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The effect of pre-emptive Ibuprofen on post- operative pain after removal of lower third molar teeth: a systematic review

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The Effect of Pre-emptive Ibuprofen on Post-Operative Pain After Removal of Lower Third Molar Teeth: A Systematic Review

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Abstract

Objective

To investigate the effect of pre-emptive ibuprofen on post-operative pain after lower third molar surgery.

Methods

A search for randomised controlled trials was undertaken across the databases MEDLINE, Embase, Cochrane CENTRAL and Dentistry and Oral Sciences Source. Citation searching was used to supplement the database search. Inclusion and exclusion criteria were used for independent double screening by two assessors.

Results

A total of 5 randomised controlled trials were included in the review. A risk of bias assessment identified some concerns in 4 of the included studies. One study was assessed as having low risk of bias. The important outcomes measured were post-operative pain intensity, total pain relief, use of rescue analgesia, time to rescue analgesia and total consumption of rescue analgesia. In 2 trials, pre-emptive ibuprofen was shown to significantly reduce pain intensity after lower third molar surgery compared with placebo. Two trials showed no significant difference between ibuprofen and placebo groups. Pre-emptive ibuprofen was shown to provide superior pain relief compared with placebo in the 1 trial measuring this outcome. Where the use of rescue medication was measured as an outcome, 2 trials showed that pre-emptive ibuprofen was superior to placebo, 1 trial showed that placebo was superior to ibuprofen and 2 trials found no significant difference between ibuprofen and placebo groups.

Conclusion

Due to the inconsistency of the results, there is insufficient evidence to support the use of pre-emptive ibuprofen for management of post-operative pain after lower third molar surgery. Further research into the effects of pre-emptive analgesia on the surgical pain pathway is required.

Introduction

Due to their anatomical position and late development, lower third molars are a common source of pain and infection. Impaction and restricted access for oral hygiene measures can cause an accumulation of bacteria around the impacted tooth which can lead

to dental caries and pericoronitis. Surgical removal of lower third molars is associated with significant risks including pain, alveolar osteitis, infection and inferior dental nerve paraesthesia [1].

Local anaesthetic administered at the time of surgery has been shown to significantly reduce early post-operative pain in oral surgery procedures carried out under general anaesthetic [2]. The most frequently used dental anaesthetic in the UK is lidocaine with adrenaline, which has duration of action of 120-300 minutes for soft tissue analgesia. Therefore the patient may be expected to remain pain-free for 2-3 hours from the start of surgery [2]. From this point, the management of post-operative pain is reliant on systemic analgesia.

A 2013 Cochrane review found high quality evidence suggesting that ibuprofen was superior to paracetamol in the management of post-operative pain and limited evidence suggesting that paracetamol and ibuprofen combined were more effective that ibuprofen alone at 6 hours after surgery [3]. Ibuprofen is a non-selective inhibitor of cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). The time to peak concentration of ibuprofen administered orally is 1 – 2 hours and the half-life is 1.8 – 2 hours [4]. It is metabolised and excreted in urine within 24 hours [5].

Pre-emptive analgesia is “an anti-nociceptive treatment applied before tissue injury to prevent peripheral and central sensitization” [6]. Due to this theoretical protective effect on the nociceptive system, pre-emptive analgesia could be more effective than similar post-operative analgesic regimes [7]. There is ongoing research in this field and animal studies have shown promising results. However, clinical trials in humans have been inconsistent and current evidence is weak [8].

Extensive research has been carried out to determine the effect of post-operative NSAIDs after lower third molar removal, but there is lack of clarity regarding effect of NSAIDs administered pre-operatively. If the peak concentration of orally administered ibuprofen is reached at 1-2 hours, a pre-emptive dose before surgery is likely to take effect during or just after the surgical procedure, which

may provide superior analgesia in the early post-operative period as well as preventing hypersensitization of the nociceptive system.

Objective

The objective of this study was to answer the question: in patients requiring removal of lower third molar teeth, does the administration of ibuprofen one hour before surgery affect experience of post-operative pain?

Methods

Eligibility criteria

Randomised controlled trials (RCTs) with adult patients having lower third molar tooth removal under local anaesthetic were included. Trials where patients were treated under general anaesthetic or conscious sedation were excluded. Only RCTs comparing the effect of pre-emptive ibuprofen with pre-emptive placebo were included. Trials where multiple doses or additional analgesic drugs were administered pre- or post-operatively were excluded.

Information sources

MEDLINE, Ovid Embase, Cochrane CENTRAL and Dentistry and Oral Sciences Source were searched. SCOPUS was used for citation searching of included studies and relevant systematic reviews.

Search strategy

Searching was carried out on 18th March 2020. The search strategy was designed with the advice of an information specialist. The strategy comprised subject headings and free text terms and synonyms for each of the concepts of lower third molars, tooth extraction, ibuprofen and pre-operative period. An RCT filter was used in MEDLINE and Embase to increase specificity [9]. No date or language restrictions were imposed.

The search strategy for each database is shown in full in Appendix 1.

Study selection

Independent double screening of the results against title and abstract and then full text was undertaken by two assessors using Rayyan [10]. There was one conflict in the decisions made and this was resolved after discussion.

Results

48 papers were excluded at title and abstract screening and 5 further papers were excluded at full text screening. Citation searching did not find any further papers for inclusion. Figure 1 shows the PRISMA flow diagram which summarises the search and screening process.

Synthesis methods

Five papers were included in the review [11, 12, 13, 14, 15]. The characteristics of each of the included studies are shown in Table 1. The five included studies varied by methodology (study design, assessment time-points) and clinical features (dosage, local anaesthetic agent, rescue analgesia). Due to this variation between a small number of studies, no clinically meaningful combined effect size

could be calculated.

The data from each of the included studies was extracted from the reports into an excel spreadsheet by the lead author for analysis. For the outcomes, the following items were extracted: pain intensity, time to rescue analgesia, total consumption of rescue analgesia and request of rescue analgesia. Results from the studies were tabulated and grouped by outcome.

Figure 1 – PRISMA 2020 flow diagram

Risk of Bias

The Cochrane Risk of Bias 2 (RoB 2) tool was used for all included papers to appraise the studies. The critical appraisal was led by the lead author and agreed by the review team. The completed assessments are included in Appendix 2.

Four of the studies were assessed as having “some concerns” overall, largely due to poor or absent reporting about randomisation and allocation concealment. In all other domains, the risk of bias was assessed as low. Figure 2 illustrates the risk of bias across the studies.

Figure 2 - Summary of Risk of Bias assessment for all included studies

Table 1 - Summary of characteristics of included studies

Study ID	**Al-Sukhun, 2012**	**Albuquerque, 2017**	**Bauer, 2012**	**Chiu, 2005**	**Morse, 2006**
Setting	Not reported	Oral and Maxillofacial surgery department, University Hospital, the Federal University of Ceara, Brazil	Outpatient clinic, School of Dentistry, Sao Paulo, Brazil	Prince Philip Dental Hospital, Hong Kong	Two government dental outpatient clinics, Fiji
Study design	Parallel group RCT	Split mouth RCT	Split mouth RCT	Split mouth RCT	Parallel group RCT
Number of participants	150 participants	36 participants 72 surgeries	47 participants 94 surgeries	54 participants	55 participants
Interventions	Celecoxib Ibuprofen	Etoricoxib Ibuprofen	Dexamethasone Ibuprofen Dexamethasone + Ibuprofen	Rofecoxib Ibuprofen	Rofecoxib Ibuprofen
Dose of ibuprofen	400mg	400mg	600mg	400mg	400mg
Control	Placebo	Placebo	Ibuprofen placebo Dexamethasone placebo	Placebo	Placebo
Local anaesthetic agent	2% lignocaine hydrochloride and 1:80,000 epinephrine	2% mepivacaine hydrochloride and epinephrine 1:100,000	2% mepivacaine hydrochloride and norepinephrine 10 g/mL	2% lignocaine hydrochloride and 1:80,000 epinephrine	% lignocaine hydrochloride and 1:80,000 epinephrine
Rescue analgesia	Paracetamol 1g	Ibuprofen 300mg	Codeine Paracetamol	Acetaminophen (Paracetamol) 500mg	Paracetamol 1g

Pain intensity

Pain intensity was measured as the primary outcome in 4 of the included studies using the VAS scale. The data retrieved for pain intensity from all included studies is shown in Table 2 and the highest score for each study is shown in bold.

Morse *et al* [15] reported significantly reduced pain intensity in the ibuprofen group compared with the placebo group at all time points measured. Albuquerque *et al* [12] reported similar findings, specifically at 2 hours and 4 hours post-operatively and reduced cumulative pain intensity at 6 hours and 12 hours post-operatively ($p<0.001$).

In the other 2 studies [13, 14] there was no statistically significant difference in pain intensity between the ibuprofen and placebo groups.

Pain intensity appears to be at its highest between 2 and 6 hours post-operatively in both groups. The data suggests that during this period, pre-emptive ibuprofen may act to reduce pain intensity. However, the difference in scores between ibuprofen and placebo groups is small (less than 1.0) in 3 studies and very variable (0.2 – 3.2) in 1 study. It is difficult to equate a difference of 3.2 on the VAS scale to an actual difference in patient experience but overall, the results suggest that the benefit of pre-emptive ibuprofen is minimal with regard to pain intensity. 12 hours after surgery, ibuprofen would have been eliminated from the blood and the benefit of pre-emptive ibuprofen is no longer evident.

Figure 3 shows pain intensity for all included studies over the first 12 hours post-operatively.

Table 2 – Pain intensity across all studies measuring this outcome

Mean VAS scores for each study (0-10) (Figures in bold are maximum reported score)								
	Albuquerque *et al* 2017		**Bauer *et al* 2012**		**Chiu *et al* 2005**		**Morse *et al* 2006**	
Time (h)	**Ibuprofen**	**Placebo**	**Ibuprofen**	**Placebo**	**Ibuprofen**	**Placebo**	**Ibuprofen**	**Placebo**
1 h before							0.90 (SD 1.90)	2.20 (SD 3.00)
Just before							0.20 (SD 0.80)	0.40 (SD 1.50)
0.5							0.40 (SD 1.20)	2.10 (SD 2.50)
1			2.00 (SD 2.40)	2.40 (SD 2.70)			0.70 (SD 1.00)	2.90 (SD 2.60)
1.5							0.90 (SD 0.90)	3.40 (SD 2.60)
2		**6.30** (SD 2.90)	2.40 (SD 2.10)	2.40 (SD 1.90)	1.18 (SD 1.49)	2.06 (SD 1.97)	1.70 (SD 1.70)	4.60 (SD 2.80)
2.5							2.00 (SD 2.30)	5.00 (SD 2.80)
3			**2.60** (SD 2.00)	**3.20** (SD 2.70)			1.90 (SD 2.10)	5.10 (SD 3.00)
3.5							2.30 (SD 1.80)	5.20 (SD 3.00)
4	**3.90** (SD 2.40)				3.16 (SD 3.26)	**4.44** (SD 2.60)	2.10 (SD 1.80)	5.30 (SD 3.00)
4.5							2.40 (SD 1.80)	5.40 (SD 3.00)
5							2.60 (SD 1.80)	5.50 (SD 3.00)
5.5							**3.00** (SD 2.30)	5.90 (SD 2.80)
6	2.60 (SD 1.80)	3.60 (SD 1.90)	2.20 (SD 1.90)	2.60 (SD 2.00)	**3.19** (SD 2.56)	4.07 (SD 2.43)	2.70 (SD 2.30)	**5.90** (SD 2.80)
8					2.89 (SD 2.49)	3.41 (SD 2.34)		
9			1.60 (SD 1.80)	1.60 (SD 2.20)				
12			1.60 (SD 1.90)	1.60 (SD 2.30)	3.17 (SD 2.53)	3.03 (SD 2.49)		
24			1.90 (SD 1.80)	1.80 (SD 2.30)	2.97 (SD 2.80)	2.50 (SD 2.56)		
48			1.50 (SD 2.10)	1.40 (SD 2.60)	2.23 (SD 2.27)	1.55 (SD 1.71)		
72			1.40 (SD 1.70)	1.50 (SD 2.40)				

Figure 3 – Scatter chart showing pain intensity over first 12 hours post-operatively

Total pain relief

Al-Sukhun *et al* [11] measured total pain relief by summing time weighted scores over 8 hours and 12 hours post-operatively. TOPAR8 and TOPAR12 scores were significantly higher (better) in the ibuprofen group compared with the placebo group ($p<0.001$). These results are shown in table 3.

Table 3 – Total pain relief (TOPAR) for all studies measuring this outcome

Total Pain Relief scores (Al-Sukhun *et al*, 2012)				
	Ibuprofen		Placebo	
	Mean	SD	Mean	SD
TOPAR 8 (0-32)	12.2	2.69	3.8	3.89
TOPAR 12 (0-48)	16.9	3.75	5.5	5.52

Time to rescue analgesia

The amount of time between the end of the surgical procedure and the participant requesting rescue analgesia was recorded as an outcome for all included studies. However, only 3 studies reported p values for this outcome and 2 reported mean values for each group [11, 12, 15].

Al-Sukhun *et al* [11] reported that the median time to rescue analgesia was significantly higher (longer) in the ibuprofen group compared with the placebo group ($p<0.001$). In contrast to this, Albuquerque *et al* [12] reported that the mean time to rescue analgesia was significantly reduced (shorter) in the ibuprofen group compared with the placebo group ($p<0.001$). Morse *et al* [15] reported no statistically significant difference in time to rescue analgesia between ibuprofen and placebo groups but did not report the p value or mean values for time.

The results for time to rescue analgesia are shown in Table 4.

Table 4 – Time to rescue analgesia for all studies measuring this outcome

Time to rescue analgesia (h)				
	Ibuprofen		Placebo	
	Mean/median	SD	Mean/median	SD
Al-Sukhun *et al*	7.0	1.48	1.5	0.21
Albuquerque *et al*	2.6	1.1	4.5	1.7

Total consumption of rescue analgesia

Two studies reported total consumption of rescue analgesia [13, 14]. Both studies showed no statistically significant difference between the ibuprofen and placebo groups. The data for this outcome was only reported by Chiu et al [14] and is shown in table 5.

Table 5 – Total consumption of rescue analgesia for all studies measuring this outcome

Total consumption of rescue analgesia (number of tablets)				
	Ibuprofen		Placebo	
	Mean	SD	Mean	SD
Chiu *et al*	5.27	4.77	4.41	3.70

Request of rescue analgesia

The proportion of participants requesting rescue analgesia was reported in 2 studies. Morse *et al* [15] reported that this was significantly reduced in the ibuprofen group compared with the placebo group (p=0.000). Data for this study was collected up to 6 hours post-operatively and there is no information about rescue analgesia requirements after this.

Al- Sukhun *et al* [11] provide data about the proportion of participants requesting rescue analgesia over 24 hours post-operatively in the ibuprofen group (55%) and placebo group

(92%) but did not report any p values for this outcome. Their findings support that of Morse *et al* [15] and suggest that pre-emptive ibuprofen provides superior post-operative analgesia to placebo. The data from both studies is shown in table 6 and figure 5.

Table 6 – Request of rescue analgesia

Request of rescue analgesia (% of participants)		
	Ibuprofen	Placebo
Al-Sukhun *et al*	55%	92%
Morse *et al*	25%	94%

Evidence quality

The GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to assess the quality of evidence generated from the review [16]. The assessment was undertaken against three outcomes: pain intensity, the use of rescue analgesia and total pain relief.

No concerns we raised when assessing study design, indirectness or publication bias. Due to the variation and contradiction within the results for pain intensity and use of rescue analgesia, the evidence was downgraded one point due to inconsistency. As total pain relief was measured as an outcome in just one study with a relatively small sample size, the evidence for total pain relief was downgraded one point due to imprecision.

For each outcome, the evidence was assessed as being of “moderate certainty”. The GRADE assessment is summarised in the form of a table in Appendix 3.

Discussion

The removal of lower third molar teeth is one of the most commonly performed surgical procedures in the NHS [17]. Due to the position of these and the surgical complexity of removal, the post-operative pain experienced is often significant and can affect quality of life [18, 19].

The subjective nature of pain and the various factors that can influence pain experience make it very difficult to measure quantitatively. This has clearly been an issue for the authors of the included studies who have used a variety of outcome measures to try to determine the effects of pre-emptive ibuprofen. The use of the VAS to measure pain intensity seems to be the simplest and most popular method used. Recording the score is straightforward for participants and the results are clear and easy to interpret [20]. TOPAR scores are generated from the individual scores of multiple outcomes, which may be confusing for participants, increasing the risk of error or bias [21]. Both tools, however, are validated and assuming that there are no significant discrepancies in baseline characteristics, they should produce accurate and reproducible data [22].

Measurement bias is also a concern for outcomes related to the use and timing of rescue analgesia. Results are directly influenced by the patient's understanding of the instructions, their pain tolerance and their inclination when it comes to taking medication. The availability of a rescue drug for trial participants experiencing uncontrolled pain is an ethical requirement. Unfortunately, once rescue analgesia has been administered, the pain experience of the participant is affected by both the experimental drug and the rescue drug and therefore accurate measurement for other outcomes, such as pain intensity, is no longer possible. Statistical methods can be used to overcome this difficulty in RCTs [23], however this has not been addressed in the studies included in this review.

The body of evidence generated from this review can be regarded with moderate certainty. The findings, however, are somewhat inconclusive and there is unquestionable inconsistency within the results. Therefore, there is insufficient evidence to support the prescription of pre-emptive ibuprofen for the management of post-operative pain after lower third molar surgery.

In order to gain a better understanding of the effects of pre-emptive ibuprofen on post-operative pain after lower third molar surgery, further RCTs are required. Multi-center studies with large sample sizes would provide better quality evidence and more accurately reflect the impact of this intervention on a wider variety of patients. Particular attention should be paid to randomisation, allocation concealment and blinding in order to reduce the risk of bias. Tools used for outcome measurement should be simple and consistent,

and consideration should be given to the effects of local anaesthesia and rescue medication when measuring pain intensity.

Transparent and comprehensive reporting is essential for clinicians to make a judgement on study quality and the clinical significance of the results. All the included studies had some missing details including information about methodology, outcome data and confidence intervals. This absent information may suggest poor conduct or inaccuracy in reporting which raises concerns about the risk of bias. This could easily be avoided by adhering to the CONSORT guidelines [24].

Investigation into the pre-emptive effects of other analgesic drugs, such as COX-2 specific NSAIDs and opioids, is also necessary to establish the optimum analgesic regime for patients undergoing lower third molar surgery. In addition to orally administered systemic analgesics, the use of long acting local anaesthetic agents, such as bupivacaine, could provide superior or prolonged management of post-operative pain compared with more commonly used lidocaine [25]. A “multi-modal” approach to post-operative pain management may provide the best results and further research on this topic would be worthwhile [26].

Despite a lack of evidence to support the benefits of pre-emptive ibuprofen, there is strong evidence to support its use for post-operative analgesia after lower third molar surgery. Ibuprofen alone is effective in the first 2 hours following surgery, but ibuprofen and paracetamol combined appear to provide more effective analgesia in the later post-operative period [3]. This evidence should be reflected in the analgesic advice given to patients undergoing this procedure to reduce post-operative morbidity and prevent accidental analgesic overdose.

Patients may still choose to self-prescribe over the counter analgesia before surgery, against advice and without regulation from a medical professional. The psychology behind this decision and the potential placebo effect, during and after surgery, could also be of interest when considering its application in clinical care. Studies investigating the psychological implications of pre-emptive analgesia may already be in existence but are not the focus of this systematic review.

Limitations

Only papers written in English were considered for inclusion in this review.
A meta-analysis of the data extracted from included studies was not possible due to the variation in study characteristics.
The review has not been registered and a protocol has not been prepared.

Conclusion

There is insufficient evidence to support the routine use of pre-emptive Ibuprofen to reduce post-operative pain. Further well-designed randomised controlled trials are required to accurately assess the value of pre-emptive analgesics.

Competing interests

The authors of this review have no competing interests to declare.

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Author Contributions

F. Gately led the systematic review and drafted the manuscript.
K. Ali provided input to the clinical context and relevance of the study.
L. Burns provided input on the search strategy, the data analysis and compliance with PRISMA guidelines.

All authors were involved in the preparation and editing of the manuscript.

Data availability statement

All data used in this review is contained within the article and supplementary information. Further information is available from the lead author upon request.

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