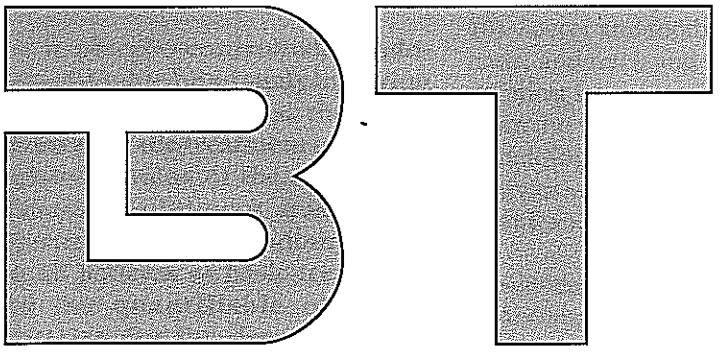
BIOLOGICAL THERAPY

JOURNAL OF BIOLOGICAL MEDICINE



reprinted from Biological Therapy,
Vol. VII, No.1, January 1989, pp.1-6

FEATURE ARTICLE

Treatment of Acute Sprains of the Ankle: A Controlled Double-Blind Trial to Test the Effectiveness of a Homeopathic Ointment

Jürgen Zell, M.D; Dr.. W.D. Connert; Prof. J. Mau; and Physiotherapist G. Feuerstake

Treatment of Acute Sprains of the Ankle: A Controlled Double-Blind Trial to Test the Effectiveness of a Homeopathic Ointment

Jüurgen Zell, M.D; Dr.. W.D. Connert; Prof. J. Mau; and Physiotherapist G. Feuerstake

Summary:

In a placebo-controlled, randomized double-blind study involving a total of 73 patients, the effectiveness of the treatment of sports-related sprains of the ankle with Traumeel ointment was tested. Electrotherapy was administered to all patients as basic treatment. As the quantifiable objective criterion for the degree of restitution of ankle mobility, the difference in total angulation of the joint - measured in extension and flexion - as calculated between affected and non-affected joints, was taken as „target criterion". Treatment was administered on an outpatient basis seven times within a period of two weeks. In both groups, the basic treatment produced an improvement in joint mobility. In the test group, this improvement (as established on the reference day stipulated prior to the start of the trial, i.e. the 10th day after injury) was as indicated by the target criterion, considerably more frequent for the Traumeel patients (p=0.03) than in the placebo group.

The authors are Jürgen Zell, MD, specialist for orthopedics, sports medicine, and chirotherapy of Idar-Oberstein; Dr.W.D. Connert of Baden-Baden; Prof. J. Mau of Tübingen; and Physiotherapist G. Feuerstake of Homburg (Saar), all of Germany.

Methods of treatment as practiced by such special therapeutic orientations as homeopathy are seldom assessed in controlled clinical testing (20). In our controlled double-blind trial, we conducted our evaluations in accordance with a test concept which fully took into acount the latest statistical requirements placed on the planning and performance of comparative clinical tests, as well as the ethical considerations of the medical profession and the circumstances encountered in typical medical practice.

Ankle sprain represents one of the most frequent sports injuries (9 and 10). Soccer and football players, gymnasts, and track and field athletes are the most frequent victims (9 and 14). From the standpoint of clinical symptomatology, the following consequences of ankle sprains are of chief significance (3 and 9):

- Soft-tissue injury
- Accompanying hematoma
- Development of joint effusion

Pain upon movement and restriction of ankle mobility are the two consequences of trauma which are of primary interest in ankle sprains, and which have greater influence on the length of time an athlete must interrupt his or her training. The quality and effectiveness of a plan of therapy, carried out by a specialist with sufficient medical insights into the pathophysiological processes involved, are all of critical importance to the athlete (11 and 17). Conventional modern first-aid treatment of sprains usually takes places in the following forms (7, 8, 16 and 17):

- Mild compression bandaging, often accompanied by the application of salve (ointment dressings)
- Immobilization
- Cold packs
- Electrotherapy

In addition to electrotherapy, local as well as oral medication in the form of anti-inflammatory and analgesic preparations is frequently administered (8, 13 and 16).

Local therapeutic medication should exhibit the following characteristics:

- Good analgesic action
- Fast resorption of edema and hematomas
- Enhancement of microcirculation, with promotion of the natural healing processes
- A minimum of side effects

Traumeel ointment fulfills all these requirements. It is a homeopathic ointment preparation, the constituents of which have anti-exudative and regenerative effects (4, 12, 15, and 18).

The mother tinctures and the attenuations of all of the 14 constituents of Traumeel ointment are prepared by reproducible techniques as specified by the detailed instruction for preparation in the Homeopathic Pharmacopoeia (HAB).

Materials and techniques of testing

The Double-Blind Method of Testing

The objective was to determine how the preparation, Traumeel ointment, influences the progress of disorders among patients with the following diagnosis:

Distortion of the articular-capsule ligaments (sprain) and of the tendons of the ankle.

Testing was to be performed of Traumeel ointment in combination with basic therapy consisting of interference-current therapy (the VARIODYN treatment) and the application of compression ointment bandages. Testing was conducted with respect to the goal criterion defined below, and to the secondary comparative criteria, as differentiated from placebo conditions.

The placebo was the ointment base of Traumeel, i.e., salve without active constituents and without therapeutic effects.
The mother tinctures and the attenuations of this product are usually encountered in a 60 - 70 % alcohol solution. A total of 3.4 g of this alcohol solution is contained in 100 g of salve. After the substances have been homogeneously worked into the ointment base, the actual product Traumeel cannot be outwardly distinguished from the placebo.

in the pilot study, the requirement is therefore at least 45 patients per group in the main test.

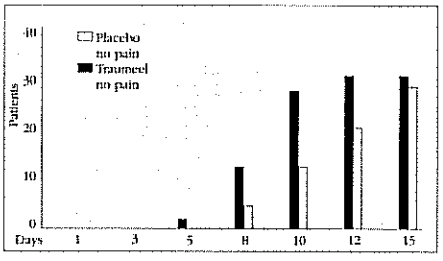


Fig. 2: Patients with no pain upon movement within two weeks after beginning of therapy with Traumeel ointment, compared with a placebo (n = 33 for Traumeel; n = 36 for placebo).

Results:

Comparability of the two groups

In the main test, 36 patients were accepted into the Traumeel group, and 37 additional patients were taken into the placebo group, again with computer-aided, randomized assignment into these two therapy groups. Owing to patients who were not accepted on grounds of falling under exclusion criteria k, l, and m as listed above, 33 were able to be evaluated for the Traumeel group, and 36 for the placebo group. The other basic data for comparison of the two groups can be seen in Table 1.

Course of therapy, as measured by the target criterion

For the upper ankle, the change in difference between the angular sums of flexion + extension for the two groups can be represented as a box-plot diagram, in the sense of explorative data analysis. The plot of median can then serve for optical comparison between the two groups in a graphical presentation; see Fig. 1. This plot reveals a difference between the groups, to the advantage of the active agent Traumeel, beginning with the fifth day after injury. This advantage over the placebo group was, furthermore, maintained throughout the course of treatment. At the tenth day after injury, calculations were able to be performed for both sides with the Wilcoxon-Mann-Whitney test, which revealed a difference between the two groups of p = 0.005. When multiplied after Bonferroni's method by 3 (i.e., the number of characteristics tested), the extremely noteworthy result of p = 0.015 was obtained. Improvement in joint mobility is naturally observed in both groups, by virtue of universal administration of basic VARIODYN therapy and by the compression bandages applied after Feuerstake (7). In the Traumeel group, however, more rapid recovery takes place as a result of the additional effects of the active ointment constituents.

In the sense of the definition of the target criterion, the significance of the difference can also be verified by counting of the succesfully and non-successfully treated patients in the two groups (see Table 2). With the aid of the exact test after Fischer, the probability for successful therapy with Traumeel is significantly greater, with p = 0.03, than that for the placebo.

Group	Success		n
	No	Yes	Total
Traumeel	16	17	33
Placebo	27	9	36

Table 2: The number of patients for whom the difference of the angular sums of flexion + extension between injured and healthy ankles decreased to 10 and less after 10 days of treatment.

Group	Success		n
	No	Yes	Total
Traumeel	5	28	33
Placebo	23	13	36

Table 3: The number of patients for whom there was no longer pain upon movement after 10 days of treatment.

Group	Success		n
	No	Yes	Total
Traumeel	8	25	33
Placebo	16	20	36

Table 4: The number of patients for whom the difference of the supination angle between injured and non-injured ankles decreased to 7 or less after 10 days of treatment.

Influence on the Secondary Comparison Criteria

To provide further assessment, the secondary comparison criteria can also be employed, with adjustment of the significance levels after Bonferroni, as already described.

For pain upon movement, Table 3 reveals a group difference on the tenth day with a significance of p less than or equal to 0.0001 (exactness in accordance with Fischer); adjusted after Bonferroni, this becomes p less than or equal to 0.0003.

Fig. 2 shows the development in the number of patients without movement pain throughout the entire course of therapy.

For the inversion angle (supination), Table 4 reveals the following, in the sense of the definition: a difference between the groups on the tenth day with p = 0.13 (exactness in accordance with Fischer). For this characteristic, however, the difference here is not significant, even before adjustment.

Discussion of results

Strict Double-Blind Conduct of Testing

The organization of this test, and the manner in which the two preparations were presented and employed, guaranteed strict double-blind conduct of testing. Such rigorousness of testing was a methodological necessity owing to the therapeutic effectiveness of the basic VARIODYN treatment administered to both groups and, in turn, the expected slight differences in recovery between the Traumeel and placebo groups. Even experienced test personnel were not able to tell the difference between Traumeel and the placebo in their appearance, odor, and tactile impressions.

Verification of Effectiveness with the Aid of Biometry

The question of course remains open as to the manner in which the active constituents in Traumeel reach the site of injury through the skin. The actual diffusion barrier in this case is the stratum corneum, the permeation of which requires that a substance possess both hydrophilic as well as lipophilic characteristics.

The human skin is, furthermore, not equally permeable at all points on the body. For a preparation with several active components, the circumstances involved dictate that pharmacokinetic questions concerning the action of such constituents be exactly answered, only with great difficulty, if at all. In recent time, to be sure, there have been a goodly number of models and

Criterion for Selection of the Patients Studied

For identification of the target criterion for the main test, a pilot test was first conducted: 47 patients in two groups (Traumeel and placebo), with randomized assignment of effective/placebo therapy in accordance with a computer program.

Patients were selected from victims up to the age of 30 with sprains of the upper and lower ankle areas (talocruralis and talocalcaneonavicularis articulations) as suffered while engaged in sports activities. Outpatients therapy was provided in the Department of Physical Therapy of the University Hospital of Homburg (Saar), Germany. The patients were not allowed to engage in sports for the duration of the therapy.

Patients who fell into the following categories were excluded from this study:

a. Patients with joint injuries on both sides, or with multiple joint injuries on the same side.
b. Patients who had been injured more than 24 hours before the opportunity of their inclusion in the test.
c. Patients with prior injuries at the same joint within six months before the test began.
d. Patients with open wounds and the danger of infection.
e. Patients with bone fractures.
f. Patients for whom local or systematic long-term therapy with non-steroid anti-inflammatory medication was deemed necessary.
g. Patients for whom static loadbearing deficiency of the joints concerned was present, on either a hereditary or an acquired basis.
h. Patients with degeneratively predamaged joints, chronic joint disorders, or post-operative joint conditions.
i. Persons in poor physical condition and patients who did not engage in sport.
j. Pregnant patients.
k. Patients for whom the Movement-Pain Score was less than 2 at the time that the initial test was conducted.
l. Patients for whom the difference was less than 20 degrees between the injured and non-injured joints, for the angular sum from flexion plus extension, at the time that the initial test was conducted.
m. Patients for whom the difference was less then 15 degrees between the injured and non-injured ankles for the inversion angle at the time that the initial test was conducted.

Plan of Therapy

The duration of therapy did not exceed 14 days. Patients were instructed to visit the clinic for in-patient treatment on the first, third, fifth, eighth, tenth, twelfth, and fifteenth days after the injury. In all cases, the same therapist made the measurements, evaluated the conditions, and administered the medication. By virtue of this arrangement, uniform quality of treatment and evaluation, and patient compliance were ensured in all cases. Approximately 10 to 12 grams of salve were administered in the form of applying a compression ointment bandage in accordance with the lesion concerned, and the basic VARIODYN treatment was conducted.

The Traumeel and the placebo ointments were provided in identical packaging and could not be distinguished by either patients or therapist. The assignment of Traumeel and placebo was performed by a computer-generated randomizing program and consecutive treatment numbers were accordingly issued. The sequence of entry of the patients into testing determined the respective assignment to a treatment number and, in turn, to one of the two test groups. Where required, the therapy was continued past the fifteenth day. For purposes of statistical evaluation, however, only findings until the fifteenth day were considered. In the event that a patient recovered completely before the fifteenth day, his or her last examination was considered to be equivalent to the post-treatment examination. For patients with requirements for longer treatment, the post-treatment examination was considered to take place on the nineteenth day. Patients for whom a change in medication was necessary for various reasons, for whom total immobilization of the injured joint became necessary, or who had to be admitted to the hospital on an in-patient basis, were also no further studied.

Recording of Data

Upon initial examination, fundamental data such as age, body size, weight, and duration of symptoms before acceptance into the study were recorded. Data on patient pain were recorded each time medication was administered in the consecutive examination/treatment sessions. Immobile pain, pain upon movement, and pain upon pressure were reported on a three-point scale with the score values of 0 = no pain, 1 = mild pain, and 2 = severe pain. Clinical findings were recorded in the form of the following measurements: skin temperature above the injured joint, circumference of the joint to indicate the degree of swelling, and joint mobility in accordance with the neutral-null method (by means of a goniometer with precision of ± 3). The degree of maximum possible active joint movement as carried out by the patient himself was measured as linear displacement, and the difference was taken between this maximum reading and the corresponding measurement made on the opposite non-injured joint at the time of admission to testing.

The movement deflection for the upper ankle (talocruralis articulation) is this sum of the angular measurement for flexion plus extension. For the lower ankle (talocalcaneonavicularis joint), differentiation is made between the eversion and the inversion angles.

Target Criterion

It was determined from the measured values of the clinical findings from the pilot study that the skin temperature and the degree of swelling do not represent sufficiently precise characteristics for assessment of the course of therapy for the medical treatment of sprains. Only the following factors were found to be adequately precise to afford a basis for evaluation of sprain therapy:

- The angular sum taken from flexion and extension tests, in determination of joint mobility.

- The inversion angle (supination).
- The degree of pain suffered upon movement.

On the basis of the results of measurements in the pilot test, the target criterion was initially defined as follows before the beginning of the main test:

- Individually successful therapy within 8-10 days (i.e., up to the forth consecutive examination).

One characteristic which satisfactorily quantifies the degree of restoration of complete joint mobility for the upper ankle (talocruralis articulation) is the difference between the angular sum of flexion + extension for the injured and for the non-injured joints. The result 0 here represents equal mobility of both ankles. The error measurement in these tests was ± 10.

Characteristic	Group	
	Traumeel n = 33	Placebo n = 36
Female	n = 8	n = 11
Male	n = 25	n = 25
Age in years	23 ± 5	22 ± 4
Height in cm	175 ± 6	175 ± 6
Weight in kg	70 ± 8	70 ± 6.5
Time in hours between the injury and the beginning of therapy	10.8 ± 3.5	10.5 ± 3.2

Table 1: Comparability of the groups in the main test

Further definition of target criterion:

- The therapy was assessed to have been successful in the difference in the angular sums between injured and non-injured ankles decreased to 10 or less by the fourth consecutive examination/therapy visit (i.e., after approximately 10 days).

Formulation of the target criterion in this matter requires that the following conditions prevail:

- Upon initial acceptance for therapy, all patients demonstrate a substantial difference in the angular sums (flexion + extension) between injured and non-injured ankles: at least 20.
- This difference does not increase again to values above 10 during the fifth and sixth examination/therapy visits.

Secondary Comparison Criteria

- Pain upon movement:

Only major changes in the degree of pain allow results to be obtained on a basis which can be expected to be reliably reproducible. Formulation of the criterion of success here:

- The therapy was assessed to have been successful if the score recorded for pain upon movement decreased from 2 at the initial (acceptance) examination to 0 at the fourth consecutive examination/therapy visit.

Successful data are compared in both groups treated. This applies under the condition that all patients demonstrate a score of 2 upon the acceptance examination, and that the score not increase again by the fifth and sixth examinations.

- Inversion (supination):

Errors in measurement of the angular differences amount to approximately ± 7. A considerable angular difference around 15 was measured in many cases in the pilot test. Further formulation of the criterion of success:

- The therapy was assessed to have been successful if the angular difference between injured and non-injured ankles in the measurement for the inversion decreased to 7 or less by the time of the fourth consecutive examination/therapy visit.

Comparison was made of the success quotas for both groups being treated.

The above applies under the conditions that all patients demonstrate an angular difference of at least 15 upon being admitted, and that the angular difference not increase to 7 or more by the fifth and sixth visits.

Test Statistics

Clinically relevant difference: A rate of successfully treated patients of 0.2 (pl = 0.2), with a confidence interval of 95 % for the true probability of success of 0.03-0.60, was expected for the placebo control group in the main test, as predicted from assessment of the pilot test. For Traumeel, the actual medication administered, results would be considered clinically relevant only in the event of a very definite difference with respect to the placebo: Delta P = 0.40 would be considered adequate here.

Statistical model: The null hypothesis would be p1 = p2. Level : a = 0.05. Statistical power of the double-sided test: 1 - ß = 0.90. On the basis of calculations performed on the results of the pilot test, 35 cases capable of evaluation are required per group in the main test. With a statistical invalidity rate of 0.20

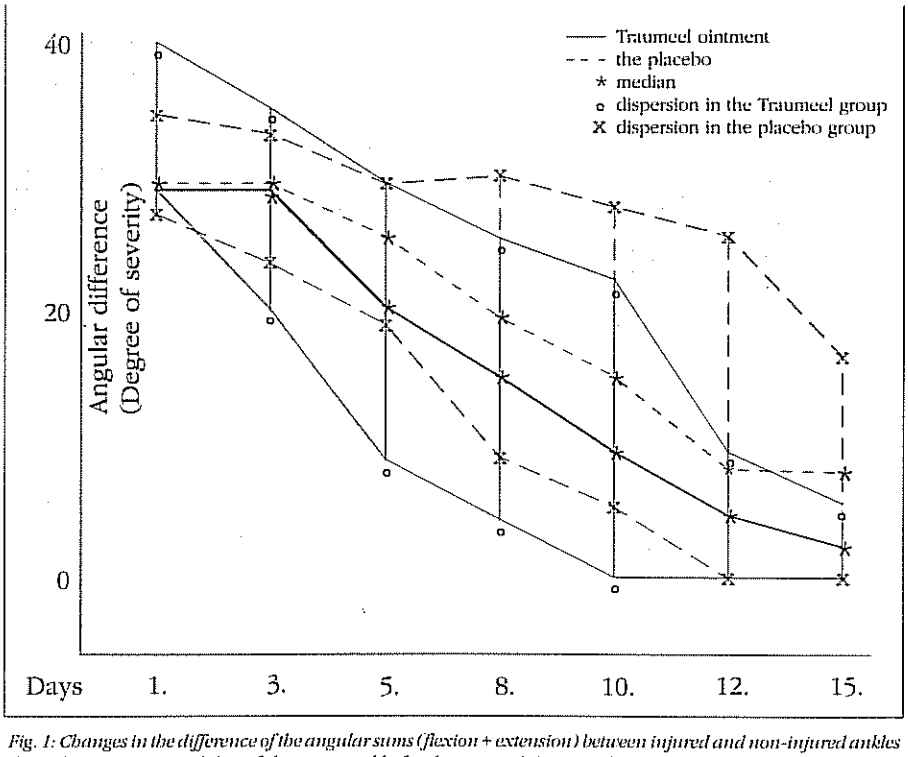


Fig. 1: Changes in the difference of the angular sums (flexion + extension) between injured and non-injured ankles through increase in mobility of the upper ankle for therapy with Traumeel ointment and for treatment with a placebo.

experimental investigations directed toward the answer to these questions. The mean saturation flux through human skin for atropine, to take one example, is 0.01 ug/cm² • h (in accordance with source 1), whereas for hydrocortisone the percutaneous absorption rate at the ankle is only approximately one-eighth that measured at the armpit (4).

According to Chlud (5), there are for a great number of NSAID's pharmacokinetically confirmed investigation data which attest that administered drugs undergo a concentration process in the following parts of the body after they have passed through the layers of the skin: the subcutis, the fasciae lying below, the musculi, the synovial bursae, the tendons and ligaments, the articular capsules, and the synovial fluid. At the same time, only very slight amounts of such administered drugs are found in the blood, an observation which rules out systemic action. In the case of therapeutic agents which contain natural constituents prepared without chemical alteration, it is impossible in the vast majority of cases to assess each of the individual agents involved - many of which are as yet unknown - for their pharmacokinetic characteristics. Entirely apart from these difficulties remains, in addition, the question of pharmacodynamic phenomena. Consequently, it appears more effective to subject the preparation in toto to an investigation of its effectiveness.

As the results of this pioneering clinical test have demonstrated, the techniques of modern biometry indeed make it possible to subject a preparation of this nature to just such an assessment of its effectiveness.

Literature

1. Asche H. Schweiz. Rundsch. Med. (Praxis) 1985; 11:3.
2. Bartek M.J, LaBudde J.A, Maibach H.I. J. Invest Dermatil. 1972; 58:116.
3. Biener K, Fasler S. Sportunfälle, Huber, Bern/Stuttgart/ Wien 1978.
4. Casper J, Foerstel G. Erfahrungen mit Traumeel in Klinik und Praxis, Therapiewoche 1986; 17: 892.
5. Chlud K. Diagnostik und Therapie rheumat. Erkrankungen: Perkutane Rheumatherapie mit NSAR. Vortrag auf d. 39. Therapiewoche, Karlsruhe, 2. Sept. 1987.
6. Fenner H. Wirkstoffe zur Behandlung rheumat. Erkrankungen, mediamed 1984.
7. Feuerstake G, Heisel J. Muskel, Sehnen u. Gelenksverletzungen. Allgemeinmedizin 1984; 60: 530-533.
8. Frank K. Traumatologie des Sports. Thieme, Stuttgart, 1980.
9. Groh H, Groh P. Sportverletzungen u. Sportschäden. Luitpold-Werke, München, 1976.
10. Jäger M, Wirth C.J. Praxis d. Orthopädie. Thieme, Stuttgart, 1986.
11. Lindner J. Die Rolle der terminalen Strombahn bei der Entzündung. Therapiewoche 1982; 32: 4675-4689.
12. Mergen H. Therapie posttraumatischer Schwellungen mit Traumeel. Münch. med. Wschr. 1970; 111: 298.
13. Peterson L, Renstrom P. Verletzungen im Sport DAV 1987.
14. Pförringer W, Rosemeyer B, Bär H.W. Sporttraumatologie, perimed, Erlangen 1981.
15. Schubert K. Traumeelsalbe in d. Traumatologie des praktischen Arztes. Homotoxin-J. 1967; 6: 281.
16. Schwerdtner H.P. Sportverletzungen. permimed. Erlangen 1982.
17. Seissiger L, Wallner H. Traumon Gel bei stumpfen Traumen. Therapiewoche 1984; 34: 5045-5059.
18. Thiel W. Die Behandlung von Sportverletzungen und Sportschäden mit Traumeel. Biol. Med. 1986: 15,4,163.
19. Wagenhäuser F.J. Nutzen und Risiken der Antirheumatika. Eular, Basel 1985.
20. Wagner J, Jurcic K, Doenicke A, Rosenhuber E, Behrens N. Die Beeinflussung der Phagozytosefähigkeit von Granulozyten durch homöopathische Arzneipräparate. Arneim. Forsch./Drug Res. 1986; 36 (II): 1421-1425.

Contact with the authors is possible through the following address:

Dr. med. Jürgen Zell
Hauptstr. 110
6580 Idar-Oberstein
Germany

Special printing, by permission, of an article which originally appeared in Fortschritte der Medizin, an international magazine for medical science, founded in 1882 by Carl Friedlander and Robert Koch:

Volume 106, Issue 5, pp 96/62-100/70 (1988), copyright by Urban & Vogler, Munich.