



Effect of Nonsteroidal Anti-inflammatory Drug as an Oral Premedication on the Anesthetic Success of Inferior Alveolar Nerve Block in Treatment of Irreversible Pulpitis: A Systematic Review with Meta-analysis and Trial Sequential Analysis

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Abstract

Introduction: Successful anesthesia with an inferior alveolar nerve block (IANB) is imperative for treating patients with irreversible pulpitis in mandibular teeth. This systematic review assessed the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) as oral premedications on the success of IANBs in irreversible pulpitis. **Methods:** Three databases were searched to identify randomized clinical trials (RCTs) published up until September 2017. Retrieved RCTs were evaluated using the revised Cochrane Risk of Bias Tool. The primary efficacy outcome of interest was the success rate of IANB anesthesia. Meta-analytic estimates (risk ratio [RR] with 95% confidence intervals [CIs]) performed using a random effects model and publication bias determined using funnel plot analysis were assessed. Random errors were evaluated with trial sequential analyses, and the quality of evidence was appraised using a Grading of Recommendations, Assessment, Development and Evaluation approach. **Results:** Thirteen RCTs ($N = 1034$) were included. Eight studies had low risk of bias. Statistical analysis of good-quality RCTs showed a significant beneficial effect of any NSAID in increasing the anesthetic success of IANBs compared with placebo (RR = 1.92; 95% CI, 1.55–2.38). Subgroup analyses showed a similar beneficial effect for ibuprofen, diclofenac, and ketorolac (RR = 1.83 [95% CI, 1.43–2.35], RR = 2.56 [95% CI, 1.46–4.50], and RR = 2.07 [95% CI, 1.47–2.90], respectively). Dose-dependent ibuprofen >400 mg/d (RR = 1.85; 95% CI, 1.39–2.45) was shown to be effective; however, ibuprofen ≤400 mg/d showed no association (RR = 1.78; 95% CI, 0.90–3.55). TSA

confirmed conclusive evidence for a beneficial effect of NSAIDs for IANB premedication. The Grading of Recommendations, Assessment, Development and Evaluation approach did not reveal any concerns regarding the quality of the results. **Conclusions:** Oral premedication with NSAIDs and ibuprofen (>400 mg/d) increased the anesthetic success of IANBs in patients with irreversible pulpitis. (*J Endod* 2018;44:914–922)

Key Words

Diclofenac, ibuprofen, inferior alveolar nerve block, irreversible pulpitis, ketorolac, nonsteroidal anti-inflammatory drugs, meta-analysis, systematic review

The successful management of pain during root canal treatment is important for both patients and dentists (1). Achieving adequate pulpal anesthesia is a major concern for patients with irreversible pulpitis during endodontic therapy (2). The inferior alveolar nerve block (IANB) technique is commonly used to achieve pulpal anesthesia in mandibular teeth. It was observed that the failure rate for IANB was between 43% and 83% in patients with irreversible pulpitis (3–9). Failure of the IANB in teeth with irreversible pulpitis has been mainly attributed to the presence of inflammation in the pulp (10). Inflammation is mediated through the production of prostaglandins from arachidonic acid in cell membranes by the action of cyclooxygenase enzymes. Prostaglandins are involved in the development and amplification of pain (10, 11). The increased sensitization of nociceptors as a result of pulpal inflammation adversely affects the effect of anesthetics (10–12). Pain during access opening and instrumentation caused by anesthetic failure was even recorded in patients who had demonstrated positive signs of anesthesia such as numbness in the lower lip and the tip of the tongue (13, 14). Thus, lip numbness was shown not to be always related to successful pulpal

Significance

Oral premedication with NSAIDs increases the anesthetic efficacy of inferior alveolar nerve blocks in patients with irreversible pulpitis. Ibuprofen (>400 mg) showed higher anesthetic efficacy compared with other NSAIDs.

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anesthesia. Therefore, it is paramount to increase the success rate of the IANB block during root canal treatment.

The success rate of mandibular anesthesia for pain-free endodontic access and instrumentation in teeth with irreversible pulpitis can be increased by using supplemental buccal infiltration (15), periodontal ligament injection (16), intraosseous anesthesia (17), and oral premedication (18–22). Previous meta-analyses (MAs) showed that the use of oral premedication (nonsteroidal anti-inflammatory drugs [NSAIDs]) increased the anesthetic success of IANBs in teeth with irreversible pulpitis (18–22). However, among the latest 4 reviews, 2 studies (19, 20) did not include all available RCTs, whereas the remaining reviews did not exclusively evaluate NSAIDs.

Random errors can affect the validity of MAs when conducted with fewer than adequate RCTs and an inadequate sample size, leading to ambiguous conclusions. Random errors rather than the true intervention effect can also result in positive outcomes (23, 24). Trial sequential analysis (TSA) is an important tool that assesses the risk of random errors and determines the required sample size to evaluate whether the evidence in an MA is conclusive (23, 25). TSA also estimates the “optimal information size,” which is akin to the sample size of a large adequate trial that an MA mimics (23, 25). Previously published SRs and MAs on the success of IANBs did not evaluate the risk of random errors and did not grade the quality of evidence using The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for reliability. GRADE evaluates the quality of evidence and assesses the strength of recommendations from MAs in an objective and systematic manner (26, 27). With multiple MAs being performed for the same research question at periodic intervals, it is important to assess the need and benefit of future MAs.

Furthermore, although previous SRs have shown the efficacy and safety of ibuprofen, none evaluated the dose-response effect of ibuprofen. The objective of this SR and MA was to update the evidence on the effect of NSAIDs, especially ibuprofen, by using an MA with TSA. The specific research questions were as follows:

1. In adult patients with irreversible pulpitis (population), do oral NSAIDs as premedication (intervention), when compared with placebo (comparison), increase the anesthetic success of IANBs (outcome) in RCTs (study design) with conclusive evidence?
2. Which is the most effective dose of ibuprofen (≤ 400 mg or >400 mg) compared with placebo in increasing the anesthetic success of IANBs in adult patients with irreversible pulpitis with conclusive evidence?

Methods

Study Design

This SR and MA to determine the effect of premedication of NSAIDs on anesthetic success in patients with irreversible pulpitis was prepared and conducted following the *Cochrane Handbook for Systematic Reviews of Interventions* (28). The reporting of this SR and MA was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (29).

Search Strategy and Study Selection

A systematic literature search of the PubMed, EBSCOhost, and Scopus databases up until September 9, 2017, was conducted to identify relevant studies. The search terms used were (((((premedication) OR preoperative medications) OR NSAID) OR non steroidal anti inflammatory agents)) AND ((inferior alveolar nerve block) OR irreversible pulpitis). The clinical trial registry (www.clinicaltrials.gov) was searched, and the reference lists of published SRs, textbooks, and

selected articles were checked for studies not identified from the database search. Title and abstract screening followed by full-text assessment were undertaken by 2 independent reviewers (V.N. and S.P.). Reviewers resolved disagreements by discussion, and 1 of 2 arbitrators (S.V. and N.T.) adjudicated any unsolved disagreements.

Inclusion Criteria

RCTs that evaluated the effect of any NSAIDs as an oral premedication on the efficacy of IANBs in achieving anesthesia in adult patients with irreversible pulpitis and undergoing nonsurgical root canal therapy in mandibular posterior teeth were selected. Interventions of interest were any NSAIDs as a premedication alone at any dose and a placebo as a comparator. Data from RCTs that reported the efficacy of combinations of NSAIDs with other anti-inflammatory drugs or analgesics in the analysis were excluded. The primary efficacy outcome of interest was the success rate of IANB anesthesia, which was assessed based on the experience of pain during access preparation and root canal instrumentation.

Data Extraction and Quality Assessment

Relevant data were extracted by 2 independent calibrated reviewers (S.P. and V.N.) using a standardized extraction form. The extracted data included study characteristics, patient characteristics, interventions, outcomes, and other relevant findings. Any missing information was obtained by contacting the authors. Any discrepancy was resolved by a review team discussion or by 1 of the arbitrators (N.T.). Two reviewers (S.V. and V.N.) independently assessed the risk of bias within each study using the revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0) (30). Bias because of the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias were evaluated to classify the selected studies into RCTs with a low risk of bias, some concerns, and a high risk of bias (30). Any discrepancy in the assessment of the risk of bias was concluded by review team discussion or by 1 of the arbitrators.

Statistical Analysis

The MA was performed using a random effects model to estimate effect sizes such as the pooled risk ratio (RR) and 95% confidence intervals (CIs) incorporating within- and between-study heterogeneity (28). I^2 statistics were used to evaluate heterogeneity among trials. An estimate greater than 50% was considered to be substantial heterogeneity. To report the efficacy of individual NSAIDs, for which at least 2 data sets were available for the MA, a subgroup analysis was conducted. These subgroup analyses investigated the dose-response effect of ibuprofen on the primary outcome by classifying studies into 2 groups: high dose (ibuprofen >400 mg) and low dose (ibuprofen ≤ 400 mg). Sensitivity analyses were performed for the primary outcome by restricting studies with a low risk of bias and using a fixed effects model. Analyses were performed using STATA 14.1 software (StataCorp, College Station, TX). Publication bias was assessed using funnel plot asymmetry and Egger regression tests (31).

TSA was conducted using the TSA software package available from Copenhagen Trial Unit (Copenhagen, Denmark) at <http://www.ctu.dk> (25) to assess the risks of random errors in the MA. The GRADE approach was used to rate the quality of evidence of estimates (high, moderate, low, and very low) derived from the MA using GRADEpro GDT software (<https://www.gradepro.org>) (26, 27). Reviewers (S.V. and N.T.) independently assessed the confidence in effect estimates for primary outcome using the following categories: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

TABLE 1. Characteristics of the Included Studies

| No. | Author, year | Age (years) (mean ± SD) | Male (n) | Female (n) | Local anesthetic agent | Drugs | Dosage | Total sample (N) | Success rate (n/%) | | |
|-----|--------------------------------------|----------------------------|-------------|---------------|---|-------------------------|--------|------------------------|--------------------------|----|---------|
| 1 | Aggarwal et al, 2010 (44) | 30 ± 8 | 10 | 12 | 1.8 mL 2% lidocaine/ 1:100,000 epinephrine | Ibuprofen | 300 mg | 22 | 6/27.3% | | |
| | | 29 ± 8 | 12 | 11 | | Ketorolac | 10 mg | 23 | 9/39.1% | | |
| | | 26 ± 9 | 14 | 10 | | Placebo | — | 24 | 7/29.2% | | |
| 2 | Oleson et al, 2010 (13) | 32 ± 8 | 20 | 29 | IANB: 3.6 mL 2% lidocaine/ 1:100,000 epinephrine plus long buccal injection: 0.9 mL 2% lidocaine/ 1:100,000 epinephrine | Ibuprofen | 800 mg | 49 | 20/40.8% | | |
| | | 33 ± 12 | 25 | 26 | | Placebo | — | 51 | 18/35.3% | | |
| 3 | Parirokh et al, 2010 (43) | 26.2 ± 9.5 | 26 | 24 | 1.8 mL 2% lidocaine/ 1:80,000 epinephrine | Ibuprofen | 600 mg | 50 | 39/78.0% | | |
| | | 26.2 ± 5.7 | 23 | 27 | | Indomethacin | 75 mg | 50 | 31/62.0% | | |
| | | 25.9 ± 6 | 22 | 28 | | Placebo | — | 50 | 16/32.0% | | |
| 4 | Prasanna et al, 2011 (41) | 26 ± 9 | 22 | 16 | 1.8 mL 2% lidocaine/ 1:200,000 epinephrine | Lornoxicam | 8 mg | 38 | 28/73.7% | | |
| | | 30 ± 6 | 15 | 23 | | Diclofenac potassium | 50 mg | 38 | 24/63.2% | | |
| 5 | Singh et al, 2011 (42) | 28 ± 7 | 18 | 20 | 2% lignocaine/ 1:200,000 adrenaline (volume not stated) | Placebo | — | 38 | 10/26.3% | | |
| | | NR | NR | NR | | Ibuprofen | 600 mg | 7 | 4/57.1% | | |
| | | | | | | Ketorolac | 10 mg | 7 | 5/71.4% | | |
| 6 | Paul et al, 2011 (40) | 30.4 ± 9.83 | 12 | 8 | 1.8 mL 2% lidocaine/ 1:100,000 epinephrine | Placebo | — | 7 | 2/28.6% | | |
| | | 31.7 ± 8.93 | 11 | 9 | | Aceclofenac | 100 mg | 20 | 13/65.0% | | |
| 7 | Wali et al, 2012 (39) | Adults | 42 | 38 | 1.8 mL 2% lidocaine/ 1:200,000 epinephrine | Placebo | — | 20 | 7/35.0% | | |
| | | | | | | Piroxicam | 20 mg | 20 | 18/90.0% | | |
| | | | | | | Diclofenac potassium | 50 mg | 20 | 15/75.0% | | |
| 8 | Jena & Shashirekha, 2013 (38) | 38.8 ± 12.01 | 14 | 6 | 2% lignocaine/ 1:200,000 adrenaline (volume not stated) | Naproxen sodium | 550 mg | 20 | 7/35.0% | | |
| | | 33 ± 10.33 | 11 | 9 | | Placebo | — | 20 | 2/10.0% | | |
| | | 34 ± 12.49 | 13 | 7 | | Ibuprofen | 600 mg | 20 | 11/55.0% | | |
| 9 | Shahi et al, 2013 (37) | >18 | 30 | 25 | 1.8 mL 2% lidocaine/ 1:80,000 epinephrine | Ketorolac | 10 mg | 20 | 14/70.0% | | |
| | | | 30 | 25 | | Placebo | — | 20 | 8/40.0% | | |
| 10 | Madani et al, 2013 (36) | 26.47 ± 10.58 | 5 | 10 | 1.8 mL 2% lidocaine/ 1:80,000 epinephrine | Ibuprofen | 400 mg | 55 | 14/25.5% | | |
| | | 28.8 ± 10.91 | 8 | 7 | | Placebo | — | 55 | 7/12.7% | | |
| | | 22.8 ± 8.53 | 8 | 7 | | Ibuprofen | 400 mg | 15 | 10/66.7% | | |
| 11 | Noguera-Gonzalez et al, 2013 (35) | 18–56 | 10 | 15 | 1.8 mL 2% mepivacaine/ 1:100,000 epinephrine | Gelofen | 400 mg | 15 | 7/46.7% | | |
| | | 19–68 | 8 | 17 | | Placebo | — | 15 | 3/20.0% | | |
| 12 | Saha et al, 2016 (34) | 30.85 ± 8.67 | 23 | 19 | 1.8 mL 2% lidocaine/ 1:200,000 epinephrine | Ibuprofen | 600 mg | 25 | 18/72.0% | | |
| | | 30.4 ± 8.69 | 20 | 22 | | Ketorolac | 10 mg | 42 | 32/76.2% | | |
| | | | | | | Diclofenac potassium | 50 mg | 42 | 23/54.8% | | |
| 13 | Shantiaee et al, 2013 (33) | 30.73 ± 7.83 | 22 | 20 | 1.8 mL 2% lidocaine/ 1:100,000 adrenaline | Placebo | — | 42 | 12/28.6% | | |
| | | 32.78 ± 9.55 | 10 | 13 | | Meloxicam | 7.5 mg | 23 | 16/69.6% | | |
| | | 31.7 ± 8.04 | 10 | 13 | | Ibuprofen | 600 mg | 23 | 20/87.0% | | |
| | | 32.22 ± 8.87 | 13 | 10 | | | | Placebo | — | 23 | 8/34.8% |

NR, not reported.

Results

A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram depicting study selection, inclusion, and exclusion at each screening phase is depicted in [Supplemental Figure S1](#) (available online at www.jendodon.com). A total of 118 studies were identified; 14 potentially eligible studies were reviewed in full text. Of the 14 RCTs identified after full-text review, 1 was excluded (32) because the anesthetic efficacy was not evaluated during access preparation. This resulted in a final number of 13 studies that evaluated the effect of any NSAIDs on the efficacy of IANBs in achieving anesthesia in patients with irreversible pulpitis (13, 33–44).

Characteristics of the Included Studies

Table 1 describes the characteristics of all studies reporting the efficacy of NSAIDs in achieving the anesthetic success of IANBs. All included studies investigated both male and female sexes, with ages ranging from 14–68 years. The total sample size of all studies was N = 1174; 1034 were part of comparisons to placebo and the

remainder comparisons to various medications (eg, steroids and acetaminophen). The various NSAIDs used to increase the anesthetic efficacy of IANB were ibuprofen (300–600 mg), ketorolac (10 mg), diclofenac (50 mg), indomethacin (75 mg), lornoxicam (8 mg), piroxicam (20 mg), and naproxen sodium (550 mg). The timing of oral medication before administration of the IANB varied between 30, 45, and 60 minutes. Lignocaine/lidocaine was used as the anesthetic agent in 12 studies, whereas mepivacaine was used in 1 study (35).

Quality Assessment of the Trials

The revised Cochrane risk of bias tool (RoB 2.0) was used to determine the methodologic quality of the selected studies (30). The evaluation of the risk of bias for the included studies is provided in Table 2. Among 13 RCTs, 8 showed a low risk of bias, whereas 4 trials showed a high risk because of an inadequate randomization process and bias in the measurement outcome. For all studies, intervention provision and outcome measurement were performed at the same visit with no follow-up periods. Hence, no dropouts were reported.

TABLE 2. Risk of Bias Assessment for Included Studies

| Author, year | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall bias |
|-----------------------------------|-----------------------|--|----------------------|----------------------------|----------------------------------|--------------|
| Aggarwal et al, 2010 (44) | + | + | + | + | + | + |
| Oleson et al, 2010 (13) | + | + | + | + | + | + |
| Parirokh et al, 2010 (43) | + | + | + | + | + | + |
| Prasanna et al, 2011 (41) | + | + | + | + | + | + |
| Singh et al, 2011 (42) | - | + | + | - | + | - |
| Paul et al, 2011 (40) | - | + | + | - | + | - |
| Wali et al, 2012 (39) | - | + | + | - | + | - |
| Jena & Shashirekha, 2013 (38) | - | + | + | - | + | - |
| Shahi et al, 2013 (37) | + | + | + | + | + | + |
| Madani et al, 2013 (36) | ? | + | + | + | + | ? |
| Noguera-Gonzalez et al, 2013 (35) | + | + | + | + | + | + |
| Saha et al, 2016 (34) | + | + | + | + | + | + |
| Shantiaee et al, 2013 (33) | + | + | + | + | + | + |

+, low risk of bias; ?, some concerns; -, high risk of bias.

Effects on the Primary Efficacy Outcome

Figure 1 summarizes the random effects MA comparing premedication with NSAIDs with placebo. Of all 1034 participants for whom the success of IANB anesthesia results were available from 13 RCTs, 493

participants (47.6%) had successful anesthetic outcomes and did not experience pain during access preparation and root canal instrumentation. Quantitative pooling of the results from all RCTs showed that the use of any NSAIDs significantly increased the anesthetic success of

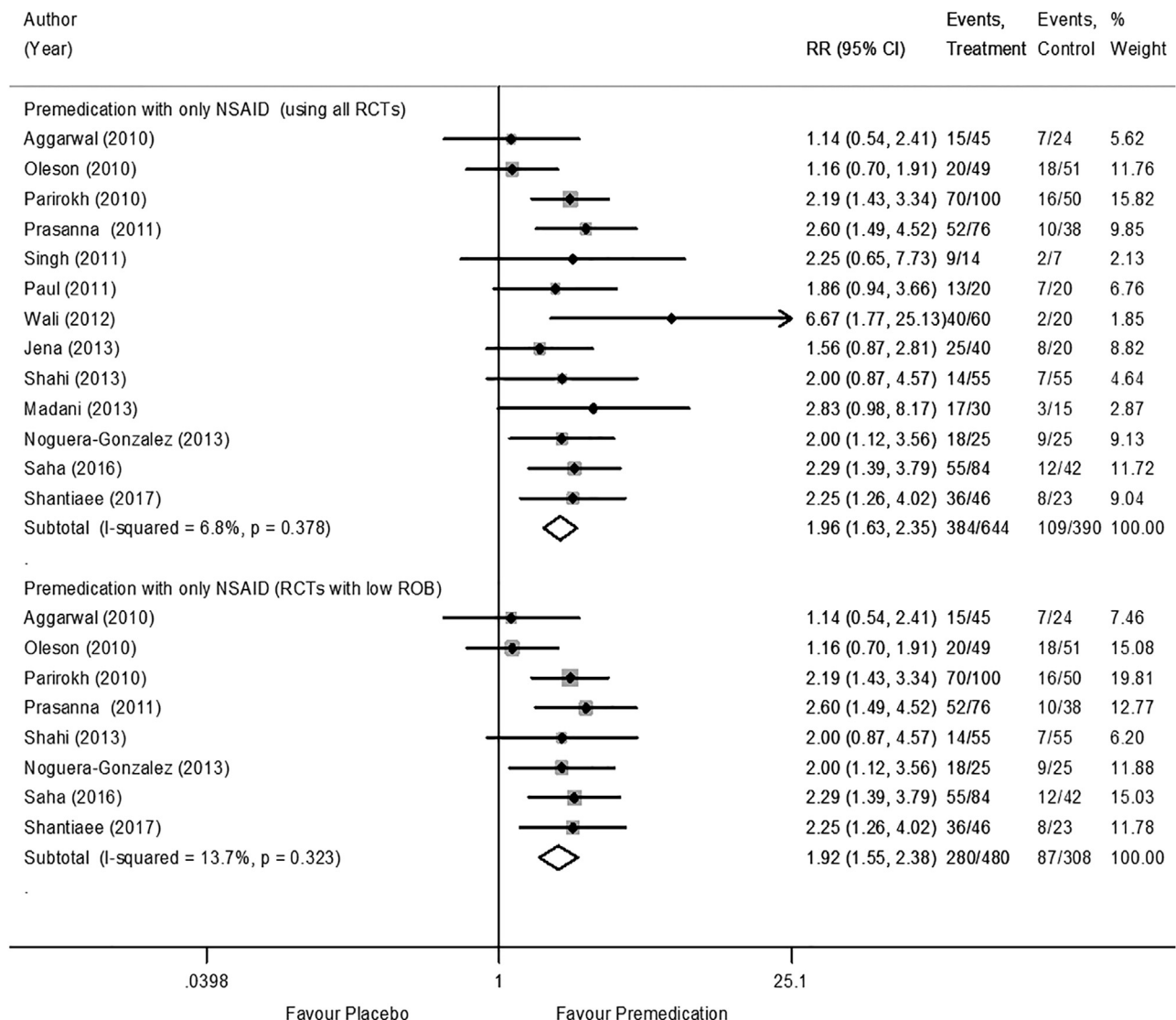


Figure 1. A forest plot of oral premedication with NSAIDs on the anesthetic success of IANBs compared with placebo. Events = success of anesthesia.

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IANB compared with placebo (RR = 1.96; 95% CI, 1.63–2.35; $I^2 = 6.8\%$). Results from a sensitivity analysis using a fixed effects model (RR = 2.07; 95% CI, 1.73–2.47; $I^2 = 6.8\%$) and restricting the analysis to only low risk of bias trials (RR = 1.92; 95% CI, 1.55–2.38; $I^2 = 13.7\%$) showed a similar magnitude of RR when compared with the main analysis. Thus, the results are reliable, and NSAIDs showed superior efficacy to placebo in all analysis.

Subgroup Analyses

To report the efficacy of individual NSAIDs, for which at least 2 data sets were available for the MA, the results of the subgroup analyses are provided in Figure 2. In the subgroup analysis of 9 trials using ibuprofen

(at any dose) as an intervention, it was found that ibuprofen had a statistically significant effect in increasing the anesthetic success of IANBs compared with placebo (RR = 1.83; 95% CI, 1.43–2.35; $I^2 = 20.8\%$). When studies were stratified based on the dose of ibuprofen, ibuprofen >400 mg/d was significantly more effective than placebo (RR = 1.85; 95% CI, 1.39–2.45; $I^2 = 26.7\%$), whereas ibuprofen ≤400 mg/d showed no statistically significant association (RR = 1.78; 95% CI, 0.90–3.55; $I^2 = 38.7\%$). Other NSAIDs, diclofenac 50 mg and ketorolac 10 mg, also showed a statistically significant effect in increasing the anesthetic success of the IANB compared with placebo (RR = 2.56; 95% CI, 1.46–4.50; $I^2 = 44.8\%$ and RR = 2.07; 95% CI, 1.47–2.90; $I^2 = 0\%$, respectively).

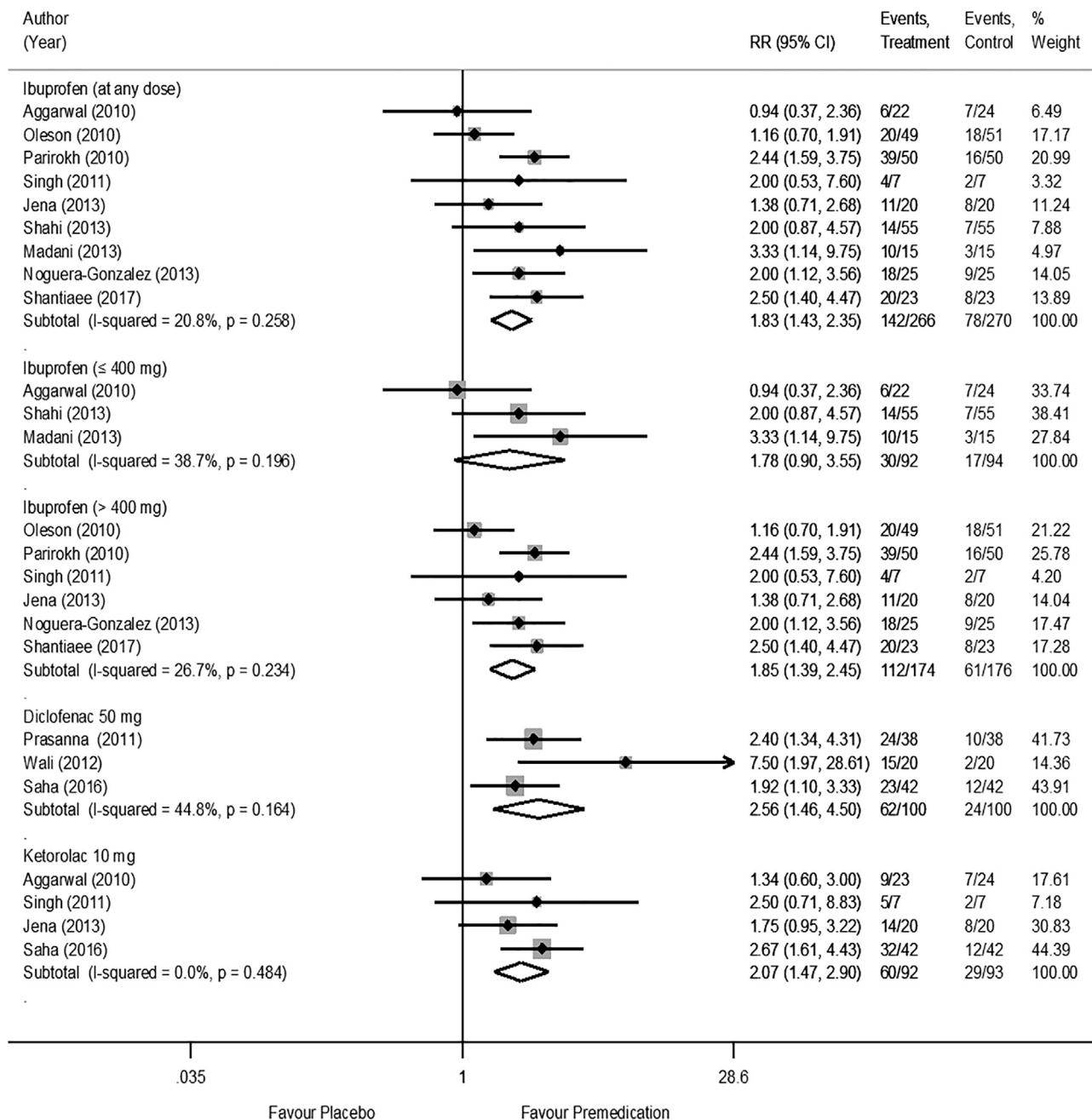


Figure 2. A forest plot on subgroup analysis of oral premedication on the anesthetic success of IANBs compared with placebo. Events = success of anesthesia.

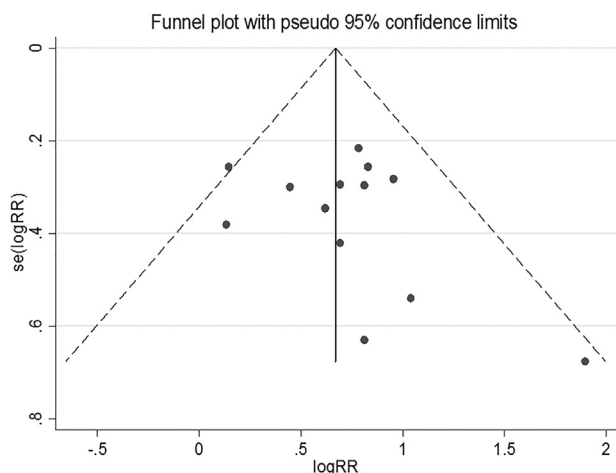


Figure 3. Publication bias (premedication with only NSAIDs using all RCTs).

Publication Bias

Based on visual inspection of the funnel plot (Fig. 3) as well as on quantitative measurement that used the Egger regression test ($P = .33$), there was weak evidence of publication bias for the main analysis (13 studies). Similarly, funnel plots and Egger regression tests showed no substantial evidence of small study effects for subgroup analyses (Egger test for small study effects: ibuprofen all RCTs, $P = .570$; ibuprofen

≤ 400 mg/d, $P = .845$; ibuprofen >400 mg/d, $P = .604$; diclofenac 50 mg, $P = .282$; and ketorolac 10 mg, $P = .366$) although the number of studies included in each comparison was small (Supplemental Figs. S2–S6 are available online at www.jendodon.com).

TSA

TSA were performed with $\alpha = 0.05$, power of 80%, and a requisite heterogeneity-adjusted information size (HIS) using a control event proportion based on the intervention effect on the success of IANB anesthesia as suggested by the low bias risk RCTs using a random effects model (25). The HIS based on the intervention effect suggested by all trials that used a random effects model was calculated to determine if it surpassed a cumulative z statistic above 1.96, which confirmed conclusive evidence for a beneficial effect of the medication. For NSAIDs, TSA for the primary efficacy outcome based on the information size adjusted for the presence of heterogeneity among 8 trials with low bias risk is shown in Figure 4. The information size ($n = 131$) surpassed with a cumulative z statistic above 1.96. This conclusively confirmed the validity of the results of the MA that NSAIDs increased the success of IANB anesthesia. TSA of other NSAID subgroups (HIS: ibuprofen at any dose [$n = 190$], ibuprofen >400 mg/d [$n = 157$], ketorolac 10 mg [$n = 88$], and diclofenac 50 mg [$n = 160$]) also showed a beneficial effect in increasing the success of IANB anesthesia. However, TSA indicated a lack of firm evidence to demonstrate or reject a beneficial effect for ibuprofen ≤ 400 mg/d. The number of patients included in the MA ($n = 186$) did not exceed the required information

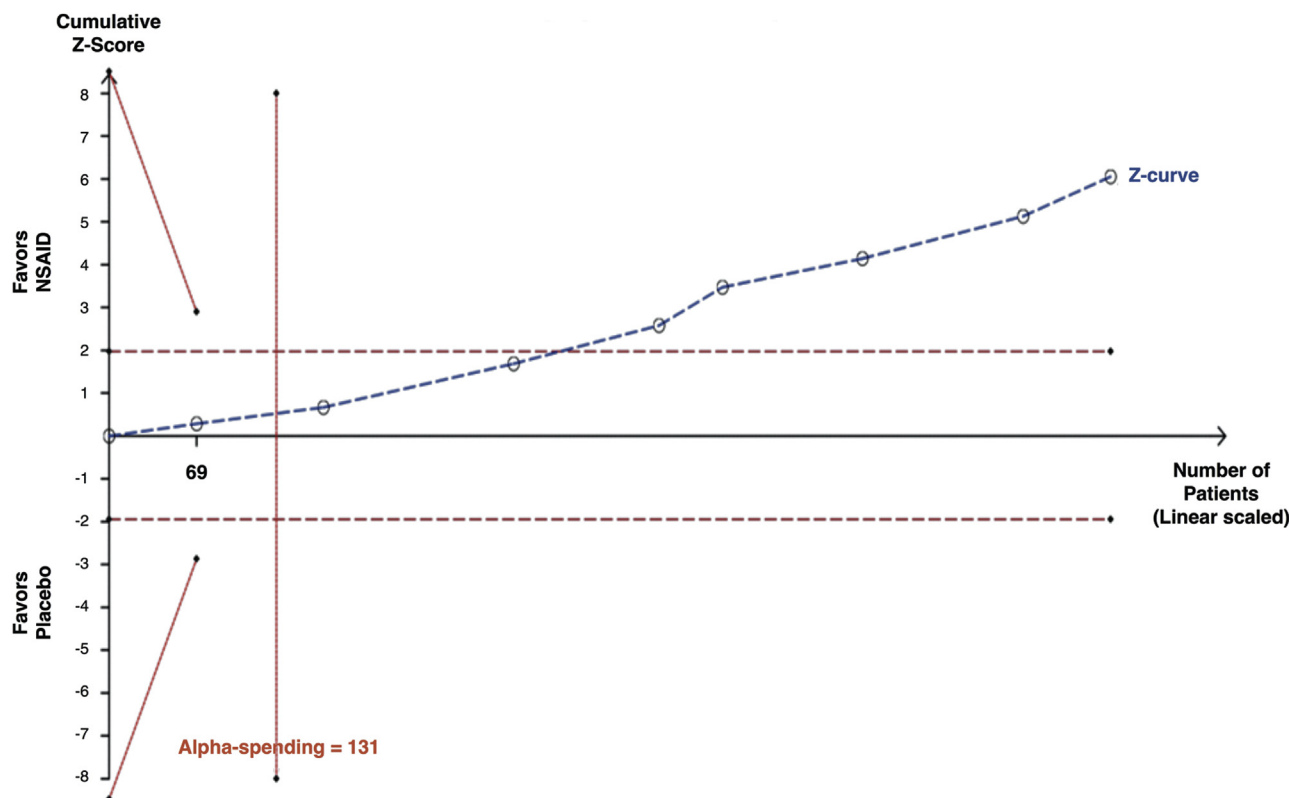


Figure 4. TSA assessing the effect of any NSAID on the anesthetic success of IANBs. TSA was calculated with a type 1 error of 5%, a type II error of 20%, and a required heterogeneity-adjusted information size ($n = 131$) based on the intervention effect suggested by the included low risk of bias trials using a random effects model for NSAIDs (RR of -92% [low bias risk trial estimate]), control group event proportion of 28.25% (median proportion of incidence of success in the control group) (Fig. 1), and a variance-based heterogeneity correction of 15%. The information size surpassed with a cumulative z statistic above 1.96, confirming conclusive evidence for a beneficial effect of NSAIDs on the success of IANBs.

TABLE 3. Quality of Evidence and a Summary of the Findings

| Quality assessment | | | | | | | Summary of findings | | | | |
|---|----------------------|---------------|--------------|-------------|--|-----------------------------|-----------------------|-----------------|--------------------------|------------------------------|--|
| No. of participants (studies) follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Overall quality of evidence | Study event rates (%) | | Relative effect (95% CI) | Anticipated absolute effects | |
| | | | | | | | With placebo | With NSAID | | Risk with placebo | Risk difference with NSAID |
| NSAIDs 788 (8 RCTs-low risk of bias) | Not serious | Not serious | Serious* | Not serious | Strong association [†] | ⊕⊕⊕⊕ High | 87/308 (28.2) | 280/480 (58.3%) | RR = 1.92 (1.5–2.38) | 282 per 1000 | 260 more per 1000 (155 more to 390 more) |
| Ibuprofen at any dose 536 (9 RCTs) | Serious [‡] | Not serious | Serious* | Not serious | Strong association dose-response gradient [§] | ⊕⊕⊕⊕ High | 78/270 (28.9) | 142/266 (53.4%) | RR = 1.83 (1.43–2.35) | 289 per 1000 | 240 more per 1000 (124 more to 390 more) |
| Ibuprofen >400 mg/d 350 (6 RCTs) | Serious [‡] | Not serious | Not serious | Not serious | Strong association dose-response gradient [§] | ⊕⊕⊕⊕ High | 61/176 (34.7) | 112/174 (64.4%) | RR = 1.85 (1.39–2.45) | 347 per 1000 | 295 more per 1000 (135 more to 503 more) |
| Diclofenac 50 mg 200 (3 RCTs) | Serious [‡] | Not serious | Not serious | Not serious | Strong association [†] | ⊕⊕⊕⊕ High | 24/100 (24.0) | 62/100 (62.0) | RR = 2.56 (1.46–4.50) | 240 per 1000 | 374 more per 1000 (110 more to 840 more) |
| Ketorolac 10 mg 185 (4 RCTs) | Serious [‡] | Not serious | Not serious | Not serious | Strong association [†] | ⊕⊕⊕⊕ High | 29/93 (31.2) | 60/92 (65.2) | RR = 2.07 (1.47–2.90) | 312 per 1000 | 334 more per 1000 (147 more to 592 more) |

CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; RCT, randomized clinical trial; RR, risk ratio.

*Indirectness because of differences in NSAIDs and dose.

[†]Strong association because of a large effect, no publication bias.

[‡]Included both low risk and high risk of bias trials.

[§]Strong association because of a large effect, dose response shown by ibuprofen, no publications bias.

size ($n = 867$), indicating that the cumulative evidence was inconclusive for ibuprofen ≤ 400 mg/d.

GRADE Summary of Evidence

The GRADE summary of findings (including the anticipated absolute effects and the strength of evidence for interventions) substantiated the evidence for efficacy of premedication as provided by the MAs (Figs. 1 and 2) and is shown in Table 3. RCTs without significant limitations were categorized high on the GRADE scale. In context with the evidence from the I^2 statistics for heterogeneity and TSA, no downgrades for inconsistency nor imprecision were implemented for any evaluation. Regarding NSAIDs, only low risk of bias trials were included. Directness assessment led to a downgrade of the evidence for a serious indirectness observed in regard to the differences in NSAIDs and their respective doses. However, the evidence rating was also upgraded for a strong association because quantitative pooling of the results from the low risk of bias trials for NSAIDs showed a large effect (RR = 1.92; 95% CI, 1.55–2.38). Overall, the GRADE evaluation showed that the accumulated evidence for premedication with NSAIDs demonstrated high quality for the success of IANB anesthesia. Similar application of the GRADE methodology for other interventions with evidence of efficacy (ibuprofen at any dose, ibuprofen >400 mg/d, diclofenac 50 mg, and ketorolac 10 mg) also led to the conclusion that the accumulated evidence was of high quality.

Discussion

Our present study evaluated the effect of premedication with NSAIDs on the anesthetic success of IANBs. It is generally observed that as new evidence is produced with newer trials, an updated MA is performed. Although 5 recent MAs (18–22) evaluated a similar research question, none of these reviews answered the question whether the existing evidence conclusively resolved the issue so that there was no need for further clinical trials. Hence, in this investigation, the supplementary research question whether the existing evidence proved to be conclusive was added to the research protocol and evaluated by applying TSA. TSA is an important statistical tool that can identify the need for any future clinical trials and verify the results of an MA (23–25). The present SR provided evidence for the use of NSAIDs as a premedication for achieving anesthetic success in root canal treatment. It was found that the evidence for the use of NSAIDs as a premedication to increase the anesthetic success of IANBs in patients undergoing treatment for irreversible pulpitis was conclusive. The results of our SR and MA added significant information to previously published MAs.

Subgroup analysis revealed that ibuprofen 200–800 mg, diclofenac 50 mg, and ketorolac 10 mg was effective in achieving anesthetic success of IANBs. However, only ibuprofen >400 mg was effective in increasing the success of IANBs, whereas at a lower dose, it was not effective (a dose-response finding that is similar to earlier studies (45, 46). To the best knowledge of the authors, this is the first systematic review to report that ketorolac and diclofenac are effective in increasing the success of IANB compared with placebo by means of an MA.

The MA of all included studies and of studies with low risk of bias showed that NSAIDs were effective in increasing the anesthetic efficacy. Five of the included trials in the review had concerns regarding the randomization process (36, 38, 39, 40, 42). Randomization and allocation concealment are important parameters validating the trial process. Studies identified with high risk of bias in this aspect did not explicitly report on the randomization process or allocation concealment methods. Bias in measurement outcome is also another

aspect that affects the quality of clinical trials. This can be avoided by observing adequate blinding for both test and control groups. We observed that 4 trials did not adequately address this concern.

The results of our MA (ie, an NSAID as a premedication increases the success of IANB) were confirmed by TSA. TSA showed that there were no false results caused by random errors. Shirvani et al (21) stated that MAs of trials with small sample sizes can result in overestimation of the true effect. In our review, TSA showed that based on the calculation of information size, an adequate pooled sample size was present for the MA, yielding valid results. With the evidence provided by TSA, this MA conclusively answers the general question of efficacy of supplemental NSAIDs as a premedication for IANBs in patients being treated with irreversible pulpitis. However, future trials and new MAs will still be necessary to evaluate the efficacy of drug combinations and dose-dependent responses. In general, the field of dental research would benefit from the use of TSA because it would identify the need for further trials to answer important research questions. Researchers should assess the need of future trials in a topic by performing an MA and TSA on previously conducted trials.

Funnel plot analyses did not reveal significant publication bias for trials assessing the effect of NSAIDs in increasing anesthetic efficacy of IANBs. No publication bias was observed when separately assessing studies that evaluated the effect of ibuprofen (overall, ≤ 400 mg and >400 mg), diclofenac 50 mg, and ketorolac 10 mg. GRADE was developed by the GRADE Working Group and is a valuable tool to evaluate the relevance of the results of an MA regarding an intervention to the clinical recommendations (24, 25). Various quality and effectiveness parameters of the various RCTs included in an MA are considered to give a final score in GRADE. It was observed in our GRADE evaluations that RCTs included in MAs assessing NSAIDs in general and ibuprofen at any dose, ibuprofen >400 mg, diclofenac 50 mg, and ketorolac 10 mg achieved a high overall quality of evidence. This further confirmed that the results of our MAs of the effectiveness of NSAIDs in increasing the anesthetic success of IANB can be translated as a clinical recommendation for the benefit of patient care.

Conclusions

In summary, available evidence from RCTs suggest that oral premedication with NSAIDs increases the success rate of IANBs in patients with irreversible pulpitis. A single dose of ibuprofen >400 mg should be considered as a standard premedication in endodontics to increase the success of IANBs in patients with irreversible pulpitis. Ketorolac 10 mg and diclofenac 50 mg are also effective alternative premedications to increase anesthetic efficacy. TSA indicated that the accumulated evidence was conclusive from available trials for any NSAIDs, ibuprofen >400 mg, ketorolac 10 mg, and diclofenac 50 mg. Although ibuprofen ≤ 400 mg did not show a statistically significant effect, TSA indicated the accumulated evidence is still inconclusive. To confirm the dose-response of ibuprofen, more high-quality randomized trials comparing ibuprofen at different doses are still needed, whereas the general research question of a positive effect of oral premedication with NSAIDs for IANBs for treating patients with irreversible pulpitis has now been conclusively answered.

Acknowledgments

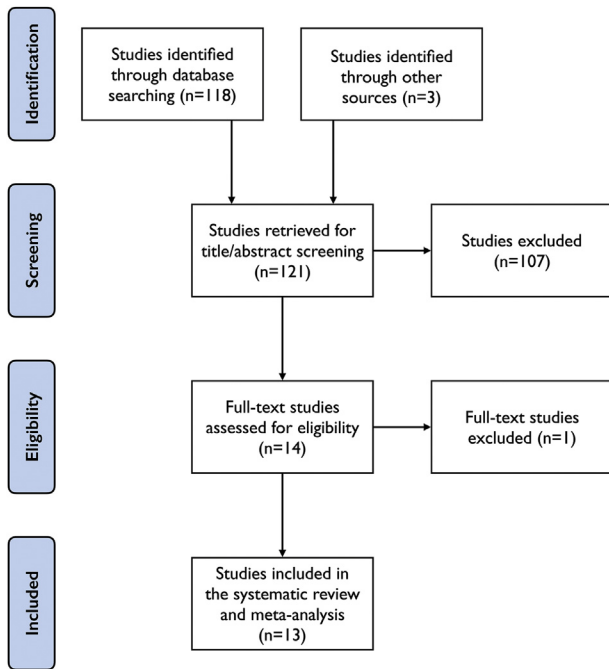
The authors deny any conflicts of interest related to this study.

Supplementary Material

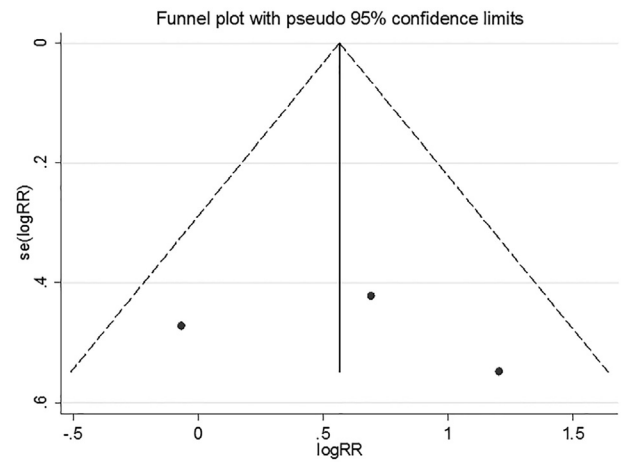
Supplementary material associated with this article can be found in the online version at www.jendodon.com (<https://doi.org/10.1016/j.joen.2018.02.017>).

References

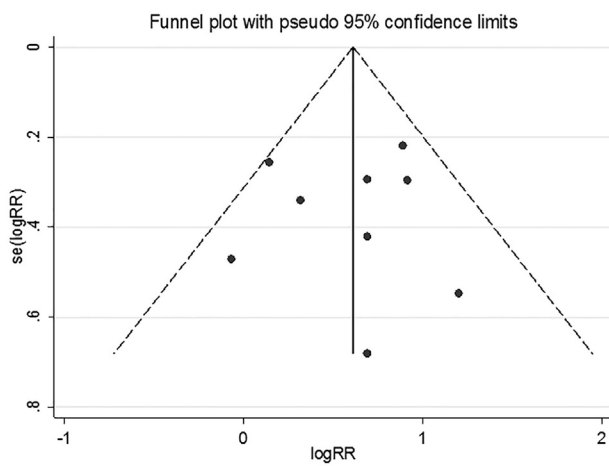
- Walton RE, Reader A, Nusstein JM. Local anesthesia. In: Torabinejad M, Walton RE, eds. *Endodontics, Principles and Practice*, 4th ed. St Louis, MO: Elsevier; 2008: 129–47.
- Drum M, Reader A, Nusstein J, Fowler S. Successful pulpal anesthesia for symptomatic irreversible pulpitis. *J Am Dent Assoc* 2017;148:267–71.
- Nusstein J, Reader A, Nist R, et al. Anesthetic efficacy of the supplemental intraosseous injection of 2% lidocaine with 1:100,000 epinephrine in irreversible pulpitis. *J Endod* 1998;24:487–91.
- Reisman D, Reader A, Nist R, et al. Anesthetic efficacy of the supplemental intraosseous injection of 3% mepivacaine in irreversible pulpitis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;84:676–82.
- Kennedy S, Reader A, Nusstein J, et al. The significance of needle deflection in success of the inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod* 2003;29:630–3.
- Claffey E, Reader A, Nusstein J, et al. Anesthetic efficacy of articaine for inferior alveolar nerve blocks in patients with irreversible pulpitis. *J Endod* 2004;30:568–71.
- Lindemann M, Reader A, Nusstein J, et al. Effect of sublingual triazolam on the success of inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod* 2008;34:1167–70.
- Aggarwal V, Singla M, Miglani S. Comparative evaluation of anesthetic efficacy of 2% lidocaine, 4% articaine, and 0.5% bupivacaine on inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a prospective, randomized, double-blind clinical trial. *J Oral Facial Pain Headache* 2017;31:124–8.
- Fowler S, Drum M, Reader A, Beck M. Anesthetic success of an inferior alveolar nerve block and supplemental articaine buccal infiltration for molars and premolars in patients with symptomatic irreversible pulpitis. *J Endod* 2016;42:390–2.
- Henry MA, Hargreaves KM. Peripheral mechanisms of odontogenic pain. *Dent Clin North Am* 2007;51:19–44.
- Dray A. Inflammatory mediators of pain. *Br J Anaesth* 1995;75:125–31.
- Hargreaves KM, Keiser K. Local anesthetic failure in endodontics. *Endod Topics* 2002;1:26–39.
- Oleson M, Drum M, Reader A, et al. Effect of preoperative ibuprofen on the success of the inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod* 2010;36:379–82.
- Khademi AA, Saatchi M, Minaiyan M, et al. Effect of preoperative alprazolam on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. *J Endod* 2012;38:1337–9.
- Aggarwal V, Jain A, Kabi D. Anesthetic efficacy of supplemental buccal and lingual infiltrations of articaine and lidocaine after an inferior alveolar nerve block in patients with irreversible pulpitis. *J Endod* 2009;35:925–9.
- Kim S. Ligamental injection: a physiological explanation of its efficacy. *J Endod* 1986; 12:486–91.
- Nusstein J, Kennedy S, Reader A, et al. Anesthetic efficacy of the supplemental X-tip intraosseous injection in patients with irreversible pulpitis. *J Endod* 2003; 29:724–8.
- Li C, Yang X, Ma X, et al. Preoperative oral nonsteroidal anti-inflammatory drugs for the success of the inferior alveolar nerve block in irreversible pulpitis treatment: a systematic review and meta-analysis based on randomized controlled trials. *Quintessence Int* 2012;43:209–19.
- Lapidus D, Goldberg J, Hobbs EH, et al. Effect of premedication to provide analgesia as a supplement to inferior alveolar nerve block in patients with irreversible pulpitis. *J Am Dent Assoc* 2016;147:427–37.
- Tupoyta P, Chailertvanitkul P, Laopaiboon M, et al. Supplementary techniques for pain control during root canal treatment of lower posterior teeth with irreversible pulpitis: a systematic review and meta-analysis. *Aust Endod J* 2017 Jul 24; <https://doi.org/10.1111/aej.12212> [Epub ahead of print].
- Shirvani A, Shamszadeh S, Eghbal MJ, et al. Effect of preoperative oral analgesics on pulpal anesthesia in patients with irreversible pulpitis—a systematic review and meta-analysis. *Clin Oral Investig* 2017;21:43–52.
- Corbella S, Taschieri S, Mannocci F, et al. Inferior alveolar nerve block for the treatment of teeth presenting with irreversible pulpitis: a systematic review of the literature and meta-analysis. *Quintessence Int* 2017;48:69–82.
- Wetterslev J, Thorlund K, Brok J, Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. *J Clin Epidemiol* 2008;61:64–75.
- Brok J, Thorlund K, Wetterslev J, Gluud C. Apparently conclusive meta-analyses may be inconclusive—trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. *Int J Epidemiol* 2009;38:287–98.
- Thorlund K, Engström J, Wetterslev J, et al. User Manual for Trial Sequential Analysis (TSA). Available at: www.ctudk/tsa/files/tsa_manual.pdf. Accessed September 22, 2017.
- Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490.
- Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Higgins JPT, Sterne JAC, Savović J, et al. A revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, eds. *Cochrane Methods 2016*. London, UK: Cochrane; 2016.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264–9.
- Higgins JP, Sterne JA, Savović J, et al. Revised tool for assessing risk of bias in randomized trials. In: Chandler J, McKenzie J, Boutron I, Welch V, eds. *Cochrane methods. Cochrane Database Syst Rev*; 2016:10 (Suppl 1).
- Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
- Modaresi J, Dianat O, Mozayeni MA. The efficacy comparison of ibuprofen, acetaminophen-codeine, and placebo premedication therapy on the depth of anesthesia during treatment of inflamed teeth. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2006;102:399–403.
- Shantiaee Y, Javaheri S, Movahhedian A, et al. Efficacy of preoperative ibuprofen and meloxicam on the success rate of inferior alveolar nerve block for teeth with irreversible pulpitis. *Int Dent J* 2017;67:85–90.
- Saha SG, Jain S, Dubey S, et al. Effect of oral premedication on the efficacy of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a prospective, double-blind, randomized controlled clinical trial. *J Clin Diagn Res* 2016;10: ZC25–9.
- Noguera-Gonzalez D, Cerda-Cristerna B, Chavarria-Bolaños D, et al. Efficacy of preoperative ibuprofen on the success of inferior alveolar nerve block in patients with symptomatic irreversible pulpitis: a randomized clinical trial. *Int Endod J* 2013;46: 1056–62.
- Madani ZS, Haddadi A, Moghadamnia A, et al. The efficacy of premedication with ibuprofen, gelofen and acetaminophen in the depth of anesthesia in mandibular molars with irreversible pulpitis. *Afr J Pharm Pharmacol* 2013;7:1841–6.
- Shahi S, Mokhtari H, Rahimi S, et al. Effect of premedication with ibuprofen and dexamethasone on success rate of inferior alveolar nerve block for teeth with asymptomatic irreversible pulpitis: a randomized clinical trial. *J Endod* 2013;39: 160–2.
- Jena A, Shashirekha G. Effect of preoperative medications on the efficacy of inferior alveolar nerve block in patients with irreversible pulpitis: a placebo-controlled clinical study. *J Conserv Dent* 2013;16:171–4.
- Wali A, Siddiqui TM, Qamar N, et al. Effectiveness of premedication with analgesics vs placebo for success of inferior alveolar nerve block in irreversible pulpitis. *Int J Prosthodont Restor Dent* 2012;2:5–9.
- Paul J, Ittyerah A, Kumar S. Effect of preoperative aceclofenac on the success of inferior alveolar nerve block in patients with irreversible pulpitis. *Indian J Dent Sci* 2011;3:1–3.
- Prasanna N, Subbarao CV, Gutmann JL. The efficacy of pre-operative oral medication of lornoxicam and diclofenac potassium on the success of inferior alveolar nerve block in patients with irreversible pulpitis: a double-blind, randomised controlled clinical trial. *Int Endod J* 2011;44:330–6.
- Singh RD, Khatter R, Bal CS. The effect of preoperative ibuprofen, combination of ibuprofen and acetaminophen, ketorolac versus placebo on the efficacy of the inferior alveolar nerve block in patients with irreversible pulpitis. *Indian J Dent Sci* 2010;2:4–6.
- Parirokh M, Ashouri R, Rekar AR, et al. The effect of premedication with ibuprofen and indomethacin on the success of inferior alveolar nerve block for teeth with irreversible pulpitis. *J Endod* 2010;36:1450–4.
- Aggarwal V, Singla M, Kabi D. Comparative evaluation of effect of preoperative oral medication of ibuprofen and ketorolac on anesthetic efficacy of inferior alveolar nerve block with lidocaine in patients with irreversible pulpitis: a prospective, double-blind, randomized clinical trial. *J Endod* 2010;36:375–8.
- McQuay HJ, Moore RA. Dose-response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. *Br J Clin Pharmacol* 2007;63:271–8.
- Schou S, Nielsen H, Nattestad A, et al. Analgesic dose-response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single-dose, randomized, placebo-controlled, and double-blind study of 304 patients. *J Clin Pharmacol* 1998;38:447–54.



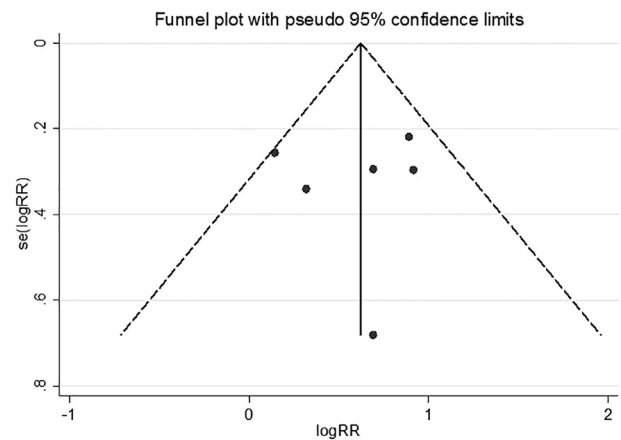
Supplemental Figure S1. Flow diagram of the search process.



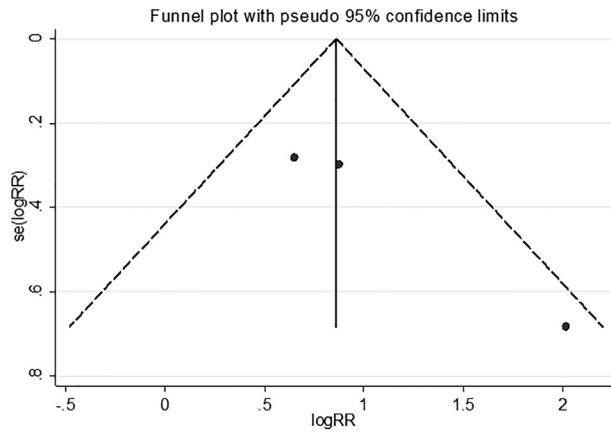
Supplemental Figure S3. Publication bias assessment for individual NSAIDs (ibuprofen \leq 400 mg/d).



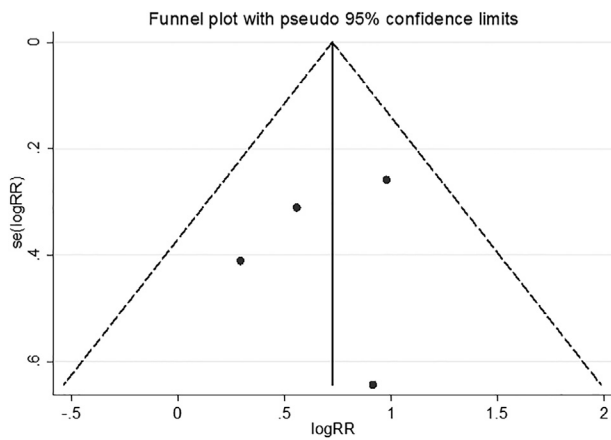
Supplemental Figure S2. Publication bias assessment (premedication with ibuprofen in all RCTs).



Supplemental Figure S4. Publication bias assessment for individual NSAIDs (ibuprofen $>$ 400 mg/d).



Supplemental Figure S5. Publication bias assessment for individual NSAIDs (diclofenac 50 mg).



Supplemental Figure S6. Publication bias assessment for individual NSAIDs (ketorolac 10 mg).