

**How to Cite:**

Khadase, P., Goyal, R., Pranam Nirangjan, A., Vaidehi, A., Chakraborty, A. J., & Kishor, A. (2022). Comparison of oral diclofenac transdermal patch versus oral diclofenac sustained release tablet as a post-operative analgesia following orthodontic extractions of premolar teeth: A randomized clinical study. *International Journal of Health Sciences*, 6(S2), 241–253.  
<https://doi.org/10.53730/ijhs.v6nS2.5003>

# **Comparison of Oral Diclofenac Transdermal Patch Versus Oral Diclofenac Sustained Release Tablet as a Post-Operative Analgesia Following Orthodontic Extractions of Premolar Teeth: A Randomized Clinical Study**

**Priyadarshani Khadase**

Department of oral and maxillofacial surgery and implantology, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Rohit Goyal**

Dept of Oral and Maxillofacial Surgery and implantology, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Pranam Nirangjan. A**

Department of oral and maxillofacial surgery and implantology, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Amba Vaidehi**

Department of preventive and pediatric dentistry, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Arka Jyoti Chakraborty**

Department of conservative dentistry and endodontics, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Avinash Kishor**

Department of orthodontics and dentofacial orthopedics, Maharaja Ganga Singh Dental College & Research Centre, located in Sri Ganganagar, Rajasthan, India

**Abstract**--Aim: This study was performed to compare the degree of post operative analgesia, patient compliance, and frequency of adverse events with the use of oral diclofenac tablets and transdermal diclofenac patch following multiple premolar extractions in patients undergoing orthodontic treatment. Materials and Methods: Thirty

young pre-orthodontic patients requiring bilateral maxillary and mandibular first premolar extractions were selected for the study. The right maxillary and mandibular first premolars were extracted first and 100mg oral diclofenac sodium sustained release tablets were prescribed to be taken thrice a day for three days. In the next appointment, the contralateral first premolars were extracted and a 100 mg transdermal diclofenac patch was applied once a day for three days. Pain relief and pain intensity with both the diclofenac formulations was recorded for each of using 5-point Verbal Pain Intensity and Pain Relief Score Charts. Results and Conclusions: Statistical analyses revealed that there was a gradual increase in pain relief scores and a gradual decrease in pain intensity scores with the use of oral diclofenac tablets as well as with the transdermal patch.

**Keywords**---analgesia, clinical study, diclofenac, post-operative, transdermal patch.

## **Introduction**

According to WHO pain has been defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (1,2,3). Pain was first explained as a protective response by René Descartes, a French philosopher in the sixteenth century, and since then, there has been rapid progress in its understanding but still the process of its management remains a challenge (4). Post extraction pain has often been a challenge for dental surgeon, with clinicians trying different analgesic modality that would provide profound analgesia and would be best tolerated by the patients, hence ensuring patient compliance (5). Over the year, opioids have been administered to allay anxiety and to reduce pain associated with surgery. Nonsteroidal anti-inflammatory drugs (NSAIDs), commonly prescribed in dental practice for the management of pain, are among the most frequently prescribed drugs worldwide. There are various routes of analgesic administration, among which oral analgesics is commonly prescribed for the management of pain. These users may develop gastrointestinal adverse effects of a sufficient degree requiring physician’s intervention.

The mechanism of action of NSAIDs is based on the inhibition cyclooxygenase 1 and 2 (COX-1 and COX-2) key enzymes in prostaglandin synthesis. Diclofenac, an NSAID is an anti-inflammatory, analgesic, and antipyretic drug, is begin used in widely for postoperative analgesic. When used through the oral route, however, only about 50% of the absorbed dose of diclofenac becomes systematically available, due to the first-pass metabolism and due to the high plasma concentration attained; oral diclofenac has the potential for significant adverse reaction, particularly those involving the gastrointestinal tract. In recent years, an increasing number of topical NSAIDs have become available, among which transdermal drug delivery system (TDDS) is the most efficient in the pain relief, with the fewer side effects and good patient compliance transdermal patches have been developed as innovative topical delivery system for diclofenac. The advantage of this route include painless, non-irritant, increased bioavailability, adverse

event, and compliance (6). The present study was carried out to evaluate and compare the degree of post-operative analgesia, patient compliance and frequency of adverse events with use of transdermal diclofenac patch and oral diclofenac in multiple premolar extractions in patients undergoing orthodontic treatment.

### **Materials and Method**

This was a proposed prospective randomized controlled trial conducted on 30 patients who visited the Department of Oral and Maxillofacial Surgery, Maharaja Ganga Singh Dental College & Research Center, Sriganganagar, Rajasthan for who required multiple premolar extractions for orthodontic purpose. The subjects belonged to both sexes and were the age range 14 to 26 years with a mean age 17.5 years. Subjects were divided into two groups.

- Group1 – patients who received diclofenac tablet for post- operative pain during tooth extraction in one side of the jaw.
- Group2 – patients who received transdermal diclofenac patch for post – operative pain during tooth extraction in opposite side of the jaw.

All the subjects included in the study had voluntarily participated in the study and had also signed informed consent and had healthy periodontal status. Subjects with grossly decayed tooth along with periapical involvement with history of allergy to NSAID, with acute peptic ulceration within six months, with history of systemic diseases like bronchial asthma, epilepsy and emotional or psychosomatic disorders were excluded from the study. Informed consent was obtained from all the patients who were enrolled for this study before the procedure and the ethical clearance for the study was provided by an institutionally approved ethical committee. A written informed consent was obtained from all the patients.

Either right or left maxillary and mandibular first premolars were first extracted in same appointment using standardized armamentarium (fig1). Following which 100 mg oral diclofenac tablets were prescribed to be taken thrice a day for period of the three days (nine tablets) or 100mg transdermal diclofenac patch was given. Each of patient were given a verbal pain intensity and pain relief score chart (both 5-point scale with value from 0 to 4) for assessing pain intensity and pain relief from each of three postoperative days.(fig2). Paracetamol 650mg tablets were permitted to be used as rescue medication and total nine tablets were provided to each patient. Subsequent right or left maxillary and mandibular first premolars were extracted and 100mg transdermal Diclofenac patch (DicloPLAST-Zuventus) was placed. Or 100mg oral diclofenac sustained release tablet (viveran SR100) was given. (fig.3 and 4). On the each of the following two days, the patch was changed and new one placed; thus placing a total of three patches over the three post-operative days (fig5). The patients were permitted to use paracetamol 650mg tablets as rescue medication during post-operative period.

### **Transdermal diclofenac patch**

The matrix controlled Diclofenac transdermal patch is flat and transparent transdermal delivery system (TDS) that provide continuous and systemic release

of Diclofenac and is designed to remain at the site of application for 24hrs. Each 50sq.cm patch contains 100mg of Diclofenac Diethylamine as its active ingredient. The device consist of polymer matrix that controls the release of the drug and an impermeable backing membrane that prevent leaching of the drug from top. The adhesives fasten the device to the skin during use. The patch delivers slow release of the drug into body over time, resulting in long term effectiveness and added convenience. subject were asked to report pain intensity score chart for three postoperative days, following to submit the 5-point pain intensity scale for evaluation and were also asked to report pain relief score chart three post-operative days, following to submit 5- point pain relief scale for evaluation. The data obtained from study subjects were statistically evaluated using Mann-Whiteny U test.



Figure 1. Armamentarium used for premolars extraction

Patient Name :  
 Age :  
 Sex :  
 OPD No . :

**Pain intensity scale**

0	-	NONE
1	-	VERY MILD PAIN
2	-	MILD PAIN
3	-	MODERATE PAIN
4	-	SEVERE PAIN

**Pain relief scale**

0	-	NONE
1	-	A LITTLE
2	-	SOME
3	-	A LOT
4	-	COMPLETE

\* Please bring the no of paracetamol tablets left on your visit to the Doctor.

Figure 2. The verbal pain intensity and pain relief score chart



Figure 3. Diclofenac Transdermal Patch (DicloPLAST)



Figure 4. Oral Diclofenac Sustained Release Tablet (Voveran SR 100)



Figure 5. Diclofenac Transdermal Patch on Patient at Right Shoulder

## Results

The patients were asked to fill the verbal pain intensity score chart and the pain relief score chart. The data collected were statistically analyzed using the mann-whitney U nonparametric test. After assessing the score charts , it was revealed that there was a gradual decrease in the pain intensity scores from day one to day three for both the oral diclofenac tablets and as well as with the transdermal patch.( table1, figure 6)

Table 1  
Score on the pain intensity scale

	Oral			Transdermal patch		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Mean (n = 30)	3.2	1.63	0.47	3.43	1.77	0.6
S. D	0.407	0.615	0.571	0.568	0.679	0.621

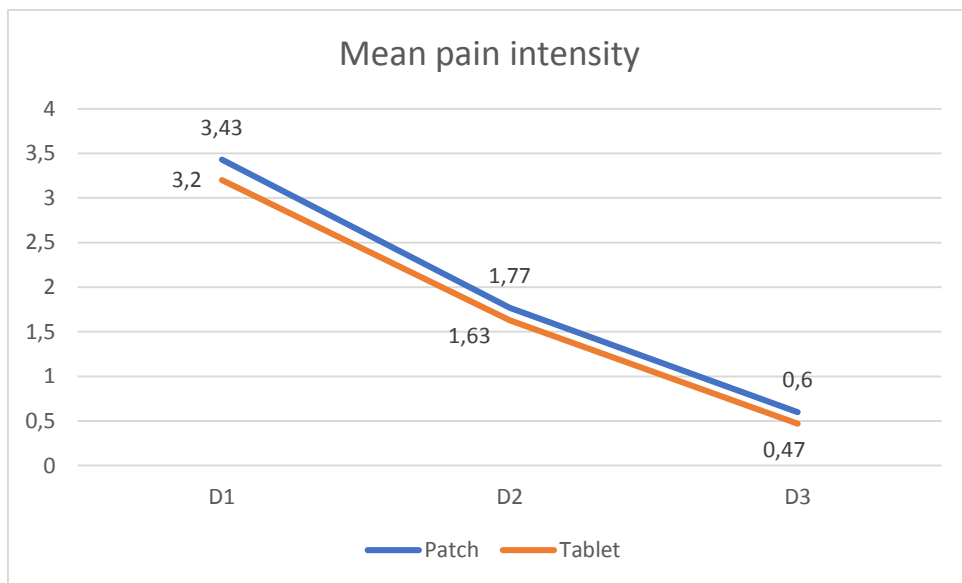


Figure 6. Mean pain intensity from day 1 to day 3.

On evaluating the chart pain relief amongst the subjects, it was observed that all patients reported of complete or almost complete pain relief by the third day of therapy with either oral diclofenac tablets or transdermal diclofenac patch. In both groups of subjects, i.e, those taking oral diclofenac tablets and those in whom the transdermal patch was placed, there was a gradual increase in pain relief scores over the three post operative days.

[Table 2, figure 7].

Table 2  
Score on the pain relief scale

	Oral			Transdermal patch		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Mean (n = 30)	1.00	2.13	3.4	1.23	2.33	3.47
S. D	0.830	0.507	0.498	0.679	0.606	0.507

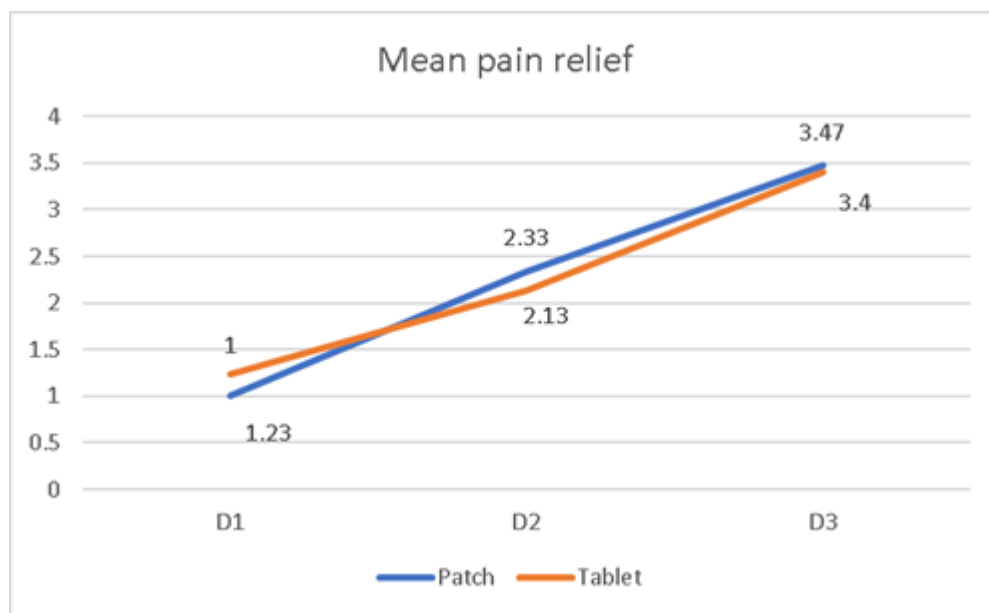


Figure 7. Mean pain relief from day 1 to day 3

The data was analyzed by statistical package for social sciences (SPSS) software. Mann-Whitney U test was done to find the statistical significance between groups. Mean verbal pain intensity of diclofenac patch for three successive days were 3.43, 1.77 and 0.60 respectively and mean verbal pain intensity of diclofenac tablets were 3.20, 1.63, 0.47 for respective three days. Mean verbal pain relief of diclofenac patch for three successive days were 1, 2.33 and 3.47 respectively and mean verbal pain relief of diclofenac tablet were 1.23, 2.13, 3.40 respectively for three successive days. Statistically result between oral diclofenac tablet and diclofenac patch on the basis of three days pain intensity and pain relief parameters are not significant.

## Discussion

Pain has been defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. The conquest over pain has been a great challenge since time immemorial; pain afflicts all living beings, and even though it is unpleasant, it has a nature of self-preservation. Pain was first explained as a protective response by René Descartes, a French philosopher in the sixteenth century, and since

then, there has been rapid progress in its understanding but still the process of its management remains a challenge. In dentistry, pain is a rather inevitable perception that often plagues both the care provider and the receiver. Various dental procedures also evoke the perception of anxiety which culminates with pain and exaggerates the perception of pain. Hence, adequate pain control and assurance is of utmost importance during and following an invasive dental procedure, such as to maintain a good rapport with the patient.

The procedure of dental extraction has been associated with an unpleasant response since time immemorial; the procedure had been used to treat a variety of illness unrelated with dental causes, and it was also used as a method of torture to obtain forced confession from a victim. Post-extraction pain control is as critical as it is during the process of extraction; the use of non-steroidal analgesic has its advantages of adequate pain control, but it has its various disadvantages of causing adverse effects inherent to the medication. These effects include gastric intolerance, multiple oral or parenteral analgesic administration, or allergic reactions to the drug itself. The attempt from the physicians' aspect is to maximize the alleviation of pain and minimizing the adverse effects associated with the drug<sup>1</sup>.

Nonsteroidal anti-inflammatory drugs (NSAIDs) block the activity of cyclooxygenase and inhibit the synthesis of prostaglandins, leading to anti-inflammatory and analgesic effects. However, it is reported that oral administration of NSAIDs subjects the drug to first pass metabolism with a significant amount being lost before it is absorbed systemically. Oral NSAIDs also cause several dose dependent adverse effects, particularly gastrointestinal effects. Alternate routes of administration of NSAIDs, in the form of topical formulations, have been developed. They are associated with a lower incidence of systemic side effects and enhanced local drug delivery to the affected tissues. Topical NSAIDs have thus established themselves as therapeutic analgesic modalities with recognized benefits and lower incidence of adverse effects.<sup>2</sup>

### **Diclofenac**

Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) taken to reduce inflammation and as an analgesic to reduce pain in conditions such as arthritis or acute injury. The name is derived from its chemical name: 2-(2,6-dichloranilino) phenylacetic acid. Diclofenac is an effective analgesic and anti-inflammatory compound with good uricosuric and antipyretic properties. It is amongst the most potent inhibitors of prostaglandin synthetase. Considering its efficacy it shows an encouraging therapeutic ratio, and has been proved to be superior to the reference drugs when comparing gastrointestinal tolerability. All metabolites are less potent compared to the parent compound (3). A newly TDDSs, also known as "patches," are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin at a programmed rate to reach the systemic circulation. The first transdermal system was approved by the Food and Drug Administration (FDA) in 1979 for the prevention of nausea and vomiting. Advantages of transdermal diclofenac patch are compared with oral and parenteral route, e.g., avoidance of the first-pass metabolism, gastrointestinal incompatibility, and predictable and extended duration of the

activity. It also provides the utilization of drugs with a short biological half-life, narrow therapeutic window, and improves physiological and pharmacological response. The mechanism of transportation of transdermal drugs is through the stratum corneum (being the uppermost layer of dead epidermal cells), viable epidermis (devoid of blood vessels), stratum lucidum, stratum granulosum, stratum spinosum, stratum germinativum, and the dermis (containing blood vessels). There are three ways in which a drug molecule can cross the intact stratum corneum, through skin appendages (transappendageal and shunt routes), intercellular lipid domain, and transcellular route.

All NSAIDs reach the targeted site of activity only after the drug enters the systemic circulation. To have an adequate local effect, oral and parenteral NSAIDs must produce relatively high systemic levels. In contrast, topically applied NSAIDs can provide direct and local relief without systemic activity. Thus, the advantage of drug delivered topically is to produce clinically meaningful results without systemic side effects or drug interactions (4). The present study included 30 patients whose age ranged from 14 years to 26 years with mean age 20 years. A similar study done by Bhaskaret al.[6] had patients whose age ranged from 14 to 16 years, with a mean age of 17.5 years and gender distribution of 28 females (84.4%) and 5 males (15.2%). This is also in accordance with Prithviet al.[1] who included twenty patients in which 13 were male (65%) and 7 (35%) were female. And sanjaytalia et al also studied 33 patients whose age ranged from 13 years to 29 years, with a mean age of 18.73 years.

Evaluation of pain is always subjective, but can be evaluated in various scales like Verbal Rating Scale, Pain Intensity Scale and Pain Relief Scale. Verbal Rating Scale is 5 pointed scale 0-4 indicating "no pain" to "severe pain" respectively. The Pain Intensity Scale is a scale similar to Verbal Rating Scale, with pain score nil pain, very mild, mild, moderate and severe pain corresponding to values 0-4. The Pain relief scale is the Pain intensity scale in reverse with the values 0-4 corresponding to complete relief and no relief respectively. In this comparative interventional study, the efficacy of Diclofenac tablet and Diclofenac transdermal patch in management of post operative pain is compared in patients with bilateral teeth extractions. This study being a cross over study all the participants were exposed to both the form of drugs (Diclofenac tablet and diclofenac patch) . This study setting provides a better platform to avoid biases. As the emergency medication used is Tab paracetamol 650mg, the parameters evaluated are postoperative pain score at intervals of 24 hours in following scales like VRS, PIS, PRS in three consecutive days and if the patient required the emergency medication, the number of paracetamol tablet consumed is calculated.

In day one, the mean pain scores in all the pain scales like VRS, PIS, PRS reduced with time in both the groups and the reduction were statistically significant in both groups (diclofenac tablet and diclofenac patch). This result was in accordance with Bhaskar et al, where he showed that in comparing post-operative pain, the mean pain score reduced with time in both the groups. pain scores on day one in all the scales seems to be lesser in group (diclofenac patch) when compared to group (diclofenac tablet) but the p value was not statistically significant. This result obtained in this study is in contradictory to the previous study by Bachalli PS et al. who showed when comparing Diclofenac patch and

Diclofenac tablet the diclofenac tablet was more effective in managing the post operative pain in first 24 hours. This contraindication can be explained with the fact that the analgesics in this study are given preemptively. The diclofenac transdermal patch was given 2 hours and diclofenac tablet was given one hour before the procedure.

On day two, the mean pain score in all the pain scales like VRS, PIS, PRS reduced with time in both the groups and the reduction of mean VRS score was significant in both groups (diclofenac tablet and diclofenac patch). On day two, though the mean pain scores in all the scales seem to be lesser in group (diclofenac patch) when compared to group (diclofenac tablet) the p value was not statistically significant. This result was similar to the result obtained by Bachalli PS et al. which states that the transdermal diclofenac and Oral Diclofenac are equally efficient in managing the post operative pain on day two. On day three, the mean pain scores in all the pain scales like VRS, PIS, PRS reduced with time in both the groups and the reduction was statistically significant in both groups (diclofenac tablet and diclofenac patch). This result was in accordance with Bhaskar et al. where he showed that in comparing post operative pain, the mean pain score reduced with time in both the groups.

In this study 2 patients required an emergency medication in Group – (diclofenac patch), and also in a comparative interventional study of Baskhar et al. about one patient out of twenty required emergency paracetamol tablet as an emergency medication in spite of transdermal patch. In this study both diclofenac tablet and transdermal diclofenac reduces the pain score on all the three days with letting the patient to go for an emergency pain medication. Though the mean pain scores for the patients in transdermal patch are lesser than the pain scores for the patients in diclofenac tablet, the differences between them are not statistically significant, thus leading to the conclusion of equal efficacy of the two medication in management of post operative pain. The results were similar to the study by Krishnan et al. who compared the efficacy of transdermal diclofenac and Oral diclofenac in third molar extraction. In this study no patients had side effects like gastric irritation from the tablet diclofenac, contradictory to study of Bhaskar et al where he reported that two of twenty patients had gastric irritation. No patients had any allergic or adverse reaction of diclofenac patch, as the patients allergic to diclofenac were excluded from the study.

## References

1. SaranyaDhanapal, NivedhitaMallisureshbabu. Efficacy of the single dose of transdermal patch as a pre-operative Analgesic in Root canal Treatment-A Randomized clinical Trial; J. Pharm. Sci. & Res Vol. 8(2),2016, 125-127.
2. HG Predel, et al. Diclofenac patch for topical treatment of acute impact injuries: a randomised, double blind, placebo controlled ,multicentre study; British Journal of Sports Medicine, July 2004
3. U PunithaGnanaSelvi, et al. Comparison of transdermal Diclofenac injection as an Analgesic Modality following Surgical Extraction of Impacted Mandibular third Molars: A cross Over Efficacy trail; international journal of scientific study | August 2016 | vol4 | issue5.

4. Sriram Krishnan et al, Transdermal diclofenac patches for control of post-extraction pain. Pilot randomized controlled double-blind study; Oral MaxillofacSurg; Springer-Verlag Berlin Heidelberg 2013.
5. Patel D, et al. Transdermal Drug Delivery System: A Review. PharmaInnov J 2012; 1(4): 78-885.
6. Lin-Fen Hsieh et al; Efficacy and Side Effects of Diclofenac Patch in Treatment of Patients with Myofascial Pain Syndrome of the Upper Trapezius| Journal of Pain and Symptom Management; Vol. 39 No. 1 January 2010
7. Sanjay Talnia, et al. Efficacy of Transdermal Diclofenac Patch as an Analgesic Following Premolar Extractions in Orthodontic Patients; Annals of Maxillofacial Surgery | Volume 10 | Issue 1 | January-June 2020.
8. DebjitBhowmik et al. Recent Trends in Challenges and Opportunities in Transdermal Drug Delivery System; www.thepharmajournal.com| Vol. 1 No. 10 2012
9. Krishnan S. Transdermal diclofenac patch for control of post-extraction pain, pilot randomized controlled double blind study. J Maxillofac Oral Surg 2015; 19(1): 5-12.
10. Bhaskar H, Kapoor P, Ragini. Comparison of transdermal diclofenac patch with oral diclofenac as an analgesic modality following multiple premolar extractions in orthodontic patients: A cross over efficacy trial. ContempClin Dent 2010;1(3):158-63.
11. Prithvi S Bachalli, et al. A comparative study of diclofenac transdermal patch against oral diclofenac for pain control following removal of mandibular impacted third molars; Association of oral and maxillofacial Surgeons of India 2009
12. Bailey BMW, et al. A double-blind comparative study of soluble aspirin and dictofenac dispersible in the control of post extraction pain after removal of impacted third molars. Int J Oral MaxillofacSurg 1993; 22. 238-41.
13. Muller M, Mascher H, Kikuta C. Diclofenac concentrations in defined tissue layers after topical administration. ClinPharmacolTher 1997; 62(3): 293-9.
14. Arora P, Mukherjee B. Design, development, physicochemical, and in vitro and in vivo evaluation of transdermal patches containing diclofenac diethylammonium salt. J Pharm Sci 91:2089-96.
15. Arthur AM, Bookman, Kate SA. Effect of a topical diclofenac solution for relieving symptoms of primary osteoarthritis of the knee: a randomized controlled trial. CMAJ. 2004;171(4):333-8.
16. Zuniga JR et al. Analgesic Safety and Efficacy of Diclofenac Sodium Soft gelson Postoperative Third Molar Extraction Pain. J Oral and MaxillofacSurg 2004;62(7): 806-15.
17. Bangbose BO, Akinwande JA, Adeyemo WL. A prospective, randomized, open label, pilot clinical trial comparing the effects of dexamethasone co-administered with Diclofenac potassium or acetaminophen and Diclofenac potassium monotherapy after third molar extraction in adults. CurrTher Res Clin Exp2006;67:230-40.
18. Carolyn J Sachs , oral analgesic for nonspecific pain, am fam physician,2005
19. Niethard FU, et al. Efficacy of topical diclofenac diethylamine gel in osteoarthritis of the knee. J Rheumatol. 32: 2384-92

20. Philip A bear et al, Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomized controlled, 6 weeks trail; biomed central; 2005.
21. Alessandri F, Lijoi D, Mistrangela E. Topical diclofenac patch for postoperative wound pain in laparoscopic gynecologic surgery: a randomized study. *J Minim Invasive Gynecol* 2006;13(3):195-200.
22. Carriches CL, Gonzalez JM, Rodriguez MD. The use of methyl-prednisolone versus diclofenac in the treatment of inflammation and trismus after surgical removal of lower third molars. *Med Oral Patol Oral Cir Bucal* 2006;11:E440-5.
23. Agarwal A, Goutham S, Gupta D, Singh U. Transdermal diclofenac vs eutectic mixture of local anesthetics for venous cannulation pain. *CAN J ANESTH* 2007;54(3):196-200.
24. Minghetti P, Cilurzo F, Casiraghi A, Montanari L, Fini A. Ex vivo study of transdermal permeation of four diclofenac salts from different vehicles. *J PharmSci* 2007;96:814-23.
25. Mastrolonardo M. Topical diclofenac 3% gel plus cryotherapy for treatment of multiple and recurrent actinic keratoses. *Clinical and Experimental Dermatology* 2009;34:33-35
26. Sen I, Mitra S, Gombar KK. Fatal anaphylactic reaction to oral diclofenac sodium. *Canadian Journal of Anaesthesia* 2001;48: 421-421
27. Hsieh et al; efficacy and side effects of diclofenac patch in treatment of patients with myofascial pain syndrome of the upper trapezius; *esevier*;2010.
28. Lionberger DR, Brennan MJ. Topical non-steroidal anti-inflammatory drugs for the treatment of pain due to soft tissue injury: diclofenac epolamine topical patch. *Pain Res* 2010; 10(3): 223-33.
29. Preetha JP, Karthika K, Rekha NR, Elshafie K. Formulation and evaluation of insitu ophthalmic gels of diclofenac sodium. *Journal of Chemical and Pharmaceutical Research* 2010;2(3):528-35.
30. Krishna R, Nataraj MS. Efficacy of single dose transdermal diclofenac patch as pre-emptive post operative analgesia: a comparison with intramuscular diclofenac. *South Afr J Anaesth Analg* 2012; 18(14):194-7.
31. Tiwari AK, Tomar GS, Ganguly S, Kapoor MC. Kounis syndrome resulting from anaphylaxis to diclofenac. *Indian J Anaesth* 2013;57:282-4.
32. Soumya Samal, Saubhagya Kumar Jena, Basanta Kumar Behera Postoperative Analgesia with Transdermal Diclofenac versus intramuscular Diclofenac – A comparative Study; *Journal of Evolution of medical and dental Sciences/ volume 2 / Issue 19 / May 13,2013 page3375-3384*
33. Khalili S et al. The effectiveness of diclofenac gel and eutectic mixture of local anesthetic cream on vein puncture pain severity with vein catheter in patient undergoing cesarean section: A randomized, double-blind, placebo-controlled trial. *Int J Appl Basic Med Res* 2014;4:46-9.
34. de Barros, Chagas PAM, Borges FA, et al. Diclofenac Potassium Transdermal Patches Using Natural Rubber Latex Biomembranes as Carrier. *Journal of Materials [Internet]*. 2015. doi:10.1155/2015/807948.
35. Osmani RA, Aloorkar NH, Ingale DJ, et al. Microsponges based novel drug delivery system for augmented arthritis therapy. *Saudi Pharmaceutical Journal: SPJ: the Official Publication of the Saudi Pharmaceutical Society*. 2015 Oct;23(5):562-572. DOI: 10.1016/j.jsps.2015.02.020. PMID: 26594124; PMCID: PMC4605913.

36. U PunithaGnanaSelvi, et al. Comparison of transdermal Diclofenac injection as an Analgesic Modality following Surgical Extraction of Impacted Mandibular third Molars: A cross Over Efficacy trail; international journal of scientific study| August 2016| vol4|issue5.
37. SaranyaDhanapal, NivedhitaMalli SureshBabu. Efficacy of the single dose of transdermal patch as a pre-operative Analgesic in Root canal Treatment – A Randomized clinical Trial; J. Pharm. Sci. & Res Vol. 8(2), 2016, 125-127.
38. Dr. IshaKaurBagga, et.al. Evaluation of efficacy, safety, and tolerability of transdermal diclofenac sodium patch for in management of postoperative pain following surgical removal of impacted mandibular third molars; International Journal of current research vol9, Issue02,pp.46168-46173, February,2017
39. Nallan CSK Chaitanya, et al. A comparative evaluation of diclofenac sodium transdermal patch, oral diclofenac sodium with intramuscular injections of diclofenac sodium in patients suffering from oral pain: A Randomized Control Trial; 2017 international Journal of pharmaceutical investigation| published by Wolter Kluwer-medknow.
40. U.S. Gupta, U.K. Bhagat and A.M. Lakra. A comparison of diclofenac patch and intramuscular diclofenac for postoperative analgesia abdominal hysterectomy under spinal anaesthesia- A Prospective, randomized clinical study.
41. VikasDiwan, et al. A comparative Evaluation of transdermal Diclofenac Sodium as an Analgesic drug following periodontal flap Surgery: A Randomized Controlled clinical study; 2019 Indian Journal of Dental Research| published by Wolters Kluwer- Medknow.
42. Kerry S. Kuehl. Review of the efficacy and Tolerability of the Diclofenac Epolamine Topical Patch 1.3% in Patients with Acute Pain Due to Soft Tissue Injuries; June 2010.
43. Shankar D, Sinha A, Anand S, Verma N, Choudhary S. Efficacy of Transdermal Diclofenac Patch and Ketoprofen Patch as Postoperative Analgesia after Extraction of First Premolars Bilaterally in Both Arches for Orthodontic Purpose: A Comparative Study. J Pharm Bioallied Sci. 2021;13 (Suppl 1):S101-S104. doi:10.4103/jpbs.JPBS\_571\_20.
44. NamanAwasthi, et al. Efficacy of transdermal ketoprofen patch and diclofenac patch in the management of post operative pain after therapeutic extraction- a clinical study. Turkish Journal of Physiotherapy and Rehabilitation; 32(3)ISSN 2651-4451 | e-ISSN 2651-446X.