

SCIENTIFIC ARTICLES

Evaluation of Periapical Injection of Ketorolac for Management of Endodontic Pain

Susan G. Penniston, DDS, MS and Kenneth M. Hargreaves, DDS, PhD

Effective pain management of the endodontic emergency patient is often a problem. Ketorolac tromethamine is the first nonsteroidal anti-inflammatory drug available for intramuscular injection in the United States. Although its analgesic efficacy is comparable with opiates after intramuscular injection, to date no study has evaluated its efficacy after intraoral periapical injection. Fifty-two endodontic emergency patients were injected (injection routes = intraoral infiltration/intramuscular deltoid) on a double-blind basis with either: (i) placebo/placebo, (ii) 30 mg ketorolac/placebo, (iii) placebo/30 mg ketorolac, or (iv) 2% mepivacaine with 1:20 K levonordefrin/placebo. Infiltration injection of ketorolac at an oral site produced significant analgesic effects, particularly in treating pain of mandibular origin. These results suggest that intraoral injection of ketorolac may prove to be a useful adjunct in the management of endodontic pain patients. Further studies are required to replicate these findings and to develop optimal treatment combinations.

Successful management of acute pain is a primary goal of all dental clinicians. It has been estimated that 50% of adults in the United States avoid routine dental care because of fear of dental pain. Endodontists in particular must often address the problem of odontalgia before they can render appropriate therapy. Once therapy is initiated, postoperative pain control is the concern.

Endodontic pain is often linked to the inflammatory process and results from the stimulation of nociceptors as well as additional central mechanisms (1, 2). Inflammation alters the response properties of nociceptors through the action of inflammatory mediators. Prostaglandins, mainly of the E series and predominantly prostaglandin E₂, have been associated with the initial stages of inflammation. They are associated with several aspects of the inflammatory process, including vasodilation (3), increased vascular

permeability (4), bone resorption (5), chemotaxis (6), and sensitization of certain primary afferent fibers (7). The hyperalgesia induced by prostaglandins probably results from reducing the stimulus threshold of polymodal nociceptors associated with C fibers (7, 8), although other mechanisms, including spinal cord effects, probably also contribute to pain perception (9).

Torabinejad and Bakland (10) implicated prostaglandins in the pathogenesis of pulpal and periapical diseases over a decade ago. Elevated levels of arachidonic acid metabolites have been reported in inflamed pulps and periapical tissues of humans and animals (10-14). Importantly, increased pulpal and periapical tissue levels of these eicosanoids are associated with the presence of pain (13, 14).

Ketorolac tromethamine is the first nonsteroidal antiinflammatory drug (NSAID) available for intramuscular injection. It is a potent inhibitor of prostaglandin synthesis. As compared with the traditional route of administration (swallowing a tablet) parenteral injection offers the theoretical advantages of a faster onset of analgesic action and greater peak serum drug levels, offering the possibility of greater analgesic effectiveness. This study determined whether ketorolac tromethamine is also effective when injected intraorally, at the site of inflammation. We compared the analgesic efficacy of ketorolac tromethamine following intraoral periapical infiltration injection with intramuscular injection of the drug in a prospective, randomized, double-blind, placebo-controlled clinical trial.

MATERIALS AND METHODS

Patients were selected from emergency patients presenting to the University of Minnesota Dental School. The inclusion criteria for the study were: (i) pain on the Heft-Parker pain scale of at least 30 mm (0 to 160 scale); (ii) patient elects root canal therapy for pain originating from a vital/nonvital tooth; (iii) patient with an ASA class I or II medical history; (iv) patient who can read and understand questionnaires; and (v) patient who provides informed consent. Patients were excluded if they fell into any of the following categories: (i) younger than 18 or older than 65 yr; (ii) analgesic ingestion within the last 4 h; (iii) history of allergy to NSAIDs, aspirin, or local anesthetics; (iv) history of ulcers, active asthma, decreased renal function, decreased hepatic function, hem-

TABLE 1. Patient Demographics

Group	n	Sex (m:f)	Mean Age (yr)	Mean Height (inches)	Mean Weight (lbs)
Placebo	14	11:3	32	69	172
Intramuscular ketorolac	10	5:5	32	68	167
Infiltration ketorolac	18	8:10	34	67	165
Mepivacaine	10	4:6	38	67	160

orrhagic disorders, and poorly controlled diabetes mellitus; (v) currently taking diuretics or anticoagulants; or (vi) pregnant or nursing.

Fifty-two patients signed a consent form outlining the procedure and its possible risks. They completed a baseline 4-point category pain scale (none, mild, moderate, and severe), a 100-mm visual analog scale (VAS), and a Heft-Parker scale for pretreatment pain. The study was a randomized, double-dummy, placebo-controlled study in which all injections were administered by a single operator. The double-dummy design simply means that all patients received both an intramuscular injection (1 ml into deltoid) and a periapical infiltration injection (1.8 ml) adjacent to the painful tooth.

Following completion of the base line pain scales, patients were randomly allocated to 1 of 4 treatment groups: (i) intramuscular placebo and periapical placebo; (ii) intramuscular ketorolac (30 mg) and periapical placebo; (iii) intramuscular placebo and periapical ketorolac (30 mg); and (iv) intramuscular placebo and periapical local anesthesia (2% mepivacaine with 1:20,000 levonordefrin). In cases where periapical swelling was present, the infiltration injection was located as close to the tooth as possible without injecting into the swelling. The intramuscular injections were given via a plastic disposable 3-ml syringe utilizing a 23-gauge needle. All infiltration injections were given with a standard dental syringe utilizing an unmarked 1.8-ml cartridge and a 30-gauge needle.

Following the drug injections, pain scores were recorded at 15, 30, 45, and 60 min. After the 60-min evaluation, all patients received local anesthesia (1.8 ml of 2% mepivacaine with 1:20,000 levonordefrin) delivered by buccal and palatal infiltration to teeth in the maxilla, or by mandibular and long buccal blocks to teeth in the mandible. A pulpotomy was performed by 1 of 3 endodontic graduate residents; ~90% of the pulpotomies were performed by the same resident (S.G.P.). Records were made of any additional local anesthetic injections required to complete the pulpotomy (e.g. type of injection and quantity of local anesthetic used). A dry cotton pellet was placed in the chamber followed by a Cavit temporary filling. Patients were given a pain diary to take home and a reserve medication packet containing 8 tablets of 200 mg ibuprofen. They were instructed to record their pain scores at 3, 4, 5, and 6 h postdrug injection time. The pain diaries were then returned by mail to the endodontic clinic.

Parametric data were analyzed by a two-way repeated measure (ANCOVA) (drug \times time) with post-hoc analysis by the post-hoc Student Newman-Keuls test. A difference was considered significant if the probability that it occurred to chance alone was $<5\%$ (i.e. $p < 0.05$). Frequency data were analyzed by the χ^2 test. Data are presented as mean \pm SE. The sample size was based on calculations using a 20% treatment effect, variance at 20 mm on the VAS, and 85% power with a two-sided test and the α set to the 0.05 level of significance.

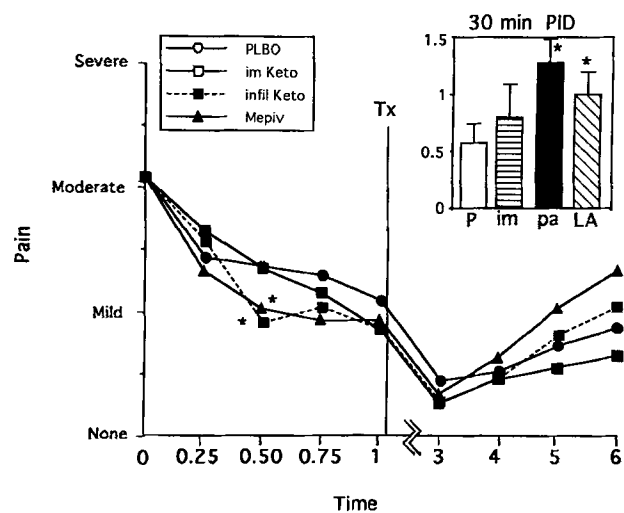


FIG 1. Combined results of maxillary and mandibular infiltration injections. Effect of 30 mg ketorolac (Keto) given by intraoral infiltration injection (■) compared with the same dose of the drug given by intramuscular injection into the deltoid muscle (□), and to saline placebo (PLBO; ○) and mepivacaine (Mepiv; ▲). Pain was measured on a 4-point category scale before, and for 60 min following administration of the various medications. After the 60-min reading, all patients received intraoral local anesthetic and a pulpotomy procedure. All patients were then discharged from the clinic and completed pain diaries from 3 through 6 h following the procedure. Inset: pain intensity difference scores (= reduction in pain from base line to 30 min) for the placebo (P), intramuscular ketorolac (im), periapical ketorolac (pa), and local anesthetic (LA) treatment groups. * $p < 0.05$ versus placebo. Error bars = SEM.

RESULTS

The similarity of the treatment groups was evaluated by comparing both patient demographics and preoperative pain levels. As illustrated in Table 1, the four treatment groups were statistically indistinguishable for the distribution of gender, mean age, height, and weight. In addition, the distribution of tooth vitality, arch location of the tooth, and anterior-posterior distribution within the arch, were not significantly different between groups (data not shown). However, there were significant differences between groups for preoperative levels of pain (as indicated by analysis of variance for each pain scale). Accordingly, the subsequent statistical analyses utilized an ANCOVA to normalize posttreatment pain reports to preoperative levels of pain. Results of the ANCOVA analyses indicated significant findings for the baseline covariant on the category pain scale ($F_{1,46} = 8.66$; $p = 0.005$), the VAS pain scale ($F_{1,24} = 14.76$; $p < 0.001$), and the Heft-Parker pain scale ($F_{1,24} = 21.23$; $p < 0.001$). For the sake of clarity, only the results from the category pain scale are presented. The results

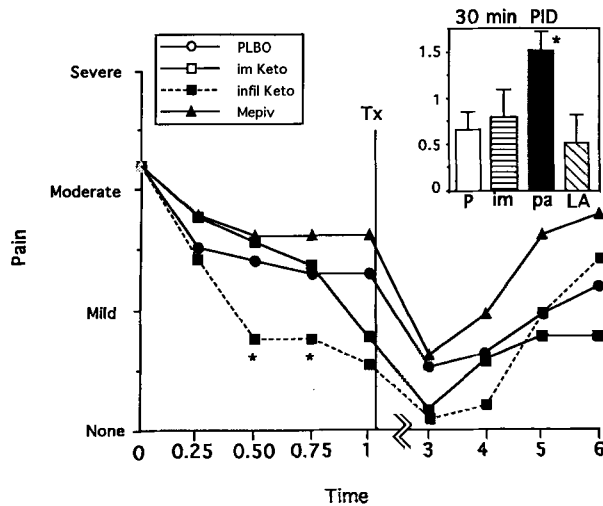


FIG 2. Results of mandibular infiltration injections. Effect of 30 mg ketorolac (Keto) given by intraoral infiltration injection (■) compared with the same dose of the drug given by intramuscular injection into the deltoid muscle (□), and to saline placebo (PLBO; ○) and mepivacaine (Mepiv; ▲). Pain was measured on a 4-point category scale before, and for 60 min following administration of the various medications. After the 60-min reading, all patients received intraoral local anesthetic and a pulpotomy procedure. All patients were then discharged from the clinic and completed pain diaries from 3 through 6 h following the procedure. *Inset*: pain intensity difference scores (= reduction in pain from base line to 30 min) for the placebo (P), intramuscular ketorolac (im), periapical ketorolac (pa), and local anesthetic (LA) treatment groups. **p* < 0.05 versus placebo. *Error bars* = SEM.

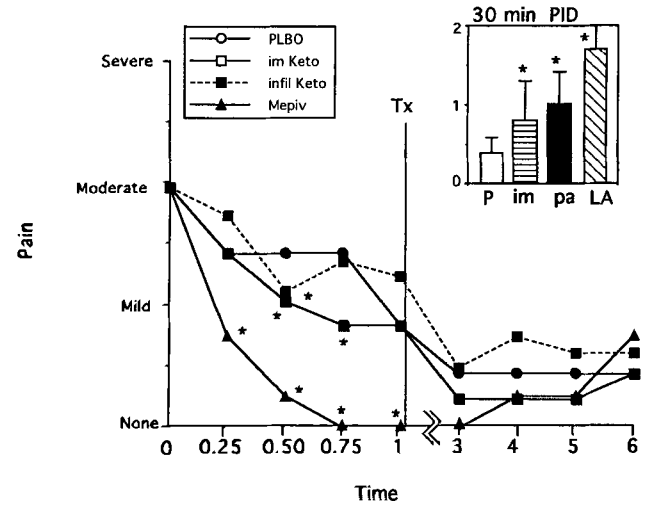


FIG 3. Results of maxillary infiltration injections. Effect of 30 mg ketorolac (Keto) given by intraoral infiltration injection (■) compared with the same dose of the drug given by intramuscular injection into the deltoid muscle (□), and to saline placebo (PLBO; ○) and mepivacaine (Mepiv; ▲). Pain was measured on a 4-point category scale before, and for 60 min following administration of the various medications. After the 60-min reading, all patients received intraoral local anesthetic and a pulpotomy procedure. All patients were then discharged from the clinic and completed pain diaries from 3 through 6 h following the procedure. *Inset*: pain intensity difference scores (= reduction in pain from base line to 30 min) for the placebo (P), intramuscular ketorolac (im), periapical ketorolac (pa), and local anesthetic (LA) treatment groups. **p* < 0.05 versus placebo. *Error bars* = SEM.

for the other pain scales were similar to those observed on the category scale.

An ANCOVA over the first 60-min period of the entire study database indicates the presence of a significant analgesic effect ($F_{21,329} = 4.06$; $p < 0.05$). Both the intraoral ketorolac and the mepivacaine groups demonstrated a significant reduction in pain at 30 min following injection (Fig. 1). The pain intensity difference (PID) scores represent the net reduction in the pain from pretreatment to the 30-min observation (Fig. 1, *inset*). The infiltration ketorolac group produced nearly twice the PID score of the placebo-treated patients. After the pulpotomy treatment, all groups reported a general decline in pain levels.

Following the initial analyses of the combined data, the population was broken out into two subgroups, as defined by pain originating in either mandibular or maxillary teeth. The results of the mandibular subpopulation analysis are presented in Fig. 2. An ANCOVA of data from the first 60 min indicates a significant analgesic effect ($F_{9,78} = 2.25$; $p < 0.05$). Post-hoc analysis of the data presented in Fig. 3 indicates that intraoral infiltration injection of ketorolac resulted in a decrease in pain, with significant analgesic effects evident at 30 and 45 min after injection. Analysis of the PID scores indicate that mandibular infiltration injection of ketorolac was about twice as effective as intramuscular injection of the same dosage of the NSAID, and nearly three times as effective as the placebo treatment group (Fig. 3, *inset*). Inspection of the results of mepivacaine injected by periapical infiltration are consistent with the clinical knowledge that infiltration injections of local anesthetics into the mandible show limited to no analgesic efficacy.

The analysis of the subpopulation of endodontic patients with

pain of maxillary origin is presented in Fig. 3. The ANCOVA indicates a significant effect for drug treatment ($F_{3,17} = 3.71$; $p < 0.05$). Post-hoc analysis of the data indicates that infiltration injection of the local anesthetic resulted in a significant reduction in base line pain over the 60-min observation period. In addition, the ketorolac groups showed modest and transient analgesic responses at the 30- and 45-min periods (Fig. 3, *inset*).

Collectively, these results indicate that intraoral infiltration injection of ketorolac results in a significant analgesic effect, with both the magnitude and duration of the response greater following injection into the mandibular arch as compared with injection in the maxillary arch. Similar results were observed on the other pain scales (data not shown).

As a separate measure of drug efficacy, we evaluated the frequency with which patients requested additional local anesthetic injections during the pulpotomy treatment. As indicated in Table 2, there was a strong tendency for treatment groups to differ in the need for additional local anesthetic injections (Chi square = 7.58; $p = 0.055$). To evaluate whether this effect was attributable to the injection of the NSAID, we combined both the intramuscular and infiltration ketorolac groups. The combined ketorolac groups required significantly less additional injections than either placebo or local anesthetic groups (Chi square = 7.117; $p < 0.05$). Separate Chi square analyses were attempted on the maxillary and mandibular subgroups from the study. However, because the frequency is <5/cell, the Chi square statistic cannot be calculated accurately.

The increased efficacy of intraoral ketorolac for treating mandibular odontogenic pain as compared with maxillary odontogenic pain was not predicted a priori. To evaluate whether patient demographic factors could have contributed to the differences in

TABLE 2. Proportion of drug-treated patients requiring additional local anesthetic injection for pulpotomy treatment

Group	All Patients			Mandibular Patients			Maxillary Patients		
	No. of Additional Injections*	n†	%	No. of Additional Injections	n	%	No. of Additional Injections	n	%
Placebo	10	14	71	7	9	78	3	5	60
Intramuscular ketorolac	2	10	20	0	5	0	2	5	40
Infiltration ketorolac	6	18	33	5	10	50	1	9	11
Mepivacaine	5	10	50	4	6	67	1	4	25

* Number of patients requesting additional local anesthetic injection.

† n, total number of patients.

TABLE 3. Comparison of periapical infiltration injection of ketorolac (30 mg) in maxillary versus mandibular arches

	Injection Pain*		Vitality†		Location‡			Base Line Pain§ (VAS)	Base Line Pain¶ (CAT)
	Yes	No	Yes	No	Anterior	Bicuspid	Molars		
Maxillary									
Ketorolac infiltration	5	3	6	2	0	1	7	65.2±8.6	2.1±0.3
Mandibular									
Ketorolac infiltration	6	4	4	6	1	2	7	59.0±8.0	2.4±0.4

* Spontaneous report of transient pain after infiltration injection.

† Response to thermal testing.

‡ Location in arch.

§ Base line (pretreatment) pain levels as measured on the 100 mm VAS (mean ± SE).

¶ Base line (pretreatment) pain levels as measured on the category (CAT) scale (mean ± SE).

analgesic efficacy, several additional parameters are presented in Table 3. Chi square analysis indicates no significant differences in either the presence of tooth vitality or the location of the tooth for the maxillary versus mandibular ketorolac infiltration groups. In addition, there were no significant differences in base line pain levels for the two groups.

There were no clinically evident signs of adverse effects or tissue toxicity at either the end of the study period or when the patients returned for definitive endodontic treatment at a subsequent appointment. Interestingly, there were reports of transient injection pain in both the maxillary and mandibular ketorolac infiltration groups, with statistically indistinguishable frequencies of occurrence (Table 3). The injection pain was brief, lasting ~3 to 5 min, and was not observed in either the placebo or mepivacaine groups. No occurrence of injection pain was noted with the intramuscular ketorolac injections.

DISCUSSION

Management of acute odontalgia is a problem faced by all dental practitioners. With the introduction of the injectable formulation of ketorolac tromethamine, it is now possible to administer a potent NSAID parenterally. The safety and relatively minimal potential for side effects with NSAIDs have been established. In some studies, ketorolac has been shown to produce analgesia comparable with 12 mg morphine sulfate when injected intramuscularly (15). However, to our knowledge, no study has examined its effectiveness when injected intraorally at the site of inflammation.

The present study determined the latency for analgesic onset, and the magnitude of analgesic efficacy after maxillary and mandibular infiltration injection in endodontic emergency patients. Infiltration injection is used routinely by dentists and might offer the advantages of rapid onset and higher tissue concentrations of the NSAID. This could provide practitioners with another option to use as an adjunct to local anesthetics in endodontic pain control.

Two theoretical advantages may be conferred by infiltration injection of NSAIDs. First, tissue drug levels should be at least similar to, and probably greatly exceed, those found after intramuscular injection, providing effective analgesia. Intraoral infiltration at the site of an inflamed tooth will bypass gastric absorption and first-pass hepatic clearance, and will minimize protein binding in plasma. Second, local infiltration injection directly at the site of inflammation may increase speed of delivery and final concentration of drug at the site of inflammation. If this form of delivery is found to provide significant pain relief, it offers an entirely new method of pain control to the endodontic community.

Our results indicate that ketorolac is an effective analgesic after periapical intraoral injection. Interestingly, mandibular infiltration injection of ketorolac produced about twice as much pain relief compared with intramuscular injection of the same dosage of the NSAID.

Following the 60-min drug study, all groups had pulpotomy performed. Our findings indicate that ~90% of patients reported some degree of pain relief in the 6-h period following the procedure; this magnitude is similar to the 96% value reported by others (16).

Ketorolac tromethamine is the first NSAID available for intramuscular injection in the United States. The recommended initial injection dose of ketorolac is 30 or 60 mg intramuscularly as a loading dose, followed by half of that dose every 6 h for up to 5 days. Injectable ketorolac should be limited to a short-term therapy (not >5 days), because the frequency and severity of adverse effects may increase with longer use. Due to reduced clearance of the drug, ketorolac should be used in reduced dosages and with caution when treating the elderly, particularly in patients with altered hepatic or renal function (17). Safety and efficacy have not been established in pregnancy, labor and delivery, nursing, and pediatric use (17).

Local injection of ketorolac tromethamine does not seem to be irritating to tissues. Local tissue effects of ketorolac injections have

been assessed by physical examination of the injection sites, and by measurement of postinjection levels of serum creatinine phosphokinase, an index of local muscle damage. Tissue tolerance was confirmed by unchanged creatinine phosphokinase values following single or repeated doses (18). The agent was not irritating when applied to the skin or the eyes (18). Thus, peripheral tissue tolerates local injections of ketorolac. The mechanism for transient pain report following intraoral injection (Table 3) is unclear. This transient side effect was not observed following intramuscular injection of ketorolac, but has been reported for other NSAIDs after local administration during corneal surgery (19).

We were quite interested in the comparison of ketorolac efficacy after maxillary or mandibular injection of the drug. It is generally accepted that local anesthetics given in the mandible via infiltration injections have little to no efficacy, possibly due to incomplete diffusion through dense mandibular bone. Whether this clinical constraint would also apply to NSAIDs has, to our knowledge, never been evaluated. The present results suggest distinct pharmacokinetic profiles exist for ketorolac as compared with a local anesthetic solution, with mandibular infiltration injection of the NSAID, but not the local anesthetic, producing significant pain relief.

The mechanism(s) mediating the difference in efficacy following injection- in mandibular versus maxillary sites are presently unknown, but could be due to tissue differences affecting pharmacodynamic or pharmacokinetic properties of ketorolac. In terms of pharmacodynamic issues, it is possible that prostanoid contribution to periapical pain could be greater in the mandible. For example, prostanoid metabolism or diffusion may differ between mandibular and maxillary sites of inflammation, possibly due to differences in relative amount of vasculature or periosteum (both can synthesize prostanoids). Alternatively, it is possible that the denser bone of the mandible permits greater tissue pressure during inflammation, leading to increased activity of prostaglandin-sensitized nociceptors. Pharmacokinetic properties that may mediate this difference in drug efficacy include greater lipophilicity for ketorolac than mepivacaine, no positively charged form of ketorolac, and the lack of a vasoconstrictor with the NSAID formulation. Further research is required to evaluate these hypotheses.

Several major conclusions can be reached from this study. First, infiltration injection of ketorolac may prove to be a useful adjunctive treatment for managing pain of endodontic origin, especially in the mandible. Second, the mechanism(s) for increased efficacy of mandibular injection versus maxillary injection is unknown, but may relate to tissue-specific differences in pharmacodynamics or pharmacokinetics. Third, further studies are required to replicate these findings and to determine the optimal treatment combinations for managing the acute endodontic emergency patient. Because

some of the infiltration injections of ketorolac were associated with transient discomfort, it may be of value for future studies to evaluate the clinical efficacy of an initial local anesthetic injection, followed by intraoral ketorolac injection, in the management of the endodontic emergency pain patient.

Drs. Penniston and Hargreaves are affiliated with the Division of Endodontics, School of Dentistry; and Dr. Hargreaves is also affiliated with the Department of Pharmacology, School of Medicine, University of Minnesota, Minneapolis, MN. Address requests for reprints to Dr. Ken Hargreaves, Division of Endodontics, School of Dentistry, University of Minnesota, 8-166 Moos Tower, Minneapolis, MN 55455.

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