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Sniffing out pain: An in vivo intranasal study of analgesic efficacy

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Abstract:

Background: Orofacial pain is a common encounter in dentistry (affecting 12% of the population) and is a primary reason for patients seeking emergency care. Dentists often prescribe oral analgesics, which have disadvantages of decreased absorption rates and delayed onset. Intranasal (IN) delivery takes advantage of a large surface area of mucosal tissue for rapid absorption. The purpose of this study was to evaluate the efficacy of IN ketorolac for endodontic pain using a randomized, double-blind, placebo-controlled parallel design study.

Materials & Methods: Twenty patients presenting with moderate to severe endodontic pain were selected to receive IN treatment with placebo (n = 10) or ketorolac (n = 10) 30 minutes before endodontic treatment was started and immediately after the completion of endodontic treatment. Baseline pain levels were recorded before IN treatment. Pain levels were also recorded at 15 and 30 minutes after the initial IN dosing (before endodontic treatment); 30 minutes after completion of endodontic treatment; and 4, 8, and 12 hours after the initial IN spray.

Results: IN ketorolac alone or with endodontic treatment showed significantly better pain relief compared with IN placebo spray alone or with endodontic treatment at 30 minutes after the first or second intranasal dose and at 4 hours after the first intranasal dose.

Conclusions: These results suggest that IN ketorolac may provide a novel and efficacious method for pain relief in endodontic pain patients.

Key Words: Endodontic pain, intra nasal, NSAID, pain survey

Introduction

The science of controlling odontogenic pain is progressing as does the understanding of the mechanisms of pain detection, processing, and perception. Pain has been described as a complex multidimensional and biopsychosocial event, which has individualized objective and subjective events, making the perception of pain very different between individuals.¹ It has been shown that the actual pain detection and processing mechanisms can differ between individuals, making one population responsive to a particular analgesic and another population nonresponsive.^{2,3} The necessity to develop a collection of analgesics and drug-delivery methods for treating odontogenic pain exists.

NSAIDs have been shown to provide more pain relief than narcotics for odontogenic pain and have little potential for dependence, yet they do exhibit a ceiling effect.⁴ Analgesics administered orally, have the main disadvantages of decreased absorption rates and delayed onset. Conversely, analgesics administered through parenteral routes have increased drug absorption and shorter times of onset. Intranasal (IN) drug delivery takes advantage of a large surface area of mucosal tissue in the nasal and sinus cavities for rapid absorption into the bloodstream.⁵ Very few analgesics, however, have been tested for IN delivery.⁶⁻⁸ In particular, no NSAIDs were previously available for the general practitioner via IN delivery. Whether IN administration of NSAIDs shows significant rapid pain control for acute endodontic pain is yet to be studied.

Ketorolac tromethamine (ketorolac) is a racemic, nonsteroidal, antiinflammatory drug (NSAID) with potent analgesic and moderate antiinflammatory activity. It is available as a water-soluble salt.⁹ The half-life of ketorolac tromethamine is 4 to 6 hours, and it is metabolized in the liver and excreted primarily via the urine.⁸ Ketorolac has

analgesia efficacy that is similar to standard dosages of morphine and meperidine.⁹ Because of its efficient ability in controlling inflammatory pain, ketorolac has been shown to decrease the need for opioids postoperatively.¹⁰ Ketorolac has also proven to be an effective analgesic in endodontic pain. Penniston and Hargreaves¹¹ used a combination of either intramuscular or intraoral injection of ketorolac, placebo, or local anesthetic (2% mepivacaine). Their results showed that after 30 minutes and 45 minutes, only the intraoral ketorolac group showed a significant reduction in pain compared with the placebo group in the mandibular arch. Interestingly, they found that the intraoral and intramuscular administration of ketorolac significantly decreased the need for supplemental anesthesia during emergency endodontic procedures.¹¹ As an alternative to intramuscular or intravenous administration, the intranasal route has recently been studied. McAleer et al⁸ showed in humans that the bioavailability of intranasal ketorolac is similar to the intramuscular route after 15-mg and 30-mg administrations. Both groups had similar time incidences of maximum plasma concentration (0.5-0.75 hours).⁸

The aim of this study was (1) to compare the preoperative analgesic efficacy of intranasal administration of ketorolac with placebo and (2) to compare the postoperative analgesic efficacy after intranasal administration of ketorolac with placebo.

Materials and Methods

The protocol for this investigation was approved by the Institutional review board. Inclusion criteria were: Patient

necrosis, or was previously treated with a periradicular diagnosis of either normal, acute periradicular periodontitis, acute periradicular abscess, chronic periradicular periodontitis, or chronic periradicular abscess; and (5) provided informed consent for endodontic treatment. Exclusion criteria included: (1) known allergies to NSAIDs; (2) patient was pregnant or breastfeeding; (3) peptic ulcer disease, cardiovascular disease, renal disease, and any bleeding disorders; (4) patient was taking pain medication for an unrelated condition; (5) patient had difficulty or was unable or unwilling to use a nasal spray and/or had any inflammation or congestion in the nose; (6) patient was unable or unwilling to complete the pain questionnaires; (7) patient was unwilling to sign consent for endodontic treatment and/or the study; and (8) severe asthma, in which they have more than one asthma attack a month and have to carry an inhaler with them at all times.

Patients presenting to the Dept. of Endodontics at St. Joseph Dental College reporting pain on the verbal numeric rating scale at a level of 3 or greater out of 10 were screened as possible candidates for the study. Before endodontic treatment, patients meeting the criteria and willing and able to participate in the study signed a consent form for study participation and for root canal treatment.

Pulpal and periradicular diagnoses were determined after radiographic and clinical examination with appropriate diagnostic testing. A demographic form was completed for each study participant. The clinical examination included the inside of the participant's nose to ensure that there was

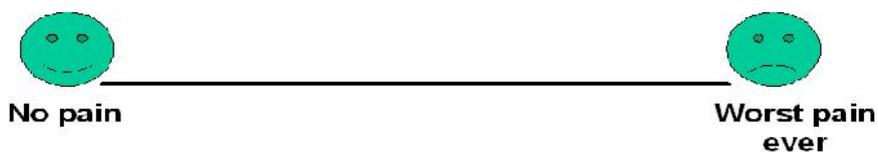


Figure 1: Visual Analog Scale.

was (1) American Society of Anesthesiologists' class I or II; (2) 18 years of age or older; (3) reported pain on the verbal numeric rating scale of 3 or greater out of 10; (4) symptoms suggestive of irreversible pulpitis, pulpal

no redness or swelling indicating inflammation. At that time, patients filled out the first pain questionnaire. On each pain questionnaire, the patient was asked to score their pain. The pain questionnaire consisted of two pain

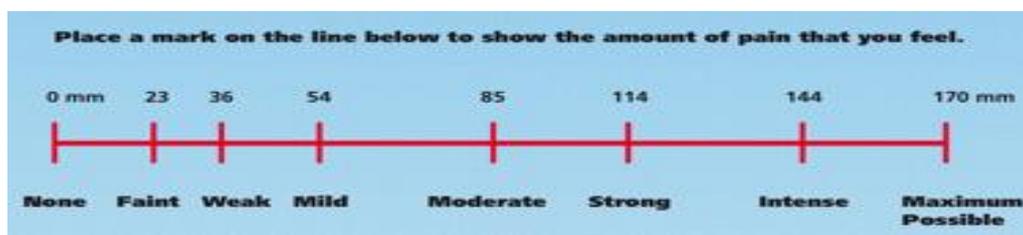


Figure 2: Heft Parker Scale.

scales: visual analog scale (VAS), and Heft-Parker. The VAS (Figure 1) consisted of a horizontal line measuring 0 mm through 100 mm, with 0 mm representing no pain and 100 mm representing the worst pain imaginable. The Heft-Parker pain scale (Figure 2) is a horizontal line measuring 0 mm to 170 mm with vertical lines intersecting it and descriptors at the vertical lines describing the severity of the pain.

Twenty patients were selected & randomly allocated (1:1) to ketorolac or placebo (saline) groups. Each nasal spray bottle looked the same and was labeled with a reference number (product provided by RUDA container, Mumbai)



Figure 3: Ketorolac (Dr. Reddy) in its injectable form.



Figure 4: Metered Dose Bottle.

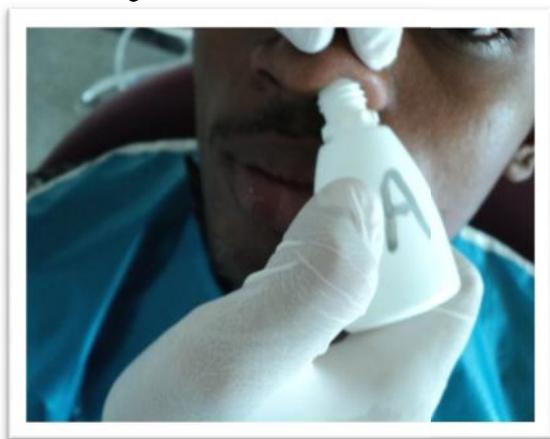


Figure 5: Intra Nasal spray.

unidentifiable to the primary investigator, co-investigators, or patient, thus achieving double blinding. After completion of the first pain questionnaire (baseline time and pain recording), patients were asked to inhale the assigned nasal spray. Ketorolac (Dr. Reddy Labs) in its injectable form (Figure 3) was used as the nasal spray at a concentration of 30 mg/mL. A total of 24 mg ketorolac was administered per patient through the study (12 mg preoperatively and 12 mg postoperatively). A metered dose bottle (Figure 4) designed to administer 0.1 mL ketorolac or placebo per spray was given to each participant. At each of two administrations, four sprays (two per each nostril) totaling 0.4 mL, were inhaled for a total dose of 12 mg of ketorolac (Figure 5). Participants were asked to use the nasal spray twice during the experiment, once 30 minutes before endodontic treatment and immediately after endodontic treatment.

Endodontic treatment then commenced with the administration of 72 mg lidocaine with 0.036 mg epinephrine. After rubber dam isolation, access cavity was done using Gates-Glidden drills and GT rotaries files (Tulsa-Dentsply; Tulsa, OK) to enlarge the orifice of each canal. Approximately 5 mL of 3% sodium hypochlorite was used throughout instrumentation. Access preparations were closed with a sterile cotton pellet and temporized (Cavit; 3M, St Paul, MN,). Once pulpal debridement/pulpectomy was completed, the patient was immediately administered the nasal spray again in the manner described previously. At the time of dismissal, patients were scheduled within 2 to 4 weeks for the completion of root canal treatment. Patients recorded their pain level again at 30 minutes after pulpal debridement and at 4 hours, 8 hours, and 24 hours from the time of initial administration of the nasal spray (Table 1). Pain questionnaires were marked for patients as to the exact time they needed to complete the remaining four

Table 1: Pain Questionnaire Timeline	
Pain survey	Time point
1	Baseline
2	15 min after nasal spray
3	30 min after nasal spray
4	30 min after 2nd nasal spray
5	4 hrs after 1st nasal spray
6	8 hrs after 1st nasal spray
7	24 hrs after 1st nasal spray

questionnaires. After completion of the 24-hour pain questionnaire, patients were instructed to return the last four questionnaires into the department. Before discharge, the patients received a patient packet containing acetaminophen 500 mg to be used as an escape medication for pain, a card with the emergency phone number, detailed instruction sheet for completing the study, 4 remaining pain questionnaires, and an envelope to return the questionnaires.

In all, patients were issued seven pain questionnaires that were to be completed at specific times, three preoperatively and four postoperatively (Table 1).

Results

Twenty-two patients were enrolled in the study-11 females and 9 males (ketorolac group size =10, placebo group size =10).

A significant difference was detected between the two study groups in the average change in pain scores from baseline over the follow-up period in ketorolac group. The time effect and interaction were not significant. The ketorolac group had larger decreases from baseline VAS values than the saline group at all time points.

well-documented history of excellent endodontic pain control with a novel intranasal delivery. When comparing the change in pain from the baseline pain levels, the ketorolac group showed a significant reduction in pain compared with the placebo group.

Parirokh et al showed that premedication with ibuprofen increased the success rates for inferior alveolar nerve block, whereas others have shown no significant increase in success rates using ibuprofen before an inferior alveolar nerve block.¹² Because of the predominant inflammatory nature of endodontic pain, NSAIDS have become the major avenue of pain control. Presently, the most convenient method of analgesic delivery in the dental office is via the oral route. The oral route has some disadvantages, including unpredictable absorption patterns, the first pass hepatic effect, and delayed onset.⁴ The time to maximal plasma concentration of intranasal ketorolac is comparable to that of the intramuscular route.⁸ Therefore, many of the disadvantages of the oral route can be avoided by using the intranasal route.

The time of onset for pain control is consistent with previous studies on intranasal ketorolac. The patients who

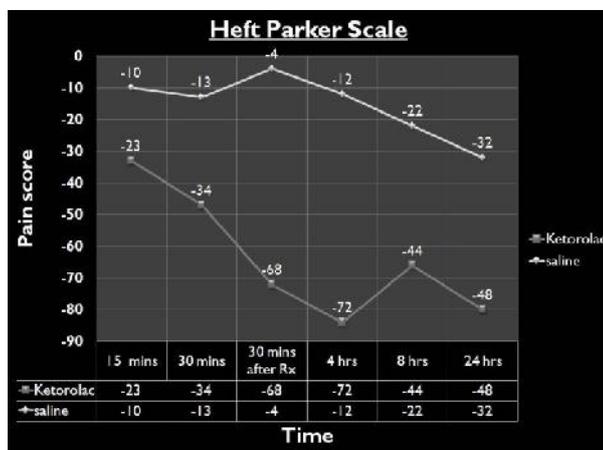


Figure 6: The Heft-Parker scale of reported pain differences for endodontic patients from baseline pain levels.

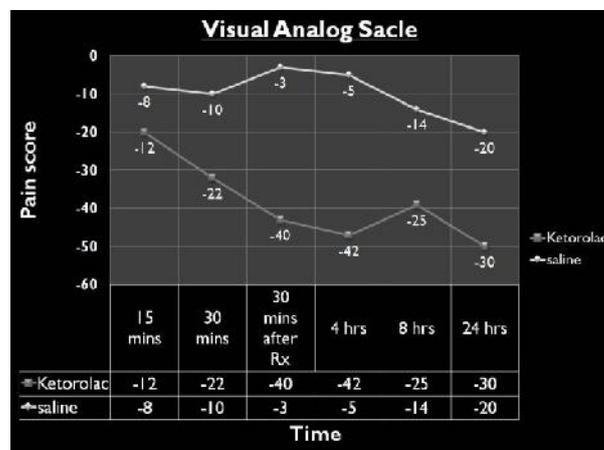


Figure 7: The visual analog scale of reported pain differences for endodontic patients from baseline pain levels.

Results from the differences in pain from baseline (pretreatment) levels with the Heft-Parker scale and Visual Analog pain scales are shown in Figures 6 and 7, respectively. Significantly greater decrease in pain from pretreatment pain were seen at timepoints 3, 4, and 5 in the Heft-Parker scale and at time points 4 and 5 using the category pain scale for the ketorolac group.

Discussion

This study evaluated the efficacy of an NSAID that has a

received ketorolac in the present study began to experience a significant change in their pain level compared with those receiving placebo by 30 minutes after the first intranasal administration of 12 mg. McAleer et al⁸ showed that the time to maximal blood concentration of the intranasal drug on human subjects was 30 to 45 minutes. The patients in the current study received local anesthesia immediately after the 30-minute post-administration pain evaluation so that the next questionnaire was filled out after endodontic

treatment (approximately 2 hours later) and 30 minutes after the second administration of intranasal ketorolac. Significant changes in the mean pain level from baseline of the ketorolac group are seen again at time points 4 and 5 (30 minutes after the second administration and 4 hours after the first administration), which is consistent with the T_{max} and $T_{1/2}$ of McAleer et al.⁸

Other investigators have recently evaluated this form of ketorolac in different pain models. Moodie et al.¹³ compared 2 different dosages of intranasal ketorolac (10 mg and 30 mg) and placebo. This study included patients who had recently experienced major surgery and were hospitalized for at least 48 hours. When patients were coherent and experienced pain, they were supplied with one of the study nasal sprays every 8 hours. If the patient's pain was not controlled, he/she had access to a rescue medication (morphine sulphate). The principal advantage of this study model was the captive study group (ie, patients were treated and evaluated while admitted to a hospital) and ready access to an effective rescue medication. Therefore, the incentive for participation in such a study design could be high.

Moodie et al showed that 30 mg intranasal ketorolac provides significantly more pain relief than 10 mg ketorolac or placebo.¹³ Thus, there is a threshold of dosage needed for significant pain control with ketorolac. The present study administered 24 mg ketorolac in two doses that were separated by endodontic treatment time (approximately 2 hours). McAleer et al⁸ showed that the bioavailability of 30 mg ketorolac administered intranasally is approximately equivalent to 20 mg administered intramuscularly. They state that the maximum efficacy of intramuscular ketorolac lies between 15 mg and 30 mg. It is conceivable that the equivalent plasma concentration from two separate doses of 12 mg ketorolac reached the threshold of optimal plasma concentration. By studying the results in the change in pain levels, it is noted that even a 12-mg intranasal dose of ketorolac began to give a significant reduction in pain compared with placebo. Therefore, in the endodontic pain model, patients began to have substantial pain relief in 30 minutes with an intranasal dosage of ketorolac that is possibly less than the intramuscular 15-mg dose. The cumulative dosage of intranasal ketorolac (24 mg over a 2- to 3-hour timeframe) in the present study is suggested to have reached the equivalent of 16 mg intramuscular ketorolac to provide additional long lasting analgesic effects (2-6 hours

postoperatively). Based on Moodie's¹³ results and the results of the present study, future studies should evaluate whether a single higher dose of ketorolac administered intranasally will provide additional pain relief with a minimal side effect profile.

There were no major adverse effects of intranasal ketorolac reported by the patients. The most common adverse report was a stinging sensation from nasal irritation at only the first dose in the ketorolac group, which subsided within 1 to 2 minutes. This is consistent with other studies involving ketorolac administration^{8,13} and has not been associated with any cytotoxic reaction.¹⁴⁻¹⁶ Other routes of administration may also cause irritation. Penniston and Hargreaves¹¹ injected 30 mg ketorolac intraorally and intramuscularly. They noted that only the patients in the intraoral ketorolac group reported injection pain (which lasted 3-5 minutes), whereas the placebo or intramuscular ketorolac group reported no such findings. The contact irritation experienced in the intranasal or intraoral route should be part of the risk-benefit explanation to the patient before the administration of ketorolac.

Conclusion

This prospective, double-blind clinical study evaluating the preoperative and postoperative effects of intranasal ketorolac for pain control showed a significant reduction in the change of mean pain scores from baseline over the follow-up time. Clinical applications of the present study could include the preoperative use of intranasal ketorolac for sustained pain relief postoperatively. Further studies in the area of intranasal ketorolac for the control of endodontic pain should include a single higher dose of ketorolac and preferably a sustained release formulation along with clinical trials with the recently Food and Drug Administration approved ketorolac nasal spray.

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