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Review Article

Pre-emptive use of non-steroids anti-inflammatory drugs for a successful inferior alveolar nerve block in patients with irreversible pulpitis: a systematic review and network meta-analysis

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Abstract: Objectives: A successful inferior alveolar nerve block is important in preventing pain during dental procedures. The purpose of this systematic review and network meta-analysis was to examine the effects of pre-emptive oral administration of non-steroids anti-inflammatory drugs (NSAIDs) for successful inferior alveolar nerve block (IANB) in patients with irreversible pulpitis. Methods: Eligible studies were searched from 14 databases and manual searching. Study inclusion, data extraction, and risk of bias assessment were performed by two reviewers in duplicate. Meta-analysis and network meta-analysis were conducted by pooling extracted data. Results: Thirty studies, involving 993 participants, were included. Traditional meta-analysis indicated that NSAIDs could significantly increase the success rate of anesthesia (SRA) by approximately 67% (RR = 1.67, 95% CI [1.44, 1.94], P<0.00001), in which ibuprofen (RR = 1.68, 95% CI [1.32, 2.14], P<0.0001, GRADE quality of evidence: high), ketorolac (1.56, [0.96, 2.55], P = 0.07, moderate), and indomethacin (1.94, [1.22, 3.06], P = 0.005, moderate) had moderate to high evidence quality. Network meta-analysis indicated that lornoxicam exerted the highest effects, compared to all other NSAIDs, followed by other drugs such as, but not limited to, diclofenac, ketorolac, ibuprofen, and acetaminophen. Conclusion: Pre-emptive administration of NSAIDs could significantly increase IANB's SAR. Lornoxicam exerted the highest effects in participants with no significant contraindications. More studies are needed to analyze indirect comparison results.

Keywords: Non-steroids anti-inflammatory drugs, inferior alveolar nerve block, network meta-analysis, irreversible pulpitis

Introduction

An effective anesthesia for the treatment of irreversible pulpitis is essential [1], but the failure of inferior alveolar nerve block (IANB) in the mandibular posterior tooth in such a case is a common problem [2]. Anesthesia failure is mainly caused by the inflammatory environment in the pulp, which further induces nociceptor activation. Other explanations include accessory innervations, bifid inferior alveolar nerves, and the special anatomical position of the mandibular canal [3, 4]. All of these factors explaining nociceptor activation have been largely accepted by scientists [5].

Inflammation of the pulp upregulates COX-2 expression, which accelerates prostaglandins production [6]. The latter can directly activate nociceptors and enhance pain [7]. Non-steroids anti-inflammatory drugs (NSAIDs) form a drug class of COX inhibitors. They inhibit the activity of COX-2 and reduce prostaglandins production with a specific or nonspecific mechanism. NSAIDs have been used for pain control for over a hundred years. Numerous studies have revealed that pre-operative use of NSAIDs can significantly increase the success rate of IANB [8-10]. Present researchers also conducted a systematic review and meta-analysis in 2011 to prove the effects of pre-emptive NSAIDs use in

patients with irreversible pulpitis [11]. However, these clinical trials and systematic reviews can only explain the efficacy of one or two specific drugs on IANB success rate increases in irreversible pulpitis, without predicting which kind of NSAIDs exerts the highest efficacy. This missing information can be found thanks to the development of network meta-analysis [12-14]. Indeed, network meta-analysis uses an appropriated indirect comparison of different treatment modalities, while they were not actually compared in clinical trials. Thus, network meta-analysis may help clinicians to choose appropriate treatments.

New evidence on this topic has emerged and systematic review methods are under constant rearrangement. Therefore, the present study performed an updated systematic review using network meta-analysis methods to explore the effects of pre-emptive oral administration of different NSAIDs on the increase of IANB successful effects in patients with irreversible pulpitis.

Methods

Two reviewers performed the study selection, data extraction, and risk of bias assessment in duplicate, according to protocol. Any discrepancies between the two reviewers were resolved through discussion. This systematic review report followed the PRISMA statement for network meta-analysis [15].

Inclusion criteria

Trials with the following criteria were included: Study design: randomized controlled trials (RCTs); Participants: at least one mandibular posterior tooth diagnosed with irreversible pulpitis requiring an endodontic treatment with IANB. The diagnostic criteria for irreversible pulpitis were: an active response to an electronic pulp test, or spontaneous pain, or a prolonged response to cold test; Intervention: pre-emptive single-dose NSAIDs oral administration; Control group: placebo or another kind of NSAID; Outcome variables: success rate of anesthesia (SRA) (if supplementary anesthesia was used, IANB should be evaluated after the initial anesthesia and SRA should be referred to the success rate of the first anesthesia), tooth sensitivity level (TSL), adverse events (AEs).

Search strategy and study selection

Electronic and manual searches were performed. Electronic searches were performed using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Chinese BioMedical Literature Database, and WHO International Clinical Trials Registry Platform on October 25, 2017.

Search strategies combined both MeSH heading words and free text words. MeSH heading words used were “pulpitis”, “anesthesia, local”, and “anti-inflammatory agents, non-steroidal”. In addition, these search strategies were combined with Cochrane Highly Sensitive Search Strategy to identify randomized trials [16].

During the study selection process, titles and abstracts were scanned to find any potentially eligible study. Full texts were obtained of any potentially eligible study to assess a final evaluation. Consistency tests were performed to check the consistency of the two reviewers, with $\kappa>0.75$ indicating excellent consistency.

Data extraction

This study created a data extraction form, piloting it on 20% of included studies. The data extraction form included: Trial design with inclusion and exclusion criteria, duration, setting and location of the study, demographic data of the participants, diagnostic criteria of irreversible pulpitis, usage of the anesthetics and NSAIDs, outcomes such as SRA, TSL and AE, and timing of measurement. Study authors were contacted in cases of important missing data.

Risk of bias assessment

Risk of bias assessment was carried out using Cochrane Collaboration’s tool for assessing risk of bias on the following domains [17]: Sequence generation; Allocation concealment; Blinding of participants and personnel; Blinding of outcome assessors; Incomplete outcome; Selective data reporting; Other bias.

Risk of bias in included studies was classified as follows: Low-low risk of bias if the 6 domains were granted as “low risk of bias”; Unclear-unclear risk of bias if one or more domains were granted as “unclear risk of bias”; and

Table 1. Characteristics of included studies

Study ID	Country	Gender (M/F)	Age	Tooth	Intervention of treatment group	IANB	Outcome	Record time
Aggarwal 2010 [21]	India	36/33	21-38	Mandibular molars	600 mg ibu/20 mg ket	1.7 ml 2% lidocaine with 1/200000 epinephrine	SRA	75 min after taking the drug, 15 min after IANB
Fuller 2014 [8]	USA	46/54	18-67	Mandibular posterior tooth	1000 mg acet + 10 mg hydro	1.3 ml 2% lidocaine with 1/100000 epinephrine and 0.9 ml for long buccal injection	SRA	75 min after taking the drug, 15 min after IANB
Ianiro 2007 [22]	USA	16/24	19-72	Mandibular posterior tooth	Acet 1g/Acet 1 g + ibu 600 mg	3.6 ml 2% lidocaine with 1/100000 epinephrine	SRA	45 min after taking the drug, 15 min after IANB
Jena 2013 [9]	India	63/37	18-65	Mandibular molars	600 mg ibu/10 mg ket/400 mg Eto + 500 mg Parac/100 mg acec + 500 mg parac	2% lidocaine with 1:100000 adrenaline	SRA	45 min after taking the drug, 15 min after IANB
Modaresi 2006 [23]	Iran	Unclear	Unclear	Mandibular teeth	400 mg ibu/600 mg acet + 40 mg codeine	1.8 ml 2% lidocaine with 1/80000 epinephrine	TSL	70 min after taking the drug, 10 min after IANB
Noguera-Gonzalez 2013 [24]	Mexico	18/32	18-68	Mandibular molars	600 mg ibu	1.8 mL of 2% mepivacaine and 1:100 000 epinephrine	SRA	75 min after taking the drug, 15 min after IANB
Oleson 2010 [25]	USA	45/55	mean = 33	Mandibular posterior tooth	800 mg ibu	two 1.8 ml 2% lidocaine with 1/100000 epinephrine and 0.9 ml for long buccal injection	SRA	75 min after taking the drug, 15 min after IANB
Parirokh 2010 [26]	Iran	71/79	18-64	Mandibular molar	600 mg ibu/75 mg indo	1.8 ml 2% lidocaine with 1/80000 epinephrine	SRA, AE	75 min after taking the drug, 15 min after IANB
Prasanna 2011 [10]	India	55/59	mean = 28	Mandibular molars	Lor 8 mg/dic 50 mg	1.8 ml 2% lidocaine with 1/200000 epinephrine	SRA	75 min after taking the drug, 15 min after IANB
Shahi 2013 [27]	Iran	86/79*	>18	Mandibular molars	400 mg ibu	1.8 mL 2% lidocaine with 1:80,000 epinephrine	SRA	75 min after taking the drug, 15 min after IANB
Simpson 2011 [28]	USA	36/64	mean = 32.5	Mandibular posterior tooth	800 mg ibu + 1000 mg acet	two 1.8 ml 2% lidocaine with 1/100000 epinephrine and 0.9 ml for long buccal injection	SRA	75 min after taking the drug, 15 min after IANB

Table 2. Risk of bias assessment in included studies

Study ID	1	2	3	4	5	6	7	Overall risk of bias
Aggarwal 2010 [21]	A	A	A	A	A	A	A	Low
Fuller 2014 [8]	A	A	A	A	A	A	A	Low
Ianiro 2007 [22]	A	A	A	A	A	A	A	Low
Jena 2013 [9]	B	B	A	A	A	A	A	Unclear
Modaresi 2006 [23]	B	B	A	B	A	A	B	Unclear
Noguera-Gonzalez 2013 [24]	A	B	A	A	A	A	A	Unclear
Oleson 2010 [25]	A	A	A	A	A	A	A	Low
Parirokh 2010 [26]	A	A	A	A	A	A	A	Low
Prasanna 2011 [10]	A	A	A	A	A	A	A	Low
Shahi 2013 [27]	A	A	A	A	A	A	A	Low
Simpson 2011 [28]	A	A	A	A	A	A	A	Low

High-high risk of bias if one or more domains were granted as "high risk of bias".

Data analysis

Meta-analysis: Review Manager 5.3 was used for traditional pair-wise meta-analysis. Statistical heterogeneity was analyzed by Cochrane's Q test and I^2 statistic. If I^2>50% and P ≤ 0.10, the heterogeneity causes were analyzed, subgroup analysis was performed, and a random-effects model was adopted for the meta-analysis. Otherwise a fixed-effects model was used for analysis. Combined results of SAR and AE are expressed as relative risks (RRs) and 95% confidence intervals (CIs). Mean difference (MD) for TSL, along with 95% Cis, was calculated. The statistical significance of the hypothesis test was set at P<0.05 (2-tailed z tests). Funnel plots and Beggs' rank correlation tests were used to detect publication bias, with funnel plot asymmetry and P<0.10 suggesting publication bias [18].

Summary of findings

Meta-analysis quality was assessed using GRADE. The specific software, GRADEprofiler, was used for assessment. Evidence from randomized controlled trials was initially considered of high quality, but confidence in the body of evidence may have decreased due to study limitations (risk of bias), directness of the evidence, heterogeneity, precision of effect estimates, and risk of publication bias. Meta-analysis quality was recorded as high, moderate, low, and very low [19].

Network meta-analysis

Network meta-analysis was performed with a random-effects model within a Bayesian framework, using the software WinBUGS1.4 [20]. Overall effects of all NSAIDs were explored based on SAR calculation with RR as the measure of treatment effects. Underlying effects were also calculated, providing relative ranking of individual drugs.

Results

Search results and study inclusion

A total of 164 records were retrieved via electronic and hand-searches (2 overlapping records were found between electronic and hand-searching). After search results screening, 143 trials were excluded, while 21 records were subjected to further assessment. After retrieving the full texts and further detailed evaluation, 11 studies were included [8-10, 21-28] (Figure S1).

Characteristics of included studies

Characteristics of included studies are shown in **Table 1**. A total of 993 participants were included. NSAIDs that were used included ibuprofen (ibu), ketorolac (ket), acetaminophen (acet), etodolac (eto), paracetamol (parac), aceclofenac (acec), indomethacin (indo), lornoxicam (lor), and diclofenac (dic). There were also some NSAIDs combinations or NSAIDs with hydrocodeine (hydro) or codeine. Ten of the included studies reported SAR [8-10, 21, 22, 24-28], while all of them defined SAR as no pain to mild pain (HP VAS ≤ 54) during the procedure. Only one study reported TSL [23] while another reported AE [26].

Risk of bias in included studies

Eight studies had low risk of bias [8, 10, 21, 22, 25-28] while the rest had unclear risk of bias [9, 23, 24]. Unclear reporting of randomization and allocation concealment was the main source of risk of bias downgrading (**Table 2**).

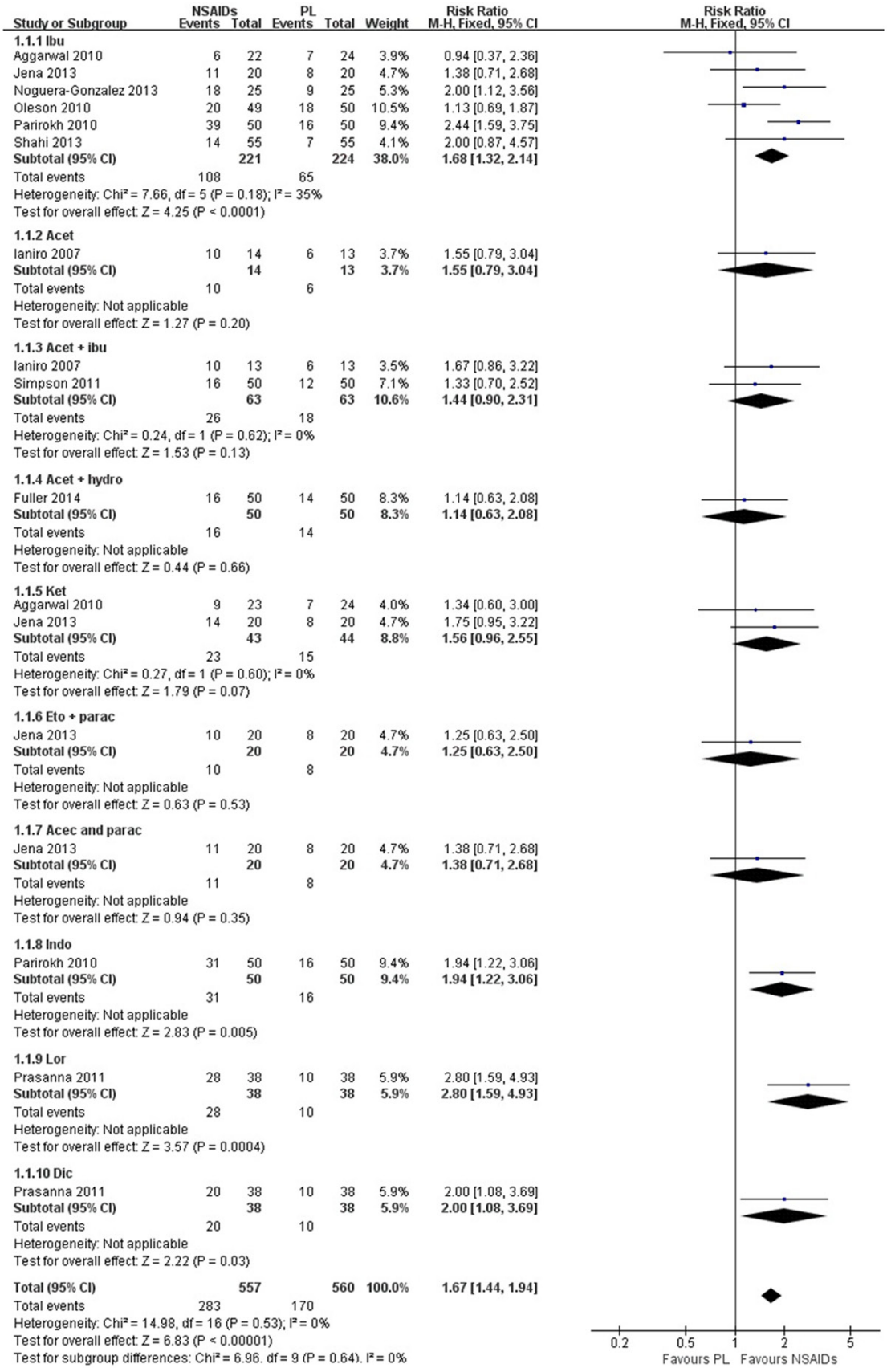

Figure 1. Meta-analysis comparing NSAIDs with PL.

Meta-analysis results and summary of findings

SAR: By pooling the data, it was found that the pre-emptive use of NSAIDs could increase SAR by approximately 67%, compared to PL, and the differences were statistically significant (RR = 1.67, 95% CI [1.44, 1.94], P<0.00001) (**Figure 1**). Funnel plots exploring publication bias exhibited a symmetry contour (Figure S2) while Beggs' test showed no significant publication bias (P = 0.897). Of all NSAIDs investigated in this study, ibu, acet, ket, indo, lor, and dic could increase SAR by at least 50%, with ibu showing a high quality of evidence and a moderate quality of evidence for indo, assessed by GRADE (**Table 3**). This study also conducted head to head comparisons to explain the advantages of one NSAID compared to another (**Table 3**; Figures S3, S4 and S5). However, based on limited evidence, only few pairwise comparisons could be made (**Figure 2**). This study lacked lots of comparisons, preventing recommendations to clinicians concerning which NSAIDs had the highest effects (**Figure 2**).

TSL Modaresi 2006 [23] showed that acet + codeine could attenuate TSL (MD = -0.07, 95% CI [-0.13, -0.01], P = 0.03).

AEs Although Parirokh 2010 [26] mentioned AE, there were not any AE values reported in any groups.

Network meta-analysis results

The blank comparisons in **Figure 2** were filled up by network meta-analysis and the present pairwise comparison was enhanced (**Table 4**). Network meta-analysis results did not significantly differ from the results in traditional meta-analysis. The effects of all NSAIDs were calculated, indicating that pre-emptive use of lor had the highest effects, followed by, but not limited to, dic, ket, and ibu (**Figure 3**).

Discussion

Pain management is of great importance in irreversible pulpitis treatment. Since pulpitis generates different pain states, endodontic procedures may add up new stimuli and increase pain levels [29]. IANB in the mandibular posterior tooth reversibly interrupts the propagation of inferior alveolar nerve impulses. However, a successful IANB is far from acceptable [2, 30]. Some studies have mentioned that, in an inflamed tooth, the IANB successful rate is under 30% [8, 21]. The activation of nociceptors by inflammatory mediators is a well-accepted explanation of IANB increased failure in patients with irreversible pulpitis [31, 32]. NSAIDs, a kind of COX inhibitors which can inhibit the production of inflammatory mediators, has been considered to increase IANB success rates, proving to be effective via oral administration [33, 34].

Numbers of studies have been conducted proving NSAIDs effects. However, none of the clinical trials available compared the effects of all NSAIDs on pulpitis, nor traditional systematic reviews and meta-analyses. These evidences reflect the limitation of a previous systematic review in which it was concluded that pre-emptive oral administration of NSAIDs might increase IANB success rates in irreversible pulpitis patients [11], but which NSAIDs exerted the highest effects could not be shown. With the introduction of network meta-analysis, this missing information can be found [35, 36].

The systematic review, therefore, was updated with the incorporation of network meta-analysis. A total of 11 studies were included, with 993 participants involved. Risk of bias in most of the studies was low, indicating high reliability. Via direct pair-wise comparison, important although limited information was retrieved (**Figure 2**). In combining all data, most of the NSAIDs showed high effects on increasing IANB SAR, by at least 50%. Via GRADE, ibu, ket, and indo had moderate to high quality effects. Thus, they are recommended in clinical practice.

Network meta-analysis revealed the missing information left by traditional meta-analysis via indirect comparison. Network meta-analysis provided a relative ranking of individual drugs, with lor exerting the highest effects, significantly increasing SAR by approximately 107% compared to PL. Acet + hydro exerted a limited effect, ranking last. Clinicians should choose available NSAIDs following the relative ranks.

However, although one study mentioned AEs in the text and no AEs were found in different groups, it was important to pay attention to IANBAEs. Many NSAIDs inhibit both COX-1 and COX-2, with the first acting as housekeeping enzymes existing in the stomach, blood, and

Table 3. Meta-analysis and GRADE results rating via direct comparison

Comparison	Intervention									
	Ibu							Color	GRADE of evidecen	
Ket	0.75 [0.48, 1.17]	Ket							High	
Acet + hydro			Acet + hydro						Moderate	
Acet				Acet					Low	
Acet + ibu				0.93 [0.59, 1.45]	Acet + ibu				Very low	
Eto + parac	1.10 [0.61, 1.99]	1.40 [0.83, 2.36]				Eto + parac				
Acec + parac	1.00 [0.57, 1.75]	1.27 [0.78, 2.08]				0.91 [0.50, 1.64]	Acec + parac			
Indo	1.26 [0.97, 1.64]							Indo		
Lor									Lor	
Dic									1.17 [0.86, 1.59]	Dic
PL	1.68 [1.32, 2.14]*	1.56 [0.96, 2.55]	1.14 [0.63, 2.08]	1.55 [0.79, 3.04]	1.44 [0.90, 2.31]	1.25 [0.63, 2.50]	1.38 [0.71, 2.68]	1.94 [1.22, 3.06]*	2.80 [1.59, 4.93]*	2.00 [1.08, 3.69]*

*P<0.05.

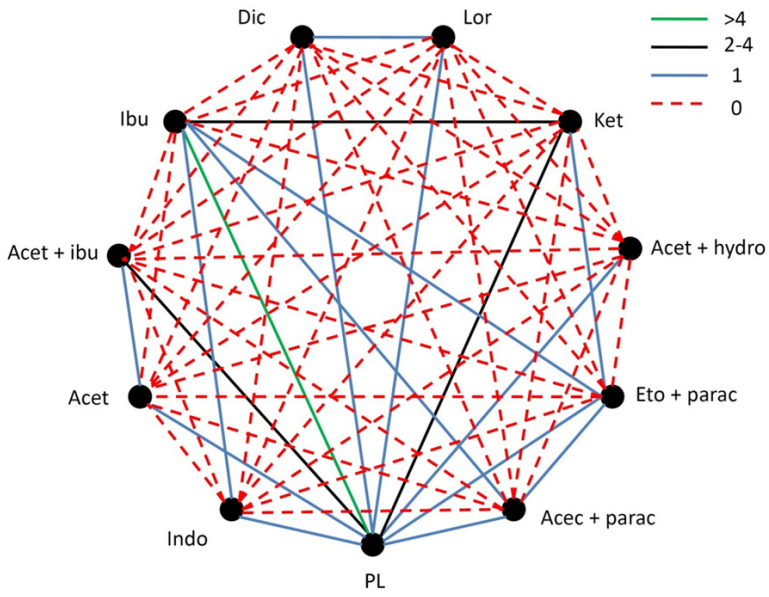

Figure 2. Network of pairwise comparisons. Red lines indicate network of indirect comparisons that should be completed using network meta-analysis.

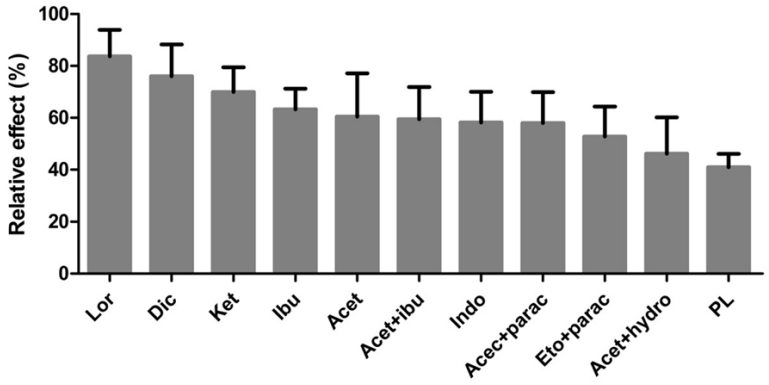

Figure 3. Relative effects of all NSAIDs and PL.

kidneys. Thus, use of these drugs may induce gastrointestinal ulceration, coagulation impairment, and renal failure [37]. Therefore, analysis of patients with irreversible pulpitis should include cases receiving only one dose of NSAIDs. Indeed, most included studies excluded participants under long-term NSAIDs treatment and other systematic diseases, such as GI ulceration and coagulation problem. Hence, one dose of NSAIDs might not have a huge impact on health, explaining the reason we did not find any AE report [38]. For patients that were excluded, the situation was different. NSAIDs were usually administered during or right after the meal, but in case of endodontic treatment, they were administered before the treatment, possibly not associated with the meal. Such improper timing of NSAIDs administration might have some impact on patients with a history of long-term NSAIDs treatment or systemic diseases [39]. Thus, results of this article can only be considered for those patients with long-term NSAIDs history or related systemic diseases. Moreover, their effects and safety in excluded patients need to be evaluated in the future.

To the best of our knowledge, this is the first network meta-analysis focusing on drug use in endodontics.

This work, however, has the following limitations. First, indirect comparison possessed lower reliability compared to direct comparisons. By simply comparing the results from direct and indirect comparison, no huge differences were found, indicating that network meta-analysis had similar reliability compared to traditional meta-analysis. Second, clinical heterogeneities in the included studies differed. The timing and dosage of drug administration, as well as the anesthetics used, were not the same among studies. However, the differences were not remarkable and could probably be ignored. Regarding ibu doses, two studies [23, 27] used 400 mg ibuprofen with a RR of2.00, while four studies [9, 21, 24, 26] used 600 mg, with a RR of 1.87. Oleson 2010 [25] introduced a dosage of 800 mg. However, Figure S1 indicates that its RR value was 1.13. There were no dose-dependent effects and variations of the RRs could mostly be explained as random error, further indicating that in this review, different dosages (but not huge differences) combination was possible. Third, there was some unclear risk of bias in included studies and sample sizes were sometimes small. Therefore,

Table 4. Results of network meta-analysis

	Intervention										
Comparison	Ibu										
Ket	0.91 [0.72, 1.16]	Ket									
Acet + hydro	1.54 [0.82, 3.24]	1.71 [0.89, 3.61]	Acet + hydro								
Acet	1.14 [0.68, 2.22]	1.26 [0.74, 2.49]	0.83 [0.29, 1.80]	Acet							
Acet + ibu	1.11 [0.73, 1.76]	1.23 [0.79, 1.97]	0.81 [0.31, 1.51]	1.04 [0.50, 1.70]	Acet + ibu						
Eto + parac	1.25 [0.87, 1.92]	1.38 [0.94, 2.14]	0.91 [0.36, 1.73]	1.20 [0.52, 2.17]	1.18 [0.65, 2.05]	Eto + parac					
Acec + parac	1.13 [0.81, 1.68]	1.24 [0.89, 1.85]	0.82 [0.33, 1.51]	1.08 [0.48, 1.89]	1.06 [0.59, 1.78]	0.93 [0.58, 1.42]	Acec + parac				
Indo	1.12 [0.80, 1.66]	1.25 [0.84, 1.93]	0.82 [0.33, 1.52]	1.08 [0.48, 1.88]	1.06 [0.59, 1.78]	0.94 [0.52, 1.52]	1.03 [0.60, 1.66]	Indo			
Lor	0.76 [0.57, 1.00]	0.84 [0.61, 1.12]	0.56 [0.23, 0.93]*	0.73 [0.34, 1.12]	0.72 [0.42, 1.03]	0.64 [0.36, 0.93]*	0.70 [0.42, 0.99]*	0.70 [0.42, 1.00]	Lor		
Dic	0.85 [0.61, 1.21]	0.94 [0.66, 1.35]	0.62 [0.25, 1.07]	0.81 [0.37, 1.35]	0.80 [0.46, 1.24]	0.71 [0.40, 1.08]	0.78 [0.46, 1.16]	0.78 [0.46, 1.17]	1.12 [0.89, 1.48]	Dic	
PL	1.56 [1.26, 1.89]*	1.72 [1.32, 2.20]*	1.13 [0.49, 1.84]	1.49 [0.71, 2.24]	1.46 [0.92, 2.05]	1.30 [0.80, 1.81]	1.42 [0.91, 1.94]	1.43 [0.92, 1.95]	2.07 [1.56, 2.67]*	1.88 [1.32, 2.47]*	

*P<0.05.

further studies should be performed using larger sample sizes.

Conclusion

Pre-emptive administration of NSAIDs could significantly increase IANB's SAR, with Ior exerting the highest effects in participants with no significant contraindications. More studies are necessary to analyze indirect comparison results.

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Disclosure of conflict of interest

None.

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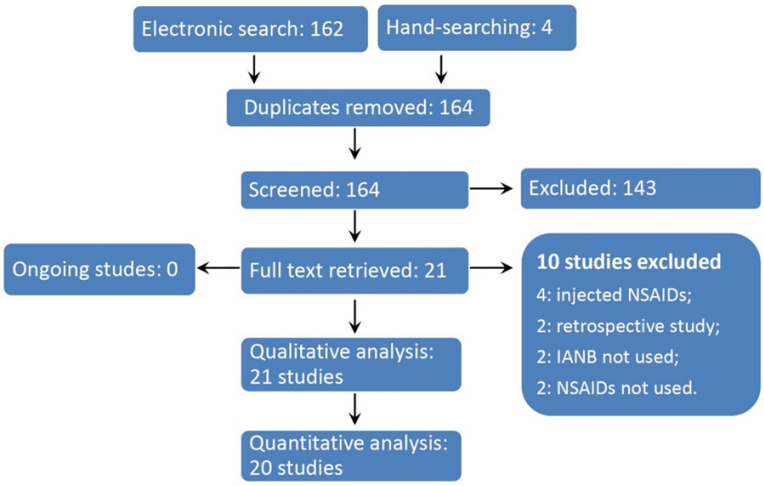

Figure S1. Flow of study inclusion.

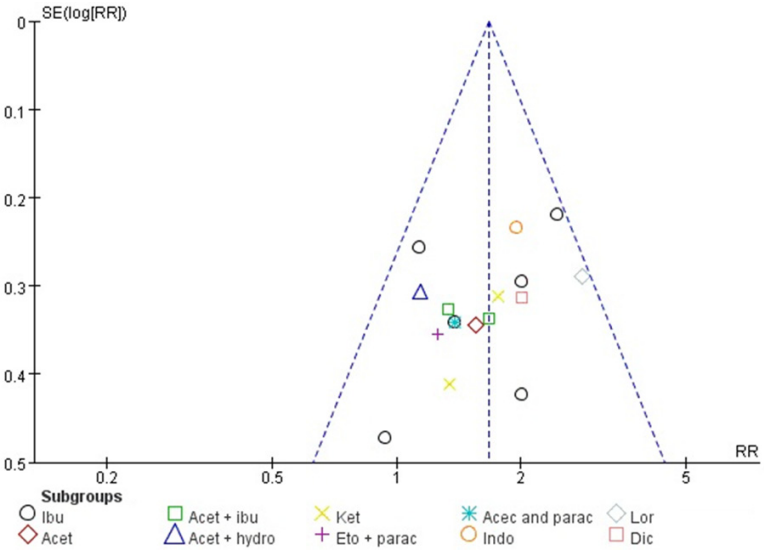

Figure S2. Funnel plot of meta-analysis comparing NSAIDs with PL.

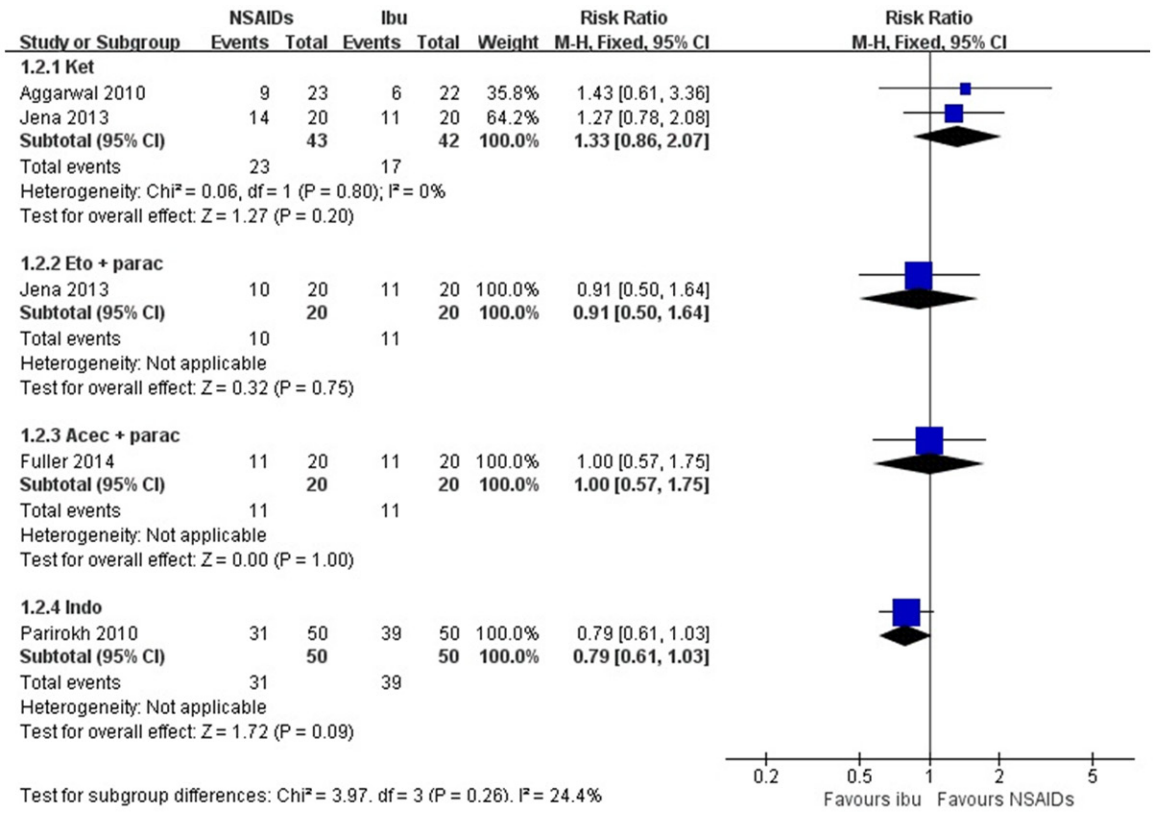

Figure S3. Meta-analysis comparing NSAIDs with ibu.

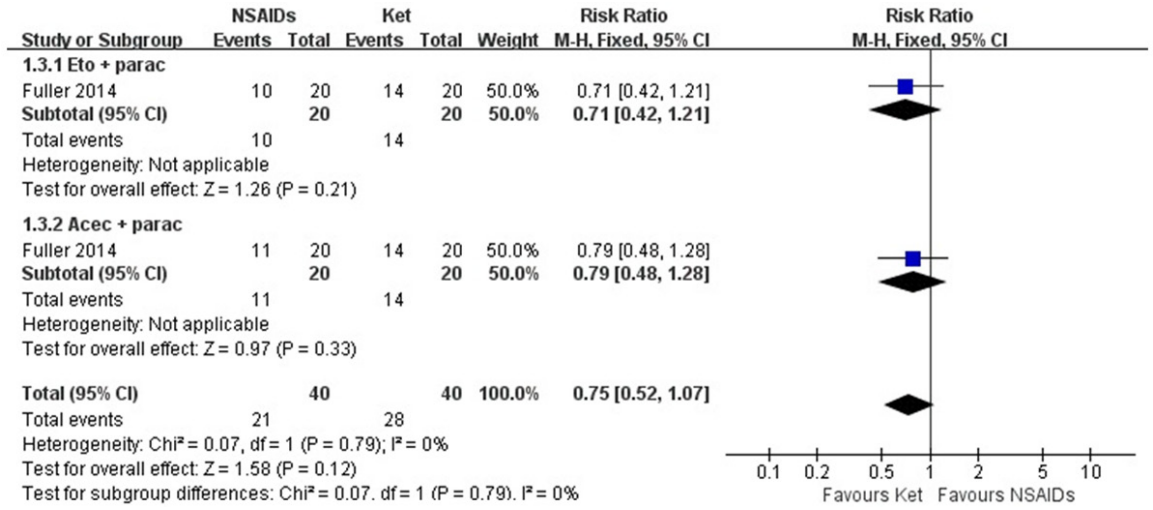

Figure S4. Meta-analysis comparing NSAIDs with ket.

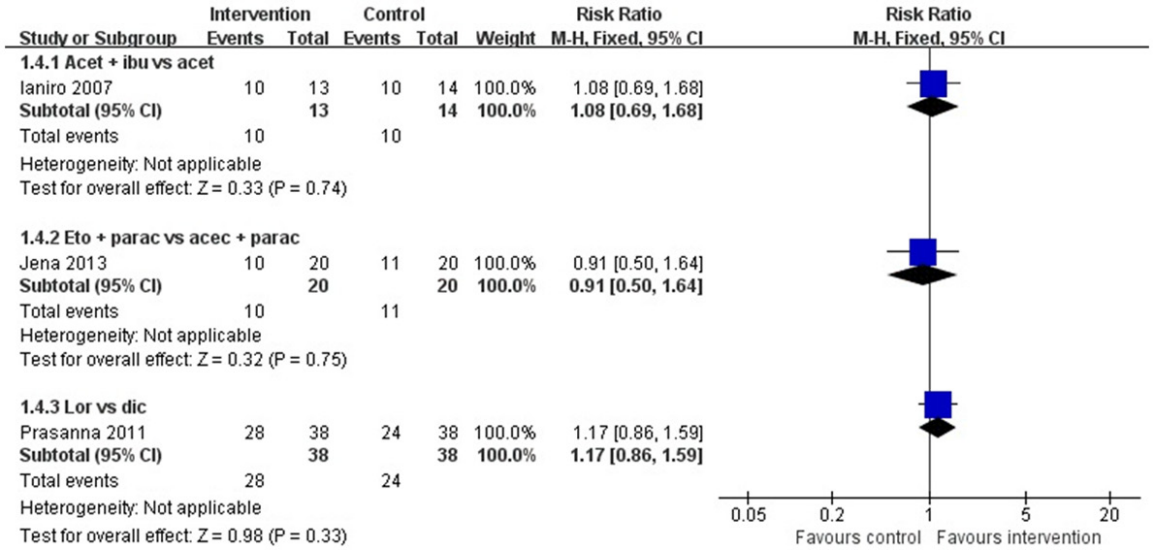

Figure S5. Other comparisons of traditional meta-analysis.