration, both oral and parenteral administration demonstrated significantly better results in comparison to the placebo at 48–72 hours ($P < 0.00001$; MD 6.26, 95% CI 3.56 to 8.96) (Fig. 7A) and at 7 days ($P < 0.00001$; MD 2.51; 95% CI 1.74 to 3.28) (Fig. 7B).

Facial swelling

It was not possible to perform a meta-analysis for oedema, due to the lack of homogeneity among the studies in terms of central tendency and dispersion measures (mean and standard deviation) and to the different techniques employed to measure this outcome. Fourteen studies demonstrated a positive effect of corticosteroids in

comparison to the placebo regarding the control of postoperative oedema^{11–14,17–22,24–27}, and two studies found no difference between corticosteroid and placebo use^{15,23}. The studies employing dexamethasone demonstrated significantly better results in comparison to the placebo for all administration routes and doses as well as both administration times (preoperative and postoperative), with the exception of one study in which no difference was found between this corticosteroid and the placebo¹⁵. Deo¹⁷ and Klongnoi et al.¹⁴ did not find a significant difference for the day 7 evaluation.

Betamethasone proved effective at controlling oedema only at 24 hours after surgery, with no significant difference on the third and seventh days (Chopra et al.²³).

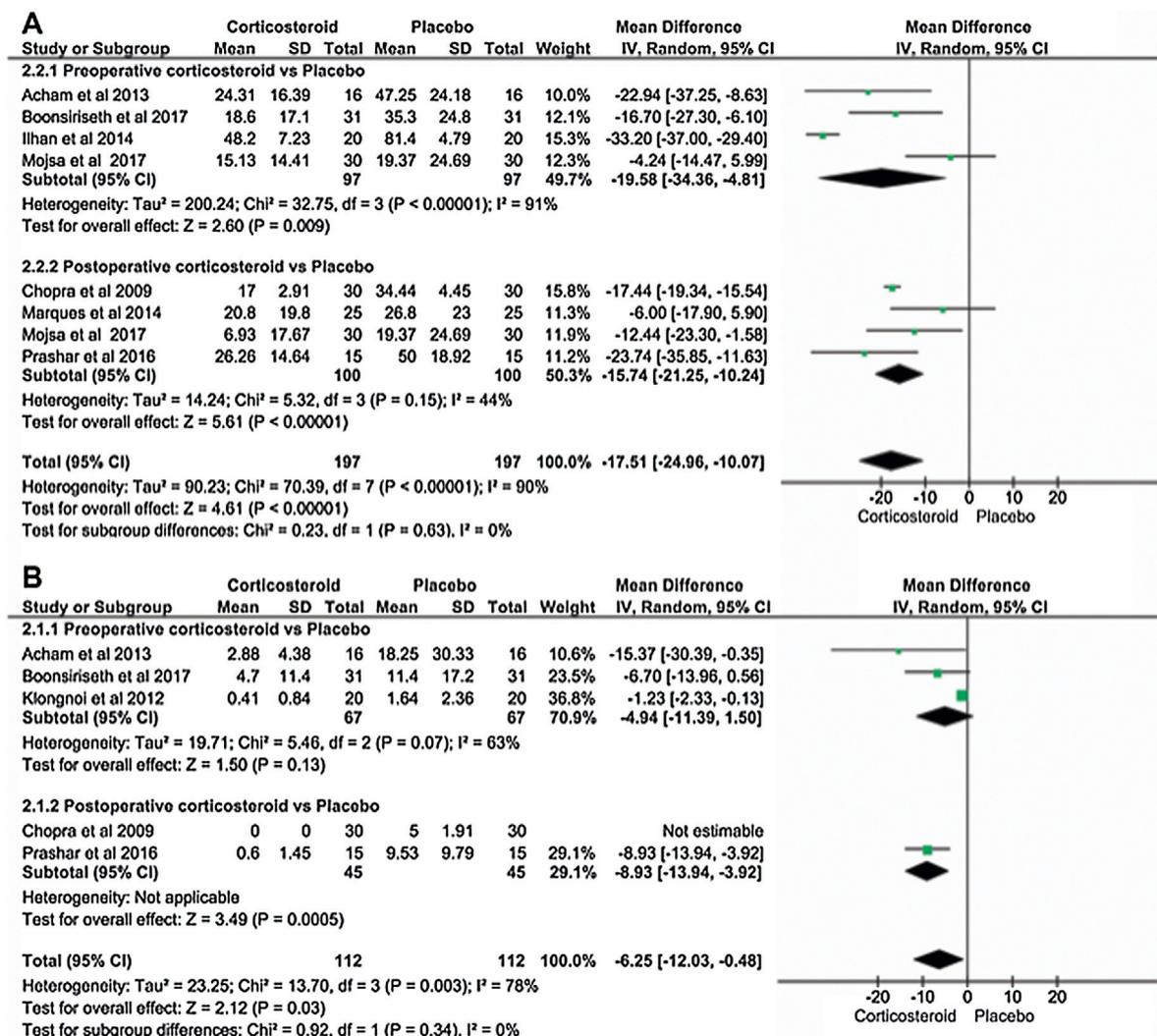


Fig. 3. Evaluation of pain according to the time of administration of the corticosteroid (preoperative or postoperative): (A) at 24 hours; (B) at 7 days.

Marques et al. found no significant difference between the group treated with beta-methasone and the placebo group²³. Methylprednisolone and prednisolone were effective at controlling postoperative oedema. Although a significant difference was found at the 48–72 hours postoperative evaluation, Buyukkurt et al.²⁷ and Esen et al.²⁴ did not find a significant difference for the day 7 evaluation.

Assessment of the risk of bias

A low risk of bias was found with regard to randomization, allocation concealment, and blinding of the patients and evaluators. With regard to incomplete outcome data and selective reporting, a risk of bias was found in six and eight studies, respectively; this was either for not describing the findings completely or for using mea-

asures that are not considered ideal for the outcomes of the study. All studies had a low risk with regard to the criterion ‘other bias’ (Fig. 8).

Discussion

This systematic review included only randomized clinical trials involving a placebo control group, since this type of design enables better control and comparability of the experimental variables and, consequently, the results are more reliable and not overestimated. This differentiates the present review from two previously published reviews that investigated the effects of corticosteroids on pain, oedema, and trismus. The reviews by Herrera-Briones et al.⁷⁶ and Ngeow and Lim⁷⁷ encompassed studies in which the control group at times was an untreated group (not sub-

mitted to any type of intervention), which certainly impaired the blinding procedure and resulted in an overestimation of the results. Moreover, the present systematic review enabled a meta-analysis for the outcomes pain and trismus with data from 10 of the 17 studies included in the quantitative analysis of the influence of corticosteroids in comparison to a placebo. Furthermore, this review includes an important subgroup analysis for the evaluation of this effect with regard to the type of drug used, time of administration, and route of administration.

The qualitative and quantitative analyses led to the rejection of the null hypothesis for all variables studied, demonstrating the effectiveness of corticosteroids in the control of pain (13 studies), oedema (14 studies), and trismus (11 studies). These effects may be explained by the action of corticosteroids

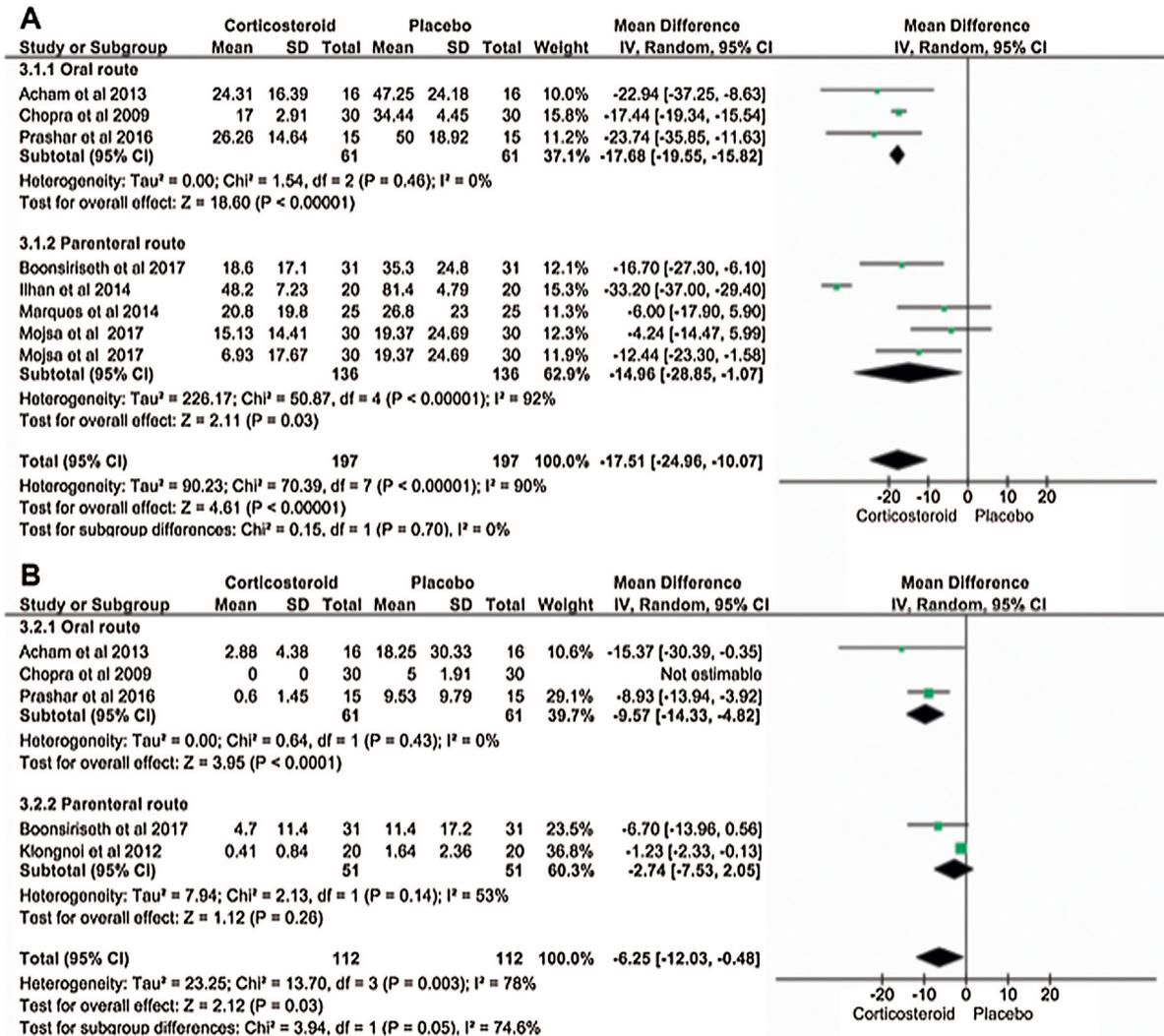


Fig. 4. Evaluation of pain according to the route of administration of the corticosteroid (oral or parenteral): (A) at 24 hours; (B) at 7 days.

on the inhibition of the enzyme phospholipase A2 and, consequently, the by-products of its action on injured tissues, such as prostaglandins, leukotrienes, and bradykinin. When the levels of these inflammatory mediators are diminished, the result is less oedema and consequently less pain and trismus^{21,78}.

Three of the four studies that found no significant difference between corticosteroids and a placebo with regard to pain administered the drugs using the submucosal route^{17,21,23}. In the study by Mojisa et al., however, the lack of a difference only occurred when the corticosteroid was administered preoperatively²¹. In the study by Marques et al., who performed the submucosal administration of betamethasone, no positive effects of the corticosteroid were found with regard to any of the outcomes²³. According to Moraschini et al., when the submucosal route is selected, larger doses of corticosteroids

may be necessary, especially if administration of the drug is performed in the preoperative phase, since the use of a flap and tissue displacement can affect the concentration of the drug and its absorption into the blood stream⁷⁹.

No significant effect of the corticosteroid was found with regard to any of the outcomes in the study conducted by Bortoluzzi et al.¹⁵. However, that study failed to clarify the randomization and allocation strategies and did not provide mean and standard deviation values, which precluded its inclusion in the quantitative analysis. Moreover, a VAS was used not only to measure pain, but also to measure oedema and trismus, rather than employing more objective measures of these outcomes, such as measurements of particular anatomical points on the face and the interincisal distance.

Corticosteroids proved to be satisfactory for the control of postoperative oedema

in the most critical period of the inflammatory process. As expected, this effect was diminished by the day 7 evaluation, but nonetheless remained significant in six studies.

With regard to the drug, dexamethasone and methylprednisolone have been shown to be effective in the control of pain, oedema, and trismus after the surgical removal of impacted third molars, and should be the drugs of choice. Only two studies evaluated the effect of betamethasone^{22,23}. Chopra et al. found positive results in comparison to the placebo with regard to pain, swelling, and trismus²². Further clinical trials involving betamethasone are needed to enable a better estimation of its effects.

The studies that continued the use of corticosteroids in the postoperative period did not present better results than those in which a single dose was employed^{12,22,26}. Therefore, the maintenance of use is not

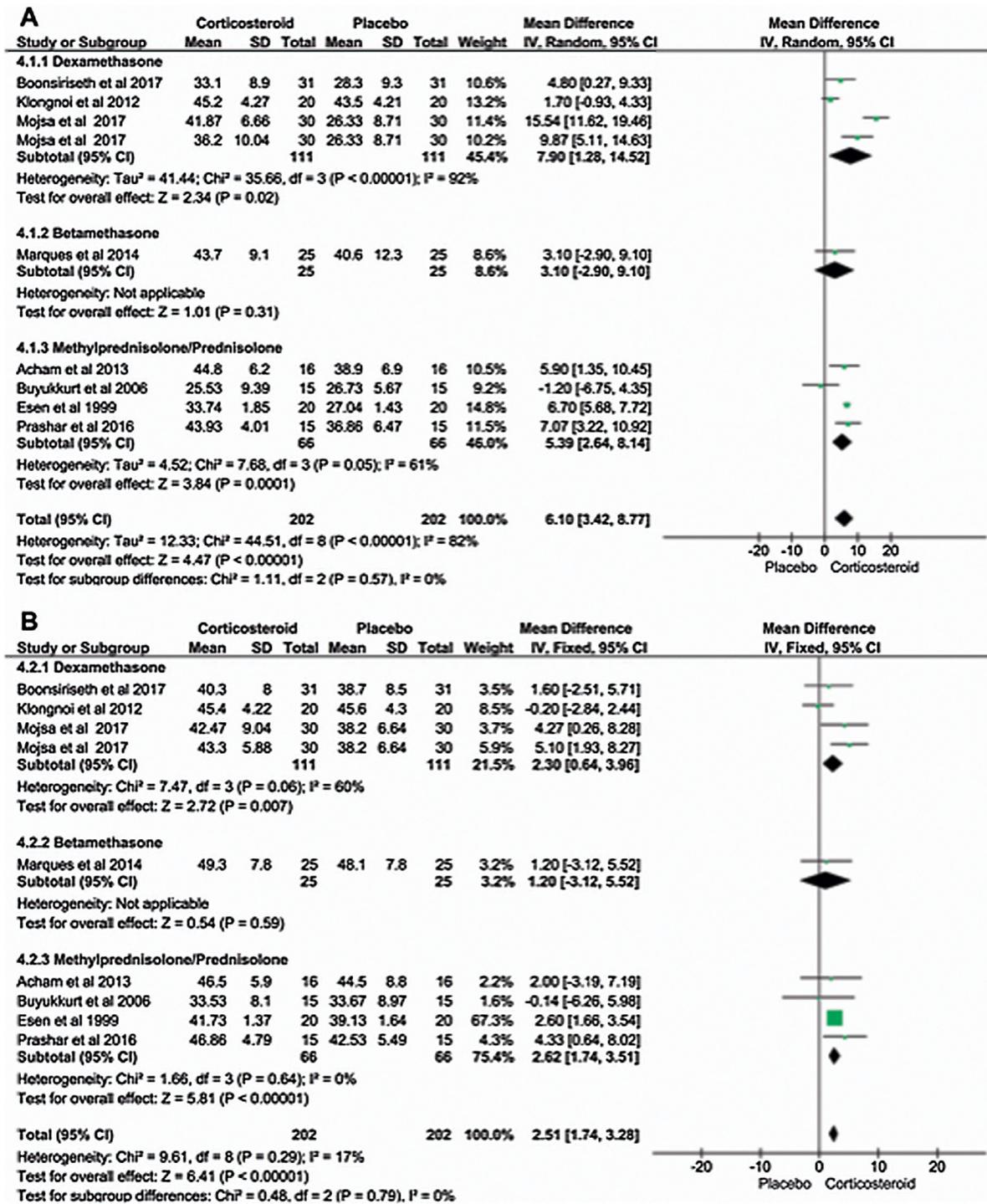


Fig. 5. Evaluation of trismus according to the drug administered: (A) at 48–72 hours; (B) at 7 days.

justified. This is an important point to stress, as the prolonged use of corticosteroids is associated with adverse side effects and even short-term use can lead to adrenal suppression and a reduction in the secretion of endogenous cortisol²⁴, which is an extremely important hormone to the functioning of the organism.

Based on the results of the quantitative analysis, preoperative and postoperative administration of corticosteroid were equally effective in the control of postoperative pain at 24 hours after surgery. For trismus, however, administering a corticosteroid in the preoperative period achieved better results than postoperative adminis-

tration at evaluations conducted 48–72 hours after surgery. The better performance of the drug administered preoperatively with regard to trismus may be explained by the fact that the corticosteroid is made available to the organism prior to tissue injury. Although the meta-analysis suggested better results when the drug

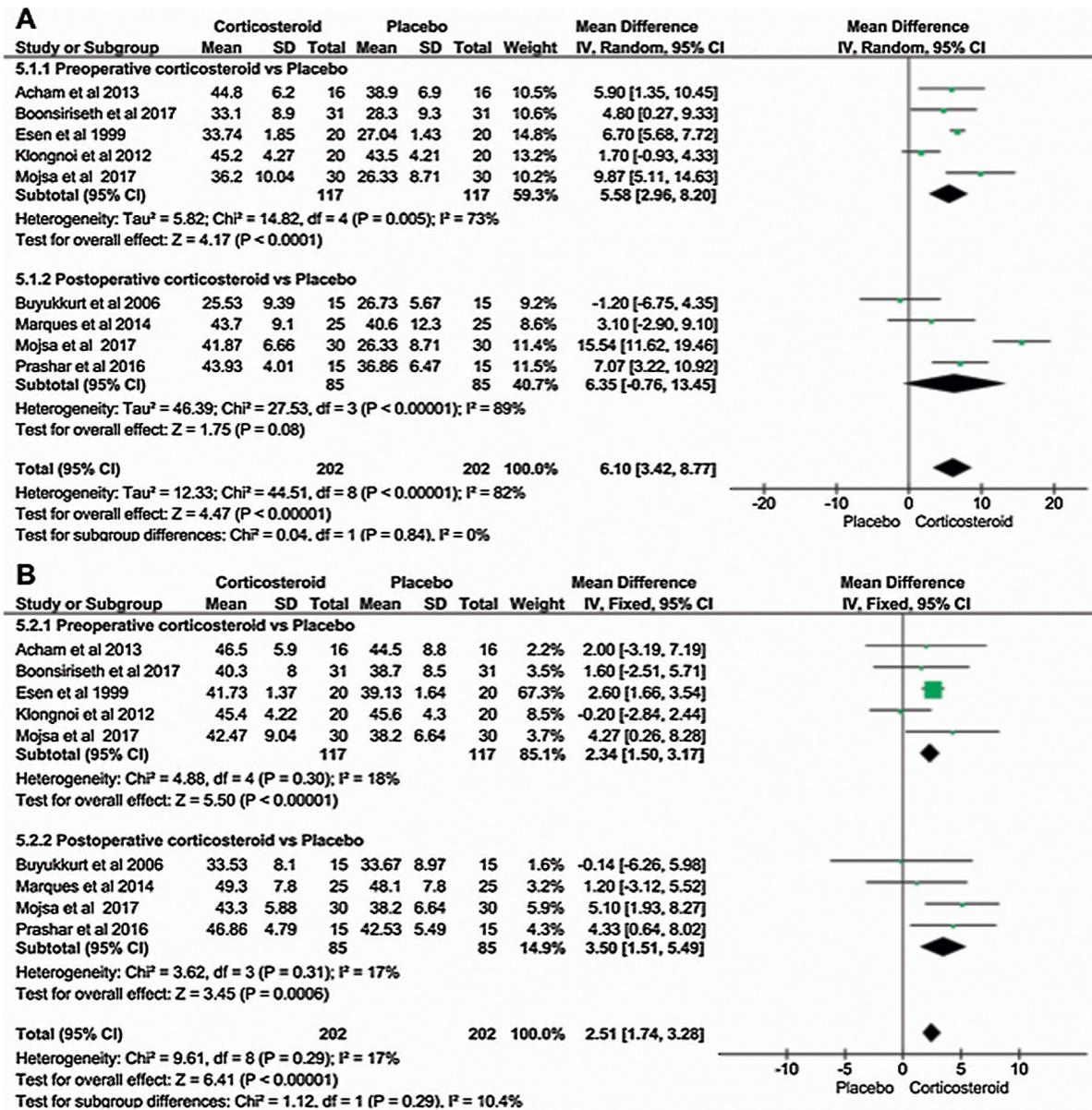


Fig. 6. Evaluation of trismus according to the time of administration of the corticosteroid (preoperative or postoperative): (A) at 48–72 hours; (B) at 7 days.

was administered in the preoperative period, further clinical trials should be conducted to enable better comparison of the two administration times to a placebo group.

Moraschini et al. performed a meta-analysis to evaluate the effectiveness of dexamethasone administered through the submucosal route and found results favouring the corticosteroid for pain and oedema, but no difference was found in comparison to the control group with regard to trismus⁷⁹. Seven of the eight studies included in this former review had an untreated control group, which could have led to an overestimation of the results. The present systematic review does not lend

support to the encouragement of submucosal administration, as the results demonstrated no difference between the corticosteroid administered in this manner when compared to the placebo for any of the outcomes in the studies conducted by Marques et al.²³, Pappalardo et al.¹³, and Mojsa et al.²¹ (preoperative administration of corticosteroid). Moreover, Deo found no difference in the evaluation of pain¹⁷. In contrast, the oral and parenteral administration routes were equally satisfactory in the period considered the most critical with regard to inflammatory activity.

In the studies analyzed, oedema was evaluated based on facial measurements, the analysis of photographs, ultrasound,

computed tomography, and subjective clinical observations (Likert scales and VAS). Standardization of the evaluation of oedema is needed in future clinical trials to enable the quantification of the effect of corticosteroids on this outcome. Moreover, not all studies selected evaluated the preoperative and postoperative (48–72 h and 7 days) periods, which rendered meta-analysis unviable.

The analysis of the use of rescue medication constitutes an additional parameter for the evaluation of pain. In the present study, it was not possible to evaluate pain based on this variable due to the lack of data and standardization in the evaluation times in the studies analyzed.

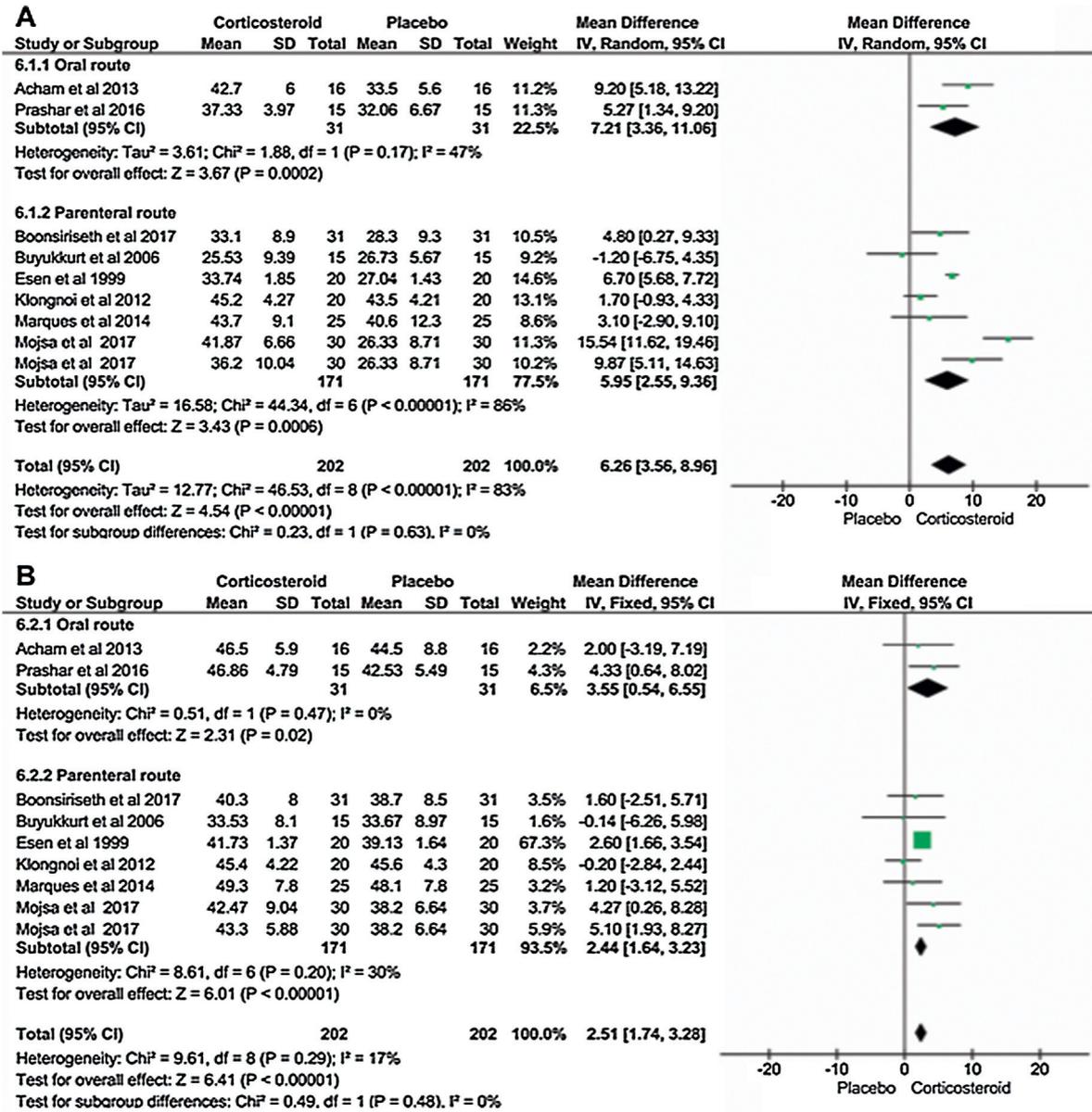


Fig. 7. Evaluation of trismus according to the route of administration of the corticosteroid (oral or parenteral): (A) at 48–72 hours; (B) at 7 days.

Posology is one of the factors that can influence the results of corticosteroid use. However, it was not possible to determine the effect of the dose of the corticosteroids on the control of postoperative pain, oedema, and trismus. The meta-analysis showed the existence of high heterogeneity between the studies, confirmed by the heterogeneity test and the *I*² statistic, which undoubtedly resulted from the great variability in the corticosteroid doses employed. The majority of studies that made use of dexamethasone employed a dose of 8 mg. However, positive results were also achieved with a dose of 4 mg. Other drugs were used without any stan-

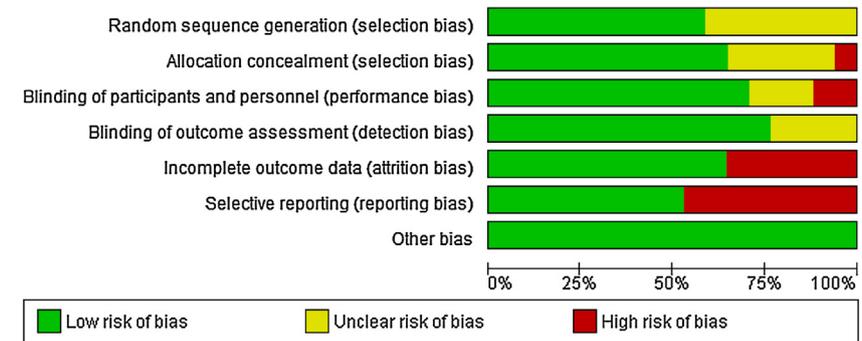


Fig. 8. Risk of bias.

andardization. Betamethasone was used at doses of 0.5 mg²² and 12 mg²³, prednisolone was used at a dose of 25 mg²⁷, and methylprednisolone was used at doses of 8 mg¹², 32 mg²⁶, 40 mg²⁵, 60 mg²⁵, 80 mg^{11,25}, and 125 mg²⁴. Thus, further randomized controlled clinical trials comparing different doses of the same drug to a placebo group are needed.

Although only randomized clinical trials were included in the present review, one of the limitations of this study is the high risk of bias found regarding two of the criteria of the Cochrane Collaboration tool for the assessment of randomized clinical trials (incomplete outcome data and selective reporting), which rendered the incorporation of some articles into the quantitative analysis unviable.

The use of corticosteroids had a positive effect with regard to the control of the pain, oedema, and trismus associated with the surgical removal of impacted mandibular third molars in the majority of studies included in this systematic review. With the exception of the submucosal route, the route of administration did not seem to influence the results, making the oral route an easy and excellent option. The administration of a corticosteroid in the preoperative phase was superior to its use in the postoperative phase for the control of trismus.

Acknowledgements. The authors are grateful to the Brazilian fostering agency Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES; Coordination for the Advancement of Higher Education Personnel), as well as the authors Izabela Mojsa and Saroj Prasad Deo for making available data not found in the articles reporting their studies, which enabled the inclusion of these studies in the meta-analysis.

Funding. No source of funding.

Competing interests. No competing interests.

Ethical approval. Not required.

Patient consent. Not required.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online

version, at <https://doi.org/10.1016/j.ijom.2018.05.023>.

References

- Goyal M, Marya K, Jhamb A, Chawla S, Sonoo PR, Singh V, Aggarwal A. Comparative evaluation of surgical outcome after removal of impacted mandibular third molars using a Piezotome or a conventional handpiece: a prospective study. *Br J Oral Maxillofac Surg* 2012;**40**:456–561. <http://dx.doi.org/10.1016/j.bjoms.2011.10.010>.
- Piersanti L, Dilorenzo M, Monaco G, Marchetti JC. Piezosurgery or conventional rotary instruments for inferior third molar extractions? *Oral Maxillofac Surg* 2014;**72**:1647–52. <http://dx.doi.org/10.1016/j.joms.2014.04.032>.
- McGrath C, Comfort MB, Lo EC, Luo Y. Patient-centred outcome measures in oral surgery: validity and sensitivity. *Br J Oral Maxillofac Surg* 2003;**41**:43–7.
- Kazancioglu HO, Kurklu E, Ezirganli S. Effects of ozone therapy on pain, swelling, and trismus following third molar surgery. *Int J Oral Maxillofac Surg* 2014;**43**:644–8. <http://dx.doi.org/10.1016/j.ijom.2013.11.006>.
- Ong CK, Lirk P, Seymour RA, Jenkins BJ. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. *Anesth Analg* 2005;**100**:757–73.
- Montgomery MT, Hogg JP, Roberts DL, Redding SW. The use of glucocorticosteroids to lessen the inflammatory sequelae following third molar surgery. *J Oral Maxillofac Surg* 1990;**48**:179.
- Dionne RA, Gordon SM, Rowan J, Kent A, Brahim JS. Dexamethasone suppresses peripheral prostanoid levels without analgesia in a clinical model of acute inflammation. *Oral Maxillofac Surg* 2003;**61**:997–1003.
- Moher D, Liberati A, Tetzlaff J, Altman DG, GPRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;**151**:264–9. <http://dx.doi.org/10.7326/0003-4819-151-4-200908180-00135>.
- Egger M, Smith GD. Principles of and procedures for systematic reviews. In: Egger M, Smith GD, Altman AG, editors. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books; 2003. p. 23–42.
- Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;**33**:159–74.
- Ilhan O, Agacayak KS, Gulsun B, Koparal M, Gunes N. A comparison of the effects of methylprednisolone and tenoxicam on pain, edema, and trismus after impacted lower third molar extraction. *Med Sci Monit* 2014;**20**:147–52. <http://dx.doi.org/10.12659/MSM.890239>.
- Prashar DV, Pahwa D, Kalia V, Jindal G, Kaur R. A comparative evaluation of the effect of diclofenac sodium with and without per-orally administered methylprednisolone on the sequelae of impacted mandibular third molar removal: a cohort randomized double-blind clinical trial. *Indian J Dent* 2016;**7**:11–6. <http://dx.doi.org/10.4103/0975-962X.158187>.
- Pappalardo S, Puzzo S, Cappello V, Mstrangelo F, Adamo G, Caraffa A, Tete S. The efficacy of four ways of administering dexamethasone during surgical extraction of partially impacted lower third molars. *Eur J Inflamm* 2007;**4**:151–8.
- Klongnoi B, Kaewpradub P, Boonsiriseth K, Wongsirichat N. Effect of single dose preoperative intramuscular dexamethasone injection on lower impacted third molar surgery. *J Oral Maxillofac Surg* 2012;**41**:376–9. <http://dx.doi.org/10.1016/j.ijom.2011.12.014>.
- Bortoluzzi MC, Capella DL, Barbieri T, Pagliarini M, Cavalieri T, Manfro R. A single dose of amoxicillin and dexamethasone for prevention of postoperative complications in third molar surgery: a randomized, double-blind, placebo controlled clinical trial. *J Clin Med Res* 2013;**4**:26–33. <http://dx.doi.org/10.4021/jocmr1160w>.
- Simone JL, Jorge WA, Horliana AC, Canaval TG, Tortamano IP. Comparative analysis of preemptive analgesic effect of dexamethasone and diclofenac following third molar surgery. *Braz Oral Res* 2013;**27**:266–71. <http://dx.doi.org/10.1590/S1806-83242013005000012>.
- Deo SP. Single-dose of submucosal injection of dexamethasone affects the post operative quality of life after third molar surgery. *J Maxillofac Oral Surg* 2016;**15**:367–75. <http://dx.doi.org/10.1007/s12663-015-0846-6>.
- Dereci O, Tüzüner-Öncül AM, Kocer G, Yüce E, Askar M, Öztürk A. Efficacy of immediate postoperative intramuscular dexamethasone injection on postoperative swelling after mandibular impacted third molar surgery: a preliminary split-mouth study. *J Pak Med Assoc* 2016;**66**:320–3.
- Al-Dajani M. Can preoperative intramuscular single-dose dexamethasone improve patient-centered outcomes following third molar surgery? *J Oral Maxillofac Surg* 2017;**31**:1–11. <http://dx.doi.org/10.1016/j.joms.2017.03.037>.
- Boonsiriseth K, Latt MM, Kiattavorncharoen S, Pairuchvej V, Wongsirichat N. Dexamethasone injection into the pterygomandibular space in lower third molar surgery. *Int J Oral Maxillofac Surg* 2017;**46**:899–904. <http://dx.doi.org/10.1016/j.ijom.2017.02.1266>.
- Mojsa IM, Pokrowiecki R, Lipczynski K, Czerwonka D, Szczeklik K, Zaleska M. Effect of submucosal dexamethasone injection on postoperative pain, oedema, and trismus

- following mandibular third molar surgery: a prospective, randomized, double-blind clinical trial. *Int J Oral Maxillofac Surg* 2017;**46**:424–530. <http://dx.doi.org/10.1016/j.ijom.2016.11.006>.
22. Chopra D, Rehan HS, Mehra P, Kakkar AK. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of paracetamol, serratiopeptidase, ibuprofen and betamethasone using the dental impaction pain model. *Int J Oral Maxillofac Surg* 2009;**38**:350–5. <http://dx.doi.org/10.1016/j.ijom.2008.12.013>.
 23. Marques J, Pié-Sánchez P, Figueiredo R, Valmaseda-Castellón E, Gay-Escoda C. Effect of the local administration of betamethasone on pain, swelling and trismus after impacted lower third molar extraction. A randomized, triple blinded, controlled trial. *Med Oral Patol Oral Cir Bucal* 2014;**9**:e49–54. <http://dx.doi.org/10.4317/medoral.19280>.
 24. Esen E, Tasar F, Akhan O. Determination of the anti-inflammatory effects of methylprednisolone on the sequelae of third molar surgery. *Oral Maxillofac Surg* 1999;**57**:1201–6.
 25. Acham S, Klampfl A, Truschneegg A, Kirmeier R, Sandner-Kiesling A, Jakse N. Beneficial effect of methylprednisolone after mandibular third molar surgery: a randomized, double-blind, placebo-controlled split-mouth trial. *Clin Oral Invest* 2013;**17**:1693–700. <http://dx.doi.org/10.1007/s00784-012-0867-1>.
 26. Christensen J, Matzen LH, Vaeth M, Wenzel A, Schou S. Efficiency of bupivacaine versus lidocaine and methylprednisolone versus placebo to reduce postoperative pain and swelling after surgical removal of mandibular third molars: a randomized, double-blinded, crossover clinical trial. *J Oral Maxillofac Surg* 2013;**71**:1490–9. <http://dx.doi.org/10.1016/j.joms.2013.05.001>.
 27. Buyukkurt MC, Gungormus M, Kaya O. The effect of a single dose prednisolone with and without diclofenac on pain, trismus, and swelling after removal of mandibular third molars. *J Oral Maxillofac Surg* 2006;**64**:1761–6. <http://dx.doi.org/10.1016/j.joms.2005.11.107>.
 28. Markovic A, Todorovic L. Effectiveness of dexamethasone and low-power laser in minimizing oedema after third molar surgery: a clinical trial. *Int J Oral Maxillofac Surg* 2007;**36**:226–9. <http://dx.doi.org/10.1016/j.ijom.2006.10.006>.
 29. Bauer HC, Duarte FL, Horliana AC, Tortamano IP, Perez FE, Simone JL, Jorge WA. *Oral Maxillofac Surg* 2013;**17**:165–71. <http://dx.doi.org/10.1007/s10006-012-0360-7>.
 30. Messer EJ, Keller JJ. The use of intraoral dexamethasone after extraction of mandibular third molars. *Oral Surg Oral Med Oral Pathol* 1975;**40**:594–8.
 31. Carriches CL, González JM, Rodríguez MD. The use of methylprednisolone versus diclofenac in the treatment of inflammation and trismus after surgical removal of lower third molars. *Med Oral Patol Oral Cir Bucal* 2006;**11**:e440–5.
 32. Graziani F, D' Aiuto F, Arduino PG, Tonelli M, Gabriele M. Perioperative dexamethasone reduces post-surgical sequelae of wisdom tooth removal. A split-mouth randomized double-masked clinical trial. *Int J Oral Maxillofac Surg* 2006;**35**:241–6. <http://dx.doi.org/10.1016/j.ijom.2005.07.010>.
 33. Micó-Llorens JM, Satorres-Nieto M, Gargallo-Albiol J, Arnabat-Domínguez J, Berini-Aytés L, Gay-Escoda C. Efficacy of methylprednisolone in controlling complications after impacted lower third molar surgical extraction. *Eur J Clin Pharmacol* 2006;**62**:693–8. <http://dx.doi.org/10.1007/s00228-006-0164-5>.
 34. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M, Farronato D, Santoro F. Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. *J Oral Maxillofac Surg* 2007;**65**:2218–26. <http://dx.doi.org/10.1016/j.joms.2006.11.036>.
 35. Vegas-Bustamante E, Micó-Llorens J, Gargallo-Albiol J, Satorres-Nieto M, Berini-Aytés L, Gay-Escoda C. Efficacy of methylprednisolone injected into the masseter muscle following the surgical extraction of impacted lower third molars. *Int J Oral Maxillofac Surg* 2008;**37**:260–3. <http://dx.doi.org/10.1016/j.ijom.2007.07.018>.
 36. Zandi M. Comparison of corticosteroids and rubber drain for reduction of sequelae after third molar surgery. *Oral Maxillofac Surg* 2008;**12**:29–33. <http://dx.doi.org/10.1007/s10006-008-0096-6>.
 37. Kang SH, Choi YS, Byun IY, Kim MK. Effect of preoperative prednisolone on clinical postoperative symptoms after surgical extractions of mandibular third molars. *Aust Dent J* 2010;**45**:462–7. <http://dx.doi.org/10.1111/j.1834-7819.2010.01271.x>.
 38. Majid OW. Submucosal dexamethasone injection improves quality of life measures after third molar surgery: a comparative study. *J Oral Maxillofac Surg* 2011;**69**:2289–97. <http://dx.doi.org/10.1016/j.joms.2011.01.037>.
 39. Antunes AA, Avelar RL, Neto EC, Frota R, Dias E. Effect of two routes of administration of dexamethasone on pain, edema, and trismus in impacted lower third molar surgery. *Oral Maxillofac Surg* 2011;**15**:217–23. <http://dx.doi.org/10.1007/s10006-011-0290-9>.
 40. Majid OW, Mahmood WK. Effect of submucosal and intramuscular dexamethasone on postoperative sequelae after third molar surgery: comparative study. *Br J Oral Maxillofac Surg* 2011;**49**:647–52. <http://dx.doi.org/10.1016/j.bjoms.2010.09.021>.
 41. Bhargava D, Sreekumar K, Rastogi S, Deshpande A, Chakravorty N. A prospective randomized double-blind study to assess the latency and efficacy of Twin-mix and 2% lignocaine with 1:200,000 epinephrine in surgical removal of impacted mandibular third molars: a pilot study. *Oral Maxillofac Surg* 2013;**17**:275–80. <http://dx.doi.org/10.1007/s10006-012-0372-3>.
 42. Majid OW, Mahmood WK. Use of dexamethasone to minimise post-operative sequelae after third molar surgery: comparison of five different routes of administration. *Oral Surg* 2013;**6**:200–8. <http://dx.doi.org/10.1111/ors.12049>.
 43. Nair RB, Rahman NM, Ummar M, Hafiz KA, Issac JK, Sameer KM. Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. *J Contemp Dent Pract* 2013;**14**:401–4.
 44. Bhargava D, Sreekumar K, Deshpande A. Effects of intra-space injection of Twin mix versus intraoral-submucosal, intramuscular, intravenous and per-oral administration of dexamethasone on post-operative sequelae after mandibular impacted third molar surgery: a preliminary clinical comparative study. *Oral Maxillofac Surg* 2014;**18**:293–6. <http://dx.doi.org/10.1007/s10006-013-0412-7>.
 45. Ehsan A, Bukhari SG, Manzoor AA, Junaid M. Effects of pre-operative submucosal dexamethasone injection on the postoperative swelling and trismus following surgical extraction of mandibular third molar. *J Coll Physicians Surg Pak* 2014;**24**:489–92.
 46. Nandini GD. Eventuality of dexamethasone injected intra-massetrically on post operative sequel following the surgical extraction of impacted mandibular third molars: a prospective study. *J Maxillofac Oral Surg* 2016;**15**:456–60. <http://dx.doi.org/10.1007/s12663-015-0847-5>.
 47. Sabhlok S, Kenjale P, Mony D, Khatri IH, Kumar PH. Randomized controlled trial to evaluate the efficacy of oral dexamethasone and intramuscular dexamethasone in mandibular third molar surgeries. *J Clin Diagn Res* 2015;**9**:48–51. <http://dx.doi.org/10.7860/JCDR/2015/13930.6813>.
 48. Zerener T, Aydintug YS, Sencimen M, Bayar GR, Yazici M, Altug HA, Missir AF, Acikel C. Clinical comparison of submucosal injection of dexamethasone and triamcinolone acetate on postoperative discomfort after third molar surgery. *Quintessence Int* 2015;**46**:317–26. <http://dx.doi.org/10.3290/j.qi.a33281>.
 49. Ibikunle AA, Adeyemo WA, Ladeinde AL. Oral health-related quality of life following third molar surgery with either oral administration or submucosal injection of prednisolone. *Oral Maxillofac Surg* 2016;**20**:343–

52. <http://dx.doi.org/10.1007/s10006-016-0571-4>.
50. Saravanan K, Kannan R, John RR, Kumar CN. A single pre operative dose of sub mucosal dexamethasone is effective in improving post operative quality of life in the surgical management of impacted third molars: a comparative randomised prospective study. *J Maxillofac Oral Surg* 2016;**15**:67–71. <http://dx.doi.org/10.1007/s12663-015-0795-0>.
51. Ghensi P, Cucchi A, Creminelli L, Tomasi C, Zavan B, Maiorana C. Effect of oral administration of bromelain on postoperative discomfort after third molar surgery. *J Craniofac Surg* 2017;**28**:e191–7. <http://dx.doi.org/10.1097/SCS.00000000000003154>.
52. Neupert LE, Lee LJ, Philput CB, Gordon LJ. Evaluation of dexamethasone for reduction of postsurgical sequelae of third molar removal. *J Oral Maxillofac Surg* 1992;**40**:1177–82.
53. Skjelbred P, Loken P. Reduction of pain and swelling by a corticosteroid injected 3 hours after surgery. *Eur J Clin Pharmacol* 1982;**23**:141–6.
54. Sisk AL, Bonnington GJ. Evaluation of methylprednisolone and flurbiprofen for inhibition of the postoperative inflammatory response. *Oral Surg Oral Med Oral Pathol* 1985;**60**:137–45.
55. Schmelzeisen R, Frolich JC. Prevention of postoperative swelling and pain by dexamethasone after operative removal of impacted third molar teeth. *Eur J Clin Pharmacol* 1993;**44**:275–7.
56. Holland SC. The influence of methylprednisolone on post-operative swelling following oral surgery. *Br J Oral Maxillofac Surg* 1987;**25**:293–9.
57. Tiwana PS, Foy SP, Shugars DA, Marciani RD, Conrad SM, Phillips C, White Jr RP. The impact of intravenous corticosteroids with third molar surgery in patients at high risk for delayed health-related quality of life and clinical recovery. *Oral Maxillofac Surg* 2005;**63**:45–62. <http://dx.doi.org/10.1016/j.joms.2004.01.029>.
58. Tiigimae-Saar J, Leibur E, Tamme T. The effect of prednisolone on reduction of complaints after impacted third molar removal. *Stomatologija* 2010;**12**:17–22.
59. Warraich R, Faisal M, Rana M, Shaheen A, Gellrich NC, Rana M. Evaluation of postoperative discomfort following third molar surgery using submucosal dexamethasone—a randomized observer blind prospective study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;**116**:16–22. <http://dx.doi.org/10.1016/j.oooo.2012.12.007>.
60. Beirne R, Hollander B. The effect of methylprednisolone on pain, trismus, and swelling after removal of third molars. *Oral Surg Oral Med Oral Pathol* 1986;**61**:134–8.
61. Moore PA, Brar P, Smiga ER, Costello BJ. Preemptive rofecoxib and dexamethasone for prevention of pain and trismus following third molar surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2005;**99**:e1–7. <http://dx.doi.org/10.1016/j.tripleo.2004.08.028>.
62. Campbell WI, Kendrick RW. Postoperative dental pain a comparative study of anti-inflammatory and analgesic agents. *Ulster Med J* 1991;**60**:39–43.
63. Baxandele BR, Vater M, Lavery KM. Dexamethasone reduces pain and swelling following extraction of third molar teeth. *Anaesthesia* 1993;**48**:961–4.
64. Leone M, Richard O, Antonini F, Rousseau S, Chabaane W, Guyot L, Martin C. Comparison of methylprednisolone and ketoprofen after multiple third molar extraction: a randomized controlled study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007;**103**:e7–9. <http://dx.doi.org/10.1016/j.tripleo.2006.07.005>.
65. Mehra P, Reebye U, Nadershah M, Cottrell D. Efficacy of anti-inflammatory drugs in third molar surgery: a randomized clinical trial. *Int J Oral Maxillofac Surg* 2013;**42**:835–42. <http://dx.doi.org/10.1016/j.ijom.2013.02.017>.
66. Magrin S, Megliani A, Del Fabbro M, Taschieri S, Di Marco A, Jones JM. Efficacy of corticosteroid therapy in lower third molar surgery: a prospective trial. *Ital Oral Surg* 2010;**9**:47–60. <http://dx.doi.org/10.1016/j.ios.2010.01.008>.
67. Salengro A, Berger J, Amasse L. Does dexamethasone have analgesic effect? *Le Praticien en Anesthésie Réanimation* 2009;**13**:283–6. <http://dx.doi.org/10.1016/j.pratan.2009.07.016>.
68. Carranza HO, Abanto AS, Guevara RG. Efectividad del tratamiento profiláctico con dexametasona 8y 4mg para controlar el edema poscirugía de terceros molares incluidos: ensayo clínico aleatorizado de grupos en paralelo. *Revista Española de Cirugía Oral y Maxilofacial* 2013;**3**(5):157–61. <http://dx.doi.org/10.1016/j.maxilo.2013.05.006>.
69. Christensen J, Matzen LH, Søren Schou S, Væth M, Wenzel A. Is thermography useful for assessment of postoperative inflammation after surgical removal of mandibular third molars when methylprednisolone is administered and how does it correlate with patients' perception of swelling? *Oral Maxillofac Surg* 2014;**72**:463–9. <http://dx.doi.org/10.1016/j.joms.2013.09.035>.
70. Bhargava D, Deshpande A, Khare P, Pandey SP, Thakur N. Validation of data on the use of twin mix in minor oral surgery: comparative evaluation of efficacy of twin mix versus 2% lignocaine with 1: 200000 epinephrine based on power analysis and an UV spectrometry study for chemical stability of the mixture. *Oral Maxillofac Surg* 2015;**19**:37–41. <http://dx.doi.org/10.1007/s10006-014-0446-5>.
71. Latt MM, Kiattavorncharoen S, Boonsiriseth K, Pairuchvej V, Wongsirichat N. The efficacy of dexamethasone injection on postoperative pain in lower third molar surgery. *J Dent Anesth Pain Med* 2016;**16**:95–102. <http://dx.doi.org/10.17245/jdapm.2016.16.2.95>.
72. Deo SP. Role of addition of dexamethasone to lignocaine 2% with adrenaline in dental nerve blocks for third molar surgery: a prospective randomized control trial. *Ann Maxillofac Surg* 2016;**6**:260–6. <http://dx.doi.org/10.4103/2231-0746.200341>.
73. Zwan J, Boering G, Wesseling H, Sibinga CS, Weele L. The lower third molar and antiphlogistics. *Int J Oral Surg* 1982;**11**:340–50.
74. Koçer G, Yuce E, Oncul AT, Dereci O, Koskan O. Effect of the route of administration of methylprednisolone on oedema and trismus in impacted lower third molar surgery. *Int J Oral Maxillofac Surg* 2014;**43**:639–43. <http://dx.doi.org/10.1016/j.ijom.2013.11.005>.
75. Alcântara CE, Falci SG, Oliveira-Ferreira F, Santos CR, Pinheiro ML. Pre-emptive effect of dexamethasone and methylprednisolone on pain, swelling, and trismus after third molar surgery: a split-mouth randomized triple-blind clinical trial. *Int J Oral Maxillofac Surg* 2014;**43**:93–8. <http://dx.doi.org/10.1016/j.ijom.2013.05.016>.
76. Herrera-Briones FJ, Prados Sánchez E, Reyes Botella C, Vallecillo Capilla M. Update on the use of corticosteroids in third molar surgery: systematic review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2013;**116**:e342–51. <http://dx.doi.org/10.1016/j.oooo.2012.02.027>.
77. Ngeow WC, Lim D. Do corticosteroids still have a role in the management of third molar surgery? *Adv Ther* 2016;**33**:1105–39. <http://dx.doi.org/10.1007/s12325-016-0357-y>.
78. Alexander RE, Thronson RR. A review of perioperative corticosteroids use in dentoalveolar surgery. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2000;**90**:406–15. <http://dx.doi.org/10.1067/moe.2000.109778>.
79. Moraschini V, Hidalgo R, Porto Barboza ES. Effect of submucosal injection of dexamethasone after third molar surgery: a meta-analysis of randomized controlled trials. *J Oral Maxillofac Surg* 2016;**45**:232–40.

Address:

Belmiro Cavalcanti do Egito Vasconcelos
 Department of Oral and Maxillofacial Surgery
 University of Pernambuco – School of Dentistry (UPE/FOP)
 Av. General Newton Cavalcanti
 1650 – Tabatinga
 Camaragibe
 PE 54.756-220
 Brazil
 E-mail: belmirovasconcelos@gmail.com