

Research Paper

Efficacy and Safety of Oral Diclofenac Sustained release Versus Transdermal Diclofenac Patch in Chronic Musculoskeletal Pain: A Randomized, Open Label Trial

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Abstract

Introduction: To compare the efficacy, safety, and tolerability of transdermal patches of diclofenac sodium with oral diclofenac sustained release (SR) in patients of chronic musculoskeletal MSK pain conditions. **Materials and Methods:** The eligible patients were given either transdermal diclofenac patch or tablet diclofenac SR. Pain was assessed at 2 and 4 weeks using a visual analog scale. Adverse events were recorded. Patients with 18–65 years old of either gender with score of ≥ 4 on a 11-item numeric rating scale-numeric version of visual analog scale for pain with diagnosis of primary osteoarthritis (OA) of the knee or hand of at least 3 months duration, with independent radiological confirmation of OA or having pain associated with other MSK conditions such as soft-tissue rheumatism, cervical and lumbar back pain, and fibromyalgia, of at least 3 months duration were included in this study. **Results:** Transdermal diclofenac diethylamine patch and tablet diclofenac sodium sustained release (SR) do not significantly differ in the reduction of numerical rating scores at the end of 4 weeks ($P = 0.8393$). **Conclusion:** Transdermal diclofenac was equi-efficacious as tablet diclofenac sodium SR in reducing pain due to chronic MSK pain conditions.

Keywords: Nonsteroidal anti-inflammatory drugs, numerical rating score, topical

INTRODUCTION

Chronic musculoskeletal (MSK) pain is a major growing burden in the aging population.^[1] The International Association for the Study of Pain defines chronic pain as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 months). Pain in bones, joints, and muscles is very common and can often be persistent. This condition is called chronic MSK pain.^[2] Chronic MSK pain includes various painful local or regional MSK disorders such as cervical and low back pain, soft-tissue rheumatism, osteoarthritis (OA), and fibromyalgia of at least 3 months duration.^[2-4] MSK pain and arthritis are universal problems.^[5] Moderate-to-severe chronic MSK pain is an important cause of physical disability and work absence, carrying a huge economic and social cost. Therefore, it represents a relevant health problem to patients, health professionals, the health-care system, and society. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as

aspirin, ibuprofen, and diclofenac are the most commonly used pharmacological agents for symptom control in various chronic MSK pain conditions.^[1,6] Oral NSAIDs are associated with safety risks including gastrointestinal (GI) side effects,^[1] renal insufficiency, hepatic toxicity, exacerbation of asthma, sodium retention, raised blood pressure, and resistance to antihypertensive drugs, as well as increased risk of thrombotic cardiovascular events for nonaspirin agents and increased risk of intracerebral hemorrhage and other bleeding with aspirin.^[7,8] GI adverse events, such as dyspepsia, upper abdominal pain,

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and general abdominal pain, are among the most common reasons for discontinuation of oral NSAIDs therapy.^[9]

Topical NSAIDs such as gels and transdermal patches are also used for the treatment of MSK pain and are popular for their advantages such as decrease in incidence of GI adverse events. Transdermal NSAIDs seems to be attractive alternative to oral NSAIDs with the potential advantage of improving the safety profile.^[10-12] A double-blind, randomized, placebo-controlled study of myofascial pain of the upper trapezius demonstrates that diclofenac sodium patch was superior to placebo in terms of reducing visual analog (VAS) scores and improving functional outcomes and did not cause significant adverse effects.^[13]

Moreover, our literature search did not reveal any study evaluating the efficacy of transdermal patches of diclofenac in chronic MSK pain conditions. In addition, there are very limited studies directly comparing transdermal diclofenac diethylamine patch with oral diclofenac. Hence, the present study was planned with the objective of comparing efficacy, safety, and tolerability of transdermal patches of diclofenac sodium with oral diclofenac sustained release (SR) in patients of chronic MSK pain conditions.

MATERIALS AND METHODS

Study design

A randomized, open-label parallel design trial in 56 patients of chronic MSK pain after approval of Institutional Ethics Committee was conducted from January 2014 to February 2015. Patients were recruited from the orthopedics outpatient department of a tertiary care teaching hospital. Patients satisfying following inclusion and exclusion criteria were enrolled in the study.

Inclusion criteria

Patients ≥ 18 –65 years old of either gender with score of ≥ 4 on a 11-item numeric rating scale (NRS)-numeric version of VAS for pain with diagnosis of primary OA of the knee or hand of at least 3 months duration, with independent radiological confirmation of OA or having pain associated with other MSK conditions such as soft-tissue rheumatism, cervical and lumbar back pain, and fibromyalgia of at least 3 months duration.

Exclusion criteria

History of secondary OA, history of allergy or asthma related to NSAIDs, severe or uncontrolled renal, hepatic, and hematologic abnormality as detected by laboratory investigations, history suggestive of cardiovascular or neurologic disease, patients on any NSAIDs other than diclofenac sodium and pregnant and lactating mothers were excluded from the study.

Primary outcomes

Change in baseline score in NRS numeric version of VAS, patient Global Impression of Change Score (PGIC) at the end of 4 weeks and adverse events: local and systemic and particularly serious GI problems were recorded.

Secondary outcomes

1. Numbers of withdrawals: all causes and lack of efficacy were recorded
2. Treatment adherence.

Study procedure

Patients suffering from chronic MSK pain as diagnosed by orthopedician and those found meeting inclusion criteria were briefed about the study. Patient information sheet were given to all prospective participants and written informed consent in vernacular language was obtained from patients willing to participate. Subject confidentiality was maintained throughout the study. After enrollment, the data regarding age, gender, diagnosis, treatment history, and baseline clinical laboratory investigations were recorded in the case record form (CRF).

The eligible patients were randomly allocated into following two treatment groups using computer-generated table of random numbers. Group 1 received transdermal diclofenac diethylamine patch 100 mg once daily and Group 2 received tablet diclofenac sodium SR 100 mg once daily.

Instructions were given to the patient regarding the application of transdermal patch and oral diclofenac tablet. Subsequently, pain was assessed at the visit 2 (2 weeks) and visit 3 (4 weeks) using NRS and patient's global impression of change and were recorded in CRF. Adverse event if any was recorded in CRF. The patients were asked to bring the empty wrappers of patches and empty packets of tablets during follow-up visit to check adherence. Ninety percent consumption was considered as adequate adherence. Patients were given patches and tablets for 2 weeks. The patients were asked not to take any other analgesic medications during the study. Patient who were not controlled with pain were withdrawn from the study at the end of 2 weeks.

Statistical analysis

Sample size was calculated using PS software 3.1.2. The primary outcome for the power calculation was an improvement in the NRS score ($\alpha = 0.05$). The data were analyzed using Graph pad prism 5.01. The results were compared between groups by Mann–Whitney U-test. Significance of differences between baseline, follow-up visit 1 and follow-up visit 2 were assessed using Friedman test followed by Dunns Multiple Comparison *post hoc* test. PGIC scores provided by patients were tabulated according to the clinic visit and the treatment group and were compared using Mann–Whitney's U-test.

Overall, improvement in pain was calculated in percentage at the end of the study based on formula^[14] = $\frac{[\text{total pain score} - \text{total pain score on the date of assessment}]}{\text{total pain score at baseline}} \times 100$.

RESULTS

A total of 67 patients were screened for participation in the study. Of these 56 patients satisfied inclusion criteria and were randomized into two groups of twenty eight each to

receive either transdermal diclofenac diethylamine patch or tablet diclofenac SR. Out of 56 patients of chronic MSK pain, 49 patients completed the study as per protocol with regular follow-up [Figure 1]. Three patients were lost to follow-up in transdermal diclofenac diethylamine patch group, and four patients were lost to follow-up in tablet diclofenac sodium SR group. The data were analyzed using last observation carried forward method that is 49 patients were analyzed.

The baseline data of the two treatment groups were comparable with respect to the demographic and clinical parameters [Table 1]. Numerical rating score did not differ among subjects before receiving transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR [Table 2]. The reduction in numerical rating score by transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR was apparent within 2 weeks. The reduction in numerical rating scores at 2 weeks ($P < 0.0001$) and at 4 weeks ($P < 0.0001$) of therapy by transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR was statistically significant when compared with the baseline scores; however, reduction in scores was not statistically significant when scores at the end of 4 weeks were compared with scores at the end of 2 weeks [Graphs 1 and 2].

Transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR do not significantly differ in the reduction of numerical rating scores at the end of 4 weeks [Table 3]. There was no significant difference in PGIC score at the end of 4 weeks treatment between transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR [Table 4].

The percentage of adverse events was 20% with transdermal diclofenac diethylamine patch group and 29.17% with tablet diclofenac SR group. Epigastric pain/burning sensation in the abdomen was reported in 4% of patients and 16% suffered from irritation over applied area in transdermal diclofenac

diethylamine patch group. In tablet diclofenac SR group, various adverse events were dyspepsia (4.1%), abdominal pain (8.3%), epigastric pain/burning sensation in the abdomen (8.3%), giddiness and anxious (4.1%), and rash and itching over both lower limb (4.1%).

Table 1: Baseline demographic data and clinical characteristics of patients with chronic musculoskeletal pain

Characteristics	Transdermal diclofenac diethylamine patch (n=25)	Tablet diclofenac sodium SR (n=24)	P
Age (years)	46.48 (12.01)	43.04 (13.36)	0.35
Gender			
Men	17	14	
Women	8	10	
Hemoglobin (g), n (%)	12.22 (1.268)	12.08 (1.928)	0.77
Total leukocyte count (/mm ³)	5460 (1782)	6038 (2262)	0.33
Platelets (/mm ³)	258,700 (88,280)	245,300 (84,470)	0.59
Bleeding time (min)	2.191 (0.7834)	2.192 (0.6061)	0.998
Blood urea (mg/dl)	22.91 (6.394)	21.58 (4.587)	0.41
Serum creatinine (mg/dl)	0.8124 (0.2149)	0.75 (0.1414)	0.24
Serum bilirubin (mg/dl)	0.6164 (0.2231)	0.6917 (0.232)	0.25
SGOT (IU/L)	20.12 (7.881)	24.04 (7.428)	0.08
SGPT (IU/L)	19.24 (6.673)	22.17 (7.761)	0.16

Values are expressed as mean (SD); Unpaired *t*-test - comparing transdermal diclofenac diethylamine patch with tablet diclofenac sodium SR. SR=Sustained release, SD=Standard deviation, SGOT=Serum glutamic oxaloacetic transaminase, SGPT=Serum glutamic pyruvic transaminase

Table 2: Baseline numerical rating score for pain in patients of chronic musculoskeletal pain

Parameters	Transdermal diclofenac diethylamine group (n=25)	Tablet diclofenac sodium SR group (n=24)	P
Numerical rating score for pain	8.16 (2.12)	7.5 (1.38)	0.09

Values are expressed as mean (SD); Mann-Whitney test comparing transdermal diclofenac diethylamine patch with tablet diclofenac sodium SR. SR= Sustained release, SD= Standard deviation

Table 3: Comparison of changes in numerical rating score from baseline to 4 weeks between transdermal diclofenac diethylamine patch and tablet diclofenac sustained release

Parameters	Transdermal diclofenac diethylamine patch (n=25)	Tablet diclofenac sodium SR (n=24)	P
Numerical rating score	3.32 (2.577)	3.375 (2.667)	0.8393

Values are expressed as mean (SD); Mann-Whitney test when transdermal diclofenac patch compared with tablet diclofenac SR. SR= Sustained release, SD= Standard deviation

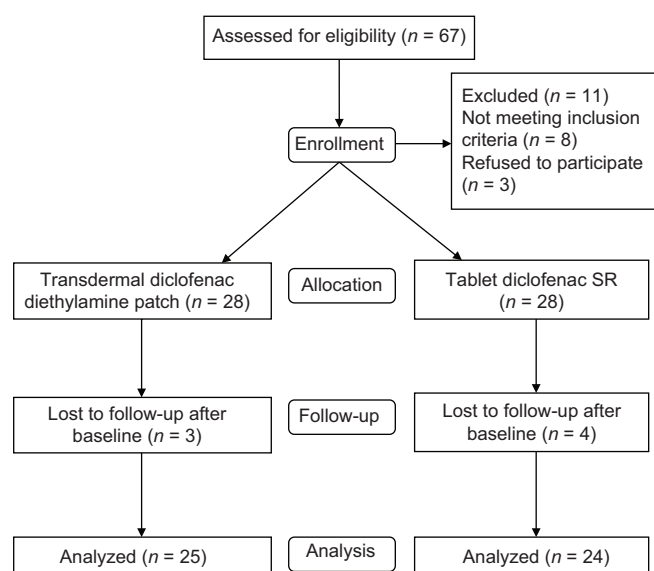
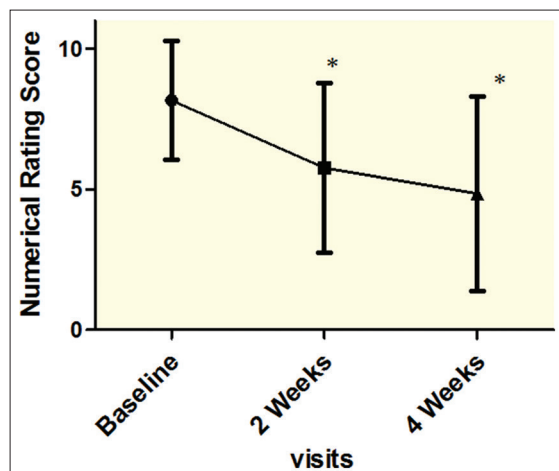


Figure 1: CONSORT certificate. $P < 0.05$ was considered as statistically significant

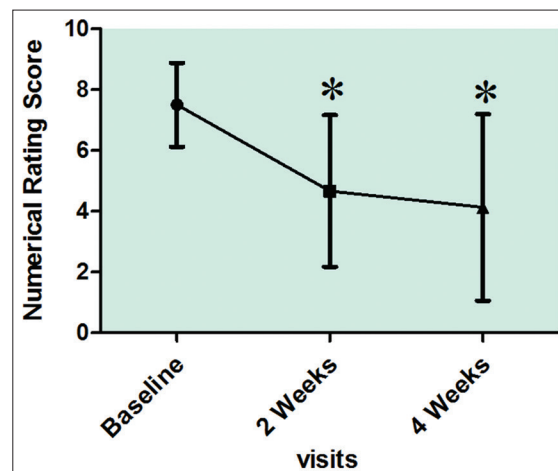
Table 4: Patients global impression of change status at the end of 4 weeks

	Very much improved	Much improved	Minimally improved	Minimally worse	Much worse	Mean score	P
Transdermal diclofenac diethylamine patch (n=25), n (%)	5 (20)	7 (28)	7 (28)	-	-	2.56	
Tablet diclofenac SR (n=24), n (%)	4 (16.67)	10 (41.67)	5 (20.83)	1 (4.17)	-	2.5	0.7715
All, n (%)	9 (36.67)	17 (69.67)	12 (48.83)	1 (4.17)	-		

Values are expressed as mean (SD); Mann–Whitney test when transdermal diclofenac patch compared with tablet diclofenac SR. SR= Sustained release, SD= Standard deviation



Graph 1: Effect of transdermal diclofenac diethyl amine patch on numeric rating scale. (n = 25) Values are expressed as mean (Standard deviation); Friedman test followed by Dunn's Multiple Comparison Test, $P < 0.0001$ when compared with baseline score



Graph 2: Effect of tablet diclofenac sodium sustained release on numeric rating scale. (n = 24) Values are expressed as mean (Standard deviation); Friedman test, * $P < 0.0001$ when compared with baseline score

DISCUSSION

Despite recent advances in the management, the chronic MSK pain remains one of the common problems. Chronic MSK pain is often associated with reduced activity, sleep disturbance, fatigue, and mood alterations and can result in severe disability. People with chronic pain often get into a “vicious circle” of problems. The pain leads to anxiety and depression, which can make the pain worse.^[4] Various treatment modalities available for chronic MSK pain include NSAIDs such as diclofenac, ibuprofen, paracetamol and aspirin, opiates, opioids, and alternative pharmacologic agents such as anti-seizure drugs and antidepressants.^[15] NSAIDs can be administered in a range of formulations such as oral, parenteral, rectal, or topical. While oral administration is the most commonly used, it has been associated with serious side effects such as GI, cardiovascular, and renal events.^[1,7] To overcome the problem associated with oral NSAIDs various topical preparations of NSAIDs in the form of gels and transdermal patches are available. Transdermal patches of salts of diclofenac approved for use for pain indications are diclofenac epolamine patch and diclofenac diethylamine patch.

One of the principle findings of our study was that the effects of transdermal diclofenac diethylamine patch in patients of chronic MSK pain were apparent within 2 weeks of treatment. The transdermal diclofenac diethylamine patch (100 mg)

produced statistically significant as well as clinically significant reduction in numerical rating scale for pain at the end of 2 weeks which continued till 2 weeks of treatment.^[16] These results confirm findings of study conducted by P. Brühlmann and Michel^[17] in OA of knee joint. Diclofenac patch resulted in a statistically significant reduction ($P < 0.01$) in VAS compared to control patch in a study by Hsieh *et al.*^[13] in myofascial pain syndrome of upper trapezius.

Topical diclofenac diffuses into the subdermal tissue. It is a small lipophilic molecule that has been shown to be capable of rapid diffusion through the skin and to distribute in blood, muscle, interstitial tissue, and synovial fluid. In the form of the 1.16% diethylamine salt (1% diclofenac sodium), absorption occurs continuously through the underlying dermis, and subcutaneous tissue to a depth of 3–4 mm and is increased by 3–10 times when an occlusive dressing is used. There is a significant direct penetration of diclofenac into skeletal muscle following multiple epicutaneous administrations. Plasma concentrations are less than tissue concentrations, thus reducing the probability of systemic adverse effects.^[13] In our study, the effects of tablet diclofenac sodium SR were apparent within 2 weeks of treatment which continued till 4 weeks. The tablet diclofenac sodium (100 mg) SR also produced statistically and clinically significant reduction in numerical rating scale for pain at the end of 4 weeks of treatment. Similar findings with diclofenac SR tablet were reported in a study conducted by Goei Thè *et al.*^[18]

In our study, when the two groups were compared for efficacy it was found that transdermal diclofenac diethylamine patch (100 mg) once daily was equally efficacious as tablet diclofenac sodium SR (100 mg) once daily at the end of 2 weeks which continued till 4 weeks in reducing pain by NRS. In this study, overall improvement in pain was calculated to be 45.03% in transdermal diclofenac diethylamine patch group and 46.38% in tablet diclofenac SR group. In a study by Farrar *et al.*, a 50% reduction in pain intensity corresponded to the highest level of patient impression of improvement.^[16] In spite of extensive literature search, no head-to-head comparative studies in chronic MSK pain between transdermal diclofenac diethylamine patch and tablet diclofenac sodium SR were found. Hence, it is difficult to compare our results with published reports. However, different studies have compared transdermal diclofenac patch with tablet diclofenac sodium SR in postoperative pain and acute pain such as pain due to extraction of tooth. In a study by Prithvi S Bachali *et al.*^[10] where in transdermal diclofenac diethylamine (100 mg) patch group provided similar analgesia as oral diclofenac (100 mg) SR following the removal of mandibular impacted third molars on second and third postoperative day as measured on VAS.

Topically, applied NSAID's are effective in decreasing both acute and chronic pain. They inhibit prostaglandin synthesis and decrease the inflammatory response. Similar efficacy of transdermal patch as that of oral diclofenac sodium is due to the similar mechanism of action that is inhibition of prostaglandin synthesis. In one study, plasma levels achieved by transdermal patch ranged between 20 and 50 ng/ml, which was lesser when compared to the oral route, but these levels were sustained for a longer time.^[10] One study has reported that the amount of drug bioavailable for targeting the sites of action is lower than oral route, but the absorbed dose appears to be adequate for therapeutic use.^[19] In one *in vitro* study carried out in rats, patches were subjected to *in vitro* permeation enhancement studies through rat skin using, an especially designed diffusion cell. The pharmacokinetic parameters calculated from blood levels of drug reveal of profile similar to a sustained-release formulation, with ability to maintain adequate plasma levels of 24 h (i.e., up to the next application).^[19]

One of the important findings of our study was that there was no significant difference between transdermal diclofenac diethylamine patch group and oral diclofenac SR group in PGIC score at the end of 4 weeks. Patient's evaluation of their global impression of change at the end of treatment was improvement (much improved and minimally improved) in their overall situation for chronic MSK pain in both the groups. In our study, 4 (16%) patients in transdermal diclofenac diethylamine group and 4 (16%) patients in tablet diclofenac SR withdrew from study due to lack of efficacy. Similar finding was reported in a study^[20] conducted in patients with OA and rheumatoid arthritis. Twenty percent of patients in transdermal diclofenac diethylamine group complained of adverse drug reactions, of which 16% patient's experienced

local irritation over applied area. The tolerability of the transdermal diclofenac diethylamine patch was otherwise good except only 4% of patients had burning sensation in abdomen. However, all the adverse drug reactions were of mild severity and disappeared on continued use. In a study conducted by P. Brühlmann and Michel^[17] for 14 days, 4 patients complained of adverse drug reactions, in the diclofenac epolamine group (2 rash, 1 pruritus, 1 nausea). None of the adverse events described in this study were judged as severe, and all symptoms resolved spontaneously. However, findings of our study showed a higher number of adverse drug reaction in comparison to above-mentioned study. This might be probably due to longer duration of treatment with transdermal diclofenac diethylamine patch which was 28 days in our study.

CONCLUSION

Our study concludes that transdermal diclofenac diethylamine patch is equi efficacious as oral diclofenac sodium SR in patients with chronic MSK pain. The treatment with transdermal diclofenac diethylamine patch has comparatively lesser percentage of GI adverse events compared to oral diclofenac sodium SR in this study. Further study of longer duration is needed to evaluate the safety of transdermal diclofenac diethylamine patch.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Schnitzer TJ. Update on guidelines for the treatment of chronic musculoskeletal pain. *Clin Rheumatol* 2006;25 Suppl 1:S22-9.
2. Santos J, Alarcão J, Fareleira F, Vaz-Carneiro A, Costa J. Tapentadol for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2015;5:CD009923.
3. Derry S, Moore RA, Rabbie R. Topical NSAIDs for chronic musculoskeletal pain in adults. *Cochrane Database Syst Rev* 2012;9:CD007400.
4. Dieppe P. Chronic musculoskeletal pain. *BMJ* 2013;346:f3146.
5. Chopra A. Disease burden of rheumatic diseases in India : COPCORD perspective. *Indian J Rheumatol* 2015;10:70-7.
6. Blower AL, Brooks A, Fenn GC, Hill A, Pearce MY, Morant S, *et al.* Emergency admissions for upper gastrointestinal disease and their relation to NSAID use. *Aliment Pharmacol Ther* 1997;11:283-91.
7. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. *Ther Clin Risk Manag* 2015;11:1061-75.
8. Gorelick PB, Weisman SM. Risk of hemorrhagic stroke with aspirin use: An update. *Stroke* 2005;36:1801-7.
9. McCarberg BH, Argoff CE. Topical diclofenac epolamine patch 1.3% for treatment of acute pain caused by soft tissue injury. *Int J Clin Pract*

- 2010;64:1546-53.
10. Bachalli PS, Nandakumar H, Srinath N. A comparative 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. 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.
12. Banning M. Topical Diclofenac: Clinical Effectiveness and Current uses in Osteoarthritis of the Knee and Soft Tissue Injuries. *Expert Opinion Pharmacotherapy* 2008;9:2921-9.
13. Hsieh LF, Hong CZ, Chern SH, Chen CC. Efficacy and side effects of diclofenac patch in treatment of patients with myofascial pain syndrome of the upper trapezius. *J Pain Symptom Manage* 2010;39:116-25.
14. Mu R, Bao CD, Chen ZW, Zheng Y, Wang GC, Zhao DB, *et al.* Efficacy and safety of loxoprofen hydrogel patch versus loxoprofen tablet in patients with knee osteoarthritis: A randomized controlled non-inferiority trial. *Clin Rheumatol* 2016;35:165-73.
15. Uhl RL, Roberts TT, Papaliadis DN, Mulligan MT, Dubin AH. Management of chronic musculoskeletal pain. *J Am Acad Orthop Surg* 2014;22:101-10.
16. Rowbotham MC. What is a “clinically meaningful” reduction in pain? *Pain* 2001;94:131-2.
17. Brühlmann P, Michel BA. Topical diclofenac patch in patients with knee osteoarthritis: A randomized, double-blind, controlled clinical trial. *Clin Exp Rheumatol* 2003;21:193-8.
18. Goei Thè HS, Lund B, Distel MR, Bluhmki E. A double-blind, randomized trial to compare meloxicam 15 mg with diclofenac 100 mg in the treatment of osteoarthritis of the knee. *Osteoarthritis Cartilage* 1997;5:283-8.
19. Reddy PR, Rajashekar SB, Karthik US. Comparing the effectiveness of transdermal diclofenac patch and intramuscular diclofenac injection in postoperative pain relief after inguinal hernia mesh repair: A randomised study in the department of general surgery. *J Evid Based Med Healthc* 2015;2:5286-92.
20. Lister BJ, Poland M, DeLapp RE. Efficacy of nabumetone versus diclofenac, naproxen, ibuprofen, and piroxicam in osteoarthritis and rheumatoid arthritis. *Am J Med* 1993;95:2S-9S.