

# *Arnica montana* Gel in Osteoarthritis of the Knee: An Open, Multicenter Clinical Trial

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## ABSTRACT

This open multicenter trial investigated the safety and efficacy of an *Arnica montana* fresh plant gel, applied twice daily, in 26 men and 53 women with mild to moderate osteoarthritis (OA) of the knee. After 3 and 6 weeks, significant decreases in median total scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) were evident in the intention-to-treat and per-protocol populations (both  $P < .0001$ ). Scores on the pain, stiffness, and function subscales also showed significant reductions at these timepoints. The overall local adverse-event rate of 7.6% included only one allergic reaction. Sixty-nine patients (87%) rated the tolerability of the gel as "good" or "fairly good," and 76% would use it again. Topical application of *Arnica montana* gel for 6 weeks was a safe, well-tolerated, and effective treatment of mild to moderate OA of the knee.

**Keywords:** *Arnica*; clinical trial; osteoarthritis; WOMAC

## INTRODUCTION

Osteoarthritis (OA) is one of the most common diseases affecting humans and a frequent cause of disability. By age 40, discrete malformations of the weight-bearing joints are evident, and by age 75, OA is virtually universal.<sup>1</sup> Women are generally more affected than

men by symptomatic OA of the hand, hip, and knee, especially after age 50.<sup>2</sup> The etiology is not known, but presumably mechanical, biologic, and biochemical interactions contribute to the progressive pathologic change in the bones and cartilages of a joint.

For the treatment of OA, oral nonsteroidal anti-inflammatory drugs (NSAIDs) are generally prescribed, but a high incidence of adverse effects, particularly involving the gastrointestinal tract, has raised questions about their use. Each year in the United States, adverse effects of oral NSAIDs cause approximately 165,000 hospitalizations and 16,500 deaths.<sup>3</sup> The economic costs of these side effects in Germany have been estimated at a quarter of a billion deutschmarks annually.<sup>4</sup> Therefore, alternatives to oral therapy are sought. Medicinal plants, whose traditional use in rheumatic conditions has been proved safe and effective, may be one option.

*Arnica montana* has been known since the 16th century as an acute topical treatment of sprains, bruises, painful swellings, and wounds.<sup>5</sup> In addition, arnica flowers have been used externally for inflammation caused by insect bites, gingivitis, and aphthous ulcers, as well as for the symptomatic relief of rheumatic complaints.<sup>6</sup>

The active ingredients of arnica flowers are the sesquiterpene lactones—helenalin and 11- $\alpha$ , 13-dihydrohelenalin and their esters—as well as acetic, isobutyric, methacrylic, and other carboxylic acids. Their main mode of action is by inhibiting the activation of transcription factor NF- $\kappa$ B, a central mediator in the inflammatory process that controls the transcription of various cytokine genes including interleukin-1, -2, -6, and -8 and tumor necrosis factor- $\alpha$ .<sup>7</sup> The traditionally known anti-inflammatory and antiphlogistic activity of *Arnica montana* can be explained by this inhibition at a very early stage of inflammation. In vitro studies have shown that even low concentrations effectively inhibit NF- $\kappa$ B.

Although arnica has a long history in folk medicine and is widely used, efficacy in a rheumatic disease has never been clinically studied. To date, only three clinical studies have been conducted with arnica gel: on the recovery of aching muscles after excessive exercise,<sup>8</sup> in patients with chronic venous insufficiency, and in patients with primary varicosis.<sup>9</sup> Arnica is also a known contact allergen,<sup>10</sup> but epidemiologic data exist only in patients with contact dermatitis.<sup>11</sup>

The present study in patients with OA of the knee is the first to test the safety and efficacy of a preparation of *Arnica montana* in a rheumatic condition and to provide data on the allergenic potential of arnica in a nonpredisposed population.

## PATIENTS AND METHODS

### Study Design

The purpose of this 6-week open multicenter trial in patients with OA of the knee was to investigate the safety and efficacy of a fresh plant preparation from *Arnica montana* flowerheads. Investigational centers were one rheumatology and rehabilitation clinic, one general hospital, and three rheumatology and six general practices in Switzerland.

The trial was approved by Swiss health authorities in July 2000 and was carried out in accordance with the European guidelines of good clinical practice and the ethical obligations of the Declaration of Helsinki.

Patients had to return to their physician for visit 2 after 21 days and for visit 3 (final) after 42 days. Adherence limits to this schedule were 5 days before and after the exact date.

## Patients

Between August 2000 and May 2001, 79 patients were enrolled. Eligibility required a diagnosis of mild to moderate arthrosis/periarthropathy of at least one knee, age between 19 and 79 years, and written informed consent.

Exclusion criteria were an allergy to asteracea, skin lesions on the knees, concurrent therapy with other antirheumatics topically applied to the knees, concurrent oral antirheumatic therapy beginning within 2 weeks prior to study inclusion, concurrent local or systemic treatment with corticosteroids or such therapy during the prior 2 weeks, concurrent infiltration therapy or local physical treatment in the study area, inflammatory bone disease, severe liver or kidney disease, malignancy, infectious diseases, suppression of the immune system, severe metabolic syndrome, and pregnancy or nursing.

## Treatment

Patients applied a thin layer of *Arnica montana* gel to the affected knee(s) in the morning and in the evening. The gel was supplied in 100-g tubes that contained 50 g of an arnica fresh plant tincture (drug extract ratio 1:20, extracting medium 50% EHOH m/m). Patients received two tubes at each visit for a treatment duration of 3 weeks.

## Measurements

Safety, the study's primary outcome variable, was determined by the occurrence of seven local symptoms (itching, burning sensation, reddening of skin, urticaria, papules, blisters, others) and any other adverse events at visits 2 and 3 and by patients' evaluation of tolerability on a four-point scale (good, fairly good, quite poor, poor).

Efficacy was assessed with the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (Likert scale, Swiss-German version 3.1).<sup>12</sup> This is a validated, self-administered, 24-item questionnaire for patients with OA of the hip or knee. Five questions concern pain; 2, joint stiffness; and 17, restrictions of every-day activities. A secondary endpoint was the aggregate WOMAC score and subscores for pain, stiffness, and function at visits 2 and 3 compared with baseline values.

In addition, patients and investigators evaluated global efficacy at the end of treatment (secondary endpoint). Investigators used a five-point scale, ranging from "very good" to "no effect." Patients used a 100-mm horizontal visual analogue scale (VAS) that ranged from "not effective at all" at the extreme left to "very effective" at the extreme right. At the final visit, patients indicated acceptability of treatment by noting whether they would take the medication again. Patients recorded the onset of treatment effect on a label on the first tube.

The investigator assessed compliance at each visit. Failure to apply the gel more than three times per week in any treatment period constituted poor compliance; failure on fewer than three occasions indicated good compliance.

## Statistical Analysis and Sample Size

All variables were descriptively analyzed with mean, median, and standard deviations. Data for the WOMAC score were not normally distributed (Shapiro-Wilk *W* test), and the Wilcoxon signed rank test (two-sided,  $\alpha=.05$ ) was used to compare the difference in the WOMAC score and subscale scores between visit 1 and visit 2 or 3.

For registration purposes, Swiss authorities demand a sample size of at least 50 for the safety assessment. With an estimated dropout rate of 35%, 80 patients had to be recruited to obtain 50 eligible cases. The intention-to-treat (ITT) population was defined as all patients who used the study preparation at least once. The per-protocol (PP) population included all patients who completed the study without protocol violations. Statistical analysis was performed by means of version 1.62 of "Analyse-it!" software (Analyse-it Software Ltd., Leeds, UK).

## RESULTS

### Patients

Eleven centers contributed 79 patients to the ITT population, whose baseline demographic characteristics are shown in Table 1.

Table 1. Baseline Demographic Characteristics

Total number of patients (ITT)	79
Patients with at least one major protocol violation	25
PP population	54
Sex, M/F	26/53
Age, y*	63.3±9.93
BMI*	28.0±4.76
Arthrosis, no. (%)	
Left knee	47 (60)
Right knee	53 (67)
Both knees	21 (27)
Patients with concomitant NSAID therapy at enrollment, no. (%)	24 (30)

\*Mean ± SD.

The PP population comprised 54 patients, as 25 participants had to be excluded because of at least one protocol violation (6 patients committed two or more violations). Reasons for exclusion were failure to adhere to the visit schedule (8 cases), use of forbidden medication (6), prohibited physical therapy (1 case), a not explicitly prohibited "medical training therapy" possibly contributing to a false-positive result (1), failure to complete the WOMAC questionnaire sufficiently for analysis of

results (10), and premature discontinuation (7). The reasons for premature discontinuation were adverse reactions not likely to be related to the study or lack of therapeutic response (3 cases each) and a request to stop treatment for personal reasons (1 patient).

Physicians assessed compliance as "good" in 94% of patients at visit 2 and in 99% at visit 3.

## Safety

Six patients experienced unexpected events which were possibly related to the study medication. All were mild or moderate local reactions at the treatment site and consisted of an allergy with red spots and itching (1 patient), a localized rash for 2 days (1), an episode of pruritus lasting for 1 hour (1), petechiae that disappeared after therapy with corticosteroid ointment (1), and dry skin, which may have been related to the galenic form of the *Arnica montana* gel (2) (Table 2).

Systemic adverse events of mild to moderate severity occurred in 14 patients and were judged unlikely to be related to the study preparation. The only serious adverse event was surgery for an inguinal hernia, and this was also unlikely to be related to the therapy.

Tolerability ratings of "good" or "fairly good" were provided by 73 patients at visit 2 and by 70 of 72 patients at visit 3. Only 2 patients at visit 3 were dissatisfied and graded the gel as "quite poor." Overall tolerability was "good" or "fairly good" for 87% of patients, and 76% would use the gel again.

Table 2. Local Adverse Reactions

Symptom	Intensity*	Symptoms Occurred After	Duration	Frequency	Counter-measure	Symptom Persisted After Treatment Ended?
Red spots, itching, allergy	Moderate	>21 d	12 d	Constant	DC treatment after 1 d of symptoms	Yes
Local rash	Mild	19 d	2 d	Temporary	None	No
Pruritus	Moderate	1 d	1 h	Temporary	None	No
Petechiae	Mild	>21 d	Unknown	Constant	Local corticoid ointment applied	No
Dry skin	Mild	1 d	Some hours	Temporary	None	No
Dry skin	Mild	1 d	During treatment	Constant	None	No

DC = discontinue.

\*Could be assessed as mild, moderate, or severe.

## Efficacy

Median values of the total WOMAC score were highly significantly decreased at visits 2 and 3, compared with visit 1, in both ITT and PP patients (Table 3). The reduction was slightly greater in the PP population, which may be subject to bias, but the result was confirmed in the ITT population (Figure). On subgroup analysis, the decrease in total WOMAC score in the 30% of patients taking concomitant analgesics did not reach statistical significance. This finding may reflect the greater severity of their disease, as indicated by a higher total WOMAC score at baseline (median: 40).

Median values for the WOMAC subscales for pain, stiffness, and function were also significantly decreased at visits 2 and 3 from baseline values in both populations (see Table 3). The maximum reduction in total and subscale scores occurred after 3 weeks at visit 2 and continued over the ensuing 3 weeks.

The positive findings of the WOMAC total and subscale scores were reflected in the global assessments by investigators and patients. On the ITT analysis, the investigators rated the efficacy of the treatment at visit 3 as "very good" or "good" in 52% of patients (41/79) and having "no effect" in only 11% (9/79). The PP analysis of 54 patients resulted in an efficacy assessment of "very good" for 9 patients and "good" for 25 patients (total: 63%); in 7 patients (13%), the gel had no effect.

On the patients' subjective assessment of efficacy (100-mm VAS), 57% of the ITT population (45/79) and 72% of the PP population (39/54) chose a rating higher than 50 mm. The corresponding median values were 70.5 mm and 74 mm.

Time to onset of effect averaged 5.9 days in the ITT and PP populations. Most patients felt an effect within 2 weeks; only six ITT patients and three PP patients recorded a later onset.

The safety and efficacy results are reflected in the patients' acceptance of treatment. Of all patients, 76% (60/79) would use the *Arnica montana* gel again; only 14% (11/79) would not.

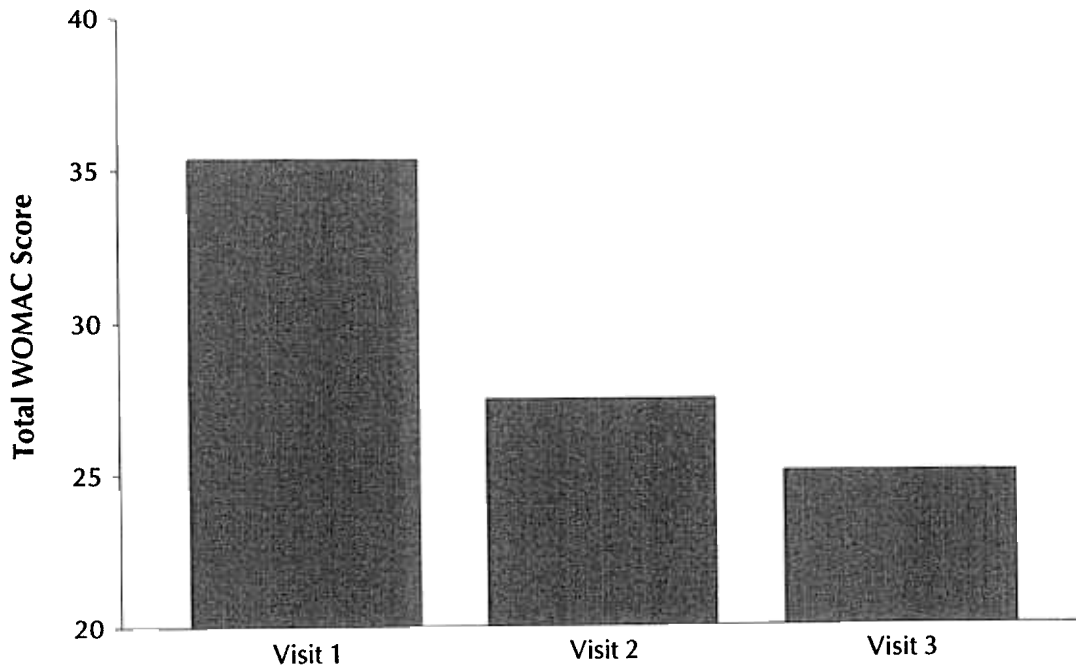
**Table 3. Median Values of WOMAC Total and Subscale Scores at Visit 1 (Day 0), Visit 2 (Day 21), and Visit 3 (Day 42)**

	Intention-to-Treat Population					Per-Protocol Population				
	No.	Total WOMAC	Pain	Subscale Stiffness	Function	No.	Total WOMAC	Pain	Subscale Stiffness	Function
Visit 1	78	36.0	7.0	3.0	26.0	54	35.5	7.0	3.0	26.0
Visit 2	72	28.6	6.0	3.0	21.0	54	27.5	6.0	3.0	21.0
Visit 3	69	28.0	5.0	2.0	21.0	54	25.0	4.5	2.0	18.5
Difference in medians between visits 1 and 2		6.0	1.5	0.5	3.5		7.4	1.9	1.0	4.5
95% CI		3.5–8.2	0.9–2.0	0.0–1.0	2.0–5.5		4.5–10.0	1.0–2.5	0.5–1.0	2.5–6.5
P value*		<.0001	.0003	.0209	.0002		.0001	.0003	.0018	.0002
Difference in medians between visits 1 and 3		8.5	2.0	1.0	6.0		10.5	2.5	1.0	7.0
95% CI		5.1–11.5	1.5–3.0	0.5–1.0	3.5–8.0		7.0–13.5	.5–3.5	0.5–1.5	4.3–9.5
P value*		<.0001	<.0001	.0006	<.0001		<.0001	<.0001	<.0001	<.0001

CI = confidence interval.

\*Two-sided Wilcoxon signed rank test for comparison against visit 1

Median values of total WOMAC score at visit 1 (day 0), visit 2 (day 21), and visit 3 (day 42) in the per-protocol population (n = 54).



\*Significantly different from visit 1,  $P < .0001$

## DISCUSSION

Topical antirheumatic therapy is indicated when the pain can be localized to only one or a few areas. Mild to moderate OA of the knee satisfies this requirement, is highly prevalent, and can be assessed with a validated instrument (WOMAC Index).

In the assessment of safety, 6 of the 79 patients experienced local reactions attributed to the *Arnica montana* gel, giving a local symptom rate of 7.6%. One meta-analysis<sup>13</sup> of 12 trials of topical antirheumatic therapy for chronic and painful conditions revealed a local adverse-effect rate of 5.9%. A review<sup>14</sup> of 17 trials with topical NSAIDs reported a rate of 9%, mostly rash or pruritus, or both, at the application site. The mean duration of treatment in these studies was only about 16 days, however. The current study of *Arnica montana* gel focused on local adverse effects by asking patients detailed questions about skin reactions. Moreover, the treatment exposure was greater, the number of patients larger, and the treatment duration longer than the average in either review. In our study, 1 patient (1.3%) reported an allergic reaction to the gel. Similarly, in a recent study of 443 consecutive patients with suspected delayed-type hypersensitivity reactions,<sup>15</sup> 5 patients (1.1%) reacted to an arnica patch test, perhaps reflecting the widespread use of arnica in soaps, lotions, ointments, and shampoos.



Efficacy was evaluated by the WOMAC Index, a validated instrument for OA of the knee that has been proposed for use in several OA guidelines.<sup>16,17</sup> To date, only one controlled trial of a topical treatment that used the WOMAC score as an efficacy parameter has been published.<sup>18</sup> Sixty-eight evaluable patients with knee OA received topical diclofenac (2% in a lecithin organogel) or placebo (gel only) for 2 weeks. No concomitant analgesic therapy was administered. The total WOMAC score was reduced by  $12.63 \pm 13.26$  in the active group and by  $3.30 \pm 17.11$  in the placebo group ( $P < .05$ ). Scores on the pain and physical function subscales were also significantly better with active treatment. That study used the WOMAC-VAS version, our study, the WOMAC-Likert version; however, the results obtained with both methods are comparable. In the present study, the decreases in total WOMAC score with the gel exceeded those with placebo and approached the reductions achieved with diclofenac. Use of concomitant analgesic therapy by some of our patients may have moderated the changes reflected in the WOMAC score.

The benign adverse-event profile and the highly positive tolerability ratings by patients in this study support the conclusion that topical *Arnica montana* gel is a safe and well-tolerated treatment for mild to moderate OA of the knee over a 6-week period. Moreover, the allergenic potential of the preparation was not as high as generally assumed. *Arnica montana* gel represents a safe and effective therapeutic option for patients with OA of the knee.

The study is the first to test arnica in a rheumatic condition and provides a scientific rationale for its widespread use in folk medicine.

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