# Efficacy of a Single Dose Transdermal Flurbiprofen Administration in Patients with Knee Osteoarthritis

## Diz Osteoartritli Hastalarda Tek Doz Transdermal Flurbiprofen Uygulamasının Etkinliği

Aliye TOSUN, MD,[a]
Mehmet BEYAZOVA, MD,[b]
Jale MERAY, MD,[b]
Figen TIRNAKSIZ,[c]
Ethem TUNCEL,[c]
İlbeyi AĞABEYOĞLU,[c]
Nesrin GÜLER[b]

[a]Clinical of Physical Medicine and Rehabilitation
Ankara Atatürk Education and Research Hospital
[b]Department of Physical Medicine and Rehabilitation,
Gazi University Faculty of Medicine,
[c]Department of Pharmaceutical Technology,
Gazi University Faculty of Pharmacy,
Ankara

Geliş Tarihi/*Received:* 16.04.2009
Kabul Tarihi/*Accepted:* 13.04.2010

Yazışma Adresi/*Correspondence:*
Aliye TOSUN, MD
Ankara Atatürk Education and Research Hospital,
Clinical of Physical Medicine and Rehabilitation, Ankara,
TÜRKİYE/TURKEY
tosunaliye@yahoo.com

**ABSTRACT Objective:** Nonsteroidal anti-inflammatory drugs (NSAID) are among the most widely prescribed agents in osteoarthritis patients, and may lead to important side-effects which increase the risk of hospitalization and death. Transdermal administration of NSAIDs can provide relief of pain locally with relatively less side effects. This study was aimed to evaluate the efficacy of a single administration of 40 mg transdermal flurbiprofen on pain and on strength of quadriceps and hamstring muscles in patients with knee osteoarthritis. **Material and Methods:** This study is a double blind, placebo-controlled cross-over preliminary study. Transdermal flurbiprofen and placebo patches were administered to the 24 patients with knee osteoarthritis. Knee pain was evaluated using a visual analog scale (VAS) and the strength of quadriceps and hamstring muscles using an isokinetic dynamometer. **Results:** Mean VAS scores reduced from 5.3 ± 1.7 to 4.7 ± 1.6 (p= 0.88) after placebo administration, and from 5.4 ± 1.9 to 3.9 ± 1.7 (p= 0.04) following flurbiprofen administration. Peak torque and total work values of flexor and extensor muscles of knee did not differ statistically after flurbiprofen or placebo administrations. **Conclusion:** Pain significantly reduced after single dose of transdermal flurbiprofen patch. However, no significant difference in isokinetic assessment parameters was observed in the present study. To assess the effects of transdermal flurbiprofen and its efficacy on knee pain and function, further controlled studies in larger groups of patients with different doses of flurbiprofen are recommended.

**Key Words:** Osteoarthritis, knee; administration, cutaneous; anti-inflammatory agents, non-steroidal; pain; muscle strength

**ÖZET Amaç:** Osteoartritli hastalarda en çok reçete edilen ilaçlar arasında yer alan nonsteroidal antienflamatuar ilaçlar (NSAİİ), hospitalizasyon ve ölüm riskinin artmasına yol açan önemli yan etkilere neden olabilir. NSAİİ'ın transdermal uygulaması göreceli olarak azalmış yan etki ile beraber lokal ağrının azalmasını sağlayabilir. Bu çalışma ile diz osteoartritli hastalarda 40 mg flurbiprofenin transdermal uygulamasının ağrı, kuadriseps ve hamstring kas gücü üzerindeki etkinliğinin araştırılması amaçlandı. **Gereç ve Yöntemler:** Bu çalışma çift-kör, plasebo kontrollü bir çapraz ön-çalışmadır. Yirmi dört diz osteoartritli hastaya transdermal flurbiprofen ve plasebo uygulaması yapıldı. Diz ağrısı görsel analog skala (VAS) ile, diz kuadriseps ve hamstring kas güçleri ise izokinetik dinamometre kullanılarak değerlendirildi. **Bulgular:** Ortalama VAS skorları plasebo alan grupta 5.3 ± 1.7'dan 4.7±1.6 değerine düşerken (p= 0.88), flurbiprofen alımından sonra 5.4 ± 1.9'dan 3.9 ± 1.7 değerine geriledi (p= 0.04). Flurbiprofen ve plasebo uygulamasından sonra diz fleksör ve ekstansör kaslarının pik tork ve total iş değerlerinde istatistiksel fark yoktu. **Sonuç:** Transdermal flurbiprofen uygulamasından sonra ağrıda anlamlı azalma oldu. Ancak, izokinetik değerlendirme parametrelerinde anlamlı bir farklılık izlenmedi. Transdermal flurbiprofenin diz ağrısı ve fonksiyonları üzerine etkileri ve etkinliğini saptamak amacıyla, daha geniş hasta gruplarında ve flurbiprofenin farklı dozları ile yapılacak daha ileri kontrollü çalışmalar gereklidir.

**Anahtar Kelimeler:** Osteoartrit, diz; ilaç verme, ciltten; anti-enflamatuar ajanlar, steroid olmayan; ağrı; kas kuvveti



**Turkiye Klinikleri J Med Sci 2010;30(6):1911-6**

Osteoarthritis (OA) is a chronic degenerative joint disease characterized by softening and loss of articular cartilage, sclerosis and eburnation of subchondral bone, osteophytes and subchondral cysts.[1] Being one of the most common reasons of chronic pain and causing considerable disability, osteoarthritis is an important public health problem with substantial social and economic aspects.[2] Pain is the most common symptom in patients and the treatment aims relieving of joint pain and improving the mobility. Analgesics, anti-inflammatory agents, antispasmodics, and depot-corticosteroids are among medications used to treat symptoms in OA.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) have both analgesic and anti-inflammatory activity and are among the most widely prescribed agents in rheumatic diseases. However, these drugs have important gastrointestinal, hepatic, renal, cardiovascular, and allergic toxicities which increase the risk of hospitalization and death. NSAIDs especially tend to cause gastric irritation, gastric, and duodenal ulcers and may lead to ulcer-related bleeding.[4-6]

Transdermal administration of NSAIDs may have some advantages such as relief of pain with relatively less systemic side effects. Furthermore, by transdermal administration of drugs, a constant therapeutic level in biophase can be achieved and easy application of the drug formulation promotes a good compliance.[7] In some studies, topical formulations of NSAIDs were found to be more effective compared to placebo, and reported adverse events were usually localized to the area of administration.[8,9] Transdermal 40 mg flurbiprofen was found adequately effective with low levels of adverse events.[10,11] This study aimed to evaluate the efficacy of a single dose of 40 mg transdermal flurbiprofen on pain and strength of flexor and extensor muscles of knee in patients with knee osteoarthritis.

## MATERIALS AND METHODS

### STUDY DESIGN

The present study is a double blind and placebo-controlled crossover study. Local ethics committee approved all study procedures. Primary outcome of the study was the efficacy of transdermal 40 mg flurbiprofen application on knee pain, and secondary outcome was the improvement of strength of quadriceps (extensors of knee) and hamstring (flexors of knee) muscles due to the alleviation of pain.

### PARTICIPANTS

Twenty-four patients (three men, 21 women; mean age 49.8 ± 7.9 years) who admitted to the Physical Medicine and Rehabilitation outpatient clinic with knee pain and satisfied the clinical criteria for osteoarthritis of the knee were randomly included in to the study.[12] Subsequently, antero-posterior weight-bearing radiographs of both knees were obtained and evaluated with the Kellgren-Lawrence grading scale.[13] Patients with grade 3 or grade 4 OA were excluded from the study. There were no limitations in the knee range of motion of the patients. After informing about the study, all participants completed their written consents. Demographic and clinical characteristics of the patients are presented in Table 1.

### ASSESSMENT

#### Pain and Function

Knee pain before and 6 hours after transdermal patch application was evaluated using a visual analog scale (VAS) (0, no pain; 10, unbearable pain) by the same investigator.

#### Isokinetic Assessment

The tests were carried out by the same investigator using an isokinetic dynamometer (Cybex Norm, Ronkonkoma, New York). Subjects were placed on the seat with backrest at 90° angle. Thigh, pelvis and trunk were stabilized by straps. Support lever

**TABLE 1:** Demographic and clinical characteristics of patients.

| | | |
|---|---|---|
| Age (years, mean ± SD) | | 49.8 ± 7.9 |
| Weight (kg, mean ± SD) | | 75.9 ± 11.2 |
| Body-mass index (kg/m$^2$, mean ± SD) | | 27.6 ± 3.9 |
| Sex (n) | Male | 3 |
| | Female | 21 |
| Kellgren-Lawrence grading scale (n) | Grade 1 | 5 |
| | Grade 2 | 19 |

was attached just proximal to the lateral malleolus by a padded cuff. Axis of the rotation of dynamometer was positioned just lateral to the lateral femoral epicondyle. Range of motion of the knee joint was assessed and mechanical stops were fixed according to the guidelines of the device. Gravity correction was obtained. Extensor and flexor muscles of knee were tested and peak torque and total work values were recorded at 180°/sec angular velocity in both legs. After performing four consecutive warming trials, 20 maximal flexion and extension concentric contractions were performed before and six hours after application of transdermal patches.

### DRUG ADMINISTRATION

The study was conducted in double-blind crossover manner. Transdermal patches of flurbiprofen and placebo were prepared at Gazi University Faculty of Pharmacy, Department of Pharmaceutical Technology, and numeric codes were stuck onto the patches. Transdermal patches (one containing 40 mg flurbiprofen, the other with identical appearance, and base formulation without flurbiprofen) were administered to the symptomatic knees of the patients (15 right, nine left) by clinical investigators. Placebo was administered to half of the patients and flurbiprofen to the other half. Flurbiprofen was administered to the first half who got placebo initially and placebo to second half according to the predetermined numeric codes. Since the elimination half-life of flurbiprofen is approximately six hours and excretion of flurbiprofen is 88% to 98% complete 24 hours after the last dose, three-days wash-out period was left between interventions. Clinical investigators and patients were blinded about the contents of the patches. The patches were identical in size, appearance, color and odor. Placebo administrations to patients constituted the control group of the study. No other analgesic, anti-inflammatory drug or any other analgesic treatment option was used throughout the study period starting 36 hours before the study. All of the patients were evaluated during the same and the following day of the application of transdermal patches for any adverse events. After completing the study, data analysis were performed by clinical investigators and pharmacologists.

### STATISTICAL ANALYSIS

A computer-based statistics program (SPSS 11.5 and NCSS 2007 statistical software) was used. In order to compare peak torque, total work and VAS pain scores before and after flurbiprofen administration and before and after placebo application, crossover analysis using t-tests was used. The results were expressed as mean ± SD. The significance level was set at a "P" value less than 0.05.

## RESULTS

All participants completed the study. VAS scores for pain; peak torque and total work values of flexor and extensor muscles of knee were assessed before and six hours after application of transdermal patches. Mean VAS scores were reduced from 5.3 ± 1.7 to 4.7 ± 1.6 (p= 0.88) after placebo application (Table 2) and from 5.4 ± 1.9 to 3.9 ± 1.7 (p= 0.04) after 40 mg of flurbiprofen application (Table 3). Carry-over effect was not observed. Peak torque and total work values of flexor and extensor muscles of knee did not show a significant difference, neither after flurbiprofen nor after placebo administrations (Tables 2 and 3). Power analysis of the study was given in Table 4. Only one patient complained about epigastric pain after both placebo and flurbiprofen administrations. No other side effects were reported.

## DISCUSSION

This study aimed to evaluate the efficacy of a single transdermal dose of 40 mg flurbiprofen on pain and strength of knee muscles in patients with knee osteoarthritis. A statistically significant decrease in mean VAS scores was observed with flurbiprofen administration.VAS scores also decreased with placebo administration, however this was statistically insignificant. Namely, transdermal patch of flurbiprofen was found to be effective in pain-relief. The difference in peak torque and total work values of flexor and extensor muscles of knee was not significant, both after flurbiprofen and after placebo administrations.

**TABLE 2:** Comparison of peak torque, total work and VAS values with placebo administration.

| | Pre-placebo mean value | Post-placebo mean value | Parameter | Estimated effect | P value | Lower 95% confidence limit | Upper 95% confidence limit |
|---|---|---|---|---|---|---|---|
| Flx-PT | 26.1 ± 9.9 | 27.2 ± 10.9 | Treatment | -0.04 | 0.97 | -2.32 | -2.25 |
| | | | Carryover | 2.78 | 0.75 | -15.40 | 20.97 |
| Ext-PT | 46.3 ± 12.7 | 48.8 ± 13.6 | Treatment | -1.16 | 0.47 | -4.47 | 2.14 |
| | | | Carryover | 2.82 | 0.79 | -19.1 | 24.8 |
| Flx-TW | 24.6 ± 13.7 | 25.4 ± 14.1 | Treatment | -0.49 | 0.72 | -3.32 | 2.34 |
| | | | Carryover | 1.08 | 0.93 | -23.9 | 26.13 |
| Ext-TW | 50.1 ± 17.7 | 52.5 ± 18.4 | Treatment | -1.16 | 0.47 | -4.47 | 2.14 |
| | | | Carryover | 2.82 | 0.79 | -19.16 | 24.80 |
| VAS | 5.3 ± 1.7 | 4.7 ± 1.6 | Treatment | -0.03 | 0.88 | -0.38 | 0.32 |
| | | | Carryover | -1.87 | 0.14 | -4.43 | 0.68 |

Flx: Knee flexor muscles; Ext: Knee extensor muscles; PT: Peak torque (Ft-lb's); TW: Total work (Ft-lb's); VAS: Visual analog scale.

**TABLE 3:** Comparison of peak torque, total work and VAS values with flurbiprofen administration.

| | Pre-flurbiprofen mean value | Post-flurbiprofen mean value | Parameter | Estimated effect | P value | Lower 95% confidence limit | Upper 95% confidence limit |
|---|---|---|---|---|---|---|---|
| Flx-PT | 26.9 ± 11.2 | 28.3 ± 11.9 | Treatment | 0.33 | 0.68 | -1.31 | 1.97 |
| | | | Carryover | 8.98 | 0.33 | -9.79 | 27.74 |
| Ext-PT | 46.7 ± 13.1 | 49.5 ± 15.6 | Treatment | 1.21 | 0.42 | -1.90 | 4.32 |
| | | | Carryover | 9.64 | 0.39 | -13.45 | 32.73 |
| Flx-TW | 25.4 ± 14.4 | 26.2 ± 14.8 | Treatment | 0.87 | 0.35 | -1.00 | 2.74 |
| | | | Carryover | 7.98 | 0.51 | -16.78 | 32.73 |
| Ext-TW | 50.5 ± 17.2 | 53.2 ± 20.7 | Treatment | 1.65 | 0.38 | -2.17 | 5.48 |
| | | | Carryover | 8.76 | 0.57 | -22.48 | 40.00 |
| VAS | 5.4 ± 1.9 | 3.9 ± 1.7 | Treatment | -0.50 | 0.04* | -1.00 | 0.00 |
| | | | Carryover | -1.83 | 0.18 | -4.54 | 0.89 |

Flx: Knee flexor muscles; Ext: Knee extensor muscles; PT: Peak torque (Ft-lb's); TW: Total work (Ft-lb's); VAS: Visual analog scale.

Transdermal administration of NSAIDs have some advantages such as local relief of pain with relatively less systemic side effects. Previous studies focused on the efficacy of topical applications of NSAIDs in soft tissue injuries.[8,9] Russel investigated the efficacy and tolerability of piroxicam 0.5% topical gel and compared it with placebo treatment in acute musculoskeletal injuries.[8] Patients were treated for a minimum of seven days with piroxicam (20 mg/day) or placebo gel. That study showed a significant difference between the piroxicam and placebo with similar tolerability, and concluded that piroxicam gel treatment was effective for patients suffering from musculoskeletal injuries. Galer

**TABLE 4:** Power analysis.

| | | Power | Effect Size |
|---|---|---|---|
| Flx-PT | PLB | 0.24 | 0.41 |
| | FLB | 0.99 | 1.73 |
| Ext-PT | PLB | 0.14 | 0.28 |
| | FLB | 0.88 | 0.96 |
| Flx-TW | PLB | 0.07 | 0.13 |
| | FLB | 0.99 | 1.33 |
| Ext-TW | PLB | 0.08 | 1.18 |
| | FLB | 0.63 | 0.71 |
| VAS | PLB | 0.99 | 1.77 |
| | FLB | 0.92 | 1.05 |

Flx: Knee flexor muscles; Ext: Knee extensor muscles; PT: Peak torque; TW: Total work; VAS: Visual analog scale., PLB: Placebo, FLB: Flurbiprofen.

et al. investigated the efficacy and safety of topical diclofenac epolamine patch and compared it with placebo for the treatment of pain associated with acute minor sports injuries applied twice daily for two weeks.[9] Diclofenac epolamine patch was found to be superior to placebo in relieving pain without any significant differences in safety or side effects, and it was concluded that diclofenac patch was an effective and safe pain-reliever for treatment of pain secondary to minor sports injuries. Poul et al. evaluated the efficacy and tolerability of local action transcutaneous (LAT) flurbiprofen 40 mg twice daily and compared it with placebo in patients with soft tissue lesions for two weeks.[10] Flurbiprofen LAT was found to be an effective and acceptable treatment for soft tissue lesions with low levels of adverse events. Martens investigated the efficacy and safety of flurbiprofen LAT 40 mg patches applied at 12-hourly intervals and compared it with diclofenac sodium tablets 50 mg twice daily for two weeks in the treatment of soft-tissue rheumatism.[11] Treatment with flurbiprofen LAT patch was found to be superior to diclofenac in terms of both efficacy and gastrointestinal tolerability. However to our knowledge, acute/near term analgesic efficacy of a single dose of transdermal flurbiprofen was not previously evaluated. We observed that transdermal patch of flurbiprofen was effective in acute pain-relief at a single dose in patients with knee osteoarthritis. The expectation of the patient with pain is immediate pain relief and subsequent improvement in physical function. The patient's compliance to the medical treatment is directly related with his/her satisfaction. Acute analgesic efficacy of a NSAID may enhance the compliance of the patient to the medication. We assume that transdermal flurbiprofen might provide advantages in these aspects along with reduced systemic side effects.

Pain is believed to have a role in functional performance and isokinetic assessments of patients with knee pain were performed in some studies in assessment of pain. We aimed to measure the knee muscle strength using Cybex Norm Isokinetic Dynamometer in order to assess the analgesic effect of the drug objectively. The most frequently used isokinetic measurement is been peak torque. Other muscle function parameters including peak work, peak power, angle-specific torque measurements were also evaluated, but their routine use is not recommended.[14,15] We evaluated the peak torques and total work of flexor and extensor muscles of knee. We expected to find an increase in these parameters as a result of pain reduction, and re-assessed the patients 6 hours after application of patches, taking the half-life of the drug into consideration. However, a significant difference was not seen in measured parameters either after flurbiprofen or after placebo administrations. Lankhorst et al. evaluated 39 patients with knee osteoarthritis and found that pain score during isokinetic extension at 180/sec was the single best independent variable for the mean pain score.[16] However they mentioned that torque values and torque production can also be modified by the patient's will and concluded that isometric and isokinetic concentric torque measurements could not be considered as reliable predictors of functional capacity.[16] Gür and Çakın also reported that isokinetic concentric and eccentric torques were unsatisfactory predictors of functional capacity and pain.[17] The present study did not show any significant differences in isokinetic concentric torques at 180°/sec angular velocity, although patients defined a decrease in pain after both placebo and flurbiprofen administrations.

In conclusion, we found significant reductions in pain scores after application of flurbiprofen patches. However, no significant difference in isokinetic assessment parameters was observed. The small number of participants and application of a single dose of transdermal flurbiprofen are the limitations of the study. To assess the effects and side effects of transdermal flurbiprofen and its efficacy on knee pain and function in knee osteoarthritis, further controlled studies in larger groups of patients with different doses of flurbiprofen are needed.

There was no conflicts of interest that could have influenced the reporting of the experimental data or conclusions in this manuscript.

## REFERENCES


1. Hough AJ. Pathology of osteoarthritis. In: Koopman WJ, Moreland LW, eds. Arthritis and Allied Conditions. 15thed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 2169-98.
2. İnanıcı F. [What is social and economic burden of osteoarthritis?] Turkiye Klinikleri J PM&R-Special Topics 2008;1(2):33-9.
3. Lozada CJ, Altman RD. Management of osteoarthritis. In: Koopman WJ, Moreland LW, eds. Arthritis and Allied Conditions. 15thed. Philadelphia: Lippincott Williams & Wilkins; 2005.p. 2257-76.
4. Sundy JS. Nonsteroidal anti-inflammatory drugs. In: Koopman WJ, Moreland LW, eds. Arthritis and Allied Conditions. 15thed. Philadelphia: Lippincott Williams & Wilkins; 2005.p. 679-704.
5. Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. Arch Intern Med 1994;154(1):42-6.
6. Deniz G, Saygı Ş. [The clinical importance of selective inhibitors of COX-2 and new antiinflammatory agents without gastrointestinal toxicity]. Turkiye Klinikleri J Med Sci 2000;20(2):102-6.
7. Ridout G, Santus GC, Guy RH. Pharmokinetic considerations in the use of newer transdermal formulations. Clinical Pharmokinetics 1988;15(2):114-31.
8. Russel AL. Piroxicam 0.5% topical gel compared to placebo in the treatment of acute soft tissue injuries: a double-blind study comparing efficacy and safety. Clin Invest Med 1991;14(1):35-43.
9. Galer BS, Rowbotham M, Perander J, Devers A, Friedman E. Topical diclofenac patch relieves minor sports injury pain: results of a multicenter controlled clinical trial. J Pain Symptom Manage 2000;19(4):287-94.
10. Poul J, West J, Buchanan N, Grahame R. Local action transcutaneous flurbiprofen in the treatment of soft tissue rheumatism. Br J Rheumatol 1993;32(11):1000-3.
11. Martens M. Efficacy and tolerability of a topical NSAID patch (local action transcutaneous flurbiprofen) and oral diclofenac in the treatment of soft-tissue rheumatism. Clin Rheumatol 1997;16(1):25-31.
12. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of Osteoarthritis of the Knee. Arthritis Rheum 1986;29(8):1039-49.
13. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis 1957;16(4):494-501.
14. Kannus P. Normality, variability and predictability of work, power and torque acceleration energy with respect to peak torque in isokinetic muscle testing. Int J Sports Med 1992;13(3):249-56.
15. Kannus P, Yasuda K. Value of isokinetic angle-specific torque measurements in normal and injured knees. Med Sci Sports Exerc 1992;24(3):292-7.
16. Lankhorst GJ, Van de Stadt RJ, Van der Korst JK. The relationships of functional capacity, pain and isometric and isokinetic torque in osteoarthrosis of the knee. Scand J Rehab Med 1985;17(4):167-72.
17. Gür H, Çakın N. Muscle mass, isokinetic torque and functional capacity in women with osteoarthritis of the knee. Arch Phys Med Rehabil 2003;84(10):1534-41.