Trolamine Salicylate Cream in Osteoarthritis of the Knee

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• **Twenty-five patients with symptomatic osteoarthritis (OA) of the knee were treated topically for one week with either 10% trolamine salicylate cream or placebo cream in a randomized double-blind crossover study. No significant difference was found in subjective or objective measures of pain relief between the treatment and control groups. Eight patients preferred "active" test cream, six preferred placebo, and 11 had no preference. No side effects were reported. Topically applied 10% trolamine salicylate cream did not relieve the pain of OA of the knee any more than did placebo.**

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TOPICAL application of ointments for the relief of pain dates back to the Babylon-Assyria era, about 3000 to 5000 BC.[1]

Ten percent trolamine salicylate is the primary ingredient in a number of proprietary products used to treat common muscle and rheumatic pain. A double-blind comparison between oral aspirin and topical trolamine salicylate cream[2] showed that the latter is at least as effective as 650 mg of aspirin for the relief of arthritic pain and that it tends to provide relief more quickly, have fewer side effects, and be less likely to lead to discontinuation of treatment. However, in that study, patients did not serve as their own controls, measures of efficacy were unreliable or overly subjective, and inappropriate statistical tests were used to analyze results. Furthermore, small numbers of patients with different diagnoses were improperly compared.

The objective of the present study was to evaluate the effectiveness and safety of 10% trolamine salicylate cream in patients with chronic osteoarthritis (OA) of the knee.

Patients and Methods

Twenty-six patients with symptomatic OA of the knee who were undergoing treatment at the Veterans Administration Medical Center Rheumatology Clinic, Gainesville, Fla, participated in the study. All had a clinical diagnosis of OA of the knee that was not secondary to other types of arthritis or to acute trauma. All affected knees had limited motion, and all had pain that was aggravated by motion and was at least partially relieved by rest. The diagnosis was confirmed by x-ray films, taken within the preceding year, which showed at least grade 1 disease (see roentgenologic rating scale, Table 1). All patients had at least moderate pain on entry into the study.

Since the metabolic and clinical effects of salicylates are known to be dose dependent, patients were excluded from the study if they had taken any form of salicylate two days before the test period, and their conditions could not be evaluated if they took any salicylate preparation during the study period. However, patients currently receiving other forms of drug treatment for OA (ie, nonsteroidal anti-inflammatory agents) were eligible for inclusion because trolamine salicylate cream was considered adjunctive treatment in actual practice in these patients. If patients were currently using nonsteroidal anti-inflammatory drugs, they were included only if their condition had been stabilized on a stated dose of the drug for the preceding one-month period. No change in dosage or drug used was made during the study period. No other analgesic agents were taken two days before or during the test period, since those agents may affect a patient's response to pain and alter the range of motion. No patient had received an intra-articular injection of a corticosteroid within the preceding six weeks. No other form of treatment, such as external heat, exercise, or massage, was used during the study period.

Patients were randomly assigned to receive treatment with 10% trolamine salicylate cream (Myoflex, Adria Laboratories, lot E-585) or an identical, indistinguishable placebo (lot 584) consisting of the same cream base without the trolamine salicylate. Patients were instructed to apply half of a 7-g tube of cream to their most painful knee. This amount of test cream was selected because it was the maximum amount that could be applied liberally to all surfaces of the knee, yet could be rubbed until it was absorbed. All patients were instructed to apply the test cream four times daily—morning, noon, evening, and at bedtime—for seven days. Thirty 7-g tubes of test cream were dispensed to each patient. After a one-week control period, all patients used the alternative test cream for seven days. Patients were evaluated at four visits, before and after each one-week trial of each test cream. Compliance was assessed by the use of patient diaries and by the return of unused medication.

At each clinic visit, study participants were asked to assess weight-bearing pain in the chosen knee. The patients used a simple descriptive scale (SDS) and a numerical rating scale (NRS) (Table 2) to assess the pain. Some authors' believe the NRS improves discrimination over the SDS. Swelling was measured at a standard point over the patella with a flexible tape measure calibrated in millimeters. Joint tenderness was elicited by applying firm pressure over the joint margin, and responses were graded numerically (Table 2). Range of motion, both extension and flexion, was measured in degrees by use of a standard goniometer with the patient in the sitting position. Duration of morning stiffness, recorded in minutes, was based on the patients' estimates of length of time between getting up and appreciable improvement ("limbering up").

To further quantitate drug efficacy, at the start of therapy we gave each patient two standard pedometers to wear on the belt or pants. At each clinic visit, pedometer readings were recorded to assess serially the relative activity of the patient throughout the study. It was assumed that if patients had less pain, they would increase their activity, which would provide an objective measure of drug efficacy. Two pedometers were used in the event that one should fail. If both instruments appeared to have worked properly, the average of the two readings was recorded.

To quantitate the time between application of the cream and relief of pain, we asked all patients to chart each application of cream on a time line provided on a diary sheet and also to record the time after each application that some degree of

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Table 1.—Classification of Disease

Roentgenologic Rating Scale

0=Normal

1=Slight approximation of the ends of the articulating bones indicative of thinning of the articular cartilage, commonly referred to as "narrowing of the joint space"; some sharpening or pointing of the bony margins may be present

2=Moderate approximation of the ends of the articulating bones; small osteophytes, slight sclerosis of the subchondral bone, and unevenness and widening of the articular surfaces may be present

3=Marked approximation of the ends of the articulating bones and sclerosis of the subchondral bone; marginal lipping and osteophytes are seen; slight calcification of the cartilage may be seen and cysts may be present

4=Extreme sclerosis of subchondral bone and gross loss of the joint space; calcification of the cartilage may be seen and cysts may be present

ARA* Functional Class

Class 1: Complete—ability to carry on all usual duties without handicap

Class 2: Adequate for normal activities—adequate for normal activities despite handicap of discomfort or limited motion of ≥1 joints

Class 3: Limited—limited only to little or none of duties of usual occupation or self-care

Class 4: Incapacitated—largely or wholly bedridden or confined to wheelchair, little or no self-care

*ARA Indicates American Rheumatism Association.

Table 2.—Response Variable Rating Scales

C. Pain—Simple Descriptive Scale (SDS)
0=None
1=Mild
2=Moderate
3=Severe

D. Pain—Numerical Rating Scale (NRS)
Unbearable pain= 10
Less pain =≤9
No pain = 0

E. Joint Tenderness
0=Not tender
1=Tender
2=Tender and winced
3=Tender, winced, and withdrew

F. Patient Evaluation of Relief
0=None: no response
1=Poor: minimal response; unacceptable
2=Fair: definite response but could be better
3=Good: good response, but less than best possible response
4=Excellent: best possible response considering severity of disease

G. Examiner Evaluation of Relief
0=None: no response
1=Poor: minimal response; unacceptable
2=Fair: definite response but could be better
3=Good: good response, but less than best possible response
4=Excellent: best possible response considering severity of disease

pain relief was noted.

After each one-week trial, patients were asked to evaluate their response to therapy (Table 2). The examiner also rated each patient's response. Side effects were recorded. At the final clinic visit, patients were asked which treatment they preferred.

Efficacy of 10% trolamine salicylate cream was determined by comparing response-variable measurements for the active drug and placebo cream. All ordinal response variables—pain, joint tenderness, and patient and examiner evaluations of relief—were compared using the Wilcoxon matched pairs signed rank test with large sample Z test approximation.[4] All other continuous response variables—swelling, stiffness, pedometers, goniometers, and compliance—were analyzed using the one-tailed paired difference t test at an α level of .05, since the study compared the active agent with placebo for superiority. Last, in addition to using standard levels of statistical significance, we set a level of practical significance: a minimum of 20% change in final measurements could be considered clinically important.

Results

Of the 26 patients who started the study, only one patient did not complete it. In this patient, a large furuncle developed on the opposite knee unrelated to the application of test cream. Characteristics of the remaining 25 patients are summarized in Table 3. The stages of disease as assessed by the roentgenologic rating scale were as follows: stage 1, two patients; stage 2, nine patients; stage 3, eleven patients; and stage 4, three patients. Twelve patients were classified as American Rheumatism Association (ARA) functional class II (adequate for normal activities), and the remaining 13 were classified ARA class III (limited). Thirteen patients received concomitant nonsteroidal anti-inflammatory agents.

Table 3.—Patient Characteristics*

	Mean	SD	Range
Age, yr	62	8	36-72
Height, cm	175	7	160-192
Weight, kg	97	17	66-133
Duration of disease, yr	17	14	1-44

*n=25; sex: 24 men, 1 woman; race: 19 white, 6 black.

Each of the 25 patients received the active or placebo cream randomly. There were no significant statistical or practical levels of differences in any continuous response-variable measurement—range of motion (both extension and flexion), morning stiffness, and degree of activity as measured by pedometers—when 10% trolamine salicylate was compared with placebo (Table 4). The only exception was that the degree of swelling was significantly less after treatment with placebo (mean, -8 ± 12 mm) compared with active drug (1 ± 11 mm; $P=.009$). However, we do not believe this difference is clinically significant.

Similar results for ordinal response variables are summarized in Table 5. Joint tenderness, pain on both SDS and NRS, patient evaluation of relief, and examiner evaluation of relief showed no significant difference in response to trolamine salicylate cream compared with placebo. Eight patients (32%) preferred trolamine salicylate, six (24%) preferred placebo, and 11 (44%) had no preference. Only nine patients using trolamine salicylate and six patients using placebo recorded any relief in the diaries. Since this represents such a small sample, no valid conclusions could be drawn about the onset of relief.

Compliance with both treatments was exceptionally good. Mean patient compliance, defined as the number of used tubes returned divided by 28 possible applications, was 95.4% for trolamine salicylate and 89.9% for placebo. Patients were statistically more compliant with trolamine salic-

Table 4.—Continuous Response Variable Measurements

Variables	Mean Change After Treatment: 10% Trolamine Salicylate, Mean±SD	Mean Change After Treatment: Placebo, Mean±SD	P
Swelling, mm	1±11	−8±12	.009
Extension, degrees	1±8	3±7	.319
Flexion, degrees	0.0±12	−2±11	.532
Morning stiffness, min	2±11	−1±12.61	.402
Pedometers, km	12.2±9.1	14.5±13	.142

*Student's paired difference *t* test.

Table 5.—Ordinal Response Variable Measurements

Variables*	No. of Subjects Whose Response Favored: Trolamine Salicylate	Placebo	None	P†
Joint tenderness	8	10	7	NS
Pain, SDS	9	6	10	NS
Pain, NRS	14	9	2	NS
Patient evaluation of relief	10	8	7	NS
Examiner evaluation of relief	7	10	8	NS
Patient preference	8	6	11	NS

*SDS indicates simple descriptive scale; NRS, numerical rating scale.
†Wilcoxon matched pairs signed rank test with large sample *Z* test approximation (two-tailed test).

ylate than with placebo (t=−2.50; P=.02; Student's paired difference t test), which is not of clinical significance.

No side effects were reported from either treatment during the study. All patients accepted and tolerated the water-soluble cream base of both test creams without any complaints.

Comment

Osteoarthritis is a common disorder of the joints characterized by degeneration of the articular cartilage surfaces. Studies indicate that 90% of all persons aged 60 years or older have degenerative changes in the weight-bearing joints, but they are often asymptomatic.[5] At most, 25% of patients have moderate to severe disease in terms of pain and disability. The condition is age related, older patients having more extensive disease. Men and women are equally affected, as are the various races. Our population was similar to the general distribution of patients with OA in that the mean age was older than 60 years. Our subjects were predominantly men because selection was from a VA population. Female patients might respond differently to trolamine salicylate cream, but this is unlikely. These patients were chosen for their willingness to participate rather than randomly selected. Patients with irreversible cartilage damage might not be the most suitable subjects for testing an applied topical treatment. However, the difficulties are formidable in selecting a defined patient group with specified soft-tissue chronic pain disorders potentially more responsive to topical treatment.

Since trolamine salicylate cream is indicated by manufacturers for occasional and temporary relief of minor aches and pains of muscles and joints,[6] and because most standard studies of arthritis have been conducted over one- to two-week trial periods, this product was tested over a similar period. The results obtained seemed discouraging. It has been reported that approximately 35% of patients will respond to oral or injected placebos for a variety of conditions.[7] A study of arthritic patients found improvement in 41% of patients after placebo injections compared with 26% after placebo tablets.[8] Only 32% of our patients preferred the active treatment. In this study there were three possible outcomes; by chance alone, one third of the patients would be expected to pick either treatment outcome. Thus, it appears our results are consistent with those of previous reports for a placebo response and are no different than would be expected from random choice. Our concern is that if a product is promoted as being effective, it should be useful to a higher proportion of patients. Certainly, trolamine salicylate cannot replace any of the standard accepted forms of therapy for OA (eg, systemic salicylates, nonsteroidal anti-inflammatory agents).

One unique aspect of this study is the use of pedometers to attempt to quantitate degree of drug efficacy. This type of measurement has been reported previously,[9,10] but few uses of the pedometer have been made in clinical drug studies. Although no difference in motion activity was demonstrated during our study, this model may be useful for future studies.

Granted these limitations, our data indicated that there is no statistically significant evidence that 10% trolamine salicylate cream is superior to placebo in the response variables measured for these 25 patients with OA of the knee. Moreover, the clinical data show the total effect of 10% trolamine salicylate cream to be no better than that of placebo. Compliance was good in both groups, and no side effects were reported.

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