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Systematic Review and Meta-Analysis
Oral Surgery

Effect of submucosal dexamethasone injections in the prevention of postoperative pain, trismus, and oedema associated with mandibular third molar surgery: a systematic review and meta-analysis

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Abstract. The aim of this systematic review and meta-analysis was to determine whether there are clinically effective reductions in postoperative pain, oedema, and trismus following submucosal dexamethasone administration during impacted mandibular third molar surgery. An electronic database search was conducted up to and including June 2018. Randomized and quasi-randomized trials assessing the effects of submucosal dexamethasone in adult patients undergoing mandibular third molar surgery were included. The mean differences or standardized mean differences were extracted and pooled using the fixed-effects or random-effects model. Seventeen trials were included and independently assessed for risk of bias. There was low quality evidence that submucosal dexamethasone reduces early postoperative pain, early and late postoperative trismus, and late postoperative oedema after mandibular third molar extraction. Moderate quality evidence was found for the reduction of late postoperative pain and early postoperative oedema. The greatest clinical effect of submucosal dexamethasone injection during impacted

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mandibular third molar surgery was a reduction of early postoperative pain (number needed to treat (NNT) = 4) and early postoperative oedema (NNT = 5). The reduction in trismus was not clinically significant (<5 mm). Further research focusing on strengthening the quality of evidence, investigating potential harms and a definitive protocol for submucosal administration during mandibular third molar surgery is required.

Key words: meta- analyses; dexamethasone; mandibular third molar; extraction; pain; trismus; oedema.

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Third molar extractions are one of the most commonly performed procedures by dentists and oral and maxillofacial surgeons[1]. Despite improvements in surgical technique and perioperative care, the significant inflammatory reaction following an extraction is the cause of many negative postoperative sequelae. Localized inflammation in the region of the masticatory muscles can result in trismus and significant facial swelling, limiting the return to normal diet for patients. Postoperative pain is also attributable to the local damage to bone and soft tissues, with resultant inflammatory mediator release[2].

The use of anti-inflammatory agents to reduce these postoperative inflammatory sequelae has been studied, including the use of corticosteroids. However, the systemic side-effects associated with oral and intravenous corticosteroids have prompted investigation into localized corticosteroid administration[3]. Consequently, submucosal administration of corticosteroids in the perioperative period has become a target for investigation. Dexamethasone has been presented as an ideal corticosteroid due to its potency, long half-life, safety profile, and low cost[4].

Previous systematic reviews conducted in 2016 and 2017 suggested a significant reduction in postoperative pain, trismus, and oedema following submucosal dexamethasone injection[5,6]. These reviews were unable to find a clinically relevant result for all outcomes across the early and late measurements. Clinical assessment of these complications is important in both the early and late postoperative periods. Early assessments measure perioperative patient distress, which can affect oral intake and oral hygiene[7]. Late measurements are more indicative of the speed of resolution of adverse symptoms and return to function, and highlight complicated healing[7]. As interest in these areas has accelerated, there have been a number of newly published trials on this topic, necessitating an update in the literature.

The aim of this review was to evaluate whether there is a clinically significant reduction in early and late postoperative pain, trismus, and facial oedema following submucosal injection of dexamethasone when compared to placebo or no injection for impacted mandibular third molar surgery.

Materials and methods

This systematic review was conducted following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* and the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[8,9].

Protocol registration

The pre-specified protocol for this systematic review can be found in the International Prospective Register of Systematic Reviews (PROSPERO): http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018089600 (registration number CRD42018089600).

Search methods for the identification of studies

Using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), Embase, Web of Science, and Google Scholar databases, an electronic search was conducted up to and including June 2018. The search strategy followed the PICOS framework (Table 1). The references of included studies were also searched for further trials. Authors of the included studies were contacted in an attempt to identify unpublished data.

Criteria for considering studies for this review

Types of studies

This systematic review aimed to include randomized controlled trials (RCTs) and quasi-RCTs. Both parallel and crossover (split-mouth) trials were included. Reviews, case reports, clinical series, and retrospective cohort studies were excluded.

Types of participants

Included studies involved adult patients over 18 years of age undergoing mandibular third molar surgery. Trials with patients requiring the extraction of teeth other than mandibular third molars and patients taking medications with anti-inflammatory, analgesic, or immunosuppressant actions prior to extractions were excluded.

Types of interventions

Studies comparing the use of a submucosal dexamethasone injection (any dose), administered immediately before or after the extraction of mandibular third molars, with a placebo submucosal injection or no drug delivery before or after surgery were included. The injection site was in the region of the extraction, typically the buccal vestibule in the third molar region. Studies with patients receiving oral, intravenous, or intramuscular injections of dexamethasone, a submucosal injection of corticosteroids other than dexamethasone, or comparing dexamethasone with other corticosteroids or drugs (no control) were excluded.

Outcome measures

The primary outcomes were postoperative pain, trismus, and oedema measured during the early (first 3 days postoperative) and late (day 7 postoperative) postoperative period. Studies in which pain (defined by the International Association for the Study of Pain[10]) was measured with a visual analogue scale (VAS), trismus (defined as reduced mouth opening) was measured by inter-incisal difference, and oedema (defined as facial swelling) was measured by the distance between at least two facial points were included.

Selection of studies

Three authors (PO, BW, and ML) independently completed the search and screening process. Titles and abstracts were browsed for studies that met the

Table 1. Search strategy.

Search strategy		
Population	#1	(Third molar[MeSH] OR third molars[MeSH] or impacted third molar*[all fields] OR impacted tooth*[all fields] or impacted teeth*[all fields] OR wisdom teeth*[all fields] OR wisdom tooth*[all fields])
Intervention	#2	(Third molar surgery*[all fields] OR exodontia[MeSH] OR exodontia*[all fields] OR extract*[all fields] OR dexamethasone[MeSH] OR submucosal dexamethasone*[all fields] OR submucosal injection*[all fields] OR dexamethasone postoperative*[all fields] OR dexamethasone preoperative*[all fields])
Comparisons	#3	(Placebo effect[MeSH] OR control)
Outcomes	#4	(Oedema*[all fields] OR pain*[all fields] OR trismus*[all fields])
Study design		Randomized controlled trial and quasi-randomized control trials
Search combination		#1 AND #2 AND #3 AND #4
Language		No restrictions
Electronic databases		The Cochrane Register of Controlled Trials (CENTRAL), MEDLINE (PubMed), EMBASE, Web of Science and Google Scholar

eligibility criteria for study type, patients, intervention, comparison, and outcomes. Full-text articles were obtained for studies that appeared to have satisfied the eligibility criteria, or if there was insufficient information to decide from the abstract alone that the inclusion or exclusion criteria had been met. If necessary, the authors of the studies were contacted via e-mail for further clarification. Discrepancies between reviewers were resolved by a group discussion involving all three reviewers until a consensus was reached. If multiple publications from the same trial data were identified, a discussion between review authors ensued to determine which single publication was included.

Data extraction and management

Three authors (PO, BW, and ML) independently extracted data from the included studies utilizing a standardized data extraction form. The following data were extracted from each of the included articles: author, year of publication, study type, country, age, sex distribution and number of participants, grade of third molar impaction, operating time, general/local anaesthetic, drug, dose, route, injection area, timing of injection, placebo type (dose, route, injection area, timing), follow-up, outcome measured (pain, trismus, and oedema), and the scales utilized for the outcome measurements. Contact with the authors of included studies was attempted when data were insufficient or missing.

Assessment of risk of bias in included studies

Three authors (PO, BW, and ML) independently assessed the included studies for risk of bias. Quality analysis of the studies was performed using the Cochrane Collaboration tool for assessing risk of bias[8]. This tool explores six sources of bias for each study: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The risk of bias was summarized for each outcome across studies. Studies deemed at high risk of bias for a particular outcome were excluded from the meta-analysis.

Statistical analysis

The mean difference (MD) (differences in means) and standard deviation (SD) of change scores (changes from baseline) were extracted for each of the continuous outcomes (pain, trismus, oedema). Studies that compared more than two interventions (differing doses) of submucosal dexamethasone were combined into a single intervention group using the Cochrane formula for combining groups[8]. For studies that did not provide the change scores, the SDs were calculated from the provided *P*-value and samples sizes, as per Section 7.7.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*[8]. Meta-analyses were performed when at least two studies analysed the same outcome in the intervention and control groups using similar indices. The standardized mean difference (SMD) was calculated when slightly different scales were used by studies to measure the same outcome (e.g. slight variation in the measurements of facial oedema). The meta-analyses were conducted using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014)[11]. The results were pooled using the fixed-effects model or the random-effects model to calculate the MD or SMD with 95% confidence intervals (CI). When there was evidence of heterogeneity (χ^2 *P*-value <0.10) or variability due to heterogeneity ($I^2 > 40\%$), results were pooled using the random-effects model. Additional analyses were performed to re-express the SMD into the clinically relevant odds ratio (OR[8]. This was performed holding the assumption that a logistic distribution with equal standard deviation in the two comparator groups existed[8]. The ORs were then combined with the assumed control risk to obtain the absolute risk reduction and number needed to treat (NNT)[8].

Assessment of reporting bias

Selective reporting was assessed by comparing the protocol, if available publicly in clinical trial registries, with the published study. Otherwise, the methods and results sections of included trials were analysed. Trial authors were contacted in an attempt to obtain missing outcome data when selective reporting was identified. Publication bias was assessed using funnel plots for outcomes that included at least 10 trials. Outcomes that utilized the SMD as an effect measure were also not included in the funnel plot analyses, due to the correlation of SMD with the standard error and the potential to introduce error into the funnel plots.

Results

Results of the search

A total of 477 records were screened up to June 30, 2018 (Fig. 1). The search identified 205 records from Web of Science, 158 from Google Scholar, 59 from MEDLINE (PubMed), 45 from Embase, and 10 from CENTRAL. Twenty-three records were examined for potential eligibility after screening the 159 non-duplicate records. Six studies were excluded from the meta-analysis. Four were excluded due to injection of dexamethasone into alternative sites (intramuscular or pterygomandibular space)[12–15]. One study was excluded as it was confounded by amoxicillin as a covariable[16]. One further study did not clearly elucidate the methodology and was excluded as it was not possible to adequately assess eligibility[17].

Description of studies

The characteristics of the 17 studies included in this systematic review are sum-

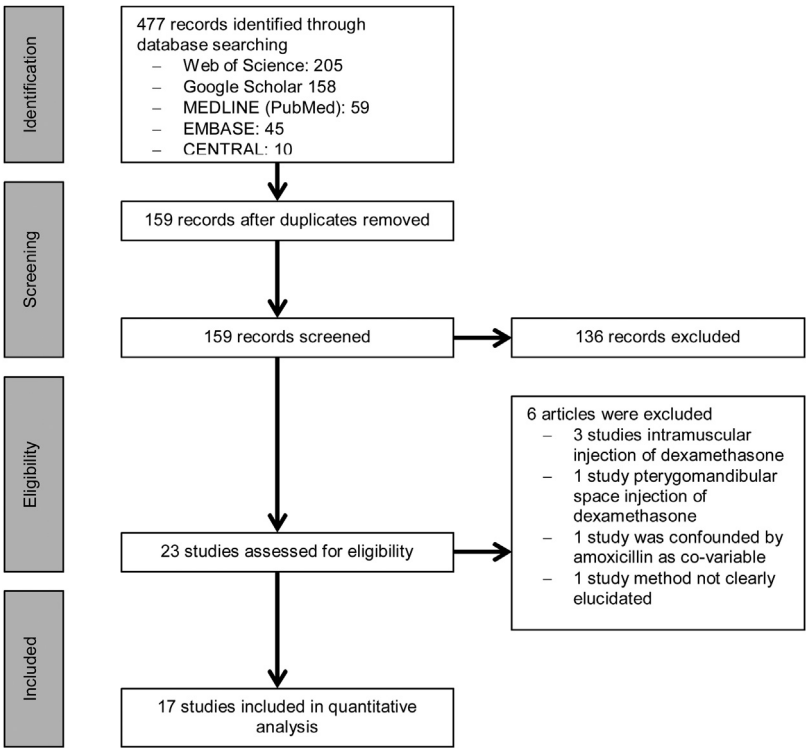


Fig. 1. Study flow diagram (PRISMA format).

marized in Table 2[4,18–33]. All included studies were RCTs or quasi-RCTs. The trials by Graziani et al.[18] and Syed et al.[19] were the only crossover (split-mouth) RCTs. The sample size of the majority of trials was small, ranging from 10 to 50 participants, for a total of 850 randomized participants, excluding split-mouth studies. The age range of the pooled population was 18 to 50 years, with a mean age of 25.7 years. There was an almost equal sex distribution, with 300 female participants and 293 male participants included in those studies reporting the sex distribution. Most investigators (14 trials) reported the class and position of impacted third molars using the Pell and Gregory classification[4,18,20–31]. Two differing doses of submucosal dexamethasone were used as an intervention, 4 mg in the majority of trials, with only three trials administering 8 mg[21,26,31]. No placebo was administered in the majority of included studies (11 trials), with only five studies administering a placebo injection (submucosal injection of normal saline) as control[21,22,24,29,31]; one study did not report the treatment used in the control group. All studies performed early and late postoperative measurement of trismus and oedema. Fifteen studies recorded early and late postoperative measurements of pain (two trials did not include any measurements of pain[4,25]).

Bias in included studies

Included trials were assessed for quality according to the Cochrane Collaboration tool for assessing risk of bias (Fig. 2). None of the included trials had a low risk of bias across all domains. However, no study was deemed at high enough risk of bias to be excluded from a particular outcome analysis.

Other potential sources of bias

A funnel plot was created for the late postoperative trismus measurement, as this outcome was the only one that included more than 10 studies in the pooled analysis. Visual interpretation of the plot (Fig. 3) demonstrated a single study outside of the funnel in the direction of a positive effect (Saravanan et al.[32]).

Effects of interventions

Pain

Seven trials with 214 participants assessed pain on the first postoperative day. Pooled data showed a significant benefit (SMD −1.16, 95% CI −1.69 to −0.63, $P <$ 0.0001) for dexamethasone when compared with placebo, with substantial evidence of heterogeneity ($I^2 = 66\%$) (Fig. 4A). For the combined assessment of pain on the third postoperative day, six trials with 194 participants were included. The pooled data showed a significant benefit for submucosal dexamethasone (SMD −1.75, 95% CI −2.74 to −0.77, $P =$ 0.0005), with considerable evidence of heterogeneity ($I^2 = 87\%$) (Fig. 4B). For day 7 postoperative, the late pain measurement, a total of nine trials were combined, including 359 participants. The pooled data demonstrated a significant effect for dexamethasone compared with placebo (SMD −0.41, 95% CI −0.62 to −0.19, $P =$ 0.0002), with minimal evidence of heterogeneity ($I^2 = 24\%$) (Fig. 4C).

The assumed control group risk was obtained from the study by Giovannacci et al., due to its recent publication, similar population and intervention, and assessment of the control group risk on the same days the pooled pain outcomes were measured[34]. Pain was less likely to occur in the submucosal dexamethasone group on the first (OR 0.48) and third (OR 0.32) postoperative days. Ten participants were required to be treated with submucosal dexamethasone to avoid pain on the first postoperative day (NNT = 10). Four participants were required to be treated with submucosal dexamethasone to avoid pain on the third postoperative day (NNT = 4). On day 7 postoperative, pain was more likely to occur in the submucosal dexamethasone group (OR 1.35), with 14 participants required to be treated for pain to occur in an additional participant (NNT = 14).

Trismus

The results for trismus were divided into early and late postoperative measurements. Early trismus included recordings from postoperative day 2 and postoperative day 3. The postoperative day 2 assessment included a total of 315 randomized participants from six studies. The postoperative day 3 assessment included a total of 154 participants from five studies. The pooled analysis of these sub-groups combined 469 participants and demonstrated a significant benefit for submucosal dexamethasone compared to placebo (MD −4.92 mm, 95% CI −7.01 to −2.84 mm, $P <$ 0.00001), with substantial evidence of heterogeneity ($I^2 = 72\%$) (Fig. 5A). The late measurement of trismus was recorded on day 7 postoperative. This analysis included 429 participants from a total of 11 studies. The late analysis of trismus also demonstrated a significant benefit for submucosal dexamethasone when compared to placebo (MD −1.41 mm, 95% CI −2.29 to −0.54 mm, $P =$ 0.001), with substantial evidence of heterogeneity ($I^2 = 68\%$) (Fig. 5B).

Table 2. Characteristics of included studies.

Authors Country	Study type	Age (years); mean ± SD or range	Sex	Number of patients	Impaction grade	Operating time (min); mean ± SD	Intervention	Injection site
Graziani et al. (2006)[18]	Crossover (split-mouth) RCT	24 ± 4	30 F	E: 14	Class I, II or III and position A or B	E: 22.3 ± 9.9	E: 4 mg SM DEX	Buccal vestibule tissues
Italy			13 M	C: 43		C: 20.5 ± 8.0	C: No drug	
Grossi et al. (2007)[26]	Parallel RCT	27.7 ± 6.5	28 F	E1: 18	Class II and position B impaction	E1: 26.8 ± 6.4	E1: 4 mg SM DEX	Buccal vestibule tissues
Italy			33 M	E2: 20		E2: 27.4 ± 6.6	E2: 8 mg SM DEX	
				C: 23		C: 27.8 ± 11	C: No drug	
Majid and Mahmood (2010)[23]	Parallel RCT	26.7 ± 6.3	11 F	E: 10	Class II or III	E: 29.6 8.3	E: 4 mg SM DEX	Buccal vestibule near site of operation
Iraq			9 M	C: 10		C: 37 ± 8.8	C: No drug	
Majid (2011)[30]	Parallel RCT	26.9 ± 6.1	13 F	E: 11	Class II or III and position B or C	E: 31 ± 9.6	E: 4 mg SM DEX	Buccal vestibule near site of operation
Iraq			9 M	C: 11		C: 36.5 ± 8.5	C: No drug	
Nair et al. (2013)[33]	Parallel RCT	>18	NR	E: 50	NR	NR	E: 4 mg SM DEX	NR
India				C: 50			C: No drug	
Warraich et al. (2013)[28]	Parallel RCT	26.9 ± 4.5	28 F	E: 50	Position B or C	E: 66.3 ± 17	E: 4 mg SM DEX	At mucogingival junction on buccal aspect of third molar
Germany			72 M	C: 50		C: 19.2 ± 18.8	C: No drug	
Bhargava et al. (2014)[27]	Parallel RCT	24.1 ± 4.3	NR	E: 10	Class II and position B	NR	E: 4 mg SM DEX	Buccal mucosa
India				C: 10			C: No drug	
Ehsan et al. (2014)[4]	Parallel RCT	18–40	NR	E: 50	Class II and position B	E: 40.62 ± 4.88	E: 4 mg SM DEX	NR
Pakistan				C: 50		C: 42.12 ± 4.54	C: No drug	
Zerener et al. (2015)[20]	Parallel RCT	23.6 ± 4.7	25 F	E: 26	Class II or III and position B or C	E: 18.8 ± 5.6	E: 4 mg SM DEX	Submucosal, 1 cm above surgical area
Turkey			27 M	C: 26		C: 17.7 ± 4.4	C: No drug	
Deo (2016)[29]	Parallel RCT	20–41	NR	E: 24	Class II or III	NR	E: 4 mg SM DEX	Buccal in proximity to the surgical site
Nepal				C: 16			C: normal saline injection	
Saravanan et al. (2016)[32]	Parallel RCT	>18	NR	E: 20	Position A and B	NR	E: 4 mg SM DEX	Distobuccal to third molar
India				C: 20			C: No drug	
Khalida et al. (2017)[25]	Parallel RCT	18–50	22 F	E: 30	Mesioangular class II and position B	NR	E: 4 mg SM DEX	Buccal aspect of molar and loose submucosa distal to third molar
Pakistan			38 M	C: 30			C: No drug	
Lim and Ngeow (2017)[22]	Parallel RCT	24 ± 4	49 F	E1: 20	Class II or position B	20.2 ± 3.5	E1: 4 mg SM DEX	Buccal submucosal area to the impacted third molar
Malaysia			11 M	E2: 20			C: normal saline solution SM injection	
				C: 20				
Mojsa et al. (2017)[24]	Parallel RCT	18–42	58 F	E1: 30	Class II position B, or class III and position B	NR	E1: 4 mg SM DEX preop. and placebo postop.	Lower buccal vestibule near the surgical site

Poland			32 M	E2: 30 C: 30			E2: placebo preop. and 4 mg SM DEX postop. C: saline SM injection preop. and postop.	
Syed et al. (2017)[19] Saudi Arabia	Crossover (split-mouth) RCT	18–45	NR	E: 10 C: 10	NR	NR	E: 4 mg SM DEX C: NR	NR
Arora et al. (2018)[21] India	Parallel RCT	NR	22 F 23 M	E1: 15 E2: 15 E: 15	Class II	NR	E1: 4 mg SM DEX E2: 8 mg SM DEX C: normal saline solution SM injection	NR
Chugh et al. (2018)[31] India	Parallel RCT	29.7	14 F 26 M	E: 23 C: 17	Position A, B or C	Range 20–35 min	E: 8 mg SM DEX C: normal saline solution SM injection	Buccal vestibule in the region of the third molar

Authors Country	Follow- up (days)	Trismus measurement used	Oedema measurement used	Pain measurement used
Graziani et al. (2006)[18] Italy	2, 7	Difference in inter-incisal distance at MMO	Distance from corner of mouth to attachment of earlobe after the bulge of cheek and distance from outer canthus of eye to angle of mandible	VAS 0–100
Grossi et al. (2007)[26] Italy	2, 7	Maximum distance between upper and lower central incisors	2 measurements from 3 reference points: tragus, pogonion, corner of mouth	The total number of analgesics taken in the first postoperative week
Majid and Mahmood (2010)[23] Iraq	1, 3, 7	Inter-incisal distance at MMO	Using measurements from 3 reference points: tragus, pogonion, corner of mouth	VAS 1–10 and the total number of analgesics taken in the first postoperative week
Majid (2011)[30] Iraq	1, 3, 7	Difference in MMO before and after operation	2 measurements: tragus–midline and gonion–lateral canthus	VAS 1–10 and the total number of analgesics taken in the first postoperative week
Nair et al. (2013)[33] India	2, 7	Maximum distance between upper and lower central incisors	Measurements made between 3 reference points: corner of mouth, pogonion, tragus	VAS 0–9
Warraich et al. (2013)[28] Germany	1, 2, 10, 28	Inter-incisal mouth opening	1 measurement: tip of tragus of right and left ear to gonion	VAS 0–10
Bhargava et al. (2014)[27] India	1, 3, 7	MMO	1 measurement: between tragus and menton	VAS 0–10
Ehsan et al. (2014)[4] Pakistan	2, 7	Inter-incisal distance	2 measurements: earlobe–corner of mouth and outer canthus–angle of mandible	NR
Zerener et al. (2015)[20] Turkey	1, 3, 7	Difference in maximal inter-incisal distance between preop. and postop. days	3 measurements from 5 reference points on face: points A–C, A–D, and B–E Point A: midpoint of tragus Point B: lateral canthus of eye Point C: corner of mouth	VAS 0–100

Table 2 (*Continued*)

Authors Country	Follow- up (days)	Trismus measurement used	Oedema measurement used	Pain measurement used
Deo (2016)[29]	Pain: 1–7	Inter-incisal distance	Point D: soft tissue pogonion Point E: angle of mandible 3 measurements: tragus–corner of mouth, tragus–pogonion, mandibular angle–ala of nose	VAS 0–10 and the total number of analgesic tablets taken in the first postoperative week
Nepal	Oedema and trismus: 2, 7			
Saravanan et al. (2016)[32]	1, 3, 7	Maximal inter-incisal mouth opening	2 measurements: tragus–midline and gonion–lateral canthus	VAS 0–100 and the total number of analgesics taken in the first postoperative week
India				
Khalida et al. (2017)[25]	2	Inter-incisal distance at maximum opening	2 measurements: tragus of ear–corner of mouth, outer canthus of eye–gonion angle on operated side	NR
Islamabad				
Lim and Ngeow (2017)[22]	1, 2, 5, 7	Maximum inter-incisal distance	Sum of the length of 2 lines along the predetermined facial reference points: outer corner of the eye–angle of the mandible, tragus of the ear–corner of the mouth	VAS 0–10 and the total number of analgesics tablets taken in the first postoperative week
Malaysia				
Mojsa et al. (2017)[24]	Pain: 1, 2, 4, 6, 8, 12, and 24 h	Maximum inter-incisal distance	3 measurements: corner of the eye–angle of the mandible, tragus–corner of the mouth, tragus–pogonion	VAS 0–100
Poland	Oedema and trismus: 2, 3, and 7 days			
Syed et al. (2017)[19]	1 h, 1 day, 7 days	Inter-incisal mouth opening	2 measurements: tragus–angle of mouth, lateral canthus of eye–angle of mouth	VAS 0–10
Saudi Arabia				
Arora et al. (2018)[21]	2, 7	Inter-incisal distance at MMO	2 measurements were made between 3 reference points: tragus, pogonion, and corner of the mouth	VAS 0–10
India				
Chugh et al. (2018)[31]	2, 7	Maximum distance between the incisal edges of the upper and lower central incisors	4 reference points: tragus, pogonion, gonion, and corner of the mouth, calculated as the sum of the 2 diagonals made between these reference points	VAS 0–10 and the total number of analgesics taken in the first postoperative week
India				

C, control group; DEX, dexamethasone; E, event group; F, female; M, male; MMO, maximum mouth opening; NR, not reported; postop., postoperative; preop., preoperative; RCT, randomized controlled trial; SD, standard deviation; SM, submucosal; VAS, visual analogue scale.

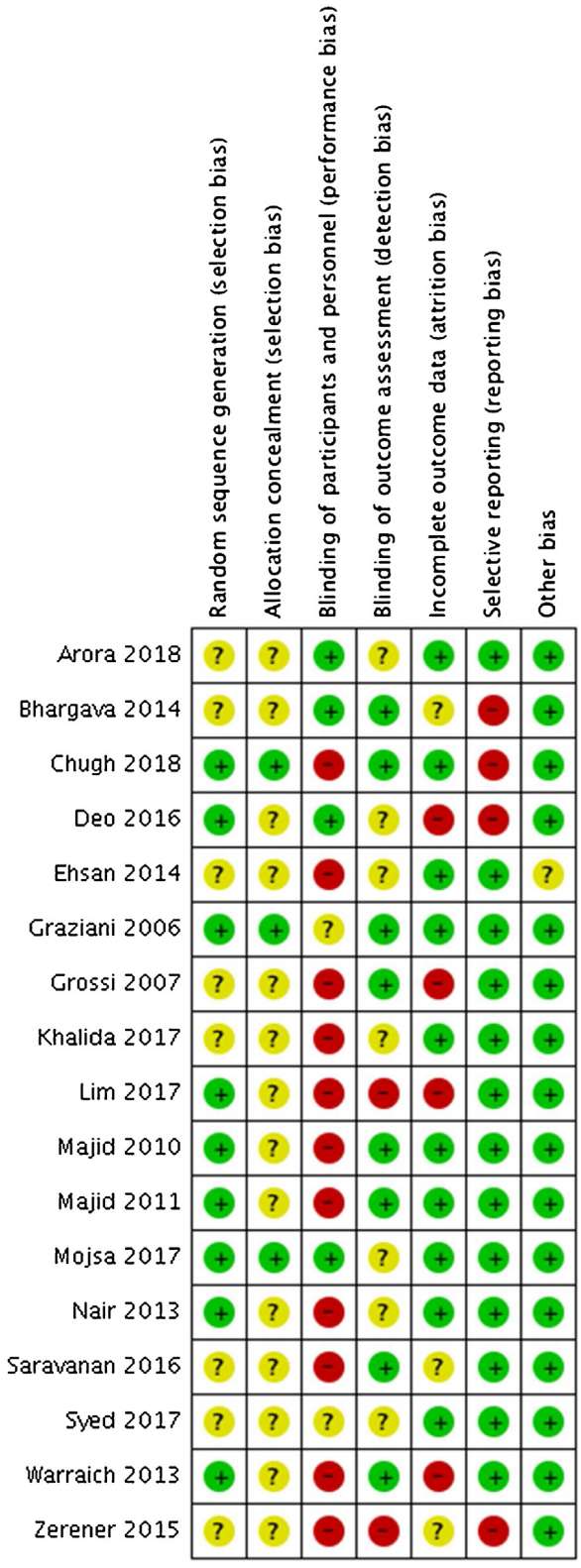


Fig. 2. Risk of bias assessment.

Oedema

The assessment of facial oedema was also divided into early and late postoperative measurements. Measurements from postoperative days 2 and 3 were combined to form the early measurement. Six studies with a total of 336 participants were pooled for the postoperative day 2 assessment. For the postoperative day 3 measurement, a total of 154 participants from five studies were analysed. The pooled analysis of these subgroups demonstrated a significant benefit for submucosal dexamethasone when compared to placebo (SMD −1.33, 95% CI −1.77 to −0.90, $P < 0.00001$), with considerable evidence of heterogeneity ($I^2 = 76\%$) (Fig. 6A). The late postoperative oedema measurement was recorded on day 7 postoperative. Ten studies with a total of 344 participants were included. The pooled analysis of the late oedema measurement also a showed significant benefit for submucosal dexamethasone compared to placebo (SMD −0.82, 95% CI −1.23 to −0.41, $P < 0.0001$), with substantial evidence of heterogeneity ($I^2 = 66\%$) (Fig. 6B).

The assumed control group risk for oedema was obtained from the studies by Micó-Llorens et al.[35] and Atalay et al.[36], due to their similar populations, interventions, and assessment of the control group risk on the same days the pooled oedema outcomes were measured. Oedema was less likely to occur in the submucosal dexamethasone group in the early postoperative period (OR 0.42). Five participants were required to be treated with submucosal dexamethasone to avoid oedema in the early postoperative period (NNT = 5). In the late postoperative period, oedema was less likely to occur in the submucosal dexamethasone group (OR 0.67), with 12 participants required to be treated with submucosal dexamethasone to avoid oedema in the late postoperative period (NNT = 12).

Discussion

Summary of main results

Across all of the early and late measurements, the pooled data demonstrated that perioperative submucosal dexamethasone resulted in decreased pain, trismus, and facial oedema following mandibular third molar surgery.

Pain

For measurements on days 1, 3, and 7 postoperative, pain was reduced in terms of the VAS score in patients who received submucosal dexamethasone compared with placebo or no intervention.

There was low quality evidence that submucosal dexamethasone injections reduced early pain in patients undergoing mandibular third molar extractions. Limitations in the design and study implementation of included trials resulted in a decrease in the quality of evidence. Five

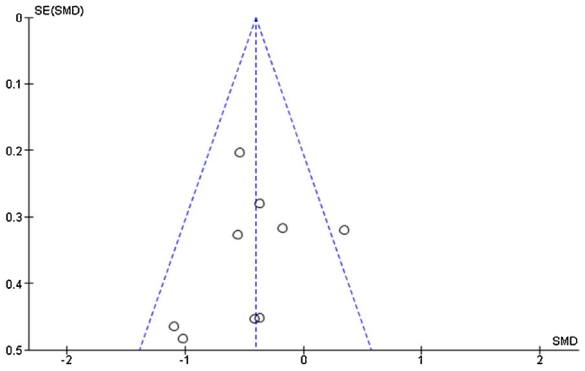
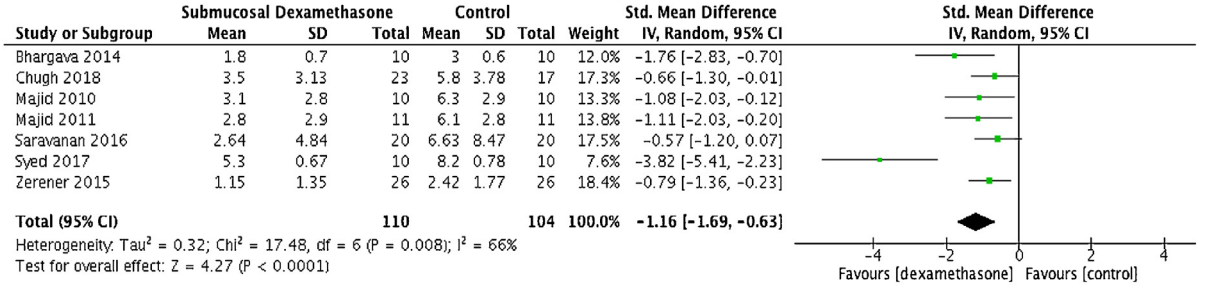


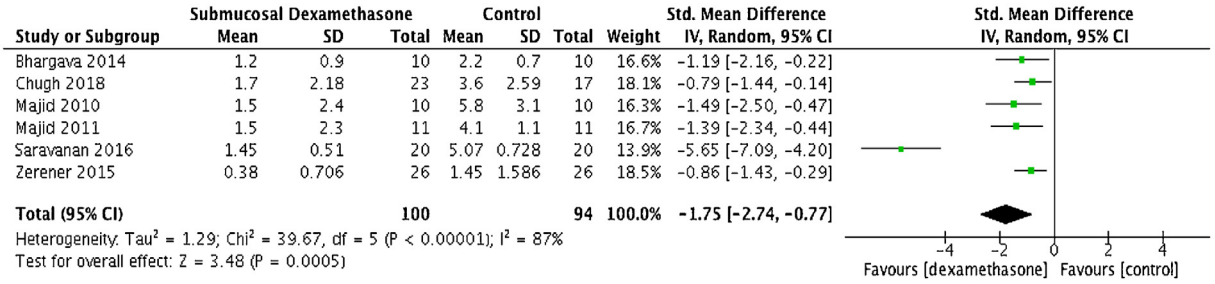
Fig. 3. Funnel plot for publication bias—trismus postoperative day 7.

of the seven studies were subject to bias through a failure to blind participants, a serious limitation when a subjective, patient-reported outcome measurement was used[20,23,30–32]. Heterogeneity was evident despite utilization of the SMD to account for the slight variation in VAS units. Heterogeneity of the combined result was largely influenced by the trial by Syed et al.[19]. This was the only trial where symptomatic participants were included and may explain the larger reduction in pain for the intervention group when compared with the other trials. The study by Syed et al. was the only crossover split-mouth trial included in this analysis, potentially giving rise to a unit-of-analysis error. The small sample sizes of included trials and the small number of pooled trials additionally contributed to heterogeneity and the relatively imprecise result.

There was low quality evidence that submucosal dexamethasone reduced pain on the third postoperative day. Again, a serious limitation in the quality of evidence resulted from five of the six included trials failing to blind participants. Heterogeneity was majorly influenced by Saravanan et al.[32] and could not be explained by clinical diversity of the participants, submucosal dexamethasone intervention, or VAS measurements. The large confidence interval of this trial suggests imprecision of the trial results for



A



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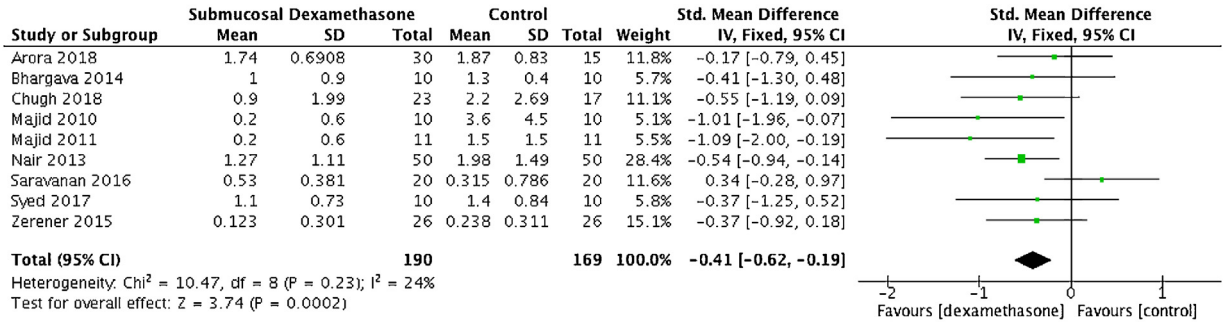

C

Fig. 4. (A) Pain postoperative day 1; (B) pain postoperative day 3; (C) pain postoperative day 7.

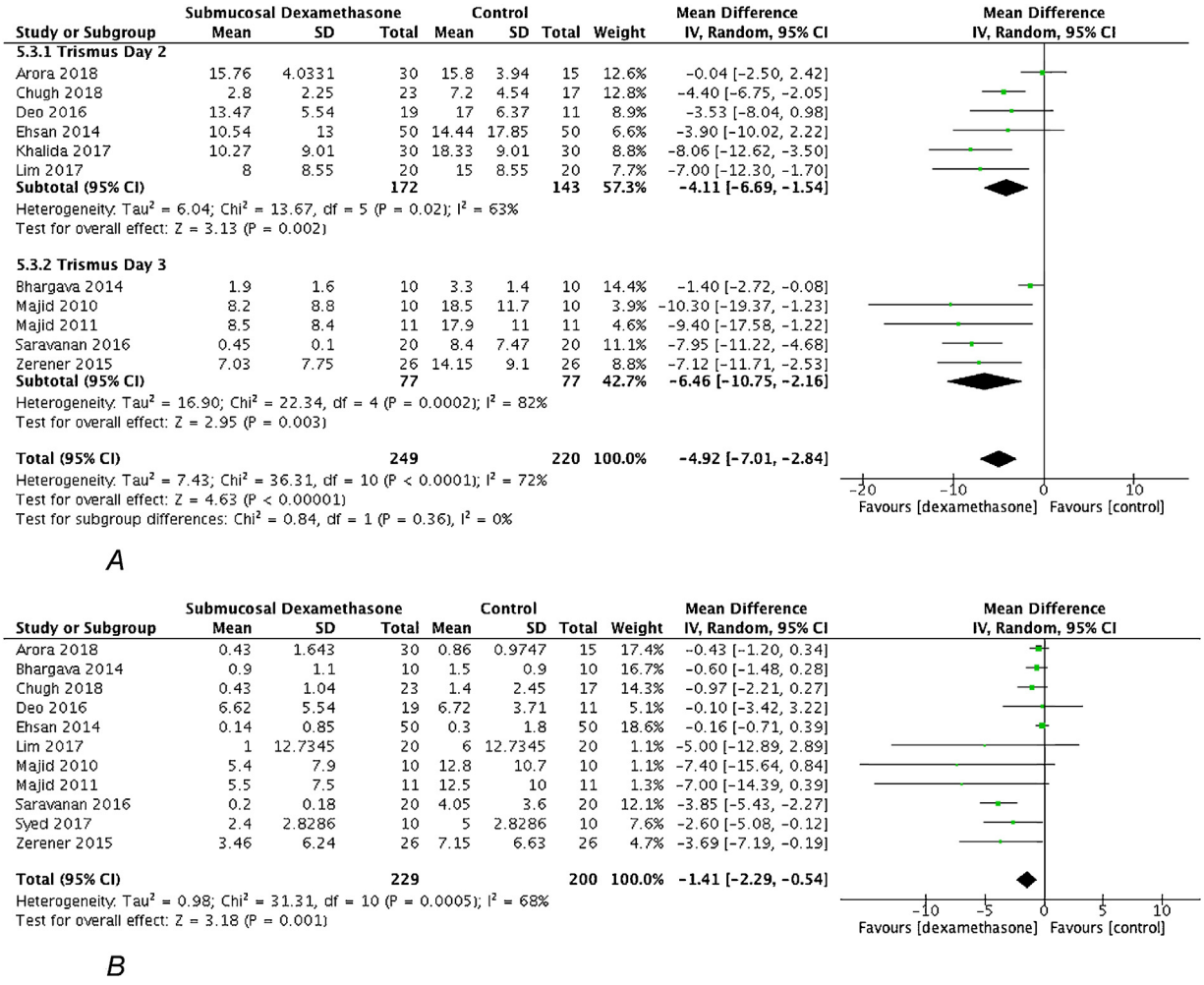

Fig. 5. (A) Early trismus (postoperative day 2 and day 3); (B) late trismus (postoperative day 7).

Saravanan et al., likely relating to limitations in their study design and a potentially biased assessment of the intervention[32]. The imprecision of the combined data for VAS on the third postoperative day is likely a product of the small sample sizes of the individual studies and the small number of trials pooled in this outcome analysis.

There was moderate quality evidence that submucosal dexamethasone reduced pain on day 7 postoperative, the late pain measurement. Design limitations of the included trials contributed to the downgrading of evidence. In particular, the lack of blinding of participants resulted in an increased risk of bias. Low heterogeneity ($I^2 = 24\%$) was observed in the pooled data and it was possible to perform a fixed-effects analysis.

The low NNT to reduce pain on the first and third postoperative days (NNT = 10 and NNT = 4, respectively), suggests that submucosal dexamethasone may be a clinically effective therapy in the early postoperative period. For the late pain measurement, although a statistically significant result was found for SMD in the meta-analysis, a clinical improvement was not identified, with the probability of more pain in the submucosal groups relative to control. The maximal inflammatory response following surgical extraction is observed during the second to third postoperative day[6]. This is seen to correlate with the present review finding that the maximal clinical effect of submucosal dexamethasone for the reduction of postoperative pain occurs in the early postoperative period. The reduction in clinical effect for submucosal dexamethasone in the late postoperative period likely relates to the decrease in the rate of pain observed in participants on day 7 postoperative and reaching the duration of effect of dexamethasone.

The number of analgesics used postoperatively was assessed in seven trials as an outcome measure for pain[22,23,26,29–32]. However, the type of analgesic differed greatly among the studies and was considered too heterogeneous to combine in a meta-analysis.

Trismus

For both early and late measurements, trismus (as measured by inter-incisal distance) was reduced for patients who received submucosal dexamethasone compared with placebo or no intervention.

There was low quality evidence that submucosal dexamethasone reduced trismus in the early postoperative period. Bias presented by the lack of blinding of the outcome assessment was deemed more important than lack of blinding of participants in the assessment of trismus. Two of the included trials failed to blind outcome assessors and it was unclear if four trials blinded assessors, contributing to the downgrading of evidence quality. The heterogeneity may partially be explained by the method for determining maximum mouth opening, with the potential to

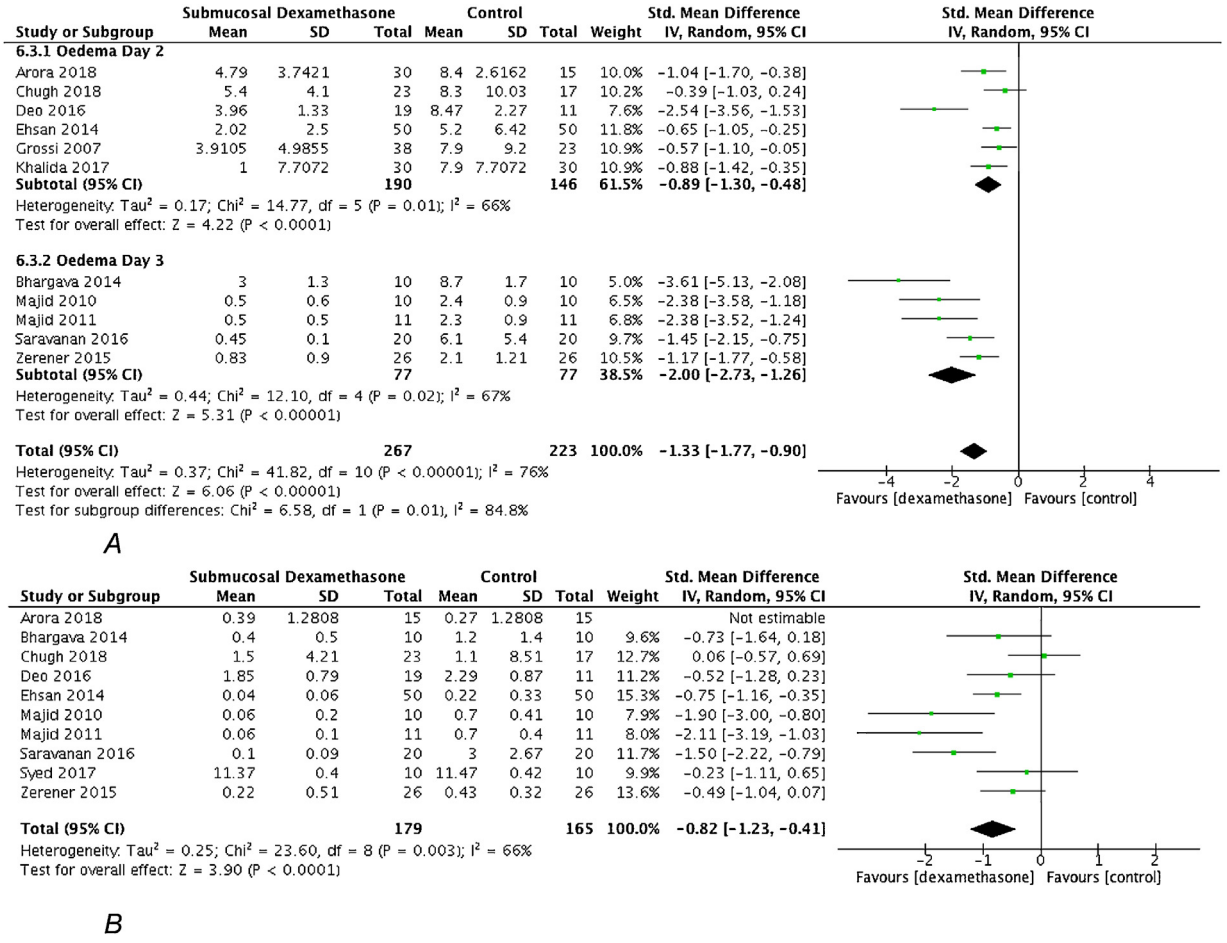

Fig. 6. (A) Early oedema (postoperative day 2 and day 3); (B) late oedema (postoperative day 7).

influence results if measurements were taken when pain was first felt, or when maximum inter-incisal distance was achieved. Imprecision of results as suggested by the wide confidence interval additionally contributed to downgrading of the quality of evidence.

There was low quality evidence that trismus was reduced in the late postoperative period following an injection of submucosal dexamethasone. As for the early measurement of trismus, the same two studies that failed to blind outcome assessors and the four studies in which blinding of assessors was unclear contributed to the downgrading of evidence. Heterogeneity was influenced by the trials by Lim and Ngeow[22], Majid and Mahmood[23], and Majid[30]. The population of the study by Lim and Ngeow differed from those of the other studies due to the predominance of female patients, which may have contributed to this heterogeneous result. The effect shown in both of the studies by Majid et al. could not be explained in terms of clinical or methodological diversity. The imprecise estimate of pooled effect reflects the heterogeneous result and additionally decreases the quality of evidence for this outcome.

Although statistically significant improvements were found for both early and late postoperative trismus, the clinical significance must be assessed. Brignardello-Petersen et al. have previously highlighted the caution required in correlating statistical and clinical significance in relation to trismus after third molar extraction[37]. The results of this meta-analysis showed an improvement in mouth opening in the submucosal dexamethasone groups of 4.92 mm and 1.41 mm in the early and late periods, respectively. The most noteworthy clinical implications of trismus include restricted speech and nutrition. Previous RCTs assessing a change in postoperative trismus have considered a difference of 5 mm to be clinically significant[38,39]. The authors' justification or citation of this value is, however, lacking. Consequently, the improvements in mouth opening reported in the present systematic review may not amount to a meaningful benefit to the patient.

Oedema

Oedema, as measured by the distance between facial points, was reduced in both the early and late measurements in the submucosal dexamethasone group when compared to placebo or no intervention.

There was moderate quality evidence that submucosal dexamethasone resulted in reduced facial oedema in the early postoperative period. Limitation in study design due to blinding of outcome assessment was deemed an important source of bias for this outcome. However, the majority of included studies displayed a low or unclear risk of bias for blinding of outcome assessors. The trial by Deo largely influenced the heterogeneity of the postoperative day 2 oedema pooled result[29]. This study was the only trial that combined three rather than two facial contour measurements. Similarly for day 3 postoperative, the trial by Bhargava et al.[27], who performed one facial contour measurement, and Zerener et al.[20], who combined three measurements, were heterogeneous to the pooled trials that analysed two measurements. The SMD were

used in an attempt to account for the heterogeneous measurements of facial oedema; however the inconsistency of results suggests that the number of facial contour measurements was a potential important modifier of facial oedema outcomes. Heterogeneity was also increased when the two subgroups for facial oedema (postoperative day 2 and postoperative day 3) were combined, suggesting a clinical or physiological difference in the daily extent of facial oedema. The small proportion of the pooled population attributed to these studies did not, however, grossly affect the precision of this result.

There was low quality evidence that submucosal dexamethasone injection reduced facial oedema in the late postoperative period. Blinding of outcome assessors was performed in the majority of included studies, reducing the potential bias from study design limitations. Heterogeneity was influenced by the results of Majid and Mahmood[23], Majid[30], and Saravanan et al.[32]. These studies all used the sum of the same two facial measurements, tragus–midline and gonion–lateral canthus, which may have estimated an increased effect compared with other measurements. The small sample sizes of the two Majid studies may also have been unrepresentative of the true effect.

The low NNTs in the early and late postoperative periods suggest that submucosal dexamethasone is an effective clinical therapy for reducing oedema following third molar surgery. The reduction in oedema was found to be greater in the early postoperative period. However, unlike pain, there was a clinically marginal effect demonstrated for the reduction of oedema in the late postoperative period. This finding suggests that the initial suppression of inflammation by dexamethasone is significant enough to result in a reduction of oedema after the duration of action of the corticosteroid has been reached.

Harm

Harm attributed to submucosal dexamethasone injection during third molar extractions was not a primary outcome of this systematic review. Interestingly, of the studies included, only one trial reported on the potential negative effects of submucosal dexamethasone[22].

Overall completeness and applicability of evidence

Despite the inclusion of 17 studies, there were limitations in the available data. Three trials were immediately excluded from meta-analysis due to the authors reporting their data graphically or in a manner that did not allow the precise mean and SD to be extracted[18,24,28]. Trial authors were contacted for the missing data; however the primary data could not be obtained for the pooled analyses. Two of the included studies did not measure pain either in terms of VAS or number of analgesics consumed. Additionally, outcomes were measured at variable times postoperatively. It was deemed that trismus and oedema measurements from the second and third postoperative days could be combined to form an early measurement of these outcomes. Similar to the combined data in the review by Moraschini et al., this decision was based on the physiological basis that the peak inflammatory response following the surgical extraction of third molars occurs over the second and third postoperative days[6]. There was therefore little clinical or physiological basis for not combining measurements from the second and third postoperative days. Pain on the other hand, as a patient-reported outcome, was considered important clinically to assess daily rather than combining into an early postoperative assessment.

The patient population, degree of third molar impaction, and surgical technique analysed were comparable to current clinical oral and maxillofacial surgical practice. The Pell and Gregory classification used to describe the degree of molar impaction, where documented, suggested a higher degree of surgical difficulty for extraction. The severity of impaction and the fact that the majority of third molar extractions were performed by oral and maxillofacial surgeons, potentially limits the applicability of the pooled results with regard to general dentists not undertaking regular impacted mandibular third molar extractions.

Quality of evidence

The quality of evidence was assessed using the GRADE framework and is presented for each outcome under the 'Summary of main results'[8]. This framework combines the risk of bias, directness of evidence, unexplained heterogeneity, precision, and publication bias to produce an overall score. Despite only including RCTs and quasi-RCTs, none of the GRADE assessments were of high quality. Evidence was predominantly downgraded due to risk of bias, most frequently relating to the lack of blinding of participants or outcome assessment. Heterogeneity and imprecision, reflecting the small number of combined trials and inadequate sample sizes, were also major contributors to the downgrading of evidence.

Potential biases in the review process

It was attempted to identify and minimize all potential biases in the review process if possible. Although there was no limitation on the language of included studies, it remains uncertain whether the search strategy was appropriate for identifying studies in languages other than English. The authors of the included studies were contacted for information regarding missing data and for potentially unpublished data; however no additional information was obtained. It was attempted to minimize duplicate publication bias. The review authors identified two trials published by Deo and only included one, as the trial data were deemed the same. However, similarities in the trials by Majid et al. may have opened the meta-analyses to duplicate publication bias, leading to an overestimation of the effect of submucosal dexamethasone in third molar surgery[23,30]. Sensitivity analyses were not performed after the exclusion of these trials, which would have improved the certainty of the intervention result.

A funnel plot was created for the late trismus outcome, as this was the only outcome for which more than 10 studies were included. Statistical testing of funnel plot asymmetry was not performed due to the narrow standard error of the included studies[40]. The single outlying study may have been a result of true heterogeneity, chance, or publication bias, a finding that likely explains the contribution of the study by Saravanan et al.[32] to the heterogeneity of outcomes[41].

Agreements and disagreements with other studies or reviews

Two previous systematic reviews have been conducted on this topic. The meta-analysis of Moraschini et al. found that submucosal dexamethasone resulted in reduced postoperative pain and facial oedema following third molar extraction[6]. This study by Moraschini et al. failed to find a statistically significant effect for the reduction of postoperative trismus[6]. In 2017, a systematic review and meta-analysis by Chen et al. found a significant effect for the reduction of early and late oedema and early trismus following submucosal dexamethasone administration[5]. No significant result was found for the reduction of late trismus, and it was not

possible to perform a meta-analysis for postoperative pain due to heterogeneity. The review by Chen et al. also utilized the SMD as the effect measure, for which the clinical interpretation of effect is difficult.

This review included seven new trials published on this topic. It was also aimed to convert the results into a clinically relevant format. Similar to Moraschini et al., the present review found a clinical benefit for the use of submucosal dexamethasone to reduce postoperative pain. It was also possible to expand upon these results to demonstrate that reductions in postoperative pain were more clinically significant in the early postoperative period. As in the 2017 review by Chen et al., the present review found a significant result for the reduction of trismus and it was also possible to demonstrate this for both early and late pooled measurements. Despite these findings, the clinical significance of the reduction of trismus may be marginal, with any potential clinical benefit more likely in the early postoperative period. Reductions in oedema were most notable in the early postoperative period, supporting the findings of the two previous reviews.

Implications for practice and research

The results suggest, with low quality of evidence, that submucosal dexamethasone may be beneficial in reducing pain and oedema in the early postoperative period for patients undergoing the extraction of significantly impacted mandibular third molars. Additional higher powered and well-conducted RCTs are required to strengthen the quality of evidence in order to guide clinical practice. Although this review examined the benefits of submucosal dexamethasone, harm was not assessed. If this intervention is to be implemented in clinical practice, further research into the potential negatives of submucosal dexamethasone must be investigated. This review did not investigate a definitive protocol in relation to the dose (4 mg or 8 mg), site, or timing of the submucosal dexamethasone injection. Further research comparing differing regimens would be useful to strengthen the clinical recommendations.

This systematic review and meta-analysis revealed a statistically significant benefit of submucosal dexamethasone when compared with placebo for the reduction of early and late postoperative pain, trismus, and oedema following the extraction of mandibular third molars. The quality of evidence was graded low or moderate according to the GRADE criteria for each outcome. The main clinical implications of submucosal dexamethasone relate to the reduction of pain and oedema in the early postoperative period. The reduction in trismus is unlikely to be of clinical significance. Further high quality RCTs are required to strengthen the quality of evidence for this intervention across all outcomes. Investigation into the potential harms and a definitive protocol for submucosal dexamethasone administration would strengthen the clinical recommendations for its use during impacted mandibular third molar extractions.

Competing interests

None.

Ethical approval

Not applicable.

Patient consent

Not required.

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