

A HOMEOPATHIC OINTMENT PREPARATION COMPARED WITH 1% DICLOFENAC GEL FOR ACUTE SYMPTOMATIC TREATMENT OF TENDINOPATHY

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Context: The incidence of tendon injuries and tendinopathy has risen substantially in the past decades.

Objective: To assess the noninferiority of therapy based on the homeopathic preparation Traumeel S ointment (Heel GmbH, Baden-Baden, Germany) compared with treatment based on diclofenac 1% gel in patients with tendinopathies of varying etiology.

Design: Nonrandomized, observational study.

Setting: Ninety-five homeopathy and conventional medical practices in Germany.

Patients: Three hundred fifty-seven patients aged 18 to 93 years with tendinopathy of varying etiology based on excessive tendon load rather than inflammation.

Interventions: Traumeel S ointment or diclofenac 1% gel for a maximum of 28 days.

Main Outcome Measures: Efficacy was measured on a four-degree scale on pain-related variables, on variables related to motility, and on overall treatment outcome. Tolerability was monitored as adverse events. Compliance was assessed by practitioner and patient on a four-degree scale.

Results: The patients groups were comparable at baseline. The changes in summary score of all pain-related variables were -5.3 ± 2.7 (all values means \pm SD) in the Traumeel group and -5.0 ± 2.7 in the control group. Changes for all motility-related variables were -4.2 ± 3.8 with Traumeel and -3.7 ± 3.4 with control therapy. The summary scores for all clinical variables were reduced by -9.5 ± 5.7 with Traumeel therapy and by -8.7 ± 5.4 with diclofenac-based treatment. Homeopathic therapy was noninferior to diclofenac therapy on all variables. For motility-related variables, there was a trend toward superiority of Traumeel. Treatments were well tolerated with no treatment-related adverse events.

Conclusions: The results suggest that Traumeel ointment is an effective alternative to nonsteroidal antiinflammatory drugs therapy for the acute symptomatic treatment of patients with tendinopathy.

Key words: Homeopathy, motility, noninferiority, NSAID, observational study

(*Explore* 2005; 1:446–452. © Elsevier Inc. 2005)

INTRODUCTION

The incidence of tendon injuries and tendinopathy has risen substantially in the past decades, mostly as a consequence of greater participation in recreational and competitive sports.¹ However, although tendinopathy is very common among athletes such as runners and those playing racquet sports, football, and volleyball, it is also frequently encountered among patients with no record of athletic activities.² The terms *tendinitis* and *tendinopathy* are frequently used in an overlapping fashion, but, strictly seen, *tendinitis* indicates only those cases of inflammatory etiology and *tendinopathy* covers a wider spectrum of tenalgias.

The current communication uses the term *tendinopathy* to cover the variety of etiologies seen. Although tendons frequently respond to repetitive overload by inflammation of their sheath,³ excessive loading during vigorous physical training is regarded as the main pathological stimulus for degeneration. Thus, medical treatment has two main objectives: to provide symptomatic relief and to moderate the inflammatory response.⁴ It is also necessary to reduce load and activity at the injured site and to correct etiological factors (training errors, limb misalignments, and muscle weaknesses) to allow for active repair of fatigue damage.

In many cases, the physician needs recourse to pharmacological medications to achieve effective symptomatic relief. Drugs used include low-dose heparin, hyaluronidase, and aprotinin,^{5,6} and, although controversial, injections of corticosteroids are also used.⁷ Nonsteroidal antiinflammatory drugs (NSAIDs) such as diclofenac sodium (Cataflam, Voltaren) are recommended and effective for the treatment of the symptoms of osteoarthritis⁸⁻¹⁰ and are commonly used to ameliorate symptoms in other musculoskeletal conditions. However, NSAIDs, at least when administered orally, carry a certain risk for significant systemic adverse effects on the gastrointestinal tract and hepatic and renal systems.¹¹⁻¹⁴ Other pharmacological approaches are similarly associated with worries about adverse effects. Heparin may in-

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Conflict of interest: M. Oberbaum has received speaking honoraria from Heel GmbH for work unrelated to that in the current presentation. The other authors have no conflicts of interest to declare.

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Table 1. Active Ingredients of Traumeel S Ointment

Source of Extract	Amount in Each Gram Traumeel Ointment (mg)
<i>Arnica montana</i> D3	15
<i>Calendula officinalis</i>	4.5
<i>Achillea millefolium</i>	0.9
<i>Chamomilla recutita</i>	1.5
<i>Symphytum officinale</i> D4	1.0
<i>Atropa belladonna</i> D1	0.5
<i>Aconitum napellus</i> D1	0.5
<i>Bellis perennis</i>	1.0
<i>Hypericum perforatum</i>	0.9
<i>Echinacea angustifolia</i>	1.5
<i>Echinacea purpurea</i>	1.5
<i>Hamamelis virginica</i>	4.5
<i>Mercurius solubilis</i> D6	0.4
<i>Hepar sulfuris</i> D6	0.25

crease bleeding, and corticosteroids, at least when administered orally, are associated with sepsis, tissue atrophy, facial flushing, and hypersensitivity reactions.⁷ Such concerns are a probable reason for the increasing interest in complementary and alternative medical (CAM) practices.⁷ In addition, recent surveys have identified musculoskeletal ailments as one area in which there are “effectiveness gaps” and a dissatisfaction with the effectiveness of conventional treatments in clinical practice.¹⁶ This limited availability of effective remedies indicates a need for wider choice of treatments. Unfortunately, the growing use of CAM has not yet been accompanied by the desirable corresponding increase in the number of clinical studies on the efficacy and safety of alternative practices, and there is a need for critical evaluations of commonly used CAM options.

Traumeel S (Traumeel; Heel GmbH, Baden-Baden Germany) has been used in the treatment of minor injuries in Germany since 1937 and is currently available in approximately 60 countries worldwide. Traumeel is a fixed combination of highly diluted herbal and mineral extracts (Table 1), prepared in accordance with the German Homeopathic Pharmacopoeia (HAB). The ingredients are further listed in the Homeopathic Pharmacopoeia of the United States (HPUS),¹⁷ and this homeopathic medication is used by practitioners and patients for the broad spectrum of symptoms associated with various traumas such as contusion, sprains, wounds, pain, inflammation, neuralgia, and others.¹⁸ It is available in a variety of dosage forms, including tablets, drops, injection solution, or ointment. Placebo-controlled trial data in varying settings suggest the efficacy and good tolerability of Traumeel in the treatment of sports injuries^{19,20} and ankle sprains.²¹ A recent work²² showed Traumeel treatment to reduce tumor necrosis factor (TNF)- α and interleukin (IL)-8 secretion by human T cells, monocytes, and gut epithelial cells in vitro.

The current study was designed to assess the noninferiority of Traumeel ointment to therapy with diclofenac 1% gel (available in the United States as Voltaren EmulGel; Novartis AG, East Hanover, NJ) in patients with tendinopathies of varying eti-

ogy. Diclofenac 1% gel is indicated for temporary relief of local pain and inflammation in acute soft-tissue injuries and localized soft-tissue rheumatism, including sprains, tendinitis, bursitis, and sports injury, and has a long record of use.

METHODS

This was a nonrandomized, observational study carried out in 95 practices in Germany from September 2003 to March 2004. Patients were included if they were >18 years of age and had either native or recurring tendinopathy of varying etiology, based on excessive tendon load rather than inflammation. Patients were excluded if they were receiving NSAID therapies (other than diclofenac 1% gel in the control group). Each center could enroll up to five patients into the study with the choice of treatment option left to the individual patients. All patients were informed about the background and purpose of the study, which was carried out with the ethical standards set forth in the Helsinki Declaration of 1975 and with the German recommendations for the planning, execution, and evaluation of observational studies (*Bundesanzeiger Federal Gazette* No. 299 of December 04, 1998).

Patients were treated with either Traumeel ointment or diclofenac 1% gel (Voltaren Emulgel, diclofenac ratiopharm gel; Ratiopharm GmbH, Ulm, Germany, or Diclophlogont; Azupharma, Gerlingem, Germany). The number of daily applications and the mode of application (simple application of ointment or ointment applied with a bandage) were not stipulated in the protocol but were to be decided for each individual patient. Treatment was to be continued for a maximum of 28 days. Efficacy was evaluated at the end of the treatment period by the physician in a dialogue with the patients. Variables were symptomatic changes, severity of tendinopathy, and an evaluation of the time to first symptomatic improvement. Symptomatic improvements were assessed on pain and on motility. Pain was graded on a scale from zero to three, in which zero represented no pain; one, mild; two, moderate; and three, severe pain. Pain was evaluated at rest, in response to local pressure, at muscle load and contraction, and as a total summary score for all pain variables. Motility was evaluated on a similar scale as degree of pain with torsional joint motion (pronation and supination), extension, flexion, rotation, abduction, and adduction. The time to first symptomatic improvement was recorded (within the first day; after two, three, or four to seven days; after >seven days; and no improvement). A global assessment of therapeutic success (graded as very good, good, moderate, none, and negative effect) was conducted at the end of treatment. Furthermore, compliance with treatment (very high, high, moderate, or low) was assessed by physicians and patients at the end of therapy.

The significance of differences between treatment groups was analyzed by analysis of variance, Mantel-Haenszel test, or Fisher exact test as appropriate. To adjust for differences between treatment groups in the distribution of variables at baseline, propensity scores were calculated according to standard methods²³ using logistic regression (procedure logistic; model option selection = forward). Patients (efficacy population; n = 357) were stratified into five strata that balance observed covariates for the treatment groups according to propensity score based on

all baseline variables. Statistical analyses were conducted using SPSS version 11 (2000) (SPSS Inc, Chicago, IL).

Noninferiority of Traumeel was defined as a situation in which the left limit of the one-sided 95% confidence interval for differences between the treatment groups should not cross the border of -0.5 score points for changes from baseline with the respective treatment with an error probability of 0.05.

RESULTS

Patients

A total of 357 patients were recruited, 160 to the Traumeel group and 197 to the diclofenac group. All patients at each center were allocated to either Traumeel or to control therapy.

Patients were comparable at baseline with regards to sex, age, height, weight, etiology, localization, severity, and duration of tendinopathy as well as in the use of prior or adjuvant therapies (Table 2). Ages ranged between 18 and 93 years in the Traumeel group and between 19 and 91 years in the control group, with a mean age of 75 years. Men and women were equally well represented in the population. The majority of tendinopathy cases (90.2% in the Traumeel group; 88.1% in the diclofenac group; $P = .60$ for between-group difference) were caused by chronic strain. Most cases in both groups were tendinopathy of the elbow, followed by wrist, ankle, and shoulder. Two thirds of patients in both groups presented with local inflammation, and around half (51.6% in the Traumeel group; 42.6% in the control group) showed local edemas at the afflicted site. In both groups, most cases were of moderate severity, with no differences in severity distribution between the groups. The only variable for which the patient groups differed significantly before adjusting for propensity score was adduction, where Traumeel patients tended toward more severe pain compared with control patients ($P = .04$ for the comparison before propensity-score adjustment). After adjusting for propensity score, these differences were no longer significant ($P = .57$).

Close to half the patient population in both groups had received previous therapy for their condition, most commonly analgesics, local anesthetics, and cryotherapy. Seventy percent of patients (69.7% in the Traumeel group; 73.2% in the control group) received adjuvant therapies during the course of the study. Most common of these were cryotherapy, stretching exercises, ultrasound, and stabilizing elastic wraps. The distribution of adjuvant therapies was not significantly different between treatment groups.

The patient disposition is given in Table 3. All enrolled patients were included in the safety population. In the Traumeel group, 38 patients (23.7%) were excluded from the efficacy analysis for protocol violations (mostly >28 days between enrollment and final evaluation visit). A smaller percentage of patients (66; 20.9%) were excluded in the diclofenac group, mostly for unallowed therapies.

Traumeel was given as an ointment; in 57 patients (46.7%), the gel was applied with a bandage. Most patients (57.4%) applied Traumeel three times daily (tid); 26.2% of patients applied Traumeel four times daily; and 15.6% of patients applied Traumeel twice daily (bid). Diclofenac was applied in different

forms: as Voltaren Emulgel (Novartis AG) in 43.0% of cases, as diclofenac ratiopharm gel (ratiopharm GmbH) in 27.7% of cases, and as Diclophlogont (Azupharma GmbH) in 9.4% of cases. The other patients received diclofenac gels from various manufacturers; the numbers of daily applications were similar to those the Traumeel group: bid in 18.3%, tid in 60.9%, and 4 times daily in 18.3%. Most patients applied gel directly; 28.5% received diclofenac with a bandage. In both groups (19.7% of Traumeel patients and 10.6% of diclofenac patients), the number of daily applications was reduced during the course of treatment.

Efficacy

Symptoms improved in both treatment groups during the course of the study. A graphic summary of changes in pain-related variables is given in Figure 1A and changes in motility-related variables in Figure 1B. The degrees of improvement were highly similar for both sets of variables, and there were very small differences between the treatment groups. The changes in summary score of all pain-related variables were -5.3 ± 2.7 (all values means \pm SD) in the Traumeel group and -5.0 ± 2.7 in the control group. Changes in summary score for all motility-related variables were -4.2 ± 3.8 with Traumeel and -3.7 ± 3.4 with control therapy. The summary scores for all clinical variables were reduced by -9.5 ± 5.7 with Traumeel therapy and by -8.7 ± 5.4 with diclofenac-based treatment. In most cases, symptoms started to improve (patients' own recordings) after three to seven days (Figure 2), and less than 10% of patients (2.5% in the Traumeel group; 7.7% in the control group) reported a lack of symptomatic improvement within the treatment period of 28 days. Only one patient in each group reported worsening of symptoms. The good results with both therapies were reflected in the global evaluation of therapies. The positive verdicts "very good" and "good" were given in 88% of Traumeel cases and 82% of control cases ($P = .09$ for the comparison between treatments).

In the noninferiority analysis (Figure 3), the left limit of the one-sided 95% confidence interval for differences between the Traumeel and control groups did not cross the border of 0.5 score points for changes from baseline for any of the analyzed variables. For most variables, differences trended toward favoring the Traumeel group. Only for supination did the point estimate favor the control group. For the motility variables extension, abduction, and adduction, as well as for the overall summary score for motility and the overall summary score for all clinical variables, the left limit of the confidence interval did not cross the line of unity. There were no significant efficacy differences between the results in treatment groups adjusted for propensity score and in the nonadjusted groups.

Tolerability

Both therapies were very well tolerated: The highest score of "very good" was reported in 92.5% of Traumeel patients and 87.9% of patients receiving control therapies. There was no difference between treatment groups in tolerability score ($P = .15$ for the comparison). Adverse events occurred in only one patient: a case of eczema reported in the diclofenac group, not considered treatment-

Table 2. Baseline Characteristics

Parameter	Traumeel (N = 122)	Control (N = 235)	P Value for Difference
Age, yr (SD)	47.8 (\pm 16.0)	47.9 (\pm 16.5)	.95
Male sex, n (%)	63 (51.6)	108 (46.0)	.32
Weight kg (\pm SD)	74.8 (\pm 11.6)	75.5 (\pm 12.2)	.61
Height cm (\pm SD)	172.4 (\pm 8.6)	171.6 (\pm 8.3)	.38
Localization of tendinopathy, n (%)			
Elbow	47 (38.5)	77 (32.8)	.29
Wrist	24 (19.7)	46 (19.6)	1.0
Ankle	18 (14.8)	39 (16.6)	.76
Shoulder	16 (13.1)	36 (15.3)	.64
Knee	13 (10.7)	24 (10.2)	1.0
Severity of tendinopathy, n (%)			.33
Mild	16 (13.1)	22 (9.4)	
Moderate	73 (59.8)	155 (66.0)	
Severe	28 (23.0)	53 (22.6)	
Duration of tendinopathy, n (%)			0.77
<1 week	55 (45.1)	121 (51.5)	
1-4 weeks	39 (32.0)	69 (29.4)	
1-6 months	16 (13.1)	24 (10.2)	
>6 months	8 (6.6)	18 (7.7)	
Previous therapy, n (%)	54 (44.3)	112 (47.7)	.66
Analgesics	29 (23.8)	75 (31.9)	
Rest	29 (23.8)	58 (24.7)	
Local anesthetics	21 (17.2)	39 (16.6)	
Cryotherapy	16 (13.1)	43 (18.3)	
Elastic wrap	14 (11.5)	25 (10.6)	
Electrotherapy	14 (11.5)	21 (8.9)	
Exercise	10 (8.2)	24 (10.2)	
Ultrasound	7 (5.7)	20 (8.5)	
Thermotherapy	3 (2.5)	17 (7.2)	
Pain-related variables, score \pm SD			
Pressure	2.1 \pm 0.7	2.1 \pm 0.7	.60
Stretch	1.9 \pm 0.8	1.9 \pm 0.8	.74
At rest	1.1 \pm 0.8	1.1 \pm 0.8	.44
Load	1.9 \pm 0.8	1.9 \pm 0.7	.92
Pronation	1.7 \pm 0.9	1.8 \pm 0.8	.74
Supination	1.7 \pm 0.8	1.6 \pm 0.9	.53
Motility variables, score \pm SD			
Extension	1.3 \pm 1.0	1.2 \pm 1.0	.31
Flexion	1.2 \pm 1.0	1.3 \pm 1.0	.80
Rotation	1.4 \pm 1.0	1.3 \pm 1.0	.69
Abduction	0.9 \pm 1.0	1.0 \pm 1.1	.55
Adduction	0.9 \pm 1.0	0.8 \pm 0.9	.04
Overall severity of tendinopathy score \pm SD	2.1 \pm 0.6	2.1 \pm 0.6	

related but leading to discontinuation of therapy. No adverse events were reported in the Traumeel group.

The tolerability was also reflected in patient compliance: In >95% of cases, compliance was reported as "very high" or "high" ($P = .48$ for comparison between treatment groups).

DISCUSSION

The main finding of the present study was that treatment based on Traumeel, an antitraumatic and antiinflammatory agent with a long history of CAM use, was as effective as commonly used 1% diclofenac gel in the treatment of tendinopathy over a period

Table 3. Patient Disposition

	Traumeel, n (%)	Control, n (%)
Recruited patients	160 (100)	297 (100)
Safety population	160 (100)	297 (100)
Protocol violators		
Final examination >28 days after enrollment	36 (22.5)	62 (13.6)
Treatment with NSAID gel not allowed in protocol	0	40 (8.8)
No data	1 (0.6)	1 (0.2)
Use of analgesics	1 (0.6)	1 (0.2)
Available for efficacy analysis	122 (76.3)	235 (79.1)
Early termination of treatment	20 (16.4)	26 (11.1)
Disappearance of symptoms	16 (13.1)	15 (6.4)
Eczema	0	1 (0.4)
Lack of efficacy	2 (1.6)	10 (4.3)
No reason given	2 (1.6)	1 (0.4)

of one month. These results might expand the choice of therapies, particularly for patients and practitioners who are uncomfortable with the use of NSAIDs.

Most patients in the current study suffered from acute rather than chronic tendinopathy, in which extrinsic factors tend to predominate, in contrast to combined intrinsic and extrinsic factors common in chronic disorders.²⁴ This was reflected in the adjuvant therapies as stretching exercises and stabilizing elastic wraps were administered to a majority of patients in both groups during the course of the study. Although Traumeel patients tended toward more severe pain compared with control patients, these adjusted differences were not significant ($P = .57$) and do not seem to have affected the use of adjuvant therapies.

The noninferiority analysis was conducted on a number of variables: One set related to pain, and one set related to motility. Overall pain scores and overall motility scores were also analyzed for noninferiority as was the summary score of all clinical variables. For none of these scores did the left-hand limit of the 95% confidence interval cross the noninferiority margin. For variables related to pain, the results tended to be more neutral than for the motility-related variables, in which none of the borders of the confidence intervals for extension, abduction, adduction and the summary score for motility crossed the line of unity. Greater benefits on motility than on pain are in line with the reported benefits of Traumeel in other studies that support antitraumatic and antiinflammatory benefits rather than analgesic effects.^{19,20,22,25}

Because the study was designed to show noninferiority and did not include a superiority hypothesis, the possibility of superiority of Traumeel over diclofenac 1% gel on motility variables cannot be answered by the current data. The same is true for the overall clinical results, in which the left-hand border of the 95% confidence interval was 0.02, favoring Traumeel treatment.

The nature of the action of Traumeel has not been analyzed in detail, but many of the ingredients are regarded as antiinflammatory (Belladonna, Aconitum, Mercurius, Hepar, Chamomilla).

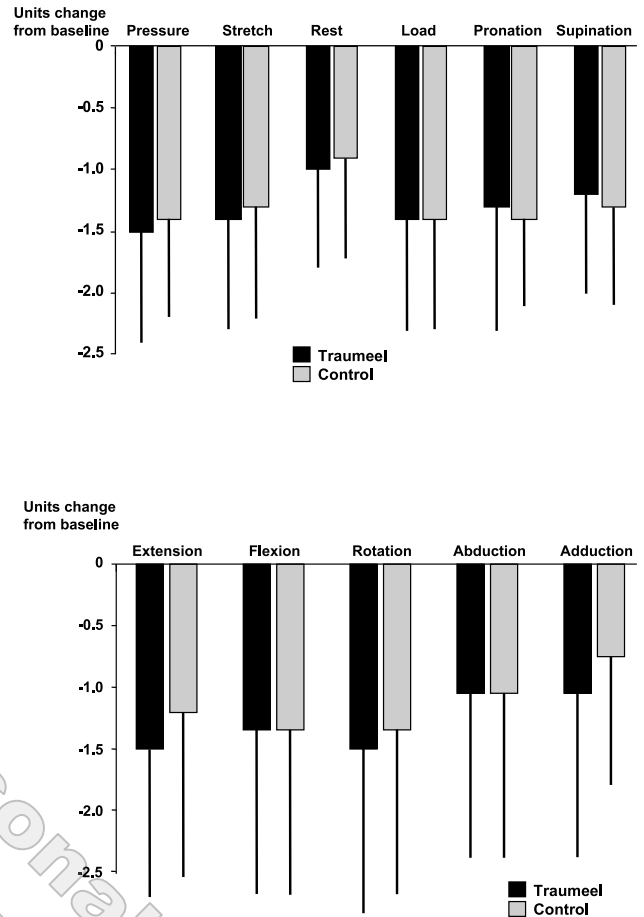


Figure 1. (A) Change from baseline to end of treatment in pain-related variables. (B) Change from baseline to end of treatment in motility-related variables. Filled bars represent the Traumeel group; shaded bars the control group. Lines indicate standard deviation.

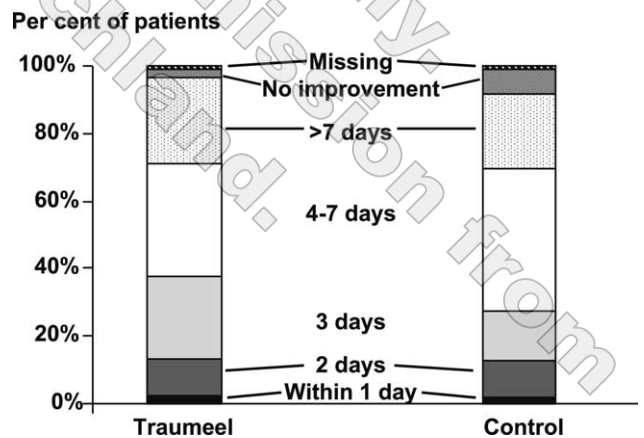


Figure 2. Time to first symptomatic improvement with Traumeel treatment (left-hand column) and diclofenac treatment (right-hand column), respectively.

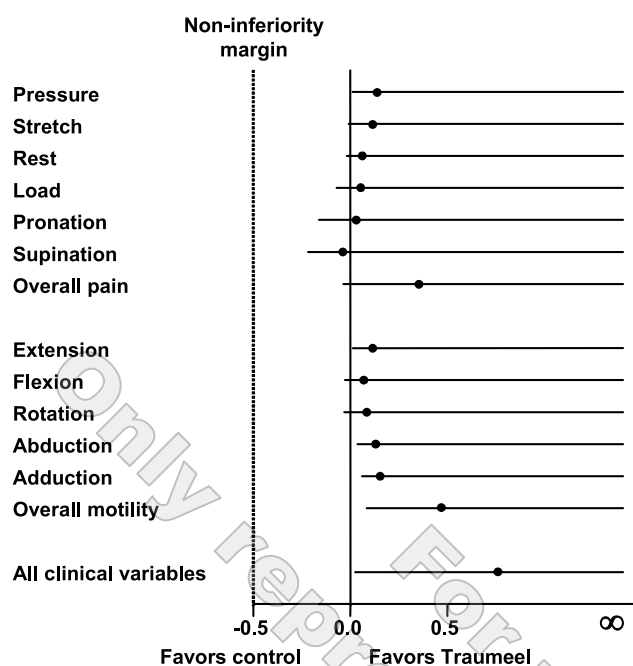


Figure 3. Point estimate and one-sided 95% confidence interval for the difference between scores for Traumeel and control for all variables. Positive values indicate a favorable effect of Traumeel; negative values favor the control group. The border of noninferiority is shown as a dotted line. The zero line indicates no differences between therapeutic effects.

milla). Other ingredients, including Arnica, Calendula, Hamamelis, and Milefolium, are believed to have antihemorrhagic properties. Arnica is one of the main remedies used in common homeopathic treatment of trauma. *Echinacea angustifolia* and *Echinacea purpurea* are thought to be immunostimulatory. Hypericum has been used in cases of neural injury.²⁵ However, as with many homeopathic therapies, the molecular basis of actions has received scant scientific attention, and further research is needed to identify which component(s) are the active compound(s). An investigation into the possibility of synergistic actions of the components would also be warranted.

Nonpharmacological tendinopathy therapies are common, but the results are mixed. Cryotherapy has been shown to be a useful intervention in the acute phase to reduce pain and the metabolic rate of the tendon⁴; deep friction massage and “Augmented soft-tissue mobilization” have reported success in chronic tendinopathy,²⁶ and the use of ultrasound to reduce the swelling has been proposed.²⁷ The need for a rational integration of CAM into medical education and practice is increasingly recognized, and the concomitant interest in a proper evidence basis for CAM practice decisions is a further sign of an ongoing paradigm shift.^{28,29}

One of the most common concerns influencing the choice of alternative practices is the possibility of adverse effects, which are perceived as less frequent with CAM therapies than with conventional treatments.¹⁶ Allergic contact dermatitis has been reported with topical NSAIDs,^{30,31} but the extent of this problem is unclear,³² and, in the current investigation, tolerability

was very good with no treatment-related adverse events and no statistically significant differences between the treatment options. The close relationship between tolerability and compliance was demonstrated by compliance ratings of the same magnitude as tolerability ratings: Compliance was reported as “very high” or “high” in >95% of cases. Because the choice of a CAM option is frequently based on perceptions rather than an evidence-based decision,¹⁶ the concordance of tolerability and compliance findings with Traumeel is reassuring.

A second factor influencing the decision to opt for CAM therapies is the phenomenon of “effectiveness gaps,” areas in which conventional treatments are not fully effective in clinical practice.¹⁶ Musculoskeletal ailments are among the conditions for which effectiveness gaps are most frequently reported.¹⁶ Although earlier studies have indicated clinical benefits of Traumeel in sports injuries,^{19,21} the still controversial status of CAM in many quarters, and the relative lack of studies in this field of medicine, are signs of the need for more data in different settings and patient populations.

Limitations

There are limitations associated with the current study. This was a nonrandomized, observational study with the associated disadvantages (possible selection and evaluation bias; possible demographic differences between treatment groups) and advantages (greater range of patient types; more closely related to clinical practice). The quantification of the variables has not been evaluated in a randomized clinical trial, and there is a risk of arbitrariness in each physician’s judgment of symptom scores. Each center allocated all patients either to Traumeel or to diclofenac therapy, and it is unlikely that physicians assigning patients to conventional therapies would have less desire to see positive results than physicians assigning patients to homeopathic therapy. Moreover, all evaluations were carried out jointly between physician and patient; this may reduce overall bias.

The definition of borders for the noninferiority test is by necessity arbitrary because no standardized evaluation system exists for severity of symptoms of tendinopathy, and there is no agreed degree of improvement that has been defined to be clinically relevant. For the current analysis, the differences between treatments were very minor or tended to favor Traumeel. This supports the stringency of the criteria used to assess noninferiority.

In conclusion, homeopathic Traumeel ointment was as effective and well tolerated as commonly used diclofenac 1% gel in the acute symptomatic treatment of tendinopathy of varying etiology. It would seem worthwhile to conduct a controlled biomedical analysis of possible mechanisms of action of Traumeel to establish a clearer role for this remedy in sport injuries.

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