Review Article

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;■:1–9)*

Key Words

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

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.

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

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0099-2399/$ - see front matter

https://doi.org/10.1016/j.joen.2018.02.017

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.