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Meta-Analysis
Oral Surgery

Does methylprednisolone improve postoperative outcomes after mandibular third molar surgery? A systematic review and meta-analysis

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Abstract. This systematic review and meta-analysis was performed to investigate whether methylprednisolone (MP) administered via any route improves postoperative outcomes (pain, trismus, and oedema) following mandibular third molar surgery. An electronic search of the PubMed, Scopus, Cochrane CENTRAL, and Google Scholar databases was performed to identify studies published in English up until January 2018. A total of 28 studies were included in the review: 25 randomized clinical trials (RCTs) and three controlled clinical trials. Studies were grouped according to the route of administration of MP for qualitative and quantitative analysis. Three studies were of 'high' quality and 22 were of 'medium' quality; three studies had a high risk of bias. Within the purview of the limitations of this review, the results showed that MP administered via any route significantly improves oedema in the early postoperative period, but has no effect on late postoperative oedema. Oral and intra-masseteric MP also seems to reduce pain and trismus in the early postoperative period. The results also indicate that oral MP may reduce late postoperative pain, while intra-masseteric MP may improve the late trismus outcome. More high quality RCTs are required to provide stronger evidence on the use of MP in third molar surgery.

Key words: prednisolone; oedema; trismus; pain; steroids; lower third molar surgery; postoperative sequelae; meta-analysis.

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The surgical removal of third molars is the most common oral surgical procedure performed worldwide. Due to the anatomical position of impacted third molars, both soft and hard tissue trauma occur during surgery[1]. With the presence of loose connective tissue and high vascularity, even a meticulous surgical technique can result in considerable postoperative

discomfort[2]. As the difficulty of the surgical extraction increases, the amount of trauma to the surgical site as well as the surrounding tissues increases proportionately. A greater amount of tissue injury leads to an increased amount of inflammation in the peri-surgical area. For healing to occur, this inflammatory process is necessary. Nevertheless, excessive inflammation often causes unnecessary pain, oedema, and trismus in the postoperative period[3]. The patient's quality of life is greatly affected, severely hampering routine activities[4].

A variety of methods have been used to prevent postoperative complications after third molar surgery, such as chlorhexidine rinses[5], systemic antibiotics[6], low-level laser therapy[7], the use of piezoelectric surgery[8], and pre-emptive pharmacotherapy, including corticosteroids[3], analgesics[9], and muscle relaxants[10]. Amongst the drugs used, researchers have shown considerable interest in the use of steroids to improve postoperative outcomes[3]. Ross and White were the first to confirm the advantage of using oral hydrocortisone against placebo in a double-blind study involving third molar surgery[11]. Corticosteroids have an inhibitory action on the enzyme phospholipase A_2, which reduces the release of arachidonic acid at the site of inflammation. This diminished amount of arachidonic acid reduces the stimulation of neutrophils to release prostaglandins and leukotrienes, and consequently there is a lower intensity of postoperative signs and symptoms[12].

The literature contains numerous studies that have used methylprednisolone (MP), betamethasone, triamcinolone, and dexamethasone in third molar surgery[3,13,14]. Among these, MP and dexamethasone are the most popular. The effect of submucosal dexamethasone in third molar surgeries has been reviewed recently[13,15]. The meta-analysis by Chen et al.[13] suggests that dexamethasone significantly reduces early and late oedema, as well as early trismus after third molar surgery, but that there is a lack of sufficient evidence regarding the effects on late trismus and pain. There remains a lack of consensus on the use of MP to improve postoperative sequelae after third molar surgery, with authors using different routes of administration of MP and reporting either no effect[2] or significant improvement in postoperative outcomes[14].

Therefore, the aim of this study was to systematically review and critically analyse the available evidence in order to answer the following clinical question: Does MP administered via any route improve postoperative outcomes (pain, trismus, and oedema) following impacted third molar surgery?

Materials and methods

Search strategy

This systematic literature review was performed following the guidelines of the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses)[16] and the *Cochrane Handbook for Systematic Reviews of Interventions*[17]. An electronic search of the PubMed, Scopus, CENTRAL (Cochrane Central Register of Controlled Trials), and Google Scholar databases was performed to identify papers published in the English language up to January 2018. Free text words and medical subject heading (MeSH) terms were used. The search strategy was conducted according to the PICOS criteria: Population, Intervention, Comparison, Outcome, and Study design. Key words for the 'population' were: molar [MeSH] OR third molar [MeSH] OR impacted tooth [MeSH]; for the 'intervention' were: methylprednisolone [MeSH] methylprednisolone succinate [MeSH] OR steroids [MeSH] OR prednisolone [MeSH] OR third molar surgery [all fields]; for the 'comparison' were: methylprednisolone [MeSH] OR placebo effect [MeSH]; for the 'outcomes' were pain [MeSH] OR oedema [MeSH] OR trismus [MeSH] OR post-operative [all fields]. Study designs searched were randomized clinical trials (RCTs) and controlled clinical trials (CCTs). The reference lists of the identified studies and relevant reviews on the subject were also scanned for additional possible studies. The clinical trials registry platforms www.clinicaltrials.gov and www.controlled-trials.com were searched for any ongoing trials.

Eligibility criteria

Inclusion criteria were the following: studies on patients requiring mandibular third molar surgery ('population'), involving the use of either preoperative, intraoperative, or postoperative MP via any route ('intervention') and comparison with the use of a placebo ('comparison'), and assessments to include pain, trismus, and/or oedema ('outcomes'). Considering only a minor difference between prednisolone and MP[18,19], studies using prednisolone were also included. The term 'MP' is generally used for both drugs in this review. Animal studies, retrospective cohort studies, clinical series, case reports, review papers, uncontrolled studies, and studies for which the full text was unavailable were excluded.

Data collection and analysis

All relevant studies were analysed separately by two reviewers (SAN and AJ) based on the inclusion criteria listed above for final selection. These two authors are also the guarantors of this study. The analysis was done first at the title and abstract level and then at the full-text level. Any disagreement was resolved by discussion with a third reviewer (IDR). Data extracted from the studies included the authors, year of publication, study type, randomization procedure, allocation concealment, use of blinding, number of patients, age and sex distribution of the sample, inclusion/exclusion criteria, classification of impacted third molars, time duration of the surgery, type of intervention, use of pre- or postoperative mouth rinse or antibiotics, outcome measures, follow-up period, and drop-outs. If necessary, the study authors were contacted via e-mail for missing data.

Risk of bias in individual studies

The risk of bias was assessed with the Cochrane Collaboration risk assessment tool for RCTs[20]. For each study, the following items were assessed for a low risk, high risk, or unclear risk of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The use of a split-mouth design was one of the factors included in the evaluation of the studies for 'other bias'.

Statistical analysis

The studies were divided into groups based on the route of administration of MP for systematic review and analysis. Final mean and standard deviation (SD) scores were used for the meta-analysis. A meta-analysis was conducted only if there were at least three studies of similar comparisons, reporting the same outcome measure. Review Manager software (RevMan, version 5.3, 2014; Nordic Cochrane Centre (Cochrane Collaboration), Copenhagen, Denmark) was used for the data analysis. A random-effects model was favoured to calculate the pooled effect of the intervention. The weighted mean difference (MD) or standard mean difference (SMD) was used to construct

forest plots of continuous data. The MD was used when the outcomes were reported on the same scale in the included studies, otherwise the SMD was used. For continuous variables, heterogeneity was evaluated using the I^2 statistic. This test estimates the percentage of variation between study results that is due to heterogeneity rather than sampling error. An I^2 value of less than 40% was considered unimportant, while a value of more than 40% was viewed as moderate to considerable heterogeneity.

Results

Search outcome

The search strategy revealed 636 records (Fig. 1). After the removal of duplicates, 157 articles were analysed by their abstracts. One hundred and fourteen articles were excluded because of non-relevance. The full text was not available for two articles[21,22], leaving a total of 41 articles for full text analysis. Twelve studies were excluded after full text review: three studies comparing MP with dexamethasone[23–25], two with diclofenac[26,27], one with serratiopeptidase[28], and one with celecoxib[29], one study comparing preoperative and postoperative administration of MP[30], one comparing intra-masseteric vs. gluteal route of administration of MP[31], one comparing two doses of MP[32], and one study that reported only the quality of life outcome[4]. The same sample was duplicated in two articles[33,34], hence only one paper was considered[33].

There were two articles by the same authors in which the research was conducted on the same sample[35,36]. In one article, swelling was measured using a patient-reported visual analogue scale (VAS)[35], while in the other article, thermography was used[36]. Since these two articles were of the same sample but with a different outcome variable reported in each paper, it was considered as a single trial. Thus, 29 articles were included in the systematic review, but with a total of 28 trials[1,2,14,33,35–59]. There were four studies where more than one route of administration of MP was compared with placebo[1,37,39,44]. Studies were grouped according to the route of administration of MP.

Quality assessment

The quality assessment of individual trials is presented in the **Supplementary Material** (File S1). Only six trials provided information on how the subjects were randomized[2,14,35,39,41,53]. A suitable method of allocation concealment was reported in eight studies[1,14,35,37,41,45,53,54]. Blinding of the participants and personnel was clearly reported in five studies[35,41,45,53,59] and blinding of outcome assessment in four[2,41,55,59]. Nine studies reported a split-mouth design[41,45,47–49,52,56,58,59], while all remaining studies used a parallel design. Based on the analysis of the methodological quality of the included studies, there were three studies of 'high' quality[35,45,59] and 22 of 'medium' quality[1,2,14,33,37–41,43,46–56,58]; three studies had a high risk of bias[42,44,57].

Characteristics of included studies

Of the 28 studies included in the review, 25 were RCTs[1,2,14,33,35–41,43,45–56,58,59] and three were CCTs[42,44,57]. Since CCTs can have differences between groups that could confound the differences in outcomes, all three CCTs, which were also trials rated with a high risk of bias, were excluded from the meta-analyses. The characteristics of all 28 studies classified according to the route of administration of MP are presented in Tables 1–5. The total numbers of patients (test group vs. placebo) reported in the studies were 488 vs. 462 for oral MP, 225 vs. 232 for intravenous (IV) MP, 88 vs. 88 for intramuscular (IM) MP, 122 vs. 119 for submucosal MP, and 128 vs. 128 for intra-masseteric MP. The dosage and time of administration of drug varied across studies. The MP dose varied from 8 mg to 80 mg via oral route, 20 mg to 125 mg via IV route, 20 mg to 40 mg via IM route, 10 mg to 40 mg via submucosal route, and 20 mg to 40 mg via intra-masseteric route.

Oral administration

In one study, combinations of lidocaine, bupivacaine, and oral MP were compared in a crossover trial[35]. To avoid bias, it was decided not to include the outcome variable 'pain' from this study in this review and meta-analysis. Of eight studies (**Supplementary Material**, File S2) comparing oral MP with placebo for the outcome variable 'pain'[37–39,41–45], five reported sufficient data for a meta-analysis[37–39,41,43]. One study had two subgroups[43]; hence there were a total of six groups for the analysis. There was a significant reduction in pain in the early postoperative period (2–3 days) with the use of oral MP (random-effects: SMD = −0.45, 95% CI −0.78 to −0.13; $P = 0.007$; $I^2 = 68\%$) (Fig. 2A). Similarly, analysis of the same studies showed a significant reduction in pain in the late postoperative period (7 days) (random-effects: SMD = −0.49, 95% CI −0.78 to −0.20; $P = 0.001$; $I^2 = 60\%$) (Fig. 2B).

The characteristics of studies reporting the outcome 'trismus' with the use of oral MP are presented in the **Supplementary Material** (File S3). Sufficient data were available in six studies for the meta-analysis[1,35,37–39,41]. Patients on oral MP had better mouth opening in the early postoperative period (random-effects: MD = 6.11, 95% CI 1.19 to 11.03; $P = 0.01$; $I^2 = 96\%$) (Fig. 2C); however there was no significant difference in mouth opening in the late postoperative period between the two groups (random-effects: MD = 2.63, 95% CI −3.29 to 8.55; $P = 0.38$; $I^2 = 97\%$) (Fig. 2D). Of the five studies not included in the meta-analysis, one used patient-reported trismus on a VAS and found no difference in the early or late postoperative period[43]. Two trials reported a significant difference in mouth opening in both the early and late postoperative period[40,42], while the other two showed no difference at both time intervals[44,45].

Ten studies (**Supplementary Material**, File S4) measured postoperative oedema with oral MP[1,36–39,41–45], of which four reported adequate data for a meta-analysis[1,37–39]. However, in one of the studies, a statistically significant difference in baseline facial measurements was seen between the experimental and control groups ($P = 0.009$)[38]. Hence, this study was excluded from the meta-analysis. The results of the remaining three studies indicated that while oral MP had a significant effect on oedema in the early postoperative period (random-effects: SMD = −0.56, 95% CI −0.84 to −0.28; $P < 0.0001$; $I^2 = 0\%$) (Fig. 2E), there was no significant difference in oedema in the late postoperative period (random-effects: SMD = −0.27, 95% CI −0.54 to 0.01; $P = 0.06$; $I^2 = 0\%$) (Fig. 2F). Of the remaining six studies[36,41–45], one used thermography, which the authors found not to be sensitive enough for the measurement of oedema[36]. One study used patient-reported oedema outcomes and found no difference in the early or late postoperative period[43]. Four trials noticed a significant difference in oedema in the early postoperative period[41,42,44,45], and two in the late postoperative period[38,44].

Intravenous administration

The outcome assessments for pain, trismus, and oedema by the studies reporting the use of IV MP are presented in the **Supplementary Material** (Files S5, S6, and S7, respectively). There was one study in which in addition to IV administration of MP, oral MP was prescribed postoperatively for 2

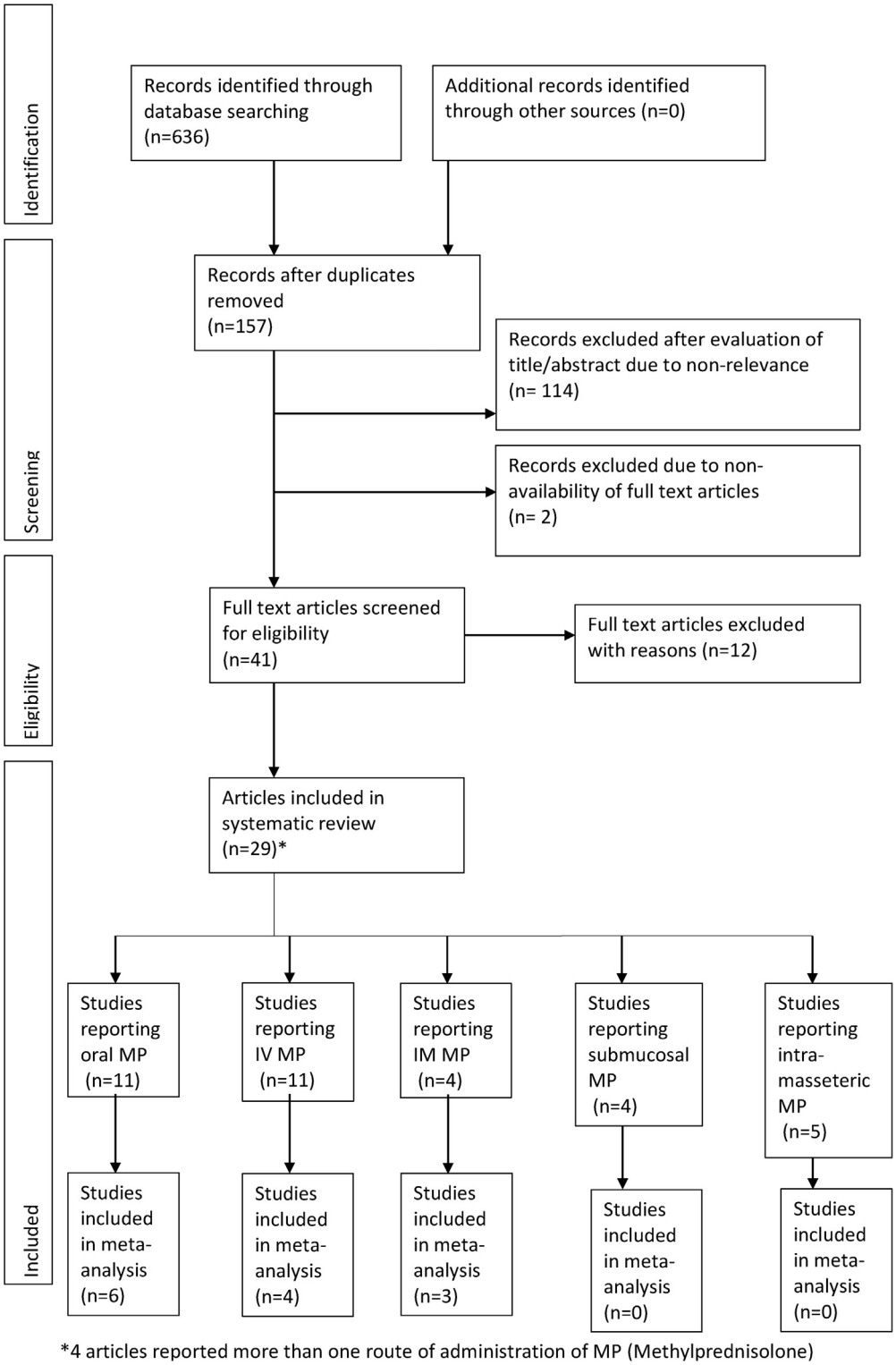

Fig. 1. Flowchart of the study selection process.

days[47]. This study was not included in the meta-analysis. With regard to the 11 studies in the IV group[1,37,46–54], there was considerable variation in the time and method of assessment of postoperative pain and oedema in addition to incomplete reporting of data. Hence a meta-analysis was not performed for these variables. Six studies reported no difference in early postoperative pain between the experimental and control groups[37,48,50,51,53,54]. Three studies reported a significant difference in pain reduction on either the first postoperative day[46,52] or during the early postoperative period[47]. Five studies reported late effects of IV MP on pain, with none demonstrating a significant difference between the groups[37,47,49,52,54].

Table 1. Characteristics of studies reporting the use of oral methylprednisolone.

Authors (year)	>Study design	Age, years[a]	Sex	Impaction type[b]	Duration of surgery, min[a]	Number of patients		Intervention	Mouth rinse used (days)	Antibiotic used (days)
						E	C			
Mukund et al.[37] (2017)	RCT	NR	NR	NR	NR	30	30	Preop. 20 mg MP	Preop.	Yes (5)
Selimović et al.[40] (2017)	RCT	18–45	19M, 41F	Class 2	NR	20	20	32 mg MP 1 h before surgery and 12 h after surgery	NR	NR
Prashar et al.[38] (2016)	RCT	19–40	NR	NR	NR	15	15	Postop. 8 mg MP every 8 h for 3 days	Preop.	NR
Ibikunle et al.[39] (2016)	RCT	28.1 ± 7.4	69M, 117F	NR	NR	62	62	Preop. 40 mg prednisolone	NR	NR
Koçer et al.[1] (2014)	RCT	29.6 ± NR	18M, 26F	NR	NR	11	11	Preop. 20 mg MP	Preop.	Yes (5)
Christensen et al.[35,36] (2013, 2014)[c]	RCT	25.04 ± 4.45	69M, 57F	NR	E: 29.26 ± 12.82 C: 32.51 ± 15.13	126[c] /124	126 /124	Preop. 32 mg; 16 mg in the morning and 16 mg in the evening on the day after surgery	Postop. (7)	Yes (7)
Acham et al.[41] (2013)	RCT	23 ± 9	6M, 10F	Class 1, 2, 3 Level A, B, C	NR	16	16	Patients with a BW <60 kg received 40 mg MP; patients with a BW 60–80 kg received 60 mg; patients with a BW >80 kg received a dosage of 80 mg; administered preop.	NR	Yes (5)
Tiigimae-Saar et al.[42] (2010)	CCT	17–63	21M, 57F	NR	15–60	38	40	Postop. 30 mg prednisolone	NR	NR
Kang et al.[43] (2010)	RCT	20–30	NR	NR	NR	G1:60 G2:64	96	G1: Preop. 10 mg prednisolone G2: Preop. 20 mg prednisolone	NR	Preop. and postop. (3)
Gataa[44] (2009)	CCT	22.05 ± NR	24M, 36F	NR	NR	20	20	Preop. 10 mg MP	NR	Yes (3)
Schultze-Mosgau et al.[45] (1995)	RCT	13–26	7M, 33F	NR	NR	26	26	32 mg MP 12 h before surgery and 12 h after surgery with ibuprofen in E group	NR	NR

BW, body weight; C, control group; CCT, controlled clinical trial; E, experimental group; F, female; G1, group 1; group 2; M, male; MP, methylprednisolone; NR, not reported; Postop., postoperative; Preop., preoperative; RCT, randomized controlled trial.

[a] Age and duration of surgery are reported as the mean ± standard deviation, or range.

[b] Pell and Gregory classification.

[c] Two papers with same sample: 126 patients evaluated for trismus and 124 patients for swelling.

Table 2. Characteristics of studies reporting the use of intravenous methylprednisolone.

Authors (year)	Study design	Age, years[a]	Sex	Impaction type[b]	Duration of surgery, min[a]	Number of patients		Intervention	Mouth rinse used (days)	Antibiotic used (days)
						E	C			
Mukund et al.[37] (2017)	RCT	NR	NR	NR	NR	30	30	Postop. 20 mg MP	Preop.	Yes (5)
Ilhan et al.[46] (2014)	RCT	18–40	19M, 41F	NR	E: 25.70 ± 0.98 C: 23.80 ± 0.79	20	20	Preop. 80 mg MP	Yes (NR)	Yes (NR)
Koçer et al.[1] (2014)	RCT	29.6 ± NR	18M, 26F	NR	NR	11	11	Postop. 20 mg MP	Preop.	Yes (5)
Kaur et al.[47] (2014)	RCT	18–40	13M, 22F	NR	NR	35	35	Preop. 125 mg MP IV followed by 16 mg oral in the evening after surgery and 6 mg oral every 8 h for 2 days	NR	NR
Esen et al.[48] (1999)	RCT	29.6 ± 0.43	9M, 11F	Class 1, 2 Level A, B	NR	20	20	Preop. 125 mg MP	NR	Yes (5)
Milles and Desjardins[49] (1993)	RCT	20–35	9M, 2F	NR	NR	11	11	16 mg oral MP 12 h preop. and 20 mg MP IV preop.	NR	No
Hyrkäs et al.[50] (1993)	RCT	24.7 ± 0.6	13M, 39F	Class 1, 2 Level A, B	NR	36	36	Preop. 40 mg MP	NR	Yes (7)
Troullos et al.[51] (1990)	RCT	21 ± 3	15M, 21F	NR	NR	9	14	Preop. 125 mg MP	NR	NR
Holland[52] (1987)	RCT	23.35 ± NR	8M, 12F	NR	E: 5.45 ± 5 C: 5.14 ± 4	20	20	Preop. 40 mg MP	NR	NR
Beirne and Hollander[53] (1986)	RCT	16–33	15M, 16F	NR	NR	15	16	Preop. 125 mg MP	NR	Yes (5)
Sisk and Bonnington[54] (1985)	RCT	19.24 ± 4.1	17M, 20F	NR	NR	18	19	Preop. 125 mg MP	NR	NR

C, control group; E, experimental group; F, female; IV, intravenous; M, male; MP, methylprednisolone; NR, not reported; Postop., postoperative; Preop., preoperative; RCT, randomized controlled trial.

[a] Age and duration of surgery are reported as the mean ± standard deviation, or range.

[b] Pell and Gregory classification.

Table 3. Characteristics of studies reporting the use of intramuscular methylprednisolone.

Authors (year)	Study design	Age, years[a]	Sex	Impaction type[b]	Duration of surgery, min[a]	Number of patients		Intervention	Mouth rinse used (days)	Antibiotic used (days)
						E	C			
Mukund et al.[37] (2017)	RCT	NR	NR	NR	NR	30	30	Postop. 20 mg MP	Preop.	Yes (5)
Eroglu et al.[55] (2015)	RCT	21.83 ± NR	13M, 23F	Class 2 Level B	16.32	12	12	Preop. 40 mg MP and 20 mg 24 h after surgery	Yes (7)	NR
Micó-Llorens et al.[56] (2006)	RCT	22 ± 2.8	15M, 16F	Class 2 Level B	E: 22 ± 6.4 C: 21.1 ± 5.4	31	31	Postop. 40 mg MP	Yes (15)	Yes (7)
Buyukkurt et al.[33] (2006)	RCT	30 ± NR	19M, 11F	NR	NR	15	15	Postop. 25 mg prednisolone	NR	Yes (5)

C, control group; E, experimental group; F, female; M, male; MP, methylprednisolone; NR, not reported; Postop., postoperative; Preop., preoperative; RCT, randomized controlled trial.
[a] Age and duration of surgery are reported as the mean ± standard deviation, or range.
[b] Pell and Gregory classification.

Table 4. Characteristics of studies reporting the use of submucosal methylprednisolone.

Authors (year)	Study design	Age, years[a]	Sex	Impaction type[b]	Duration of surgery, min[a]	Number of patients		Intervention	Injection site	Mouth rinse used (days)	Antibiotic used (days)
						E	C				
Chugh et al.[2] (2018)	RCT	29.7 ± NR	38M, 22F	Class NR Position A, B, C	20–35 min	20	17	Preop. 40 mg MP	Buccal submucosal area	Postop.	Yes (NR)
Lim and Ngeow[14] (2017)	RCT	21–39	8M, 32F	Class 2 Position B	E: 19.9 ± 3.0 C: 19.5 ± 3.3	20	20	Preop. 40 mg MP acetate	Buccal submucosal area	Preop.	Yes (5)
Ibikunle et al.[39] (2016)	RCT	28.1 ± 7.4	69M, 117F	NR	NR	62	62	Preop. 40 mg prednisolone	NR	NR	Yes (5)
Gataa[44] (2009)	CCT	22.05 ± NR	24M, 36F	NR	NR	20	20	Preop. 10 mg MP	In the gingiva at the site of surgery	NR	Yes (3)

C, control group; CCT, controlled clinical trial; E, experimental group; F, female; M, male; MP, methylprednisolone; NR, not reported; Postop., postoperative; Preop., preoperative; RCT, randomized controlled trial.
[a] Age and duration of surgery are reported as the mean ± standard deviation, or range.
[b] Pell and Gregory classification.

Table 5. Characteristics of studies reporting the use of intra-masseteric methylprednisolone.

Authors (year)	Study design	Age, years[a]	Sex	Impaction type[b]	Duration of surgery, min[a]	Number of patients		Intervention	Mouth rinse used (days)	Antibiotic used (days)
						E	C			
Mukund et al.[37] (2017)	RCT	NR	NR	NR	NR	30	30	Postop. 20 mg MP	Preop.	Yes (5)
Koçer et al.[1] (2014)	RCT	29.6 ± NR	18M, 26F	NR	NR	11	11	Postop. 20 mg MP	Preop.	Yes (5)
Chaurand-Lara and Facio-Umaña[57] (2013)	CCT	23.31 ± 10.03	14M, 18F	NR	NR	32	32	Postop. 20 mg MP acetate	NR	Yes (5)
Kaur et al.[58] (2011)	CCT	23.9 ± NR	12M, 8F	NR	NR	20	20	Postop. 20 mg MP acetate	Preop. and postop. (15)	Yes (5)
Vegas-Bustamante et al.[59] (2008)	RCT	25 ± 5	53%M 46%F	NR	NR	35	35	Postop. 40 mg MP	Postop. (15)	Yes (7)

C, control group; CCT, controlled clinical trial; E, experimental group; F, female; M, male; MP, methylprednisolone; NR, not reported; Postop., postoperative; Preop., preoperative; RCT, randomized controlled trial.

[a] Age and duration of surgery are reported as the mean ± standard deviation, or range.

[b] Pell and Gregory classification.

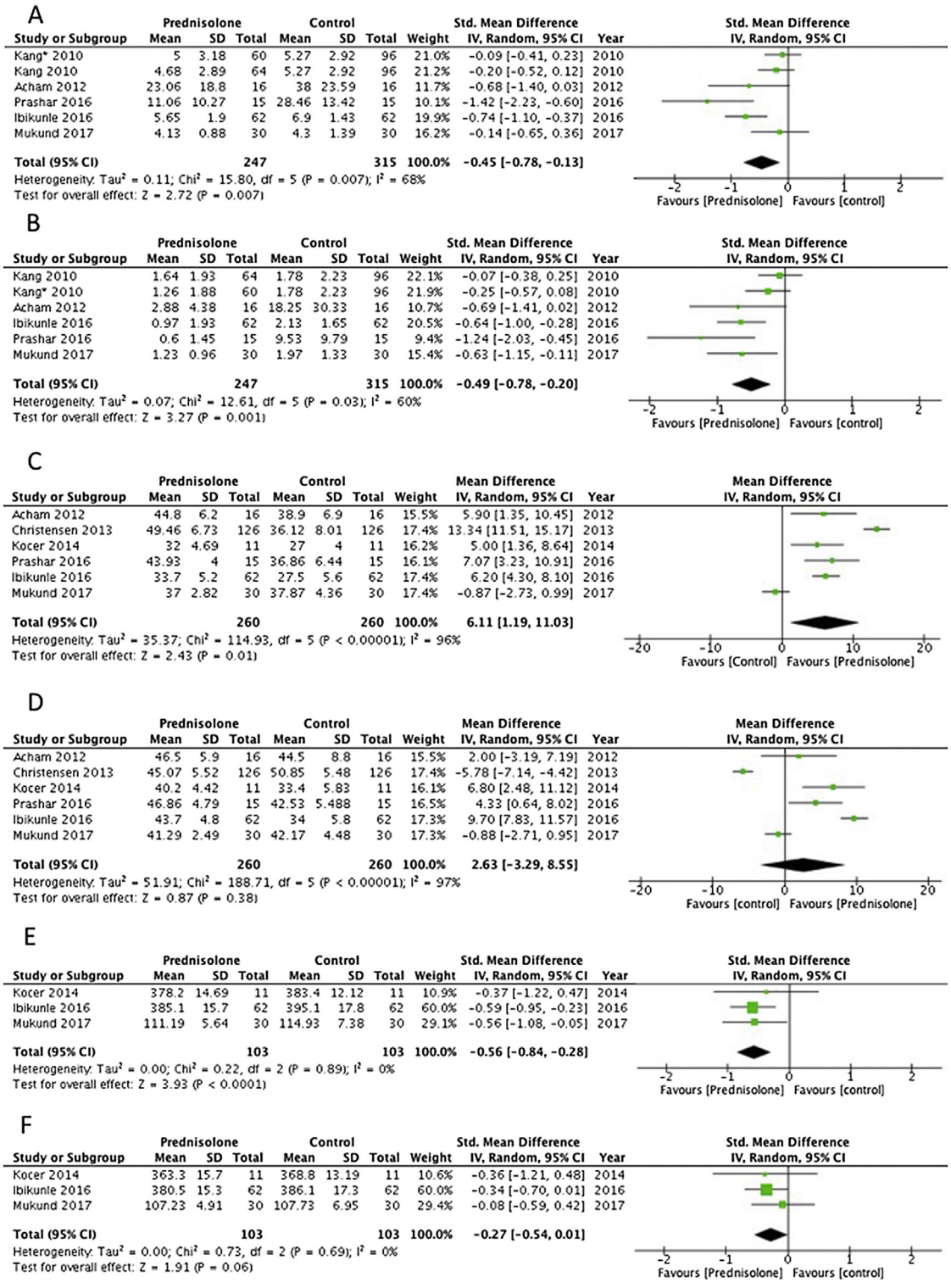

Fig. 2. Forest plot of oral methylprednisolone vs. placebo for the event (A) pain, early; (B) pain, late; (C) trismus, early; (D) trismus, late; (E) oedema, early; (F) oedema, late.

Four studies were included in the meta-analysis for trismus[1,37,48,54]. Results were insignificant for both the early (random-effects: MD = 3.15, 95% CI −2.14 to 8.44; $P = 0.24$; $I^2 = 95\%$) (Fig. 3A) and late time intervals (random-effects: MD = 2.22, 95% CI −0.95 to 5.39; $P = 0.17$; $I^2 = 85\%$) (Fig. 3B). Additionally, three studies that did not report numerical data on trismus also did not find any significant difference in mouth opening during the early[49–51] or late[49] time intervals. Two studies used the change in inter-incisal mouth opening to record trismus; one reported a significant difference[46], while the other reported no difference in the early postoperative period[53].

Nine of 10 studies that measured oedema found a significant reduction in swelling in

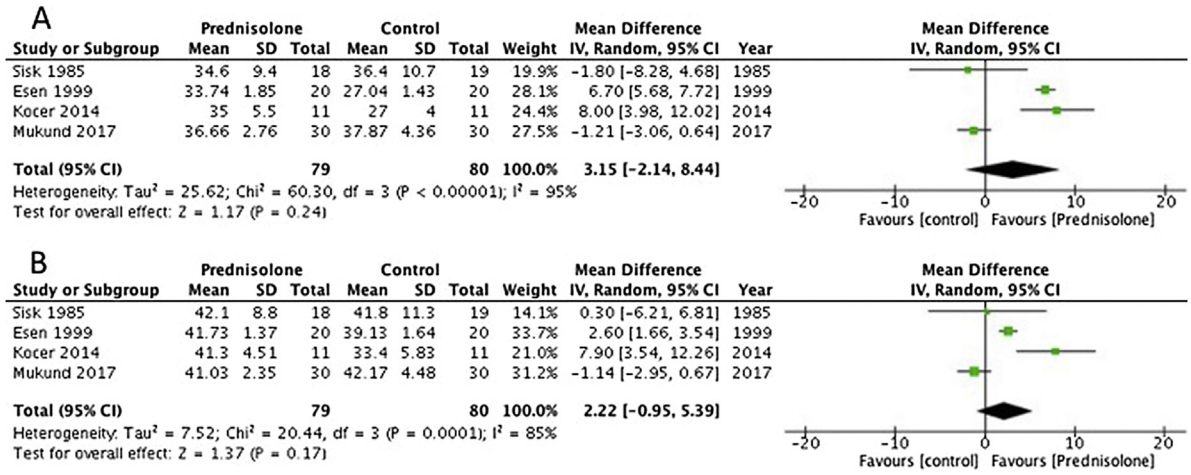

Fig. 3. Forest plot of intravenous methylprednisolone vs. placebo for the event (A) trismus, early; (B) trismus, late.

the early postoperative period[37,46–49,51–54]. Only four studies commented on late postoperative oedema, with none reporting a significant difference between the groups[37,47,52,54].

Intramuscular administration

Three studies measured postoperative pain after IM MP (**Supplementary Material**, File S8)[33,37,56]. Due to insufficient data, a meta-analysis was not conducted. The studies concluded that there was no difference in pain after IM MP either in the early[37,56] or late[37] postoperative period.

Data of three studies (**Supplementary Material**, File S8) reporting on early trismus were combined for a meta-analysis, which demonstrated no significant difference in mouth opening between the two groups (random-effects: MD = 0.40, 95% CI −3.21 to 4.02; $P = 0.83$; $I^2 = 72\%$) (Fig. 4A)[33,37,56]. Since late outcome data were unavailable for one study[56], a meta-analysis for late trismus was not performed. All of the three trials inferred that IM MP does not reduce trismus in the late postoperative period[33,37,56].

The meta-analysis of three studies (**Supplementary Material**, File S8) found a significant reduction in oedema in the early postoperative period with the use of IM MP (random-effects: MD = −3.38, 95% CI −5.12 to −1.64; $P = 0.0001$; $I^2 = 0\%$) (Fig. 4B)[33,37,56]. One study, which was not included in the analysis, that used ultrasonography to evaluate oedema, also reported a significant reduction in early swelling with the use of IM MP[55]. Three studies commented on late oedema, of which two reported no difference[37,56], while one reported a significant difference at 7 days[33].

Submucosal administration

With regard to the four studies in the submucosal group (**Supplementary Material**, File S9)[2,14,39,44], numerical data for pain, trismus, and oedema were unavailable for one study[14]. Another study could not be included in the analysis since it was a CCT with a high risk of bias[44]. Hence, a meta-analysis was not conducted for any variable. For early postoperative pain and trismus, two studies reported a significant difference between MP and placebo[14,39], while two reported no difference[2,44]. For late postoperative pain[2,14,44] and trismus[2,39,44], the majority of the studies reported no significant effect of MP. While three of four studies reported a significant effect of MP in reducing early postoperative oedema[14,39,44], there was no consensus on the reduction of late postoperative oedema.

Intra-masseteric administration

Although there were five studies comparing intra-masseteric MP with placebo[1,37,57–59], a meta-analysis could not be conducted due to differences in methods of outcome assessment amongst

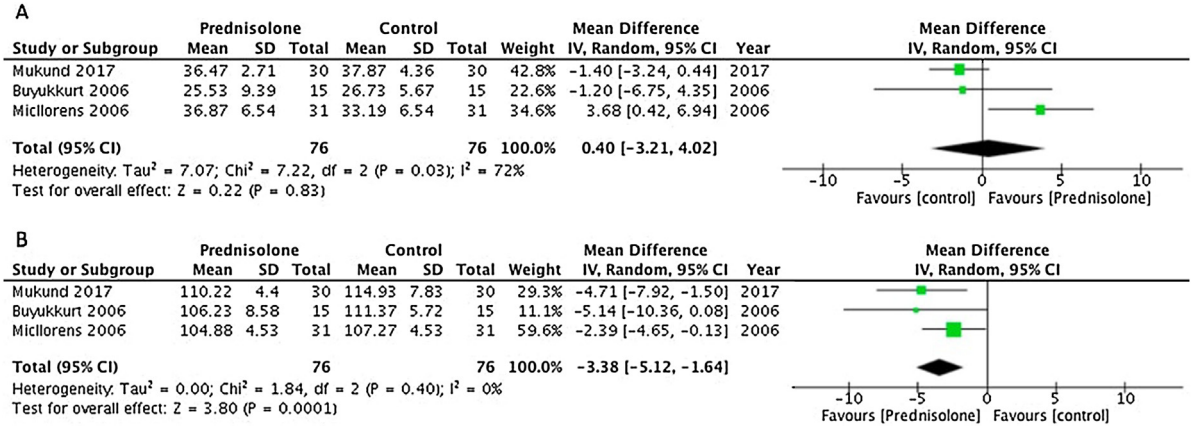

Fig. 4. Forest plot of intramuscular methylprednisolone vs. placebo for the event (A) trismus, early; (B) oedema, early.

the studies, incomplete reporting of numerical data[59], and the presence of a CCT[57] (**Supplementary Material**, File S10). The majority of the studies reported a significant reduction in pain[57–59] and trismus[1,58,59] with MP in the early postoperative period. Late pain outcomes were analysed in two trials, which found no effect of the drug[37,58]. Four trials reported late trismus outcomes[1,37,58,59], of which three noted a significant benefit with MP[1,58,59]. All five studies reported a significant reduction in early postoperative oedema with MP. However, no consensus was found for a reduction in late postoperative oedema among the five studies.

Discussion

A number of narrative reviews have been published in the literature analysing the role of corticosteroids in third molar surgeries[3,19,60]. However, none have focused specifically on MP, and no meta-analysis exploring evidence for its use has been conducted to date. The focus of this review was therefore to analyse the role of MP in improving oedema, trismus, and pain after impacted mandibular third molar surgery.

The major action of corticosteroids is suppression of all stages of inflammation. They decrease capillary vasodilatation, leukocyte migration and phagocytosis, inhibit the production of vasoactive substances such as prostaglandins and leukotrienes, and decrease the number of chemical attractants such as cytokines[2,3,19]. The overall effect is a reduction in inflammation and thereby oedema. On qualitative review and meta-analysis of the existing literature, it was found that there is a significant reduction in early postoperative oedema with the use of MP administered by any route.

For the few studies reporting no effect of MP on early postoperative oedema[2,43], the concept of 'rebound oedema' has been put forward[2]. Considering the half-life of MP, which is 12–36 h, some authors have suggested that the effect of the drug wears off rapidly and a rebound increase in swelling is seen on the second or third postoperative day[2,53]. This can occur with most forms of single-use corticosteroid, like dexamethasone sodium phosphate and MP sodium succinate, as the effect wears off in 1 day. Milles and Desjardins have suggested the use of MP acetate, which is a sustained release form of MP with a longer duration of action[49]. The use of dexamethasone, which has a longer half-life, and even the use of multiple steroid doses have been recommended to overcome this issue[14,38]. The rebound phenomenon is, however, not universally reported. Acham et al.[41] specifically studied the rebound phenomenon of MP as a secondary outcome variable. Over a follow-up period of 3 days, the authors did not find any rebound phenomenon and concluded that there is no need for multiple steroid administration. A possible explanation for this is that corticosteroids inhibit the production of prostanoids as well as neutrophils. Neutrophils could become 'deactivated' during their life-span of 1–2 days until being replaced by new neutrophils. By this time, levels of inflammatory mediators are lower and are unable to elicit another full blown inflammatory reaction[14].

Another reason for the non-effectiveness of steroids could be inadequate dosing. For a significant anti-inflammatory action, the dose should range from 80 mg to 625 mg of hydrocortisone equivalent anti-inflammatory dosage, which in the case of MP is 16–125 mg[38]. Hence, studies using only a single 10 mg dose of MP may not have found the drug to be effective[43].

The action of MP seems to wear off during the late postoperative period and MP does not appear to affect late swelling after third molar surgery when administered via any route. Of the five studies reporting improved outcomes of oedema at 7 days[14,33,38,44,58], two reported the use of MP acetate[14,58], while in one study oral steroids were administered for 3 days after surgery[38]. Thus, the action of MP was maintained for a longer time in these studies, thereby improving late outcomes of surgery.

Trismus in the postoperative period significantly affects the patient's diet and speech[24]. It has been postulated that trismus can occur as an inhibitory effect of muscle pain either from the masseter due to its proximity to the surgical site or the lateral pterygoid muscle due to prolonged mouth opening. Inhibitory feedback mechanisms from these muscles can prevent further movement of the injured site to protect the musculature, thereby causing trismus[14,19]. The results of the present study suggest that MP improves mouth opening in the early postoperative period only when administered via oral or intramasseteric route. There was a lack of consensus amongst studies reporting early outcomes of trismus with the submucosal route, with half of the studies reporting a significant difference[14,39], and the other half reporting no effect of submucosal MP[2,44]. The variance in results of this review could be due in part to the presence of other confounding factors, such as a prolonged surgical time, traumatic extraction (the majority of the studies did not mention the duration of surgery or the difficulty of extraction), accidental injection of local anaesthetic into the medial pterygoid, and the use of multiple doses of steroids in two of the oral MP studies included in the meta-analysis[35,38]. Qualitative and quantitative analysis for late trismus was conducted for the oral and IV routes, which found no evidence of MP improving outcomes. On qualitative analysis of the IM[33,37,56] and submucosal[2,39,44] routes, the majority of studies found no evidence of an improvement in late trismus. The only route of administration of MP improving both early and late trismus was found to be intra-masseteric. The direct effect of MP injected into the masseter muscle seems to be the only reasonable explanation for this effect.

Pain after third molar surgery is usually attributed to inflammatory mediators like prostaglandins and bradykinins, tension from the swelling[14,57], and neurotransmitters such as substance P, glutamate, and calcitonin gene-related peptide, which cause central sensitization of pain[61,62]. While prostanoids and swelling may be reduced by steroids, the neurotransmitter action is not blocked[14]. Pain is also dependent on several factors such as surgical trauma and the individual's pain threshold and psychological well-being, which can influence the outcomes in parallel group studies. In this review, the mode of assessment of pain in the included studies was either a VAS or the number of analgesics consumed. Since these are two very different outcome measurement tools, the data from these cannot be combined for a meta-analysis. This, combined with missing data in some studies, meant that meta-analysis was only conducted for the oral route, which suggested that oral MP significantly reduces early and late postoperative pain. Studies using IV MP reported no improvement in early or late postoperative pain (except for the studies by Holland[52] and Ilhan et al.[46], which reported an improvement in pain in the first 24 h, and the study by Kaur et al.[47], which differed in the early outcome, probably because of the use of steroids for 3 days). Only Mukund et al.[37] and Micó-Llorens et al.[56] reported pain outcomes after IM MP and found no significant difference. Amongst local injections, only intra-masseteric MP was found to reduce early postoperative pain, while both submucosal and intra-masseteric injections had no effect on late postoperative pain. The result of the pain outcome can be influenced by various confounding factors, such as the difference in use of non-steroidal anti-inflammatory drugs

(NSAIDS) amongst studies, patient compliance with NSAIDS, the difference in pain thresholds and difficulty of the extraction amongst subjects, and the use of multiple doses of steroid.

A larger number of studies were available for oral and IV MP in this review, as compared to other routes. Due to insufficient data in IV MP studies, a meta-analysis for pain was only possible for oral MP. Another possible explanation for the improvement in pain and trismus in the early postoperative period with oral MP is that higher plasma levels of the drug would have resulted at 48 h, as the oral route of administration is associated with a delayed onset of action; this could create an erratic response due to the pharmacokinetics of the drug, as compared to the other parenteral routes[3].

The oral route is in general convenient, safe, and economical for the patient, with absorption rates comparable to that of IV MP[19,41]. However, it depends greatly on patient compliance, and oral MP may cause gastrointestinal upset in some individuals. The IV route on the other hand does not depend on patient compliance, provides immediate availability of the drug, and has a predictable response. However, the effect of MP via IV route is not sustained due to early metabolism, and repeated dosing may be required. The IM route overcomes this disadvantage and can provide a prolonged duration of action of the drug, especially with MP acetate. Disadvantages include the potential for local haematoma, abscess, and necrosis; furthermore, drug absorption is dependent on the local blood flow and there may be patient discomfort due to the second injection site[3,19,30,38,41]. In order to avoid the second injection site, clinicians have used submucosal or intra-masseteric injections of MP. The surgical area is already anesthetized, making the injection painless and easy to administer. Submucosal injections provide a repository effect and act directly on the surgical site with a minimal systemic effect[2]. The intra-masseteric route of corticosteroids on the other hand is considered to be similar to the submucosal route with systemic action of the drug[19,31].

All five routes of administration of MP were used in the various studies included in this review. Comparisons between the different routes of delivery of MP for third molar surgery have not been reported frequently in the literature[1,37,39,44]. Ibikunle et al.[39] have found submucosal MP to be comparable to the use of oral MP. Koçer et al.[1] found intra-masseteric MP to be more effective than oral and IV MP. Selvaraj et al.[31] found similar outcomes with intra-masseteric and the gluteal route of administration of MP. Gataa[44] compared oral and submucosal MP and found the oral route to be more effective. Mukund et al.[37] compared the oral, IV, IM, and intra-masseteric routes and found the intra-masseteric route to be most beneficial. In the present review, oral and intra-masseteric MP were found to be most effective in improving postoperative sequelae after third molar surgery.

The results of this review are bound by some limitations. First, the strength of a systematic review and meta-analysis depends on the quality of the studies included[15]. There were only three high-quality studies with minimal bias in this review[35,45,59], with the overall quality of the literature being classified as 'medium' (Table 1). Second, not all studies could be included in the meta-analysis either due to non-availability of complete data or variations in outcome measurement tools. Only a qualitative analysis was performed for the submucosal and intra-masseteric routes, whereas meta-analysis for all three variables was possible only for the oral route of MP. Third, a standard protocol for MP administration was lacking; the studies used different routes, different doses, and different time intervals for administering the drug. Fourth, a few of the studies had a small sample size, which was as low as nine patients in the experimental group[1,49,51].

MP has been used for several years to improve postoperative outcomes after third molar extractions without any consensus on its use. This study appears to be the first comprehensive qualitative and quantitative review on the use of MP for third molar surgery. Within the purview of the limitations of this study, it is concluded that MP administered via any route significantly improves oedema in the early postoperative period, but has no effect on late postoperative oedema. Oral MP and intra-masseteric MP also seem to reduce pain and trismus in the early postoperative period. The results also indicate that oral MP may reduce late postoperative pain, while intra-masseteric MP may improve the late trismus outcome. There is a need for more high quality RCTs utilizing a standard drug administration protocol and comparing various routes of administration of MP to provide further stronger evidence on the role of MP in improving postoperative sequelae after impacted third molar surgery.

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None.

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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.2018.09.005.

References

1. Koçer G, Yuce E, Tuzuner Oncul A, 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.
2. Chugh A, Singh S, Mittal Y, Chugh V. Submucosal injection of dexamethasone and methylprednisolone for the control of postoperative sequelae after third molar surgery: randomized controlled trial. *Int J Oral Maxillofac Surg* 2018;**47**:228–33.
3. Kim K, Brar P, Jakubowski J, Kaltman S, Lopez E. The use of corticosteroids and nonsteroidal antiinflammatory medication for the management of pain and inflammation after third molar surgery: a review of the literature. *Oral Sur Oral Med Oral Pathol Oral Radiol Endod* 2009;**107**:630–40.
4. Ibikunle AA, Adeyemo WL, 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.
5. Larsen PE. The effect of a chlorhexidine rinse on the incidence of alveolar osteitis following the surgical removal of impacted mandibular third molars. *J Oral Maxillofac Surg* 1991;**49**:932–7.
6. Poeschl PW, Eckel D, Poeschl E. Postoperative prophylactic antibiotic treatment in third molar surgery—a necessity? *J Oral Maxillofac Surg* 2004;**62**:3–8.
7. Fernando S, Hill CM, Walker R. A randomised double blind comparative study of low level laser therapy following surgical extraction of lower third molar teeth. *Br J Oral Maxillofac Surg* 1993;**31**:170–2.
8. Al-Moraissi EA, Elmansi YA, Al-Sharaee YA, Alrmali AE, Alkhutari AS. Does the piezoelectric surgical technique produce fewer postoperative sequelae after lower third molar surgery than conventional rotary instruments? A systematic review and meta-

analysis. *Int J Oral Maxillofac Surg* 2016;**45**:383–91.
9. Derry S, Wiffen PJ, Moore RA. Relative efficacy of oral analgesics after third molar extraction—a 2011 update. *Br Dent J* 2011;**211**:419–20.
10. de Santana Santos T, Calazans AC, Martins-Filho PR, Silva LC, de Oliveira Silva EED, Gomes AC. Evaluation of the muscle relaxant cyclobenzaprine after third-molar extraction. *J Am Dent Assoc* 2011;**142**:1154–62.
11. Ross R, White CP. Evaluation of hydrocortisone in prevention of postoperative complications after oral surgery: a preliminary report. *J Oral Surg (Chic)* 1958;**16**:220–6.
12. Hirschmann JV. Some principles of systemic glucocorticoid therapy. *Clin Exp Dermatol* 1986;**11**:27–33.
13. Chen Q, Chen J, Hu B, Feng G, Song J. Submucosal injection of dexamethasone reduces postoperative discomfort after third-molar extraction: a systematic review and meta-analysis. *J Am Dent Assoc* 2017;**148**:81–91.
14. Lim D, Ngeow WC. A comparative study on the efficacy of submucosal injection of dexamethasone versus methylprednisolone in reducing postoperative sequelae after third molar surgery. *J Oral Maxillofac Surg* 2017;**75**:2278–86.
15. Moraschini V, Hidalgo R, Porto Barboza EdS. Effect of submucosal injection of dexamethasone after third molar surgery: a meta-analysis of randomized controlled trials. *Int J Oral Maxillofac Surg* 2016;**45**:232–40.
16. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement. *PLoS Med* 2009;**6**: e1000097.
17. Higgins JP, Green S. *Cochrane handbook for systemic reviews of interventions, version 5.1.0 (updated March 2011)*. The Cochrane Collaboration; 2011.
18. Rohatagi S, Barth J, Möllmann H, Hochhaus G, Soldner A, Möllmann C, Derendorf H. Pharmacokinetics of methylprednisolone and prednisolone after single and multiple oral administration. *J Clin Pharmacol* 1997;**37**:916–25.
19. Ngeow WC, Lim D. Do corticosteroids still have a role in the management of third molar surgery? *Adv Ther* 2016;**33**:1105–39.
20. Higgins JP, Altman DG, Sterne JA; Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: assessing risk of bias in included studies. In: Higgins JP, Green S, eds.: Cochrane handbook for systemic reviews of interventions, version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Accessed on February 1, 2018. http://www.cochrane-handbook.org
21. Bystedt H, Nordenram A. Effect of methylprednisolone on complications after removal of impacted mandibular third molars. *Swed Dent J* 1985;**9**:65–9.
22. Huffman GG. Use of methylprednisolone sodium succinate to reduce postoperative edema after removal of impacted third molars. *J Oral Surg* 1977;**35**:198–9.
23. Darawade DA, Kumar S, Mehta R, Sharma AR, Reddy GS. In search of a better option: dexamethasone versus methylprednisolone in third molar impaction surgery. *J Int Oral Health* 2014;**6**:14–7.
24. 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.
25. Loganathan S, Srinivasan H. A comparative evaluation of methylprednisolone and dexamethasone injected into the masseter muscle in surgical removal of impacted lower third molars. *Int J Curr Res Rev* 2012;**4**:2010–3.
26. López Carriches C, Martínez-González JM, Rodríguez MD. Eficacia analgósica de diclofenaco versus metilprednisolona en el control del dolor postoperatorio tras la cirugía del tercer molar inferior. *Med Oral Patol Oral Cir Bucal* 2005;**10**:432–9.
27. López Carriches C, Martínez González JM, Donado Rodríguez M. 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.
28. Chappi DM, Suresh KV, Patil MR, Desai R, Tauro DP, Bharani KN, Parkar MI, Babaji HV. Comparison of clinical efficacy of methylprednisolone and serratiopeptidase for reduction of postoperative sequelae after lower third molar surgery. *J Clin Exp Dent* 2015;**7**: e197–202.
29. Moghaddamnia AA, Nosrati K, Mehdizadeh M, Milani S, Aghvami M. A comparative study of the effect of prednisolone and celecoxib on MMO (maximum mouth opening) and pain following removal of impacted mandibular third molars. *J Maxillofac Oral Surg* 2012;**12**:184–7.
30. Vyas N, Agarwal S, Shah N, Patel D, Aapaliya P. Effect of single dose intramuscular methylprednisolone injection into the masseter muscle on the surgical extraction of impacted lower third molars: a randomized controlled trial. *Kathmandu Univ Med J (KUMJ)* 2014;**12**:4–8.
31. Selvaraj L, Hanumantha Rao S, Lankupalli AS. Comparison of efficacy of methylprednisolone injection into masseter muscle versus gluteal muscle for surgical removal of impacted lower third molar. *J Maxillofac Oral Surg* 2014;**13**:495–8.
32. Üstün Y, Erdoğan Ö., Esen E, Karsli ED. 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* 2003;**96**:535–9.
33. 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.
34. Buyukkurt CM, Gungormus M, Kaya O, Tozoğlu S. The effect of a single dose of prednisolone on pain, trismus and swelling after removal of third mandibular molars. *Pain Clin* 2005;**17**:203–7.
35. 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.
36. Christensen J, Matzen LH, 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 patientsæ perception of swelling? *J Oral Maxillofac Surg* 2014;**72**:463–9.
37. Mukund V, Singh S, Kumar S, Rath R, Tevatia S. Efficacy of various administrative techniques of methylprednisolone on oedema, trismus and pain after lower third molar surgery. *Int J Dent Res* 2017;**5**:186–90.
38. 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.
39. Ibikunle A, Adeyemo W, Ladeinde A. Effect of submucosal or oral administration of prednisolone on postoperative sequelae following surgical extraction of impacted mandibular third molar: a randomized controlled study. *Niger Med J* 2016;**57**:272–9.
40. Selimović E, Ibrahimagić-Šeper L, Šiić I, Sivić S, Huseinagić S. Prevention of trismus with different pharmacological therapies after surgical extraction of impacted mandibular third molar. *Med Glas (Zenica)* 2017;**14**:145–51.
41. Acham S, Klampfl A, Truschnegg 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.
42. 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.
43. 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;**55**:462–7.

44. Gataa IS. Evaluation of the effectiveness of two methods using methylprednisolone on post operative sequelae following lower third molar surgery. *Kufa Med J* 2009;**12**:257–66.
45. Schultze-Mosgau S, Schmelzeisen R, Frölich JC, Schmele H. Use of ibuprofen and methylprednisolone for the prevention of pain and swelling after removal of impacted third molars. *J Oral Maxillofac Surg* 1995;**53**:2–7.
46. 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.
47. Kaur N, Kumar M, Misurya R, Narula R, Neelkamal. Neeraj. Comparison of the clinical efficacy of methylprednisolone with ibuprofen and ibuprofen alone on the postoperative sequelae of surgical removal of impacted third molar. *Indian J Pain* 2014;**28**:105–10.
48. Esen E, Taşar F, Akhan O. Determination of the anti-inflammatory effects of methylprednisolone on the sequelae of third molar surgery. *J Oral Maxillofac Surg* 1999;**57**:1201–6.
49. Milles M, Desjardins PJ. Reduction of postoperative facial swelling by low-dose methylprednisolone: an experimental study. *J Oral Maxillofac Surg* 1993;**51**:987–91.
50. Hyrkäs T, Ylipaavalniemi P, Oikarinen VJ, Paakkari I. A comparison of diclofenac with and without single-dose intravenous steroid to prevent postoperative pain after third molar removal. *J Oral Maxillofac Surg* 1993;**51**:634–6.
51. Troullos ES, Hargreaves KM, Butler DP, Dionne RA. Comparison of nonsteroidal anti-inflammatory drugs, ibuprofen and flurbiprofen, with methylprednisolone and placebo for acute pain, swelling, and trismus. *JOral Maxillofac Surg* 1990;**48**:945–52.
52. Holland CS. The influence of methylprednisolone on post-operative swelling following oral surgery. *Br J Oral Maxillofac Surg* 1987;**25**:293–9.
53. Beirne OR, 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.
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. Eroglu CN, Ataoglu H, Yildirim G, Kiresi D. Comparison of the efficacy of low doses of methylprednisolone, acetaminophen, and dexketoprofen trometamol on the swelling developed after the removal of impacted third molar. *Med Oral Patol Oral Cir Bucal* 2015;**20**:e627–32.
56. 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.
57. Chaurand-Lara J, Facio-Umaña JA. Methylprednisolone injection following the surgical extraction of impacted lower third molars: a split-mouth study. *Open J Stomatol* 2013;**3**:192–6.
58. Kaur J, Sandhu S, Kaur T, Bhullar R, Sandhu Y, Parminder S. Effect of methylprednisolone on postoperative pain, swelling and trismus following the surgical removal of bilateral impacted mandibular third molars. *Indian J Compr Dent Care* 2011;**1**:36–42.
59. 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.
60. 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.
61. Takeda M, Matsumoto S, Sessle BJ, Shinoda M, Iwata K. Peripheral and central mechanisms of trigeminal neuropathic and inflammatory pain. *J Oral Biosci* 2011;**53**:318–29.
62. Chen L, Yang G, Grosser T. Prostanoids and inflammatory pain. *Prostaglandins Other Lipid Mediat* 2013;**104–105**:58–66.

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