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SYSTEMATIC REVIEW

Effects of Ibuprofen Compared to Other Premedication Drugs on the Risk and Intensity of Postendodontic Pain: A Systematic Review

Juliana L. DE GEUS, Letícia M. WAMBIER, Thaynara F. BOING, Alessandro D. LOGUERCIO, Alessandra REIS

ABSTRACT

Objective: This systematic review aims to evaluate the effects of ibuprofen compared to other drugs on the risk and intensity of postoperative pain resulting from endodontic treatment in adult patients.

Methods: A systematic search was carried out through Medline databases (Pubmed, Scopus, Web of Science, Cochrane, Lilacs, and BBO). There was no restriction on the publication year or idiom. The gray literature was explored. The Periodicos Capes Theses Databases and ProQuest Dissertations were also searched, as well as the unpublished and ongoing trials registry and the IADR abstracts (1990–2016). Solely randomized clinical trials that compared the risk or intensity of pain resulting from endodontic treatment in adult patients were included in this systematic review. The risk of bias of the articles was evaluated using the Cochrane Collaboration's tool. A random-effect meta-analysis was conducted for ibuprofen versus placebo and ibuprofen versus other drugs at 6, 8, and 24 hours. The GRADE approach was used to assess the quality of the evidence.

Results: A total of 1132 studies were identified, and only seven meet the eligibility criteria. No difference between the groups was detected in any of the meta-analysis. An exception was observed when one study was removed from the meta-analysis of pain intensity at 24 hours for ibuprofen versus placebo, favoring ibuprofen (SMD −0.67; 95% CI −1.05 to −0.17). The quality of evidence in all meta-analyses was graded as low or very low.

Conclusion: Results of the present systematic review indicate that there is no clear evidence supporting that preoperative ibuprofen is better than other drugs in reducing the risk and intensity of postendodontic pain.

Keywords: Analgesia, ibuprofen, premedication, postendodontic pain, root canal therapy, systematic review

HIGHLIGHTS

- Preoperative ibuprofen does not seem to reduce the intensity of postoperative endodontic pain.
- More RCTs with a robust methodology should be conducted as the ones available are at unclear risk of bias.
- Better reporting of RCTs is needed.

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INTRODUCTION

Endodontic postoperative pain is defined as any degree of discomfort that occurs after endodontic treatment (1). This condition is known as a flare-up, which is reported as the development of pain, tumefaction, or both, beginning within a few hours or days after the root canal preparation (2).

Postoperative pain following endodontic therapy is a clinically important issue for both patients and dentists (3). Up to 70% of patients usually experience some pain throughout the endodontic therapy (4, 5). The pain is believed to be associated with a periapical inflammatory response caused by the endodontic instrumentation or chemical substances from irrigation (6). A relevant solution would be pretreatment analgesia, minimizing the pain before the endodontic treatment is started (7); therefore, some studies investigated the role of nonsteroidal anti-inflammatory drugs (NSAID) for this purpose.

NSAIDs are effective in decreasing the pain resulting from endodontic treatments and they are commonly prescribed for this purpose (8, 9). NSAIDs appear to inhibit inflammation and induce analgesia by inhibiting the cyclooxygenase activity (COX) enzymes. There are two isoforms of COX enzymes: COX-1 and COX-2. Ibuprofen, ketoprofen, aspirin, and naproxen are nonselective NSAIDs, inhibiting both cytoprotective COX-1 enzymes and inflammatory COX-2 enzymes (10).

NSAIDs are greatly helpful in the treatment of moderate to severe postoperative pain, reducing the opioid demand and side effects, especially nausea and vomiting (11, 12). Among the NSAIDs,

ibuprofen is commonly prescribed, because it is safe, has low cost, and presents excellent analgesic and anti-inflammatory action for postoperative pain resulting from endodontic therapy (13). Some studies have compared ibuprofen with other medications, such as rofecoxib (6) and tenoxican (3), which were prescribed because they are selective COX-2 inhibitors that could promote lower incidence of side effects, such as gastritis (14). Indomethacin was also compared, because of its extensive anti-inflammatory effect (15). The use of ibuprofen as premedication before endodontic treatment has been reported to significantly reduce postoperative endodontic pain, when compared to placebo (3, 6, 15). Nevertheless, Attar et al. (7) have shown that there was no statistically significant difference in postendodontic pain between the prophylactic prescription of ibuprofen tablet, ibuprofen liquigel (400 mg), and placebo.

Against the controversial results in the literature, the objective of this systematic review was to determine whether ibuprofen as premedication significantly reduces postendodontic pain, when compared to other premedications or placebo.

MATERIALS AND METHODS

The methodology was based on previous studies published by our research group (16, 17).

Record of protocol

The protocol of this study was recorded in the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO/; CRD42016036545) according the PRISMA statement recommendations (18).

Search strategy

The search strategy, performed through the MeSH terms and keywords, was based on the following PICOS question: "Is ibuprofen effective to decrease the risk and intensity of pain after endodontic treatment in vital and nonvital teeth of adult patients?"

1. Population (P): Adult patients submitted to nonsurgical endodontic treatment
2. Intervention (I): Ibuprofen prescribed preoperatively
3. Comparison (C): Other drugs prescribed preoperatively or placebo
4. The outcome (O): Risk and intensity of postendodontic pain
5. The study design (S): Randomized clinical trials

Research was carried out on the electronic databases of MEDLINE (PubMed, Web of Science, Scopus, Cochrane Library, Latin American, and Caribbean Health Sciences Literature database [LILACS] and Brazilian Library in Dentistry [BBO]) to identify randomized clinical trials to be included in this review (Table 1), without restrictions on the publication year or idiom.

The gray literature was also explored, through the database System for Information on Grey Literature in Europe (SIGLE). The Periodicos Capes Theses Databases and ProQuest Dissertations were also searched, as well as the unpublished and ongoing trials registry (ClinicalTrials.gov, EU Clinical Trials Register, International Clinical Trials Registry Platform, Current Controlled Trials, and Rebec), beyond the IADR and their regional divisions abstracts (1990–2016).

Inclusion and exclusion criteria

Randomized clinical trials (RCTs) that used ibuprofen versus other premedication drugs in nonsurgical endodontic treatment were included. RCTs were excluded if 1) studies used only ibuprofen protocols for premedication; 2) participants used only one type of medication; 3) studies compared the association of medications; 4) the medication was prescribed after the endodontic treatment.

Study selection and data collection

First, the studies were selected by title and abstracts, according to the eligibility criteria. Duplicate articles were regarded only once. The full text of the articles was obtained if the title and abstract did not have sufficient information to include them in the study. After that, two reviewers classified those that fulfilled the inclusion criteria. An ID for each eligible study was assigned, combining the first author of the article and the year of publication. Relevant information about the study methodology and results were extracted by two authors.

When data from more than one endodontic session was provided, an average of these results was obtained. When more than one drug was included in the study, with an exception of placebo, their values were merged to make a single value.

Evaluation of risk of bias

The quality assessment of the selected studies was evaluated by two independent reviewers, through the Cochrane Collaboration's tool, to assess the risk of bias in randomized trials (19). This tool contains six items: sequence generation, allocation concealment, blinding of the outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias, if it was possible. If there were disagreements between the reviewers during the data selection and quality assessment, they were solved by discussion, and if it was necessary, by consulting a third reviewer.

In each item, the judgment involved recording a "yes," indicating that the study was at low risk of bias; a "no," indicating high risk of bias; and "unclear," indicating either missing information or uncertainty about the potential for bias. The study was at "low" risk of bias if all key domains for each outcome were at low risk of bias. If one or more key domains were classified as "unclear" or "high" risk of bias, the study was considered at unclear or high risk of bias. For the patient-focused outcomes (risk and intensity of postendodontic pain), the key domains were adequate patient blinding, sequence generation, and allocation concealment, so the studies had to be classified as "low" risk of bias in these items.

Summary measures and synthesis of the results

We used random effect models and assessed heterogeneity (which represents any kind of variability among studies) by using the Cochran Q test and I2 statistics. We carried out the analyses by using the software RevMan 5.3 (Review Manager Version 5, The Cochrane Collaboration, Copenhagen, Den-

TABLE 1. Electronic database and search strategy

Pubmed 23/09/2016 – 442 articles	
#1 endodontics[MeSH Terms] OR pulpectomy[MeSH Terms] OR root canal preparation[MeSH Terms] OR root canal therapy[MeSH Terms] OR "endodontic treatment"[Title/Abstract] OR " endodontic therapy"[Title/Abstract] OR endodontics[Title/Abstract] OR "endodontically treated teeth"[Title/Abstract] OR pulpectomy [Title/Abstract] OR "root canal preparation "[Title/Abstract] OR "root canal therapy" [Title/Abstract] OR "root canal treatment" [Title/Abstract]	**#2** ibuprofen[MeSH Terms] OR anti-inflammatory agents [MeSH Terms] OR anti-inflammatory agents, non-steroidal[MeSH Terms] OR cyclooxygenase inhibitors [MeSH Terms] OR cyclooxygenase 2 inhibitors[MeSH Terms] OR analgesics [MeSH Terms] OR analgesics, non-narcotic [MeSH Terms] OR analgesics, opioid [MeSH Terms] OR premedication [MeSH Terms] OR ibuprofen[Title/Abstract] OR anti-inflammatory [Title/Abstract] OR "cyclooxygenase inhibitors" [Title/Abstract] OR analgesic [Title/Abstract] OR premedication [Title/Abstract]
Scopus 23/09/2016 – 429 articles	
#1 (TITLE-ABS-KEY (endodontics) OR TITLE-ABS-KEY (pulpectomy) OR TITLE-ABS-KEY ("root canal preparation") OR TITLE-ABS-KEY ("root canal therapy") OR TITLE-ABS-KEY ("endodontic treatment") OR TITLE-ABS-KEY ("endodontic therapy") OR TITLE-ABS-KEY ("endodontically treated teeth"))	**#2** TITLE-ABS-KEY(ibuprofen) OR TITLE-ABS-KEY ("anti-inflammatory agent") OR TITLE-ABS-KEY ("cyclooxygenase inhibitor") OR TITLE-ABS-KEY ("cyclooxygenase 2 inhibitor") OR TITLE-ABS-KEY (analgesic) OR TITLE-ABS-KEY(premedication)
Web of Science 23/09/2016 – 80 articles	
#1 Tópico: (endodontics) ORTópico: (pulpectomy) ORTópico: ("root canal preparation") ORTópico: ("root canal therapy") ORTópico: ("endodontic treatment") ORTópico: ("endodontic therapy") ORTópico: ("endodontically treated teeth ")	**#2** Topic: (ibuprofen) OR Topic: ("anti-inflammatory agent*") OR Topic: ("cyclooxygenase inhibitor*") OR Topic: ("cyclooxygenase 2 inhibitor*") OR Topic: (analgesic*) OR Topic: (premedication)
#1 AND #2	
Lilacs and BBO 23/09/2016 – 53 articles	
#1 (MH:"endodontics" OR MH:"pulpectomy" OR MH:"root canal preparation" OR MH:" root canal therapy" OR "endodontic treatment" OR "endodontically treated teeth" OR " endodontia" OR "endodoncia" OR "pulpectomia" OR "pulpectomía" OR "tratamento de canal" OR " tratamiento de conducto" OR "tratamento endodôntico" OR "tratamiento endodóntico" OR "terapia endodôntica" OR "terapía endodóntica" OR "dentes tratados endodonticamente" OR "dientes tratados endodónticamente")	**#2** (MH:"ibuprofen" OR "anti-inflammatory agent" OR "anti-inflammatory agents" OR "cyclooxygenase inhibitor" OR "cyclooxygenase inhibitors" OR "cyclooxygenase 2 inhibitor" OR "cyclooxygenase 2 inhibitors" OR "analgesic" OR "analgesics" OR "premedication" OR "ibuprofeno" OR "agente antiinflamatório" OR "agentes antiinflamatórios" OR "agente anti-inflamatorio" OR "agentes anti-inflamatorios" OR "inibidor da ciclooxigenase" OR "inibidores da ciclooxigenase" OR "inibidor da ciclooxigenase 2" OR "inibidores da ciclooxigenase 2" OR "inhibidor de la ciclooxigenasa" OR "inhibidores de la ciclooxigenasa" OR "inhibidor de la ciclooxigenasa 2" OR "inhibidores de la ciclooxigenasa 2" OR "analgésico" OR "analgésicos" OR "pré-medicação" OR "premedicación")
#1 AND #2	

mark). A sensitivity analysis was performed to identify causes of heterogeneity if presented.

As we identified during paper screening that pain intensity was measured at different times and ibuprofen was compared with placebo or other drugs, we meta-analyzed data from two assessment periods (6/8 h and 24 hours) for ibuprofen versus placebo and ibuprofen versus other drugs. This was not pre-specified in the protocol registered in PROSPERO, as this was a finding not known before the collection of papers.

Assessment of the quality of evidence using GRADE

The quality of the evidence for each outcome across studies (body of evidence) was graded using the Grading of Recommendations: Assessment, Development and Evaluation (GRADE) (http://www.gradeworkinggroup.org/) to determine the overall strength of evidence for each meta-analysis. The GRADE approach is used to contextualize or justify intervention recommendations with four levels of evidence quality, ranging from high to very low.

TABLE 1. Electronic database and search strategy

Cochrane Library 23/06/2016 – 126 articles

#1 MeSH descriptor: [Endodontics] explode all trees
#2 MeSH descriptor: [Pulpectomy] explode all trees
#3 MeSH descriptor: [Root Canal Preparation] explode all trees

#4 MeSH descriptor: [Root Canal Therapy] explode all trees
#5 endodontics:ti,ab,kw
#5 pulpectomy:ti,ab,kw
#7 "root canal preparation":ti,ab,kw
#8 "root canal therapy":ti,ab,kw
#9 "endodontic treatment":ti,ab,kw
#10 "endodontic therapy":ti,ab,kw
#11 "endodontically treated teeth"
#12 #1 or #2 or #3 or #4 0r #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 MeSH descriptor: [Ibuprofen] explode all trees
#14 MeSH descriptor: [Anti-Inflammatory Agents] explode all trees
#15 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees
#16 MeSH descriptor: [Cyclooxygenase Inhibitors] explode all trees
#17 MeSH descriptor: [Cyclooxygenase 2 Inhibitors] explode all trees
#18 MeSH descriptor: [Analgesics] explode all trees
#19 MeSH descriptor: [Analgesics, Non-Narcotic] explode all trees
#20 MeSH descriptor: [Analgesics, Opioid] explode all trees
#21 MeSH descriptor: [Premedication] explode all trees
#22 ibuprofen:ti,ab,kw
#23 "anti-inflammatory agent*":ti,ab,kw
#24 "cyclooxygenase inhibitor*":ti,ab,kw
#25 "cyclooxygenase 2 inhibitor*":ti,ab,kw
#26 analgesic*:ti,ab,kw
#27 premedication:ti,ab,kw
#28 #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

#12 AND #28

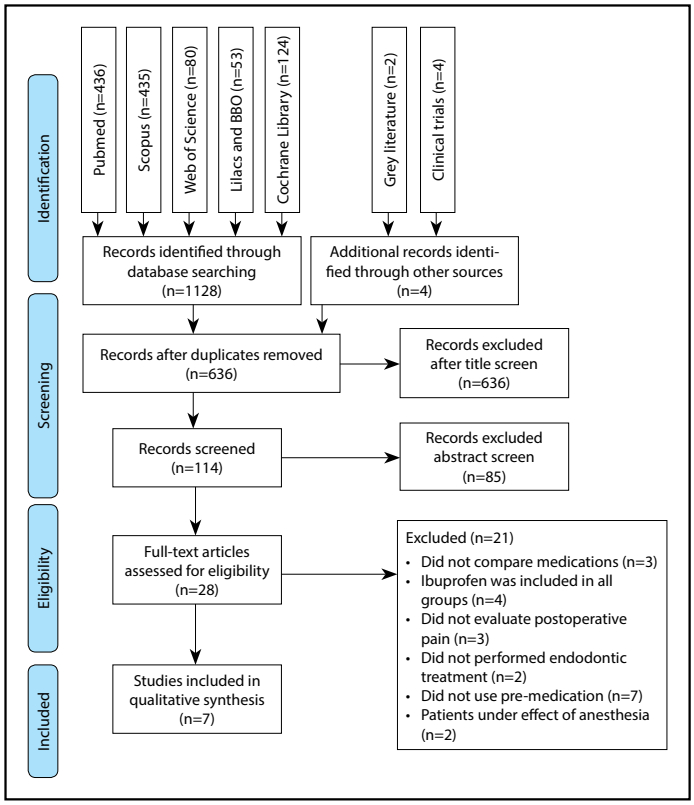

Figure 1. Flow chart diagram showing the number of articles obtained in the different phases of the study

The GRADE approach begins with the study design (RCTs or observational studies) and then addresses five reasons (risk of bias, imprecision, inconsistency, indirectness of evidence, and publication bias) for possibly rating down the quality of the evidence (1 or 2 levels) and three reasons for possibly rating up the quality (large effect, management of confounding factors, dose-response gradient) (20). Each one of these topics was assessed as "no limitation," "serious limitations," and "very serious limitations" to allow categorization of the quality of the evidence for each outcome into high, moderate, low, and very low. The "high quality" suggests that we are very confident that the true effect lies close to the estimate of the effect. On the other extreme, a "very low quality" suggests that we have very little confidence in the effect estimate, and the estimate reported can be substantially different from the one measured.

RESULTS

Study selection

Figure 1 shows the flow diagram of the study and the reasons for exclusion. A total of 1132 studies were identified, considering the databases, gray literature, and clinical trial registry. A total of 827 studies remained after the removal of duplicates. After reading the titles and abstracts, there were still 28 studies. Twenty-one were excluded after reading the full text (21–41). For qualitative analyses, only seven studies were retained (3, 6, 7, 15, 42–44), and six for meta-analysis (3, 6, 7, 15, 41, 43).

Characteristics of included articles

Study design and participants

The details of the seven studies selected are shown in Tables 2 and 3. All studies used the parallel design (3, 6, 7, 15, 42–44). All studies were performed in a university setting. Seven studies used a 0–100 visual analog scale for evaluation of pain (3, 6, 7, 15, 42–44), one study also used a 0–3 numerical rating scale (42), and another also used a Heft–Parker scale (7).

The patients per group in these studies ranged from 15 to 65. The average age of the participants was nearly 34.8 years (3, 7, 15, 44), ranging from 18 to 65 (6, 42, 43). In three out of seven studies, male participants were more frequent (6, 7, 44) while in four, females were more frequent (3, 15, 42, 43). The number of patient dropouts varied from 0 to 24 (3, 6, 7, 43, 44), and two studies did not report dropouts (15, 42).

TABLE 2. Details of the Selected Studies (Part 1)

Study ID	Study design [setting]	Pain evaluation criteria	Subject's age in mean±SD [range] (yrs.)	# of subjects male [total]	Drop-outs [# of subjects]	Groups/Drug [# of subjects]	Instrumentation protocol	Reported side effects
Arslan et al. 2011	Parallel [University]	VAS 0-100	36±n.r. [18–52]	16 [48]	0	IBUPROFEN 200 mg [16] TENOXICAM 20 mg [16] PLACEBO [16]	Crown-down technique	No
Attar et al. 2008	Parallel [n.r.]	VAS 0-100 and Heft Parker	44.1±4.6 [n.r.]	23 [39]	6	IBUPROFEN 600 mg TABLET [14] IBUPROFEN 400 mg LIQUIGEL [13] PLACEBO [12]	Crown-down technique	No
Gopikrishna & Parameswaran 2003	Parallel [University]	VAS 0-100	n.r.±n.r. [18–65]	29 [45]	0	IBUPEOFEN 600 mg [15] ROFECOXIB 50 mg [15] PLACEBO [15]	Crown-down technique	No
Mello 2014	Parallel [University]	NRS 0-3 and VAS 0-100	n.r.±n.r. [18–60]	34 [97]	n.r.	IBUPROFEN 600 mg [33] DEXAMETHASONE 4 mg [33] PLACEBO [33]	Crown-down technique	No
Menke et al. 2000	Parallel [University]	VAS 0-100	n.r.±n.r. [18–n.r.]	14 [36]	6	IBUPROFEN 600 mg [12] ETODOLAC 400 mg [12] PLACEBO [12]	n.r.	No
Mokhtari et al. 2016	Parallel [University]	VAS 0-100	23.8±2.9 [18–65]	29 [66]	n.r.	IBUPROFEN 400 mg [22] INDOMETHACIN 25 mg [22] PLACEBO [22]	Step-back technique	Yes
Ramazani et al. 2013	Parallel [University]	VAS 0-100	35.4±10 [18–65]	38 [72]	18	IBUPROFEN 400 mg [30] ZINTONA 2 g [30] PLACEBO [30]	Crown-down technique	No

ID, identification; SD, standard deviation; yrs, years; #, number; n.r., not reported; VAS, Visual Analog Scale: a 10 cm horizontal line with words "no pain" at zero and the "worst pain" at the opposite end; NRS, Numerical Rating Scale: none, mild, moderate, and severe pain

TABLE 3. Details of the Selected Studies (Part 2)

Study ID	Anesthesia salts	Tooth of endodontic treatment	Pulp condition	# of sessions	Rescue medication	Irrigation solution	Obturation technique	Endodontic cement for obturation	Time of evaluation of pain
Arslan et al. 2011	4% articaine 1:100.000 epinephrine	Incisors, premolars and molars	n.r.	1	n.r.	5.25 NaOCl+EDTA	Lateral compaction gel	Sealapex	Immediately, 6, 12, 24, 48 and 72 h after treatment
Attar et al. 2008	n.r.	n.r.	Vital or nonvital	n.r.	Paracetamol 500 mg	3 – 6 NaOCl	System B and Obtura	Roth's 801 or AH Plus	Immediately, 6, 12, 18 and 24 h after treatment
Gopikrishna & Parameswaran 2003	n.r.	Molars	Vital or nonvital	2	Paracetamol 650 mg	2.6 NaOCl +saline	n.r.	n.r.	Pretreatment, 4, 8, 12, 24, 48 and 72 h after treatment
Mello 2014	2% lidocaine 1:100.000 epinephrine	Various	Vital or nonvital	1 or 2	Paracetamol 750 mg	Saline+ Chlorexidine gel	Thermo compession	Endomethasone N	Immediately, 4, 6 and 24 h after treatment
Menke et al. 2000	n.r.	n.r.	Vital or nonvital	1	Extra medication	n.r.	n.r.	n.r.	Immediately, 4, 8, 12, 24, 48 and 72 h after treatment
Mokhtari et al. 2016	2% lidocaine 1:80.000 epinephrine	Mandibular Molar	Vital	1	Additional analgesics [n.r.]	2% NaOCl +saline	Lateral compaction	AH 26	At medication time, immediately, 8, 12 and 24 h after treatment
Ramazani et al. 2013	2% lidocaine 1:200.000 epinephrine	Mandibular Molar	Vital	1	Paracetamol 325 mg	2.5% NaOCl	Lateral compaction	AH 26	Pretreatment, 4, 8, 12, 24, 48 and 72 h after treatment

ID, identification; #, number; n.r., not reported; h, hours

The majority of studies performed the endodontic treatment in mandibular molars (6, 15, 44). However, two studies did not standardize the tooth type (3, 42), and two did not report this information (7, 43).

Root canal treatment procedures

In two studies, the authors only included vital teeth (15, 44), and in other four studies, both vital and nonvital teeth were included (6, 7, 42, 43). One study did not report the pulp condition (3). The number of clinical sessions for the endodontic therapy was variable: being only one session (3, 15, 43, 44), two clinical sessions (6), or both depending on the case (7, 42).

Lidocaine 2% was used in three studies (15, 42, 44), but 4% articaine with 1:100.000 epinephrine was also employed (3). This report was missing in three studies (6, 7, 43). The instrumentation protocol used in most of the studies was the crown-down technique (3, 6, 7, 4, 44). One study used the step-back technique (15), and one study did not report this information (43). Sodium hypochlorite in concentrations varying from 2% to 6% was the most predominant irrigation solution used (3, 6, 7, 44), but saline and chlorhexidine gel were employed in one study (42). One study did not report the irrigation solution used (43).

The obturation technique used in three studies was the lateral condensation (3, 15, 44), one used the thermo compression (42), and one used continuous wave (7). Two studies did not describe this item (6, 43). The type of endodontic cement used in obturation in two studies was resin based (15, 44), one used a zinc oxide eugenol (42), one used calcium hydroxide (3), one used a zinc oxide eugenol or resin-based cement (7), and two articles did not report the endodontic cement used (6, 43).

Preoperative analgesia

Ibuprofen concentrations of 200 mg (3), 400 mg (15, 44), and 600 mg (6, 7, 43, 44) were used. All studies used placebo in at least one of the study groups (3, 6, 7, 15, 42–44). The medications used for comparison were placebo (7) and anti-inflammatory drugs such as tenoxicam (3), rofecoxib (6), etodolac (43), indomethacin (15), corticoid dexamethasone (42), and a ginger extract (44).

Five out the seven studies used rescue medication. Extra ibuprofen doses (43) or paracetamol (6, 7, 42, 44) were administered. One study only reported that the patients used additional analgesics without specifying the type of analgesic used (15), and one study did not report this information without specifying the type of analgesic used (3).

Regarding side effects, one out of seven studies reported this information (15), and six did not report it (3, 6, 7, 42–44). The most common side effects reported were giddiness, nausea, constipation, laxity, tinnitus, blurred vision, and somnolence, without significant differences among the medications administered (15).

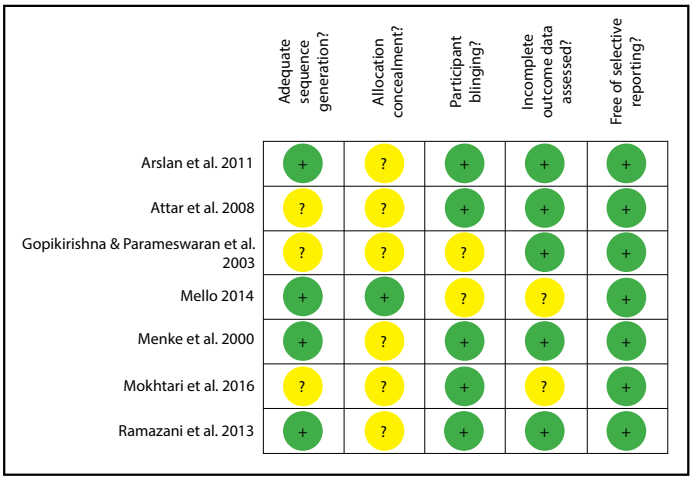

Figure2.SummaryoftheriskofbiasevaluationbasedontheCochrane Collaboration tool

Evaluation of risk of bias

The risk of bias of the selected RCTs is shown in Figure 2. Few studies reported the sequence generation, allocation concealment, and if the examiner and participant were blinded. In summary, all studies were classified as having a high or unclear risk of bias in the key domains.

Meta-analysis

Intensity of pain at 6/8 hours (ibuprofen versus other drugs)

This analysis was based on five studies (3, 6, 15, 42, 44). The standardized mean difference (SMD) was −0.24, with the 95% confidence interval (95% CI) varying from −0.65 to 0.16. This provides evidence that there was not a significant difference in the intensity of pain (p=0.24, Fig. 3). Data were not heterogeneous (chi-squared test, p=0.06; I2=57%; Fig. 3).

Intensity of pain at 24 hours (ibuprofen versus other drugs)

This analysis was based on five studies (3, 6, 15, 42, 44). The SMD was −0.01 (95% CI −0.40 to 0.39), with no significant difference between the groups (p=0.97, Fig. 4). Data were not heterogeneous (chi-square test, p=0.06; I2=55%; Fig. 4).

Intensity of pain at 6/8 hours (ibuprofen versus placebo)

This analysis was based on six studies (3, 6, 7, 15, 42, 44). No significant difference between the groups was detected (p=0.08,

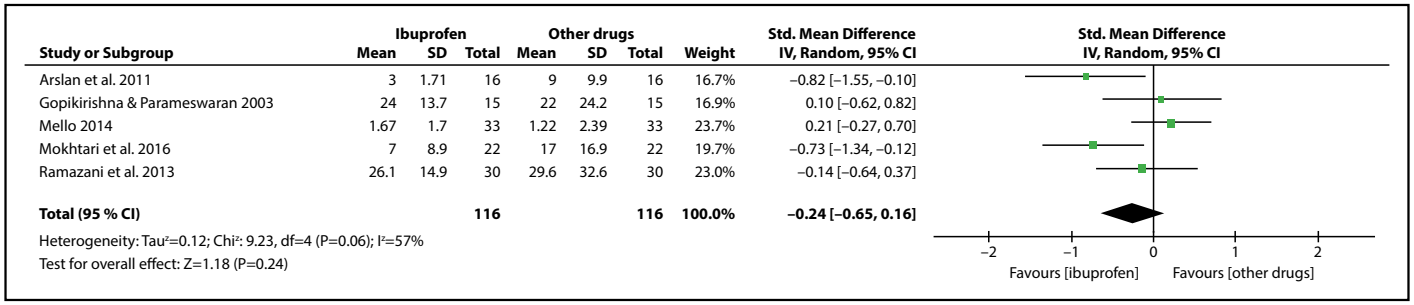

Figure 3. Forest plot of pain intensity at 6/8 h after the endodontic treatment with ibuprofen or other drugs

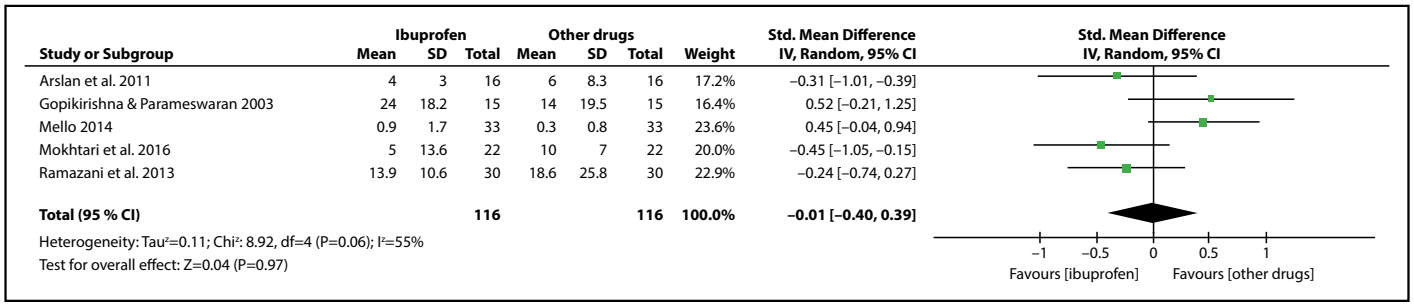

Figure 4. Forest plot of pain intensity at 24 h after the endodontic treatment with ibuprofen or other drugs

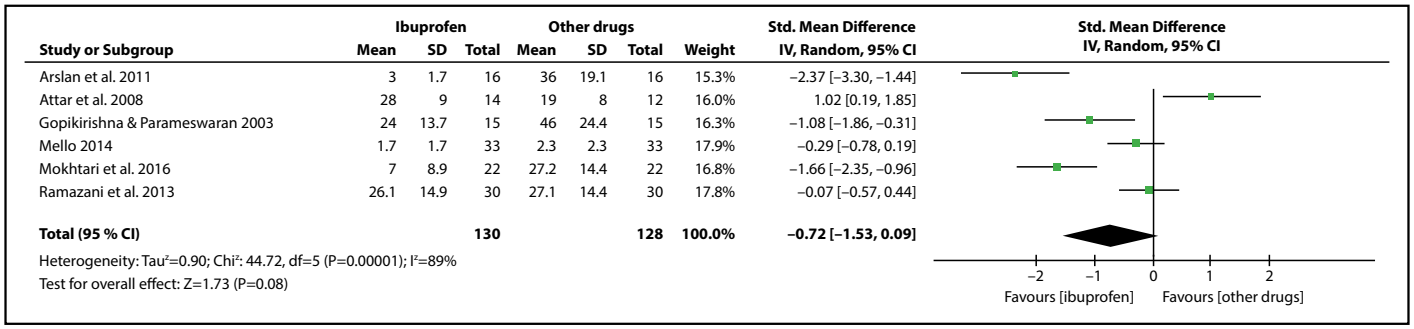

Figure 5. Forest plot of pain intensity at 6/8 h after the endodontic treatment with ibuprofen or placebo

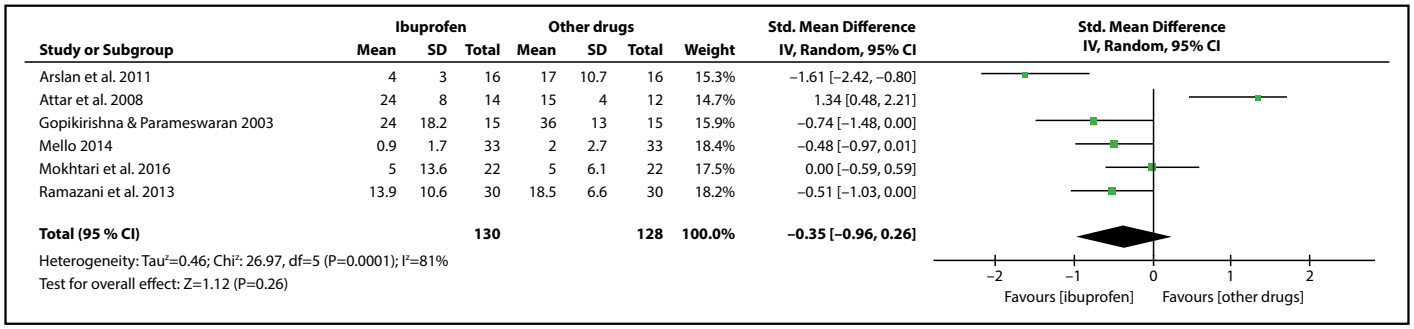

Figure 6. Forest plot of pain intensity at 24 h after the endodontic treatment with ibuprofen or placebo

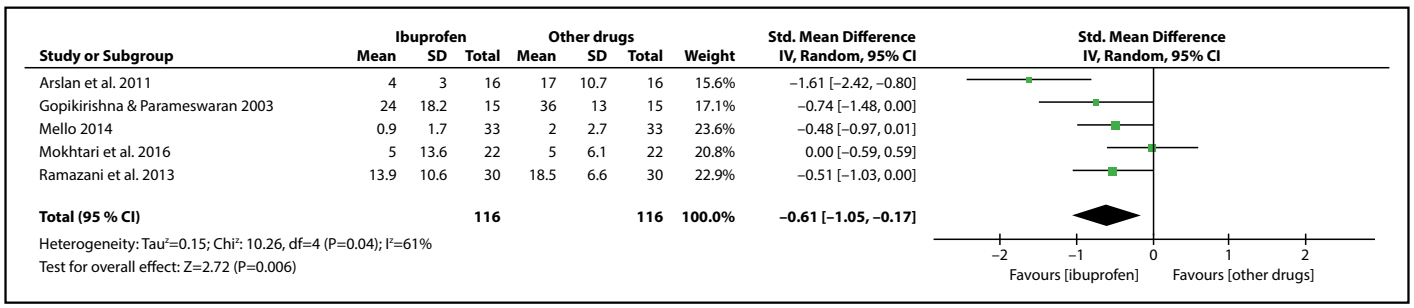

Figure 7. Forest plot of pain intensity at 24 h after the endodontic treatment with ibuprofen or placebo, after sensitivity analysis

Fig. 5) with a −0.72 SMD (95% CI −1.53 to 0.09). Data were heterogeneous (chi-squared test, p<0.00001; I2=89%; Fig. 5).

Intensity of pain at 24 hours (ibuprofen versus placebo)

This analysis was based on six studies (3, 6, 7, 15, 42, 44). The SMD was −0.35, with a 95% CI from −0.96 to 0.26. No significant difference in the intensity of pain between the groups was detected (p=0.26, Fig. 6). Data were heterogeneous (chi-squared test, p<0.0001; I2=81%; Fig. 6).

Sensitivity analysis

To find the cause of heterogeneity for the meta-analysis when ibuprofen was compared to placebo at different times, a sensitivity analysis was performed. At 6/8 hours, we did not identify the causes of the heterogeneity. At 24 hours, the study of Attar et al. (7) was the study responsible for the heterogeneity. When it was removed from the analysis, a significant difference between the groups was observed (SMD −0.67; 95% CI −1.05 to −0.17), favouring ibuprofen (Fig. 7).

Assessment of the quality of evidence

In the summary of findings in Table 4, the whole meta-analysis was graded as low or very low in the quality of evidence. The reasons for downgrading the evidence were that most RCTs were at the unclear risk of bias and imprecision with a high

TABLE 4. Summary of Findings Table

Patient or population: endodontic treatment
Intervention: ibuprofen
Comparison: other drugs/placebo

Outcomes	Anticipated absolute effects* (95% CI)				
	Risk with ibuprofen	Risk with other drugs	Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)
Intensity of pain assessed with: pain scales at 6/8 hours (ibuprofen vs other drugs)	-	SMD -0.24 SD lower (-0.65 lower to 0.16 lower)	-	232 (5 RCTs)	⊕⊕◯◯ LOW[a,c]
Intensity of pain assessed with: pain scales at 24 hours (ibuprofen vs other drugs)	-	SMD -0.01 SD higher (-0.40 lower to 0.39 higher)	-	232 (5 RCTs)	⊕⊕◯◯ LOW[a,c]
Intensity of pain assessed with: pain scales at 6/8 hours (ibuprofen vs placebo)	-	SMD -0.72 SD lower (-1.53 lower to 0.09 higher)	-	258 (6 RCTs)	⊕◯◯◯ VERY LOW[a,b,c]
Intensity of pain assessed with: pain scales at 24 hours (ibuprofen vs placebo)	-	SMD -0.35 SD lower (-0.96 lower to 0.26 higher)	-	258 (6 RCTs)	⊕◯◯◯ VERY LOW[a a,b]
Intensity of pain assessed with: pain scales at 24 hours (ibuprofen vs placebo) (sensitivity analysis)	-	SMD -0.61 SD lower (-1.05 lower to -0.17 higher)	-	232 (5 RCTs)	⊕⊕◯◯ LOW[a,c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; SMD: Standardized mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations
a. Most RCT are at "unclear" risk of bias
b. Statistical heterogeneity
c. High 95% confidence interval, which does not exclude important harm or benefit

95% CI and statistical heterogeneity (for the two meta-analyses of ibuprofen versus placebo).

DISCUSSION

Well-designed RCTs are able to minimize the influence of confounding factors on cause-and-effect relationships when compared to other clinical trial designs; hence, RCTs have a great relevance as a source of evidence (45). The randomization and concealment of allocation prevent the selection bias. The purpose of randomization is to equilibrate patients regarding factors that may or may not be known, so that any other variable, except that under investigation, may explain the differences observed between participants from different groups. Allocation concealment is performed to guarantee that the group assignment of participants is not revealed before implementation. Some methods of allocation concealment include opaque, sealed, and sequentially numbered envelopes or sequentially numbered container (46). Only one out of seven studies report the randomization method and the allocation concealment (42).

Authors usually used the terms such as "randomized groups" or "groups were randomly assigned," without additional information. The method of randomization (such as a computerized random number generator, a random-number table, coin toss, playing dice, etc.) should have been described (47). Blinding is also a key domain in RCTs. It consists in procedures that prevent study participants, operators, or outcome assessors from the knowledge of which intervention is being performed (48). Another common problem noted in the included studies is related to failures to describe who was blinded. Descriptions such as "this study was triple-blind" or "this was a double-blind clinical trial" are worthless, and readers have no way of knowing who was really blinded. Two studies did not report if patients were blinded (6, 42). The incomplete outcome data were poorly described in some studies (15, 42). The studies must describe the number of patients in each period of trial by introducing a flow chart with this information (49). None of the studies had a flow chart, which prevented us to check how many participants were actually included in the data analysis.

The CONSORT statement facilitates the critical interpretation of the results, as it recommends description of some important details of the methodology, such as the study design, the way it was conducted, and the type of analysis used. Additionally, it avoids the omission of possible systematic errors that would

compromise the validity and reliability of the results and, consequently, their applicability within the evidence-based context (18). Most of the studies evaluated did not follow the CONSORT recommendations and prevented us from evaluating important methodological aspects. In face of that, the studies were classified as being at unclear risk of bias.

Although four of eligible studies did not report dispersion measures, we imputed the data based on the coefficient of variation of the other studies. This allowed to meta-analyze the data. However, one of these studies (43) reported pain reduction, instead of the mean pain at different assessment times. For this reason, it was not included the meta-analysis.

Only one study reported the risk of pain, that is, the percentage of patients that had pain after the endodontic therapy (42). This is the reason why we could not meta-analyze the risk of pain data. Although reporting the intensity of pain is very useful, it does not tell the percentage of patients that were kept free of pain during the clinical trial. This should be reported in future studies.

In relation to the intensity of pain, no significant difference between the groups was identified in any of the assessment periods (6/8 or 24 hours), or when ibuprofen was compared with placebo or other drugs. An exception occurred when we performed a sensitivity analysis. A significant difference was found at 24 hours, favouring ibuprofen when the study by Attar et al. (7) was excluded from the analysis. Unfortunately, we could not identify important differences in the sample population of protocols of this study that could be responsible for such a finding.

Considering the differences among studies, it is worth mentioning that there are many factors that account for postoperative pain, and they are quite variable among the eligible studies. 1) The anesthetic agent: Some authors believe that articaine 4% is more effective than lidocaine 2% in inducing anesthesia when used for adjunctive periapical infiltration after an inferior alveolar nerve block (50–55). 2) Single or multiple-visit endodontic therapy: A lower pain has been demonstrated in a single visit (56–59). 3) The irrigation device: The negative apical pressure irrigation device can promote a significant decrease of postendodontic pain intensity when compared to conventional needle irrigation (60, 61). 4) The pulp condition: Teeth with pulp vitality produce a superior risk and intensity of postoperative endodontic pain if compared to necrotic teeth (62). 5) The presence of preoperative pain: A higher preoperative pain intensity is associated with a higher value of postoperative pain (22, 63). 6) Obturation technique: Alonso-Ezpeleta et al. (4) demonstrated that the Thermafil obturation technique showed higher postoperative pain level when compared to cold lateral compaction of gutta-percha and the backfill–Thermafil obturation technique. The probable reason for postoperative pain with the Thermafil technique might be the extrusion of gutta-percha.

In addition to the factors discussed above, specific preoperative factors (old age, sex, molar teeth, mandibular teeth, and the absence of periapical radiolucency) and procedures (radiograph or apex locator working length determination methods, instrumentation, irrigation, reducing the occlusion, and postoperative drugs) were associated with postoperative endodontic pain (64), are possible reasons for the different effect sizes in the different studies.

The drug to which ibuprofen was compared was another source of variation among the studies. A total of six studies compared ibuprofen versus placebo, and four of these studies compared ibuprofen versus NSAIDs.

Although there are published systematic reviews that compared the effect of medications to control postoperative endodontic pain (64, 65), the focus of our review is different. In one of these reviews (65), postoperative pain was evaluated only in patients who had preoperative pain. That is different from this study, which focused on the evaluation of the preoperative medications to control postoperative pain caused by the endodontic therapy. The authors from previous systematic review (65) also included studies that compared association of medications. We evaluated medications separately.

In another systematic review (66), the postoperative pain was evaluated in patients with irreversible pulpitis, which differs from our systematic review that included studies evaluated vital and nonvital teeth. The authors also evaluated postoperative analgesic treatments and drug combination (combination of NSAIDs with acetaminophen, tramadol, or an opioid), which differs from the present systematic review. Furthermore, a meta analysis was performed in the present study, and this was not performed.

CONCLUSION

Results of the present systematic review indicate that there is no clear evidence supporting that preoperative ibuprofen is better than other drugs in reducing the risk and intensity of postendodontic pain.

Disclosures

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