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Original Article

Comparison of Transdermal Diclofenac Patch with Intramuscular Diclofenac Injection as an Analgesic Modality Following Surgical Extraction of Impacted Mandibular Third Molars: A Cross Over Efficacy Trail

U Punitha Gnana Selvi[1], D Kamatchi[2], C Babu[3], S Keerthana[3], S Vidya Lourdu Jeeva[3]

[1]Professor and Head, Department of Dental Surgery, KAPV Government Medical College, Tiruchirappalli, Tamil Nadu, India, [2]Assistant Professor, Department of Dental Surgery, KAPV Government Medical College, Tiruchirappalli, Tamil Nadu, India, [3]Senior Intern, Department of Dental Surgery, KAPV Government Medical College, Tiruchirappalli, Tamil Nadu, India

Abstract

Introduction: The surgical removal of mandibular third molars serves as a standard model for any research pertinent to analgesia. The present study aims to analyze the effectiveness of the non-steroidal anti-inflammatory drugs, diclofenac administered by the transdermal drug delivery route as compared to intramuscular (IM) injection, in the management of post-operative pain for the standard model of surgical removal of mandibular third molars.

Materials and Methods: About 20 patients requiring bilateral mesioangular impacted mandibular third molars were selected for the study. After performing impaction surgery on right side, patients received 50-cm^2 patch, 100 mg of diclofenac diethylamine, and after 3 weeks surgical extraction on the left side was performed and postoperatively patients received injection diclofenac. The subjects were asked to report the intensity and pain relief on the verbal pain score chart for the 3 post-operative days.

Results: Diclofenac administered by either mode of delivery as transdermal patches or IM injections has similar effectiveness. The patients who had taken transdermal drug delivery had shown better compliance and also were enthusiastic of the prospect of achieving pain control without the need for oral medications.

Conclusion: The transdermal diclofenac patch is a promising analgesic modality for the management of mild to moderate pain following dental extractions, given the evidence of its established analgesic potency with a lower incidence of systemic adverse effects.

Key words: Diclofenac patch, Impaction surgery, Intramuscular diclofenac injection, Pain relief

INTRODUCTION

The contribution of non-steroidal anti-inflammatory drugs (NSAIDs) in the alleviation of pain cannot be underestimated. Right from the commonly used acetaminophen that affords relief by its antipyretic and analgesic effects in our day to day lives to diclofenac also commonly used for acute and musculoskeletal pain, the role of these drugs is indispensable. Though many adverse effects are commonly associated with the use of NSAIDs, these tools have to be applied at the right time with the right method to sculpt a pain free and comfortable experience for the patient.

It has been documented that the most common adverse effect with the use of NSAIDs by either oral or parenteral route is the gastric irritability that occurs secondary to the

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Corresponding Author: Dr. D Kamatchi, 135, Madurai Road, Manaparai - 621 306, Tiruchirappalli, Tamil Nadu, India.
Phone: +91-9842461740. E-mail: kamsdrd78@gmail.com

inhibition of the protective effects of cycloxygenase 1.[1,2] The introduction of the transdermal drug delivery system gives a solution to the question of achieving a therapeutic concentration without producing undesirable side effects. This route of administration differs from the traditional topical administration in that, after penetration of the skin barrier, the drug enters the circulation to be distributed systemically.[3] The major advantage of transdermal route is the constant drug dosage that is available and maintained in the circulation due to its sustained release properties.[4,5] Thus a stable concentration is maintained systemically without concentrated higher doses in the gastrointestinal system, the hepatic metabolism is also bypassed.[6]

The surgical removal of mandibular third molars serves as a standard model for any research pertinent to analgesia.[7] This is due the fact that surgical removal of third molars cause pain due to both incisional and inflammatory injury, thus eliciting both peripheral and central response. Also, with the surgical removal of mandibular third molars, standardization is possible to reduce the bias caused by the level of surgical difficulty.

The present study aims to analyze the effectiveness of the NSAID, diclofenac administered by the transdermal drug delivery route as compared to intramuscular (IM) injection, in the management of post-operative pain for the standard model of surgical removal of mandibular third molars.

MATERIALS AND METHODS

The study was conducted among the patients reporting at the outpatient Department of Dental Surgery, Mahatma Gandhi Memorial Government Hospital attached to KAPV Government Medical College, Tiruchirappalli.

The sample included patients of the age group of 18-30 years of both sexes who were willing for the study, with bilateral mandibular third molar impactions, Winter's classification of Class I, mesioangular in position A (Figure 1). Patients with any systemic illnesses, those under chronic steroid therapy and those with a history of peptic ulceration or known allergy to NSAIDs were excluded from the study. Accordingly, 20 patients were included in this randomized controlled study. The ethical clearance for the study was provided by an institutionally approved Ethical Committee and all subjects were informed about the nature of the study and the probable side effects from the drugs being administered. A written informed consent was obtained from all subjects. The patients were divided into Group A and Group B. Group A included patients under analgesia provided by Transdermal patch, Group B included patients under analgesia provided by IM diclofenac.

All the extractions were performed by the same operator, thus removing any operator-induced bias from the study. The extraction of third molars was performed using standardized technique (Figures 2 and 3). After performing the impaction surgery on right side, patients received 50-cm^2 patch (NuPatch-Zydus Cadilla labs), 100 mg of

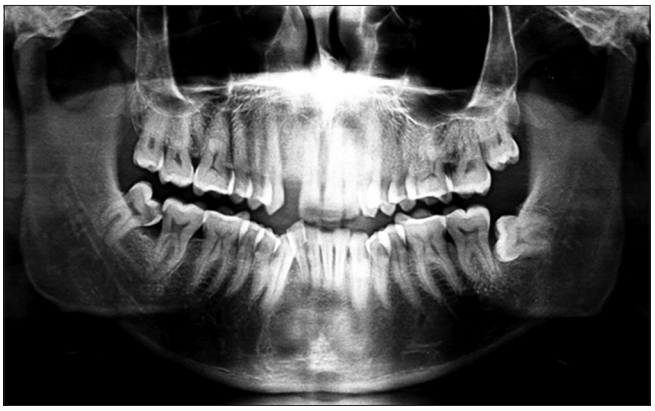


Figure 1: Radiograph showing bilateral impacted mandibular third molars

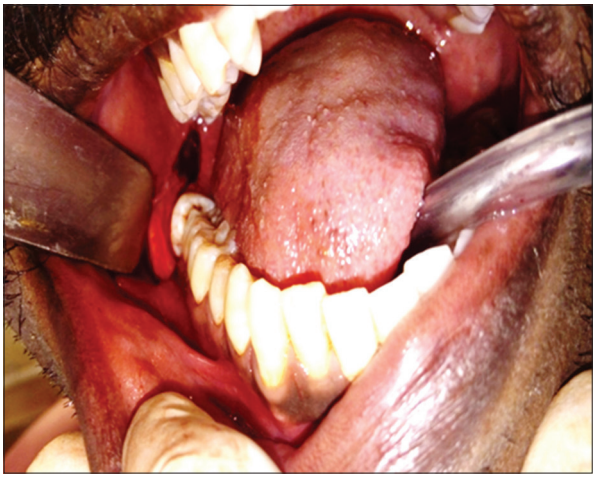


Figure 2: Incision and flap reflection during impaction surgery

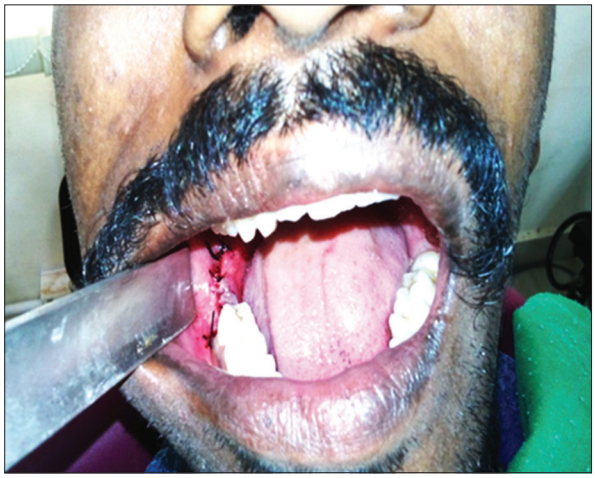


Figure 3: Placement of sutures after impaction

diclofenac diethylamine. The matrix controlled diclofenac transdermal patch is a flat and transparent transdermal delivery system that provides continuous and systemic release of diclofenac and is designed to remain at the site of application for 24 h. Each 50 cm^2 patch contains 100 mg of diclofenac diethylamine as its active ingredient (Figure 4). The device consists of a polymer matrix that controls the release of the drug and an impermeable backing membrane that prevents the leaching of drug from the top. Adhesives fasten the device to the skin during use. The patch delivers a slow release of drug into the body over time, resulting in long-term effectiveness and added convenience. On the each of the following 2 days, the patch was changed and a new one placed; thus placing a total of three patches over the 3 post-operative days. Each successive application of the transdermal patch was made on a different hairless skin area (Figure 5). Paracetamol 500 mg tablets were permitted to be used as rescue medication and a total of nine tablets were provided to each of the patients for the 3 post-operative days. Surgical extraction on the left side was performed after 3 weeks and postoperatively patients received injection diclofenac (Voveron-Novartis India, 25 mg of diclofenac). Routine antibiotics were administered at the completion of the procedure. Paracetamol 500 mg tablets were permitted to be used as rescue medication and a total of nine tablets were provided to each of the patients for the 3 post-operative days. The patients were asked to maintain a record of the number of paracetamol tablets consumed on the pain assessment charts and to return the remaining tablets to operator on their next visit.

Figure 4: Transdermal diclofenac patch-100 mg

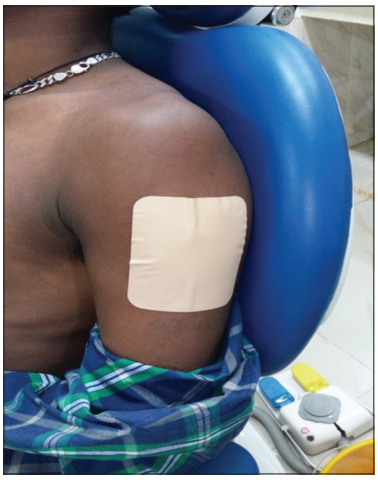


Figure 5: Transdermal patch placed over the left shoulder

The subjects were asked to report the intensity and pain relief on the verbal pain score chart for the 3 post-operative days (Tables 1 and 2). The rescue medication tablets taken, if any, were noted, and the patients were asked if they experienced any adverse effects such as gastric discomfort, nausea, vomiting, gastric acidity or burning sensation and dyspepsia, diarrhea, dizziness, and pruritis (Table 3). Accordingly, group statistics for the parameters pain relief and duration of action (Table 4) were individually analyzed and evaluated using the Mann–Whitney U test. Statistical significance was considered for a $P < 0.05$ level.

RESULTS

Pain Relief

The verbal rating scale and pain relief scale were used to analyze the post-operative pain relief. The readings were done at the 2nd, 4th, 8th, 12th h, and 24 h following the completion of the surgery. On the 2nd and 3rd post-operative days, the study medications were administered at a

Table 1: Pain relief scale

Pain score	Time	Transdermal diclofenac/IM diclofenac					
		2 h	4 h	6 h	8 h	12 h	24 h
0	None						
1	A little						
2	Some						
3	A lot						
4	Complete						

IM: Intramuscular

Table 2: Pain intensity scale

Pain score	Time	Transdermal diclofenac/IM diclofenac					
		2 h	4 h	6 h	8 h	12 h	24 h
0	None						
1	Very mild pain						
2	Mild pain						
3	Moderate pain						
4	Severe pain						

IM: Intramuscular

particular reference time and the readings done accordingly. As per the results given in Table 4, the mean pain relief at 1st day was 0.41 for Group A with a standard deviation (SD) of 0.840 and 0.64 for Group B with a SD of 1.059. The Mann–Whitney test was 112 and the significance from two-tailed *t*-test was 0.707 for both the groups. The mean pain relief at 2nd day was 1.24 for Group A with a SD of 1.149 and the mean pain relief for Group B was 1 with a SD of 1.149. The Mann–Whitney test was 91.00 with the significance by two-tailed *t*-test being 0.350 for both the groups. The mean pain relief at 3rd day was 1.40 for Group A with a SD of 0.887 and 1.00 for Group B with a SD of 0.944. The value from Mann–Whitney test was 112.00 and the significance calculated from two-tailed *t*-test was 0.847. Thus the results for post-operative pain relief were not statistically significant which as represented in Table 5 and Graph 1 showed similar level of efficacy by both patches and drugs.

Duration of Action

About 6 patients took oral medication (paracetamol tablet) at 4 h after application of patch, while 13 patients took tablets after 8 h. Only one patient took oral medication after 3 h, this could be probably due to the level of anxiety associated to the procedure. Group A had a mean duration of action of 5.070 with a SD of 1.6870, the significance of this finding by two-tailed *t*-test was 0.475. Group B had a mean duration of action for 4.586 with a SD of 1.9368, and significance form two-tailed *t*-test was 0.475. Thus, as per the representation shown in Table 6, both the groups had no statistically significant differences in terms of duration of action with Group A showing a slightly higher value than Group B which was not statistically significant.

Pain Intensity

An assessment of the intensity of pain following mandibular third molar extractions revealed that there was a gradual decrease in the pain intensity scores from day 1 to day 3 with both IM injection as well as transdermal patch (Table 7 and Graph 2). Statistical analysis using the Mann–Whitney U test however reveals that the difference in the pain intensity as well as in the pain relief provided by IM injection and transdermal patch was not statistically significant (Table 8).

Table 3: Discomforts experienced

None	Allergy	Nausea	Vomiting	Epigastric pain	Diarrhea	Headache	Dizziness

Table 4: Onset of pain: Duration of action

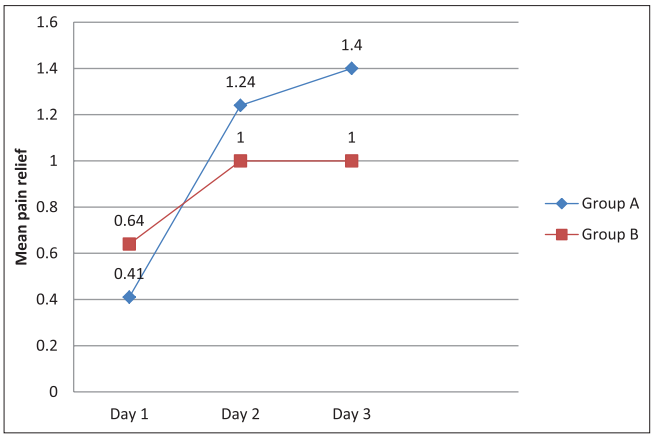
Time of drug intake/application											
	1st h	2nd h	3rd h	4th h	5th h	6th h	7th h	8th h	9th h	10th h	11th h	12th h
Pain onset												
Duration of action												

Table 5: Post-operative pain relief

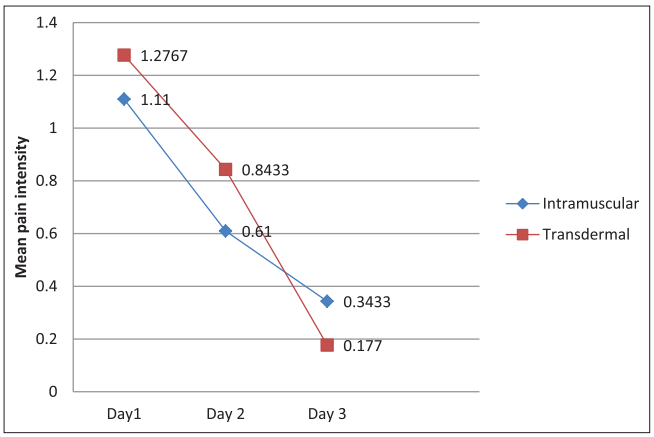
Group	Mean	Standard deviation	Significance (two-tailed)	Mann–Whitney test
Pain relief at 1st day	0.41	0.840	0.707	112.00
Group A	0.64	1.059	0.707	
Group B				
Pain relief at 2nd day	1.24	1.149	0.350	91.00
Group A	1.00	1.149	0.350	
Group B				
Pain relief at 3rd day	1.40	0.887	0.847	112.00
Group A	1.00	0.944	0.847	
Group B				

Table 6: Duration of action

Group	Mean	Standard deviation	Significance (two-tailed)
Duration of action (h)			
Group A	6.070	1.6870	0.475
Group B	5.586	1.9368	0.475



Graph 1: Variation in mean pain relief from day 1 to day 3



Graph 2: Variation in mean pain intensity from day 1 to day 3

Table 7: Score on the pain intensity scale

	Intramuscular			Transdermal system		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Mean (*n*=20)	1.1100	0.6100	0.3433	1.2767	0.8433	0.1770
SD	0.0139	0.6847	0.5567	0.7497	0.7000	0.4711

SD: Standard deviation

Table 8: Showing the Mann–Whitney U test values for pain intensity and pain relief when comparing intramuscular and transdermal diclofenac formulations

	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Mann–Whitney U	0.1000	1.2297	1.0819	1.0150	0.8675	0.1410
P value	0.328	0.233	0.294	0.280	0.420	0.260

Discomforts

Two patients when on IM diclofenac complained of gastric acidity and burning sensation. No adverse events were reported with the use of transdermal patch.

Overall Efficacy

On comparing the difference in the levels of pain duration, intensity, and pain relief experienced from day 1 to day 2 for both IM and transdermal forms of treatment, it was observed that from day 1 to day 2, 51% of the patients prescribed IM diclofenac reported of significant pain relief. On the other hand, among the patients in whom the transdermal patch was used, 67% reported of significant pain relief from day 1 to day 2 (Table 9 and Graph 3).

From the overall statistical and clinical results, are no statistically significant differences in any of these parameters between the two groups. Thus, the results show that diclofenac administered by either mode of delivery as transdermal patches or IM injections has similar effectiveness. It can be concluded that although transdermal diclofenac was an effective analgesic option, its potency in the immediate post-operative period is questionable compared to IM diclofenac and the transdermal form can be used following acute pain control with the injection form.

DISCUSSION

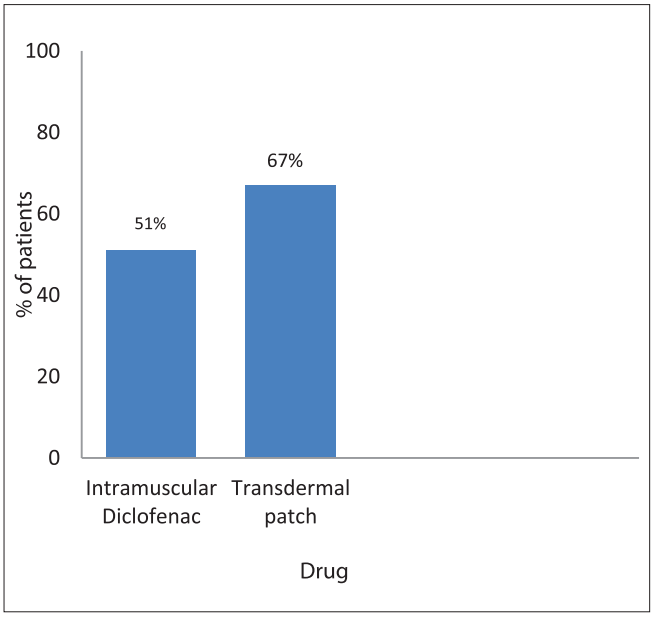
NSAIDs have the ability to reduce both pain and inflammation as a result they, are the ideal analgesic agents for the control of pain in the event of surgical removal of mandibular third molar impactions. Surgical tooth removal causes a typical type of pain which reaches peak values in the immediate extraction period and thereafter reaches moderate levels.[8] In that respect for the procedure of surgical removal of mandibular third molars, anesthesia during the procedure is important; however, adequate pain control is also important in the immediate post-operative period as the pain from surgical removal of third molar reaches its peak level in the immediate post-operative period. In this study, we had standardized the level of difficulty of the procedure, operator variability, and patient inclusion and exclusion criteria.

The results of our study for show that the pain relief at 1st, 2nd, and 3rd day for patches is seen by the pain scores of 0.41, 1.24, and 1.40, respectively, whereas for IM diclofenac, the values are 0.64, 1.00, and 1.00. Though these two ranges of values show no statistically significant difference and are not statistically significant, the mild variations between these values show that in the 4th h when the action of local anesthetic is completely reversed, diclofenac injection have shown better pain management, probably due to the sufficient plasma levels available to combat the post-operative pain. However, at the 6th h, patches appear to show better pain control probably because they had achieved a more constant therapeutically effective concentration by this time comparable to injectable form.[3] These results observed in our study are similar to the results seen in the studies done by Bhaskar *et al.*,[9] Bachalli *et al.*,[10] and Krishna.[11] In the study by Bhaskar *et al.*,[9] IM

Table 9: Efficacy of the treatment

	Effective	Not effective	Total
Injection	10	10	20
Patch	13	7	20
Total	23	17	40

Injection event rate=51.00%, patch event rate=67.00%, injection event odds=100.00%, patch event odds=185.71%



Graph 3: Distribution of patients reporting significant pain relief from day 1 to day 3

diclofenac had shown better pain management in the first post-operative day compared to transdermal diclofenac patches for patients undergoing therapeutic extraction of premolars. The results also showed that while 51% of the subjects on IM diclofenac showed a pain relief on the 2nd post-operative day, 67% of the patients on transdermal patches showed pain relief on the 2nd post-operative day. However, there was a complete pain relief in both the groups on the 3rd post-operative day. Similar results were also observed in a study by Bachalli *et al.*,[10] it was seen that the pain relief at 2 h was significantly better with administration of IM diclofenac compared to transdermal patches in patients undergoing surgical removal of impacted mandibular third molar. There was no statistically significant difference between either routes of administration in the pain relief score on the measurement taken subsequently for 3 consecutive days. There was also difference in the pain level of the patients when they had opted for an analgesic. While some patients had taken an analgesic when only little pain had been experienced, others waited for a higher intensity of pain before they had taken the analgesic. The results for two forms of diclofenac had been similar in another study by Krishna,[11] where 100 mg of transdermal patches had been administered at start of the surgery and 75 mg of IM diclofenac was given half an hour before the completion of the procedure in patients undergoing orthopedic limb surgery, there was no statistically significant difference in the visual analog scale between the two groups at 2 h. However, at 6 h, 15 patients in the transdermal group and 13 patients in the oral group showed a pain intensity score of 2. The results of this study had shown that both transdermal diclofenac and IM diclofenac had shown similar pain relief. In a similar study by Krishna[11] comparing transdermal diclofenac and IM diclofenac for orthopedic limb surgery, the duration of action for transdermal patches had been for 8 h and 6 min and for IM diclofenac had been for 7 h and 28 min.

In the study by Bhaskar *et al.*,[9] they also concluded in his study that diclofenac transdermal patches were well tolerated by the patients, 2 patients had reported gastric irritation and nausea following the intake of oral diclofenac tablets. In a meta analyses by Mason *et al.*,[12] it has been shown that topical NSAIDs do not show any serious gastrointestinal injury or increased chances of renal failure. Also in a study by Naesdal *et al.*,[13] it has been shown that the overall gastrointestinal complications such as ulcer and dyspepsia were statistically significantly lower with the use of topical NSAIDs due to their lower systemic concentrations. Apart from the discomforts, the patients who had taken transdermal drug delivery had shown better compliance and also were enthusiastic of the prospect of achieving pain control without the need for oral medications, as was previously experienced in the study by Bhaskar *et al.*[9]

CONCLUSION

The transdermal diclofenac patch seems to be a promising analgesic modality for the management of mild to moderate pain following dental extractions, given the evidence of its established analgesic potency with a lower incidence of systemic adverse effects. Transdermal diclofenac therapy may have a role to play in post-traumatic pain, perhaps with an increased strength of the analgesic drug in the transdermal patch. However, longer clinical trials with a larger sample need to be conducted before the real scope of the transdermal diclofenac patch for surgical dental extractions can be clearly defined.

REFERENCES

1. Deer TR, Leong MS, Ray AL, Buvanendran A, Gordin V, Kim PS, *et al.* Treatment of Chronic Pain by Medical Aproaches: The American Academy of Pain Medicine Textbook on Patient Management. New York, NY: The American Academy of Pain; 2014. p. 33-42.
2. Tripathi KD. Essentials of Medical Pharmacology. 6th ed. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd.; 1985. p. 184-202.
3. Shingade GM, Quazi A, Sabale PM, Grampurohit ND, Gadhave MV.

Review on: Recent trend on transdermal drug delivery system. J Drug Deliv Ther 2012;2:66-75.
4. Pragya Y, Rastogi V. Transdermal patches: A synergistic approach of drug delivery For NSAIDs. Int J Pharm Sci Res 2012;3:2897-909.
5. Patel D, Chaudhary SA, Parmar B, Bhura N. Transdermal drug delivery system: A review. Pharm Innov 2012;1:78-87.
6. Bajaj S, Whiteman A, Brandner B. Transdermal drug delivery in pain management. Contin Educ Anaesth Crit Care Pain 2011;11:39-43.
7. Trindade PA, Giglio FP, Colombini-Ishikiriama BL, Calvo AM, Modena KC, Ribeiro DA, *et al*. Sublingual ketorolac and sublingual piroxicam are equally effective for postoperative pain, trismus, and swelling management in lower third molar removal. Oral Surg Oral Med Oral Pathol Oral Radiol 2012;114:28-33.
8. Yamashita Y, Sano N, Shimohira D, Danjo A, Goto M. A parallel-group comparison study of celecoxib with loxoprofen sodium in third mandibular molar extraction patients. Int J Oral Maxillofac Surg 2014;43:1509-13.
9. 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. Contemp Clin Dent 2010;1:158-63.
10. Bachalli PS, Nandakumar H, Srinath N. A comparitive study of diclofenac transdermal patch against oral diclofenac for pain control following removal of mandibular impacted third molars. J Maxillofac Oral Surg 2009;8:167-72.
11. Krishna R. Efficacy of a single dose of a transdermal diclofenac patch as preemptive postoperative analgesia: A comparison with intramuscular diclofenac. South Afr J Anaesth Analg 2012;18:194-7.
12. Mason L, Moore RA, Edwards JE, Derry S, McQuay HJ. Topical NSAIDs for acute pain: A meta-analysis. BMC Fam Pract 2004;5:10.
13. Naesdal J, Brown K. NSAID-associated adverse effects and acid control aids to prevent them: A review of current treatment options. Drug Saf 2006;29:119-32.

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