Treatment of Arthritis with Topical Capsaicin: A Double-Blind Trial

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ABSTRACT

The neuropeptide substance P has been implicated in the pathogenesis of inflammation and pain in arthritis. In this double-blind randomized study, 70 patients with osteoarthritis (OA) and 31 with rheumatoid arthritis (RA) received capsaicin (a substance P depletor) or placebo for four weeks. The patients were instructed to apply 0.025% capsaicin cream or its vehicle (placebo) to painful knees four times daily. Pain relief was assessed using visual analog scales for pain and relief, a categorical pain scale, and physicians' global evaluations. Most of the patients continued to receive concomitant arthritis medications. Significantly more relief of pain was reported by the capsaicin-treated patients than the placebo patients throughout the study; after four weeks of capsaicin treatment, RA and OA patients demonstrated mean reductions in pain of

0149-2918/91/$3.50

57% and 33%, respectively. These reductions in pain were statistically significant compared with those reported with placebo ($P = 0.003$ and $P = 0.033$, respectively). According to the global evaluations, 80% of the capsaicin-treated patients experienced a reduction in pain after two weeks of treatment. Transient burning was felt at the sites of drug application by 23 of the 52 capsaicin-treated patients; two patients withdrew from treatment because of this side effect. It is concluded that capsaicin cream is a safe and effective treatment for arthritis.

INTRODUCTION

Endogenous neuropeptides have recently been implicated in the pathogenesis and modulation of inflammation and pain in arthritis.[1–8] The neuropeptide most closely associated with the arthritis process is the undecapeptide substance P (SP),[6–10] which has been demonstrated to have diverse effects on immunologic and inflammatory reactions.[11–13] SP-containing afferent fibers richly innervate joints, and are related to the severity of joint inflammation in experimental adjuvant-induced arthritis in animals.[8,14] SP levels are elevated in inflamed joints of polyarthritic rats,[7] and a direct correlation has been demonstrated between the release of SP in specific joints and the extent of inflammation in those joints.[7,8] SP also stimulates synoviocytes to produce prostaglandins and collagenase,[7] which have been shown to produce pain and joint destruction.

The role of SP in the development and morbidity of arthritis has stimulated interest in the use of capsaicin, a potent depletor of SP,[15–20] in the treatment of arthritis.[8,11,21] Experimental feline antigen-induced arthritis has been demonstrated to be moderated by administration of intra-articular capsaicin.[21] Since local administration of capsaicin to the peripheral sensory endings in the skin results in the depletion of SP from the whole neuron both peripherally (including nerve endings supplying the joints) and centrally,[22] we postulated that capsaicin applied to the skin overlying affected joints might relieve the pain of arthritis and improve patients' functioning.

The present study was designed to evaluate the effects of 0.025% capsaicin cream on pain in patients with either osteoarthritis (OA) or rheumatoid arthritis (RA).

PATIENTS AND METHODS

Patients with primary OA (n = 70) or RA (n = 31) affecting one or both knee joints participated in this four-week, randomized, double-blind, placebo-controlled, multicenter study. All patients gave their written informed consent prior to participation, and the study protocol was approved by all of the institutional review boards of the participating institutions. All patients had to be at least 18 years of age and have moderate to very severe knee pain as evaluated by investigators using a categorical pain scale (0 = none, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe).

Patients with RA had to have at least three of the American College of Rheumatology (American Rheumatism Association) criteria[23] for classic definite or probable RA. Patients with OA were diagnosed based on physical examination and radiologic changes typical of OA, accompanied by negative laboratory test results for other causes of arthritis.

Table I. Physician's global evaluation of pain.

Completely gone (score 3)	Patient has experienced no knee pain from arthritis for three or more days
Much better (2)	Patient has experienced considerable improvement on study medication, but some continuing pain is still noted
Slightly better (1)	Patient has experienced some slight but noticeable decrease in pain, but considerable pain still remains
Same (0)	There has been essentially no change in the patient's condition since the day-1 visit
Worse (−1)	Pain is more intensive, more frequent, and/or more extensive than at day 1

Patients were allowed to take standard oral arthritis medications during the study provided that the doses were stabilized before study start and the medications continued without interruption during the study. Intra-articular corticosteroid injections to the knees were prohibited during three weeks before the study and to its end. Application of topical medications (including corticosteroids) to the knees was prohibited during seven days before the study and to its end. Patients undergoing physical therapy or using nondrug treatments such as braces were enrolled provided that the regimens remained unchanged during the study. No skin disorders were present in the knee selected for treatment.

Study Design

At the baseline visit, a medical history was taken and a physical examination was performed. Severity of knee pain was rated from none to very severe. In cases of bilateral disease, the most painful knee was selected for treatment. The patients were then randomly assigned to receive either 0.025% capsaicin* or placebo (vehicle cream).

Before the patients began using the study medication, they assessed their level of pain by using a 100-mm horizontal visual analog scale (VAS) labeled "no pain" and "worst pain imaginable" at the two terminals. At each follow-up visit, patients reassessed their pain using this scale and, in addition, marked a vertical VAS to quantify pain relief. One terminus of this vertical scale was labeled "no relief of pain" and the other was labeled "complete relief of pain." These visual scales have been used extensively in other studies and considerable data support both their reliability and validity.[24,25] At each follow-up visit (ie, at 1, 2, and 4 weeks), the investigator completed a physician's global evaluation of the patient's response to treatment (Table I) and evaluated knee pain according to the same categorical scale as at baseline. Patients were interviewed at each visit to assess side effects, compliance, and use of concomitant medications.

*Trademark: Zostrix® (GenDerm Corporation, Lincolnshire, Illinois).

During the four-week study, patients applied the assigned drug four times daily to the front, back, and both sides of the selected knee. The knee that had not been selected for treatment was left untreated. The patients were instructed to apply the study drug for the duration of the study even if the pain had resolved, and to wash their hands after drug application and to avoid contact with broken or irritated skin, eyes, or mucous membranes.

Statistical Analyses

Where appropriate, Fisher's Exact Test, the Cochran-Mantel-Haenszel test, and Student's *t* test were used on baseline variables to test the hypothesis of no treatment effect. Pain variables were analyzed by multivariate (repeated measures) analysis of variance. The SAS general linear models procedure was used to test the multivariate hypothesis of greater treatment effect with capsaicin treatment than with vehicle treatment. Time-treatment interactions within subjects were also tested. All pain variables were assessed for treatment effects at each visit by univariate analyses (Student's *t* tests). The Wilcoxon rank sum test was used on measures of categorical pain to test for treatment effects at each visit. Changes from baseline were used for analyses of categorical pain. Percentage changes from baseline were used for analyses of VAS pain. Actual values were used in the analyses of global evaluation and VAS relief.

RESULTS

The pretreatment characteristics of the 101 patients are shown in Table II. Most had experienced moderate to very severe knee pain, and almost all patients (93 of 101) were using concomitant arthritis medications at the baseline visit; these medications were continued during the study. Patients assigned to the capsaicin or placebo groups were similar at baseline, except that, among the OA patients, the VAS pain score was significantly higher in the capsaicin than the placebo group. Ninety-three patients, 29 with RA (14 capsaicin, 15 placebo) and 64 with OA (34 capsaicin, 30 placebo), completed the four-week study. Of the eight patients who did not complete the study (four capsaicin, four placebo), two capsaicin-treated patients dropped out because of adverse experiences, while the other noncompleters failed to comply with the study protocol.

The results of the physician's global evaluation are shown in Figure 1 and Table III. Knee pain improved significantly more in OA and RA patients treated with capsaicin than placebo. This difference was statistically significant in the RA group ($P = 0.027$) and the OA group ($P = 0.023$). Sixty-nine percent of the capsaicin-treated patients in both the OA and RA groups demonstrated improvement after only one week of treatment, and this improvement was maintained throughout the study. A high placebo response rate was noted in both the OA and RA groups at week 1 (48% of OA patients and 33% of RA patients improved) and throughout the study, with an additional increase at week 4 for the RA patients. A higher proportion of RA than OA patients treated with capsaicin showed improvement from week 2 through week 4.

Figure 2 and Table III show the mean percentage reductions in knee pain as

Table II. Pretreatment patient characteristics.

	Osteoarthritis		Rheumatoid Arthritis	
	Capsaicin (n = 36)	Placebo (n = 34)	Capsaicin (n = 16)	Placebo (n = 15)
Men/women	15/21	10/24	2/14	4/11
Mean age (years)	62	60	52	56
Range	31–74	35–82	20–79	28–77
Duration of arthritis (mean ± SEM years)	6.5 ± 0.8	7.4 ± 1.4	6.4 ± 1.3	9.7 ± 2.3
Severity of knee pain				
Categorical scale (% patients)				
None or mild	0	6	0	0
Moderate	47	53	75	80
Severe	36	41	25	20
Very severe	17	0	0	0
Visual analog scale for pain (mean ± SEM mm)	67 ± 3*	52 ± 4*	57 ± 4	55 ± 4
Use of concomitant arthritis medications (% patients)	83	97	94	100
NSAIDs	64	68	88	80
Analgesics	28	44	25	27
Corticosteroids	3	3	25	40
Gold	0	0	13	13
Immunosuppressive agents	0	0	6	13
Other	14	15	31	47

NSAID = nonsteroidal anti-inflammatory drug.
*$P < 0.05$ for treatment comparisons.

measured by the patient-rated VAS scale. Capsaicin was significantly superior to placebo during the treatment period for both OA ($P = 0.033$) and RA ($P = 0.003$) patients. Capsaicin was significantly superior to placebo after one week of treatment in RA patients and after two weeks in OA patients. This superiority was maintained at each study visit throughout the treatment period in RA patients, and was only slightly reduced in the OA patients at week 4. In the capsaicin-treated patients, pain reduction ranged from 21% at week 1 to 33% at week 4 in the OA group and from 31% to 57% in the RA group. Capsaicin-treated patients with RA had a greater reduction in knee pain than did OA patients. A moderate placebo effect was noted in both groups, which remained around 16% for OA patients and then increased to 32% in the RA group at week 4. The results of the VAS pain relief scales were similar to those of the VAS pain scale, but significant comparisons with placebo occurred only in the RA patients ($P = 0.016$).

After one week of treatment, the capsaicin-treated patients in the OA and RA groups reported a significantly greater reduction in categorical pain severity than did placebo patients (Tables III and IV). The superiority of capsaicin over placebo was maintained at each visit throughout the study in both patient groups. The capsaicin patients also reported a significantly greater overall pain reduction than did placebo patients in the RA ($P = 0.009$) and OA ($P = 0.020$) groups.

Burning at the site of application was reported by 44% of the capsaicin-treated patients and by one placebo patient. Most of these reactions were mild and

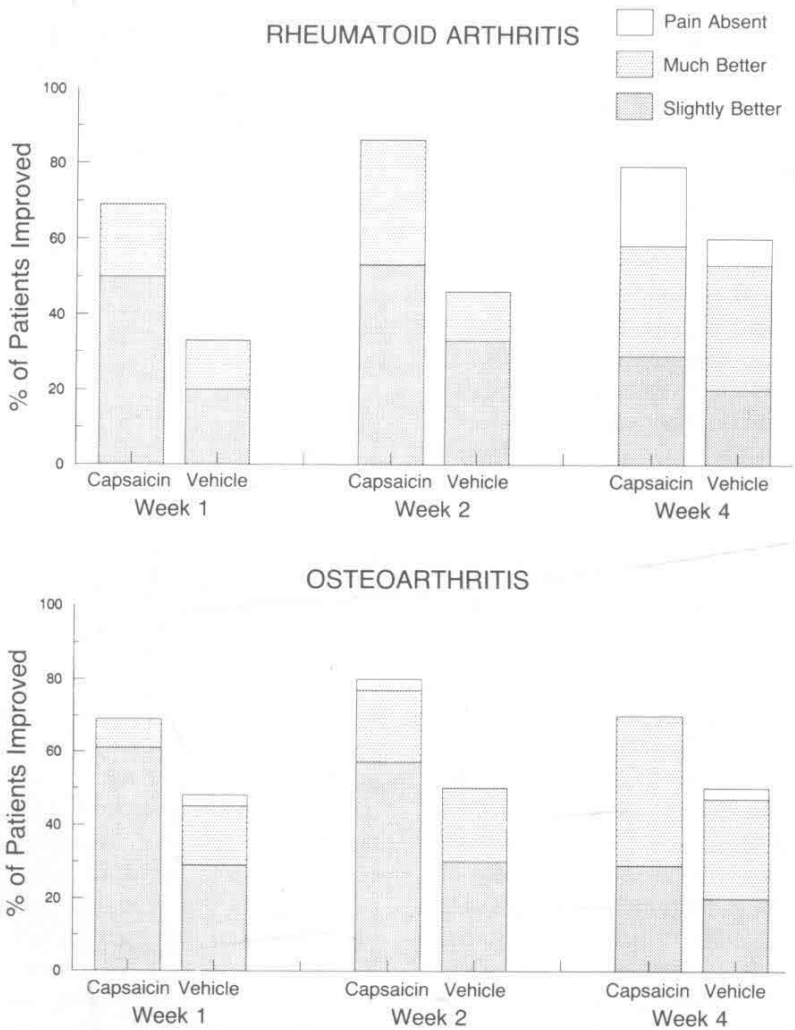

Figure 1. Physicians' global evaluations of patients with rheumatoid arthritis and osteoarthritis treated with capsaicin or placebo (vehicle) for four weeks.

transient. Two patients treated with capsaicin dropped out of the study after two weeks because of mild or moderate burning. Other reported adverse experiences were more numerous in the placebo-treated group, including migraine, cramps, back pain, and rhinitis, and were determined not to be associated with use of the study drug.

Since the significantly higher incidence of burning experienced by capsaicin-treated patients could compromise the blinding of the study, and thus favor a positive response to capsaicin, we performed a repeated-measures analysis (two-tailed) of the physician's global evaluation, comparing the response of capsaicin patients with burning versus those without burning. The analysis demonstrated that there was no difference in drug response between these two groups ($P = 0.65$). In fact, patients with burning responded slightly more poorly than did those without burning. Thus burning ap-

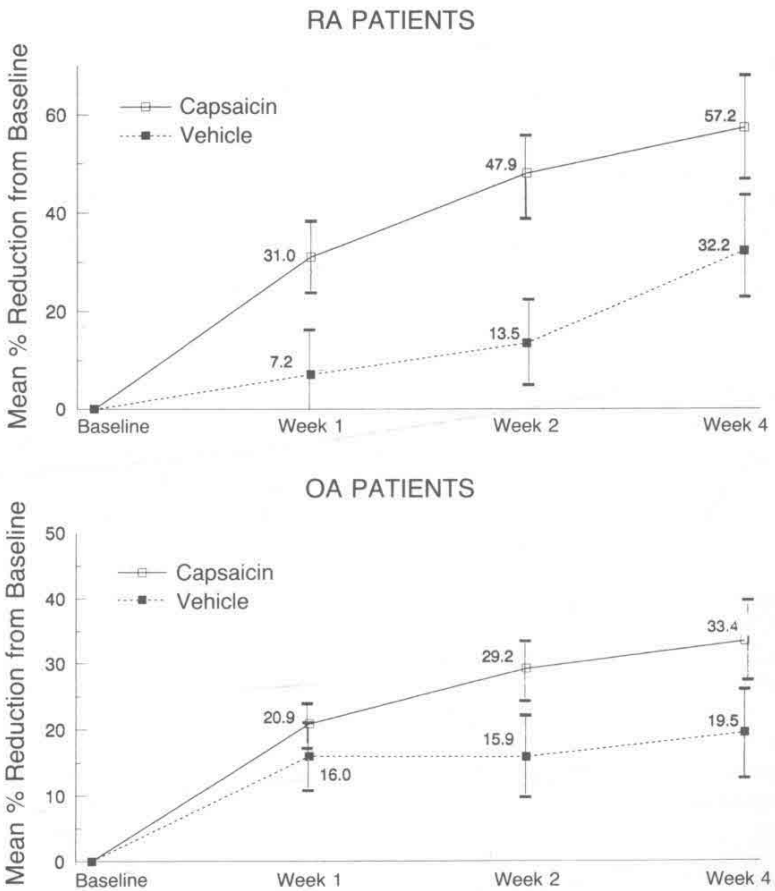

Figure 2. Percentage reductions in pain in patients with rheumatoid arthritis (RA) and osteoarthritis (OA) treated with capsaicin or placebo (vehicle) for four weeks.

Table III. Mean (±SEM) global evaluation scores and reductions from baseline in visual analog scale (VAS) for pain and categorical scale pain scores in patients with osteoarthritis and rheumatoid arthritis treated with capsaicin or placebo for four weeks.

	Baseline	Week 1	Week 2	Week 4	*P*
Osteoarthritis					
Global evaluation					
Capsaicin	—	0.78±0.10	1.00±0.14	1.09±0.15	0.023
Placebo	—	0.65±0.17	0.60±0.17	0.70±0.20	
P		0.088	0.030	0.051	
VAS pain scores (% reduction from baseline)					
Capsaicin	66.6±2.9	20.9±3.7*	29.2±4.6*	33.4±5.0*	0.033
Placebo	50.5±4.4	16.0±4.7*	15.9±5.8*	19.5±8.0*	
P	0.004	0.106	0.026	0.061	
Categorical scores (reduction from baseline)					
Capsaicin	2.69±0.12	0.58±0.13*	0.77±0.15*	0.88±0.14	0.020
Placebo	2.32±0.13	0.39±0.12*	0.37±0.14*	0.53±0.18*	
P	0.091	0.047	0.017	0.053	
Rheumatoid Arthritis					
Global evaluation					
Capsaicin	—	0.88±0.18	1.20±0.17	1.43±0.33	0.027
Placebo	—	0.40±0.21	0.60±0.19	0.07±0.27	
P		0.048	0.006	0.137	
VAS pain scores (% reduction from baseline)					
Capsaicin	56.7±3.9	31.0±6.8*	47.9±7.4*	57.2±9.7*	0.003
Placebo	55.0±4.0	7.2±8.3	13.5±7.2*	32.2±9.6*	
P	0.765	0.034	0.001	0.019	
Categorical scores (reduction from baseline)					
Capsaicin	2.25±0.11	0.50±0.16*	0.73±0.18*	1.00±0.26*	0.009
Placebo	2.20±0.11	0.13±0.13	0.13±0.09	0.53±0.17*	
P	0.743	0.040	0.003	0.042	

*$P<0.05$ vs baseline.

Table IV. Pain severity (categorical scale) in patients with osteoarthritis and rheumatoid arthritis treated with capsaicin (C) or placebo (P) for four weeks.

	Baseline		Week 1		Week 2		Week 4	
Pain Severity	C	P	C	P	C	P	C	P
Osteoarthritis								
	(n = 36)	(34)	(35)	(30)	(36)	(31)	(34)	(30)
	%	%	%	%	%	%	%	%
None	0	3	0	3	3	3	0	7
Slight	0	3	23	13	25	26	41	37
Moderate	47	53	49	67	50	48	41	33
Severe	33	41	29	13	19	23	15	17
Very severe	19	0	0	3	3	0	3	7
*P**			0.185		0.035		0.060	
Rheumatoid Arthritis								
	(n = 16)	(15)	(16)	(15)	(15)	(15)	(14)	(15)
	%	%	%	%	%	%	%	%
None	0	0	0	0	0	0	21	7
Slight	0	0	31	13	47	7	36	27
Moderate	75	80	63	67	53	80	36	60
Severe	25	20	6	20	0	13	7	7
Very severe	0	0	0	0	0	0	0	0
*P**			0.055		0.004		0.093	

*Wilcoxon rank sum test.

peared to play no role in determining treatment outcome.

DISCUSSION

Clinical associations between neural stimuli and RA have long been known,[26,27] but only recently has the contribution of neurogenic factors been recognized as a key to understanding the pathophysiology of arthritis. RA is considered a symmetric disease, but focal neurologic lesions usually alter its bilateral symmetry.[26,27] For example, patients who sustain paralyzing lesions of the central or peripheral nervous system rarely manifest inflammatory synovitis in the paretic limb if RA subsequently develops.[27] Similarly, bilaterally symmetric experimental adjuvant-induced arthritis in rats can be rendered unilateral by section of the sciatic nerve prior to adjuvant administration.[4]

These findings have suggested that neuromodulators contribute to the development and maintenance of the chronic inflammatory state observed in arthritic disease.[1-8] Of the neuropeptides probably involved in arthritic disease, SP, the neuropeptide principally responsible for transmission of pain in afferent nerve

fibers, has been most directly implicated in the exacerbation of the arthritic state.[11–14] These data suggest that an agent capable of antagonizing SP might be effective in the treatment of arthritis.

Capsaicin (trans-8-methyl-n-vanillyl-6-nonenamide) is an alkaloid derived from seeds and membranes of plants of the Nightshade family. Capsaicin has been shown[17,21] to enhance SP release and inhibit or prevent its reaccumulation from cell bodies and nerve terminals in the central and peripheral nervous systems. Local application of capsaicin results in depletion of SP from the whole neuron.[21] Initially, axonal transport is blocked and, subsequently, SP synthesis is reduced[17,21] The effect may be similar to cutting or ligating a nerve, which also depletes the SP content of the neuron. Capsaicin is remarkably specific for type C primary afferent neurons. Capsaicin also has been shown[28] to reduce voltage-gated calcium currents in type C neurons, and could thus elevate thresholds for the release of SP and other neurotransmitters.

Over the last five years, topical capsaicin has been shown to be a useful treatment for the relief of a variety of peripheral pain syndromes, including postherpetic neuralgia,[29–32] postmastectomy pain,[33] amputation-stump pain,[34] and diabetic neuropathy.[35] The results of the present study demonstrate that 0.025% capsaicin cream appears to be an effective analgesic for treating arthritis pain with minimal side effects. Significant pain relief was experienced by both OA and RA patients after just one week of treatment, and this relief was maintained throughout the four-week course of the study.

Although most patients exhibited a clinically significant reduction in pain during capsaicin administration, complete relief of pain was rarely observed. After four weeks of treatment, OA patients reported a 33% mean decrease in pain and RA patients a 57% mean decrease. The VAS pain relief scales showed similar trends; however, this scale is not as accurate a measure of pain because the patient is required to compare the pain present at each study visit with the pain present at baseline (weeks earlier). Pain is not only a very common symptom in arthritis, it is also an important contributor to the morbidity of patients with arthritis.[4] A strong correlation has been demonstrated[36] between the degree of pain experienced by RA patients and their physical and psychological disability.

Mild to moderate burning at the site of capsaicin application was reported in nearly 44% of the arthritis patients treated with topical capsaicin. It was the only side effect directly attributed to capsaicin. This burning was usually noted on initial applications of capsaicin, and diminished or vanished with repeated applications. It has been suggested[28] that the burning sensation experienced with initial applications of capsaicin is due to an augmented release of SP from sensory nerve endings into the skin. Topically applied capsaicin appears to have a very short duration of action,[21] and it may be necessary to apply the drug at least three or four times daily to produce or maintain pain relief. Less frequent application prevents the total depletion and inhibition of synthesis and transport of SP, decreasing clinical efficacy while increasing local discomfort.

It should be noted that most of the arthritis patients treated in this study were taking concomitant antiarthritic medications before and during the study.

These medications ranged from aspirin and nonsteroidal anti-inflammatory drugs to prednisone, methotrexate, and penicillamine. The pain reduction that occurred in patients on concomitant medications indicates that capsaicin can be useful in enhancing pain control when added to standard arthritis therapeutic regimens.

Older patients, the principal sufferers from arthritis, generally have other diseases and frequently require one or more systemic medications unrelated to their arthritis management. Coupled with the potent systemic analgesic, anti-inflammatory, and immunosuppressant agents required for their arthritis, the possibility of serious drug interactions or undesirable side effects is substantial in these patients. Consequently, a topical treatment, devoid of the potential of drug interactions or serious systemic side effects, may be of benefit for these older patients.

The present study was designed principally to evaluate the effects of topical capsaicin in relieving arthritis pain. No attempt was made to assess the possible effects of capsaicin on joint inflammation. Since SP has known inflammatory effects in the joint and can activate synovial cells to produce other mediators of joint inflammation and destruction, further studies to ascertain capsaicin's effects on joint inflammation appear warranted.

In summary, capsaicin cream was shown to significantly reduce pain in OA and RA patients without the risk of the systemic side effects or adverse drug interactions associated with systemic therapies. Topical capsaicin appears valuable as an adjuvant to current arthritis treatments in order to enhance pain control, and appears to be a useful therapeutic option in the management of arthritis pain.

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