Topical Diclofenac versus Placebo: A Double Blind, Randomized Clinical Trial in Patients with Osteoarthritis of the Knee

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ABSTRACT. ***Objective.*** To assess the efficacy and safety of a topical formulation of 2% diclofenac in lecithin organogel in the treatment of pain associated with mild to moderate osteoarthritis (OA) of the knee.

Methods. Seventy patients completed a double blind, randomized, placebo controlled, parallel group design 2 week clinical trial. Patient responses to disease-specific (WOMAC VA3.0) and quality of life (Medical Outcome Survey SF-36) health status measures were assessed. Global assessments were also made at baseline and post-treatment. The physician conducted a global assessment and range of motion of the knee at baseline and post-treatment.

Results. T tests on the aggregated WOMAC total score and aggregated subscale scores revealed significant improvement ($p < 0.05$) on the aggregated total score and the pain, stiffness, and physical function subscales from baseline to post-treatment for the active treatment group versus the placebo group. Analysis of gain scores from the aggregated WOMAC total score and aggregated subscale scores also revealed that this improvement was significantly greater than the improvement recorded by the placebo treatment group on the aggregated total and the pain and physical function subscale scores. Other efficacy measures exhibited no significant differences between or within treatment groups.

Conclusion. A topical formulation of 2% diclofenac in a lecithin organogel appears to have therapeutic value in patients with mild to moderate OA of the knee as determined by responses from the WOMAC (VA3.0) osteoarthritis health status measure. (J Rheumatol 1999;26:2659–63)

Key Indexing Terms:
OSTEOARTHRITIS CLINICAL TRIALS TOPICAL
DICLOFENAC LECITHIN WOMAC OSTEOARTHRITIS INDEX

Osteoarthritis (OA) is characterized by progressive degeneration of articular cartilage. Lifestyle, occupation, age, and possibly genetic factors may be of etiologic importance[1]. Treatment of OA involves a multifaceted approach including patient education, rest, medication, physiotherapy, occupational therapy, and in selected patients, use of intraarticular steroid injections or surgical intervention. However, the mainstay of management is with oral nonsteroidal antiinflammatory drugs (NSAID)[2,3]. Other approaches have been used to treat mild to moderate OA of the knee in an attempt to decrease side effects, including analgesics such as acetaminophen[4], topical capsaicin creams, or topical NSAID formulations[5,6].

Experience with topical NSAID has been gained through use in ophthalmology[6] and acute soft tissue injuries[5,7], with scarce information available on efficacy and safety in OA[8-11]. Applied topically, these drugs are formulated to penetrate the stratum corneum in amounts sufficient to exert therapeutic activity because of tissue concentrations of drug attained in the skin, subcutaneous fatty tissue, and muscle, while being associated with low plasma levels[12]. However, the evidence is inconclusive with respect to deep tissues such as the synovium[13]. Poor correlations between plasma levels and therapeutic effect, good correlations between plasma levels and toxicity, and good correlations between local tissue levels and therapeutic effect all suggest that local depots of NSAID may improve the therapeutic window for this class of agents[14]. In one instance, 4.7 µg/g ketoprofen in intraarticular adipose tissue, 2.4 µg/g in capsular sample, and 1.4 µg/g in synovial fluid of the knee joint were measured after topical gel administration[15], while 0.5% piroxicam or 3% felbinac gels yielded clinical improvement in patients with traumatic injuries and knee OA and muscular pain[16]. Topical NSAID can provide an effective alternative for management of pain by delivering drug locally, without the gastrointestinal (GI) complications associated with many oral NSAID[17]. Oral NSAID account for a high percentage of reported serious adverse drug reactions, with the incidence rate in the elderly 2-fold higher than in younger populations[18,19], a major concern when treating OA. Although topical NSAID formulations may cost more than conventional dosage forms, this approach could likely reduce the secondary costs of treating NSAID related side effects, e.g., GI ulceration[20,21]. The adverse event profile for NSAID

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delivered topically is not eliminated entirely since there is usually minimal systemic exposure.

Efficacy of topical NSAID in knee OA appears to be good. A double blind, placebo controlled trial carried out on 155 adult patients showed that diclofenac plasters significantly reduced overall pain and night pain[8]. In a single-blind study, 97 patients were treated topically with either diclofenac gel or piroxicam gel, with the treating physician assessing efficacy of both formulations as "good" or "excellent" in 80% of patients[11]. Although some cases of GI bleeding associated with using topical NSAID have been reported[22], large case control studies have shown that use of topical NSAID is not related to GI bleeding[19,23]. The efficiency of drug delivered topically to lower skin structures is largely dependent on the nature of the drug and vehicle, as well as skin integrity and hydration. Following topical administration of an oil in water (o/w) emulsion gel or a solution gel of diclofenac, the maximum plasma concentrations were 10% of that reached after intramuscular injection, and C_{max} of the solution gel was almost twice that of the emulsion gel and was reached in a shorter time[24]. Alternatively, using a sub-micron o/w emulsion vehicle plasma levels of diclofenac achieved were about 40% greater compared to the conventional topical formulations of diclofenac, attributable to the dual effects of smaller particle size and the penetration enhancement abilities of phospholipids[25].

The use of phospholipid systems in topical diclofenac delivery is gaining acceptance because of a good tolerability profile in addition to enhanced penetration of drug through the stratum corneum[25,26]. Lecithin organogels, which are phospholipid emulsion systems, have also been advocated in the topical delivery of diclofenac, although only evidence of *in vitro* testing has been available to predict percutaneous absorption[27,28].

Our primary objective was to assess efficacy and safety of a topical formulation of 2% diclofenac compounded in a lecithin organogel base in patients with mild to moderate OA of the knee.

MATERIALS AND METHODS

Diclofenac sodium powder was obtained from Wiler Fine Chemicals (London, ON, Canada). The vehicle used was PHLOJEL®, a pluronic lecithin organogel base (J.A.R. Pharmaceuticals Ltd., Edmonton, AB, Canada).

The trial was a double blind, randomized, placebo controlled, parallel groups design approved by the Caritas Health Group Research Steering Committee in Edmonton, Alberta, Canada. Treatment groups received PHLOJEL® ("the gel") containing 2% diclofenac as the active gel and the gel alone as placebo. Inclusion criteria for enrollment were age > 35 years, symptomatic and radiologic OA of the knee requiring daily drug therapy, disease duration of at least 3 months, and clinical laboratory, hematological, biochemical, and urinalysis values within ± 10% of normal range.

Exclusion criteria were: stage 4 OA; recent or current alcohol abuse, drug dependency, or serious psychological disease; women who were pregnant, lactating, or of child-bearing potential not using an effective form of birth control; subjects with a significant history of allergies, corticosteroid, or hyaluronic acid injections of target knee within one month prior to enrollment; hypersensitivity to an NSAID; local skin disease; prior joint replacement surgery on the target knee; patients who had started physiotherapy in the preceding 2 weeks or had anticipated stopping or starting physiotherapy during the trial, those who had donated blood in the previous 56 days or undergone multiple blood sampling 30 days before study outset, and those who possessed a language or psychological barrier. Patients were discontinued if there was significant intercurrent illness, adverse event or surgery, or symptoms/signs indicating possible toxicity. Patients, investigators, clinical assessors, and laboratory and statistical analysts were unaware which study medication (placebo or active drug) patients were given. Adverse events were noted throughout the duration of the trial and categorized by frequency, severity, and relationship to medication.

Patients were required to visit at Week 0 (screening), at Week 1 (baseline enrollment), and at Week 3 (post-treatment). At Weeks 0 and 3, a medical history, examination, and blood and urine sampling were performed. At Weeks 1 and 3, a series of clinical assessments was taken including: WOMAC (Western Ontario and McMaster Universities) Osteoarthritis Index, visual analog scale, Version A3.0 (disease-specific assessment), physician and patient global assessments, knee range of motion (ROM), and the Medical Outcome Survey Short Form-36 Health Survey (quality-of-life assessment).

During the screening visit, eligible patients were instructed to stop their current NSAID therapy between 3 and 7 days prior to the enrollment visit. Patients were given a supply of 500 mg acetaminophen tablets during the screening visit with a dose regimen of 2 tablets per dose for control of pain not to exceed 8 tablets per day. No other concomitant medications for treating OA were allowed.

If a patient met the necessary flare criteria (persistent symptoms of OA requiring daily use of medication) during the washout period, final enrollment in the study was confirmed. Patients were randomly assigned to either placebo or active treatments after a computer generated randomization scheme. Patients received a 2 week supply of 500 mg acetaminophen tablets and the assigned study medication. The medication was self-administered 3 times daily at about the same time intervals for 2 weeks. The amount of gel administered (2.5 g) was controlled by applying a level scoop of gel to the target knee. Patients rubbed the gel over the affected area with 2 fingers for between 5 and 20 s. The target knee was not occluded. Patients were allowed to maintain normal physical activities. Application of the study medication was to be avoided for 1 h before and after strenuous activity or bathing.

A total of less than 60 ml of blood per patient was collected during the study. Blood and urine samples were collected during screening and post-treatment visits for clinical laboratory testing (Dynacare Kasper Medical Laboratories, Edmonton, AB, Canada).

Descriptive statistics and frequencies were determined for each variable at each time period. Chi-squared tests and t tests were used to determine significant differences within and between treatment groups at baseline and post-treatment. Gain score analysis was chosen a priori to determine whether there were any significant differences between treatment groups in their improvement from baseline to post-treatment based on responses to the WOMAC, the primary outcome variable. This is an appropriate statistical method if the subjects are drawn randomly from defined populations and if the purpose of the study is to compare these populations with respect to average gain, trend, or other intrasubject contrast[29]. The analysis of efficacy included all 74 patients as the intent to treat group; however, some of the patients failed to complete many of the post-treatment measurements. Results of all patients admitted to the study were included in the analysis of safety. Incidences of adverse events were recorded for each treatment group.

RESULTS

There were 88 patients screened for the clinical trial. Twelve patients did not meet specified entry criteria (7 did not possess the necessary OA inclusion criteria, 4 did not want to fulfill the stated study obligations or were unavailable for the length of study, one was unable to sufficiently understand English to participate). Two patients met the entry criteria at the screen-

ing visit but did not wish to continue after the washout period. Hence, 74 patients that were randomized at the enrollment visit remained; of these, 70 completed the clinical trial. Two patients (placebo group) had not completed all visits, one (placebo group) was terminated from the study due to a protocol violation (applied medication to wrong location), and one (active group) was withdrawn from the study after 5 days of medication due to a rash.

Demographic and clinical baseline characteristics are given in Tables 1 and 2, respectively. There were no significant differences between groups on baseline characteristics of age, sex, height, weight, race, type of symptomatic involvement, presence of chronic co-morbidity and acute intermittent illness, knee selection, American College of Rheumatology grade, and duration of OA. Both Patient and Physician Global Assessments and knee ROM measurements exhibited no significant differences between groups at baseline. There was no significant difference between groups at baseline on the subjects' responses to the questions in the 2 health care measurement instruments used, the WOMAC and SF-36.

The WOMAC Osteoarthritis Index was considered to be the primary measurement instrument for determination of efficacy (Table 3). Although no significant differences were found between the groups at baseline or post-treatment on the aggregated WOMAC and sub-scale (pain, stiffness, physical function) scores, there was a significant improvement within the active group from baseline to post-treatment on 21 of 24 individual item scores, the 3 WOMAC subscale scores, and aggregated total score. There was a significant improvement within the placebo group from baseline to post-treatment in 3 of 24 individual item scores, but no significant improvement in the 3 subscale scores and the aggregated total score.

The difference in scores from baseline to post-treatment of each group was determined, and the mean change was then compared between groups using an independent samples t test. The change in mean item response scores on the WOMAC aggregated and Pain and Physical Function subscales for the active group was significantly different from that in the mean item response scores for the placebo group. As indicated by their responses on the WOMAC, the active group experienced significantly less pain and a significantly greater degree of physical functioning after treatment and this improvement was significantly greater than that experienced by the placebo group using these measures.

Physician and Patient Global Assessment and knee ROM measurements at post-treatment exhibited no significant differences between groups. Valuations of Patient Global Assessment were generally higher than those of Physician Global Assessment, indicating belief in a greater severity of disease by the patient than by the physician. There was no significant difference between groups at post-treatment on any SF-36 individual measurement.

Comparison within groups of pretreatment versus post-treatment Patient and Physician Global Assessment (Table 4)

Table 1. Baseline demographic factors by group.

Variable	Active	Placebo
Sex		
F/M, n	23/15	22/14
Race		
Caucasian, n	37	35
Other, n	1	1
Age, mean ± SD	60.4 ± 14.6	63.6 ± 10.7
Height (cm), mean ± SD	165.0 ± 10.6	163.9 ± 14.6
Weight (kg), mean ± SD	87.7 ± 22.2	89.5 ± 20.4

Table 2. Baseline clinical factors by group.

Variable	Active, n	Placebo, n
Target knee		
Left	14	14
Right	23	22
Symptomatic involvement		
Bilateral	28	29
Unilateral left	4	2
Unilateral right	6	5
Chronic co-morbidity, Y/N	21/16	16/19
Acute intermittent illness, Y/N	2/35	4/32
ACR Grade		
1	1	0
2	6	10
3	25	23
4	4	3
Duration of OA (mo), mean ± SD	129.0 ± 172	143.0 ± 152

Table 3. WOMAC total and subscale item mean scores by group.

	Active, n = 34 X ± SD	Placebo, n = 34 X ± SD
WOMAC total		
Pretreatment	46.25 ± 16.13	41.04 ± 16.47
Post-treatment	33.62 ± 17.8	37.74 ± 20.33
Pre-post change**	−12.63 ± 13.26*	−3.30 ± 17.11
Pain subscale		
Pretreatment	44.68 ± 17.50	39.77 ± 17.89
Post-treatment	28.19 ± 18.31	35.42 ± 19.86
Pre-post change**	−16.49 ± 15.16*	−4.35 ± 22.55
Stiffness subscale		
Pretreatment	49.06 ± 18.60	47.56 ± 20.72
Post-treatment	40.49 ± 22.10	46.09 ± 24.48
Pre-post change	−8.57 ± 20.11*	−1.47 ± 19.04
Physical function subscale		
Pretreatment	46.37 ± 16.51	40.61 ± 18.14
Post-treatment	34.41 ± 18.14	37.44 ± 21.16
Pre-post change**	−11.96 ± 13.37*	−3.17 ± 17.72

*p = 0.05 level within treatment.
**p = 0.05 level between treatments.

Table 4. Patient and physician global assessment by treatment*.

	Baseline		Post-Treatment	
	Active, n (%)	Placebo, n (%)	Active, n (%)	Placebo, n (%)
Patient				
None	0 (0)	0 (0)	5 (13)	2 (6)
Mild	8 (21)	7 (19)	7 (18)	7 (18)
Moderate	23 (61)	24 (67)	18 (46)	23 (59)
Severe	7 (18)	5 (14)	6 (15)	1 (3)
Physician				
None	0 (0)	0 (0)	4 (12)	2 (7)
Mild	12 (34)	13 (38)	14 (42)	11 (37)
Moderate	18 (51)	19 (56)	8 (24)	15 (50)
Severe	5 (14)	2 (14)	7 (21)	2 (7)

*Assessments were not provided for every patient.

and knee ROM measures showed no significant difference for either active or placebo groups even though both patients and physician claimed improvement in post-treatment evaluation. Comparisons within groups of pretreatment versus post-treatment SF-36 measures showed no significant difference in either active or placebo groups.

There was no significant difference between groups in numbers of reported cases of adverse events. The active group had 6 cases (4 rash, 1 nausea and cramps, 1 case of hirsutism) and the placebo group had 9 cases (5 rash, 2 nausea, 1 numbness, 1 complaint of pruritis). All cases in both groups were mild in severity and did not require immediate treatment. One patient in the active drug treatment group reporting a rash was withdrawn from the study by the clinical investigator.

DISCUSSION

In general, patients tend to express concern about the rationale of taking oral medications when the area exhibiting pain can be localized. OA of the knee has been treated by a number of methods and interest continues among physicians and patients for topical treatments.

A significant difference was found between the active and placebo gel groups in the magnitude of change of the WOMAC data over the course of treatment. Although both groups improved, it was apparent that the diclofenac gel contributed to a more positive change in patient pain and physical functioning. This disease-specific instrument (WOMAC) detects improvements due to a specific intervention (diclofenac gel) and confirms the usefulness of the intervention on a patient's pain, stiffness, and physical functioning due to a particular disease (OA of knee). Lack of significant findings for the generic measure (SF-36) indicates that elderly patients continue to be disabled by their pain and reduced physical functioning, suggesting that addressing one condition may not significantly improve overall functioning.

Other measurements such as the Patient and Physician Global Assessments showed no significant differences between treatment groups even though there was an apparent tendency to favor the active gel. Dreiser and Tisne-Camus[8] describe significant improvement in pain measures for diclofenac plasters, but the WOMAC test, which is specifically geared toward OA of the knee, was not applied. The modest number of adverse events (greater in the placebo group) and associated mild severity in the present study are in agreement with previous reports[8,30].

Use of the WOMAC as a criterion of treatment success or failure in OA may be meritorious in view of recent trends of regulatory agencies to increase emphasis on direct patient impressions. Direct recordings of rating scales of comfort, flexibility, and pain measures should encourage patients to become more aware of the treatment process.

Future studies involving topical delivery of diclofenac should make comparisons of PHLOJEL® with other bases and topical treatments, evaluate chronic usage, and optimize dosage range and dose intervals. Efficacy of topical diclofenac for the treatment of acute tissue and joint trauma, such as sports related injuries, is another active area of interest. From results of this double blind, placebo controlled randomized study, topical diclofenac delivery appears to have therapeutic value in treatment of OA of the knee as determined by the WOMAC Osteoarthritis Index, a disease-specific, patient administered subjective measure.

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