Longterm Efficacy of Topical Nonsteroidal Antiinflammatory Drugs in Knee Osteoarthritis: Metaanalysis of Randomized Placebo Controlled Clinical Trials

SHIBADAS BISWAL, BIKASH MEDHI, and PROMILA PANDHI

ABSTRACT. ***Objective***. To evaluate the longterm efficacy of topical therapies for pain control in primary knee osteoarthritis (OA).

Methods. Systematic literature search was carried out from January 1, 1966, to December 31, 2004, in Pubmed, Medline, Embase, and Cochrane database. Manual searches of related journals in the National Medical Library (New Delhi, India), the library of our institute, and conference abstracts were also carried out. We included randomized controlled clinical trials of 4 weeks or more comparing any topical nonsteroidal antiinflammatory drug (NSAID) with placebo or vehicle. Effect size for pain control was estimated.

Results. Out of 172 citations, 4 studies fulfilled all the specified criteria. Four of them compared topical NSAID with placebo or vehicle. Pooled effect of topical NSAID measured at 4 weeks or beyond was superior to placebo/vehicle in pain relief (mean effect size –0.28, 95% CI –0.42 to –0.14).

Conclusion. Topical NSAID are effective for pain relief in knee OA for a longer duration; however, this may not hold true for all the preparations. (J Rheumatol 2006;33:1841–4)

Key Indexing Terms:
TOPICAL NONSTEROIDAL ANTIINFLAMMATORY DRUGS
KNEE OSTEOARTHRITIS PAIN LONG TERM

Knee osteoarthritis (OA) is a chronic degenerative disease where pain is the most predominant symptom[1]. Nonsteroidal antiinflammatory drugs (NSAID), widely used for pain relief in this chronic condition, are associated with distressing gastrointestinal complications, which may be life-threatening[2]. Selective cyclooxygenase 2 (COX-2) inhibitors, which seem to be more "gut friendly," were developed for these chronic NSAID users[3]. Nevertheless, an association of COX-2 with increased cardiovascular mortality is reducing their use, with some COX-2 already phased out by manufacturers, while the fate of others remains uncertain[4,5].

With respect to other therapeutic options, topical therapies may be a reliable alternative. Most of the preparations contain NSAID, including ibuprofen, ketoprofen, diclofenac sodium, etc., while others contain cetylated fatty acids, chondroitin, glucosamine, and so on[6-8]. The efficacy of topical NSAID in clinical studies has been inconsistent[8-12]. Tugwell, *et al*[10] showed the statistical and clinical equivalence of oral and topical diclofenac, while Sandelin, *et al*[11] demonstrated that topical eltenac is not better than placebo in knee OA.

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Most studies involving topical NSAID for OA are small and of short duration; drawing any valid conclusions from them may be erroneous. In a quantitative review, Moore, *et al*[13] demonstrated that topical NSAID are significantly better than placebo in chronic conditions such as arthritis, with a number needed to treat of 3.1. A metaanalysis by Lin, *et al*[14] shows that even though topical NSAID for OA are effective for a period of 2 weeks, efficacy is not sustained beyond that. In the present metaanalysis, we considered studies of at least 4 weeks' duration and involving only knee OA to evaluate efficacy of topical NSAID for a long duration (4 weeks or more).

MATERIALS AND METHODS

A systematic literature search was carried out from January 1, 1966, to December 31, 2004, in Pubmed, Medline, Embase, and the Cochrane database using the search words osteoarthritis, knee osteoarthritis, topical therapy, topical NSAID, gel, ointment, sprays, generic name of drugs, knee, arthritis, pain relief, clinical trial, and randomized controlled trial. The reference list of original reports and review articles was checked to identify the desired studies. We also manually searched related journals in the National Medical Library (New Delhi), the library of our institute, and 2003 and 2004 conference abstracts of international societies such as the British Society for Rheumatology and the American College of Rheumatology.

Inclusion and exclusion criteria. We included randomized controlled clinical trials comparing any topical NSAID with placebo or vehicle. Studies satisfying the following were selected.

Inclusion criteria

1. Patients having primary knee OA with radiological evidence
2. Study duration of 4 weeks or more
3. Primary efficacy endpoint is the pain score

Exclusion criteria

1. Nonarthritic joint pain
2. Mixed patient population such as OA and rheumatoid arthritis
3. Patients using any other therapies along with topical NSAID except for rescue medication
4. Patients having OA of joints other than knee
5. Topical therapies other than NSAID

Data extraction and outcome measures. Data were extracted in a specially designed format. The only outcome measure was pain score at final scheduled followup.

Statistical analysis. From individual studies we obtained the number of patients in treatment and control groups, and mean and standard deviation (SD) of the final pain scores. As pain measurement scales were different in different trials, we converted each score to a percentage of the scale used in the particular study. Effect size between the placebo and the active treatment arm was estimated with RevMan software (Version 4.2). Differences in the pain scores between the active treatment and placebo or vehicle at the end of the treatment were analyzed by the software to calculate the effect size only. We calculated pooled effect size in both fixed-effect and random-effect models. Heterogeneity was evaluated by applying chi-square and I-square statistics as well as by funnel plot. Association was evaluated between time and effect size by Spearman rank correlation.

RESULTS

Out of 172 citations, 71 were duplicate citations from different databases. We identified 21 randomized controlled clinical trials among 101 relevant publications. Another 12 studies were excluded because the duration was less than 4 weeks. Additional exclusions: 2 studies because other diseases or other joints were studied, 2 studies for not having topical therapy as control group, and one for having topical therapy other than NSAID. Four studies fulfilled all the specified criteria (Figure 1). All are English language reports published within the last 5 years, except one published in 1997. Except for one (sponsorship not mentioned), studies were sponsored partially or fully by pharmaceutical houses (Table 1).

Effect on pain scores. The pooled effect size of topical NSAID measured at 4 weeks or beyond was superior (effect size 0.28) to placebo/vehicle in pain relief (Table 2, Figure 2).

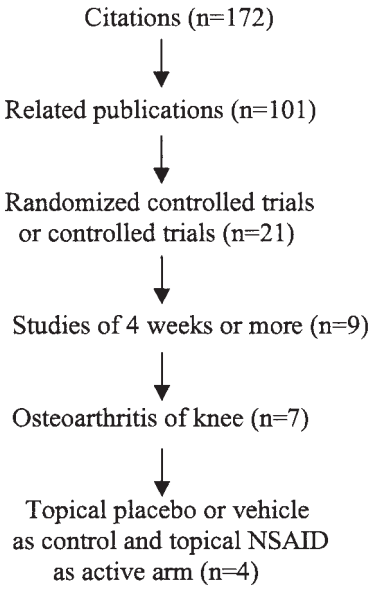

Figure 1. Selection of randomized controlled trials.

Test of heterogeneity. Studies had no variability in treatment effects as evident by the chi-square and I-square statistics. A similar finding is also evident using a funnel plot (Table 2, Figure 3).

Correlation between effect size and time. No correlation was observed between effect size and duration of treatment (Figure 4).

DISCUSSION

Our metaanalysis demonstrates efficacy of topical NSAID in pain relief of knee OA at 4 weeks or beyond. Therefore, it can be chosen as a proven therapeutic modality for a long duration in this chronic painful condition.

We selected only knee OA because efficacy may vary at different sites, given that topical NSAID act by achieving higher local concentrations[17-20]. There were only 2 topical NSAID preparations: diclofenac and eltenac. Eltenac is structurally similar and more potent, with enhanced skin permeability[11]. Mean age, disease site, gender distribution, and absence of any significant heterogeneity in effect size across the studies connotes uniformity and strength in the results.

Duration of studies varied from 4 to 12 weeks. There was no statistically significant correlation between efficacy and duration of treatment. This implies that the efficacy may not diminish with time. Compared to the effect size (0.41) at 2 weeks in the metaanalysis by Lin, *et al*[13], efficacy at 4 weeks in our analysis (0.28) is lower. This may point to a diminishing effect over time. But we did not find a similar trend. Generally, this effect size would be considered small to medium, but taking into account the context of the intervention, it may be highly meaningful, looking at its side effect profile, minimal resource utilization, and little imposition on the patients.

All the studies are relatively newer ones. Reliability in newer studies lies in their rigorous design, adequate power, and long duration of treatment. Penetration of the skin barrier has been a constant hindrance to development of topical therapies. Structural modifications (eltenac)[11] or the use of carriers such as dimethyl sulfoxide (DMSO)[10,16] has abated this problem to some extent.

In the most robust trial, Roth, *et al*[16] studied over 300 patients for a span of 12 weeks. Superiority over vehicle control was demonstrated for all defined efficacy variables, including WOMAC (Western Ontario and McMaster University Osteoarthritis Index), pain, physical function, and stiffness subscales, as well as pain on waking and patient global assessment. Efficacy variables after treatment with topical diclofenac ranged from 35% to 46% over baseline values, comparable to conventional oral diclofenac treatment of OA.

The adverse effect profiles are mostly local skin reactions (dryness, pruritus, rash), which are generally well tolerated and self-limiting[6-16]. As they do not significantly increase the

Table 1. Characteristics of randomized clinical trials comparing various topical NSAID with placebo or vehicle in knee OA. Values are number or mean (SD) unless otherwise indicated.

Trial*	Final Scheduled Followup, wks	Age, Active Treatment Group/ Control Group, yrs	Women, Active Treatment Group/ Control Group, %	Active Treatment	Control	Baseline Pain/Final Pain Score, Active Treatment, %	Baseline Pain Score/ Final Pain Score, Control, %	Effect Size (95% CI)
Bookman 2004[15]	4	62.5 (11.5)/ 60.8 (11.4)	62/61	Topical diclofenac, 84	Placebo, 84	45.5 (17.5)/26 (23)	47 (18)/34.5 (22.5)	–0.37 (–0.68, –0.07)
Ottillinger 2001[12]	6	66 (8)/67 (7)	82/76	Eltenac gel, 59	Placebo, 59	54.54 (24.1)/ 34.84 (24.0)	54.05 (21.1)/ 37.97 (22.3)	–0.13 (–0.50, 0.23)
Sandelin 1997[11]	4	61 (8.3)/61 (7.8)	62.1/69.6	Eltenac gel, 124	Placebo, 79	48 (21.5)/28 (20.7)	53 (22.2)/32 (24.1)	–0.18 (–0.57, 0.22)
Roth 2004[16]	12	63.4 (10.5)/ 64.9 (10.6)	68.9/66.7	Topical diclofenac, 163	Vehicle†, 159	65 (16.5)/35.5 (23.5)	64.5 (17)/43 (24)	–0.31 (–0.53, –0.09)

* Double blind parallel trial design for all studies. † Dimethyl sulphoxide as vehicle.

Table 2. Pooled effect sizes of pain control comparing topical therapies/topical NSAID with placebo or vehicle in controlled clinical trials of 4 weeks or more.

Comparison	No. of Trials	No. of Patients	Pooled Effect Size (95% CI)	Chi-square Significance of Heterogeneity	I-square
Topical NSAID vs placebo or vehicle	4	709	–0.28 (–0.42, –0.14)	p = 0.72	0%

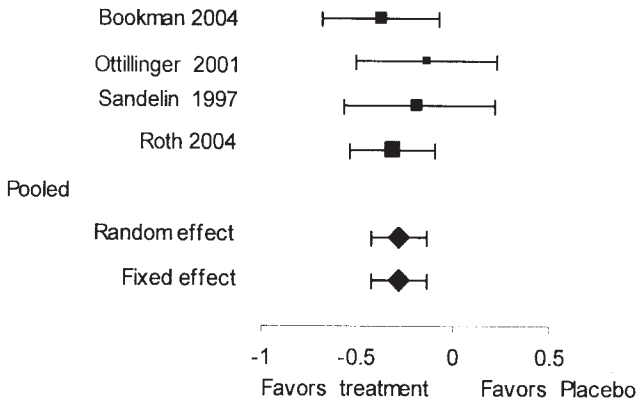

Figure 2. Effect sizes (95% confidence intervals) in pain relief between topical therapies or nonsteroidal antiinflammatory drugs (NSAID) and placebo or vehicle.

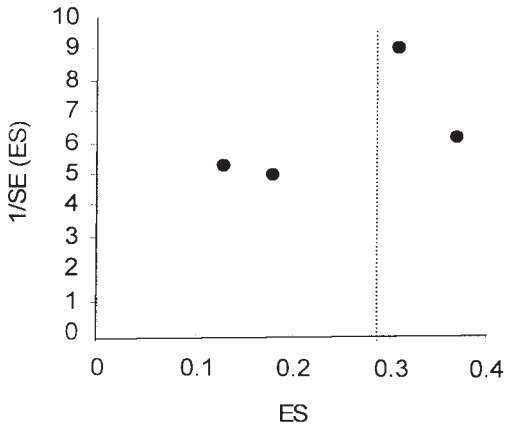

Figure 3. Funnel plot of randomized controlled trials comparing topical NSAID with placebo or vehicle. ES: effect size, SE: standard error. Test for heterogeneity: chi-square = 1.32, df = 3 (p = 0.72), I-square = 0%.

levels of the active drug in plasma (rather they increase local tissue concentrations), further studies need to be carried out to explore whether topical NSAID can be safely combined with oral regimens. Moreover, a number of studies report equivocal efficacy in oral and topical NSAID, even over a long duration[10,11].

The major limitation of our work is lack of an adequate number of studies. Second, the efficacy endpoint was measured at different times in different studies. We presume this would have diluted the results rather than overstating them, on the premise of efficacy decreasing over time. As our meta-analysis involves only a few types of preparations, extrapolating results to all NSAID may be erroneous. However, our results throw light on the persistence of effect when used over a longer term.

In conclusion, topical NSAID are effective for pain relief in knee osteoarthritis for a longer duration; however, this finding may not hold true for all the preparations.

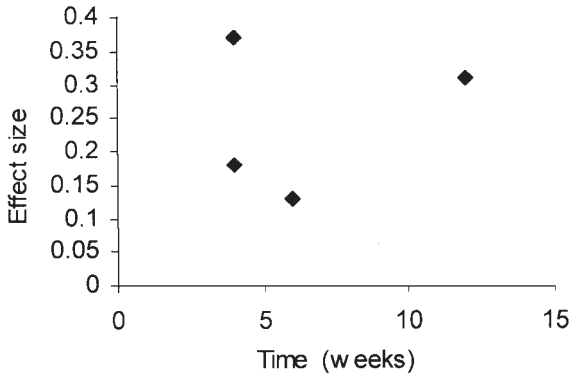

Figure 4. Time trend in effect size.

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