Original Article

Comparative evaluation of efficacy of diclofenac and ketoprofen administered using transdermal drug delivery route in management of post endodontic pain: A randomized controlled clinical trial

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Abstract

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used as a postoperative medication after endodontic treatment. The introduction of transdermal patches aided in reducing the discomfort caused by medication prescribed through the oral route.

Aim: This study aims to compare the efficacy of transdermal patches of diclofenac and ketoprofen for postendodontic pain control.

Materials and Methods: Thirty patients with symptomatic irreversible pulpitis in singlerooted teeth of either arch were endodontically treated by a single endodontist. Oral diclofenac for Group I and transdermal diclofenac patch for Group II and transdermal ketoprofen patch for Group III were administered as postendodontic analgesics. Visual Analog Scale chart was used to record pain intensity preoperatively and at intervals of 4, 8, and 24 h postoperatively. Paracetamol 500 mg tablets were provided as rescue medication.

Statistical Analysis: Repeated Measure ANOVA.

Results: There was a significant decrease in the postoperative pain intensity scores for both transdermal groups. The postoperative scores gradually decreased from day 1 to day 2. Six out of ten patients who had received diclofenac tablets complained of gastric discomfort.

Conclusion: Both transdermal ketoprofen and diclofenac patches were effective than oral diclofenac tablet and can be used as an alternative and effective analgesic for postendodontic pain management, especially in patients with gastric discomfort.

Keywords: Ketoprofen; nonsteroidal anti-inflammatory drugs; postendodontic pain; transdermal patch

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INTRODUCTION

Postoperative pain following endodontic intervention has often been a nemesis for the operator and the patient alike due to the considerable amount of inflammatory response

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involved.[1] It has been reported that up to 80% of patients who had preoperative pain continued to experience pain after endodontic therapy, with pain levels ranging from mild to severe.[2] Pain is typically higher in the first 48 h and gradually becomes better with time, generally subsiding away after 7–10 days.[3]

Management of postoperative pain still remains the subject of ongoing study, with more advanced formulations and treatment approaches continuously replacing the antiquated ones.[1] Numerous approaches, including opioids, glucocorticoids, long-acting local anesthetics, and nonsteroidal anti-inflammatory drugs (NSAIDs), have been recommended to lessen pain. Non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed for moderately painful conditions.[4] NSAIDs work by inhibiting prostaglandin production and cyclooxygenase activity to provide anti-inflammatory and analgesic effects.[5,6]

The mechanism of action of NSAIDs is inhibition of COX thereby reduction of prostaglandin production. Prostaglandins are compounds synthesized from the dietary essential fatty acids primarily linoleic acid which is metabolized to arachidonic acid and are collectively known as "eicosanoids."[7] Prostaglandins are mucoprotective and ulcer healing agents. They form a cytoprotective layer and increase the secretion of bicarbonate ions that neutralize gastric acidity. Conventional NSAIDs possess the nonselective inhibitory action of COX, which leads to a reduction in bicarbonate secretion and reduced mucous production.[7,8] In addition, it has antiplasmid activity, the ability to change the expression of genes encoding transport or binding proteins, and the ability to downregulate efflux pumps, all of which have the ability to have bacteriostatic effects.[9,10]

Since the majority of NSAIDs are weak organic acids with low pKa values, they remain in equilibrium in the stomach and are significantly absorbed from the stomach. However, once they penetrate the stomach cells' cell membranes, they encounter a fundamental pH condition called "trapping" of the medications inside the cell. This topical effect is considered an important mechanism of gastroduodenal damage associated with NSAIDs use, for example, ulcers, severe bleeding, perforation, and obstruction.[8]

These analgesics are administered through a variety of routes and each has its own positive and negative aspects. The drug delivery system's goal is to quickly and sustainably supply the required drug concentration throughout the dosage by delivering an effective therapeutic quantity of the medication to the target site of action in the body. Even though oral administration has notable advantage of easy administration, it also carries significant drawbacks – namely poor bioavailability due to hepatic metabolism (first pass mechanism), gastric discomfort, and the inclination to yield rapid blood level surges (both high and low).[11,12]

To overcome this, the transdermal drug delivery system (TDDS) was emerged so as to achieve improved therapeutic efficacy, safety of drugs by more precise spatial and temporal placement within the body thereby reducing both size and number of doses and also increased its effectiveness with optimum dose concentrations.[12]

Hence, the present study aimed to compare the efficacy of diclofenac and ketoprofen administered using a transdermal drug delivery route for the management of postendodontic pain. The null hypothesis was that there would be no significant difference among the pain scores after the administration of different NSAIDs through the transdermal route.

MATERIALS AND METHODS

Source of data

Patients were selected from the Department of Conservative Dentistry and Endodontics. Before the study began, the Institutional Ethics Committee granted approval for it (no: PMVIDS and RC/IEC/ENDO/PR/541-22). The investigation was registered in the Indian Clinical Trials Registry (no: CTRI/2023/06/054464). Subject's confidentiality and anonymity were secured.

Inclusion criteria

- Patients between the ages of 18 and 45 years, of both sexes, are included
- Patients with symptomatic irreversible pulpitis reported discomfort in single-rooted lower premolar teeth in either jaw
- An intraoral periapical radiograph of selected teeth ought to exhibit intact lamina dura and no periapical radiolucency
- Teeth with lack of any anatomical challenges, such as canal calcifications, with no foreseen procedural complications.

Exclusion criteria

- Teeth with associated periodontal conditions
- People who have previously experienced adverse responses to diclofenac and ketoprofen or other nonsteroidal anti inflammatory drugs (NSAIDs), such as bronchospasm, shock, and urticarial
- Patients who had active duodenal or stomach ulcers in 6 months before
- Patients receiving NSAIDs or corticosteroids during the study
- People with a history of illnesses such as bronchial asthma, epilepsy, inflammatory bowel disease, severe liver or renal insufficiency, dengue fever, and mental or psychological issues
- Women who are pregnant and breastfeeding
- Patients with a history of receiving antibiotics during the study.

Study design

The sample size was estimated using the G*power software (version 3.1.9.3 designed for Macintosh, developed by Heinrich Heine University in Dusseldorf, Germany) as part of an a prior sample size assessment within the F tests category, based on the previous literature, wherein at an effect size of 0.624, 95% confidence interval, and a power of 0.80, the estimated sample size is 30 (with 10 in each group). Patients who reported to the Department of Conservative Dentistry and Endodontics with complaints of tooth discomfort were examined and 30 patients were chosen based on the inclusion and exclusion criteria [Table 1]. It was a Randomized controlled clinical trial with concurrent parallel grouping. The current study adhered to all ethical standards and the rules outlined in the Helsinki Declaration and fulfills the CONSORT guidelines.

The patients were informed about the study's methodology and the potential negative effects of the medications being used. All patients provided their voluntarily informed written consent. Each patient's brief medical history was acquired to rule out any underlying illnesses and drug hypersensitivity. Each patient was given a Visual Analog Scale (VAS) and was asked to score their discomfort before treatment. Patients with a baseline score of more than 3 were included in the study.

The tooth was anesthetized using 2% lignocaine with 1:200,000 adrenaline and isolated using a rubber dam. An access cavity was established using Endo Access burs, the coronal portion of each canal was flared, and the pulp was removed with a barbed broach. A K-file of #10 size (Mani Inc., Tochigi, Japan) was submissively inserted up to the apical foramen to evaluate canal patency. Biomechanical preparation was done using the crown down technique up to 25–6% followed by obturation using AH PLUS sealer.

Single-visit endodontic treatment was performed by a single endodontist who was blinded to the patient's placement in the experimental group. A second researcher divided the patients into two groups once endodontic therapy was finished.

Sequentially numbered, sealed, opaque envelopes were used as the method of concealment for the patient's group.

The three groups ($n = 10$) were:

- Group I-Oral diclofenac tablet (Voveran 50 mg, Novartis India Limited, India) twice daily for 2 days
- Group II-Transdermal diclofenac patch (Diclo-plast, 100 mg, ZuVentus Healthcare Ltd, Sparsha Pharma International Pvt Ltd, Telangana, India) once daily for 2 days
- Group III-Transdermal ketoprofen patch (Keto-plast, 100 mg, ZuVentus Healthcare Ltd, Sparsha Pharma International Pvt Ltd, Telangana, India) once daily for 2 days.

Patients received the patch on their right forearm immediately after root canal treatment. On the following day, they were instructed to swap out the patch for a fresh one and apply it to their left forearm. Each patient received four Paracip (Paracetamol 500 mg-Cipla Ltd, Mumbai, India), which can be used as rescue medication if necessary. At 4, 8, 12, and 24 h following the procedure, recipients were asked to indicate their level of pain on the VAS chart (scale = 0–10).

Statistical analysis

Data were entered into SPSS version 20 (IBM Corp., Armonk, NY, USA) for statistical analysis after being processed in Microsoft Excel. For continuous data, descriptive analysis was used to determine the mean and standard deviation. The Repeated Measure ANOVA was used to analyze the comparisons between groups.

RESULTS

Pretreatment pain levels among treatment groups were assessed and recorded as >3 on VAS chart. An evaluation of the pain intensity following endodontic therapy revealed a significant decrease in the postoperative pain intensity scores. The scores gradually decreased with oral and transdermal diclofenac and ketoprofen formulations. There was highly significant statistical difference between the three intervention groups in relation to pain recorded using the VAS as $P < 0.05$ for both the days at 4, 8, 12, and 24 h postoperatively 2 days [Table 2].

Six out of ten patients who had received diclofenac tablets reported gastric discomfort, One out of ten patients who had received diclofenac patch reported gastric discomfort whereas none of the patients with ketoprofen patch reported any discomfort [Table 3]. Two patients from Group 2 consumed paracetamol tablets as rescue medication. No local irritation was reported by patients at the site of transdermal patch application.

DISCUSSION

Patients generally relate dental care with pain and the experience of poorly managed pain related to dental treatment leads them to maintain a strategic distance from or defer treatment. The management of postendodontic pain has always been a field for endless research with better formulations and modalities persistently replacing antiquated ones. NSAIDs are medications that are frequently given in the field of dentistry to relieve pain.[11,13,14]

The extensive use of prescribed and over-the-counter NSAIDs is associated with significant adverse effect. A newly TDDSs, commonly referred to as "patches," are dosage forms created to release a therapeutically

Table 1: Inter-group comparison for postendodontic pain management for the 2 postoperative days at different time intervals by repeated measure ANOVA

	Mean±SD					*P*
	Baseline	4 h	8 h	24 h	Day 2	
Group 1	7.40±0.54	6.20±0.44	5.4±1.34	4±0.00	2.0±0.00	0.04*
Group 2	7.60±0.89	5±0.0	2.8±0.44	1.4±0.89	0.6±0.54	0.00*
Group 3	7±0.70	5.6±0.54	3.6±0.89	2.2±0.83	1±0.00	0.00*
P	0.455	0.142	0.04*	0.02*	0.001*	

*0.00 – highly significant. Repeated measure ANOVA; $P<0.05$ considered statistically significant. SD: Standard deviation

Table 2: Inter-group comparison for the occurrence of gastric discomfort

Group	Gastric discomfort	
	Present	Absent
Group 1	6	4
Group 2	1	9
Group 3	0	10

Table 3: Frequency distribution of study population

Group	Male/female	Mean age (range in years)	Tooth number
I	6/4	29.3 (18–45)	35, 44
II	7/3	26.2 (18–45)	34, 35
III	3/7	25.8 (18–45)	45, 35

appropriate amount of medication over a patient's skin at a predetermined rate to achieve systemic circulation.[15-17] Advantages of the transdermal patch are avoidance of the firstpass metabolism, gastrointestinal incompatibility, and predictable and extended duration of the activity.[18,19]

In addition, it enables the use of medications with a limited therapeutic window and short biological half-life, and it enhances pharmacological and physiological response. Transdermal drugs are transported through passing through the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, stratum germinativum, and the dermis, which has blood vessels.[18,20] Transdermal patches make medicine administration effortlessly painless, especially for patients who are afraid of needles. They have sustained plasma levels that are equivalent to those of oral medications.[19,21]

The three ways in which a drug molecule can cross the intact stratum corneum, is through skin appendages (trans appendageal and shunt routes), intercellular lipid domain, and transcellular route.[18,22] The advantage of drug delivered topically is to produce clinically meaningful results without systemic side effects or drug interactions.[23]

Diclofenac is a common NSAID used for postoperative pain management. Mangal *et al*. conducted a study to compare the effectiveness of transdermal diclofenac patch against oral diclofenac for postendodontic pain control, and the authors concluded that transdermal diclofenac patch was as effective as an oral diclofenac tablet and could be used as an alternative and effective analgesic for postendodontic pain management, particularly in patients with gastric discomfort.[11]

Similarly, Bhaskar *et al*. compared oral versus transdermal diclofenac administration and observed that patients were comfortable using transdermal patch which provided potent analgesia.[23]

The specific aim of this study was to show whether ketoprofen patch is comparable to the conventionally used diclofenac patch in terms of postoperative analgesia, to record the dosage and number of rescue analgesia consumption in the postoperative 24 h.

The mechanism of action of ketoprofen is the inhibition of enzyme cyclooxygenase and also produces analgesic effect by a central mechanism inhibiting the spinal cord nociceptor reflex activity, thereby reducing the central sensitization in the spinal cord.[24,25]

To provide postoperative analgesia in patients having lower limb orthopaedic surgery, Verma R *et al*. examined the effectiveness of single-dose transdermal patches of diclofenac and ketoprofen. Through this observation, they concluded that both ketoprofen and diclofenac provided postoperative analgesia with less number of rescue analgesic consumption when ketoprofen was applied compared to the diclofenac patch group.[26]

Another placebo-controlled study compared the effectiveness of transdermal diclofenac and ketoprofen patches in reducing the VAS score during venous cannulation and concluded that both patches were effective, with lower pain scores in patients receiving ketoprofen.[27,28]

In general, ketoprofen is found to be more potent as compared to diclofenac, though ketoprofen is not popularly used in clinical practice despite its documented potent action. The probable reason could be the unavailability of the ketoprofen patch as compared to diclofenac patch. In terms of efficacy, ketoprofen supersedes diclofenac when administered as transdermal medication.[27]

To conclude, both the transdermal patches for ketoprofen and diclofenac were successful in reducing postendodontic

pain. Two patients receiving diclofenac patch required rescue analgesic as compared to ketoprofen, making it inferior in terms of patient comfort postprocedure.

Transdermal drug delivery is considered a safer method for pain management postoperatively as it avoids gastrointestinal complications by evading the first-pass metabolism associated with oral administration; it also eludes trypanophobia associated with invasive intramuscular or Intravenous route of injection.[29,30]

Limitations

- The outcomes of this patient-dependent investigation could have depended on the patients' subjectively reported score values. As a result, the bias of the participant could not be removed from the research
- An NSAID ketoprofen was not compared for two routes of administration in the study. Further investigation can be done using different pharmacological drugs.

CONCLUSION

Within the limitations of the study, it was concluded that the transdermal ketoprofen patch was more effective than oral and transdermal diclofenac for postendodontic pain management. Furthermore, transdermal patch users reported no unpleasant pain. In light of this, the transdermal diclofenac patch can be utilized as an additional and efficient analgesic for postendodontic pain treatment, particularly in patients with gastrointestinal difficulties. Hence, this study widens the horizons for future research.

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Conflicts of interest

There are no conflicts of interest.

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