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Efficacy of Transdermal Ketoprofen for Delayed Onset Muscle Soreness

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Objective: To determine the efficacy of transdermal ketoprofen in reducing delayed-onset muscle soreness (DOMS), limiting systemic absorption, and improving postexercise function following repetitive muscle contraction.

Design: Double-blind, placebo-controlled clinical trial.

Setting: OrthoMed, University of California at San Diego, La Jolla, CA, U.S.A.

Participants: Thirty-two healthy males 18 to 35 years old.

Interventions: Subjects performed a leg extension and flexion exercise program designed to create DOMS in quadriceps muscles. Subjects were randomly assigned to receive any combination of transdermal ketoprofen or placebo cream, applied TID, to their right and left quadriceps.

Main Outcome Measures: Subjective measure of DOMS in quadriceps muscles, serum ketoprofen levels, strength index scores (a measure of postexercise function), and adverse reactions were assessed at baseline, 24 hours, and 48 hours.

Results: Within-subjects analysis (n = 16) showed a significant reduction in DOMS scores in legs receiving transdermal ketoprofen compared with legs receiving placebo cream ($P = 0.002$ at 48 hours and 0.000 at 24 and 48 hours combined). Between-subjects analysis (n = 16) showed a marginally significant reduction in DOMS scores at 48 hours ($P = 0.05$ in right legs and 0.053 in left legs). Systemic absorption was minimal, with serum ketoprofen levels in the ng/mL range. No differences in strength index scores were observed. No adverse reactions were reported.

Conclusions: Transdermal ketoprofen appears to be effective in reducing self-reported DOMS after repetitive muscle contraction, particularly after 48 hours. Systemic absorption of the drug was minimal. Treatment did not appear to have any effect on postexercise function, and there were no reported adverse reactions.

Key Words: transdermal, ketoprofen, NSAID, DOMS

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INTRODUCTION

Ketoprofen (Orudis, Oruvail; Wyeth-Ayerest Laboratories) is a nonsteroidal anti-inflammatory drug (NSAID) used as an antipyretic, to provide analgesia, and to treat inflammation.[1] Oral NSAIDs, like ketoprofen, are the most commonly used medications in the United States and worldwide.[2] They are frequently used for relief of muscular discomfort, such as that found in delayed-onset muscle soreness (DOMS).[3] However, there are significant systemic side effects (gastrointestinal, liver, renal, hematologic, and so forth) associated with the use of oral NSAIDs.[4] Most common and significant among these adverse effects is gastrointestinal irritation. This constitutes a considerable and costly counterbalance to the substantial beneficial effects of NSAIDs. Annually, an estimated 103,000 patients with arthritides are hospitalized in the United States for NSAID-induced gastrointestinal complications, accounting for more than $2 billion in health care costs.[5]

If an effective transdermal method of NSAID delivery were available, these limitations of oral delivery could be avoided. Further, a transdermal delivery system would have the advantage of delivering NSAIDs directly to the desired location. Thus, an effective local concentration could be achieved, while systemic absorption and its complications would be avoided.[6,7] To this end, transdermal NSAID applications are known to achieve therapeutic soft tissue concentrations, while serum concentrations tend to be less than 10% of those achieved with oral NSAIDs.[8] Moreover, adverse reactions unique to transdermal preparations, such as local skin reactions, are reported to be rare.[9] Interestingly, there are vast international experiences with transdermal ketoprofen in the medical literature.

Moore et al[9] performed a meta-analysis of 86 trials involving 10,160 patients. They reviewed the effectiveness and safety of all topical NSAIDs in acute and chronic pain conditions. They concluded that in both

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acute and chronic conditions, the incidences of local and systemic adverse events related to the topical drug were low, and the adverse effects were no different from those of placebo. They stated that topical NSAIDs were effective in relieving pain in acute and chronic conditions, based on a comprehensive analysis of all the relevant data. This study, written 5 years ago, is by far the most exhaustive in the literature and includes randomized controlled trials and both acute and chronic pain conditions.

Vaile and Davis,[8] in another review of the current literature, concluded that there had been a sufficient number of studies of soft tissue conditions to demonstrate the superiority of topical NSAIDs over placebo and to suggest equivalent efficacy in comparison with oral NSAIDs. The adverse event profile of topical agents was reasonable in minimizing cutaneous effects in only up to 2% of patients and tended to be self-limiting. Gastrointestinal events appeared from the existing literature to be rare and minor. However, this review admitted that there have not been adequate trials comparing transdermal NSAIDs with other local treatments used for acute soft tissue injuries, and there have been few trials supporting efficacy in arthritis.

Most recently, in 2001, Steen et al[10] developed a model for muscle pain to evaluate the efficacy of a topical and peroral ketoprofen not commercially available in the United States. Using this model for the precipitation of muscle pain rather than DOMS, Steen et al[10] found that a dose for dose comparison with peroral and topical ketoprofen found that peroral provided a greater degree of pain relief in muscle. The pain relief of the topical preparation was more rapidly reached but more transient. Steen et al[10] used a 2.5% commercial concentration of ketoprofen with a different topical penetrating agent than that used in the present study.

Despite these studies and the potential advantages, transdermal formulations of NSAIDs are not commercially available in the United States. They are only available by a physician's prescription, customized individually for a patient, filled in a compounding pharmacy. The current study examines a novel, patented pluronic lecithin organogel (PLO) transdermal delivery system. This system combines 2 separate transdermal delivery vehicles that have proven successful in the past: pluronic acid[11,12] and lecithin.[13] Similar PLO delivery systems have provided effective transdermal penetration of drugs across the skin.[14,15]

Ketoprofen, as opposed to other NSAIDs, was chosen for the study due to its safety profile. According to Avouac and Teule,[16] ketoprofen, for its incidence of gastrointestinal complaints per million prescriptions, ranked seventh among 19 NSAIDs in its last 5 years of marketing in the United Kingdom. Ketoprofen has been associated with very low incidence of renal, hepatic, or cutaneous reactions. The study concluded that ketoprofen, in 15 years of use in Europe, had an excellent safety profile.

Delayed-onset muscle soreness is defined as skeletal muscle discomfort that peaks 24 to 48 hours after exercise.[3] It is a common form of muscle pain experienced by exercising adults and athletes. Oral NSAIDs are among the treatment methods used to relieve severe DOMS. Further, many individuals chronically use oral NSAIDs to attenuate DOMS, making the systemic side effects more probable. Thus, DOMS constitutes a setting in which efficacious transdermal NSAID delivery may prove advantageous.

Clinically, DOMS is a common but self-limiting condition that often requires no treatment. It is thought that pretreatment with topical NSAIDs could be prophylactic for DOMS. It is the sensation of discomfort that is most evident in skeletal muscle 1 to 2 days after exercise. MacIntyre et al[3] have reported that the soreness usually subsides within 5 to 7 days after exercise with no treatment. The soreness has been reported to be most evident at the muscle–tendon junction initially and spreads throughout the muscle. It has been suggested that the soreness may occur as a result of the mechanical factors inherent to the eccentric activity followed by an acute inflammatory response. The present study evaluates the effectiveness of a 10% ketoprofen PLO formulation in reducing DOMS, limiting systemic absorption, improving postexercise function, and avoiding adverse reactions in quadriceps muscles following repetitive muscle contraction.

METHODS

Subjects and Experimental Protocol

Thirty-two male subjects were recruited for this double blind, placebo-controlled clinical trial. Recruitment was based on age (18–35 years), exercise history, and absence of significant health risk factors. Women were not included to avoid any fertility or pregnancy complications. Subjects were instructed to avoid all nonessential medications, including NSAIDs, for the week prior to the study and throughout the study. Similarly, subjects were instructed to refrain from exercise beyond their normal level of activity and to avoid the use of heat, ice, massage, and other forms of soreness relief.

Day 1 (Baseline; Time = 0)

A detailed exercise and health history questionnaire was administered before the intervention to obtain standard demographic information, including normal exercise frequency, duration, and intensity. All subjects then underwent a physical examination to rule out any significant biomechanical abnormality. Baseline quadriceps soreness (DOMS) was assessed using a subjective scale, with 0 representing "no soreness" and 10 representing "worst soreness" (Fig. 1). Subjects marked the scale according to their current level of quadriceps soreness. A separate scale was marked for the left and right quadriceps.

To create DOMS, a knee extension and flexion exercise load was carried out for each leg using the UCSD Department of Orthopaedics MedX (MedX 96, Inc., 1401 NE 77th Street, Ocala, FL 34479) clinical fatigue response testing protocol.[17] To perform the fatigue response test, subjects were seated in a MedX knee machine and restrained to isolate the target quadriceps muscle. Whether a given subject began with the right or left leg was randomized. Subjects then performed a series of maximal effort isometric contractions at 6 knee

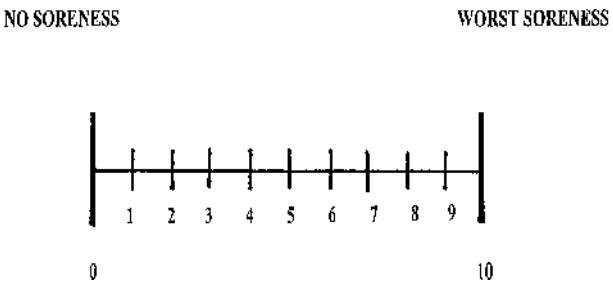

FIGURE 1. Delayed-onset muscle soreness scale.

joint angles through a pain-free range of motion: at 96°, 78°, 60°, 42°, 24°, and 6°.

After a brief rest, subjects performed as many dynamic variable resistance knee extension and flexion repetitions as possible at 40% of the peak torque generated during the isometric test. This weight load was calculated separately for each leg to ensure that similar DOMS was created in both quadriceps muscles of each subject. Each repetition was performed through the full pain-free range of motion (from 96° to 6°) in a slow, controlled manner. Subjects performed the concentric portion of the repetition for 2 seconds, paused at full contraction for 1 second, and then completed the eccentric portion over a 4-second period (for a total of 7 seconds per repetition). Repetitions were performed until subjects were unable to move the weight load through the full range of motion within the allotted 7 seconds—that is, they reached volitional fatigue.

Immediately following the dynamic repetitions (within 1 minute), subjects performed maximal effort isometric contractions at the same knee joint angles selected for the previous isometric contractions. This entire procedure was then repeated as the subject performed a second set of exercises. The same protocol was then used on the subject's opposite leg. Data on peak isometric torque, dynamic repetition weight load, and number of dynamic repetitions were recorded for later analysis.

Delayed-onset muscle soreness was not confirmed by any biochemical marker. Instead, we accepted the complaints of pain by the subjects as adequate proof of the cause and effect relationship of the exercise performed.

Immediately following the exercise (t = 0), transdermal ketoprofen or placebo creams were applied to subjects' quadriceps muscles. The transdermal ketoprofen, designed by Trans-Pharma Pharmaceutical Co., was a 10% ketoprofen formulation of PLO cream. The placebo consisted of the PLO cream alone. Subjects were randomized into 4 groups so that they could apply any combination of intervention and placebo to their right and left quadriceps (Table 1). Subjects applied the same combination of intervention and placebo throughout the study. To maintain consistency, the application area (an 8 cm × 13 cm rectangle) was marked on subjects' quadriceps muscles. A premeasured dose of 1 g cream was applied to each leg per application, with the medicated cream containing 100 mg ketoprofen. Subsequently, subjects were instructed to apply the cream every 8 hours. Thus, on the first day, cream was applied at 0, 8, and 16 hours from the time of exercise.

Day 2 (Time = 24)

A repeat subjective soreness scale questionnaire was administered to evaluate quadriceps DOMS at 24 hours postexercise. Blood samples were drawn to measure systemic absorption of ketoprofen. For each subject, 10 mL blood was collected in EDTA tubes, centrifuged for 10 minutes, and the serum harvested and frozen for later analysis. Using the exercise load described, subjects then underwent a repeat MedX fatigue response test to assess postexercise function and create further DOMS. Once again, the cream was applied immediately following exercise and every 8 hours thereafter (ie, at 24, 32, and 40 hours from the time of the initial exercise load).

Day 3 (Time = 48)

A repeat subjective soreness scale questionnaire was administered to evaluate quadriceps DOMS at 48 hours. Serum samples were drawn to measure systemic absorption of ketoprofen at 48 hours.

Analytical Methods

Serum ketoprofen levels at 24 and 48 hours were measured by National Medical Services using a liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method. The normal analytical method for the quantitation of serum ketoprofen, high-performance liquid chromatography with ultraviolet detection, was not sensitive enough to detect the low serum concentrations found in the study. Thus, LC/MS/MS was chosen for its high sensitivity and selectivity. Blinded standards were run to confirm the accuracy of the method. The quantitation limit of serum ketoprofen was 10 ng/mL.

As a measure of postexercise function, a strength index (SI) was calculated from the isometric contraction data collected during the 2 exercise sessions. The SI was defined as the area under the curve of knee joint angles versus peak force generated at each joint angle during the isometric tests (Fig. 2). The difference between the SI before and the SI after dynamic repetition sets represented the fatiguing effect of the dynamic exercise. Comparisons of the change in the SI were then made between the different treatment groups.

Statistical Analysis

T tests were used to make 2 types of comparisons. One was within subjects who used transdermal ketoprofen on 1 leg and placebo cream on the other leg (n = 16). The other type was between subjects who used transdermal ketoprofen on both legs (n = 8) and subjects who used

TABLE 1. *Treatment groups*

Group Number	Right Leg Treatment	Left Leg Treatment
1 (n = 8)	Transdermal ketoprofen	Transdermal ketoprofen
2 (n = 8)	Placebo cream	Placebo cream
3 (n = 8)	Transdermal ketoprofen	Placebo cream
4 (n = 8)	Placebo cream	Transdermal ketoprofen

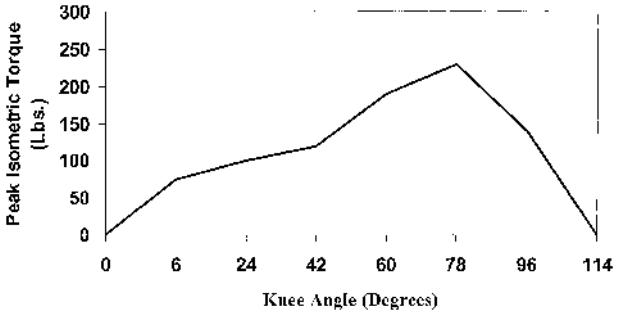

FIGURE 2. Strength index (SI). SI, a measure of postexercise function, was defined as the area under the curve generated during isometric tests.

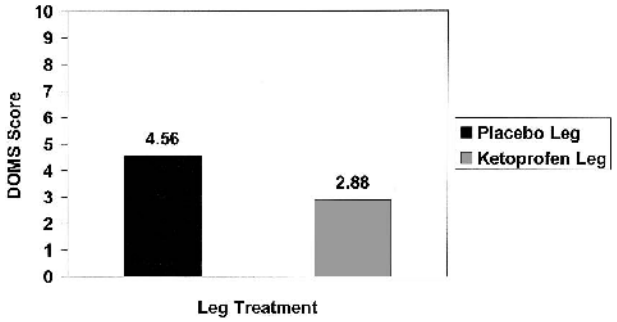

FIGURE 3. Mean delayed-onset muscle soreness (DOMS) scores at 48 hours for within-subjects comparisons.

placebo cream on both legs (n = 8). Comparisons were performed at baseline, 24 hours, 48 hours, and 24 and 48 hours combined. In addition, standardized regression analysis was run to examine factors influencing the change in SI scores.

RESULTS

Effectiveness of Transdermal Ketoprofen in Reducing Delayed-onset Muscle Soreness

Within-subjects comparisons are shown in Table 2. At 48 hours, subjects (n = 16) reported a mean reduction in DOMS scores of 37% in legs receiving transdermal ketoprofen compared with legs receiving placebo cream ($P = 0.002$) (Fig. 3). When DOMS scores at 24 and 48 hours were combined (n = 32), subjects reported a mean reduction in soreness of 33% in ketoprofen-treated legs compared with placebo-treated legs ($P = 0.000$) (Fig. 4). Results at 24 hours showed a similar trend but were only marginally significant ($P = 0.068$).

Between-subjects comparisons are shown in Table 3. At 48 hours, subjects in the transdermal ketoprofen-treated group reported a mean reduction in DOMS scores of 45% in right legs (n = 16, $P = 0.05$) and 43% in left legs (n = 16, $P = 0.053$) compared with subjects in the placebo-treated group (Figs. 5 and 6, respectively). Results at 24 hours and 24 and 48 hours combined showed a similar trend but were not significant.

TABLE 2. *Within-subjects comparison of delayed-onset muscle soreness scores**

Time	Ketoprofen Leg DOMS Score Mean (SD)	Placebo Leg DOMS Score Mean (SD)	*P*
Baseline (n = 16)	0.31 (0.60)	0.31 (0.60)	1.000
24 h (n = 16)	2.69 (1.62)	3.69 (2.12)	0.068
48 h (n = 16)	2.88 (1.36)	4.56 (2.53)	0.002
24 and 48 h (n = 32)	2.78 (1.48)	4.13 (2.34)	0.000

* Subjects applied transdermal ketoprofen to 1 leg and placebo cream to the other.

DOMS indicates delayed-onset muscle soreness.

Age, Body Mass Index, and Exercise History as Factors Modifying the Effectiveness of Transdermal Ketoprofen

No differences were observed among any of the treatment groups with respect to age, body mass index, or exercise history (Table 4).

At 24 hours, DOMS scores were significantly higher in the left legs of subjects receiving placebo cream who were younger than 24 years, subjects who exercised 3 days or fewer per week, and subjects whose normal exercise was of mild intensity (Table 5).

At 48 hours, DOMS scores were significantly higher in the right and left legs of subjects receiving placebo cream who were younger than 24 years and subjects whose normal exercise was of moderate intensity. DOMS scores were significantly higher in the right legs of subjects receiving placebo cream who had a body mass index less than 24.0 kg/m^2. DOMS scores were significantly higher in the left legs of subjects receiving placebo cream who had a body mass index of 24.0 kg/m^2 or greater and subjects whose normal exercise was of mild intensity (Table 5).

Systemic Absorption of Transdermal Ketoprofen

The systemic absorption of transdermal ketoprofen was minimal (Figs. 7, 8). Serum ketoprofen levels were in the ng/mL range, with a mean of 39 ng/mL at 24 hours and 53 ng/mL at 48 hours for those applying transdermal ketoprofen to both legs (n = 8). For those applying transdermal ketoprofen to 1 leg and placebo to the other (n = 16), the mean serum ketoprofen levels at 24 and 48

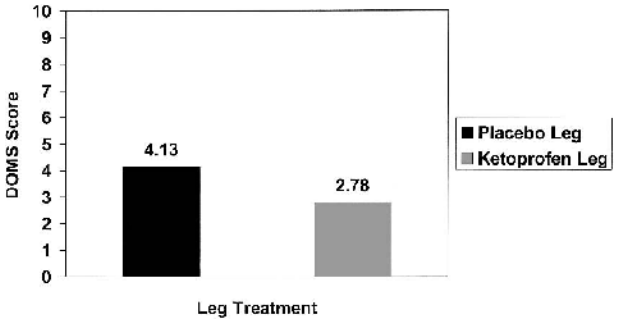

FIGURE 4. Mean delayed-onset muscle soreness (DOMS) scores at 24 and 48 hours combined for within-subjects comparisons.

TABLE 3. *Between-subjects comparison of delayed-onset muscle soreness scores**

Time	Ketoprofen Group DOMS Score Mean (SD)	Placebo Group DOMS Score Mean (SD)	*P*
Right leg			
Baseline (n = 16)	0.38 (1.06)	0.38 (0.74)	1.000
24 h (n = 16)	3.38 (1.51)	3.88 (2.23)	0.608
48 h (n = 16)	3.00 (1.77)	5.50 (2.78)	0.050
24 and 48 h (n = 32)	3.18 (1.60)	4.69 (2.58)	0.057
Left leg			
Baseline (n = 16)	0.38 (1.06)	0.38 (0.74)	1.000
24 h (n = 16)	3.50 (1.69)	3.50 (1.85)	1.000
48 h (n = 16)	3.00 (2.20)	5.25 (2.05)	0.053
24 and 48 h (n = 32)	3.25 (1.92)	4.38 (2.09)	0.123

* Subjects applied either transdermal ketoprofen or placebo cream to both legs.

DOMS indicates delayed-onset muscle soreness.

hours were 23.8 ng/mL and 30.7 ng/mL, respectively. As expected, serum ketoprofen levels in those who applied placebo to both legs (n = 8) were below the 10 ng/mL detection limit.

There was a trend toward higher serum ketoprofen in subjects who received transdermal ketoprofen on both legs versus 1 leg. However, these differences were not statistically significant ($P = 0.08$ at 24 hours and $P = 0.0768$ at 48 hours).

Effect of Transdermal Ketoprofen on Postexercise Function

No differences were observed in SI scores of legs receiving transdermal ketoprofen and legs receiving placebo cream (Table 6). After 24 hours of treatment, no differences were observed in reduction of SI scores following dynamic repetitions (Table 7).

Predictors of the Change in Strength Index Scores After Each Set of Dynamic Repetitions

At 24 hours, changes in SI scores in the right leg were associated with the following variables:

(1) Normal exercise frequency and difference between SI after first dynamic repetition set and SI after second set ($r = 0.46$, $P = 0.009$)

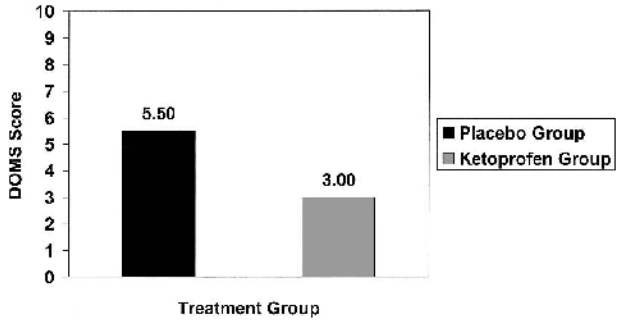

FIGURE 5. Mean delayed-onset muscle soreness (DOMS) scores in right legs at 48 hours for between-subjects comparisons.

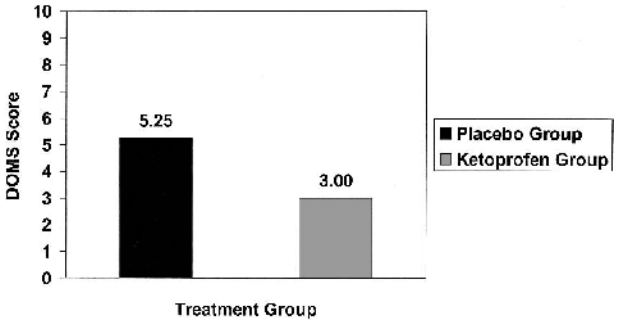

FIGURE 6. Mean delayed-onset muscle soreness (DOMS) scores in left legs at 48 hours for between-subjects comparisons.

(2) Normal exercise frequency and difference between baseline SI and SI after second dynamic repetition set ($r = 0.37$, $P = 0.037$)

At 24 hours, changes in SI scores in the left leg were associated with the following variables:

(1) Serum ketoprofen levels at 48 hours and difference between SI after first dynamic repetition set and SI after second set ($r = -0.42$, $P = 0.016$)
(2) Baseline SI score and difference between baseline SI and SI after first dynamic repetition set ($r = -0.39$, $P = 0.027$)
(3) Baseline SI score and difference between baseline SI and SI after second dynamic repetition set ($r = -0.42$, $P = 0.017$)

After controlling for all potential covariates, the only significant independent predictor of changes in SI scores was the baseline SI score at 24 hours (Table 8).

Collectively, these variables account for a significant percentage of the variance in change in SI scores between the first and second sets of dynamic repetitions in both legs. However, after controlling for potential covariates, neither DOMS scores nor serum ketoprofen levels predict for changes in SI scores at 24 hours in either leg.

Adverse Reactions to Transdermal Ketoprofen and the Pluronic Lecithin Organogel Delivery System

According to questionnaires administered at 24 and 48 hours, there were no reports of adverse reactions to transdermal ketoprofen, nor to placebo cream.

DISCUSSION

The current study evaluated the efficacy of transdermal ketoprofen in 4 main areas. First, it assessed the ability of the drug to achieve therapeutic soft tissue concentrations, as evidenced by DOMS scores. Second, it judged the ability of the transdermal preparation to minimize systemic absorption, as measured by serum ketoprofen levels. Third, it evaluated the ability of the drug to improve postexercise function, as determined by SI scores. Finally, it assessed the ability of the drug to avoid adverse reactions unique to transdermal preparations, such as local skin reactions.

TABLE 4. *Physical characteristics and exercise history of treatment groups*

Physical Characteristic or Exercise History	Ketoprofen Both Legs (n = 8)	Ketoprofen Right Leg, Placebo Left Leg (n = 8)	Placebo Right Leg, Ketoprofen Left Leg (n = 8)	Placebo Both Legs (n = 8)
Mean age, y (SD)	25.5 (5.5)	22.9 (3.1)	24.5 (3.3)	23.8 (1.9)
Mean body mass index, kg/m^2 (SD)	24.2 (2.7)	23.0 (4.6)	25.4 (3.0)	26.0 (3.5)
Mean exercise frequency, d/wk (SD)	3.9 (1.5)	3.4 (1.5)	2.4 (0.9)	4.1 (1.6)
Mean exercise duration				
% ≤45 min	37.5	62.5	62.5	25.0
% >45 min	62.5	37.5	37.5	75.0
Mean exercise intensity				
% mild	0.0	25.0	25.0	0.0
% moderate	100.0	62.5	62.5	75.0
% strenuous	0.0	12.5	12.5	25.0

Transdermal ketoprofen appeared to be effective in alleviating self-reported DOMS in isolated quadriceps muscles following repetitive muscle contraction, particularly after 48 hours. This relief of DOMS appears to be secondary to the effects of the drug. In the current double-blind, placebo-controlled clinical trial, no other medications or pain relief measures were allowed. The effects of the transdermal ketoprofen could not be attributed to massage during application, as the placebo cream was applied in an identical manner. Statistical analysis showed no difference between treatment groups with respect to age, body mass index, or exercise history. Transdermal ketoprofen appears to be more effective in younger adults—those younger than 24 years—than in older adults. Body mass index and exercise history also appear to have some influence on treatment effective-

TABLE 5. *Mean delayed-onset muscle soreness scores of leg treatment by physical characteristics and exercise history*

Physical Characteristic or Exercise History	DOMS Scores at 24 h Mean (SD)		DOMS Scores at 48 h Mean (SD)	
	Ketoprofen Legs	Placebo Legs	Ketoprofen Legs	Placebo Legs
Right legs				
Overall age	3.1 (1.4)	3.6 (2.0)	3.0 (1.6)	4.9 (2.7)*
<24 y	2.9 (1.6)	3.3 (2.4)	2.4 (1.7)	4.5 (2.6)*
≥24 y	3.2 (1.3)	3.8 (1.9)	3.4 (1.4)	4.6 (2.8)
Body mass index				
<24.0 kg/m^2	2.8 (0.8)	3.6 (1.3)	2.7 (1.40	6.2 (1.5)‡
≥24.0 kg/m^2	3.5 (2.1)	3.6 (2.3)	3.5 (1.9)	4.4 (2.9)
Exercise frequency				
≤3 d/wk	3.3 (1.0)	3.5 (1.7)	3.6 (1.5)	4.7 (2.3)
≥4 d/wk	2.9 (1.7)	4.0 (2.8)	2.6 (1.6)	5.4 (3.6)
Exercise duration				
≤45 min	2.9 (0.6)	4.0 (2.2)	3.1 (1.1)	5.4 (3.3)
>45 min	3.3 (1.9)	3.3 (1.9)	2.9 (2.0)	4.6 (2.2)
Exercise intensity				
Mild	3.5 (0.7)	2.5 (3.5)	3.5 (2.1)	2.5 (2.1)
Moderate	2.9 (1.5)	4.2 (1.9)	2.8 (1.5)	5.6 (2.9)†
Strenuous	4.0 (0.0)	2.3 (0.6)	5.0 (0.0)	4.0 (0.0)
Left legs				
Overall age	3.1 (1.8)	3.8 (2.1)	2.8 (1.8)	5.3 (2.4)†
<24 y	2.0 (1.2)	5.1 (2.0)*	1.7 (1.2)	7.0 (1.5)‡
≥24 y	3.7 (1.6)	2.7 (1.4)	3.5 (1.7)	3.9 (2.0)
Body mass index				
<24.0 kg/m^2	2.4 (1.3)	4.3 (2.3)	3.1 (2.0)	5.3 (2.8)
≥24.0 kg/m^2	3.6 (2.1)	3.3 (1.9)	2.6 (1.6)	5.3 (2.1)†
Exercise frequency				
≤3 d/wk	3.0 (1.80	5.0 (1.7)*	2.7 (1.6)	6.6 (1.6)‡
≤4 d/wk	3.2 (2.0)	2.8 (1.9)	3.0 (2.2)	4.2 (2.4)
Exercise duration				
≤45 min	2.9 (1.6)	3.7 (2.1)	2.8 (1.8)	5.3 (3.0)
>45 min	3.3 (2.2)	3.8 (2.2)	2.9 (1.8)	5.2 (2.0)*
Exercise intensity				
Mild	1.0 (1.4)	7.0 (0.0)*	1.5 (0.7)	8.0 (1.4)*
Moderate	3.5 (1.7)	3.5 (1.9)	3.1 (1.8)	4.9 (2.5)*
Strenuous	1.0 (0.0)	2.7 (1.2)	2.0 (0.0)	4.7 (1.5)

* $P < 0.05$; † $P < 0.01$; ‡ $P < 0.001$.
DOMS indicates delayed-onset muscle soreness.

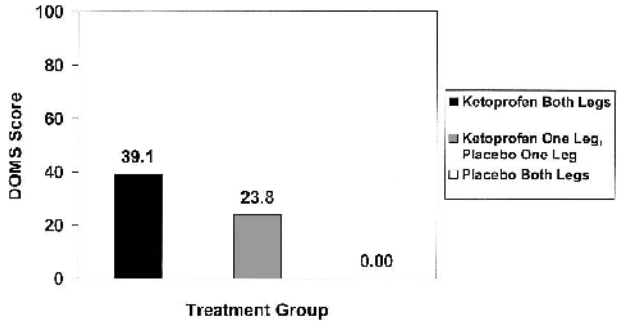

FIGURE 7. Systemic absorption of transdermal ketoprofen at 24 hours. DOMS indicates delayed-onset muscle soreness.

ness, although this can not be stated with certainty given the large number of multiple comparisons conducted. However, these variables do not account for the significantly lower DOMS scores in legs receiving transdermal ketoprofen.

There were both advantages and disadvantages to using DOMS as a model to assess the efficacy of the drug. The DOMS model allowed the distinction to be made between the local and systemic effects of the transdermal drug. Specifically, within-subjects analysis allowed subjects to serve as their own controls. Thus, if relief of DOMS was due to systemic absorption, then both ketoprofen-treated and placebo-treated legs would have decreased soreness. No such crossover effect was seen. Within-subjects analysis also eliminated the potential confounding variables of differential pain tolerance and subjective assessment of soreness that may exist in between-subjects comparisons. These confounding variables may account for the marginally significant results at 48 hours in between-subject analysis and the lack of significant results in such comparisons at 24 hours and 24 and 48 hours combined.

The study followed subjects for 48 hours after the initial exercise session. This time frame corresponded to the peak of DOMS.[3] However, further studies are needed to evaluate the efficacy of long-term treatment with transdermal ketoprofen. In addition, by using the DOMS model, the study evaluated an acute inflammatory, painful condition. Further study is needed to evaluate the efficacy of the drug in treating chronic inflammatory, painful conditions.

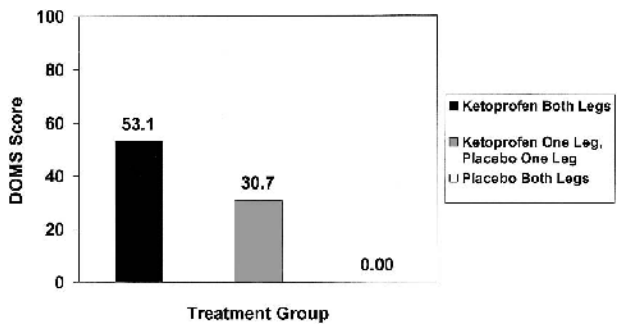

FIGURE 8. Systemic absorption of transdermal ketoprofen at 48 hours. DOMS indicates delayed-onset muscle soreness.

TABLE 6. *Strength index scores at 24 hours*

Time of Isometric Contractions	Ketoprofen Legs Strength Index Mean lb (SD)	Placebo Legs Strength Index Mean lb (SD)
Right leg		
Baseline	9482.9 (2548.1)	8721.0 (3391.6)
After first set of dynamic repetitions	8690.4 (3624.5)	7924.3 (2940.6)
After second set of dynamic repetitions	8984.1 (3706.9)	7712.3 (2534.6)
Left leg		
Baseline	8821.8 (3066.2)	9372.6 (3427.0)
After first set of dynamic repetitions	7896.9 (3426.9)	8699.8 (2956.7)
After second set of dynamic repetitions	7631.1 (3187.5)	8286.0 (2689.7)

While DOMS is a common indication for NSAIDs, there are many other common uses for NSAIDs that may or may not lend themselves to a transdermal preparation. In addition, the efficacious results seen in the treatment of DOMS may not necessarily translate to the treatment of pathologic states, such as muscle tears or sprains. Further, the present study examined subjects in good health. Again, the results may not hold true for patients who have chronic medical conditions, such as arthritis.

The small patient pool in this study may cast doubt on its validity. However, it is a testament to the efficacy of the drug that there was statistical significance in spite of the small patient pool. The arm of the study that featured blinded patients comparing their own legs with drugs against placebo was significant and argues against a small sample flaw. However, a study in addition to the report by Steen,[10] using this specific topical preparation, comparing it to oral ketoprofen, is a logical follow-up.

Thus, despite the encouraging results, further study is needed to evaluate how transdermal NSAIDs may be used in the future. Nonetheless, the results of the present study indicate that physicians should consider prescribing transdermal NSAIDs for the treatment of certain conditions.

As evidenced by decreased DOMS scores, the transdermal preparation of ketoprofen was able to achieve therapeutic local soft tissue concentrations. However, systemic absorption of the drug was minimal (in the ng/mL range). This may be compared with peak plasma levels of orally administered ketoprofen, which are in the mg/mL range, with a mean of 2.4 mg/mL for Orudis and 3.4 mg/mL for Oruvail.[17] Therefore, systemic absorption of transdermal ketoprofen is approximately 2 orders of magnitude less than that of oral ketoprofen. These results are encouraging in that, intuitively, it would follow that limiting systemic absorption would minimize the adverse effects of NSAIDs. In fact, 1 study has shown that patients with acute upper gastrointestinal hemorrhage had significantly higher plasma NSAID levels.[18] However, the current study did not evaluate the incidence of NSAID side effects. Thus, while the results are statistically significant, it may not be stated with complete confidence that the low systemic absorption of transdermal

TABLE 7. *Changes in strength index scores at 24 hours*

Time of Change in Strength Index	Ketoprofen Legs Change in Strength Index Mean lb (SD)	Placebo Legs Change in Strength Index Mean lb (SD)
Right leg		
Difference between baseline and after first set	792.5 (1734.2)	796.8 (1390.2)
Difference between after first set and after second set	–293.7 (985.1)	212.0 (938.9)
Difference between baseline and after second set	498.8 (1953.2)	1008.8 (1678.4)
Left leg		
Difference between baseline and after first set	924.8 (1096.2)	672.9 (1074.3)
Difference between after first set and after second set	265.8 (899.8)	413.8 (1262.5)
Difference between baseline and after second set	1190.6 (1091.4)	1086.6 (1895.4)

ketoprofen will prevent the occurrence of NSAID side effects. Long-term study is necessary to monitor for these adverse effects.

In addition, although systemic absorption was limited, people who are hypersensitive to NSAIDs or who have severe gastrointestinal problems may experience adverse reactions at lower serum NSAID levels. Further study is necessary to evaluate the safety of transdermal NSAIDs in such patients. Nonetheless, the low serum ketoprofen levels seen in the study are encouraging and point toward a method of NSAID delivery in patients who cannot tolerate oral NSAIDs or who are at a high risk of developing complications.

Conservative calculations estimate that 103,000 patients annually are hospitalized for NSAID-related gastrointestinal complications.[5] At least 16,500 NSAID-related deaths occur each year among arthritis patients alone.[5] With drugs such as ketoprofen, due to the transdermal delivery system, the stomach is avoided during the absorption process, which eliminates the first-pass effect. The drug is not metabolized by the liver, and the gastrointestinal effects most common with NSAIDs are minimized.

Evans et al,[7] in a case-control study published in 1995, concluded that topical nonsteroidal anti-inflammatory drugs were not statistically associated with upper gastrointestinal bleeding and perforation. After adjustment for the confounding effects of the concomitant use of oral anti-inflammatory and ulcer healing drugs, Hernandez-Diaz and Rodriguez[20] in 2000 confirmed a known fact that history of peptic ulcer disease has the highest absolute risk. Also, the increased risk was maintained during NSAID treatment and returned to baseline once treatment stopped. A clear dose response was observed.

Wolfe et al[5] reported that although previous reports suggested that the morbidity associated with NSAID use diminishes over time, a recent study by Singh[21] indicates that the risk of NSAID-associated hemorrhage remains constant over an extended period of observation. In fact, he also reports that after ingestion of an NSAID, ultrastructural damage to the gastric surface epithelium occurs within minutes, and gross endoscopically detectable hemorrhages and erosions in the gastroduodenal epithelium occur within several hours.

Despite its effectiveness in alleviating DOMS, transdermal ketoprofen had no significant effect on postexercise function. However, this finding may be accounted for by some potential confounding variables. For one, per the UCSD Department of Orthopaedics' MedX clinical fatigue response testing, the change in SI scores, a measure of the fatiguing effect of the dynamic exercise, reflected the characteristics of subjects' quadriceps

TABLE 8. *Standardized regression coefficients (betas) of change in strength index scores on physical characteristics, exercise history, treatment group, and delayed-onset muscle soreness scores*

	Right Legs			Left Legs		
	Δ1	Δ2	Δ3	Δ1	Δ2	Δ3
Age	–0.21	0.16	–0.09	–0.27	0.15	–0.08
Body mass index	0.12	0.31	0.27	–0.05	0.21	0.12
Exercise frequency	0.10	0.44	0.32	0.17	0.21	0.27
Exercise duration	0.18	–0.09	0.10	0.14	0.19	0.24
Exercise intensity	0.13	0.06	0.14	–0.17	0.23	0.04
Treatment group	–0.03	–0.32	–0.20	0.16	<0.01	0.12
Delayed-onset muscle soreness score	0.24	0.03	0.22	–0.15	0.19	0.03
Serum ketoprofen level	0.21	0.10	0.23	0.16	0.21	0.26
Baseline strength index score	–0.21	–0.47*	–0.43	–0.29	–0.69†	–0.69†
R^2	0.20	0.49*	0.40	0.16	0.51*	0.36

* $P < 0.05$; † $P < 0.01$.

Δ1 indicates difference between strength index after first set of dynamic repetitions and baseline; Δ2, difference between strength index after second set of dynamic repetitions and after first set; Δ3, differences between strength index after second set of dynamic repetitions and baseline.

muscles. Thus, the amount of fatigue varied among individuals and was indicative of the fiber-type characteristics of the knee extensor musculature. Further, there may not be a relationship between DOMS and loss of muscle strength, because the timing of the 2 differ: while loss of muscle force occurs immediately following dynamic exercise, DOMS peaks at 24 to 48 hours postexercise.[3] This finding may be supported by the data that neither DOMS scores nor serum ketoprofen levels predict for changes in SIs at 24 hours. The lack of improvement in postexercise function is significant in that transdermal ketoprofen does not appear to be an ergogenic agent and, as such, would not confer a competitive advantage.

The current study reported no adverse reactions to the transdermal ketoprofen. However, as the present study included only healthy males and treatment was over a 48-hour period, these results may not generalize to other populations or over longer periods. Treatment and follow-up longer than 48 hours perhaps might have produced more long lasting benefits or uncovered as yet unreported adverse events.

There may be some potential limitations to transdermal delivery systems, as transdermal creams have been known to cause local irritation at the site of administration.[8] One of the known adverse effects of ketoprofen is photosensitivity. Veyrac et al[21] in 2002 reported on a French nationwide pharmacovigilant survey collated for 5 years regarding a commercial ketoprofen gel. There was a frequency of 1.3% to 2.8% photosensitivity reactions. Seventy-five percent of the cutaneous side effects appeared in the summer, and 50% were reported as photosensitivity. The frequency of this photosensitivity is accounted for by its chemical structure and the variety of chemical reactions to phototoxic effects. Widespread and repeated use of topical ketoprofen may lead to sensitization that would incur a greater risk of systemic allergic reactions or worsen the reaction to other drugs recognized to induce cross-reactions. Patients should be advised of this adverse risk. However, among the NSAIDs, ketoprofen is the main drug involved in this photoallergic contact dermatitis.[22,23] The PLO delivery system used in the current study contains lecithin. Thus, patients who are sensitive to egg whites may have an allergic reaction. Thus, further study is necessary to monitor for side effects unique to transdermal preparations.

CONCLUSIONS

This study is very much in accord with the current literature and study conclusions. As mentioned, Moore et al[9] in an exhaustive meta-analysis that involved 10,160 patients concluded similarly that topical nonsteroidal anti-inflammatory drugs were effective in relieving pain in acute and chronic conditions.

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