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Effect of single dose pretreatment analgesia with three different analgesics on postoperative endodontic pain: A randomized clinical trial

Priyank Sethi, Manish Agarwal, Hemant Ramesh Chourasia, Mahesh Pratap Singh

Department of Conservative Dentistry and Endodontics, Peoples College of Dental Sciences and Research Centre, Bhopal, Madhya Pradesh, India

Abstract

Introduction: One of the aims of root canal treatment is to prevent or eliminate pain. Postoperative endodontic pain control continues to be a significant challenge.

Aim: To compare and evaluate the effect of single oral dose of 100 mg of tapentadol, 400 mg of etodolac, or 10 mg of ketorolac as a pretreatment analgesic for the prevention and control of postoperative endodontic pain in patients with symptomatic irreversible pulpitis. The incidence of side effects was recorded as secondary outcome.

Materials and Methods: Sixty emergency patients with moderate to severe pain, diagnosed with symptomatic irreversible pulpitis were randomly allocated (1:1:1) to any of the three groups; tapentadol, etodolac, or ketorolac. Medications were administered 30 min before beginning of the endodontic treatment. Patients recorded pain intensity on 10 cm visual analog scale (VAS) after treatment, for upto 24 h.

Results: At 24 h, mean \pm standard deviation (SD) of VAS scores (in cm) for tapentadol, etodolac, and ketorolac were 0.89 ± 0.83 , 2.68 ± 2.29 , and 0.42 ± 0.69 , respectively. Kruskal-Wallis (K-W) test showed significant difference among the three groups ($P = 0.001$). Mann-Whitney test showed significantly lower VAS scores in tapentadol and ketorolac than etodolac group ($P = 0.013$ and 0.001 , respectively).

Conclusions: Single oral dose of 10 mg of ketorolac and 100mg of tapentadol as a pretreatment analgesic significantly reduced postoperative endodontic pain in patients with symptomatic irreversible pulpitis when compared to 400 mg of etodolac.

Keywords: Analgesia; etodolac; ketorolac; postoperative endodontic pain; pretreatment analgesia; tapentadol

INTRODUCTION

When most individuals seek root canal therapy, pain is already present and is the most common reason for patient reporting to the dental office. A significant relationship exists between pre- and post-endodontic pain. Up to 80% of patients with preoperative pain continue to report mild to severe pain after endodontic treatment.^[1,2] Thus, prevention and management of postoperative endodontic pain becomes an integral part of endodontic treatment. Preparing patients about the expected postoperative endodontic pain and prescribing medications can increase patient confidence, pain threshold, and can improve their attitude towards the endodontic therapy.^[3,4]

Need of the hour is to develop new pain management strategies with optimal analgesic therapy for acute pain management with minimum incidence of side effects. However, a definitive anti-inflammatory and analgesic protocol to prevent and control the occurrence of postoperative endodontic pain has not yet been established.^[5] Preoperative administration of some analgesics has shown to reduce the onset of postoperative pain.^[6,7]

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit prostaglandin synthesis by decreasing the activity of the enzyme, cyclooxygenase (Cox) 1 and 2. Many NSAIDs like ibuprofen, aspirin,^[8] flurbiprofen,^[9] ketorolac,^[10,11] and etodolac^[12] have shown to produce significant reductions

Address for correspondence:

Dr. Priyank Sethi, Department of Conservative Dentistry and Endodontics, Peoples College of Dental Sciences and Research Centre, Bhopal - 462 037, Madhya Pradesh, India.

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in dental pain using clinical trials. Etodolac has a high affinity to block the Cox-2 enzyme,^[13] but its ability to control post-endodontic pain when administered prophylactically has not been analyzed much. Ketorolac has shown high efficacy in inhibiting Cox enzyme and has analgesic efficacy that is similar to standard dosages of morphine and meperidine.^[14]

However, patients having gastrointestinal ulcers, bleeding abnormalities, bronchospasm, and liver function changes are contraindicated to NSAIDs. In these cases, opioids like tramadol have shown to produce significant reductions in dental pain using clinical trials.^[9]

Many opioids still possess issues of drug dependency, withdrawal symptoms, and seizure-like side effects. Tapentadol is a centrally acting opioid analgesic with two modes of action, combining μ -opioid agonist and norepinephrine reuptake inhibition (NRI) in a single molecule with the rationale to produce an opioid-sparing effect. But this promising analgesic has not been tested much in endodontic pain models.

The purpose of this study was to evaluate postoperative pain in patients diagnosed with symptomatic irreversible pulpitis, receiving endodontic treatment after pretreatment analgesia with single oral dose of either 100 mg of tapentadol, 400 mg of etodolac, or 10 mg of ketorolac for the management of postoperative endodontic pain. Null hypothesis tested was that there exists no significant difference among the three groups in postoperative endodontic pain management.

MATERIALS AND METHODS

This research protocol was approved by the Institutional Ethical Committee. Patients reporting to the postgraduate endodontic clinic from 11 September 2012 to 05 February 2013, within the age group of 18-60 years were enrolled for the study. Demographic details and thorough case history was recorded with stress on medical and drug histories. Clinical examinations, including thermal (cold) test, electrical pulp testing, periodontal assessments, and radiographic examinations were performed.

Sixty patients diagnosed with symptomatic irreversible pulpitis in multirooted teeth with baseline pain scores greater than 3 cm on visual analog scale (VAS) were included in the study. Exclusion criteria were any drugs taken within the last 8 h; patients under any currently acting analgesics; patients with any systemic or mental illness, pregnant or lactating mothers; patients with acute endodontic abscess, periodontal diseases, and retreatment cases; and any known allergy or sensitivity to the study groups.

Selected patients signed an informed consent prepared on World Health Organization (WHO) Guidelines,^[15] which outlined the study procedure. A sample size of 17 patients per group was calculated based on the results of the pilot study to achieve 95% confidence interval (two-sided) and 90% power of the study. Considering the dropouts, a final sample size of 20 patients per group was decided.

The selected patients were randomly assigned (1:1:1) [Figure 1] to any of the three study groups: Group 1- tapentadol (Tydol 100 mg - Ranbaxy Laboratories Ltd), Group 2- etodolac (Etura 400 mg - Dr Reddy's Pvt Ltd), and Group 3- ketorolac (Ketanov 10 mg - Ranbaxy Laboratories Ltd). Single oral dose of medication was provided 30 min before the initiation of endodontic therapy. Food intake was withheld for next 3 h and patients were allowed only drinking water, so as to prevent injury to the oral tissues by biting on the areas that are anesthetized.

In this clinical trial, all medications were sealed in coded packets by a staff nurse, who was blinded to the aim and research protocol. All the drug packets were coded with randomly generated area pincodes of six digits on Microsoft Excel Sheet 2007. The packets were maintained by an investigator, who was blinded to the drugs and the coding protocol. He supervised the patients while taking the oral medications. Endodontic therapy, in all cases was performed by an endodontic postgraduate resident who was also blinded to the coding protocol.

Each patient was anesthetized with 2ml of xylocaine 2% with adrenaline 1:200,000, AstraZeneca, India followed by rubber dam isolation and access cavity preparation.

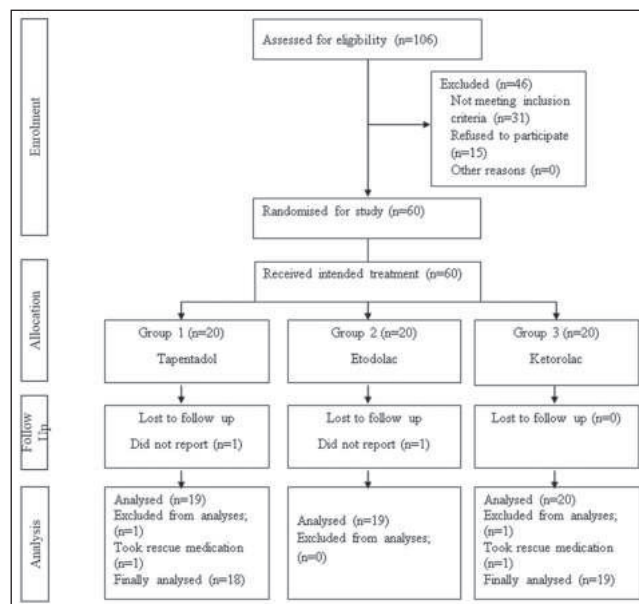


Figure 1: CONSORT flow chart: Flow of patients through each stage. CONSORT = Consolidated Standards of Reporting Trials

Working length was determined with Root ZX mini apex locator (J. Morita, USA) and periapical radiographs. Cleaning and shaping was done using passive step-back technique to enlarge the canal to a minimum apical size of #30 file or larger depending on the size of the canal. Sodium hypochlorite (2.5%) and normal saline were used as irrigants. Finally, canals were dried with paper points and the access cavities were restored temporarily with Cavit (3M ESPE, St Paul, MN, USA).

Each patient was provided with a postoperative pain questionnaire having VAS and side effect chart. Patients were encouraged to make immediate postoperative pain measurement (0 h) in order to ensure patient understanding of the pain questionnaire. Patients were instructed to complete the questionnaire at 0, 6, 12, 18, and 24 h after completion of root canal treatment. Pain intensity was recorded using VAS, which consisted of a 10-cm line anchored by two extremes, “no pain” and “pain as bad as it could be”.^[16] Patients were asked to make a mark on the line that represented their level of perceived pain. All common side effects mentioned by drug manufacturers were included in the side effect chart as none, mild, moderate, and severe.^[17] Side effects included were nausea, vomiting, diarrhea, constipation, heartburn, stomach pain, dizziness, headache, drowsiness, skin itching, and blurred vision. Patients were also provided with escape medication (Tab. Ibugesic 600 mg, Cipla Ltd, India) and were instructed to take medication in case of severe pain and report immediately. However, these patients were excluded from the analysis [Table 1].

All the statistical calculations were made through the Statistical Package for Social Science (SPSS) version 17. The three test groups were compared at baseline for age using one-way analysis of variance (ANOVA); for gender and tooth location using Pearson chi-square test; and for VAS score of preoperative pain using Kruskal-Wallis (K-W) test. To compare VAS scores of the three test groups at 0, 6, 12, 18, and 24 h; K-W test was applied. When K-W test showed significant difference, Mann-Whitney U test was applied for pairwise comparisons. *P*-value less than 0.05 was considered statistically significant. However, as the number of patients who reported side effects were very less [Table 2], no statistical tests could be performed.

RESULTS

Table 1 shows the number of patients analyzed (*n* = 56) and the number of patients excluded (*n* = 4) from the analysis. These were excluded because of the homogeneity of noncompliance between the study groups and lack of evidence of severity of pain scores amongst them. The number of noncompliance samples was almost equal amongst the groups. Otherwise, excluding the

Table 1: Number of patients excluded from the analysis

Patients	Group 1	Group 2	Group 3
	Tapentadol	Etodolac	Ketorolac
Took escape medication	1	0	1
Did not report back	1	1	0
Total number of patients excluded	2	1	1
Total number of patients analyzed	18	19	19

Table 2: Severity-wise distribution of reported side effects

Side effects	Severity	Group 1	Group 2	Group 3
		Tapentadol <i>n</i> = 18	Etodolac <i>n</i> = 19	Ketorolac <i>n</i> = 19
Nausea	Mild	2	1	0
	Moderate	1	0	0
	Severe	1	0	0
Vomiting	Mild	0	0	0
	Moderate	2	0	0
	Severe	0	1	0
Headache	Mild	1	2	1
	Moderate	2	1	0
	Severe	1	1	0
Dizziness	Mild	1	4	1
	Moderate	2	0	0
	Severe	1	0	0
Heartburn	Mild	0	0	0
	Moderate	2	1	0
	Severe	0	0	0

noncompliance samples was not allowed. The analysis was carried out on the VAS scores of 56 fully compliant samples with demographic data.

No significant differences were seen among the three groups with respect to preoperative pain scores, age, gender, and tooth location; as shown in Table 3. All patients reported postoperative pain at the 0, 6, 12, 18, and 24 h time intervals. Table 4 shows the mean and standard deviations (SDs) of VAS scores for tapentadol, etodolac, and ketorolac at different time intervals. At 0 and 24 h, the VAS scores of tapentadol and ketorolac groups were significantly lower than etodolac group. At 6, 12, and 18 h; ketorolac group showed significantly lower VAS scores than tapentadol group; and VAS scores in tapentadol and ketorolac groups were significantly lower than etodolac group [Figure 2]. Table 2 shows number of patients reporting incidence of side effects.

DISCUSSION

Postoperative endodontic pain control continues to be a significant challenge. Amongst all dental procedures, endodontic treatment produces more frequent and severe postoperative pain.^[18] Endodontic treatment itself can trigger production of prostaglandins due to the trauma of severing the pulp and the irritation of the periodontal ligament (PDL) subsequent to establishing patency, cleaning, and shaping. This inflammatory process in the periradicular areas of the tooth after treatment can

Table 3: Demographic data

Variables	Group 1	Group 2	Group 3	P-value
	Tapentadol n = 18	Etodolac n = 19	Ketorolac n = 19	
VAS score of preoperative pain (cm); mean±SD	6.33±1.33	6.26±1.48	6.16±1.30	0.947 ns
Age (years); mean±SD	31.67±10.72	30.11±7.86	30.74±12.05	0.899 ns
Gender (male:female)	12:6	10:9	13:6	0.547 ns
Tooth (upper:lower)	07:11	08:11	08:11	0.974 ns

SD: Standard deviation, n: Number of patients, ns: Not significant

Table 4: Comparison of mean and standard deviations of VAS scores (cm)

Time intervals (hours)	Group 1 Tapentadol, n = 18	Group 2 Etodolac, n = 19	Group 3 Ketorolac n = 19	P-value	Mann-Whitney U test (significant difference)
	Mean±SD	Mean±SD	Mean±SD		
0	0.72±0.67	2.00±1.67	0.84±1.71	0.018	1,3<2
6	1.17±1.04	2.53±1.58	0.53±1.17	0.000	3<1; 1,3<2
12	1.17±1.10	2.58±1.86	0.42±0.77	0.000	3<1; 1,3<2
18	1.06±1.39	2.95±2.15	0.37±0.68	0.000	3<1; 1,3<2
24	0.89±0.83	2.68±2.29	0.42±0.69	0.001	1,3<2

K-W test = Kruskal-Wallis test

produce postoperative pain.^[19] Moreover, postoperative pain is more likely to occur within the first 24 h following endodontic treatment.^[20] Management of postoperative pain is multifactorial and should be aimed at reducing the peripheral and central components of hyperalgesia with endodontic and pharmacological therapy.

Reduction of postoperative endodontic pain after pretreatment analgesia with NSAIDs has been well proved in both oral surgery^[6] and endodontic models.^[21] Pretreatment analgesia with NSAIDs before endodontic treatment can block the Cox pathway and might block the pain sensation before it even originates.^[7]

In the present study, pretreatment analgesia was given to patients diagnosed with symptomatic irreversible pulpitis and without any signs and symptoms of apical periodontitis. Patients with tenderness on vertical percussion were excluded from the study, as such patients may require additional medication to relieve postoperative endodontic pain.^[7]

Ketorolac, peripherally inhibits prostaglandin synthesis resulting in a decreased amount of prostaglandin to sensitize pain receptors. Oral ketorolac is completely absorbed, with a mean peak plasma concentration occurring at an average of 44 min after a single 10-mg dose.^[22] Oral formulation of 10 and 20 mg ketorolac as postoperative doses provided the same analgesia as 400 mg ibuprofen, and significantly

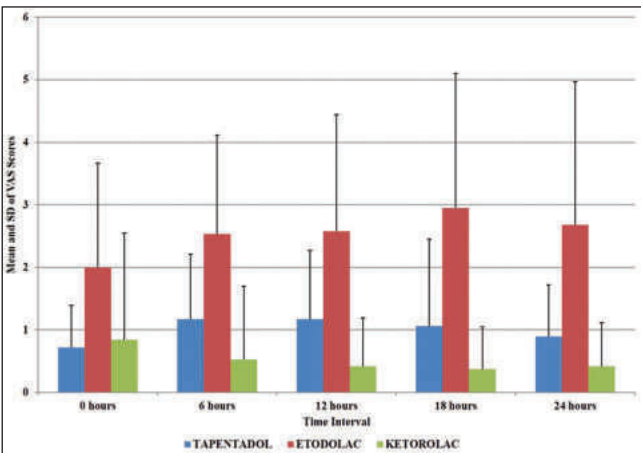


Figure 2: Mean and standard deviations of VAS scores. VAS = Visual analog scale

better analgesia than acetaminophen and acetaminophen codeine combinations.^[23]

Etodolac has proven to be effective for postoperative pain management in oral surgery models with minimal gastrointestinal irritation due to selective sparing of cytoprotective prostaglandins.^[24]

Tapentadol activates the opioid receptors, particularly the μ -opioid receptor (MOR), which is one of the main options for the treatment of moderate-to-severe pain. Consistent with the rationale above, tapentadol has demonstrated potent analgesia in acute and chronic pain along with a substantially improved gastrointestinal sideeffect profile in clinical studies.^[25]

Results of the present study demonstrate that pretreatment analgesia with ketorolac significantly decreased postoperative endodontic pain when compared to tapentadol and etodolac at 6, 12, and 18 h. Tapentadol and ketorolac were significantly better than etodolac at 0 and 24 h, but no significant difference was found between both of them. Etodolac showed significantly higher VAS scores. This finding may suggest that etodolac might not have a high affinity for the inflammatory components of an endodontic pain in comparison to ketorolac and tapentadol. None of the medications showed any higher incidence of side effects [Table 2] and were relatively safe.

CONCLUSIONS

Within the limitations of the study, pretreatment analgesia with single oral dose of 10 mg of ketorolac and 100 mg of tapentadol when given 30 min before endodontic treatment showed substantial reduction in postoperative pain when compared with 400 mg of etodolac. This might be helpful to prevent postoperative endodontic pain,

especially in patients with a low pain threshold. Further studies examining different clinical conditions, single-versus multiple-visit endodontic treatment, modes of drug delivery, and use of immediate release and sustained release drugs should be carried out to elucidate the potential of these drugs in the context of endodontic pain.

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