TITLE: Ketorolac for Pain Management: A Review of the Clinical Evidence

DATE: 30 June 2014

CONTEXT AND POLICY ISSUES

Non-steroidal anti-inflammatory drugs (NSAIDs) play an important role in the pain management in various clinical conditions such as headaches, menstrual disorders, postoperative pain, spinal and soft tissue pain, rheumatoid arthritis (RA), osteoarthritis (OA), and ankylosing spondylitis (AS) by blocking cyclooxygenase (COX) enzymes that are needed to produce prostaglandin.[1,2]

Ketorolac tromethamine (Toradol) is a NSAID available in Canada that is administered by either oral tablets or intramuscular injection,[3] though this review will focus solely on oral administration. Oral Toradol has a Health Canada indication for short-term management (not to exceed 5 days for post-surgical patients or 7 days for patients with musculoskeletal pain) of moderate to moderately severe acute pain, including post-surgical pain, acute musculoskeletal trauma pain and post-partum uterine cramping pain.[3] The recommended dose for oral administration is 10 mg every 4 to 6 hours, not exceeding 40 mg per day.[3] Common side effects include rash, ringing in the ears, headaches, dizziness, drowsiness, abdominal pain, nausea, diarrhea, constipation, heartburn, and fluid retention.[4] Toradol, like most NSAIDs, is commonly associated with gastrointestinal bleeding.[4] In view of the concern regarding the potential safety risks and uncertainty of additional benefits compared with other NSAIDs, this report aims to review the clinical effectiveness of oral ketorolac for management of dental, non-dental, and non-cancer pain.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of oral ketorolac for management of dental pain?

2. What is the clinical effectiveness of oral ketorolac for management of non-cancer, non-dental pain?

KEY FINDINGS

Limited evidence suggested that oral ketorolac compared with other NSAIDS demonstrated a similar profile in dental, non-dental, and non-cancer pain reduction.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and non-randomized studies containing safety data. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2004 and May 30, 2014.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed for relevance. Full texts of any relevant titles or abstracts were retrieved, and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with dental pain Patients with non-cancer, non-dental pain
Intervention	Oral Ketorolac (Toradol)
Comparator	Other NSAIDs
Outcomes	Clinical effectiveness (e.g. pain reduction, QoL), safety and harms (e.g. cardiovascular events, GI bleeding, other adverse events)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria in Table 1, if they were published prior to January 2004, if they were duplicate publications of the same study, or if they were referenced in a selected systematic review.

Critical Appraisal of Individual Studies

The quality of the included RCTs was assessed using the Scottish Intercollegiate Guidelines Network (SIGN50) methodology checklist.[5] Numeric scores were not calculated. Instead, the strengths and limitations of the study are summarized and presented.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 482 citations. Upon screening titles and abstracts, 406 citations were excluded and 22 potentially relevant articles were retrieved for full-text review. No additional potentially relevant reports were retrieved from the grey literature and by hand search. Of the 22 potentially relevant reports 18 were excluded. Four RCTs[6-9] met the inclusion criteria. The process of study selection is outlined in the PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

A detailed summary of the included study and guidelines is provided in Appendix 2.

Dental Pain

Jena et al., 2013[6]

A randomized, double-blinded study design was conducted. A total of 100 patients (63 males) between the ages of 18 and 65 years in acute pain with mandibular molar teeth diagnosed as acute irreversible pulpitis were included. Patients must have been in good health with vital mandibular molar teeth actively experiencing moderate-to-severe pain (≥85 mm) as determined by a Heft-Parker Visual Analogue Scale (VAS). Patients also must have had a prolonged response to cold testing. Patients were excluded if they had an allergy to ibuprofen, ketorolac, etodolac, aceclofenac, or paracetamol, if they had no response to cold testing or periradicular pathosis (other than a widened periodontal ligament), if they had a history of significant medical problems, gastrointestinal problems, syndrome of nasal polyps, angioedema or bronchospastic reactivity to aspirin or other NSAIDs, taken central nervous system (CNS) depressants (including alcohol or any analgesic medications) within the last 48 hours or if they were pregnant. Patients were randomized to one of five groups: 1) placebo with sugar coated pills, 2) Ibuprofen (600 mg) (n=20), 3) Ketorolac (10 mg) (n=20), 4) combination of etodolac with paracetamol (400 mg + 500mg) (n=20), and 5) combination of aceclofenac with paracetamol (100 mg + 500mg) (n=20). Before receiving administration of anesthesia, patients underwent cold testing using Green Endo ice spray to determine level of pain using the 170mm Heft-Parker VAS scale with 0 mm representing no pain and 170mm the worst possible pain. Treatment was provided 30 minutes prior to the administration of anesthesia. Inferior alveolar nerve block (IANB) was administered using 2% lidocaine with 1:100,000 adrenaline. The teeth were isolated with a rubber dam, and a conventional access opening was initiated. The treatment consisted of three phases: access into dentin, access into the pulp chamber, and instrumentation of the canals. Patients were instructed to rate pain during endodontic treatment with the Heft-Parker VAS. Statistical testing using analysis of variance (ANOVA) was used to compare between group differences.

Aggarwal et al., 2010[7]

A randomized, double-blinded study design was conducted. A total of 69 patients (14 males) between the ages of 21 and 35 years who reported to the dental emergency department with acute pain with mandibular molar teeth were included. Patients must have had active pain in a mandibular molar, prolonged response to cold testing with an ice stick and an electric pulp tester, and absence of any periapical radiolucency on radiographs, with the exception for a widened periodontal ligament and a vital coronal pulp on access opening. Patients were excluded if they had an allergy, sensitivity, or contraindications to any opioid or non-opioid analgesic, history of active peptic ulcer within the preceding 12 months, history of bleeding problems or anticoagulant use within the last month, pregnant or breast-feeding, a history of known or suspected drug abuse, and if NSAIDs were taken within 12 hours prior to the administration of the study medication. Patients were also excluded if they had active pain in more than 1 mandibular molar. Patients were randomized to one of three groups: 1) placebo capsules (n=24), 2) Ibuprofen (300 mg) (n=22), and 3) Ketorolac (10 mg) (n=23). All patients received standard IANB injection using 1.8mL of 2% lidocaine with 1:200,000 epinephrine one hour after oral administration of study treatment. Patients were asked to rate their pain on the 170mm Heft-Parker VAS 15 minutes after initial IANB. Patients were excluded from the study when the block was considered unsuccessful (if lip numbness was not recorded within 15 minutes). Treated teeth were isolated with a rubber dam. During the procedure, patients were instructed to raise their hand when pain was experienced, and treatment was stopped. Patients were again asked to rate the pain on Heft-Parker VAS. The extent of access preparation and/or instrumentation was recorded as “within dentin”, “within pulpal space”, and “instrumentation of canals”. Statistical testing for anesthetic success (defined as Heft-Parker VAS score > 54 mm) was conducted using chi-square tests.

Non-dental/Non-cancer Pain

Ortiz et al., 2010[8]

A randomized, double-blinded study design was conducted. A total of 49 patients (proportion of males/females not provided) between the ages of 18 and 55 years with closed ankle fractures hospitalized in the trauma service were included. Patients must had acute pain ≥ 5 cm according to a 10-cm VAS ranging from 0 (no pain) to 10 (worst pain), good health determined by clinical history, without sanguineous dyscrasias or hypersensitivity to study treatment. No specific exclusion criteria were provided. At 24 hours post-treatment, patients rated their pain with a Likert scale (0 representing complete relief; no pain during treatment; 1 representing slight relief, pain intermittently throughout the study, which is very tolerable; 2 representing moderate relief, pain intermittently throughout the study, which causes inconvenience and discomfort to the patient, but not leaving the study; and 3 representing no pain subsided with treatment) at baseline and were randomized to one of three groups: 1) ketorolac (10mg) (n=15), 2) etoricoxib (60 mg) (n=17), and 3) diclofenac (70 mg) (n=17) all taken orally twice daily. Patients’ measurements for pain were recorded at 0, 2, 4, 8, 12 and 24 hours using the VAS.

Kaeding et al., 2004[9]

A randomized study design was conducted. A total of 50 patients (34 males) between the ages of 14 and 46 years who underwent acute or chronic anterior cruciate ligament (ACL) reconstruction surgery were included. No specific inclusion criteria were provided. Patients were

excluded if they were pregnant women, had a history of gastrointestinal bleeding, ulceration, were allergic to NSAIDs, had renal disease or coagulation disorders, or if they were undergoing multi-ligament reconstruction or meniscal repair. Patients were randomized to one of two groups: 1) rofecoxib (50 mg orally while in the preoperative holding area and 50 mg orally every morning thereafter for 5 days) (n=25), or 2) ketorolac (30 mg intravenously intraoperatively and 10 mg orally four times daily for first 5 postoperative days) (n=25). At baseline, patients rated their pain using a VAS ranging from 1 (extremely poor) to 5 (extremely good, no pain) in the preoperative holding area. All patients received standardized anesthesia both intraoperatively and postoperatively and were prescribed oxycodone (1 or 2 tablets orally every 3 hours as needed for breakthrough pain). Patients' pain scores (VAS) and severity of side effects were measured at 5 days post-surgery. Statistical analyses were conducted using Student t tests for continuous data, and Fisher exact test for discrete data.

Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 3.

In regards to the RCTs pertaining to dental pain, the methodological quality of Jenna et al.[6] was poor as the randomization and concealment methods were not adequately described, blinding procedures were not adequately described, and baseline patients characteristics were not well reported. No sample size calculation was provided, thus it remains unclear whether the study was adequately powered to detect meaningful differences. The proportion of patients actually completing the study was unclear. The RCT by Aggarwal et al.[7] was of high methodology quality as an appropriate and clearly focused research question was posed, the only difference between treatment groups was the treatment under investigation, and randomization, concealment methods, and blinding procedures were well described. A sample size calculation was provided and indicated that the study was adequately powered. A list of both inclusion and exclusion criteria was provided. However, results did not demonstrate statistical significance.

Both non-dental/non-cancer RCTs were of poor methodological quality. The RCT by Ortiz et al.[8] did not adequately describe randomization, concealment methods and blinding procedures. Baseline characteristics were not well reported, and it was unclear how many patients were originally randomized in the study. Statistical testing was performed, though the tests used were not specified and patient exclusion criteria were not provided. The RCT by Kaeding et al.[9] did not blind participants which may have impacted the subjective pain outcome measures. Though randomization methods were well described, and baseline patient characteristics were reported, statistical measures of dispersion and confidence intervals were not provided. Specific inclusion criteria were not provided and none of the results demonstrated statistical significance. Oxycodone use among the ketorolac group was greater compared with the rofecoxib group, thus it is unclear whether this affected pain score results.

Summary of Findings

A summary of the main study findings can be found in Appendix 4.

As seen in Appendix 4 Table 1, The RCT by Jena et al.[6] (n=100) revealed, despite having the highest mean (SD) Heft-Parker VAS score before local anesthesia, the ketorolac group had the lowest mean (SD) Heft-Parker VAS score during endodontic treatment (27.80 [47.02]) compared with the ibuprofen (46.30 [54.23]), etodolac plus paracetamol (46.50 [51.10]),

aceclofencac (39.85 [52.02]) and placebo (62.35 [55.37]) groups. Differences between groups were not statistically significant. Although no statistical analyses were performed for pain type, the proportion of patients who experienced “no pain” was greatest in the ketorolac group (70%) compared to the other treatment groups, while the lowest proportion of patients experiencing “severe pain” (Hefter-Parker VAS score 86mm to 170mm) was also in the ketorolac group (20%).

As seen in Appendix 4 Table 2, The RCT by Aggarwal et al., 2010[7] (n=69) revealed that the proportion of patients experiencing “mild pain” (Heft-Parker VAS score < 54 mm) was lower in the ibuprofen group (27%) during endodontic treatment. The proportion of patients experiencing “moderate pain” (Heft-Parker VAS score 54mm to 114mm) during endodontic treatment was lowest among the ibuprofen group for within dentin (25%), and placebo group for within pulpal space (12%) and for instrumentation of canals (12%) . The proportion of patients experiencing “severe pain” (Heft-Parker VAS score > 114 mm) during endodontic treatment was lower among the placebo group for within dentin (18%), and the ketorolac group for within pulpal space (7%) and for instrumentation of canals (7%). Between-group differences were not statistically significant.

As seen in Appendix 4 Table 3, The RCT by Ortiz et al. 2010[8] (n=49) revealed that etoricoxib group had the lowest (less pain) mean (SE) VAS pain score (20.1 [4.3]) compared with the other treatment groups at 24 hours post-treatment, while the mean (SE) Likert scale scores were both similarly greater (less pain) among the ketorolac (1.13 [0.8]) and etoricoxib (1.13 [0.9]) compared with placebo (1.07 [0.7]) at 24 hours post-treatment. Though it was unclear what statistical methods were used, the investigators stated that between-group differences were not statistically significant.

As seen in Appendix 4 Table 4, The RCT by Kaeding et al. 2004[9] (n=50) revealed that rofecoxib group had greater (less pain) mean VAS scores (3.57) compared with the ketorolac group (3.49) at 5 days post-operation. The mean change from baseline (0.13) and overall daily pain mean VAS score (4.09) was also greater in the rofecoxib group. The rofecoxib group used less oxycodone (mean change of -2.52 pills per day) compared with the ketorolac group (mean change of -1.86 pills per day). The proportion of patients experiencing incision-site bleeding was greater among the ketorolac group (28%) compared with the rofecoxib group (8%), while a greater proportion of patients experienced nausea in the rofecoxib group (28%) compared with the ketorolac group (16%). Between-group differences were not statistically significant.

Limitations

As the majority of included were of poor methodological quality, results should be interpreted with caution. Given the lack of detail regarding the randomization, concealment methods and blinding processes in several of the included studies, the validity of the subjective pain outcome results is uncertain. With four studies being retrieved, the literature pertaining to effectiveness and safety of oral ketorolac compared with other NSAIDS is limited. No studies measuring long-term effects such as health-related quality of life were retrieved. Furthermore, three of the four included studies were conducted in either India or Mexico, thus generalizability of the findings to the Canadian population is uncertain.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Limited evidence suggested that oral ketorolac compared with other NSAIDS demonstrated a similar profile in dental, non-dental and non-cancer pain reduction, though no results demonstrated statistical significance. There remains an unmet need for high quality trials, and further research measuring the clinical effectiveness and safety of oral ketorolac compared with other NSAIDs.

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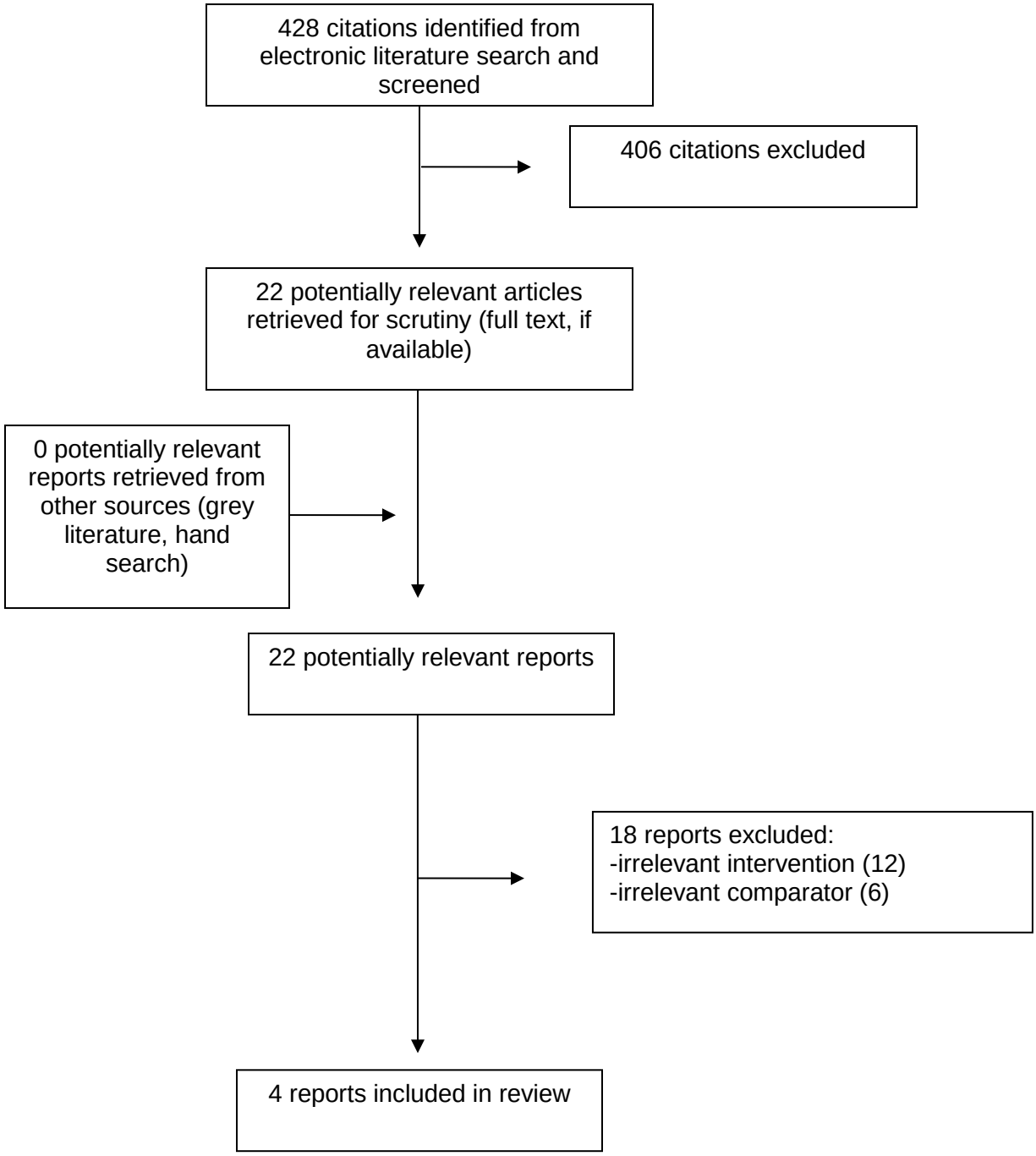
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country,	Study Design, N	Patient Characteristics	Intervention	Comparator Group	Clinical Endpoints
Dental Pain					
Jena, 2013[6] India	Single centre, 5-arm, double-blind randomized controlled trial N= 100	Endodontic emergency patients, aged 19 to 65, with acute pain with mandibular molar teeth (first or second molar) diagnosed as acute irreversible pulpitis.	Ketorolac (10 mg p.o) 30 minutes before conventional IANB anesthesia	1. Placebo (sugar coated pills p.o) 2. Ibuprofen (600 mg p.o) 3. combination of Etodolac with Paracetamol (400 mg + 500 mg p.o) 4. combination of aceclofenac with paracetamol (100 mg + 500 mg p.o) 30 minutes before conventional IANB anesthesia	1. Pain (Heft-Parker VAS score) before local anesthesia 2. Pain (Heft-Parker VAS score) during endodontic treatment
Aggarwal, 2010[7] India	Single centre, 3-arm, double-blind, randomized controlled trial N=69	Endodontic emergency patients, aged 21 to 38, with acute pain with mandibular molar teeth (first or second molar)	Ketorolac (10 mg p.o) 60 minutes before conventional IANB anesthesia	1. Placebo (starch filled capsule p.o) 2. Ibuprofen (300 mg p.o) 60 minutes before conventional IANB anesthesia	Pain (Heft-Parker VAS score) during endodontic treatment
Non-dental/Non-cancer Pain					
Ortiz, 2010[8] Mexico	Single centre, 3-arm, double-blind, randomized controlled trial N=49	Patients with closed ankle fractures ranging in age from 18 to 55 years, with acute pain ≥ 5 cm according to a 10-cm visual analog scale (VAS; 0 = no pain and 10 = worst pain)	Ketorolac (10 mg p.o) twice daily	1. Etoricoxib (60 mg p.o) 2. Diclofenac (70 mg p.o) twice daily	Pain (VAS) from baseline to 24 hours

First Author, Publication Year, Country,	Study Design, N	Patient Characteristics	Intervention	Comparator Group	Clinical Endpoints
Kaeding, 2004[9] United States	Single centre, 2-arm, randomized controlled trial N=50	Patients aged 15 to 46 years, who had acute or chronic ACL reconstruction with hamstring autograft	Ketorolac (30 mg i.v) intraoperatively plus ketorolac (10 mg p.o) four times daily for first 5 postoperative days	Rofecoxib (50 mg p.o) in preoperative holding plus 50 mg once daily for 5 days	Pain (VAS score) Oxycodone use Incision site bleeding Nausea Diarrhea

IANB= inferior alveolar nerve block; P.O= oral administration; VAS = visual analogue scale

APPENDIX 3: Summary of Critical Appraisal of Included Clinical and Cost Studies

Strengths	Limitations
SIGN50[5]	
Dental Pain	
Jena et al., 2013[6]	
• Appropriate and clearly focused research question • Initial pain was similar between groups at baseline • Inclusion criteria, study interventions, outcome measures clearly described	• Randomization and concealment methods were not adequately described • Blinding procedures were not adequately described • Baseline patient characteristics were not well reported • Unclear whether all patients completed the study and if the analysis was based on intention to treat. • None of the results demonstrated statistical significance
Aggarwal, 2010[7]	
• Appropriate and clearly focused research question • Only difference between groups is treatment under investigation • Randomization and concealment methods were well described • Blinding procedures were well described • Baseline patient characteristics were reported • Power and sample size calculation provided • Inclusion criteria, study interventions, outcome measures clearly described • Low discontinuation rate	• None of the results demonstrated statistical significance
Non-Dental/Non-Cancer	
Ortiz, 2010[8]	
• Appropriate and clearly focused research question	• Randomization and concealment methods were not adequately described • Blinding procedures were not adequately described • Baseline patient characteristics were not well reported • Unclear how many patients were originally randomized in the study • Statistical analyses methods not provided • Exclusion criteria not provided

Strengths	Limitations
Kaeding et al., 2004[9]	
• Appropriate and clearly focused research question • Randomization methods were well described • Baseline patient characteristics were reported	• Patients were not blinded, only nurse assessor was blinded • Statistical measures of dispersion and confidence intervals were not provided • None of the results demonstrated statistical significance • Only exclusion criteria was specified

APPENDIX 4: Main Study Findings

Table 1: Main Findings from Jena et al., 2013[6]

	Treatment				
	Ketorolac (n=20)	Ibuprofen (n=20)	Etodolac + Paracetamol (n=20)	Aceclofenac (n=20)	Placebo (n=20)
Pain before local anesthesia- Heft-Parker VAS score (mm)					
Mean (SD)	128.00 (20.17)	122.05 (17.19)	125.05 (22.59)	125.30 (25.57)	119.05 (15.76)
Pain during endodontic treatment- Heft-Parker VAS score (mm)					
Mean (SD)	27.80 (47.02)	46.30 (54.23)	46.50 (51.10)	39.85 (52.02)	62.35 (55.37)
Level of pain - Heft-Parker VAS score, n(%)					
No Pain (0mm)	14(70)	1(55)	10(50)	11(55)	8(40)
Mild (1mm to 54mm)	2(10)	0	1(5)	3(15)	0
Moderate (55mm to 85mm)	0	3(15)	4(20)	1(5)	3(15)
Severe (86mm to 170mm)	4(20)	6(30)	5(25)	5(25)	9(45)

VAS = visual analogue scale
a= Heft-Parker VAS scale ranging from 1 to 170 mm, where 0mm = no pain, 1mm to 54mm = mild pain, 54 mm to 114mm = moderate pain, and > 114mm = severe pain

Table 2: Main Findings from Aggarwal et al., 2010[7]

	Treatment		
	Ketorolac (n=23)	Ibuprofen (n=22)	Placebo (n=24)
Mild Pain (Heft-Parker VAS score < 54 mm) during endodontic treatment			
n (%)	9 (39)	6 (27)	7 (29)
Moderate Pain (Heft-Parker VAS score 54mm to 114mm) during endodontic treatment			
Within dentin n/N (%)	4/14 (29)	4/16 (25)	5/17 (29)
Within pulpal space n/N (%)	3/14 (21)	2/16 (13)	2/17 (12)
Instrumentation of canals n/N (%)	2/14 (14)	2/16 (13)	2/17 (12)
Severe Pain (Heft-Parker VAS score > 114 mm) during endodontic treatment			
Within dentin n/N (%)	3/14 (21)	5/16 (31)	3/17 (18)
Within pulpal space n/N (%)	1/14 (7)	3/16 (19)	4/17 (24)
Instrumentation of canals n/N (%)	1/14 (7)	2/16 (13)	1/17 (6)

VAS = visual analogue scale
a= Heft-Parker VAS scale ranging from 1 to 170 mm, where 0mm = no pain, 1mm to 54mm = mild pain, 54 mm to 114mm = moderate pain, and > 114mm = severe pain

Table 3: Main Findings from Ortiz et al. 2010[8]

	Treatment		
	Ketorolac (n=15)	Etoricoxib (n=17)	Diclofenac (n=17)
Pain at 24h post-treatment (VAS mm)[a]			
Mean (SE)	21.2 (4.3)	20.1 (4.5)	21.9 (5)
Pain at 24h post-treatment (Likert Scale)[b]			
Mean (SE)	1.13 (0.8)	1.13 (0.9)	1.07 (0.7)

SE = standard error; VAS = visual analogue scale

a= visual analogue scale ranged from 0 (no pain) to 10 (worst pain)

b = 1 represents slight relief, pain intermittently throughout the study; 2 represents moderate relief, pain intermittently throughout the study, and 3 represents no pain subsided with treatment

Table 4: Main Findings from Kaeding et al. 2004[9]

Treatment		
	Ketorolac (n=25)	Rofecoxib (n=25)
Pain 5 days post-operation (VAS)[a]		
Mean (SD)	3.49 (NR)	3.57 (NR)
Mean change from baseline (SD)	-0.24 (NR)	0.13 (NR)
Overall Daily Pain (VAS)[a]		
Mean (SD)	3.76 (NR)	4.09 (NR)
Adverse Events		
Incision-site bleeding, n (%)	7 (28)	2 (8)
Nausea, n (%)	4 (16)	7 (28)

NR = not reported; SD = standard deviation; VAS = visual analogue scale

a = visual analogue scale ranging from 1 representing great pain to 5 representing no pain