



www.bioinformation.net
Volume 22(9)



Research Article

Received September 00, 2026; Revised September 00, 2026; Accepted September 00, 2026, Published September 00, 2026

DOI: 10.6026/973206300225695

SJIF 2026 (Scientific Journal Impact Factor for 2026) = 8.478

2022 Impact Factor (2023 Clarivate Inc. release) is 1.9

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Citation: Kumari *et al.* Bioinformation 22(9): 5695-5700 (2026)

Transdermal versus oral analgesics for post-endodontic pain management: A randomised control trial in India

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Abstract:

Post-endodontic pain remains a significant clinical challenge. Hence, eighty adults requiring single-visit treatment received oral or transdermal analgesics. Post-operative pain was assessed using Visual Analog Scale scores. Transdermal Ketoprofen patches showed a sustained analgesic effect. Thus, transdermal delivery provides effective, prolonged post-endodontic pain relief.

Keywords: Analgesics, fentanyl, ketoprofen, post-endodontic pain, root canal treatment, transdermal drug delivery

Background:

Post-endodontic pain remains a significant clinical challenge despite advances in rotary instrumentation, irrigation protocols, obturation techniques [1, 2]. The incidence of post-operative pain ranges from 3% to 58%, reflecting variations in pre-operative status, microbial load, host immune response and procedural factors [3, 4]. Clinical studies have demonstrated that post-operative and interappointment pain may persist despite contemporary treatment protocols [5]. Tissue injury activates phospholipase A2 to release arachidonic acid from cell membrane phospholipids. It leads to prostaglandin E2 (PGE2) synthesis, which sensitizes peripheral nociceptors and is a key mediator of pain and hyperalgesia. Inflammatory agents including bradykinin, substance P, histamine and cytokines such as interleukin-1 (IL-1) and tumor necrosis factor- α (TNF- α) contribute to vasodilation, increased vascular permeability and intensified nociceptive signalling [5]. NSAIDs reduce post-endodontic pain by inhibiting cyclooxygenase enzymes and diminishing prostaglandin production. COX-1 mediates physiological functions such as gastric mucosal defense and platelet aggregation, whereas COX-2 is primarily associated with inflammation and pain. Blockage of these pathways decreases peripheral sensitization and prevents pain transmission [6]. Oral analgesics are widely used because of their convenience, rapid onset of action and established efficacy [7-9]. However, their use is associated with several limitations, including hepatic first-pass metabolism and fluctuations in plasma drug concentrations. In addition, NSAIDs are associated with an increased risk of gastrointestinal irritation, renal impairment and cardiovascular adverse effects; whereas excessive paracetamol use may result in hepatotoxicity. Repeated dosing may further contribute to variable analgesic effects and reduced patient compliance [7]. The transdermal drug delivery system offers an alternative approach by providing controlled and sustained release of drugs through the skin into the systemic circulation. Drug absorption occurs primarily through passive diffusion across the stratum corneum and is influenced by molecular size, lipophilicity and concentration gradient. Transdermal systems maintain stable plasma drug concentrations, bypass first-pass metabolism and may reduce systemic adverse effects while improving patient compliance [10]. Transdermal NSAIDs such as ketoprofen and diclofenac have showed effective analgesic activity in both acute and chronic pain conditions, with fewer gastrointestinal adverse

effects compared with oral formulations. Similarly, transdermal fentanyl patches provide prolonged opioid analgesia through sustained drug release and have been widely used in pain management [11]. Therefore, it is of interest to compare the analgesic efficacy and safety of oral diclofenac and ibuprofen with transdermal ketoprofen and fentanyl patches following single-visit root canal treatment.

Materials and Methods:

This randomized, parallel-arm, superiority trial featuring blinded outcome-data assessment and a 1:1:1:1 allocation ratio was approved by the Institutional Ethics Committee (IEC/P-541/2024) and registered with ClinicalTrials.gov (NCT07610265). Participant recruitment was conducted from April 2024 to October 2025. Written informed consent was obtained from all participants before enrollment and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki (1975), as revised in 2000. The study was reported according to the CONSORT 2010 guidelines. Subjects were arbitrarily divided to four treatment groups using a computer-generated randomization sequence. Distribution concealment was done using sequentially numbered opaque sealed envelopes (SNOSE). Owing to the obvious differences between oral medications and transdermal patches, participant and operator blinding were not feasible. Pain scores were self-recorded by participants, whereas data extraction and statistical analysis were performed by an investigator blinded to group allocation. No changes to the methodology or eligibility criteria were made after trial commencement.

Sample size calculation:

Sample size was calculated using G*Power software (version 3.1.9.7; Heinrich Heine University, Düsseldorf, Germany) based on the primary outcome of post-operative pain intensity measured using the Visual Analog Scale (VAS). Using an F-test for repeated-measures ANOVA (within-between interaction), four intervention groups, five repeated measurements, a significance level of 0.05 and 80% power, a minimum sample of 80 participants (20 per group) was calculated. The estimated effect size was derived from the randomized clinical trial by Karunakar *et al.* [12] evaluating transdermal analgesics following endodontic treatment. Systemically healthy patients aged 18-60 years presenting with moderate-to-severe preoperative pain

(VAS ≥ 4) associated with symptomatic irreversible pulpitis, with or without symptomatic apical periodontitis, in multi-rooted permanent teeth requiring single-visit root canal treatment were eligible. Exclusion criteria included hypersensitivity to study medications, active peptic ulcer disease, current NSAID or corticosteroid therapy, bronchial asthma, epilepsy, inflammatory bowel disease, severe hepatic or renal disease, pregnancy, lactation, psychiatric disorders, recent antibiotic therapy and teeth requiring retreatment, presenting with root fracture, root resorption, advanced periodontal involvement, or considered non-restorable.

Clinical procedure:

All procedure was done by a single trained clinician under standardized aseptic conditions. Baseline pain intensity was recorded using the Visual Analog Scale (VAS). Local anesthesia was achieved with 2% lignocaine containing adrenaline (1:100,000) (Lignox, Indoco Remedies Ltd., India), followed by rubber dam (Waldent Instruments, India) isolation. Access cavities were prepared using sterile Endo Access burs (Dentsply Maillefer, Switzerland) and canal patency was established with #10 K-files (Mani Inc., Japan). Working length was established using an electronic apex locator (Root ZX II, J. Morita Corp., Japan) and confirmed radiographically. Biomechanical preparation was performed using rotary nickel-titanium instruments (Wal-Flex S-Blue rotary file system, Waldent Innovations Pvt. Ltd., New Delhi, India) to a final apical preparation of size 25/.04. Canals were irrigated with 3% sodium hypochlorite (Prime Dental Products Pvt. Ltd., Mumbai, India) throughout instrumentation, followed by 17% EDTA (RC Help, Prime Dental Products Pvt. Ltd., India) and a final saline rinse. After drying with sterile paper points (Dentsply Maillefer, Switzerland), obturation was completed during the same visit using gutta-percha (Dentsply Maillefer, Ballaigues, Switzerland) and resin sealer (AH Plus, Dentsply DeTrey GmbH, Germany) by the lateral condensation technique. A post-operative radiograph confirmed the quality of obturation before placement of a temporary restoration (Cavit-G, 3M ESPE, and Germany).

Intervention:

Immediately after treatment, participants received the allocated analgesic regimen:

- [1] **Group 1:** Oral diclofenac sodium 50 mg (Reactin, Novartis India) every 8 hours for 48 hours.
- [2] **Group 2:** Oral ibuprofen 400 mg (Abbott Healthcare Pvt. Ltd., India) every 8 hours for 48 hours.
- [3] **Group 3:** Ketoprofen 30 mg transdermal patch (Ketoplast, Zuventus Healthcare Ltd., India) applied immediately after treatment and replaced after 24 hours.
- [4] **Group 4:** Fentanyl 25 $\mu\text{g/h}$ transdermal patch (ThermiFent-P®, Sparsha Pharma International Pvt. Ltd., and Telangana, India) applied immediately after treatment and maintained for 48 hours. Fentanyl was included solely as a pharmacological comparator to evaluate the analgesic potential of sustained transdermal opioid delivery and should not be interpreted as a recommendation for routine

opioid use following endodontic treatment. The lowest commercially available transdermal fentanyl patch strength (25 $\mu\text{g/h}$) was selected to minimize opioid exposure while allowing evaluation of sustained transdermal analgesia under controlled clinical conditions. Before patch application, patients and an accompanying family member received standardized verbal instructions regarding recognition of opioid-related adverse effects and were advised to seek immediate medical care if warning symptoms occurred. This outpatient protocol was IEC-approved, given fentanyl's low single-patch dose in healthy ASA I participants and structured caregiver safety counseling. Paracetamol 650 mg was prescribed as rescue medication when pain became intolerable (VAS ≥ 4), with a minimum dosing interval of six hours and a maximum daily dose of 3g. Rescue analgesic consumption was recorded throughout the study period.

Outcome assessment:

The primary outcome was post-operative pain intensity measured using a 10-cm Visual Analog Scale (VAS) [13]. Recorded at 6, 12, 24 and 48 hours after treatment. Secondary outcomes included rescue analgesic consumption and adverse events. Participants completed standardized pain diaries and telephone follow-up at 24 hours was performed to encourage compliance and document adverse events. No pre-defined outcomes were modified after trial commencement.

Statistical analysis:

Data were evaluated with/ IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Prior to analysis, normality of VAS score distributions was assessed using the Shapiro-Wilk test. Evaluation was done using ANOVA and Chi-square test at $P < 0.05$.

Results:

A total of 80 participants were enrolled and randomly allocated into four treatment groups ($n = 20$ per group). All participants completed the study and were included in the final analysis. SD = standard deviation; VAS = Visual Analog Scale. Continuous variables were compared using one-way ANOVA and categorical variables were compared using the Pearson chi-square test. Baseline demographic and clinical characteristics were comparable among the four groups, with no statistically significant differences in age, sex, tooth type, clinical diagnosis, or baseline VAS scores (Table 1). Baseline pain intensity was also comparable among the treatment groups (one-way ANOVA, $p = 0.991$). Values are presented as mean $\pm$ SD. Mixed-design ANOVA with Greenhouse-Geisser correction showed significant effects of time ($F = 419.827$, $P < 0.001$, partial $\eta^2 = 0.847$), treatment group ($F = 2.939$, $P = 0.038$, partial $\eta^2 = 0.104$) and the treatment group $\times$ time interaction ($F = 10.856$, $P < 0.001$, partial $\eta^2 = 0.300$). Bonferroni-adjusted pairwise comparisons were used for post hoc analyses mean post-operative VAS scores decreased progressively over the 48-hour follow-up period in all treatment groups (Table 2). Oral ibuprofen demonstrated the

lowest mean VAS score during the early post-operative period (6 hours), whereas the transdermal ketoprofen and transdermal fentanyl groups exhibited lower mean pain scores at 24 and 48 hours, consistent with a more sustained analgesic effect. Mixed-design ANOVA with Greenhouse-Geisser correction demonstrated a significant main effect of time ($F(2.19, 166.19) = 419.827$, $p < 0.001$, partial $\eta^2 = 0.847$), confirming a progressive reduction in post-operative pain throughout the study period. A significant main effect of treatment group was also observed ($F(3, 76) = 2.939$, $p = 0.038$, partial $\eta^2 = 0.104$). Furthermore, a significant treatment group $\times$ time interaction was identified ($F(6.56, 166.19) = 10.856$, $p < 0.001$, partial $\eta^2 = 0.300$), indicating that the pattern of pain reduction differed significantly among the four analgesic regimens over time. Post-hoc Bonferroni-adjusted comparisons were performed to further explore the significant interaction. Values are presented as n (%). Pain severity was categorized as no pain (VAS = 0), mild (VAS = 1-3), moderate (VAS = 4-6) and severe (VAS = 7-10). Pearson's Chi-square test was used for comparisons unless otherwise noted. * $P < 0.05$ indicates statistical significance. For pain severity at 48 hours (Panel A), the Pearson chi-square result ($\chi^2 = 14.624$, $df = 9$, $p = 0.102$) is reported alongside the Fisher-Freeman-Halton

exact test ($p = 0.110$), which gave a consistent result and is more appropriate given the sparse cell counts in this 4 $\times$ 4 table. Regarding the secondary outcomes, pain severity at 48 hours did not differ significantly among the treatment groups (Fisher-Freeman-Halton exact test, $p = 0.110$). However, rescue analgesic requirements differed significantly between groups. During the first 12 hours, rescue medication use was more frequent in the transdermal groups than in the oral analgesic groups ($\chi^2 = 13.033$, $p = 0.005$), reflecting the delayed onset of transdermal drug delivery. Conversely, during the 12-48-hour period, rescue analgesic consumption was significantly lower in the transdermal groups, particularly in the transdermal fentanyl group ($\chi^2 = 14.936$, $p = 0.002$), consistent with their prolonged analgesic effect (Table 3). Distribution of reported side effects among the study groups. Gastric discomfort was more frequently observed in Groups I and II, whereas nausea was most commonly reported in Group IV. The incidence of both side effects differed significantly among the study group adverse effects included gastric discomfort in the oral analgesic groups and nausea in the transdermal fentanyl group. No serious adverse events, respiratory depression, or patch-related complications were observed during the study period.

Table 1: Baseline demographic and clinical characteristics of the study population

Variable	Oral (n=20)	Diclofenac Oral (n=20)	Ibuprofen Transdermal (n=20)	Ketoprofen Transdermal (n=20)	Fentanyl	P value
Age (years), Mean $\pm$ SD	33.8 $\pm$ 8.1		34.6 $\pm$ 7.8	35.1 $\pm$ 8.5	34.2 $\pm$ 7.9	0.964
Gender, n (%)						0.951
Male	11 (55.0)	10 (50.0)	11 (55.0)	10 (50.0)		
Female	9 (45.0)	10 (50.0)	9 (45.0)	10 (50.0)		
Tooth treated, n (%)						0.982
Maxillary molar	9 (45.0)	8 (40.0)	9 (45.0)	8 (40.0)		
Mandibular molar	11 (55.0)	12 (60.0)	11 (55.0)	12 (60.0)		
Preoperative diagnosis, n (%)						0.988
Symptomatic irreversible pulpitis	14 (70.0)	15 (75.0)	14 (70.0)	15 (75.0)		
Symptomatic apical periodontitis	6 (30.0)	5 (25.0)	6 (30.0)	5 (25.0)		
Preoperative VAS score (Mean $\pm$ SD)	7.75 $\pm$ 0.91	7.80 $\pm$ 0.89	7.70 $\pm$ 0.92	7.75 $\pm$ 0.85		0.991

Table 2: Mean Visual Analog Scale (VAS) pain scores across treatment groups at different post-operative time points

Time	Oral Diclofenac	Oral Ibuprofen	Transdermal Ketoprofen	Transdermal Fentanyl
Baseline	7.75 $\pm$ 0.91	7.80 $\pm$ 0.89	7.70 $\pm$ 0.92	7.75 $\pm$ 0.85
6 hours	4.95 $\pm$ 0.72	4.25 $\pm$ 0.72	5.70 $\pm$ 0.66	5.95 $\pm$ 0.83
12 hours	4.45 $\pm$ 1.28	4.30 $\pm$ 1.22	3.80 $\pm$ 1.45	3.65 $\pm$ 1.45
24 hours	3.60 $\pm$ 1.50	3.65 $\pm$ 1.50	2.45 $\pm$ 1.50	2.10 $\pm$ 1.45
48 hours	3.10 $\pm$ 1.21	2.95 $\pm$ 1.40	1.80 $\pm$ 1.44	1.30 $\pm$ 1.26

Table 3: Secondary clinical outcomes: Pain severity and rescue analgesic requirement

Pain category	Oral Diclofenac	Oral Ibuprofen	Transdermal Ketoprofen	Transdermal Fentanyl	χ^2	P Value
No pain	0 (0%)	0 (0%)	3 (15%)	5 (25%)	14.624	0.102
Mild	6 (30%)	8 (40%)	8 (40%)	10 (50%)		
Moderate	8 (40%)	7 (35%)	5 (25%)	3 (15%)		
Severe	6 (30%)	5 (25%)	4 (20%)	2 (10%)		
B. Rescue analgesic requirement						
Time interval (Yes)	Oral Diclofenac	Oral Ibuprofen	Transdermal Ketoprofen	Transdermal Fentanyl	χ^2	P Value
	n(%)	n(%)	n(%)	n(%)		
0-12 h	6 (30.0)	5 (25.0)	14 (70.0)	13 (65.0)	13.033	0.005*
12-48 h	11 (55.0)	14 (70.0)	6 (30.0)	3 (15.0)	14.936	0.002*

Discussion:

Post-endodontic pain is a multifactorial inflammatory condition resulting from mechanical, microbial and chemical irritation during root canal therapy. Pain is primarily mediated by inflammatory mediators such as prostaglandins, bradykinin and cytokines, which contribute to nociceptor sensitization [4]. In the present study, both oral and transdermal drug delivery systems were effective in reducing post-operative pain, as evidenced by the significant reduction in VAS scores over time in all groups. Oral ibuprofen demonstrated superior early post-operative pain control at 6 hours in the present study [8]. Whereas transdermal ketoprofen and fentanyl patches showed a more sustained analgesic effect from 12 to 48 hours, with fentanyl showing the lowest pain scores at later time points. This pattern may reflect the rapid systemic absorption and onset of action of orally administered NSAIDs, whereas transdermal systems require an initial absorption phase before achieving optimal therapeutic concentrations. Similar post-operative pain findings have been reported in randomized clinical trials evaluating different endodontic treatment protocols, further supporting the concept that effective pain control is an important determinant of treatment success and patient satisfaction. The prolonged analgesic efficacy observed with transdermal ketoprofen is consistent with previous randomized clinical studies. Karunakar *et al.* reported significantly lower post-operative pain scores with transdermal ketoprofen than diclofenac following root canal treatment, while Pandey *et al.* showed superior post-operative pain control with ketoprofen patches compared with diclofenac after orthodontic extractions [12, 13]. Similarly, Sharma *et al.* observed effective post-operative analgesia with transdermal ketoprofen following mandibular fracture surgery [14]. Collectively, these studies support the sustained analgesic profile of transdermal ketoprofen observed in the present investigation. These observations may be attributed to the controlled release characteristics of transdermal delivery systems, which maintain relatively stable plasma drug concentrations while avoiding first-pass hepatic metabolism [15]. Transdermal fentanyl has a delayed onset of action, with therapeutic plasma concentrations generally achieved after 12–16 hours, explaining its limited analgesic benefit during the early post-operative period. These pharmacokinetic characteristics are well documented in previous studies of transdermal drug delivery and opioid pharmacology [16, 17]. As noted under Intervention, fentanyl served solely as a pharmacological comparator; opioids should be reserved for exceptional circumstances where non-opioid analgesics are contraindicated or ineffective, in accordance with current evidence-based recommendations [18]. The sustained analgesic effect observed with transdermal fentanyl is supported by previous studies in oral surgery. Hazra *et al.* [19] showed lower post-operative pain scores and reduced rescue analgesic consumption with transdermal fentanyl compared with diclofenac patches following mandibular third molar surgery. Adverse events observed in the present study were consistent with the established pharmacological profiles of the study drugs. Oral NSAIDs were associated with more frequent gastrointestinal discomfort whereas transdermal preparations produced fewer

gastrointestinal adverse effects. Mild nausea occurred more frequently in the fentanyl group, but no serious opioid-related adverse events or participant withdrawals were observed during the study period, consistent with reports emphasizing the importance of safety monitoring during analgesic therapy [17]. Zadsirjan *et al.* concluded that, post endodontic pain decreased by both Ketoprofen and ibuprofen efficiently [20]. According to Modi *et al.* oral diclofenac tablets had less pain at two hours after surgery, but transdermal diclofenac patches had less pain at twenty-four hours [21]. For the treatment of postoperative endodontic pain, Murugan *et al.* found that a transdermal patch used after treatment would be more beneficial than oral diclofenac [22]. Kararia *et al.* concluded that root-end cavity fillings sealing potential was same for both MTA and retroplast groups [23]. The strengths of this study include its randomized design, blinded outcome-data assessment, standardized treatment protocol and complete follow-up of all participants. However, several limitations should be acknowledged, including the single-center setting, relatively small sample size, short follow-up duration and the inability to blind participants because of the obvious differences between oral medications and transdermal patches. Although no serious opioid-related adverse events were observed, safety monitoring in the transdermal fentanyl group was limited to pre-application counseling of patients and accompanying family members, together with a structured telephone follow-up at 24 hours assessing sedation and respiratory status. Objective monitoring, including oxygen saturation, respiratory rate and validated sedation scales, was not performed. As fentanyl was administered as a low-dose single patch to carefully screened ASA I patients without respiratory or CNS risk factors and participants were instructed to remove the patch and seek immediate medical care if warning signs developed, the absence of serious adverse events should be interpreted as reassuring within this controlled, low-risk population rather than as definitive evidence of safety. Although this approach was approved by the Institutional Ethics Committee, future studies should incorporate objective safety monitoring to strengthen the evidence base. Post-operative pain was assessed using patient-reported VAS scores and the subjective nature of pain perception may have contributed to interindividual variability. In addition, the inclusion of fentanyl may limit the generalizability of the findings to routine endodontic practice. Overall, both oral and transdermal analgesics effectively reduced post-endodontic pain following single-visit root canal treatment. Oral ibuprofen provided superior early pain control at 6 hours, whereas transdermal ketoprofen demonstrated sustained analgesic efficacy from 12 to 48 hours, suggesting that it may be a promising non-opioid alternative for appropriately selected patients. Further multicenter randomized controlled trials with larger sample sizes, longer follow-up and standardized safety monitoring are needed to confirm these findings and improve their clinical applicability.

Conclusion:

Ketoprofen showed clinically relevant sustained analgesia with few gastrointestinal adverse effects. Oral NSAIDs showed superior analgesia during the early post-operative period. These findings suggest that transdermal ketoprofen may represent a potential alternative for selected patients requiring prolonged post-operative analgesia. However, large multicenter randomized clinical trials are required before routine clinical adoption.

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