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ORIGINAL ARTICLE

Beneficial effect of methylprednisolone after mandibular third molar surgery: a randomized, double-blind, placebo-controlled split-mouth trial

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Abstract
Objectives Third molar (M3) removal is the model most frequently used for pain trials in oral surgery. Corticosteroids are frequently administered to reduce trismus and swelling after dentoalveolar surgical procedures. The purpose of this investigation was to evaluate the influence of a single, preoperative oral application of methylprednisolone on postoperative trismus, pain intensity, and the subjective need for analgesic medication after surgical removal of impacted mandibular M3 (LM3).
Materials and methods Sixteen healthy patients requiring similar bilateral surgical LM3 removal were included in a prospective, randomized, placebo-controlled, double-blind study in a split-mouth design. At random, each patient received either weight-dependent methylprednisolone (40–80 mg) or a placebo orally 1 h prior to surgery. In each case, the right and left LM3 were treated in independent visits. Trismus, swelling, pain measured on a 100-mm visual analog scale, and the postoperative demand of analgesics were assessed.
Results Statistical analysis indicates a significant reduction of trismus, swelling, pain intensity, and patient-controlled intake of analgesics during the whole postsurgical period of investigation (first to seventh day).
Conclusions The results of this study suggest that a single preoperative weight-dependent administration of methylprednisolone is a safe and effective concept for diminishing postoperative discomfort, pain intensity, and the total intake of analgesics after wisdom tooth extractions.
Clinical relevance In case of missing contraindications, the preoperative administration of methylprednisolone is recommended, a routine medication for more extended procedures in oral surgery.

Keywords Third molar surgery · Methylprednisolone · Corticosteroids · Postsurgical pain · Analgesic therapy

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Introduction

Dentoalveolar interventions are generally associated with postoperative pain of variable intensity, swelling of the facial soft tissues, and reduced mouth opening [1–4]. Most sequelae are based on an individually varying physiological inflammatory response in the perisurgical area [5–10], depending on the degree of tissue trauma and the extent of bone manipulation [9–11]. Immediate implications are mild to moderate pain and, as a consequence, an increased analgesic request for several days.

The surgical removal of an impacted third lower molar (LM3) is a very common surgical procedure in clinical practice and a well-documented model for investigating the efficacy of analgesics for postoperative pain management in oral surgery [1, 2, 5–18].

Corticosteroids, like methylprednisolone, dexamethasone, or betamethasone, are potent and widely used inhibitors of inflammation because of their suppressive impact on the synthesis and release of inflammatory tissue mediators [10–13, 19, 20]. A significant reduction of edema and

trismus following steroid application after mandibular third molar (LM3) removals has been reported [2, 8, 14–17, 21, 22] as well as a decrease in post-interventional pain [9, 11]. Therefore, several investigators have stated that corticosteroids are effective adjuncts in peri-operative pain management, although steroids do not have a clinically significant analgesic impact themselves [9, 18, 23]. However, the administration of these drugs must be limited in time and dosage [13] to minimize the risk of potential side effects such as adrenal suppression, hyperglycemia, infections, or delayed wound healing [5, 7, 8].

The pre-emptive analgesic effect of steroids in oral surgery has been assessed in an inconsistent way in scientific papers. In addition, previous studies did not sufficiently focus on patients' post-interventional pain and their need for pain treatment. Furthermore, there exists no consensus regarding agent, route, timing, duration, and dosage of administration.

The purpose of this clinical trial was to evaluate the effect of a single dose of methylprednisolone orally administrated preoperatively on the postoperative sequelae and the post-interventional demand of analgesics after third molar removal.

Patients and methods

Ethics

The study protocol and the informed consent form were approved by the Research and Ethics Committee of the Medical University Graz, Austria (no.19-086 ex 07/08) and by the European Community Clinical Trial System at the European Medicines Agency for the Monitoring of Clinical Trials in Europe (no. 2007-006252-19). The trial adhered to Good Clinical Practice guidelines, including the Declaration of Helsinki.

All patients were informed about possible risks and benefits associated with the intervention and study medication. A detailed written informed consent according to the WMA Declaration of Helsinki (www.wma.net/en/30publications/10policies/b3/index.html) was signed at least 24 h before surgery.

Study design

A prospective, randomized, placebo-controlled study in a split-mouth design was conducted. Inclusion and exclusion criteria are presented in the following:

Inclusion criteria

- Adults of both gender (age<30 years);
- To date asymptomatic LM3;
- On panoramic radiographs, symmetrically impacted LM3 of moderate surgical difficulty according to Pederson et al. [24] (Table 1); and
- Patient's written informed consent.

Exclusion criteria

- Contraindications for the use of the study medication;
- Significant stomatognathic disorders;
- Acute facial traumata;
- Significant medical history (e.g., anaphylaxis, gastrointestinal disease, severe systemic diseases or adverse health conditions, hematological disease, deficiency of coagulation, etc.);
- Pregnancy and breast feeding; and
- Contraindications for oral surgery (e.g., acute signs and symptoms of infection in the surgical area) itself.

Pregnancy was excluded using hCG midstream urine test kit (hCG-Pregnancy Test®; Dia-Chrom, Vienna, Austria).

Study variables

The primary aim of this trial was to assess the influence of a preoperative administration of methylprednisolone on mouth-opening ability, pain, and the summative ad libitum dosage of non-steroidal anti-inflammatory drug (NSAID) analgesics after LM3 removals. As a secondary aim, the gradient of facial swelling, in particular, a rebound phenomenon after anti-inflammatory medication, as well as the incidence of complications and adverse drug reactions were recorded.

Table 1 Pederson [24] Difficulty Index (PDI) for the surgical removal of impacted mandibular third molars

Spatial relationship	
Mesioangular	1
Horizontal/transverse	2
Vertical	3
Distoangular	4
Depth	
High occlusal level (level A)	1
Medium occlusal level (level B)	2
Deep occlusal level (level C)	3
Ramus relationship/available space	
Sufficient space (class 1)	1
Reduced space (class 2)	2
No space (class 3)	3
Difficulty Index (Σ points)	
Very difficult	8–10
Moderately difficult	5–7
Slightly difficult	3–4

Sample size

Sample size calculation was performed taking into account the results of the study of Schultze-Mosgau et al. [8]. They reported a reduction in swelling of 56 % and in pain perception of 67.7 % following oral perioperative application of methylprednisolone. Based on these findings, the sample size calculation revealed, for a study collective of maximum homogeneity (Table 2), a need of 16 individuals, each with symmetrically impacted lower wisdom teeth of strictly comparable position and surgical level of difficulty (power, 0.8; alpha, 0.05).

Randomization and crossover design (split-mouth)

Patients were randomized for treatment group and surgeon by computerized tables prepared in advance. The side of the initial LM3 removal was defined by the patient.

Both surgical appointments of each patient were fixed separately with a time interval of at least 3 weeks. Both LM3 of the same patient were removed by the same surgeon.

Patients who received treatment A at the first LM3 removal received treatment B at the second surgical appointment, and vice versa.

Medication and blinding

Medication and data collection of the clinical investigation were double-blinded. The blinding (medication A and B) was carried out by the local clinical pharmacy preparing steroid (verum) and placebo capsules of identical type and aspect and similar flavor. The dosage of methylprednisolone (MP) was applied depending on patients' body weight. For the verum test phase, patients with a body weight less than 60 kg received 40 mg MP; patients with 60–80 kg received 60 mg MP, whereas patients with more than 80 kg body weight, a dosage of 80 mg MP was administered.

In advance of the first surgical appointment, patients received compound A or B containing either steroid or placebo according to the patient's randomization. The remaining compound containing the different receptacle was applied within the second surgical intervention obligatorily.

Four investigators were involved strictly following the protocol: One applied the medication; two accomplished the surgical third lower molar removal, and one evaluated the study parameters perioperatively. Both surgeons and examiners were blinded and not allowed to disclose their knowledge and suspicions.

Study protocol, assessments, and data acquisition

Demographic data including age, gender, body weight, health history, and current medications were recorded (Table 2).

Preoperative protocol On the day of surgery, the stomatognathic system was examined according to Krough-Poulsen [25]. The surgical area was inspected for inflammatory symptoms, i.e., mucosal swelling, hyperemia, or exudation. One hour prior to surgery, the maximum mouth opening ability was examined. Therefore, the inter-incisal distance (millimeters) between the mesial corners of the upper and lower right central incisors at maximum opening of the jaws was recorded as baseline-reference for evaluation of postoperative trismus.

Additionally, facial width was measured using a modification [8] of the non-invasive tape measuring method first-described by Gabka and Matsumara [26]. Three distances between five anatomic reference points were evaluated: length between lateral corner of the eye and angle of the mandible, between tragus and lateral corner of the mouth, and between tragus and soft tissue pogonion.

In advance of the first intervention, patients received the study medication as described previously. One hour prior to surgery, the capsule was administered.

Surgical technique The LM3 removal was performed under local anesthesia by two experienced surgeons in an outpatient unit at the Department of Oral Surgery and Radiology, Medical University Graz, Austria. For mandibular nerve block and local infiltration, articaine (Ultracain dental forte® with 1:100,000 epinephrine, Sanofi Aventis, Vienna, Austria) was used. The surgical procedure was performed standardized via an envelope flap access [27, 28] following crestal and buccal osteotomy, tooth section and removal, and finally, wound closure by suturing. Both sides of each patient were dealt with the same surgeon in separate visits. The duration of surgery was recorded.

Table 2 Demographics and surgical variables

		Steroid group	Placebo group
Count of probands	Total (female, male)	16 (10, 6)	16 (10, 6)
Age, years	Mean (SD)	23, 9 (3, 3)	23, 9 (3, 3)
Body weight, kg	Mean (SD)	65, 5 (8, 4)	65, 5 (8, 4)
Surgical difficulty, Pederson°	Mean (SD)	6, 1 (0, 7)	6, 0 (0, 7)

Postoperative protocol All patients obtained facial cool packs immediately after surgery. For the post-interventional period, patients received a standardized scheme of antibiotic (amoxicillin 875 mg+clavulanic acid 125 mg, Augmentin® 1 g bid, GlaxoSmithKline Pharma, Vienna, Austria; for 5 days) and analgesic therapy (dexibuprofen, Seractil Forte® 400 mg, Gebro Pharma, Fieberbrunn, Austria; as required). To prevent gastrointestinal ulcera, a proton pump inhibitor (pantoprazole, Pantoloc® 20 mg, Nycomed Pharma, Vienna, Austria; once a day for 7 days) was applied [29].

Follow up Follow-up visits were conducted on the first, third, and seventh post-surgical day. Each visit, trismus was evaluated by measuring the inter-incisal distance at maximum mouth opening in relation to the preoperative account. Facial swelling was recorded as described previously. The presence of paresthesia, fatigue, wound infection, or further complications was also noted.

Furthermore, patients were advised to record pain intensity using a simplified 100-mm visual analogue scale (VAS)—with marginal values "0" for "no pain" and "10" for "maximum pain intensity"—three times a day (morning/noon/evening) for 7 days and to document their analgesic doses taken ad libitum for the whole period of investigation. The surgical routine and the study protocol were completed by the suture removal on day 7.

Statistics

All statistical analyses used general linear model with repeated measurements running SPSS 15.0 statistical analysis system for Windows (SPSS Inc., Chicago, IL, USA; campus license). $P<0.05$ was considered as statistically significant.

Results

Demographic and surgical data

Age, gender, and body weight as presented in Table 2 were included in the statistical analyses but did not implicate any significant influence on the investigated study parameters. The difficulty of the removed impacted LM3 scored from 5 to 7 (Table 2) according to the Pederson Difficulty Index [24] (Table 1). The duration of the surgeries did not vary relevantly.

Trismus

Data analysis revealed a significant difference between the steroid group and placebo group on the first ($P=0.001$) and third ($P=0.001$) post-interventional days (Table 3). The restriction of the mouth opening in the steroid group (day 1, 10.3 %; day 3, 5.4 %) was less than in the placebo group (day 1, 31.3 %; day 3, 20.4 %). On the seventh day after surgery, maximal inter-incisal opening approximated the preoperative situation in both groups ($P=0.462$) (Fig. 1).

Pain intensity

Throughout the whole study period, VAS pain scores of the steroid group revealed a significant lower level ($P=0.001$) than in the placebo group (Table 4). The steroid group's mean graph started and ended more than 10 mm lower than the placebo group's graph on a 100 mm scale. Both scores decreased significantly over time ($P=0.05$).

Analgesic drug demand

For the whole study period, analgesic intake in the steroid group was significantly ($P=0.019$) decreased compared with the placebo group (Fig. 2). The mean of daily analgesic doses diminished in both groups significantly over time ($P=0.001$).

Swelling

The evaluation of swelling was not a primary aim of this study. Nevertheless, the measurement of all investigated anatomic distances revealed a reduced increase in steroid group compared with placebo group at which day 1 and day 3 showed a significant difference between the two groups ($P=0.001$). No rebound phenomenon was observed.

Complications and side effects

Over the entire observation period, we did not observe any drug-related adverse side effects or local post-operative complications, neither in the steroid nor in the placebo group. Wound healing was similar for each side.

Discussion

This study is presenting a significantly reduced request of pain medication after a single preoperative steroid application for up to 7 days after surgical wisdom tooth removals. A great number of papers about clinical evaluations support the decisive therapeutic role of steroids in reducing post-surgical discomfort in oral surgery. To our knowledge, no previous report documents a significant reduction of postoperative analgesics demand, although a multitude of studies confirm a considerable relief of pain and trismus after third molar surgery as a result of a steroid medication [2, 5–13, 15–18, 20–23, 29–34].

Generally, dexamethasone (DM) and MP are the preferred steroids due to their mainly glucocorticoid and

Table 3 Mouth opening ability (millimeters inter-incisal distance)

	Steroid group							Placebo group						
Time	Mean	SD	Min	Max	Median	95 % CI		Mean	SD	Min	Max	Median	95 % CI	
Preop	47.7	7.3	36.6	63.6	47.3	43.8	51.2	48.9	6.2	40.5	59.7	47.8	45.6	52.2
Day 1	42.7	6.0	32.7	53.1	42.4	39.4	45.9	33.5	5.6	27.0	47.4	33.4	30.4	36.5
Day 3	44.8	6.2	34.4	56.3	43.4	41.5	48.1	38.9	6.9	29.9	54.2	37.6	35.2	42.5
Day 7	46.5	5.9	37.9	55.8	46.7	43.3	49.6	44.5	8.8	32.1	58.7	40.8	39.8	49.2

minimal mineralocorticoid effects [20, 24]. Esen et al. [22] and Graziani et al. [13] suggest the short-acting MP for short-term medication and moderate dosage to avoid postoperative complications. Instead of MP, some authors prefer the use of the longer-acting DM, because of its extended intermediate duration of action, described as 12 to 36 h [32], or reapplied administration of steroids up to 3 days [12, 16, 18, 30, 33].

A persuasive argument for the use of DM is the prevention of a swelling rebound on the second and third postoperative days. However, by using MP, we did not observe any swelling rebound in our study group, and, according to our results, we can state that, in cases of average surgical removal of wisdom teeth, there was no need for multiple steroid application [30].

Various routes of application (PO, IV, IM, submucosal) have been advocated. Esen et al. [22] observed a significant decrease of edema, besides trismus and facial pain, in patients receiving a single pre-interventional administration of 125 mg MP intravenously. Graziani et al. [13] compared the intraoperative application of an endo-alveolar powder or submucosal injection into the operation site and observed an effective reduction of postoperative sequelae. Grossi et al. [20] chose the route of submucosal injection of DM intraoperatively. The intramuscular route of steroid application has also been shown to decrease sequelae in the immediate post-interventional period [11]. But there are several stringent reasons to avoid the intramusculous application of steroids, viz., (1) a slower onset of action highly dependent on the rate of blood flow at the site of administration [9]; (2) an increased risk of adrenal suppression is described [5, 17, 22], and (3) local complications such as necrosis, hematoma, and abscess can be adverse results of intramuscular injections.

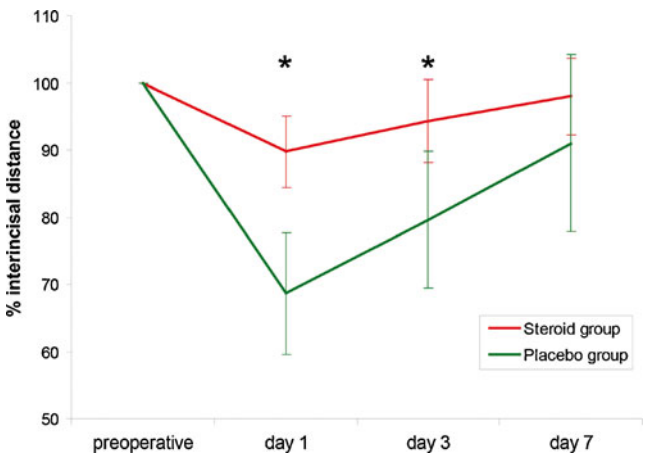

Fig. 1 *Graph* of steroid and placebo group demonstrating the trends of postoperative trismus in relation to the preoperative inter-incisal distance (100 %)

As a result of the instant plasma drug concentration, the intravenous application is frequently considered to be the most effective route of medication [9, 17, 22, 33].

However, steroids such as DM and MP have a very high enteral absorption rate ensuring an effective reduction of post-interventional sequelae [35, 36] comparable with intravenous application [8, 14, 17, 18]. As the mode of administration does not affect the efficacy of corticosteroids significantly, the oral route can be preferred due to its comfortable handling.

Regarding the dosage, Huffman et al. [30] did not observe any statistically significant clinical differences between the administration of 40 or 125 mg MP IV. Filho et al. [21] reported a significant reduction of trismus and swelling after wisdom tooth removals in both study groups using 4 or 8 mg of DM PO 1 h prior to surgery. Eight milligrams DM promoted greater effects than half the dose, but the investigators saw no influence on pain control. Grossi et al. [20] compared the same doses (4 and 8 mg of DM) and placebo as submucosal injections intraoperatively into the operative site. Facial edema was significantly reduced in both DM groups on the second postoperative day, but increasing the dose did not provide any further benefit. Additionally, they observed no significant effect on pain and trismus. Üstün et al. [5] compared the efficacy of two intravenous dosages of methylprednisolone. No significant benefit of 3 mg/kg MP in comparison with 1.5 mg/kg was detected. However, all these working groups compared rather high dosages, each effective in pain and swelling control for common oral surgery. On the other hand, Schultze-Mosgau et al. [8] noted a decrease in swelling of 56 % and in pain perception of 67.7 % after a perioperative application of 64 mg methylprednisolone PO. And, as Milles

Table 4 Pain intensity evaluated on a 100-mm visible analogue scale (VAS)

		Steroid group						Placebo group					
		Min	Max	Mean	SD	CI 95 %		Min	Max	Mean	SD	CI 95 %	
Day 1	Morning	0	52	24.31	16.39	16.28	32.34	4	94	47.25	24.18	35.40	59.10
	Noon	0	68	23.38	18.97	14.08	32.67	3	96	40.88	22.81	29.70	52.05
	Evening	0	52	20.44	16.98	12.12	28.76	0	75	39.19	25.49	26.70	51.68
Day 2	Morning	0	62	23.06	18.80	13.85	32.28	0	94	38.00	23.59	26.44	49.56
	Noon	0	42	13.38	14.04	6.49	20.26	0	59	28.94	14.90	21.64	36.24
	Evening	0	51	16.81	17.90	8.04	25.58	0	58	29.94	18.29	20.98	38.90
Day 3	Morning	0	58	14.13	15.37	6.59	21.66	0	48	23.88	14.01	17.01	30.74
	Noon	0	64	12.88	17.83	4.14	21.61	0	41	22.63	11.95	16.77	28.48
	Evening	0	63	14.94	17.45	6.39	23.49	0	55	24.19	15.92	16.39	31.99
Day 4	Morning	0	37	11.13	12.24	5.13	17.12	0	37	17.94	12.37	11.87	24.00
	Noon	0	39	10.25	12.49	4.13	16.37	0	34	17.63	10.86	12.30	22.95
	Evening	0	32	10.31	12.08	4.40	16.23	2	50	21.25	16.18	13.32	29.18
Day 5	Morning	0	25	7.88	7.92	4.00	11.75	0	35	12.19	11.00	6.80	17.58
	Noon	0	28	7.63	8.45	3.48	11.77	0	38	11.00	9.83	6.19	15.81
	Evening	0	34	7.88	9.72	3.11	12.64	0	48	17.50	15.92	9.70	25.30
Day 6	Morning	0	18	4.81	6.23	1.76	7.87	0	81	16.19	20.74	6.03	26.35
	Noon	0	34	5.00	8.94	0.62	9.38	0	92	13.19	22.51	2.16	24.22
	Evening	0	33	7.44	9.94	2.57	12.31	0	94	18.06	24.26	6.17	29.95
Day 7	Morning	0	12	2.88	4.38	0.73	5.02	0	100	18.25	30.33	3.39	33.11

CI confidence interval

and Desjardins [18] still noted, a significant reduction in swelling (42 % to 19 % decrease) during days 1–3 after M3 removal using 16 mg MP orally the evening before surgery and 20 mg MP intravenously immediately prior to surgery, it might be concluded that higher doses of corticosteroids are generally not necessary to achieve a significant clinical benefit.

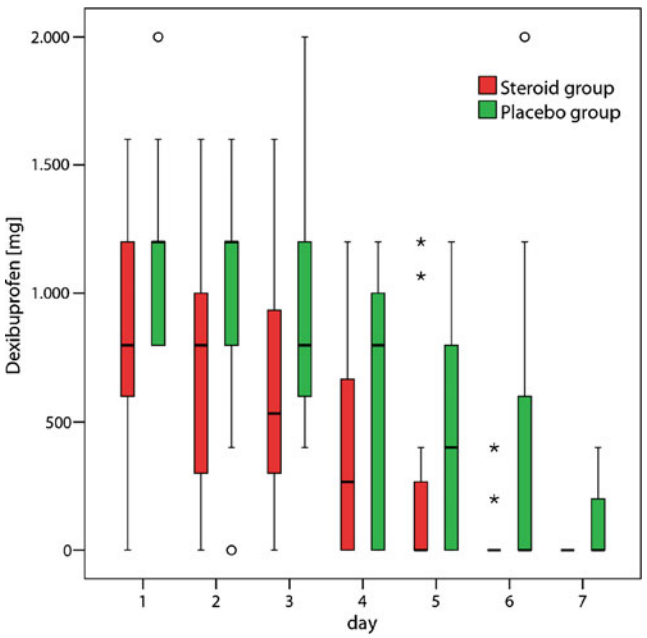

Fig. 2 *Box plot* illustrating the progression of the daily overall analgesics consumption (milligrams dexibuprofen) in steroid and placebo groups

Optimal therapeutic doses are generally identified in terms of drug per kilogram of patients' body weight [5, 30, 35]. The aforementioned concept of our study followed this premise.

Our study shows good clinical results of a preoperative administration of an anti-inflammatorily acting steroid with preventive impact in combination with NSAIDs postoperatively. Buyukkurt et al. [11] (immediately postoperative prednisolone+diclofenac IM), Bamgbose et al. [14] (pre- and postoperative DM IV+diclofenac PO), and Hargreaves et al. [35] (preoperative DM+Ketorelac IV) examined this co-administration of corticosteroids and NSAIDs on postoperative pain, trismus, and edema and concluded that a perioperative combination therapy is more effective in decreasing post-interventional sequelae. In contrast to their study designs, we solely chose the oral route, splitting the administration of steroid and NSAIDs and achieved similar results.

The spectrum of dosages of steroids and routes of administration is diverging, but there is one well-established consensus throughout most studies. Steroids have to be applied before tissue injury occurs [35–37] to achieve an adequate

tissue level in the immediate postoperative period [5, 12]. Some authors strongly recommend the administration at least 2 h preoperatively [17, 35, 36]. Filho et al. [21] reports the administration 1 h prior to surgery PO. Huffmann [30] reports a reduced post-interventional facial swelling in patients applying MP (125 mg IV) immediately before M3 surgery.

One may argue the small sample size is a weakness of our study. This sample size is the result of the calculation basing on the publication of Schultze-Mosgau et al. [8], reporting a reduction in swelling of 56 % and in pain perception of 67.7 %. The calculation was correct as illustrated by the significant results regarding all reported variables. This may be supported by the stringent study design, the homogenous study sample, and the intra-individual comparison of two medications in two identical surgical interventions, as well as a result of the highly potent anti-inflammatory impact of the study medication.

Conclusion

The findings of the present study indicate that a single, preoperative, oral administration of methylprednisolone is a suitable preventive measure to diminish postoperative discomfort and the need for pain medication. For clinical practice, our study supports the routine application of steroids for medium-sized and larger procedures in oral surgery. Hence, study models using other standardized oral surgical procedures (e.g., osseous augmentations like sinus lift) should be conducted to confirm the clinical benefit of steroids in oral and maxillofacial surgery.

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Conflict of interest The authors declare that they have no conflict of interest.

References

1. Kirmeier R, Truschnegg A, Payer M, Acham S, Schulz K, Jakse N (2007) Evaluation of muscle relaxant of sequelae of third molar surgery: a pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 104:e8–e14
2. Zandi M (2008) Comparison of corticosteroids and rubber drain for reduction of sequelae after third molar surgery. J Oral Maxillofac Surg 12:29–33
3. Martin MV, Kanatas AN, Hardy P (2005) Antibiotic prophylaxis and third molar surgery. Br Dent J 198:327–330
4. Yuasa H, Kawai T, Sugiura M (2004) Classification of surgical difficulty in extracting impacted third molars. Br J Oral Maxillofac Surg 40:26–31
5. Üstün Y, Erdogan Ö, Esen E, Karsli E (2003) Comparison of the effects of 2 doses of methylprednisolone on pain, swelling, and trismus after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 96:535–539
6. Douglass LJ (1999) Determination of the anti-Inflammatory effects of methylprednisolone on the sequelae of third molar surgery. J Oral Maxillofac Surg 57:1206–1208
7. Lopez-Carriches C, Martinez-Gonzalez JM, Donaldo-Rodriguez M (2006) 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 11:E440–445
8. Schultze-Mosgau S, Schmelzeisen R, Frölich JC, Schmele H (1995) Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 53:2–7
9. Kim K, Brar P, Jakubowski J, Kaltman S, Lopez E (2009) The use of corticosteroids and nonsteroidal anti-inflammatory medication for the management of pain and inflammation after third molar surgery: a review of the literature. Oral Surg Oral Med oral Pathol Oral Radiol Endod 107:630–640
10. Markovic MR, Brady MF, Ding EL, Dodson TB (2008) Corticosteroids reduce postoperative morbidity after third molar surgery: a systematic review and meta-analysis. J Oral Maxillofac Surg 66:1881–1894
11. Buyukkurt MC, Gungormus M, Omer K (2006) 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 64:1761–1766
12. Alexander RC, Trondson RR (2000) A review of perioperative corticosteroid use in dentoalveolar surgery. Oral Surg Oral Med oral Pathol Oral Radiol Endod 90:406–415
13. Graziani F, D'Aiuto F, Arduino PG, Tonelli M, Gabriele M (2006) Perioperative dexamethasone reduces post-surgical sequelae of wisdom tooth removal. A split-mouth randomized double-masked clinical trial. Int J Oral Maxillofac Surg 35:241–246
14. Bamgbose BO, Akinwande JA, Adeyemo WL, Ladeinde AL, Arotiba GT, Ogunlewe MO (2005) Effects of co-administered dexamethasone and diclofenac potassium on pain, swelling and trismus following third molar surgery. Head & Face Medicine 1:11
15. Ordulu M, Aktas I, Yalcin S, Azak AN, Evlioglu G, Disci R, Emes Y (2006) Comparative study of the effect of tube drainage versus methylprednisolone after third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 101:e96–e100
16. Moore PA, Brar P, Smiga ER, Costello BJ (2005) Preemptive rofecoxib and dexamethasone for prevention of pain and trismus following third molar surgery. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 99(2):E1–E7
17. Mico-Llorens JM, Satorres-Nieto M, Gargallo-Albiol J, Arnabat-Dominguez J, Berini-Aytes L, Gay-Escoda C (2006) Efficacy of methylprednisolone in controlling complications after impacted lower third molar surgical extraction. Eur J Clin Pharmacol 62:693–698
18. Milles M, Desjardins PJ (1993) Reduction of postoperative facial swelling by low-dose methylprednisolone. J Oral Maxillofac Surg 51:987–991
19. Kawamura M, Hatanaka K, Saito M, Ogino M, Ono T, Ogino K, Matsuo S, Harada Y (2000) Are the anti-inflammatory effects of dexamethasone responsible for inhibition of the induction of enzymes involved in prostanoid formation in rat carrageenin-induced pleurisy? Eur J Pharmacol 400:127–135
20. Grossi GB, Maiorana C, Garramone RA, Borgonovo A, Beretta M, Farronato D, Santoro F (2007) Effect of submucosal injection of dexamethasone on postoperative discomfort after third molar surgery: a prospective study. J Oral Maxillofac Surg 65:2218–2226

21. Filho JRL, Maurette PE, Allais M, Cotinho M, Fernandes C (2008) Clinical comparative study of the effectiveness of two dosages of dexamethasone to control postoperative swelling, trismus and pain after the surgical extraction of mandibular impacted third molars. Med Oral Pathol Oral Cir Bucal 13:E129–E132
22. Esen E, Tasar F, Akhan O (1999) Determination of the anti-inflammatory effects of methylprednisolone on the sequelae of third molar surgery. J Oral Maxillofac Surg 57:1201–1206
23. Beirne OR, Hollander B (1986) The effect of methylprednisolone on pain, trismus, and swelling after removal of third molars. Oral Surg Oral Med Oral Pathol 61(2):134–138
24. Pederson GW (1988) Oral surgery. WB Saunders, Philadelphia, Cited in: Koerner KR. The removal of impacted third molars—principles and procedures. Dent Clin North Am 1994;38:255–278
25. Krogh-Poulsen WG, Olsson A (1966) Occlusal disharmonies *and dysfunction of the stomatognathic system*. Dent Clin North Am 11:627–635
26. Gabka J, Matsumura T (1971) *Measuring techniques* and clinical testing. 34. Of an anti-inflammatory agent (tantum). Munch Med Wochenschr 113:198–203
27. Jakse N, Bankaoglu V, Wimmer G, Eskici A, Pertl C (2002) Primary wound healing after lower third molar surgery: evaluation of 2 different flap designs. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 93:7–12
28. Pajarola GF, Jaquiery C, Lambrecht JT, Sailer HF (1994) The extraction of retained mandibular wisdom teeth (II). The surgical technique, follow-up and complications. Schweiz Monatsschr Zahnmed 104:1520–1534
29. Piper JM, Ray WA, Daugherty JR, Griffin MR (1991) Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Annals of Internal Medicine 114(9):735–740
30. Huffmann G (1977) Use of methylprednisolone sodium succinate to reduce postoperative edema after removal of impacted third molars. J Oral Surg 35:198–199
31. Leone M, Richard O, Antonini F, Rousseau S, Chabaane W, Guyot L, Martin C (2007) Comparison of methylprednisolone and ketoprofen after multiple third molar extraction: a randomized controlled study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 103(1):e7–e9
32. Lopez-Carriches C, Martinez-Gonzalez JM, Donado-Rodriguez M (2005) Analgesic efficacy of diclofenac versus methylprednisolone in the control of postoperative pain after surgical removal of lower third molars. Med Oral Patol Oral Cir bucal 10:432–439
33. Schaberg SJ, Stuller CB, Edwards SM (1984) Effect of methylprednisolone on swelling after orthognathic surgery. J Oral Maxillofac Surg 42:356–361
34. Holland CS (1987) The influence of methylprednisolone on postoperative swelling following oral surgery. Br J Oral Maxillofac Surg 25:293
35. Hargreaves KM (1995) Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. J Oral Maxillofac Surg 53:7–8
36. Bahn SL (1982) Glucocorticosteroids in dentistry. J Am Dent Assoc 105:476–481
37. Hargreaves KM, Costello A (1990) Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. Clin Pharmacol Ther 48:168–178