Nonsteroidal Anti-inflammatory Drugs for Managing Postoperative Endodontic Pain in Patients Who Present with Preoperative Pain: A Systematic Review and Meta-analysis

Elizabeth A. Smith, DDS, J. Gordon Marshall, DMD,* Shelley S. Selph, MD, MPH,† Dale R. Barker, DDS,* and Christine M. Sedgley, MDS, MDSc, PhD**

Abstract

Introduction: Nonsteroidal anti-inflammatory drugs (NSAIDs) have been commonly used to treat endodontic postoperative pain. The purpose of this study was to address the following Population, Intervention, Comparator, Outcome, Timing, Study design and setting question: in patients with preoperative pain who undergo initial orthograde endodontic treatment, what is the comparative efficacy of NSAIDS compared with nonnarcotic analgesics or placebo in reducing postoperative pain and the incidence of adverse events. **Methods:** Ovid MEDLINE (1946–December 15, 2015), the Cochrane Database of Systematic Reviews (2005–December 15, 2015), and the Cochrane Central Register of Controlled Trials (to December 15, 2015) were searched using included drugs, indications, and study designs as search terms. Hand searches in texts were also conducted. Two independent reviewers assessed eligibility for inclusion, extracted data, and assessed quality using the risk of bias tool. L'Abbe plots were used for qualitative review. Where applicable, meta-analysis was conducted on the pooled effect size (ES). **Results:** Two thousand two hundred eighty-four studies were identified through the database searches; 405 full-text articles were assessed. Fifteen articles met the inclusion criteria; qualitative analysis revealed all studies had a moderate to high risk of bias. Ibuprofen was the most studied NSAID. The L'Abbe plots showed that NSAIDS are effective at relieving postoperative endodontic pain overall. Meta-analysis showed that ibuprofen 600 mg is more effective than placebo at 6 hours postoperatively (ES = 10.50, P = .037), and ibuprofen 600 mg + acetaminophen 1000 mg combination is more effective than placebo (ES = 34.89, P = .000) but not significantly different than ibuprofen (ES = 13.94, P = .317). Five studies reported patients experiencing adverse events such as drowsiness, dizziness, nausea, and emesis; 2 studies reported that patients experienced no adverse events. **Conclusions:** A combination of ibuprofen 600 mg and acetaminophen 1000 mg is more effective than placebo but not significantly different than ibuprofen 600 mg at 6 hours postoperatively. Ibuprofen 600 mg is more effective than placebo at 6 hours postoperatively; however, there are insufficient data to recommend the most effective NSAID, dose amount, or dose interval for the relief of postoperative endodontic pain of longer duration in patients with preoperative pain. *(J Endod 2017;43:7–15)*

Key Words

Acetaminophen, endodontics, ibuprofen, meta-analysis, nonsteroidal anti-inflammatory drugs, pain, systematic review

Significance

This systematic review provides evidence that ibuprofen and ibuprofen plus acetaminophen combinations provide greater pain relief than placebo after orthograde endodontic treatment. It also emphasizes the need for increased rigor in endodontic pain research.

The primary reason people seek endodontic treatment is for the relief of pain caused by bacterial infection and subsequent inflammation (1). Although pain is diminished after treatment, there may be residual symptoms because of the effects of inflammation. Endodontic treatment includes the management of postoperative pain and symptoms that address both the patient's primary concern and potential long-term complications such as chronic pain (2, 3). A variety of drugs have been used to manage postoperative pain and often include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and combinations of drugs (4).

Pain after endodontic treatment is largely unpreventable. NSAIDs are one of the most recommended classes of pain relievers in dentistry today (5, 6). NSAIDs function by inhibiting the cyclooxygenase enzymes and preventing the generation of new prostaglandin molecules, but they have no effect against existing molecules in circulation (7).

Systematic reviews are a way to synthesize and combine data from numerous studies evaluating a common outcome (6). Holstein and Niederman (8) published a systematic

From the *Department of Endodontology, School of Dentistry and †Pacific Northwest Evidence-based Practice Center, Oregon Health and Science University, Portland, Oregon.

Address requests for reprints to Dr Christine M. Sedgley, Department of Endodontology, School of Dentistry, Oregon Health and Science University, 2730 SW Moody Ave, Portland, OR 97201-5042. E-mail address: sedgley@ohsu.edu

0099-2399/$ - see front matter

http://dx.doi.org/10.1016/j.joen.2016.09.010

review on the use of NSAIDs for treating postoperative endodontic pain in 2002 and found the most effective analgesics were a combination of flurbiprofen and tramadol or a combined regimen of preoperative and postoperative flurbiprofen. The purpose of this systematic review was to update the review from 2002 using studies published over the past 14 years, with a focus on the comparative efficacy of NSAIDs alone or in combination with other analgesics and other non-narcotic drugs for postoperative endodontic discomfort in patients who present with pretreatment pain. This study addresses the following Population, Intervention, Comparator, Outcome, Timing, Study question: in patients with preoperative pain who undergo initial orthograde endodontic treatment, what is the comparative efficacy of NSAIDS alone or in combination with other analgesics compared with placebo or non-narcotic analgesics in reducing postoperative pain and the incidence of adverse events.

Materials and Methods

This systematic review was undertaken using recommended guidelines (9). A review protocol was written and registered with the public registry of systematic reviews PROSPERO (CRD42015019532).

Literature Search

The literature search of the Ovid MEDLINE and Ovid OLDMEDLINE, Ovid MEDLINE In-Process & Other Non-Indexed Citations, EBM Reviews–Cochrane Central Register of Controlled Trials, and EBM Reviews–Cochrane Database of Systematic Reviews included articles published from inception through December 2014. The search criteria included key words for NSAIDs and endodontic postoperative pain. Hand searching was performed on reference lists of relevant textbooks. Gray literature was also searched through www.clinicaltrials.gov. The search was repeated on December 15, 2015.

Randomized controlled trials were included if they enrolled patients who presented with endodontic pain and received a diagnosis of pulpal pathosis necessitating initial nonsurgical endodontic treatment, compared postoperative treatment with an NSAID or other non-narcotic analgesic or placebo, and measured pre- and postoperative pain. Exclusion criteria included nonrandomized studies and systematic reviews, animal studies, the use of a nonendodontic pain model, and treatment that required multiple visits.

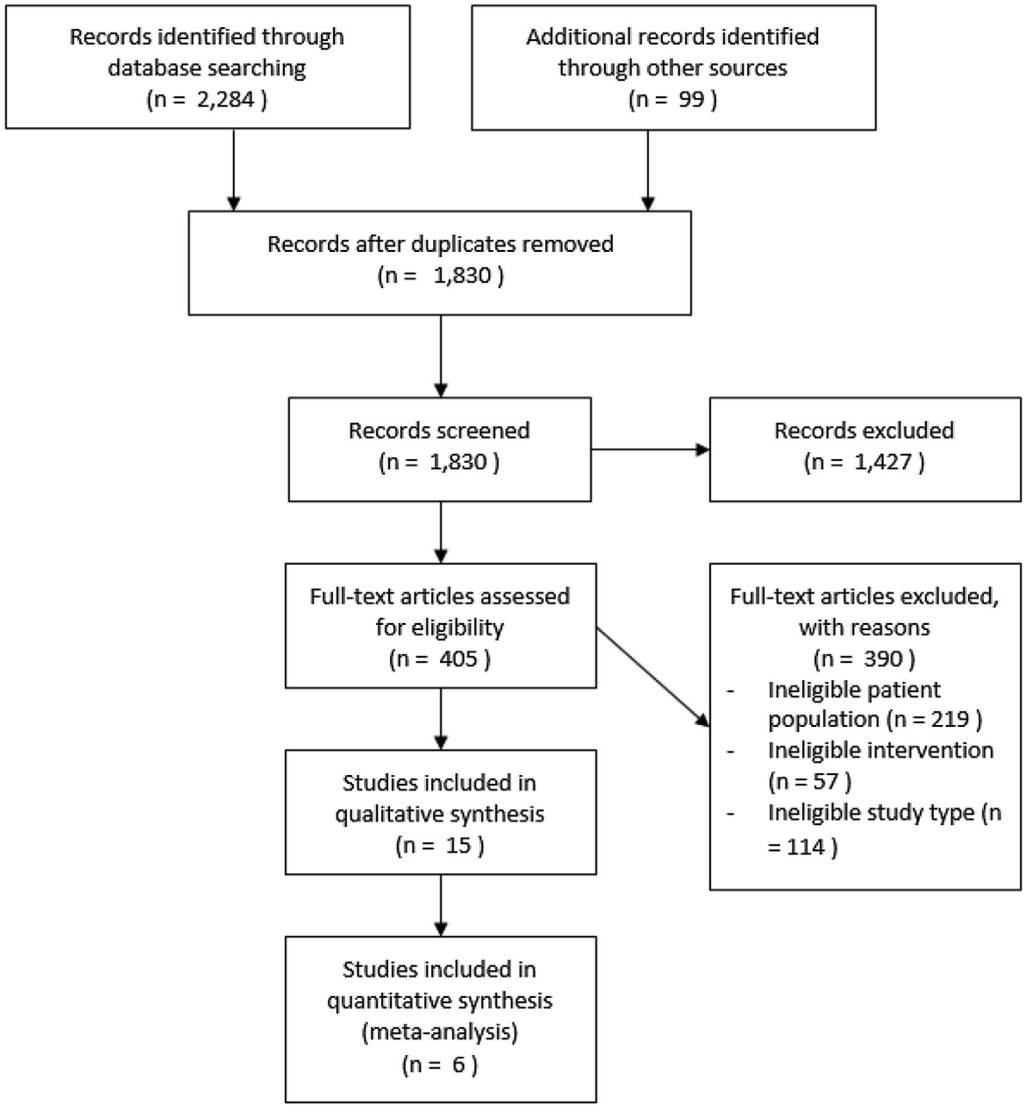

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.

Study Selection, Quality Assessment, and Data Extraction

Two independent reviewers provided evaluations at all stages. Titles and abstracts returned by the initial database search were initially screened. Relevant abstracts were retrieved as full-text articles and read to assess their relevance, and selected studies underwent data extraction. Quality assessment of included studies was performed using the Cochrane risk of bias tool (10). Each study was evaluated as low, moderate, or high risk of bias in the categories of randomization; allocation concealment; and blinding of the participants, providers, and assessors. Any disagreements between evaluators were resolved by a third party. After data abstraction and quality assessment, the strength of evidence was evaluated based on the Agency for Healthcare Research and Quality Evidence-based Practice Centers strength of evidence methodology (11).

Data Extraction and Statistical Analysis

Data were extracted on treatment drugs, dosing, dosing schedules of drug administration, pain measurement, and pain severity. When data graphs and figures were inadequately labeled, jTechDig software (jTechDig, Boston, MA, open source software) was used to identify precise values. All data were converted to a standardized 100-mm visual analog scale (VAS) scale for meta-analysis. L'Abbe plots were derived from the adjusted change in pain relief scores.

Meta-analyses were conducted when appropriate based on the heterogeneity among studies in design, patient population, interventions, and outcomes using the Dersimonian-Laird random effects model with Stata 14 (StataCorp LP, College Station, TX). After meta-analysis, the display r(seES) command (Stata14) was used to retrieve the standard error of the effect size, which was used for indirect analysis, and performed on data that could be related using placebo as a common comparator. When meta-analysis could not be performed, the data were summarized qualitatively.

Results

Summary of Included Studies

Electronic and manual searches identified 2284 studies (Fig. 1). After deduplication, 1731 records remained, and 99 further records were identified through hand searching. Two independent reviewers read 1830 abstracts; 1427 records were excluded in the first pass, and 403 records were retrieved. After the assessment of full texts, 15 articles pertaining to postoperative endodontic pain management with NSAIDs were identified (12–26).

A variety of drugs were included (Table 1). Baseline demographic data were provided by most studies (13–20, 23–26). Those that did provide patient characteristics reported a mean age of 40 years, with a range of 18–80 years (12–14, 17, 19–21, 24, 26). The population was 55% male and 45% female. Two studies reported ethnicity (13, 17), with 83% white patients, 11% black patients, and 6% Hispanic or Asian patients. The mean baseline pain for all studies was 59 on a 100-mm VAS, with a range from 12.85 to 85.47. Six studies categorized treated teeth by tooth type and arch type and reported an equal distribution of incisors, premolars, and molars; there were 52% maxillary teeth and 48% mandibular teeth (12, 14, 17, 19, 24, 26). Characteristics of the included studies are provided in Table 2.

Qualitative Review

Major differences between the studies selected included treatment drugs, dose of medication, population type, sample size, preoperative diagnosis, time of drug administration, and time of outcome variable measurement. The overall quality of the articles was poor, with 8 of the 15 studies having a high risk of bias. Sequence generation, allocation concealment, and blinding of parties was often alluded to but not specified and was assessed as unclear (Fig. 2). There was low strength of evidence to recommend ibuprofen plus acetaminophen over placebo and low strength of evidence to recommend ibuprofen over placebo. There was insufficient evidence to draw conclusions regarding the best non-narcotic analgesic regimen for postoperative endodontic treatment pain overall (Table 3).

L'Abbe plots were generated for all treatment drugs at time points 6, 12, and 24 hours postoperatively in Supplemental Figures S1–S3. The L'Abbe plots illustrate that NSAIDs are effective at relieving postoperative endodontic pain. The top 5 drugs in terms of greatest decrease in pain relative to placebo are found in Figure 3. Ibuprofen, flurbiprofen, and ibuprofen plus acetaminophen combinations were represented in multiple trials. General observations include a trend toward increased pain from 6 to 12 hours in all groups, which may represent the peak pain levels postanesthesia.

Eight studies did not report adverse events. Of the 7 that did publish details on harms encountered during the study, 2 reported no side effects noted by patients taking placebo, tenoxicam 20 mg, ibuprofen 200 mg, meloxicam 15 mg, and piroxicam 20 mg (13, 22). The remaining 5 studies classified the side effects as pertaining to the central nervous system or the gastrointestinal

TABLE 1. Included Drugs

Drug	Recommended daily dosing for mild to moderate pain	Half-life	Duration	Maximum daily dose
Acetaminophen	650 mg every 4–6 h	2 hours	4–6 hours	3250 mg (OTC recommendation)
Ibuprofen	400 mg every 6–8 h	2 hours	6–8 hours	3200 mg
Aspirin	325–650 mg every 4–6 h	3 hours	4–6 hours	4000 mg
Naproxen	500 mg every 12 h	12–17 hours	<12 hours	1250 mg on day 1 and then 1000 mg
Flurbiprofen	100 mg every 12 h	5.7 hours	—	300 mg
Ketoprofen	50 mg every 6 h	2–4 hours	6 hours	300 mg
Ketorolac	20 mg initial dose and then 10 mg every 4–6 h	2–6 hours	4–6 hours	40 mg
Meloxicam	7.5 mg every day	15–20 hours	—	15 mg
Piroxicam	20 mg every day	50 hours	—	20 mg
Etodolac	300 mg every 8–12 h	6.4 hours	5–6 hours	1200 mg
Tenoxicam*				
Rofecoxib*				

OTC, over-the-counter.

*Not available in the US.

TABLE 2. Characteristics of Included Studies

Author, year	Treatment groups (*n*)	Time of delivery	Time of pain evaluation (hours postoperative)	Outcome variable	Inclusion criteria	Treatment*	Escape drug	Baseline VAS†	6 H VAS†	12 H VAS†	24 H VAS†
Arslan, 2011 (12)	Placebo (16) Tenoxicam 20 mg (16) Ibuprofen 200 mg (16)	PRE	B, 0, 6, 12, 24, 48, 72	100-mm VAS	50 VAS, DNS	NS-RCT	Extra dose of the treatment medication	85.5 82.6 83.2	35.1 7.92 2.83	19.8 9.62 15.3	16.4 4.09 3.49
Attar, 2008 (13)	Placebo (12) Ibuprofen 600-mg tablet (14) Ibuprofen 600-mg liqui-gel (13)	PRE	B, 0, 6, 12, 18, 24	100-mm VAS, 170-mm HPC, VAS-C	30 VAS, DNS	NS-RCT	Tylenol ES (McNeil Consumer Healthcare Division, Fort Washington, PA) (500 mg)	65.6 64.7 65.9	17.9 26.2 28.1	20.4 24 31.8	11.9 23.5 21.6
Baradaran, 2014 (14)	Placebo (15) Ibuprofen 400 mg (15) Ibuprofen 400 mg + alprazolam 0.5 mg (15)	POST	B, 4, 6, 12, 24, 48, 72	10-cm VAS	SIP	Two visit NS-RCT	Acetaminophen 650 mg	82.0 76.0 82.0	38.0 30.0 23.3	36.0 25.3 23.3	15.8 10.7 13.3
Battrum, 1996 (15)	Placebo (10) Ketorolac 10 mg PO (10)	Every 6 h	B, 6, 24	100-mm VAS, 6 PIS, 4 VPR	SIP, NEC, SAP	NS-RCT	Ketorolac 10 mg	12.9 40.2	14.7 5.14	—	12.9 5.14
Doroschak, 1999 (16)	Placebo (12) Flurbiprofen 50 mg (12)	Every 6 h	B, 6, 24, 36, 48, 60	4 PIS, 100-mm VAS, HP	30 VAS, SIP, NEC, NORM, AAP, SAP, AAA	Pulpectomy	Acetaminophen 650 mg	66.2 70.6	42.8 36.6	—	26 20
Flath, 1987 (17)	Placebo (29) Preoperative placebo, postoperative flurbiprofen 100 mg (30) Pre-operative flurbiprofen 100 mg, post-operative placebo (28) Flurbiprofen (29)	PRE, 3 h POST	B, 3, 7, 24, hours after initial dose	4 PIS, 100-mm VAS, 5 VPR	DNS	Pulpectomy	—	48.97 37.06 33.09 41.03	—	—	30 11.91 18.53 6.18
Gopikrishna, 2003 (18)	Placebo (15) Rofecoxib 50 mg (15) Ibuprofen 600 mg (15)	PRE	B, 4, 8, 12, 24, 48, 72	100-mm VAS	30 VAS, DNS	Pulpectomy	Acetaminophen 650 mg	72.6 76.3 75.1	—	55.4 21.7 45.9	35.3 13.1 25.0
Mehrvarzfar, 2012 (19)	Placebo (25) Naproxen 500 mg (25) Ibuprofen 200 mg + acetaminophen 325 mg + 40 mg caffeine (25)	POST	B, 6, 12, 24	10-point VAS	SIP, NORM	Pulpectomy	—	4.7 5.8 4.8	4.8 0.8 0.6	3.7 0.5 0.7	3.2 0.7 0.4
Menhinick, 2004 (20)	Placebo (19) Ibuprofen 600 mg (20) Ibuprofen 600 mg + acetaminophen 1000 mg (18)	PRE	B, 1, 2, 3, 4, 6, 8	100-mm VAS	50 VAS, SIP, NEC, NORM, SAP, AAP	Pulpectomy	Acetaminophen 300 mg + codeine 30 mg	80.0 69.0 81.0	35.8 20.8 0.0	—	—
Nekoofar, 2003 (21)	Placebo (17) Meloxicam 15 mg (17) Piroxicam 20 mg (17)	POST	B, 8, 24	9-cm VAS	5-cm VAS. DNS	NS-RCT	—	6.4 7.3 6.7	—	—	1.2 1.0 1.9
Rogers, 1999 (22)	Placebo (12) Ibuprofen 600 mg (12)	POST	B, 6, 12, 24, 48	150-mm VAS	SIP, normal pulp	NS-RCT	—	23.6 28.4	39.4 28.8	28.3 22.1	18.3 12.5

Ryan, 2008 (23)	Placebo (14)	PRE, every 6 h	B, 0, 6, 12, 18, 24	100-mm VAS	30 VAS, SIP, NEC	NS-RCT	—		70.7	49.5	47.9	27.4
	Ibuprofen 600 mg (15)								68.0	17.0	18.2	12.4
Sethi, 2014 (24)	Etodolac 400 mg (19)	PRE, every 6 h	B, 0, 6, 12, 18, 24 hours after RCT	10-cm VAS	3-cm VAS, SIP	NS-RCT	Ibuprofen 600 mg		62.6	25.3	25.8	26.8
	Ketorolac 10 mg PO (19)								61.6	5.3	4.2	4.2
Torabinejad, 1994 (25)‡	Placebo (53)	POST, every 6 h	B, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72	Modified 90-mm VAS	DNS	NS-RCT	—		7.6	4.9	3.5	2.4
	Salicylic acid 650 mg (50)								8.44	2.79	1.77	2.05
	Acetaminophen 650 mg (57)											
	Ibuprofen 400 mg (57)											
	Ketoprofen 50 mg (53)											
	Acetaminophen 325 mg + codeine 60 mg (48)											
Wells, 2011 (26)	Ibuprofen 600 mg (36)	POST, every 6 h	B, 1, 24, 48, 72, 96, 120	170-mm HP VAS	SAP	NS-RCT	Hydrocodone 5 mm + acetaminophen 500 mg		130.1	—	—	62.7
	Ibuprofen 600 mg + acetaminophen 1000 mg (35)								118.3			54.6

3-cm VAS, pain ≥3 on a 10-cm VAS; 5-cm VAS, pain ≥5 on a 9-cm VAS; 30 VAS, pain ≥30 on 100-mm VAS; 50 VAS, pain ≥50 on 100-mm VAS; AAA, acute apical abscess; AAP, asymptomatic apical periodontitis; B, baseline; DNS, diagnoses not specified; HPC, Heft Parker categoric scale; NEC, pulpal necrosis; NORM, normal periapical tissues; PIS, pain intensity scale; POST, postoperative dose; SAP, symptomatic apical periodontitis; SIP, symptomatic irreversible pulpitis; VAS, visual analog scale; VAS-C, visual analog scale–categoric; VPR, verbal pain relief scale.

*VAS scores are for patients with endodontic pain and a diagnosis of pulpal pathosis necessitating initial nonsurgical endodontic treatment and who underwent pulpectomy/cleaning and shaping or completion of single-visit RCT.

†VAS scores have been converted to a 100-mm scale.

‡For Torabinejad (25), data are available for placebo and ketoprofen groups only.

system. Other side effects were noted (eg, xerostomia, rash, and wheezing) (Table 4). In studies that analyzed the side effects by treatment group, the placebo group had the same or greater incidence of side effects as at least one of the experimental drug groups (17–19, 21, 26).

Nine studies reported supplying or recommending a rescue medication or "escape drug" including varying doses of acetaminophen, acetaminophen 300 mg + codeine 30 mg, and acetaminophen 500 mg + hydrocodone 5 mg. Seven studies reported that patients needed supplemental medication or used the rescue medication (Table 4).

Quantitative Review

Several studies included a measure of variance, facilitating the inclusion of these data in a meta-analysis (13, 14, 16–21, 23–26). Five of the 15 studies were included in a meta-analysis (18–20, 23, 26). The remaining studies did not provide sufficient information to be included in a meta-analysis or were dissimilar to the included studies in population enrolled or intervention.

Meta-analysis indicated a trend for greater pain reduction on the VAS with ibuprofen compared with placebo at 6 hours after treatment (mean difference = 10.5; 95% confidence interval, 0.61–20.39; $I^2 = 62\%$) (Fig. 4*A*). In an indirect analysis of ibuprofen 600 mg versus naproxen 500 mg using the placebo group as a common comparator at 6 hours post-treatment, naproxen 500 mg reduced pain scores on the VAS 30.5 points more than ibuprofen 600 mg ($P = .052$). An indirect analysis of ibuprofen 600 mg and ketoprofen 50 mg at 6 hours showed that ketoprofen 50 mg reduced pain scores on the VAS 22.28 points more than ibuprofen 600 mg ($P = .156$); however, neither of these were significant.

Ibuprofen plus acetaminophen combinations were significantly more effective than placebo at 6 hours; ibuprofen plus acetaminophen reduced pain by 34.89 VAS points more than placebo ($P = .00$, $I^2 = 20.8\%$) (Fig. 4*B*). Comparing ibuprofen plus acetaminophen with ibuprofen at all time points, ibuprofen plus acetaminophen reduced pain by 13.94 VAS points more than ibuprofen, but it was not statistically significant ($P = .317$, $I^2 = 83.4\%$) (Fig. 4*C*).

Discussion

The goal of this study was to consolidate the available information on NSAID use for treating postoperative endodontic pain. To the authors' knowledge, this is the first systematic review of NSAID use for endodontic purposes that focuses on NSAIDs and nonopioid analgesic combination drugs. In patients with preoperative pain who undergo initial orthograde endodontic treatment, ibuprofen was found to be the most studied NSAID in the endodontic literature and was found to be significantly more effective than placebo at relieving pain 6 hours after treatment. The combination of ibuprofen plus acetominophen was also found to be significantly more effective than placebo but not significantly more effective than ibuprofen alone at reducing pain 6 hours after treatment. However, the available evidence on nonsteroidal pain relief after endodontic treatment was generally sparse, of low quality, and considered insufficient to draw broad conclusions regarding the comparative effectiveness of NSAIDS. Additional research comprised of larger, well-conducted randomized trials comparing one NSAID with another is needed to reach definitive conclusions.

Historically, acetaminophen has not been classified as an NSAID, and the mechanism for its analgesic action has been unknown (27). New evidence suggests that, similar to NSAIDS, acetaminophen functions in part by blocking prostaglandin synthesis through the inhibition

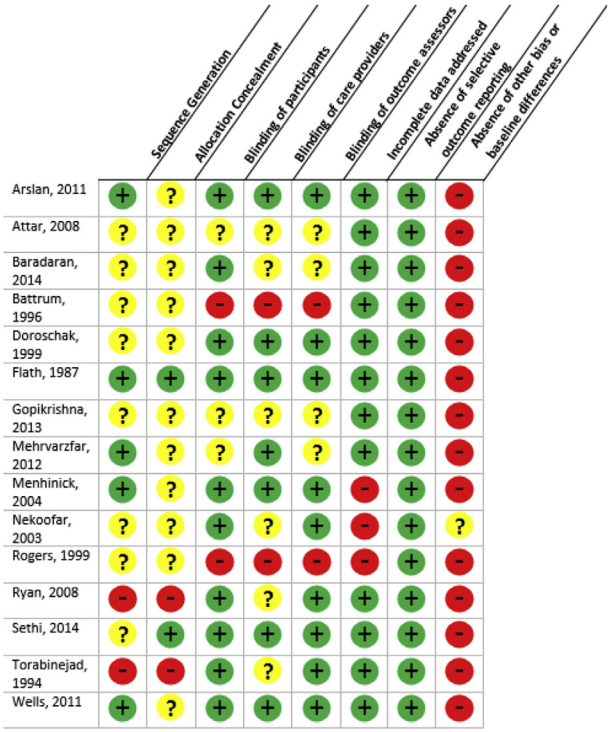

Figure 2. Risk of bias assessment.

of cyclooxygenase 1 and cyclooxygenase 2, with additional activity linked to the central nervous system via endogenous neurotransmitter systems (27, 28). Acetaminophen is considered to have fewer gastrointestinal and cardiovascular side effects than NSAIDs. Its number needed to treat is higher than other NSAIDs, with acetaminophen 500 mg having a number needed to treat of 3.5 on the Oxford League table. Recent evidence suggests that combining ibuprofen and acetaminophen has a greater analgesic effect than either drug alone (29).

This information provides growing evidence that ibuprofen and ibuprofen plus acetaminophen combinations are effective at relieving pain of endodontic origin in the hours after root canal therapy. Previously, the core of the pain literature applied to endodontics came from an oral surgery or medical pain perspective, which might not be germane to pain of endodontic origin. A patient needing root canal treatment may have had preexisting pain for an extended duration and that pain may have undergone centralization and progressed from acute to chronic (30, 31). Analgesic drug regimens that are effective in cases of acute pain may not be as helpful in cases of chronic pain. The endodontic pain studies looked at a variety of NSAIDs separately but rarely compared them with each other. In addition to differences in the quality of pain, analgesic research studies using an oral surgery model tend to have different baseline population characteristics than for an endodontic model; patients seeking third molar extraction are more likely to be young and healthy and have no or mild preoperative pain.

There is pharmacologic evidence that the combination of ibuprofen and acetaminophen is better than either drug alone for pain relief. Ibuprofen and acetaminophen are synergistic rather than merely additive according to a recent report by Miranda et al (32). The findings by Miranda et al also bring to light other NSAIDs that might benefit from coadministration with acetaminophen, and it may be worth comparing their efficacy with ibuprofen/acetaminophen; a combination with significant synergy may outperform ibuprofen.

Ibuprofen plus acetaminophen combinations were not more effective than ibuprofen alone (20, 26), but they were more effective than placebo (19, 20). The 2 studies that compared ibuprofen plus acetaminophen with ibuprofen do not agree; this may be caused by differences in the inclusion criteria regarding the baseline diagnosis. One of the 2 studies that compared ibuprofen plus acetaminophen with placebo (19) actually studied a combination of ibuprofen plus acetaminophen plus caffeine 40 mg (Novafen; Brown & Burk, Richmond, UK). In the present review, it was determined that Novafen could be included in the meta-analysis because of findings from the Cochrane review that doses of caffeine less than 100 mg have no additional benefit to analgesics (33).

The inclusion criteria were designed to identify studies that analyze analgesic treatment groups in patients for whom relief of postoperative endodontic pain that is expected to be moderate to severe and for whom pain relief is more urgently required. The exclusion criteria were designed to eliminate studies that did not adjust for confounding factors that can attenuate postoperative pain. An example of this is in the number of treatment visits. The number of treatment visits does not impact postoperative pain (1), but the stage of treatment does; there is more postoperative pain after cleaning and shaping of the root canal system than after obturation of the root canal system (25).

Several studies were included (12–14, 18–21, 23, 24, 26) that were not included in the previous systematic review (8). It should be noted that certain NSAIDS in included studies are no longer available in the United States (Table 1) (eg, rofecoxib, a

TABLE 3. Strength of Evidence for Postoperative Pain Reduction

Study set	Domains					Grade for strength of evidence
	Number of studies and participants	Study limitations	Directness	Consistency	Precision	
Ibuprofen 600 mg versus placebo	3 RCTs n = 98	High	Direct	Consistent	Imprecise	Low
Ibuprofen 600 mg versus Ibuprofen 600 mg plus acetaminophen 1000 mg	2 RCTs n = 109	High	Direct	Inconsistent	Imprecise	Insufficient
Ibuprofen 600 mg plus acetaminophen 1000 mg versus placebo	2 RCTs n = 87	High	Direct	Consistent	Imprecise	Low
Indirect analysis of naproxen 500 mg to ibuprofen 600 mg	4 RCTs n = 148	High	Indirect	Inconsistent	Imprecise	Insufficient
Indirect analysis of ketoprofen 50 mg to ibuprofen 600 mg	4 RCTs n = 204	High	Indirect	Inconsistent	Imprecise	Insufficient
Overall data set	15 RCTs n = 1107	High	Direct	Inconsistent	Imprecise	Insufficient

Study limitations, high, medium, or low; Directness, direct or indirect; Consistency, consistent, inconsistent, or unknown; Precision, precise or imprecise; Strength of evidence, high, medium, low, or insufficient.

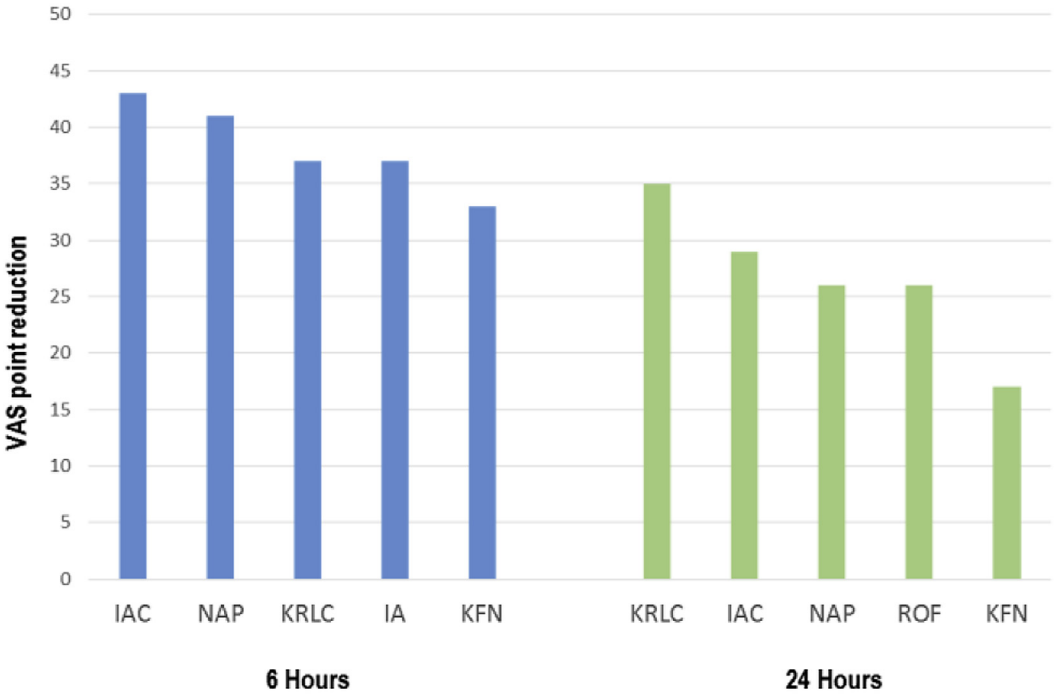

Figure 3. Efficacy of drugs relative to placebo by VAS point reduction.

cyclooxygenase 2 NSAID was withdrawn from the market in the United States in 2004 because of reports of serious heart disease after use [23]). This is also the first time NSAIDs used in alleviating postoperative endodontic pain have been subjected to a quantitative comparison and meta-analysis.

The most obvious limitation of this review is the small number of included studies and that the sample size of all the included studies available for meta-analysis was small, ranging from $n = 12$ to $n = 36$. The scarcity of studies available in the endodontic literature is a severe limitation. Additionally, trial authors often did not report a statistical measure of postoperative pain variability such as standard deviation or confidence limits, which made their inclusion in meta-analyses difficult. Other limitations include the significant heterogeneity in the included studies; the trials differed in the timing of drug administrations, the dose, and the time after administration when the effect was measured. For example, although Attar et al (13) administered ibuprofen liqui-gel and tablet forms at approximately 15 and 30 minutes, respectively, before accessing

TABLE 4. Incidence of Adverse Events

Adverse events	Drugs involved	References
None experienced	Placebo Tenoxicam 20 mg Ibuprofen 200 mg	12, 21
Not reported by study		13, 14, 15, 18, 19, 22, 23, 26
GI	Placebo Flurbiprofen 50 mg, 100 mg Ibuprofen 400 mg, 600 mg Ibuprofen 600 mg + acetaminophen 1000 mg Etodolac 400 mg Salicylic acid 650 mg Ketoprofen 50 mg	16, 17, 20, 24, 25
CNS	Placebo Flurbiprofen 50 mg, 100 mg Ibuprofen 400 mg, 600 mg Ibuprofen 600 mg + acetaminophen 1000 mg Etodolac 400 mg Ketorolac 10 mg Salicylic acid 650 mg Ketoprofen 50 mg	16, 17, 20, 24, 25
Other	Placebo Flurbiprofen 50 mg, 100 mg Ibuprofen 600 mg	16, 17, 20

GI, gastrointestinal side effects such as nausea, emesis, and dyspepsia; CNS, central nervous system side effects such as sedation, light-headedness, headache, and euphoria; Other, side effects such as xerostomia, "felt warm," tachycardia, "itchy," sweating, rash, wheezing, and tightness in chest.

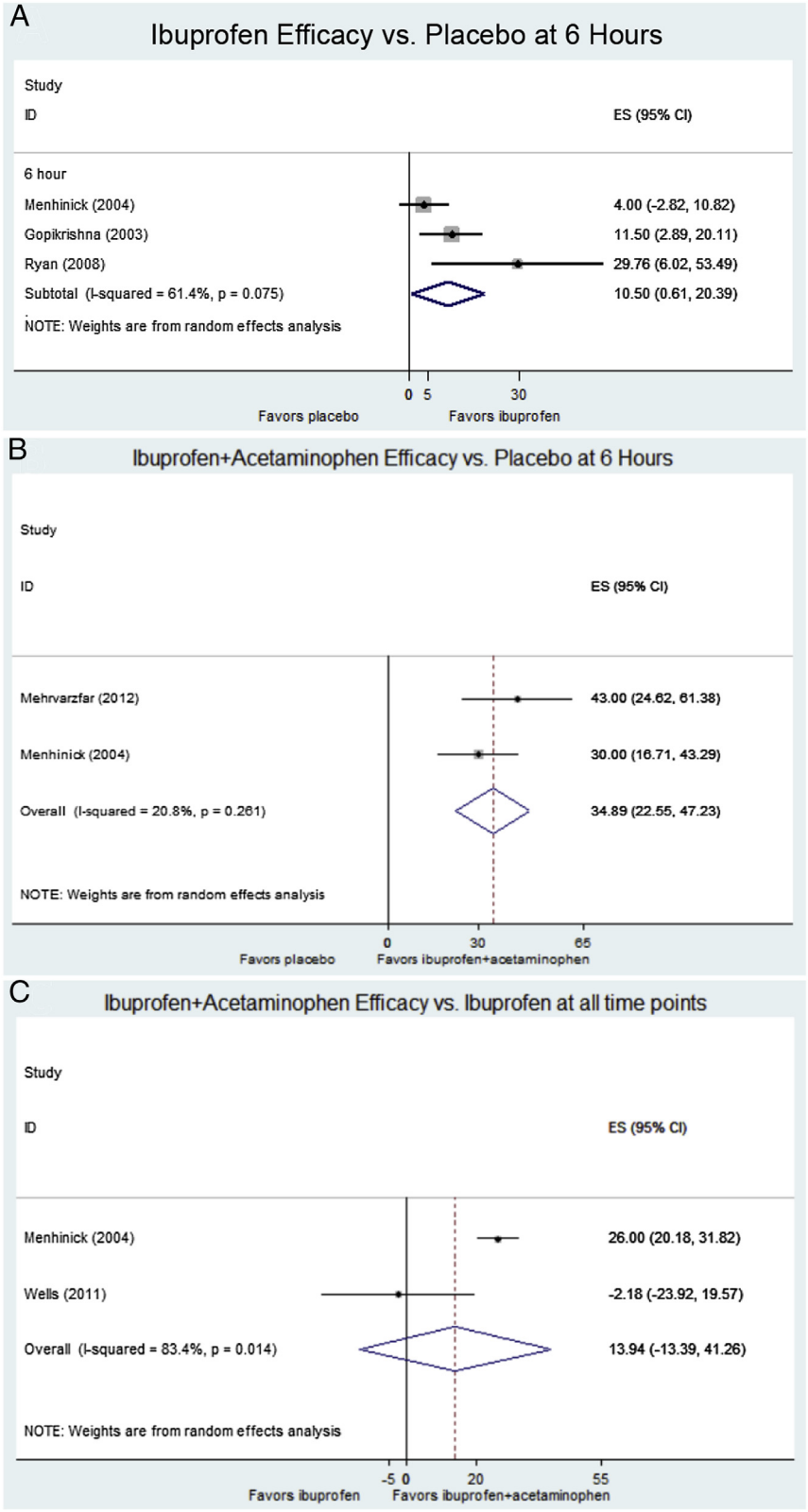

Figure 4. Meta-analysis. Forest plots of (*A*) ibuprofen versus placebo at 6 hours, (*B*) ibuprofen + acetaminophen versus placebo at 6 hours, and (*C*) ibuprofen + acetaminophen versus ibuprofen at all time points.

and instrumenting the root canal, there was much heterogeneity and an absence of standardization regarding the timing of pretreatment and post-treatment drug delivery.

This review highlights some of the needs for future endodontic pain research. Primarily, additional studies are needed that analyze endodontic pain, with larger sample sizes for increased statistical

power. The latest study to be published in a recognized peer-reviewed endodontic journal was Mehrvarzfar et al (19), which was published in 2012. Basic standards for materials and methods need to be implemented that make logical sense and match clinical practice; this includes determining a standard on the clock dose regimen to be a prophylactic dose and a maintenance dose every 6 hours. Improved standards also include measuring pain relief at regular intervals for at least 3 days; Genet et al (34) found that severe postoperative pain was usually reduced to a tolerable level within 3 days. The patients included in future randomized controlled trials should have moderate to severe preoperative pain and a consistent preoperative diagnosis that includes periapical symptoms.

Conclusion

As it stands, the dental literature lacks specificity in its reporting and clarity in its results. Ibuprofen is the most studied NSAID, which at a dose of 600 mg is more effective at relieving pain than placebo at 6 hours after endodontic treatment. Ibuprofen 600 mg + acetaminophen 1000 mg is significantly more effective than placebo at 6 hours. There is low strength of evidence to recommend ibuprofen or ibuprofen plus acetaminophen over placebo. Based on preliminary information, ketoprofen 50 mg and naproxen 500 mg might be more effective than ibuprofen 600 mg at 6 hours postoperative. At this time, there are insufficient data to recommend the most effective NSAID, dose amount, or dose interval for relieving postoperative endodontic pain in patients with preoperative pain.

Acknowledgments

Supported by the OHSU Department of Endodontology Les Morgan Endowment Fund and a resident research grant from the American Association of Endodontists Foundation.

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 (http://dx.doi.org/10.1016/j.joen.2016.09.010).

References

1. O'Keefe EM. Pain in endodontic therapy: preliminary study. J Endod 1976;2:315–9.
2. Polycarpou N, Ng YL, Canavan D, et al. Prevalence of persistent pain after endodontic treatment and factors affecting its occurrence in cases with complete radiographic healing. Int Endod J 2005;38:169–78.
3. Nixdorf DR, Moana-Filho EJ, Law AS, et al. Frequency of persistent tooth pain after root canal therapy: a systematic review and meta-analysis. J Endod 2010;36:224–30.
4. Whitten BH, Gardiner DL, Jeansonne BG, Lemon RR. Current trends in endodontic treatment: report of a national survey. J Am Dent Assoc 1996;127:1333–41.
5. Yingling NM, Byrne BE, Hartwell GR. Antibiotic use by members of the American Association of Endodontists in the year 2000: report of a national survey. J Endod 2002;28:396–404.
6. Mulrow CD. Rationale for systematic reviews. BMJ 1994;309:597–9.
7. Rainsford KD. Anti-inflammatory drugs in the 21st century. Subcell Biochem 2007;42:3–27.
8. Holstein A, H K, Niederman R. Evaluation of NSAIDS for treating post-endodontic pain, a systematic review. Endod Topics 2002;3:3–13.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6:e1000100.
10. Higgins JPT, Green S., eds Table 8.5.a: The Cochrane Collaboration's tool for assessing risk of biasohr. Available at: http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm. Accessed March 20, 2015.
11. Berkman ND, Lohr K, Ansari M, et al. *Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update*. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
12. Arslan H, Topcuoglu HS, Aladag H. Effectiveness of tenoxicam and ibuprofen for pain prevention following endodontic therapy in comparison to placebo: a randomized double-blind clinical trial. J Oral Sci 2011;53:157–61.
13. Attar S, Bowles WR, Baisden MK, et al. Evaluation of pretreatment analgesia and endodontic treatment for postoperative endodontic pain. J Endod 2008;34:652–5.
14. Baradaran M, Hamidi MR, Moghimi Firoozabad MR, et al. Alprazolam role in the analgesic effect of ibuprofen on postendodontic pain. Caspian J Intern Med 2014;5:196–201.
15. Battrum D, Gutmann J. Efficacy of ketorolac in the management of pain associated with root canal treatment. J Can Dent Assoc 1996;62:36–42.
16. Doroschak AM, Bowles WR, Hargreaves KM. Evaluation of the combination of flurbiprofen and tramadol for management of endodontic pain. J Endod 1999;25:660–3.
17. Flath RK, Hicks ML, Dionne RA, Pelleu GB Jr. Pain suppression after pulpectomy with preoperative flurbiprofen. J Endod 1987;13:339–47.
18. Gopikrishna V, Parameswaran A. Effectiveness of prophylactic use of rofecoxib in comparison with ibuprofen on postendodontic pain. J Endod 2003;29:62–4.
19. Mehrvarzfar P, Abbott PV, Saghiri MA, et al. Effects of three oral analgesics on postoperative pain following root canal preparation: a controlled clinical trial. Int Endod J 2012;45:76–82.
20. Menhinick KA, Gutmann JL, Regan JD, et al. The efficacy of pain control following nonsurgical root canal treatment using ibuprofen or a combination of ibuprofen and acetaminophen in a randomized, double-blind, placebo-controlled study. Int Endod J 2004;37:531–41.
21. Nekoofar MH, Sadeghipanah M, Dehpour AR. Evaluation of meloxicam (A cox-2 inhibitor) for management of postoperative endodontic pain: a double-blind placebo-controlled study. J Endod 2003;29:634–7.
22. Rogers MJ, Johnson BR, Remeikis NA, BeGole EA. Comparison of effect of intracanal use of ketorolac tromethamine and dexamethasone with oral ibuprofen on post treatment endodontic pain. J Endod 1999;25:381–4.
23. Ryan JL, Jureidini B, Hodges JS, et al. Gender differences in analgesia for endodontic pain. J Endod 2008;34:552–6.
24. Sethi P, Agarwal M, Chourasia HR, Singh MP. Effect of single dose pretreatment analgesia with three different analgesics on postoperative endodontic pain: a randomized clinical trial. J Conserv Dent 2014;17:517–21.
25. Torabinejad M, Cymerman JJ, Frankson M, et al. Effectiveness of various medications on postoperative pain following complete instrumentation. J Endod 1994;20:345–54.
26. Wells LK, Drum M, Nusstein J, et al. Efficacy of Ibuprofen and ibuprofen/acetaminophen on postoperative pain in symptomatic patients with a pulpal diagnosis of necrosis. J Endod 2011;37:1608–12.
27. Aminoshariae A, Khan A. Acetaminophen: old drug, new issues. J Endod 2015;41:588–93.
28. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. Paediatr Anaesth 2008;18:915–21.
29. Merry AF, Gibbs RD, Edwards J, et al. Combined acetaminophen and ibuprofen for pain relief after oral surgery in adults: a randomized controlled trial. Br J Anaesth 2010;104:80–8.
30. Nasri-Heir C, Khan J, Benoliel R, et al. Altered pain modulation in patients with persistent postendodontic pain. Pain 2015;156:2032–41.
31. Nixdorf DR, Law AS, Lindquist K, et al. Frequency, impact, and predictors of persistent pain after root canal treatment: a national dental PBRN study. Pain 2016;157:159–65.
32. Miranda HF, Puig MM, Prieto JC, Pinardi G. Synergism between paracetamol and nonsteroidal anti-inflammatory drugs in experimental acute pain. Pain 2006;121:22–8.
33. Derry CJ, Derry S, Moore RA. Caffeine as an analgesic adjuvant for acute pain in adults. Cochrane Database Syst Rev 2012;3:CD009281.
34. Genet JM, Wesselink PR, Thoden van Velzen SK. The incidence of preoperative and postoperative pain in endodontic therapy. Int Endod J 1986;19:221–9.