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THE HOMEOPATHIC PREPARATION TRAUMEEL® S COMPARED WITH NSAIDS FOR SYMPTOMATIC TREATMENT OF EPICONDYLITIS

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ABSTRACT

Objective: To compare the homeopathic remedy Traumeel® S with standard NSAID therapy for effects on symptomatic relief in patients with diagnosed epicondylitis.

Methods: An observational, non-randomized study over 2 weeks in 184 patients with diagnosed epicondylitis from 38 primary care centers in Germany. At the start of the study, patients were given initial injections of either Traumeel® S or NSAID (unspecified; mainly diclofenac). Traumeel® S patients might have other Traumeel® S injections and other treatments were allowed, e.g. oral analgesics (in the NSAID group only) or physiotherapy. Treatments were evaluated on clinically relevant variables: three pain variables (local pressure pain, pain with movements, pain at rest) and two mobility variables (change in extensional joint mobility and change in torsional joint mobility).

Results: Both treatments significantly improved scores on all five variables with no significant differences in time to onset of action. Traumeel® S was equivalent to NSAIDs on all evaluated variables and was significantly superior to NSAID therapy on the variables pain at rest ($p < 0.01$), torsional joint mobility ($p < 0.01$), and extensional joint mobility ($p < 0.05$). Patients' verdicts on the global outcome reflected the results, with the terms "very good" or "good" given by 71.0% of patients in the Traumeel® S group versus 44.2% of patients receiving NSAIDs. Tolerability was good in all groups.

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Conclusion: Traumeel® S represents an appealing and well-tolerated alternative to NSAIDs for symptomatic treatment of epicondylitis.

Keywords: Non-inferiority; Observational study; Trauma; Propensity score.

INTRODUCTION

Epicondylitis was described as early as 1873[19] and has been known as "tennis elbow" for over a century,[13] although in practice, less than 1/10 of incidences occur among tennis players and most cases are work-related.[7, 16]

Despite its long history, there is a lack of consensus on the best treatment of epicondylitis and there have been few methodologically rigorous trials of treatments.[2, 11] This situation is reflected in the large number of proposed treatments historically[4] and in the variety of recommendations. Most of the debate regards long-term outcomes, however, and recommendations for the initial phase of treatment generally stress symptomatic relief.[8] As the control of pain and trauma is an integral part of the management scheme,[7] the choice of initial therapy is highly relevant.

Traumeel® S (Heel GmbH, Baden-Baden, Germany) is a homeopathic-complex remedy, used to treat trauma, inflammation, and degenerative processes. Traumeel® S has been sold over the counter in pharmacies in Germany, Austria and Switzerland for over 50 years and the ingredients are officially listed in the Homeopathic Pharmacopoeia of the United States.[20] It contains extracts from plants and minerals, all of them highly diluted (10^{-1} to 10^{-6} of the stem solution; Table 1). Anti-inflammatory and analgesic effects of Traumeel® S have been demonstrated in clinical trials as well as in experimental models *in vivo*, including the carrageenin-induced edema test and the adjuvant arthritis test.[5, 15]

The current report describes the results of a study comparing Traumeel® S with NSAIDs for non-inferiority in the treatment of epicondylitis in patients aged 14–88 years. Homeopathic remedies are prescribed to a very wide range of patients, from which follows that the populations enrolled into randomized trials (which exclude patients not meeting certain predefined criteria) may not be representative of the broad spectrum of individuals treated in clinical practice.[17] To avoid this bias, the study used a non-randomized approach. The relationship between observational and experimental studies is widely considered to be complementary, not alternative.[3]

Table 1 Traumeel® S Ingredients.

Source of Extract	Volume in Every Ampoule (2.2 ml) of Traumeel® S
Arnica montana	2.2×10^{-2} µl
Calendula officinalis	2.2×10^{-2} µl
Achillea millefolium	2.2×10^{-3} µl
Chamomilla recutita	2.2×10^{-3} µl
Symphytum officinale	2.2×10^{-6} µl
Atropa belladonna	2.2×10^{-2} µl
Aconitum napellus	1.3×10^{-2} µl
Bellis perennis	1.1×10^{-2} µl
Hypericum perforatum	6.6×10^{-3} µl
Echinacea angustifolia	5.5×10^{-3} µl
Echinacea purpurea	5.5×10^{-3} µl
Hamamelis virginica	2.2×10^{-2} µl
Mercurius solubilis	1.1×10^{-6} µl
Hepar sulfuris	2.2×10^{-6} µl

METHODS

The study was designed to assess the non-inferiority of Traumeel® S to NSAID therapy. For

this observational, non-randomized study in 38 centers, 184 patients with diagnosed epicondylitis were recruited over a six-month period. In order for each practitioner's evaluations of effects of Traumeel® S and NSAID to be as neutral as possible, each center planned to treat 3 patients with Traumeel® S and 3 with NSAID (unspecified; mainly diclofenac), both administered by injection. NSAIDs were applied systemically, primarily intramuscularly, whereas Traumeel® S was given as local infiltration. As the study was non-randomized, the choice of treatment option was left to the individual patients. Other treatments were allowed, e.g. oral analgesics or physiotherapy. Patients in the Traumeel® S group were allowed further Traumeel® S injections, but no oral NSAIDs. Evaluations of treatments were conducted at weeks 1 and 2.

All patients were informed about the background and purpose of the study, which was conducted in full compliance with the principles of the Declaration of Helsinki.

Traumeel® S was provided by Biologische Heilmittel HEEL GmbH (Baden-Baden, Germany) in sterile 2.2 ml ampoules. The composition of the Traumeel® S preparation is shown in Table 1. Solutions of Traumeel® S were prepared according to the German homeopathic pharmacopoeia.

Treatment efficacy was evaluated on five scores, three for pain and two for joint mobility. Change in pain was assessed as change in: (a) local pressure pain; (b) pain with movements; and (c) pain at rest. Change in joint mobility was evaluated as change in extensional joint mobility and change in torsional joint mobility (for pronation and supination). Pain was evaluated on a five-point scale, where 0 = no pain, 1 = light, 2 = moderate, 3 = strong and 4 = severe. Joint mobility was evaluated on a four-point scale, where 1 = normal, 2 = lightly impaired, 3 = moderately impaired and 4 = heavily impaired. The basis for evaluating changes with treatment were the differences between scores at enrolment and at examinations.

In addition, the administering physician carried out a global assessment of efficacy on three variables: (a) time point of first improvement of symptoms (after the first injection, after 1, 2, 3, 4–7 days, after more than one week, no improvement); (b) global outcome of therapy (very successful, successful, moderate, unsuccessful, negative); and (c) physician-assessed compliance (very high, high, moderate, low). These variables were measured at the beginning of the study and at weeks 1 and 2.

Statistical Methods

For the comparison between treatments, non-inferiority was assessed using the results from the 2-week examination. Non-inferiority was defined as a situation where the left border of the 97.5% confidence interval for the difference between the groups does not cross the boundary of 10% of the maximal possible change in the respective measurement. For pain, this corresponded to a boundary of –0.4 (five-point scale 0–4) and for joint mobility a boundary of –0.3 (four-point scale 1–4). Data evaluations were done using SAS 6.12.

To achieve a closer relevance to actual clinical practice than controlled randomized double-blind trials, the study used a non-randomized cohort approach. In this kind of study, the principal investigator has no control over the treatment assignment and there is the possibility of relevant differences in observed co-variates between the treatment groups. In a study with a homeopathic remedy, the characteristics of the patient group opting for the homeopathic treatment may differ from that of patients choosing allopathic medications. To balance the co-variates in the two groups and reduce bias, we applied the

Table 2 Baseline Characteristics.

Variable	Traumeel S (n = 86)	NSAIDs (n = 77)	Test
Sex n (%)			$p = 0.635$[a]
Female	43 (50.0)	36 (46.8)	
Male	40 (46.5)	40 (51.9)	
Age years (mean ± SD)	n = 81	n = 76	
	48.6 (15.1)	45.8 (12.1)	$p = 0.203$[b]
Height cm (mean ± SD)	n = 85	n = 73	
	169.5 (±8.4)	170.7 (±7.6)	$p = 0.352$[b]
Weight (mean ± SD)	n = 85	n = 72	
	71.8 (±12.4)	74.1 (±15.2)	$p = 0.296$[b]
Smokers n (%)	17 (19.77)	26 (33.77)	$p = 0.051$[a]
Habitual alcohol users n (%)	23 (26.74)	17 (22.08)	$p = 0.585$[a]
Epicondylitis variety n (%)			$p = 0.003$[c]
Humeri radialis	64 (74.4)	69 (89.6)	
Humeri ulnaris	13 (15.1)	8 (10.4)	
Humeri radialis and ulnaris	8 (9.3)	0 (0.0)	
Unknown	1 (1.2)	0 (0.0)	
Severity (%)			$p = 0.434$[c]
Mild	3 (3.5)	4 (5.2)	
Moderate	33 (38.4)	23 (29.9)	
High	45 (52.3)	43 (55.8)	
Very high	5 (5.8)	7 (9.1)	
Symptoms (%)			$p = 0.816$[c]
Acute	35 (40.70)	35 (45.45)	
Chronic	29 (33.72)	26 (33.77)	
Relapsing	19 (22.09)	15 (19.48)	
Unknown	3 (3.49)	1(1.30)	
Duration of epicondylitis (%)			$p = 0.839$[c]
< 1 week	17 (19.77)	11 (14.29)	
1–2 weeks	22 (25.58)	28 (36.36)	
3–4 weeks	20 (23.26)	12 (15.58)	
> 4 weeks	25 (29.07)	23 (29.87)	
Unknown	2 (2.33)	3 (3.90)	

[a]Chi-square test
[b]Analysis of variance
[c]Mantel-Haenszel test

established methodology of propensity-score (PS) analysis to construct matched strata that balance observed co-variates.[6, 18]

Treatment groups were compared after adjustment for PS using a two-way ANOVA model for co-variates based on interval data and Cochran–Mantel–Haenszel test for co-variates with dichotomous values.

This was not a confirmatory study and thus, every individual efficacy and safety criterion was assessed. Therefore, a multivariate analysis was not carried out.

RESULTS

Patients

A total of 184 patients were recruited. Of these, 106 received Traumeel® S and 78 NSAIDs. Although the study design prescribed that each center should recruit 3 patients to each treatment, in the evaluation this requirement was relaxed to allow for different distributions of patients into the treatment groups. All enrolled patients were included in the safety analysis. The study populations were similar at baseline (Table 2).

The efficacy analysis was carried out on 163 patients, 86 of whom received Traumeel® S and 77 NSAIDs. Twenty patients at 7 centers receiving Traumeel® S and one patient receiving NSAID were excluded as their recruiting centers failed to recruit patients into the opposite treatment group. A total of 6 patients (7%) in the Traumeel® S group and 15 (19.5%) in the NSAID group discontinued the study. Of these, the majority of patients (3 in the Traumeel® S group, 8 in the NSAID group) cited spontaneous disappearance of symptoms as the reason for discontinuing. Only 2 patients, both in the NSAID group, discontinued because of treatment-related adverse events.

The major NSAID injected in the NSAID group was diclofenac, which was used by 51.9% of the patients in this group. Tenoxicam was used by 16.9% and other NSAIDs (bufexamax, propacetamol, piroxicam or unspecified) by the remaining patients. Parallel oral NSAID therapy was given to 41.6% of patients in the NSAID group. Non-NSAID anestethics, mostly procaine/lidocaine, were taken by 15.6% of patients in the NSAID group.

In the Traumeel® S group, patients were allowed further Traumeel® S injections, oral Traumeel® S, or other oral homeopathic therapies (Ferrum Homaccord, pyrogenium, Rhus tox. globule). Such treatments were given to 26.4% of patients in this group. Other homeopathic therapies such as Traumeel® S gel or lavender oil were taken by 4.7% of patients in the Traumeel® S group.

Treatment Effects

As the baseline differences between treatment groups were so small, the PS-adjustments changed the results only marginally and had no effect on the overall analysis. Hence, unadjusted data are presented here. Similar degrees of improvements were seen in all 5 evaluated variables with both Traumeel® S and NSAID treatments (Fig. 1). As shown in Fig. 1, there were no significant differences between Traumeel® S and NSAID in time to onset of action; improvements of similar magnitude were seen in the first week in both treatment groups. Symptoms continued to improve with treatment in both groups over the course of the study assessed on all five variables. Patients in the Traumeel® S group showed markedly greater improvements in the variables pain at rest, change in extensional joint mobility and change in torsional joint mobility than the comparator group, particularly in the second week of treatment.

The non-inferiority analysis, which used scores from the 2-week examination, showed Traumeel® S to be non-inferior as well as equivalent to NSAID on all five evaluated variables, with a

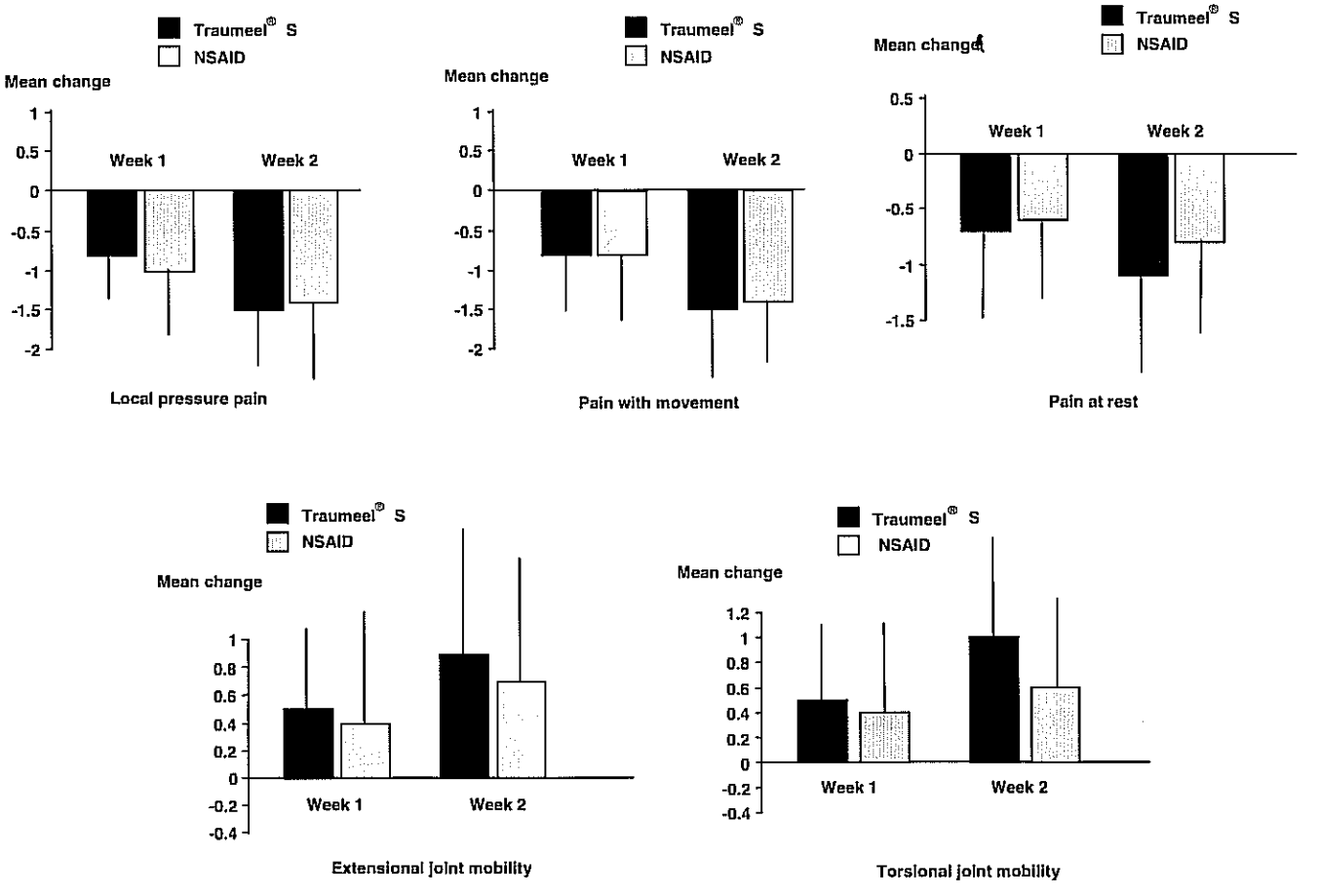

Fig. 1 Evaluation of the change in symptoms over time with Traumeel® S and NSAIDs respectively, for the five variables included in the study. Negative values for pain indicate improvement in symptoms. Bars are SD.

trend towards superiority of Traumeel® S on all variables (Fig. 2). The analysis of the scores for pain at rest, change in extensional joint mobility and change in torsional joint mobility indicated a statistically significant superiority of Traumeel® S, although it was not the primary aim of the study to demonstrate this.

The global assessment of therapies also favored Traumeel® S over NSAIDs (Fig. 3). Treatment was given the verdicts "very good" and "good" (indicating total disappearance of symptoms and marked improvements, respectively) by 71.0% of patients receiving Traumeel® S compared with 44.2% of patients receiving NSAIDs (p = 0.013 for comparison between treatment groups). Physician-assessed compliance did not differ significantly between the groups, but there was a trend towards better compliance with Traumeel® S. In this group, compliance was reported as "very high" or "high" in 91.9% of patients compared with 80.6% in the NSAID group (p = 0.11).

Tolerability

Both treatments were well-tolerated, but there were significant differences in favor of Traumeel® S. Whereas 87.7% of patients receiving Traumeel® S reported the highest "very good" tolerability, only 44.9% in the NSAID group reported similar

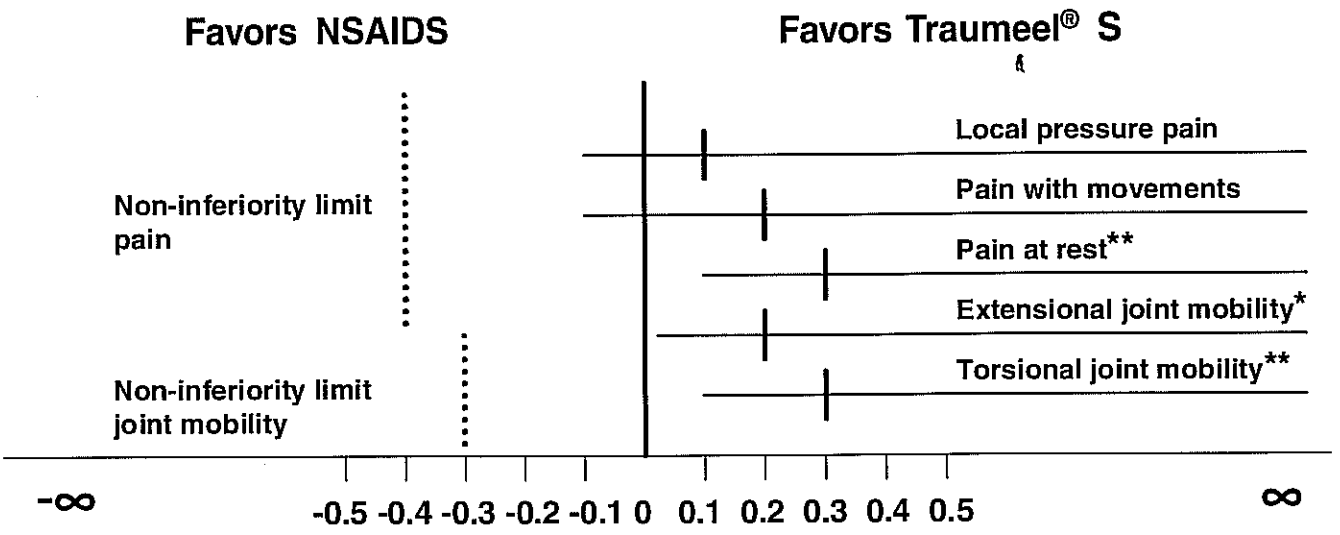

Fig. 2 Mean difference ±97.5% confidence interval between symptom scores after two weeks for NSAID (n = 77) and Traumeel® S (n = 86). The dotted vertical lines indicate the border for non-inferiority. * indicates statistically significant superiority of Traumeel® S at $p < 0.05$; ** indicates significant superiority of Traumeel® S at $p < 0.01$.

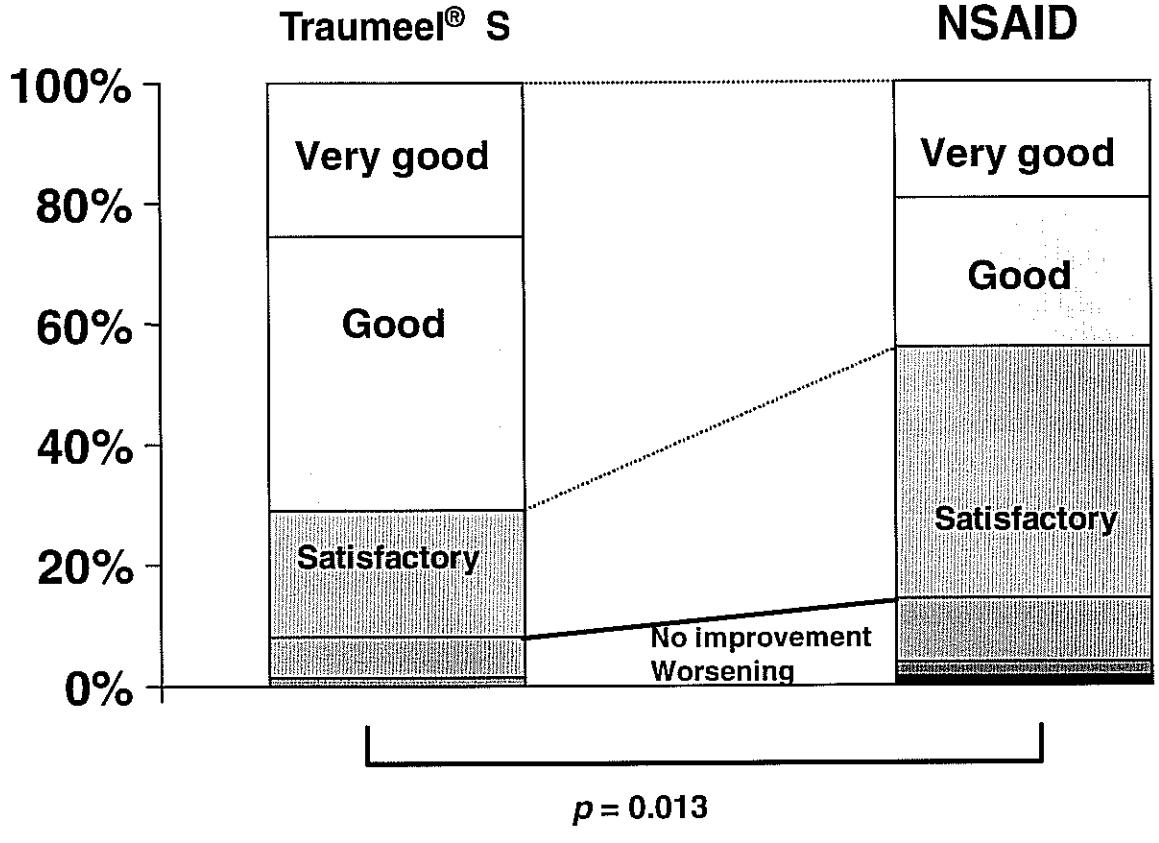

Fig. 3 Global evaluation of the outcomes of therapy in the Traumeel® S and NSAID treatment groups, respectively.

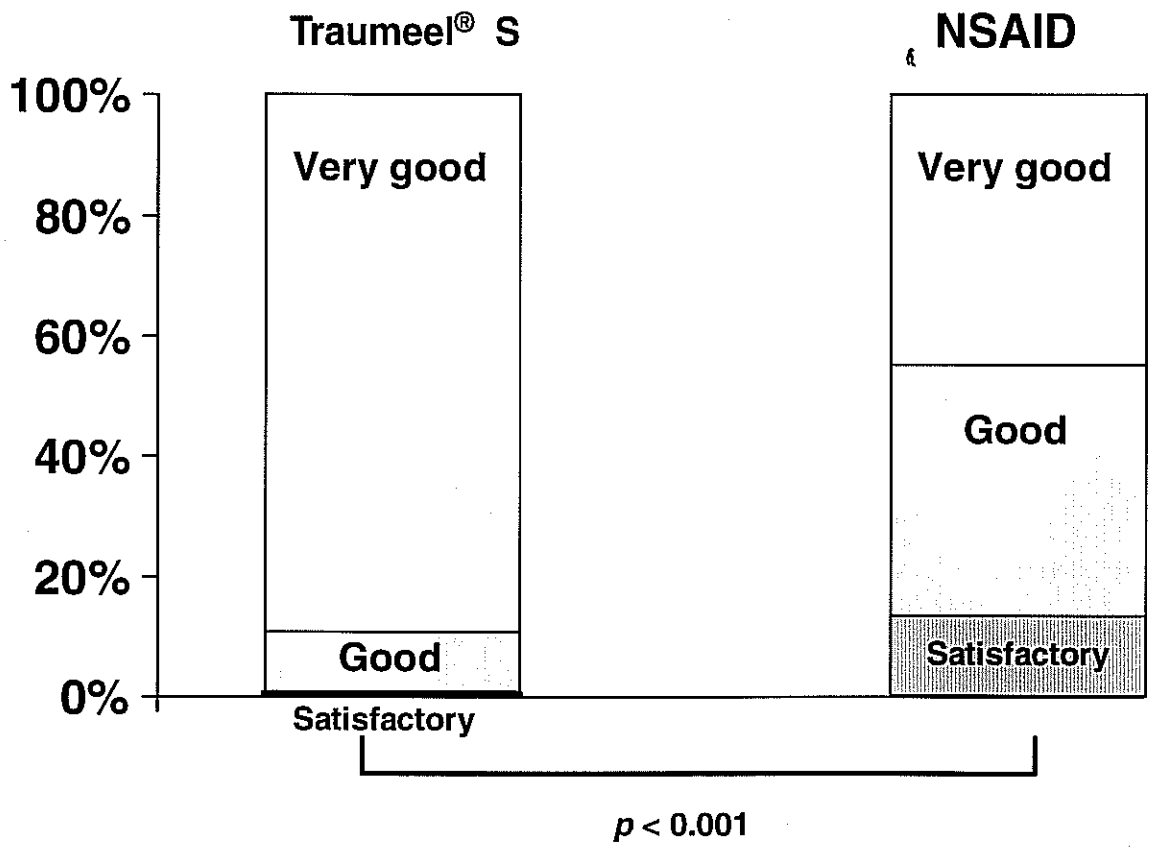

Fig. 4 Global evaluation of tolerability in the Traumeel® S and NSAID treatment groups, respectively.

tolerability (Fig. 4). Only 3 adverse events were reported during the study, all in the NSAID group. Two of these (both adverse dermal reactions believed to be treatment-associated) led to the patients' discontinuing treatment. Discontinuation rates were overall low. In the Traumeel® S group, 7% did not continue the full two weeks; for the NSAID group the number was higher (19.5%).

DISCUSSION

This study demonstrated the non-inferiority of the homeopathic-complex remedy Traumeel® S to NSAIDs for the localized short-term treatment of epicondylitis. Treatments were evaluated on five variables relevant to symptomatic relief. Although the study was designed to assess non-inferiority, the analysis showed Traumeel® S to be equivalent to NSAIDs on all variables and tended towards superiority on the variables pain at rest, extensional joint mobility and torsional joint mobility.

There are a number of strategies for the symptomatic treatment of epicondylitis and the current study can be viewed as comparing a homeopathic strategy with one based on NSAID injections. This focus on strategies is reflected in the observational, non-randomized design of the trial, which carries strengths and weaknesses. Among the strengths is the inclusion of patients and treatments reflecting varying clinical practices, rather than the narrow range (typically between 49% and 91% of screened patients[14]) included in randomized clinical studies. This is particularly relevant to homeopathic strategies,

which are used in a very broad range of patients. The disadvantage is the possible lack of stringency in results and the introduction of potential confounders into the analysis. However, we believe the current non-inferiority results to be quite robust. The oral treatments allowed after the initial injection of study medications were highly unlikely to have affected the analysis to any great extent, as they were only used in the NSAID group and cannot have effected the Traumeel® S patients. The reverse is the case for oral homeopathic remedies which were used in less than 1/3 of patients in the Traumeel® S group and not at all in the NSAID group. In the majority of these cases the treatment was oral Traumeel® S.

Although there is always a risk of subjectivity in the evaluations of variables in this kind of trials, the equivalence of Traumeel® S to NSAIDs on all variables support the robustness of the results and further indicates that in these patient groups, the homeopathic remedy would be an alternative to established treatments directed at providing symptomatic relief. Patients' assessments of the global effects of therapies reflected the benefits on individual variables; 71.0% of patients receiving Traumeel® S reported "very good" or "good" results. In the NSAID group, these verdicts were given by 44.2% of patients.

Non-randomized studies risk exhibiting a greater variation of sample composition than randomized trials. However, in the current study, the populations were highly similar, as seen by the fact that adjusting for propensity score had no influence on the evaluation of the respective treatments.

The control of pain and trauma is an integral part of the management scheme for epicondylitis and NSAIDs, commonly diclofenac, have long been part of the clinician's armamentarium. Traumeel® S is widely used in homeopathic practice to treat trauma, inflammation and degenerative processes. The anti-traumatic effects of Traumeel® S have been subject to small-scale studies which generally report good efficacy and excellent tolerability.[12, 21] However, these comparisons were with placebo, or comparisons between two Traumeel® S preparations, and do not yield information on Traumeel® S therapy compared with other standard anti-traumatic agents.

A possible advantage with Traumeel® S over other symptomatic treatments such as NSAIDs or corticosteroids is the tolerability profile of the homeopathic remedy. Traumeel® S has a long record of use in Europe and the US, and tolerability has been reported as excellent (manufacturer's own data). In contrast, corticosteroid use is associated with post-injection pain and possible peptic ulcerations,[2] and NSAIDs use is well known to be associated with gastrointestinal ulcers and ulcer complications. In the current study, both treatments were well tolerated if evaluated on adverse events, and no gastrointestinal problems were reported with either therapy. However, when patients' own assessments on tolerability were compared, there was a major difference in favor of Traumeel® S.

The long-term effects of NSAIDs and corticosteroids in the treatment of epicondylitis are debated and several investigators claim that benefits are only temporary, reducing pain but not affecting the healing process.[1, 9, 10] The general strengthening effects of Traumeel® S have not been studied in a controlled way and the duration of the current investigation was too short to reach conclusions as to beneficial long-term effects. It would be most interesting to assess, in a controlled fashion, the possible benefits of Traumeel® S on long-term outcomes in epicondylitis.

In summary, for patients opting for a homeopathic remedy rather than NSAID treatment, Traumeel® S appears to be an appealing alternative to current therapies directed at pro-

viding symptomatic relief in the early treatment of epicondylitis. Traumeel® S was equivalent or superior to NSAID therapy in reducing pain and improving mobility. Tolerability, both in terms of adverse events and on patients' own assessments, was comparable between the treatment groups.

CONFLICT OF INTEREST

This study was supported by a grant from Biologische Heilmittel Heel, GmbH. With the exception of Dr. Weiser, who is an employee of Heel GmbH, the authors have no relationship to the sponsor to disclose.

CONSENT

As this was a non-randomized, observational study, patients had full disclosure of treatments and a formal informed consent was not required.

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