Comparative evaluation of transdermal diclofenac patch and oral diclofenac as an analgesic modality following root coverage procedures

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Diclofenac sodium is a nonsteroidal anti-inflammatory drug and is effective in the management of pain following periodontal surgery. However, oral administration of diclofenac can lead to gastrointestinal (GI) complications. To overcome these drawbacks, diclofenac is formulated as a transdermal patch, which delivers the drug into systemic circulation through skin. Twenty patients were selected for root coverage procedures with subepithelial connective tissue grafts bilaterally. Following the surgical procedure on the control sites, oral diclofenac sodium 100 mg was administered QD for 3 days. Following the surgical procedure on the contralateral test site, a transdermal diclofenac patch (TDP) was applied every 24 hours for 3 days. The TDP was effective in postoperative pain control following root coverage procedures with subepithelial connective tissue grafts. Pain tolerance was higher with the TDP as compared to oral administration, as it did not cause any GI complications.

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P ostoparative pain is the most commonly encountered sequel following periodontal surgery.1 The degree of pain intensity may alter depending on the category of the periodontal surgical procedure.2 Soft tissue grafting procedures such as free gingival grafts and subepithelial connective tissue grafts (SCTGs) have been associated with a higher incidence of postoperative pain.3,4 Therefore, the postoperative management of pain following these procedures is of utmost importance to gain the patient’s comfort and compliance, and the administration of analgesics is one of the most routinely employed methods to relieve pain.

Conventional analgesics fall under 2 main classes: opioids and nonopioids. Although opioids are effective analgesics with no analgesic effect ceiling, their usefulness is often limited due to their adverse effects. Nonopioids include nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis and thus inflammation. NSAIDs provide excellent analgesia for mild to moderate pain. They are particularly useful in the initial management of pain that has an inflammatory component. However, NSAIDs have a maximal dose or ceiling effect for their analgesic effect.

NSAIDs are the most widely used analgesics in medicine and dentistry to treat mild to moderate pain.5-11 In dentistry, NSAIDs are effective in the management of acute dental pain, chronic orofacial pain, and endodontic pain.7,11 Moreover, NSAIDs are commonly prescribed to minimize postoperative pain following dental extractions and periodontal surgical procedures.12-18 NSAIDs act by blocking the cyclooxygenase (COX) enzyme, which mediates the inflammatory changes by the production of prostaglandins (PGs) from arachidonic acid. Among the NSAIDs, diclofenac sodium is widely used due to its potent anti-inflammatory and analgesic properties.19 Diclofenac competitively inhibits the binding of arachidonic acid with COX in a dose-dependent manner. This results in decreased production of PGs, which in turn reduces postoperative inflammation, edema, and pain. However, when administered orally, diclofenac experiences a considerable first pass metabolism, with its bioavailability ranging from 54% to 90%.20 Thus oral diclofenac has a greater potential to cause adverse reactions due to its high plasma concentrations.21

Gastrointestinal (GI) complications are the most common adverse effects seen with NSAIDs. NSAIDs induce the injury of GI mucosa by 3 key mechanisms. First, NSAIDs inhibit the COX-1 enzyme, leading to a significant reduction in the synthesis of PG, which in turn may impair the GI mucosal defense.22 Second, since PGs are potent vasodilators, inhibition of their synthesis may contribute to increased vascular tone. The third mechanism is the ability of NSAIDs to reduce the gastric mucosal blood flow.23,24 These changes in the gastric microcirculation can lead to ischemia reperfusion-associated damage in the GI tract.25 Moreover, NSAIDs increase the number of neutrophils adhering to the vascular endothelium in the GI microcirculation, which has been shown to be a crucial factor in the development of ulcers.26

To overcome the adverse effects of oral NSAIDs, recent research has focused on the development of topical drug delivery systems. Among topical formulations, the transdermal drug delivery system (TDDS) has offered promising results in postoperative pain control.27-29 Furthermore, the controlled penetration of drug across the skin allows for more uniform serum drug concentrations, thereby reducing the risk of systemic adverse reactions.30 In a TDDS, the active ingredients of the drug are absorbed from the skin and into systemic circulation. Currently, TDDSs are available for a variety of clinical conditions.31-33

The transdermal diclofenac patch (TDP) is a drug delivery system shown to be effective in controlling postoperative pain following dental extractions and third molar impactions.27,28 No significant GI adverse effects have been reported following the use of these patches. However, very limited data is available in the literature on the transdermal delivery of drugs following periodontal surgical procedures.
It is a well-known fact that subepithelial connective tissue graft (SCTG) procedures are associated with significant postsurgical pain. This study aimed to compare and evaluate the analgesic efficacy of diclofenac sodium when administered by oral and transdermal routes following root coverage procedures with SCTGs.

### Materials and methods

A split-mouth study was designed involving 20 healthy subjects (10 males and 10 females) ranging in age from 18 to 35 years. This study was performed from February 2012 to June 2012 in the Department of Periodontics, Krishnadevaraya College of Dental Sciences and Hospital, Bangalore, India. Prior to enrollment in the study, the treatment protocol was explained to all patients and a signed informed consent was obtained. The ethical committee of the Krishnadevaraya College of Dental Sciences and Hospital, affiliated to the Rajiv Ghandi University of Health Sciences, India, approved the study, and the guidelines of the Helsinki Declaration of 1975 (as revised in 2000) were followed.

Patients were selected based on the following inclusion criteria: bilateral Miller’s Class I or Class II labial or buccal gingival recession defects with recession height ≤2 mm, width of keratinized gingiva ≤2 mm apical to recession, and the maintenance of good oral hygiene following initial Phase I therapy. Patients with a history of NSAID allergy, gastric discomfort, and/or systemic diseases such as bronchial asthma or epilepsy were excluded.

Prior to the surgery, medical and dental histories were recorded from all patients. Routine blood investigations were also carried out. Clinical parameters such as recession height, recession depth, and width of keratinized gingiva were measured. SCTGs were used to cover the denuded root surfaces and to augment the width of keratinized gingiva. A partial thickness flap was raised at the recipient site with 2 vertical releasing incisions 1-2 mm away from the gingival margin of the adjacent teeth. The flap was extended beyond the alveolar mucosa to the mucogingival junction to allow its coronal movement. Connective tissue grafts (CTGs) were harvested from the palate by means of horizontal incisions 5-6 mm away from the gingival margins of premolars and molars, with mean dimensions of 14 (length) x 10 (width) x 1 mm (thickness). The CTG was placed on the denuded root surface and periosteal suturing was completed. To cover the graft with the outer portion of the partial thickness flap, sling suturing with 5-0 absorbable (Ethicon, Inc.) sutures was used. All patients underwent root coverage procedures with SCTGs bilaterally, with a minimum time interval of 2 weeks between the procedures. In each patient, surgical sites were randomly divided into test and control sites. Following the surgical procedure on the control sites, oral diclofenac sodium 100 mg QD for 3 days was administered. Following the surgical procedure on the contralateral test site, a TDP was applied on skin devoid of hair. Each patch was placed on the site of application for 24 hours. Hence, 3 patches were used for the first 3 postoperative days. The applications of the TDP on Postoperative Days 2 and 3 were made on different hairless skin areas.

The TDP is a matrix-controlled device used to relieve mild to moderate postoperative pain. The TDP is available in 2 strengths, 100 and 200 mg, in sizes 50 and 75 cm², respectively. The plasma concentrations attained by the TDPs range from 20 to 50 ng/ml. Since the plasma concentrations are low, the patches have a reduced risk of GI complications, such as gastric or peptic ulcers, dyspepsia, and hemorrhage.

A Visual Analog Scale (VAS) was used for assessment of pain in the present study. The VAS is a simple, efficient, and widely used pain assessment scale in clinical and research studies. The VAS consists of a 10 cm horizontal or vertical line with the 2 endpoints marked ‘no pain’ and ‘worst pain’. The patients assigned scores on the 10 cm line at a point that corresponded to their perceived current level of pain intensity. The pain intensities were scaled as mild (from 0 to 4 cm), moderate (>4 to 7 cm), and severe (>7 to 10 cm). Since VAS is a subjective measure of pain, it may produce wide variations when comparing across a group of individuals at 1 time point. To minimize these inter-individual variations, the authors utilized a split-mouth study design, in which patients act as their own controls. During the treatment period, patients were assessed for pain intensity at baseline (immediately before the TDP was applied), then 2, 4, 8, 12, 24, 48, and 72 hours postsurgically. In addition to pain intensity, adverse effects such as gastric discomfort, nausea, burning sensation, and pruritis were dichotomously recorded by noting the presence or absence of each adverse effect.

A 2-sided independent t-test was performed using data provided from a study by Al-Hezaimi et al. This study was chosen because the method of pain

<table>
<thead>
<tr>
<th>Time point postsurgery</th>
<th>Control group</th>
<th>Test group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline)</td>
<td>7.46 (0.70)</td>
<td>7.60 (0.84)</td>
<td>0.842</td>
</tr>
<tr>
<td>2</td>
<td>5.75 (1.25)</td>
<td>3.60 (0.70)</td>
<td>0.001*</td>
</tr>
<tr>
<td>4</td>
<td>4.60 (1.33)</td>
<td>3.00 (1.37)</td>
<td>0.001*</td>
</tr>
<tr>
<td>8</td>
<td>3.20 (1.32)</td>
<td>2.50 (0.92)</td>
<td>0.564</td>
</tr>
<tr>
<td>12</td>
<td>2.20 (0.85)</td>
<td>1.70 (1.07)</td>
<td>0.352</td>
</tr>
<tr>
<td>24</td>
<td>1.50 (1.05)</td>
<td>1.00 (0.95)</td>
<td>0.525</td>
</tr>
<tr>
<td>48</td>
<td>1.00 (0.85)</td>
<td>0.65 (0.95)</td>
<td>0.455</td>
</tr>
<tr>
<td>72</td>
<td>0.60 (0.79)</td>
<td>0.30 (0.88)</td>
<td>0.065</td>
</tr>
</tbody>
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*Significant differences observed at P < 0.05.
control used (adhesive patch) and pain control assessment (by visual analog scale) were similar to the present study. A sample size of 20 patients was required in order to obtain 90% power with a P value set at 0.05. Paired t-tests were used to compare the results of the 2 groups at each time interval (95% level of confidence). The mean and standard deviation of pain intensity of the test and control groups are shown in the Table.

**Results**
A significant reduction in pain intensity was observed only in the test (TDP) group at the 2-hour and 4-hour postsurgical intervals (P < 0.05). Although the reduction in pain intensity was better with the TDP at all points in time, after 4 hours postsurgery, the reduction was deemed not statistically significant. Three patients in the control (oral diclofenac) group complained of mild gastric discomfort. No adverse effects were noted in the test group.

**Discussion**
The SCTG is a frequently used surgical procedure for root coverage due to its high predictability, shortened healing time, and tissue color match. However, this procedure requires a second surgical site that may cause patient discomfort due to a significant increase in the risk of postoperative complications such as pain, swelling, and hemorrhage. Consequently, the management of these postoperative complications is crucial for the patient’s comfort. NSAIDs are effective in reducing pain and swelling following periodontal surgeries due to their potent analgesic and anti-inflammatory properties.

To the best of the authors’ knowledge, this is one of the first studies documented in the literature that uses TDP for the postoperative management of pain following periodontal plastic procedures. This study comparatively evaluated the analgesic efficacy and patient tolerance of the TDP vs oral diclofenac following root coverage procedures with SCTG. The TDP (100 mg QD) was found to be more effective than oral diclofenac (100 mg QD) for postsurgical analgesia. In contrast, Bachalli et al reported diclofenac sodium administered orally provided slightly better analgesia compared to transdermal administration on Postoperative Day 1. However, no statistical difference was observed on the second and third postsurgical days.

Bhaskar et al reported that when used for postdental extraction analgesia, both oral and transdermal diclofenac showed similar analgesic efficacy. Recent studies have shown that the TDP is as effective as intramuscular diclofenac for postoperative analgesia following orthopedic and laparoscopic surgeries. Currently, there are no studies comparing the analgesic efficacy of TDP with opioids.

Diclofenac sodium is a nonselective COX inhibitor, that is, it inhibits both COX-1 and COX-2 enzymes. Thus, treatment with diclofenac may lead to COX-1-mediated adverse effects, such as gastric irritation, hepatotoxicity, nephrotoxicity, and blood dyscrasias. To overcome these adverse effects and to maximize the efficacy of diclofenac, the drug was formulated in the form of a TDP. The diclofenac patch was the first NSAID approved for transdermal delivery.

The principal components of a transdermal patch are a polymer matrix that aids in the controlled release of the drug from the reservoir, a liner that protects the patch during storage and must be removed prior to use of the patch, an adhesive that adheres the patch to the skin, and a backing layer that protects the patch from the outer environment. Release of a drug from a transdermal patch and its transport to the systemic circulation is a multistep process, which involves diffusion of the drug from the reservoir to the rate-controlling membrane on to the stratum corneum. The drug is absorbed by the stratum corneum, then it penetrates through the epidermis, resulting in uptake by the local capillary network in the dermis and finally systemic circulation.

TDDSs can be employed for several medical conditions, such as scopolamine for motion sickness, clonidine for hypertension, nitroglycerin for angina pectoris, fentanyl for chronic visceral pain, diclofenac for mild to moderate pain, nicotinе to aid in smoking cessation, lidocaine for anesthesia, oestriadiol for hormone replacement, and testosterone for hypogonadism. When Funk et al used the TDP for postoperative shoulder pain, it was equally effective as oral diclofenac.

In the present study, the TDP did not result in any adverse effects, whereas 3 patients complained of mild gastric discomfort when diclofenac was administered orally. One important fact to note in the present study is that the TDP was not applied over the same site during subsequent patient visits. Therefore, no signs of local irritation at the site of patch application were observed. However, Agarwal et al found localized erythema or pruritus at the site of application of the transdermal patch when it was used for the attenuation of venous cannulation. Transdermal patches offer several advantages over oral administration, including ease of application, sustained drug delivery, lower incidence of adverse effects, prolonged duration of action, avoidance of first pass metabolism, increased therapeutic efficacy, and, in some cases, improved patient compliance due to not having to take multiple oral doses daily.

**Conclusion**
Within the limitations of the present study, a TDP was effective in the postoperative pain control following root coverage procedures with SCTGs. Patient tolerance was better with the TDP, as it did not cause any GI complications. However, there might be a possibility of bias as there was no placebo or blinded effect in the present study. To overcome these limitations, placebo-controlled studies with larger sample sizes are required to validate the findings of this study.

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**Disclaimer**
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