Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following dental implant placement

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The aim of this study was to compare the efficacy and safety of transdermal and oral routes of diclofenac for postoperative pain management in patients undergoing dental implant placement. Twenty systemically healthy, partially edentulous patients who required dental implants bilaterally in the mandibular first molar region were included. While the patient was under local anesthesia, an implant was placed in the mandibular first molar region of one quadrant. After a minimum of 4 weeks, an implant was placed in the contralateral quadrant under local anesthesia. Patients were prescribed 50 mg of oral diclofenac, taken twice daily for 3 days, following implant placement on the first side and a 100-mg diclofenac transdermal patch, placed once daily for 3 days, after surgery on the contralateral side. Postoperative pain was documented using the Numeric Rating Scale, Verbal Rating Scale, and Pain Relief Scale. Demographic, intraoperative, and postoperative characteristics were comparable in all the patients. The data obtained with the 3 subjective scales were analyzed by the Mann-Whitney test. No statistically significant differences in scores were discerned between the oral and transdermal routes of diclofenac delivery. None of the patients developed any adverse effects when using the transdermal patch, whereas 3 patients reported gastric irritation and a mild burning sensation when taking oral diclofenac. Thus, while the efficacy of transdermal and oral diclofenac for postoperative pain management was similar, the safety of the transdermal diclofenac patches was evidently superior. Further research with larger patient samples is necessary, but delivery of diclofenac through a transdermal route is a promising approach to the management of postoperative pain.

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Rehabilitation of partially and completely edentulous areas with dental implants is well established, with numerous advantages over conventional procedures. A recent meta-analysis demonstrated a 95.2% survival rate and 84.9% success rate in single-crown–supported implants, signifying the predictability of this treatment modality.[1] The pain following implant surgery is categorized generally as mild to moderate and generally is at its maximum level 5-6 hours postpostoperatively.[2] If appropriate surgical guidelines—including precise incision, gentle tissue handling, heat control with copious irrigation during osteotomy preparation, intermittent drilling pressure, and end-to-end closure of sutures—are followed prudently, postoperative pain can be mitigated considerably. Operator experience, interventions involving regenerative procedures, placement of a greater number of implants, female predilection, older age, and smoking are some of the other significant factors found to influence the severity of implant postoperative pain.[3]

Managing postoperative pain is a major concern for the surgeon, and an oral route of analgesic administration is the most widely practiced method. Nevertheless, oral analgesics have been associated with potential complications, such as a high risk of gastrointestinal (GI), renovascular, and/or cardiovascular adverse effects.[4-6] The incidence of GI complications is high, especially in the elderly and patients on long-term drug regimens.[4] Gastrointestinal bleeding and GI ulcers account for 16% of reported adverse effects.[5] Although diagnosed less frequently than bleeding and ulcers, dyspepsia is also prevalent (40%) and constitutes a major clinical burden, warranting the use of comedications such as proton pump inhibitors.[4,6]

Cognizance of these adverse effects related to anesthesia is increasing, and exploratory research in the analgesic field is aimed at the reduction or elimination of adverse reactions to postoperative pain management. In the light of the aforementioned complications associated with oral nonsteroidal anti-inflammatory drugs (NSAIDs), interest in research on suitable alternative routes has been renewed.

One attractive alternative is the use of a topical therapeutic system, known for its efficacy in various medical fields and offering other distinct advantages. The most commonly available topical analgesic agents are NSAIDs, local anesthetics (such as lidocaine), counterirritants (such as methyl salicylate), and camphor.[7] The objective of topical analgesic therapy is to attain a comparable analgesic effect with fewer adverse effects than oral analgesics. The serum level of the drug achieved with topical analgesics is relatively low, and thus systemic side

Table 1. Mean NRS scores of patients receiving oral or transdermal diclofenac after implant placement surgery.

Time PS (h)	Delivery	Mean	SD	SEM	Mean diff	*Z*	*P*
2	Transdermal	0.70	0.73	0.16	0.200	−0.841	0.400
	Oral	0.50	0.61	0.14			
4	Transdermal	0.35	0.49	0.11	0.000	0.000	1.000
	Oral	0.35	0.49	0.11			
8	Transdermal	0.10	0.31	0.07	0.050	−0.593	0.553
	Oral	0.05	0.22	0.05			
12	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
24	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
48	Transdermal	0.05	0.22	0.05	0.000	0.000	1.000
	Oral	0.05	0.22	0.05			
72	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			

Abbreviations: diff, difference; NRS, Numeric Rating Scale; PS, postsurgery; SEM, standard error of the mean.

Table 2. Mean VRS scores of patients receiving oral or transdermal diclofenac after implant placement surgery.

Time PS (h)	Delivery	Mean	SD	SEM	Mean diff	*Z*	*P*
2	Transdermal	0.70	0.73	0.16	0.150	−0.672	0.502
	Oral	0.55	0.69	0.15			
4	Transdermal	0.15	0.37	0.08	0.050	−0.472	0.637
	Oral	0.10	0.31	0.07			
8	Transdermal	0.00	0.00	0.00	−0.050	−1.000	0.317
	Oral	0.05	0.22	0.05			
12	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
24	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
48	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
72	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			

Abbreviations: diff, difference; PS, postsurgery; SEM, standard error of the mean; VRS, Verbal Rating Scale.

effects and drug-drug interactions are reduced.[7] In addition, bypassing the first-pass metabolism considerably reduces the total drug dosage needed.

In the last few decades, transdermal patches have gained popularity as an effective analgesic modality, owing to advantages such as ease of application; reduced risk of dose dumping compared with cream, ointment, and gel forms of topical delivery; constant and prolonged duration of action; self-administration capability; and ease of termination.[8] These advantages also lead to better patient compliance. A topical NSAID confers clinically effective analgesia at a reduced plasma concentration compared to that of an oral NSAID. Bockow et al showed the analgesic effectiveness of intranasal ketorolac in dental implant placement–induced postsurgical pain.[9] However, about 36% of their subjects reported a brief stinging of the mucosa.

Table 3. Mean PRS scores of patients receiving oral or transdermal diclofenac after implant placement surgery.

Time PS (h)	Delivery	Mean	SD	SEM	Mean diff	*Z*	*P*
2	Transdermal	0.60	0.68	0.15	0.000	0.000	1.000
	Oral	0.60	0.68	0.15			
4	Transdermal	0.20	0.41	0.09	0.050	−0.411	0.681
	Oral	0.15	0.37	0.08			
8	Transdermal	0.05	0.22	0.05	−0.050	−0.593	0.553
	Oral	0.10	0.31	0.07			
12	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
24	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
48	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			
72	Transdermal	0.00	0.00	0.00	0.000	0.000	1.000
	Oral	0.00	0.00	0.00			

Abbreviations: diff, difference; PRS, Pain Relief Scale; PS, postsurgery; SEM, standard error of the mean.

Diclofenac, a hydrophilic NSAID with favorable physiochemical properties, is widely used both orally and topically for effective pain relief. Various topical formulations of diclofenac have been studied, including patch, gel, and solution; the patches exhibited more controlled release.[10] The purpose of the present study was to compare and evaluate the analgesic efficacy and safety of diclofenac diethylamine transdermal patches and oral diclofenac sodium tablets in postoperative pain management following implant placement.

Materials and methods

A prospective, split-mouth, simple, randomized, open-label study was designed to assess the analgesic effect of a diclofenac transdermal patch and oral diclofenac for acute postoperative pain management after implant surgery, utilizing self-rated pain scores and rescue analgesics. The study protocol was approved by the Institutional Review Board, Bapuji Dental College & Hospital, Davangere, India, and conducted in accordance with the Declaration of Helsinki, as revised in 2002.[11] After obtaining informed written consent from all the subjects, 9 men and 11 women, aged 30-65 years (mean, 45 years), were enrolled. Systemically healthy patients with bilaterally missing mandibular first molars requiring conventional implant placement were included. Exclusion criteria included an allergy to NSAIDs, the presence of a bleeding disorder, any contraindication to implant placement, and the current concomitant use of any sedative that might have interfered with the results. Routine hematologic tests were completed, and preoperative radiographs were obtained.

Following general surgical guidelines, 40 implants (2 in each patient) were placed by a single implantologist. An inferior alveolar nerve block was employed to achieve anesthesia in all subjects. The 2 implant placement surgeries were performed a minimum of 4 weeks apart in all patients. Endosseous implant placement was performed by raising the mucoperiosteal flap, and sequential osteotomies were accomplished using a new surgical bur in all cases. Maintenance of the same irrigation protocol and intermittent drilling pressure was carefully monitored throughout all the procedures. Regenerative procedures were not required in any of the patients. Standardization was maintained by placing implants with similar diameter and using comparable torque application in the same patient bilaterally. None of the patients received any premedication. Antibiotics were not prescribed after the surgery.

Following implant placement on 1 side, 50 mg of oral diclofenac sodium (Voveran, Novartis India), twice daily for 3 days, was prescribed. When the same patient returned for the surgery on the contralateral side, a 100-mg diclofenac diethylamine transdermal patch (Diclo-Touch, Sparsha Pharma) was placed once daily for 3 days. The transdermal patches were administered 30 minutes after the surgery. The allocation of side to be treated first in each patient was randomly selected by coin toss. In accordance with the manufacturer's instructions, the patch was applied on the upper chest area below the clavicle on the same side as the surgery, preferably in an area devoid of hair. Patients were instructed to replace the patch every 24 hours. After transdermal patch placement, each of the patients was provided with a total of 9 paracetamol tablets (500 mg) for the 3 postoperative days, to be used as rescue medication. Patients were instructed to return the rescue analgesics if their use was not required.

The Numeric Rating Scale (NRS), Verbal Rating Scale (VRS), and Pain Relief Scale (PRS) were the 3 subjective scales used to record the patient's postoperative pain level.[12] Directions were given to the patients to assign scores for each parameter at 2, 4, 8, 12, 24, 48, and 72 hours postoperatively, and responses were collected at the day 3 follow-up visit. Occurrence of any allergic reaction (such as local erythematous rash, skin irritation, or

Chart 1. Reduction in mean NRS scores from baseline (2 hours).

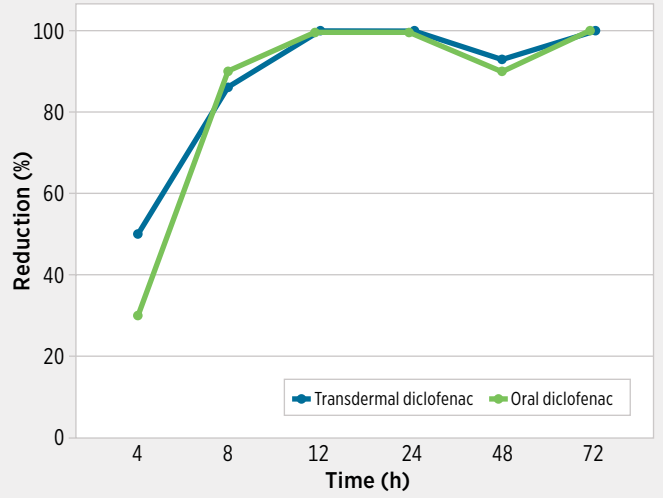
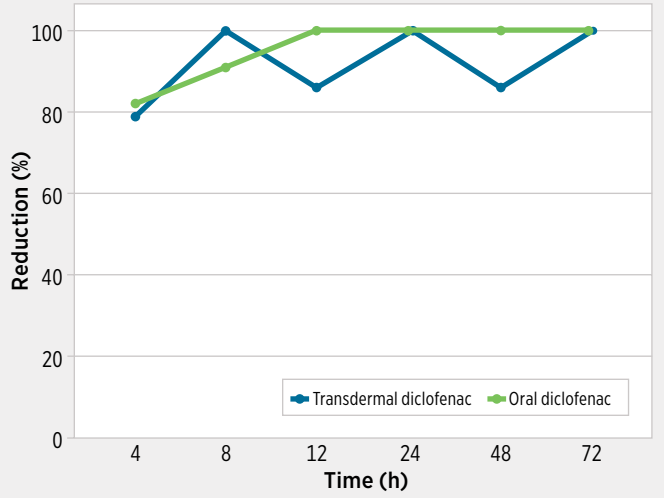


Chart 2. Reduction in mean VRS scores from baseline (2 hours).



itching) and other systemic adverse effects was recorded individually, as part of a questionnaire completed at all the specified time intervals in both study periods. The patient's preferred modality of drug administration was recorded in the questionnaire at the end of the second study period.

Analysis of the data was performed in SPSS for Windows software package (version 13.0.0, IBM Corporation). Means and standard deviations were computed, and the significance of differences in the NRS, VRS, and PRS scores of the transdermal and oral drug delivery systems was tabulated utilizing the Mann-Whitney test.

Results

All the patients were found to be similar with regard to demographic data (age and sex) and intraoperative course of the surgeries. On statistical evaluation of the 3 scales, the *P* value suggested that there was no significant difference between the 2 routes of diclofenac at any of the time intervals (Tables 1-3). The reductions in pain levels over time are depicted in Charts 1-3.

None of the patients developed any adverse effects when using the transdermal patches, whereas 3 patients reported gastric irritation and a mild burning sensation during use of the oral diclofenac. None of the patients required the use of rescue analgesics during transdermal drug delivery. All but 2 of the patients were of the opinion that transdermal drug delivery was much more comfortable in terms of usage and compliance.

Discussion

The use of topical NSAIDs for acute pain relief is one of the most controversial issues in analgesic practice. While they are commonly prescribed in some parts of the world (such as Western Europe), in other areas they are almost regarded as a placebo.[13] A systematic review has confirmed the efficacy of topical NSAIDs compared to that of placebo in both acute and chronic pain management.[14] Analgesic patches are one of the well-established approaches to topical NSAID administration. Unlike other conventional topical formulations, such as gels, creams, or ointments, transdermal patches have the advantage of providing constant and continuous delivery of the drug in a controlled manner for an extended period of time.

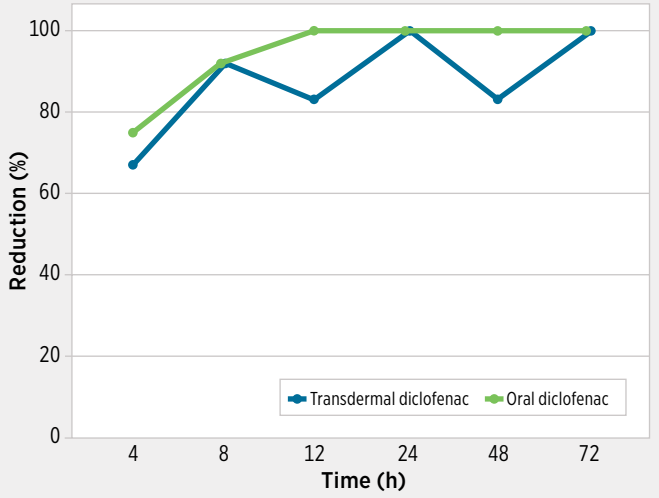
For a transdermal route to be effective, intact skin is a prerequisite for penetration of the drug. Upon reaching the deeper layers of the skin, the drug can be absorbed by blood, reach the site of inflammation, or penetrate deeper in order to exert its action. The threshold quantity of the drug in the site of inflammation also has to be achieved in order to obtain adequate analgesia.

Plasma concentration of a topically applied NSAID was found to reach only a fractional level (less than 5%) of that achieved after oral administration.[15] A lower plasma drug concentration limits the systemic side effects and has an auxiliary advantage of improved action at the site of inflammation.[13] Transdermal delivery is associated with a lesser incidence of GI adverse effects and is particularly useful in patients unable to tolerate an oral route. However, no such reduction was documented with occurrences of heart and renal failure, which have been connected to oral NSAID usage.[13] Furthermore, the incidence of local side effects was found to be minimal with topical applications.[16]

Diclofenac, a benzeneacetic acid derivative, is one of the most frequently prescribed NSAIDs after periodontal and implant surgical procedures. Commonly administered doses are 75 mg and 150 mg, taken in divided parts daily. Diclofenac comprises the ideal characteristics for transdermal application: smaller dose, poor bioavailability, and short biological half-life. The bioavailability of diclofenac transdermal patches is 1% that of oral diclofenac; the elimination half-life is 12 hours compared with the 1.2-2.0 hours associated with oral delivery. Brewer et al investigated the GI safety of diclofenac topical patches and concluded that they are well tolerated and could be utilized as an alternative to short-term NSAIDs.[17]

Topical diclofenac patches have been extensively used in pain management in other surgical fields with well-recognized safety performance, promptness, efficacy, and tolerance. The efficacy of a diclofenac patch in the management of acute pain related to

Chart 3. Reduction in mean PRS scores from baseline (2 hours).



soft tissue injury was evaluated by Kuehl et al, who established it to be satisfactory in this regard.[18] A meta-analysis on the safety profile of topical diclofenac confirmed its excellent tolerability in treatment of acute and chronic musculoskeletal conditions.[19] The distinctive characteristics of diclofenac have been found to be appropriate for the strong demands of therapeutics for neuropathic orofacial pain.[20] The effectiveness of diclofenac patches in postoperative pain management has been well-documented after laparoscopic, gall bladder, and gynecologic surgery as well as in the treatment of osteoarthritis.[21,22]

In the dental field, topical diclofenac patches are an established analgesic modality. Their capabilities for managing postoperative morbidity after tooth extraction have been explored.[23-25] The research has shown that a diclofenac transdermal drug delivery system showed promising outcomes and could be a safe alternative for oral diclofenac.[23-25] Recently, another study aiming to compare the analgesic efficacy of transdermal diclofenac and oral diclofenac following subepithelial connective tissue grafting for root coverage procedures concluded that satisfactory pain management was established via the transdermal route.[26]

In the current study, diclofenac was assessed in both topical and oral forms in 20 patients undergoing implant placement bilaterally. The oral drug was prescribed after the first surgical appointment, and a transdermal patch was prescribed after the second surgical appointment in the same patient. This clinical setting was especially useful in assessing the analgesic efficacy of the 2 drug routes because all the patients belonged to the same age group, the sex ratio was maintained, the same type of surgery was performed on both sides (with attention given to standardization of the protocol), and the patients acted as their own controls, thus eliminating any bias from differences in pain perception.

Contradictory views exist regarding the prescription of antibiotics following implant surgery. Nolan et al conducted a randomized clinical trial concerning antibiotic use in implant surgery and advocated the use of prophylactic antibiotics to improve implant survival rate while reducing postoperative morbidity.[27] On the other hand, researchers conducting another clinical trial opposed the use of systemic antibiotics during implant surgery; the authors claimed that there were no additional improvements in patient-reported outcomes or incidence of postoperative morbidity.[28] In the present clinical study, neither presurgical nor postsurgical systemic antibiotics were administered.

In the present study, oral diclofenac (50 mg twice daily for 3 days) was given as a standard to compare the efficacy and safety profile of topical diclofenac patches. The handling properties of the patch were satisfactory, and the patches were simple to administer. When using the transdermal diclofenac patches, patients reported adequate pain relief both clinically and statistically, with results comparable to those for oral diclofenac. In terms of safety profile, the common adverse reaction associated with transdermal patches is mild local skin reactions, including pruritus, erythema, petechiae, phototoxicity, and photoallergy.[29] In a study of 1344 patients, fewer than 3.1% experienced such cutaneous reactions.[30] In the present study, transdermal patches did not elicit any local allergic reactions or systemic adverse effects. However, 3 patients experienced mild gastric irritation when using oral diclofenac.

The outcome of the current study corroborates previous studies evaluating the safety and analgesic efficacy of transdermal diclofenac patches for various other surgical applications.[21,22] Thus, a topical diclofenac diethylamine (100-mg) transdermal patch is superior to the oral route in terms of safety and demonstrates the same efficacy. Topical diclofenac patches offer an efficacious, safe, well-tolerated, patient-compliant treatment modality that is an effective alternative to conventional oral diclofenac treatment.

Advancements and technological breakthroughs are paving the way for improving the delivery of drugs via a transdermal route with a minimal risk profile as well as greater patient tolerance, compliance, and satisfaction. Numerous methods are being tested to improve drug penetration, including penetration enhancers, liposomes, transfersomes, ethosomes, and iontophoresis.[31] In view of the complications associated with the oral route of administration, future research should be directed at optimizing topical analgesic formulations.

Conclusion

Postoperative pain management plays a critical role in a patient's recovery and improving patient compliance. Taking into account the efficacy of diclofenac formulations generally, and diclofenac diethylamine transdermal patches in particular, with their associated reduction in cutaneous side effects and low systemic toxicity, transdermal delivery of analgesics presents a viable treatment option for postoperative pain management following implant surgery. Further studies that have larger patient samples and that evaluate application of transdermal analgesics for other areas of implant dentistry are necessary to explore this delivery route further.

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