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A Comparison of Ketorolac Tromethamine and Acetaminophen Codeine in the Management of Acute Apical Periodontitis

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Effective management of severe endodontic pain is often a major problem. The analgesic effect of ketorolac tromethamine (Toradol, 10 mg po) was compared with acetaminophen codeine (325 mg/15 mg po) in patients with severe pain due to acute apical periodontitis in a double-blind clinical study. A total of 66 patients presenting with severe pain (defined as 7 cm and more using a visual analog scale) were randomly assigned to receive either ketorolac tromethamine or acetaminophen codeine (33 patients in each group), and recorded their pain score once every 10 min for 90 min after administration. Results indicate that patients in the ketorolac group had significantly less pain than those who received acetaminophen codeine ($p = 0.005$).

Pain control is a major stage of all dental practice, in particular root canal therapy. Endodontic pain is often associated with the inflammatory process. Inflammation alters the response of nociceptors through the action of inflammatory mediators (1). Prostaglandins (PGs), mainly of the E series (PGE_2) have been linked to several aspects of the inflammatory process, including vascular dilation, vascular stasis, and pain (2). McNicholas et al. (3) showed that acute periapical lesions have higher concentrations of PGE_2 than chronic lesions and confirm the role of PGs in the pathogenesis of human periapical disease. Importantly, increased concentration of these eicosanoids in pulpal and periapical tissues are associated with the presence of pain.

Ketorolac tromethamine (Toradol; Syntex Laboratories, Inc., Palo Alto, CA) is a new nonopioid analgesic, a nonsteroidal anti-inflammatory drug (NSAID). Ketorolac is a member of the pyrrolo–pyrrole group of NSAIDs and exerts its effect by inhibiting the cyclo-oxygenase enzyme system that metabolizes arachidonic acid to PGs (4–6).

Ketorolac has been used successfully in the treatment of postoperative surgical pain and other types of acute pain. In previous investigations, ketorolac has been found to be significantly more effective than meperidine, aspirin, acetaminophen, acetaminophen codeine, and acetaminophen hydrocodone for the relief of postoperative pain following major dental surgeries (4, 6).

Curtis et al. (7) also compared intramuscular use of ketorolac with placebo for the relief of severe odontogenic pain. Results indicate that patients in the ketorolac group had significantly less pain than those receiving placebo.

Penniston et al. (8) suggested intraoral injection of ketorolac as a useful adjunct in the management of endodontic pain.

The purpose of this study was to compare the analgesic effect of ketorolac with that of acetaminophen codeine for the relief of pain due to presence of acute apical periodontitis (AAP).

MATERIALS AND METHODS

Sixty-six patients participated in this single-dose, double-blind study. All of the patients presented with signs and symptoms of severe AAP to the Dental School of Tehran University and two private dental clinics. Severe AAP is defined as a condition in which the involved tooth is exquisitely painful to touch and there is no overt swelling, but a grossly painful tooth elevated in its socket (9).

Patients were screened at entry according to the degree of their base line pain, which was determined with the use of a visual analog scale (VAS) (10). The VAS consisted of a line of 10 cm length with 0 (0 cm) signifying no pain and 10 cm representing the worst pain imaginable. Patients marked a score on the line to indicate their pain intensity. A patient with signs and symptoms of AAP was considered to be eligible for the study, if he/she placed a mark at the 7 cm or above level. To reduce the variables, only those patients with preoperative AAP due to the extension of pulpal disease into periapical tissue were considered. Those having AAP caused by endodontic procedures or occlusal trauma were excluded. All of the patients could read and understand questionaires. Patients were excluded if they fell into any of the following categories: (a) age <16 years or >65 years, (b) ingestion of analgesic within the last 4 h of their visit, (c) history of allergy to NSAIDs or aspirin, (d) history of peptic ulcer disease, (e) history of renal or hepatic disease, (f) hemorrhagic disorders, and (g) pregnancy or breast feeding.

Using a double-blind protocol, patients were randomly given either ketorolac (10 mg po) or acetaminophen codeine (325 mg/15 mg po). The drugs were encapsulated and packaged in identical, opaque, brown capsules. After administration, each patient was monitored at 10-min intervals for 90 min. Using the VAS, their

TABLE 1. Demographic, clinical and diagnostic data

Gender	Female (41%)
	Male (59%)
Age	<21 (6%)
	21–39 (65%)
	40–59 (29%)
	>60 (0%)
Marital status	Single (27%)
	Married (73%)
	Divorced (0%)
Systemic disease	Yes (8%)
	No (92%)
Periodontal problems	Yes (6%)
	No (94%)
Crown status	Restoration (16%)
	Caries (79%)
	Intact (2%)
	Tooth as an abutment (3%)
Pulp status	Vital (0%)
	Nonvital (100%)
Radiographic manifestations	Apical or lateral radiolucency (14%)
	Normal (46%)
	Thickened PDL (38%)
	External resorption (2%)
	Internal resorption (0%)
	Root fracture (0%)
Sensitivity on palpation and/ or percussion	Yes (100%)
	No (0%)
Tooth mobility	Yes (8%)
	No (92%)

PDL, periodontal ligament.

subjective pain intensity was determined. They were also evaluated for possible side effects at each interval.

Immediately following the experimental period, each patient received the appropriate dental treatment to eliminate the source of his/her pain.

Upon completion of the study, data were analyzed by Epi-Info software with a regression analysis method. For each group, scatter diagrams and regression lines according to scatter diagrams were drawn. The values of "a" and "b" in line equations, $y = bx + a$ were specified and then analyzed with the t test.

RESULTS

Of the 66 patients enrolled in the study, three patients were excluded because they could not complete the requirements specified in the study. Sixty-three patients (31 ketorolac and 32 acetaminophen codeine) were included in the study.

Demographic data and the parameters related to the study are summarized in Table 1. The mean pain intensity at 10-min intervals for both groups are shown in Table 2.

Similarities of the treatment groups were evaluated by comparing both patient demographics and preoperative pain level. Two groups were statistically identical in regard to gender, mean age, and the location of the tooth (maxilla or mandible). At initial VAS recording (time 0), there was no significant difference between the experimental groups ($p > 0.1$).

TABLE 2. Mean pain intensity in 10-min intervals

Time	Ketorolac	Acetaminophen Codeine
0	7.8710	7.9375
10	7.3226	7.5938
20	6.4516	7.2500
30	5.5806	6.8438
40	4.4839	6.2188
50	3.5161	5.8125
60	2.7419	5.3750
70	1.9355	5.0625
80	1.3871	4.6250
90	1.0000	4.3438

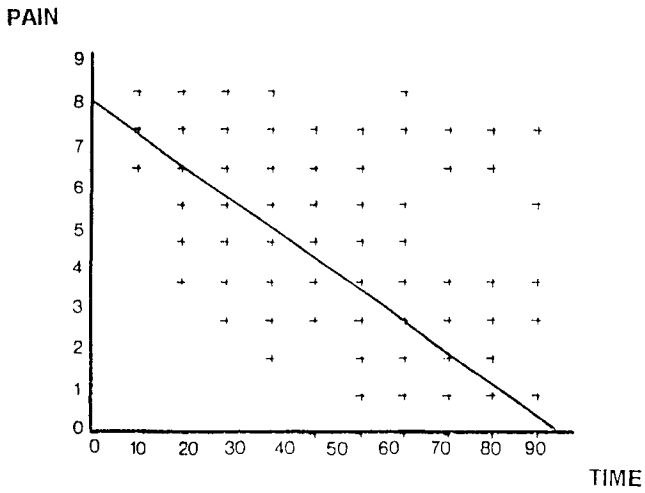

FIG 1. Scatter diagram and regression line, ketorolac tromethamine.

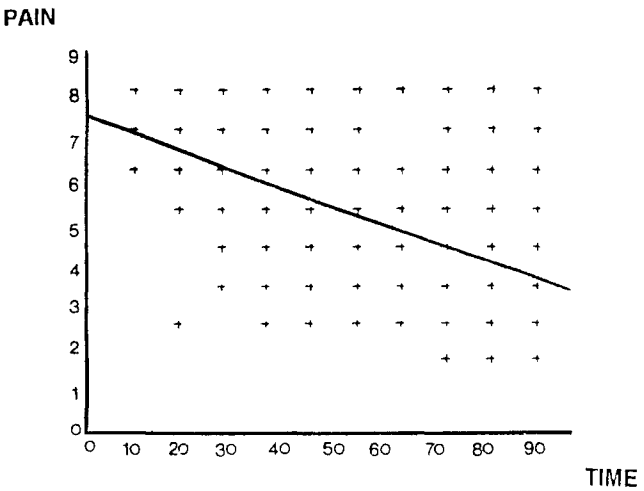

FIG 2. Scatter diagram and regression line, acetaminophen codeine.

The effectiveness of drugs in reducing pain intensity was analyzed by regression analysis. Scatter diagrams and regression lines are shown in Figs. 1 and 2. There is a significant difference between two drugs, and ketorolac was shown to be more effective than acetaminophen codeine to relieve pain due to AAP (t test, $p = 0.005$).

A statistically significant difference was found between the two groups when comparing VAS scores at 90 min (t test, $p = 0.05$).

No side effects were reported by patients in either experimental groups.

DISCUSSION

The use of new NSAIDs, such as ketorolac tromethamine, in the control of dental pain has been the subject of recent publication (6). The beneficial effect of these drugs has been described in many controlled clinical studies (6, 11–13). Minor surgical operation, like removal of the impacted third molar, has been one of the successful application of these drugs. However, in these studies, other causes of odontogenic pain, especially endodontic pain, are less considered.

In this study, pain due to the AAP as a model was used. This is a common complaint in dentistry, and the patient seeks emergency treatment (9). The aim of this study was not the introduction of a new treatment method for AAP, because the standard treatment for this condition is root canal therapy (9). It seems that there are few studies in the literature that deal with the use of ketorolac in acute odontalgia (7, 8). This study seems to be unique in two ways. First, the drugs are used in a specific model of dental pain, namely AAP, whereas in previous studies all forms of odontalgia had been considered, without specifying the precise features of pain or the condition of the pulp and periapical regions. On the other hand, this is the first study that has used oral ketorolac in the treatment of AAP. In this study, a placebo was not used. It is not moral to use a placebo, because the pain model is too severe to be tolerated by the patients.

As mentioned before, ketorolac is an NSAID and acts by inhibiting PG production (4, 6), which will in turn relieve pain due to pulpal and periapical inflammation. This can explain the results of this study. Previous reports have shown that the inhibitory effect of ketorolac on cyclo-oxygenase (5, 6) is more peripheral when compared with acetaminophen, which seems to have a more central effect (14). On the other hand, the inhibiting effect of acetaminophen on cyclo-oxygenase is poor, and its effect on PGs production is less than ketorolac. This could explain the significant difference between these two drugs in this study.

The results of this study correlate with the results of a study by Forbes et al. (12), who compared the effect of oral ketorolac on patients who had surgery of the third molar with acetaminophen codeine. Another study by Vangen et al. (15) showed that the effect of a 10 mg oral dose of ketorolac in moderate to severe gynecological pain is similar to a dose of 1000 mg/60 mg of acetaminophen codeine. Considering the difference in the pain model, this may not be a proper comparison; nevertheless, the analgesic effect of 10 mg of oral ketorolac is significantly greater than acetaminophen codeine (325 mg/15 mg) in AAP. Although a significant difference may exist between ketorolac and acetaminophen codeine, the latter has also been an effective analgesic in AAP.

In this study, no side effect was found for the two drugs; but, in the study by Frick et al. (13) that used a single oral dose of 10 mg ketorolac, a small percentage of complications were reported. Chronic use of ketorolac increases the risk of gastrointestinal bleeding and ulceration. Because of increased risk of gastrointestinal problems, ketorolac should be used only for a limited duration (1 to 3 days) (6).

Penniston and Hargreaves (8) used a periapical injection of ketorolac to relieve odontalgia. They reported better symptom control in the mandible compared with the maxilla, and suggested that tissue differences may affect the pharmacodynamics and pharmacokinetics of ketorolac. In regard to pharmacodynamics, it may be that prostanoids are more effective in the mandible. For example, there may be differences in metabolism or distribution in the maxilla, compared with the mandible. On the other hand, the more dense mandible may cause more pressure during inflammation and cause an increase in the activity of sensitized PG receptors. The type of drug administration in Penniston's study is different from this study and their hypothesis, considering that the difference of pharmacodynamics of ketorolac in the mandible and maxilla has not yet been proved. In this study, a statistical analysis for the distribution of the location of teeth (maxilla or mandible) was done, and there was not any significant difference. Even if the effect of ketorolac would be greater in the mandibular teeth, compared with the maxillary teeth, using the abovementioned statistical test, the results would still be valid.

Acute endodontic pain, whether acute pulpulgia or AAP is dependent on the inflammatory process and immunological reactions. Thus, the use of analgesic drugs with an anti-inflammatory effect could help toward the successful control of pain. Although in this study the analgesic effect of the drug in AAP prior to any treatment was evaluated, other studies have shown that pulpalgia and pain during or after endodontic treatment appointments have similar etiologies (2). It can be supposed that the use of ketorolac may control this type of pain as well. Further studies are required to evaluate the clinical efficacy of this drug in the management of other types of endodontic pain with other types of drug administrations, such as intramuscular or intraoral injection.

Finally, considering the results of the present and previous studies, ketorolac can be regarded as a potent analgesic drug with few side effects. Regardless of its high cost, ketorolac can be used for pain control in dentistry, especially for endodontic pain.

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