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Effectiveness of pre-operative oral corticosteroids in reducing pain, trismus and oedema following lower third molar extractions: a systematic review

Running title: Pre-operative oral corticosteroids and lower third molar extractions

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ABSTRACT

Aim: To determine if a single pre-operative dose of oral corticosteroids would be effective in reducing pain, trismus and oedema following lower third molar surgical extraction. Secondary outcomes of interest were post-operative complications such as infections.

Methods: Searching was conducted using Embase, MEDLINE, DOSS, CINAHL and CENTRAL for randomised controlled trials. Four studies which compared pre-operative oral corticosteroids to placebo prior to lower third molar surgical extractions were eligible for inclusion.

Results: All studies were judged to be at unclear risk of bias. All studies tested the efficacy of 8mg dexamethasone 60-90 minutes prior to surgical extractions. Whilst three studies showed improvement in pain visual analogue scale (VAS) scores in the dexamethasone groups, two were not statistically significant. One study found no improvement in pain scores on VAS. One study found no difference in either trismus or oedema. One study reported one occurrence of post-operative alveolar infection in the dexamethasone group and one occurrence of alveolar osteitis in the placebo group.

Conclusion: While there seems to be an improvement in pain scores on VAS, these results are not clinically significant. Post-operative analgesia plays a more important role clinically.

• **Key words:** Third molar, corticosteroids, oral surgery, pain, trismus, oedema

INTRODUCTION

Inflammatory complications including pain, swelling, trismus, and alveolar osteitis are recognised sequalae of surgical removal of mandibular third molars and adversely affect the quality of life[1]. Apart from individual variations, the severity of inflammatory response is often related to the difficulty and duration of the surgical procedure[2, 3, 4]. Postoperative pain following third molar removal in outpatient settings is first reported once local anaesthesia has subsided and is managed routinely with oral analgesics[5]. Other measures to minimise post-operative inflammatory complications include antibiotics[6]; chlorhexidine[7]; corticosteroids; cryotherapy[8]; ozone and platelet-rich plasma[9].

Corticosteroids have been used in dentistry since the 1950s and continue to be used in contemporary oral surgery[10, 11]. The use of corticosteroids has been found to reduce post-surgical inflammation and pain by inhibiting vascular dilation and reducing the transudation of fluids[12]. This is made possible by inhibiting leukocyte chemotaxis and the suppression of the production of inflammatory mediators, such as prostaglandins and leukotrienes[12, 13]. Although corticosteroid use may potentially increase the risk of post-surgical wound infection, such events are rare following administration of a single dose of corticosteroid as prescribed in oral surgery[13, 14].

Corticosteroids are available in numerous preparations and routes of administration, with dexamethasone, betamethasone and methylprednisolone being the most commonly used corticosteroids as they

have the longest duration of action[15]. Corticosteroids may be administered orally, intramuscularly into the masseter muscle, submucosally into the pterygomandibular space, and intravenously. Parenteral administration is most effective in reducing inflammation and pain[16].

There is evidence from systematic reviews and meta analyses that the pre-operative use of oral corticosteroids leads to favourable outcomes following lower third molar surgery. Although the effectiveness of corticosteroid has been evaluated in several systematic reviews, these studies considered all routes of administration, dosages and preparations[12, 15, 16]. Existing evidence suggests that oral administration is comparable to parenteral administration, with the exception of submucosal administration[12]. A single, pre-operative dose of oral corticosteroids offers potential benefit of ease of administration and this aspect has not been evaluated in previous reviews.

The aim of this systematic review was to investigate the effectiveness of a single pre-operative dose of oral corticosteroids in reducing pain, trismus, and oedema following lower third molar surgical removal.

METHODS

Eligibility criteria

Only randomised controlled trials that studied the effects of a single pre-operative dose of oral corticosteroids prior to lower third molar extractions were included in this review. Studies which focused on parenteral corticosteroids, multiple doses of corticosteroids and other oral surgical procedures were excluded. Furthermore, the use of prophylactic antibiotics was also excluded. The use of pre-operative and post-operative analgesics was not excluded if both intervention and control groups received similar drug regimens.

Information sources

The following biomedical databases were searched: Embase, MEDLINE, DOSS, CINAHL and CENTRAL. Trial registries and OpenGrey were used to search for unpublished articles. SCOPUS was used to search the references of the most recent systematic review on this topic[12].

Search

Searching was conducted in March 2019. The search comprised terms for dental extractions or surgery combined with terms for corticosteroids, including common misspellings of their names. Both free text terms for synonyms and subject headings were used according to their availability in the databases. The search strategy was developed under the guidance of an information specialist. There were no restrictions on date or language of publication. The full search strategy may be found in Appendix A.

Study selection

Results were independently screened on title and abstract and on full text by two reviewers and conflicts were resolved by discussion. Data was extracted from the included studies using the Cochrane Collaboration data extraction forms[17] against the following items: study design, sample size, timing of corticosteroid administration, type of local anaesthesia, surgical time, analgesics required, outcome measures and their results. The results were extracted from the groups of interest which compared dexamethasone versus placebo.

RESULTS

Full text screening led to exclusion of 23 articles. The PRISMA flow diagram[18] is illustrated in Figure 1 with reasons for the full text exclusions.

A total number of 4 randomised controlled trials satisfied the inclusion and exclusion criteria for the review and are listed in Table 1. Bauer et al.[19] conducted a split mouth study which compared the effects of ibuprofen with and without dexamethasone versus placebo. Bortoluzzi et al.[20] compared the effects of dexamethasone, with and without amoxicillin versus placebo prior to lower third molar extractions. Lisboa et al.[21] conducted a randomised controlled trial comparing 4 drugs: ibuprofen with arginine, etoricoxib, and dexamethasone versus placebo. Simone et al.[22] compared dexamethasone and diclofenac sodium versus placebo. Table 2 illustrates the characteristics of the included studies.

Risk of bias

Following appraisal using the Cochrane Risk of Bias tool[17], all four studies[19, 20, 21, 22] were judged to have an unclear overall risk of bias. Bauer et al.[19] did not report on all of the time points proposed in their methodology, and therefore was deemed to have a high risk of reporting bias. Lisboa et al. [21] had multiple areas of unclear risk bias throughout the study, but these may be attributed to poor reporting. Simone et al.[22] was judged to be at high risk of attrition bias due to the exclusion of some patients from the analysis. Bortoluzzi et al.[20] was judged to have an unclear risk of bias in the areas of selection, detection, attrition and reporting bias. It was for these reasons

that the overall risk was unclear. A visual representation of the risk of bias can be found in Figure 2.

Pain

The visual analogue scale (VAS), was used to measure pain in all four studies, with Bauer et al.[19], Bortoluzzi et al.[20] and Simone et al.[22] using the VAS scale to report the outcomes and Lisboa et al.[21] using a similar 101-point scale. The VAS scores reported in all four studies have been converted to a 0-10 scale for ease of readability and can be seen in Figure 3.

The results show an improved response in pain with the use of corticosteroids in three studies[19, 21, 22].

The Bauer et al.[19] results for pain VAS scores showed no statistical significance. Furthermore, Bauer et al.[19] found there to be no statistically significant difference between the dexamethasone and ibuprofen groups versus ibuprofen alone in regard to the total number or rescue analgesics consumed.

Lisboa et al.[21] observed a statistically significant difference between dexamethasone and the higher placebo scores at 4 hours post-operatively in both pain VAS and 4-point verbal scale scores. Furthermore, a significantly higher number of analgesics were taken post-operatively in the placebo group than in the dexamethasone group.

Simone et al.[22] found no statistically significant difference between the dexamethasone and placebo groups in hourly pain scores. However, they

did find significantly more pain in the placebo group when the mean of the scores were observed across the whole evaluation period.

Bortoluzzi et al.[20] found no statistically significant difference between the dexamethasone and placebo groups in either pain, trismus, oedema.

Rescue medication

Bauer et al.[19], Lisboa et al.[21] and Simone et al.[22] reported the number of analgesics taken, which can be found in table 3. Patients in both groups in the Bortoluzzi et al.[20] study were prescribed a regimen of acetaminophen 750 mg 4 times a day and sodium diclofenac 50 mg 3 times a day for the duration of the follow up period. Bauer et al.[19] reported conflicting numbers of rescue analgesics. In one visual representation, the control group (ibuprofen and placebo) was reported to have taken a total of approximately 21 analgesics in a 72-hour period, and in another visual representation, participants had only taken 3 in a 72-hour period which appears to be conflicting.

Oedema and trismus

Bortoluzzi et al.[20] was the only study to measure oedema and trismus. Oedema was measured on a VAS scale of 0-100 which was self-reported by the patients in each group. The results show that there was no significant difference between the intervention and the control groups (Figure 4).

Trismus was defined as half of normal mouth opening[20]. Trismus was measured as a binary “yes” or “no” by both the patient and the clinician post-extraction. Therefore, the assessment of “half of normal mouth

opening" appears to be subjective and may be unreliable. It may have been beneficial if studies adopted a standardised technique to measure these outcomes[23, 24, 25, 26]. The results are shown in Table 4.

Post-operative complications

Three studies[19, 21, 22] recorded no complications in the intervention or the control groups. Bortoluzzi et al. reported that 1 patient in the dexamethasone group suffered from alveolar infection, and 1 patient from the placebo group suffered from alveolar osteitis[20].

DISCUSSION

Removal of impacted third molars is one of the most commonly undertaken surgical procedures[27]. Postoperative inflammatory complications following removal of mandibular third molars may have a significant impact on the quality of life for patients[28]. A variety of measures have been evaluated to reduce the intensity of postoperative inflammatory sequalae[1]. Although pharmacological therapy with corticosteroids has been reported to be one of the most effective options to reduce postoperative swelling, variations in the timing of administration, dosage, and route of administration pose difficulties in comparability of the results to draw reliable inferences[29]. Existing evidence has already identified the benefits of injectable corticosteroids in third molar surgery[12, 13]. Furthermore, previous reviews that have studied oral corticosteroids have not differentiated between the dosages and have noted the difficulty in meta-analysis due to heterogeneity[12, 16, 30]. There was lack of clarity regarding the value of oral administration which provided the rationale for the current systematic review.

A critique of evidence from our systematic review is summarised below along with comparisons with the wider literature followed by the implications of the findings in contemporary clinical practice.

Quality of the evidence

The GRADE (Grading of Recommendations, Assessment, Development and Evaluation) tool was used in order to assess the quality of the evidence[31]. This can be found in Table 5. The outcomes pain, number of rescue analgesics and post-operative complications were indicated as low certainty, due to serious limitations with both risk of bias and indirectness. Indirectness was measured as a serious limitation due to the differences in interventions[32]. In the Bauer et al.[19] study, ibuprofen was given pre-operatively as an adjunct in both the dexamethasone and placebo groups, whereas the other studies used of dexamethasone alone. Furthermore, the parameters imposed by the Bauer et al.[19] and Simone et al.[22] studies in regard to surgical time, limits the applicability.

The GRADE assessment of both the trismus and oedema outcomes were judged as moderate certainty due to risk of bias of the Bortoluzzi et al.[20] study, as this was the only paper to report these outcomes.

Difference in interventions

The Bauer et al.[19] results showed the least overall pain VAS scores among all four studies as seen in Figure 3. This may be due to the difference in the treatment group, as Bauer et al.[19] used both ibuprofen and dexamethasone in combination as their intervention group, versus ibuprofen and placebo as their control group. This may indicate the increased efficacy of corticosteroids in combination with a non-steroidal anti-inflammatory drug (NSAID) which has shown promising effects in managing post-operative pain in oral surgery[8]. In fact, some studies have observed the qualities of

corticosteroids taken in conjunction with analgesics and had found them to be beneficial [33, 34].

Analgesics used post-operatively

Dual therapy has been proven to be more effective than single drug preparations when attempting to control post-operative pain[35, 36]. This would therefore affect the VAS pain scores, as demonstrated by the Lisboa et al.[21] participants experiencing more post-operative pain due to the single drug therapy and the low dosage in comparison to the other studies. Conversely, in the Bauer et al.[19] and Bortoluzzi et al.[20] studies, patients reported lower VAS scores (Figure 3). Furthermore, in the Bortoluzzi et al.[20] study, patients were prescribed a regimen of rescue medication, which may additionally explain why their results do not show an improvement (Figure 3). Further analyses of both Bauer et al.[19] and Lisboa et al.[21] show the VAS scores of the intervention group equalling or surpassing the controls in the 6-hour to the 12-hour mark post-surgery (Figure 3). This could be attributed to the use of the rescue medication during this period, which Bauer et al.[19] had noted in their study.

Depth of impaction and difficulty

It has been shown that the difficulty and depth of third molar impaction can increase symptoms of post-operative pain, oedema and trismus[2]. Bortoluzzi et al.[20] reported the number of patients who had "difficult" extractions and the classification of impaction according to the Pell and Gregory classification[26]. The dexamethasone group had had 3 more patients requiring deeper and more difficult extractions than the placebo group

which can further explain why the dexamethasone group showed a higher pain/oedema score than placebo. This conforms to the literature, where a prospective study found that Pell and Gregory Class III Position A had a higher incidence of pain (37.5%)[37].

Bauer et al.[19] did not report on the distribution of patients according to depth of impaction, only that all patients had "semi-impacted" lower third molars, which can be inferred to be Position A (highest point of the third molar above or equal to the occlusal plane) or Position B (highest point of the third molar between the occlusal place and the cemento-enamel junction of the lower second molar) impactions. This does not account for the amount of the ramus impacting the third molar (Class I, II, III)[38]. Therefore, this leaves room for potential variability in the participants, as we cannot accurately infer how much bone removal was required and therefore how much trauma the patients may have experienced.

Lisboa et al.[21] and Simone et al.[22] did not report on the depth of impaction, except that Lisboa et al. reported that stratification was undertaken according to Pell and Gregory's classification[21], which would have evenly distributed the impacted cases between the groups.

Local anaesthetic

The literature suggests the potential interaction of corticosteroids when used in combination with a local anaesthetic[39, 40], however, they are usually administered parenterally, and it is unclear if the benefits would apply with the use of oral corticosteroids. The only paper to report the amount of anaesthetic administered to the participants was Bauer et al.[19] and can be

found in Table 2. The studies did not report if the anaesthetics were administered via infiltration or an inferior alveolar nerve block or a combination of these.

The variability in type and dosage of anaesthetic used may be important, especially in the first few hours following treatment. The duration of soft tissue anaesthesia of articaine 4% is said to be longer than lidocaine 2% followed by mepivacaine 2%, and a difference is also noted whether or not local anaesthetics were delivered via nerve block or infiltration[41, 42].

This is reflected in the VAS scores seen in Figure 3. We see that the highest points of pain occur in the 3 to 6-hour mark following extraction. The use of different types of anaesthetic and dosages would then lead to discrepancies especially within this time period.

Surgical time

In clinical practice, the difficulty of a surgical extraction could be influenced by mouth-opening, depth of impaction, difficulty of achieving effective anaesthesia, root morphology, among others[43]. Surgical time has been shown to be a significant cause of pain trismus and oedema, with a close relationship to the depth of impaction[44].

The amount of time spent during the surgical procedure would affect the results, as this would directly translate to higher amounts of trauma experienced by the participants[1]. Bauer et al.[19] and Bortoluzzi et al.[20] reported similar surgical times for both the intervention and the control groups. Lisboa et al.[21] and Simone et al.[22], did not report these figures,

although Simone et al. excluded patients who required increased surgical time, but did not define the time-scale[22].

Timing of dexamethasone administration

Both Bauer et al.[19] and Simone et al.[22] prescribed dexamethasone to patients 1 hour before the procedure, while Lisboa et al.[21] administered the drug 90 minutes before the procedure. Bortoluzzi et al.[20] reported a range of 60 to 90 minutes before the procedure. While this is a difference in methodology amongst the studies, this may not greatly affect the results, as dexamethasone concentrations in serum tend to be highest at around 2 hours post-ingestion[45].

Clinical relevance

Both Bauer et al.[19] and Simone et al.[22] excluded patients with a history of pericoronitis. Furthermore, Bortoluzzi et al.[20] and Simone et al.[22] only included American Society of Anaesthesiologists (ASA) grade 1 patients and excluded patients classified as ASA 2. This could limit the relevance of these studies to routine clinical practise, as pericoronitis is one of the main indications for extraction of lower third molars[46] and more patients with complex medical histories are increasingly being treated[47].

When considering pain as an outcome measure, it is important to quantify a clinically meaningful change. A 30% reduction in pain is used as a benchmark in regards to its effect on patients' quality of life, and therefore considered clinically significant[48]. Moreover, a score of 30 or less on a 0-100 VAS is generally considered to be manageable by patients[49]. Bauer et al.[19],

Bortoluzzi et al.[20], and Simone et al.[22] all had relatively low VAS scores spread amongst all groups, and hence the differences in scores between these groups are not clinically significant. Lisboa et al.[21] on the other hand observed a clinically significant change at the 6th hour post operatively when compared to placebo, with the placebo having a 0-10 VAS score of 6, compared to the dexamethasone score of 3.5. Therefore, it could be interpreted that dexamethasone has a clinically significant effect on pain at the 6-hour mark.

Limitations of the review

It should be noted that the studies included in this review had multiple areas that were of unclear risk of bias. Furthermore, there was data that had not been reported by some of studies in the review. The number of clinicians conducting the surgeries were not reported by Lisboa et al.[21] or Simone et al.[22], while Bauer et al.[19] reported that one operator conducted the surgical procedures, and a final year Dentistry student as the operator in the Bortoluzzi et al.[20] study. Moreover, sample size calculations were not reported by Lisboa et al.[21] and Bortoluzzi et al.[20], while Bauer et al.[19] and Simone et al.[22] reported that 22 patients and 17 patients were needed in each group respectively to achieve a power of 90%. However, the placebo group in the Simone et al.[22] study was under powered.

Implications for Clinical Practice

Preoperative oral corticosteroids during surgical removal of third molars are not used in the UK for a variety of reasons. A significant proportion of patients who require surgical removal of mandibular third molars are

treated under general anaesthesia or intravenous sedation. These patients have intravenous access established prior to the surgical procedure and administration of injectable corticosteroids through the existing intravenous access is straightforward, when indicated.

Oral administration is only relevant for patients treated in outpatient settings in general and specialist practice as it offers an alternate option. However, several factors may limit the use of corticosteroids in general practice in primary care. Firstly, in spite of their potential benefits, corticosteroids should be administered sparing and only when clinically indicated by the difficulty of the surgical procedure. Given that complicated third molars are generally referred to secondary care in the UK, it is unlikely that GDPs will be undertaking these procedures. Secondly, GDPs working in the National Health Service (NHS) are not authorised to prescribe oral or injectable corticosteroids[50].

In the UK, the only setting where preoperative oral corticosteroids may be used is outpatient clinics in secondary care. However, following administration of local anaesthesia, sub-mucosal injection of corticosteroids in painless and shows rapid systemic distribution. Moreover, oral corticosteroids may show variable absorption and would warrant patient compliance as well as careful planning of the timing of surgery for optimal outcomes. These factors may leave little merit in the widespread use of oral corticosteroids in outpatient hospital settings.

Nevertheless, the practise of third molar removal may vary internationally and GDPs may undertake this procedure routinely in some countries. These trends may be related limited availability of specialist oral surgeons or

financial constraints of patients to afford specialist care. Preoperative oral corticosteroids may be considered under such circumstances, but their appropriate use would require further evidence based on well-designed randomised-controlled trials.

Conclusion

This review concludes that pre-operative oral administration of 8 mg of dexamethasone has little benefit to a patient undergoing lower third molar surgical extraction. The benefit of post-operative rescue analgesia seems to be more important and clinically relevant than a single dose of dexamethasone pre-operatively, with the use of NSAIDs being studied extensively[35]. Quantifying the effect of higher or lower doses of dexamethasone would be beneficial to establish if there indeed is a dose-effect relationship. In fact, two previous clinical trials noted that a dose of 10 to 23 mg of the dexamethasone equivalent is best used to achieve the highest effect in reducing pain post-operatively[51, 52]. Moreover, the evidence suggests that there may be a benefit to use pre-operative NSAIDs and corticosteroids in combination for lower third molar extractions[53]. The efficacy of pre-operative combination of NSAIDs and corticosteroids needs to be explored further.

There is insufficient evidence to establish the benefits of corticosteroids in the reduction of oedema and trismus. Furthermore, there is insufficient evidence to determine an association between the surgical time for lower third molar extraction and the use of corticosteroids.

Conflict of Interest

We declare that we have no conflict of interest.

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