

**Evaluation of Efficacy, Safety And Tolerability of Transdermal Diclofenac Sodium Patch When Compared To Oral Diclofenac Sodium, For Pain Relief Following Minor Oral Surgical Procedures.**

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Conflicts of Interest: Nil

Abstract**Aim**

To compare efficacy, safety and tolerability of transdermal diclofenac sodium patch with oral diclofenac sodium for pain relief.

Method

100 participants requiring minor surgical procedures like Bilateral orthodontic premolar extractions, Bilateral surgical removal of third molars, Multiple extractions (U/L first/second molar), Bilateral preprosthetic surgery or any other minor surgical procedures that require staged surgical innervation bilaterally were selected for the study.

Surgical procedure on one side was done and oral Diclofenac sodium (75mg SR) b.i.d was given for 3 days. Then after a week, patient was called for the other side surgical procedure. 60 minutes before procedure, Transdermal patch of Diclofenac sodium 200mg (Nupatch) was applied on Trapezius muscle. Then the procedure was done and patient was asked to change

patch every 24 hours for the next 2 days. Modified Visual Analogue Scale (VAS) “Faces visual analogue pain scale”, was used to record the pain postoperatively, it is a four point scale, with values from 0-3.

Patients were also questioned about adverse effects (Gastro intestinal disturbances, headache, dizziness, allergic reactions erythema, induration, edema).

Results and Conclusion

Statistical analysis revealed that on Day 1 and 2, study subjects who were taking transdermal diclofenac show mild pain relief whereas subjects who were taking oral diclofenac showed better pain relief for moderate pain and results were found to be statistically significant. (p-value = 0.027, S). On day 3, complete pain relief in the groups who were taking oral diclofenac and there were moderate pain relief who were taking transdermal diclofenac but not statistically significant (p-value=0.208). Also, our results indicate higher tolerability and less adverse effects of transdermal diclofenac patch than oral diclofenac

following minor oral surgical procedures. The results indicated that transdermal diclofenac sodium can be used as an alternative form of pain control following minor oral surgical procedures.

Keywords: diclofenac sodium, transdermal patch, minor surgical procedures.

Introduction

Sound maxillofacial surgery practice demands excellent post operative analgesia or pain control. Dental care with pain or unsuccessfully managed pain makes patients reluctant towards seeking proper treatment.

Post surgical pain with inflammatory response often cannot redress the balance between surgeons and patients.

It is best managed by the most common analgesic Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).¹

Analgesic drugs can be delivered by different routes, including oral, parenteral, inhalation and transdermal. Drugs administered orally are lost substantially as they carry the risk of first pass metabolism before absorption. Parenteral delivery of drugs is often painful and there is sudden increase of drug concentration level in the plasma that could lead to adverse effects.² Most commonly patients are subjected to a course of oral analgesics be it NSAIDs/or a combination of NSAIDs and opioids as a measure of post operative analgesia. With drawbacks such as high first pass metabolism, poor taste, gastric irritation/acidity/ peptic ulcer, respiratory depression, nausea and vomiting, constipation, dependence associated with these commonly prescribed analgesics, it is but natural that we look for alternate drugs/ mode of drug delivery.¹

With the progress of medical science many alternate and novel routes of drug administration have been evolved, which can evade gastrointestinal tract. Transdermal route is an excellent example for this. It is applied to the skin to deliver sufficient quantity of drug to exert systemic effect

in form of patch or device. Transdermal route have various advantages, one of which is, the drug bypasses the liver metabolism after absorption thereby avoiding the gastrointestinal irritation for e.g. it has good patient acceptance, eliminates the need to take tablet at regular intervals and provides steady plasma profile.³

The Diclofenac transdermal patch is a newly introduced delivery system for Diclofenac and is available in India since 2005.⁴ In contrast to conventional topical formulations such as creams or gels, patches permit a constant and continuous delivery of the active ingredient to the affected area by means of occlusive bandage and slow release of the drug.^{5,6,7}

This study aims to compare the effectiveness of transdermal diclofenac patch in managing the post operative pain following minor oral surgical procedures in comparison with the standard oral dosage.

Material and method

The present study was carried out in Department of Oral and Maxillofacial Surgery, Vyas Dental College and Hospital, Jodhpur on an outpatient basis. Patients requiring minor oral surgical procedures under local anesthesia on an outpatient basis were included in the study. The procedures included, minor surgical procedures like Bilateral orthodontic premolar extractions, Bilateral surgical removal of third molars, Multiple extractions (U/L first/second molar), Bilateral preprosthetic surgery or any other minor surgical procedures that require staged surgical innervation bilaterally. Study events were explained to the patients and a written consent was obtained before inclusion in the trial. A detailed case history and medical condition of the patients were recorded.

Inclusion criteria:

Both male and female patients of all age groups who required any of the following procedures like,

1. Bilateral orthodontic premolar extractions,
2. Bilateral surgical removal of third molars
3. Multiple extractions (U/L first/second molar)
4. Bilateral preprosthetic surgery or
5. Any other surgical procedures that require staged surgical intervention bilaterally.

Exclusion criteria:

1. Pregnant and lactating women
2. Patients with blood coagulation disorders
3. Patients allergic to diclofenac or any other NSAIDs
4. Patients who are mentally retarded or unable to communicate
5. Immunocompromised patients
6. Patients with known skin disorders
7. Patients with history of analgesic intake or alcohol within the previous 24 hours.

Armamentarium



Fig 1: Armamentarium for minor surgical procedures



Fig 2: Tab Voveran SR 75mg



Fig 3: Transdermal diclofenac patch – 200mg

Orally active medication of diclofenac sodium (75 mg twice daily dosage; Voveran, Novartis, India) and active drug of diclofenac diethyl amine incorporated in the patch (Nupatch, 200 mg; Zydus Cadila, India). The medicated patch had identical dimensions of 10×7.5 cm (75 cm²).

Method

Data were collected from 100 patients reporting to Department of Oral and Maxillofacial surgery, Vyas Dental College and Hospital, Jodhpur from January 2015 onwards. Where 40 patients were treated for therapeutic bilateral orthodontic premolar extractions, 50 patients treated for bilateral impacted third molars, 5 patients were treated for bilateral preprosthetic surgeries and 5 patients were treated for multiple extractions. The procedures were explained in detail to the patient and written informed consent was obtained. Pre – operative evaluation included

case history, consent and routine radiographic and hematological investigations if needed.

Surgical procedure on one side was done and oral Diclofenac sodium (75mg SR) b.i.d was given for 3 days. Then after a week, patient was called for the other side surgical procedure. 60 minutes before procedure, Transdermal patch of Diclofenac sodium 200mg (Nupatch) was applied on Trapezius muscle. Then the procedure was done and patient was asked to change patch every 24 hours for the next 2 days.



Fig 4 : Transdermal patch applied on Trapezius muscle

Modified Visual Analogue Scale (VAS) “Faces visual analogue pain scale”, was used to record the pain postoperatively, it is a four point scale, with values from 0-3. In this scale, the interpretation for the values was complete relief for a score of 0 and no relief for a score of 3. Patients were also questioned about adverse effects (Gastro intestinal disturbances, headache, dizziness, allergic reactions erythema, induration, edema).

Results

Table 1: Distribution of study subjects selected

Variable	No. of Patients	Percentage
Bilateral orthodontic premolar extraction	40	40%

Bilateral surgical removal of third molar	50	50%
Bilateral preprosthetic surgery	5	5%
Multiple extractions (U/L first / second molar)	5	5%
Total	100	100%

Graph 1: Distribution of study subjects selected

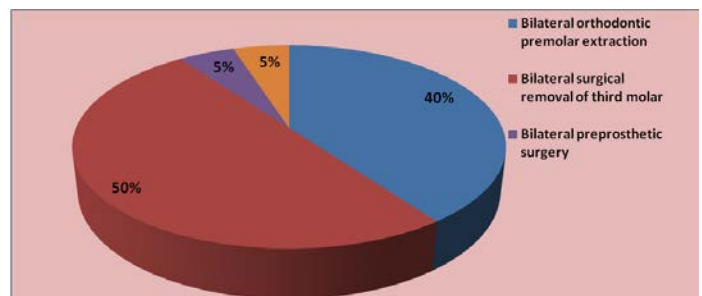


Table 1, Graph 1 : Shows distribution of study subjects among total 100 patients, where 40 patients (40%) were treated for bilateral orthodontic premolar extraction, 50 patients (50%) were treated for bilateral surgical removal of third molar, 5 patients (5%) were treated for bilateral preprosthetic surgery and 5 patients (5%) were treated for Multiple extractions.

Table 2: Distribution of study subjects according to gender

Gender		
Male	63	63%
Female	37	37%

Graph 2: Distribution of study subjects according to gender

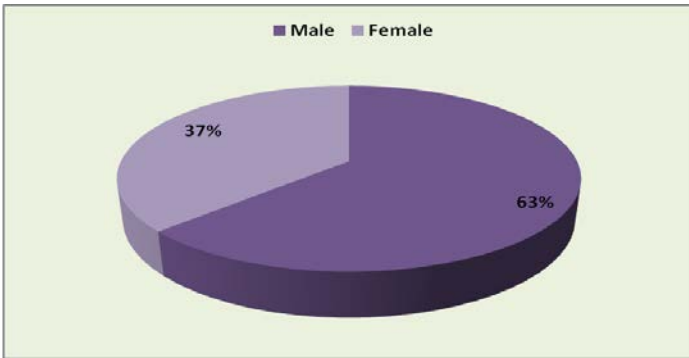


Table 2, Graph 2: Shows Distribution of study subjects according to gender there were 63 male patients (63%) and 37 female patients out of total 100 patients.

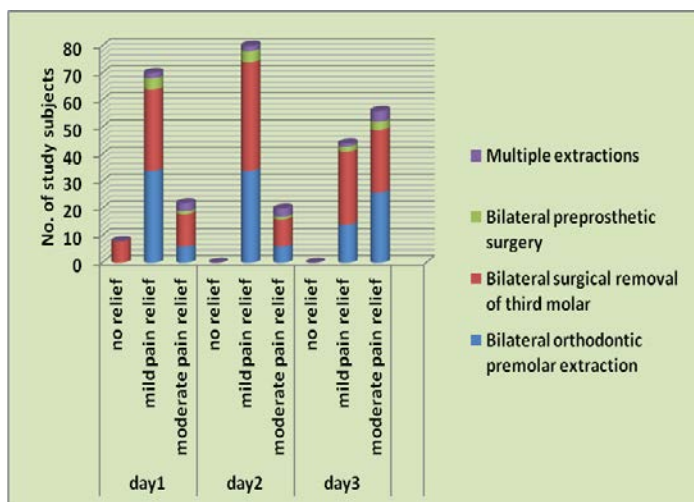
Table 3: Comparison of the efficacy of transdermal Diclofenac patch with oral Diclofenac for pain relief following minor oral surgical procedures.

Pain Relief	None	Mild	Moderate	Chi square-value	p-value
Day1					
Transdermal diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	34(34%)	6(6%)	10.928	0.091
Bilateral surgical removal of third molar	8(8%)	30(30%)	12(12%)		
Bilateral preprosthetic surgery	0(0%)	4(4%)	1(1%)		
Multiple extractions	0(0%)	2(2%)	3(3%)		
Oral diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	9(9%)	31(31%)	12.169	0.007
Bilateral surgical removal of third molar	0(0%)	28(28%)	22(22%)		
Bilateral preprosthetic surgery	0(0%)	1(1%)	4(4%)		
Multiple extractions	0(0%)	1(1%)	4(4%)		
Day2					
Transdermal diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	34(34%)	6(6%)	5.625	0.131
Bilateral surgical removal of third molar	0(0%)	40(40%)	10(10%)		
Bilateral preprosthetic surgery	0(0%)	4(4%)	1(1%)		
Multiple extractions	0(0%)	2(2%)	3(3%)		
Oral diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	3(3%)	37(37%)	3.862	0.027
Bilateral surgical removal of third molar	0(0%)	10(10%)	30(30%)		
Bilateral preprosthetic surgery	0(0%)	0(0%)	5(5%)		
Multiple extractions	0(0%)	1(1%)	4(4%)		

Day3					
Transdermal diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	14(34.6%)	26(11.4%)	4.545	0.208
Bilateral surgical removal of third molar	0(0%)	27(19.3%)	23(31.7%)		
Bilateral preprosthetic surgery	0(0%)	2(0%)	3(0%)		
Multiple extractions	0(0%)	1(0%)	4(0%)		
Oral diclofenac					
Bilateral orthodontic premolar extraction	0(0%)	0(0%)	40(0%)	---	---
Bilateral surgical removal of third molar	0(0%)	0(0%)	50(0%)		
Bilateral preprosthetic surgery	0(0%)	0(0%)	5(0%)		
Multiple extractions	0(0%)	0(0%)	5(0%)		

Graph 3, 4: Comparison of the efficacy of transdermal diclofenac patch with oral diclofenac for pain relief following minor oral surgical procedures.

Transdermal patch



Oral Diclofenac

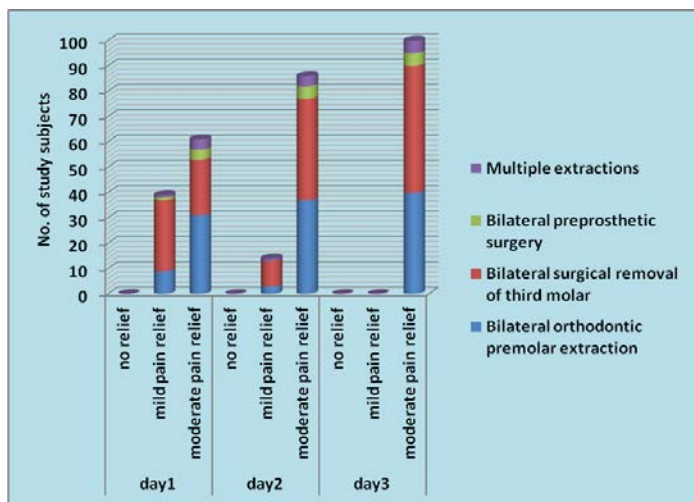


Table 3, Graph 3,4: Shows Comparison between the efficacy of transdermal Diclofenac patch with oral Diclofenac for pain relief following minor oral surgical procedures.

On Day 1 and 2, study subjects who were taking transdermal diclofenac show mild pain relief where as subjects who were taking oral diclofenac showed better pain relief for moderate pain and results were found to be statistically significant. (p-value = 0.027, S).

On day 3, complete pain relief in the groups who were taking oral diclofenac and there were moderate pain relief who were taking transdermal diclofenac but not statistically significant (p-value=0.208).

Table 4: Association between transdermal diclofenac patch with oral diclofenac for tolerability following minor oral surgical procedures

Tolerability	Oral diclofenac	Transdermal diclofenac	Chi square -value	p-value	Significance
Fair	57(28.5%)	14(7.0%)	40.140	0.002	S
Good	23(11.5%)	44(22%)			
Excellent	20(10%)	42(21%)			

Graph 5: Frequency of transdermal diclofenac patch and oral diclofenac for tolerability following minor oral surgical procedures.

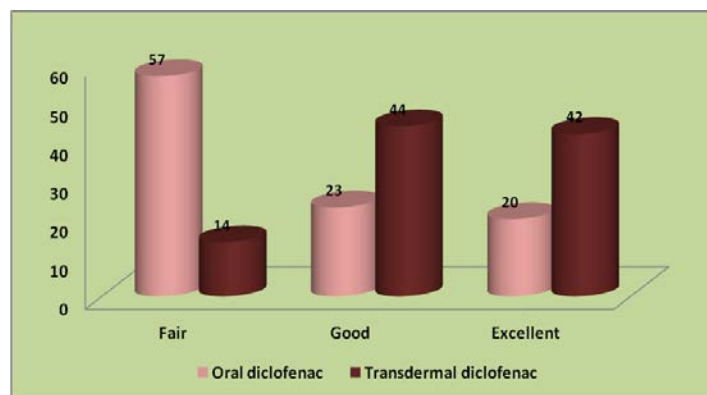
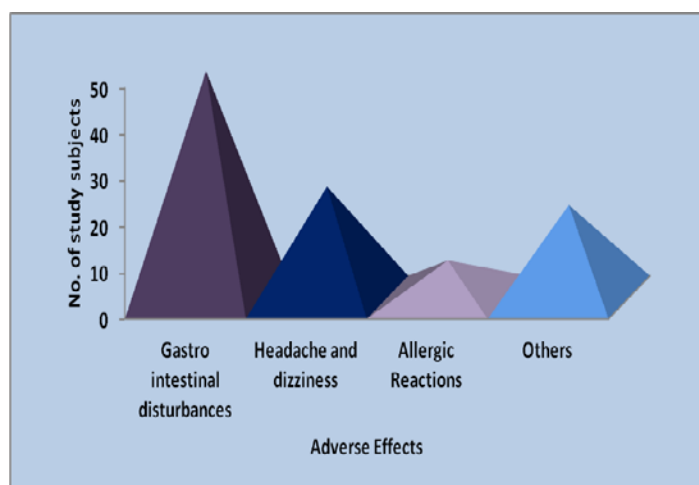


Table 4, Graph 5: Shows association between transdermal diclofenac patch with oral diclofenac for tolerability following minor oral surgical procedures. Study subjects who were taking transdermal diclofenac showed excellent tolerability compared to oral diclofenac and results found to be statistically significant. (p-value= 0.002, S)

Table 5: Frequency of adverse effects after application of transdermal diclofenac patch and oral diclofenac following minor oral surgical procedures

Adverse Effects	No. of study subjects	Percentage
Transdermal diclofenac		
Erythema	6	(5.9%)
Induration	13	(30.7%)
Edema	0	(0%)
Others	0	(0%)
Oral diclofenac		
Gastro intestinal disturbances	49	(48.5%)
Headache and dizziness	24	(23.8%)
Allergic Reactions	8	(7.9%)
Others	20	(19.8%)

Graph 6: Frequency of adverse effects after application of oral diclofenac following minor oral surgical procedures



Graph 7: Frequency of adverse effects after application of transdermal diclofenac patch following minor oral surgical procedures

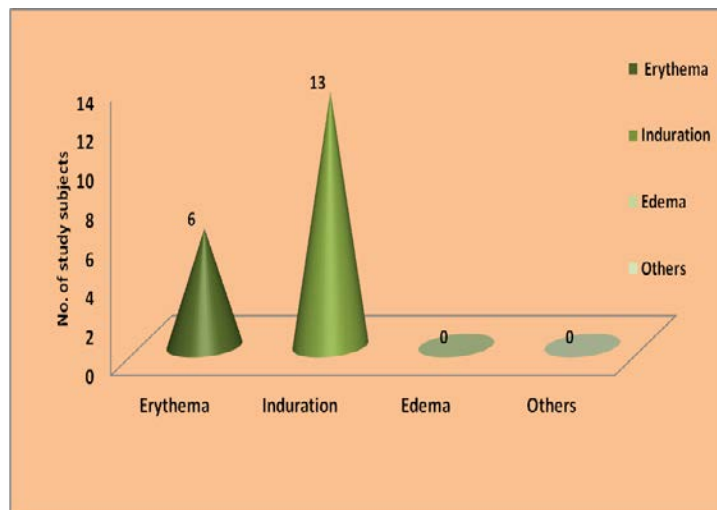


Table 5 , Graph 6,7: Shows adverse effects after application of transdermal diclofenac patch and oral diclofenac following minor oral surgical procedures. There were 100 (50%) subjects who had taken transdermal diclofenac. Out of them, 13 got induration and 6 got erythema as adverse effects. There were 100 (50%) subjects who had taken oral Diclofenac. Out of them, 49 got Gastro intestinal disturbances, 24 got headache and dizziness, 8 got allergic reactions and 20 got other adverse effects.

Discussion

Dental pain management is an important aspect in the routine dental practice; its management defines a practitioner’s clinical calibre and acumen.⁸

Non steroidal anti inflammatory drugs (NSAIDs) are among the most widely used medications in the world because of their demonstrated efficacy in reducing pain and inflammation⁹. Their efficacy has been documented in a number of clinical disorders, including osteo-arthritis, rheumatoid arthritis, ankylosing spondylitis, gout, dysmenorrhea, dental pain and headache.¹⁰⁻¹⁵ NSAIDs are commonly used for postoperative pain relief. NSAIDs exert anti - inflammatory and analgesic effects by inhibiting prostaglandin synthesis and through inhibition of the activity of cyclooxygenase (COX). When Diclofenac

is administered by oral route it is completely absorbed from gastrointestinal tract. Nearly 50% of the absorbed drug dose is systematically available due to first pass metabolism. Peak plasma concentration is generally achieved in approximately 1 hour in fasting normal healthy volunteers.

Clinically, efficacy of specific drugs of NSAIDs is no different. But these drugs have certain side effects like gastrointestinal bleeding, thrombotic cardiovascular events, renal and platelet.^{16,17} Diclofenac is an NSAID that inhibits both peripheral and central pain. As a cyclooxygenase inhibitor, it reduces the release of inflammatory mediators in the cyclooxygenase pathway, resulting in reduction of inflammation and pain sensation.¹⁵ Although effective at relieving pain and inflammation, diclofenac is associated with a significant risk of serious gastro intestinal adverse events and potential cardio vascular side effects.^{18,19}

Diclofenac is one such drug that is extensively used in dentistry and oral surgery for the management of post-operative pain in the form of tablets, suppositories, or parenteral preparations. Its use as an analgesic through a transdermal route has rarely been verified for the relief of dental pain. Its use through the oral and parenteral route is associated with various adverse effects that have been documented.^{20,21}

Transdermal drug system is itself a unique delivery method which is substituting traditional methods of drug delivery. The patch which is applied delivers the drug through the skin. First important layer is stratum corneum as its composition keeps the water within the body and do not let foreign substance to enter. Then dermis layer which is covered with epidermis has system of capillaries that transfer blood to the entire body. Furthermore, if the drug is able to penetrate through stratum corneum via passive diffusion, it can enter blood stream. The high

concentration of the patch releases slowly in blood as low concentration thereby the drug will keep diffusing for long period of time and maintain the constant concentration level of drug in blood.⁶⁰ The transdermal drug delivery offers several advantages as it avoids the need for intravenous or intramuscular drug administration, and is an option in patients who are unable to swallow oral medications.²³

We conducted a study to compare the analgesic efficacy, safety and tolerability of transdermal Diclofenac patch with oral Diclofenac sodium for postoperative analgesia in patients scheduled for extraction due various reasons.

It was found from the present study that efficacy of oral diclofenac in relieving the pain was superior as compared to transdermal diclofenac. In favour to our present study, Bachalli et al also reported that diclofenac sodium administered orally provided slightly better analgesia compared to transdermal administration on Postoperative Day1. However, statistical difference was also observed on the second and third postoperative days.² But, in contrast, Bhaskar et al. found that when used for postdental extraction analgesia, both oral and transdermal diclofenac exhibited similar analgesic efficacy.²⁴ Recent studies have shown that the transdermal administration is as effective as intramuscular diclofenac for postoperative analgesia following orthopedic and laproscopic surgeries.^{25,26} An important concern with regard to transdermal drugs is the prolonged duration of onset and offset, typically 12-24 hours unlike oral or intramuscular medications, which can be used as needed for pain control or nausea.²⁶ Transdermal diclofenac sodium patch has been shown to achieve better bioavailability with no marked peak to trough fluctuations. The diclofenac transdermal patch bioavailability is nearly 1% that of oral diclofenac, with half-life of 12hours.

Conclusion

The study concludes that transdermal diclofenac sodium can be used as an alternative form of pain managing mechanism following minor oral surgical procedures like orthodontic premolar removal, but in cases like third molar removal or preprosthetic surgeries where analgesic potency of transdermal patch will be less immediately, oral diclofenac will be more suitable, following which transdermal route can be used for pain control. Patient tolerance was better with the transdermal Patch, as it did not cause any GI complications or other systemic adverse reactions. This supports the previous findings that the lower plasma concentration achieved with topical NSAIDs application is associated with reduction in systemic adverse effects.

Limitation

There might be a possibility of bias as there was no placebo or blinding effect in the present study. To overcome these limitations, placebo-controlled studies with larger sample sizes should be done to validate these findings.

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