Treating Osteoarthritis of the Knee with a Homeopathic Preparation

Results of a Randomized, Controlled, Clinical Trial in Comparison to Hyaluronic Acid

G. Nahler, H. Metelmann, and H. Sperber

Key words

arthritis, homeopathy, Zeel® compositum, hyaluronic acid

Abstract

This multicentric, randomized, single-blind, controlled study compared the efficacy and tolerance of Zeel® compositum and Hyalart® brand of hyaluronic acid in the treatment of patients with osteoarthritis of the knee. Over the five-week course of the study, each patient received either 10 injections of Zeel® compositum (two 2 ml intra-articular injections per week) or 5 injections of Hyalart® (one 2 ml intra-articular injection per week). Key parameters were the intensity of pain in the arthritic joint during active movement, and the global assessment of tolerance, both as reported by the patient. Out of a total of 121 patients, the data on 114 (2 treatment groups of 57 patients each) were suitable for statistical analysis. Zeel® compositum and Hyalart® proved to be equally efficacious in treating patients with either milder or more severe pain. Undesirable incidents occurred in 6 patients receiving Zeel® compositum and in 13 of those receiving Hyalart®. In both treatment groups, the most frequently reported side effects were signs of local inflammation or irritation after the intra-articular injections.

Introduction

Osteoarthritis of the knee is a painful, degenerative joint disease that occurs in approximately 10% of all individuals over the age of 65 and in approximately 2% of the total adult population.[1,2] At present there is no effective means of treating the cause. Depending on the stage of the illness, however, good therapeutic results can be achieved with non-steroidal anti-inflammatories, corticosteroids, hyaluronic acid, homeopathic remedies, and organ lysates. Age-related cartilage degeneration is a crucial factor in the development of arthritis, since all bradytrophic tissues—due in large part to the fact that they are poorly supplied with blood vessels—are subject to regressive aging processes with increasing loss of elasticity. Because of the chronic and generally progressive nature of the disease, the best possible ratio of therapeutic efficacy to risk of undesirable side effects is a prime consideration in the selection of pharmaceutical therapy.

The goal of this multicenter, randomized, controlled, single-blind, clinical-equivalence study was to prove the therapeutic efficacy of Zeel® compositum in treating knee arthritis. According to the symptom pictures of its individual ingredients (Rhus toxicodendron, Arnica montana, Solanum dulcamara, Sanguinaria canadensis, and Sulphur), Zeel® compositum, a combination homeopathic preparation, is appropriate for effectively alleviating arthritic symptoms with little risk.[a] Hyalart® brand of hyaluronic acid (a polysaccharide and a natural component of synovial fluid) was selected as the comparative drug.[b] Controlled studies have demonstrated the therapeutic efficacy of Hyalart® in treating arthritis.[3,4,5,6] Because Hyalart® is visibly more viscous than Zeel® compositum and because the manufacturer recommends less frequent applications than are recommended for Zeel® compositum, it was not possible to conduct this trial on a strict double-blind basis, so it was conducted as a single-blind study. Additional injections of a placebo to equalize application frequencies between the two drugs were rejected as unethical.

Editor's note: The formula of the complex homeopathic preparation featured in this study, Zeel® compositum, is not available in the U.S. In the U.S., Zeel® is distributed as ointment, tablets, and oral vials, all of which contain the same ingredients of Zeel® compositum, plus others.

Methodology

Between July 1994 and February 1995, 12 orthopedic physicians in active practice in Germany and Austria accepted a total of 121 patients of both sexes with primary osteoarthritis of the knee into this clinical trial.

Criteria for inclusion were:

- presence of primary (idiopathic) arthritis, verified by:
  - pain in one or both knees;
  - a typical X-ray (medial narrowing of the joint cavity, peripheral osteophyte development, compact ossification of subchondral bone)
  - chronic pain in one or both knee joints for at least three months, with no sign of acute inflammation

[a]Zeel® compositum is manufactured by Biologische Heilmittel Heel GmbH, Baden-Baden, Germany.

[b]Hyalart® is manufactured by Bayer AG, Leverkusen, Germany.

- written statement of patient consent.

Criteria for exclusion were:

- age <35 or >85 years
- arthritis resulting from prior deformations, injuries, or metabolic causes (secondary arthritis)
- other ailments with symptoms similar to arthritis of the knee, such as arthritis of the hip, varicosis, bone and muscle disorders, rheumatoid arthritis
- signs of acute inflammation (acute active arthritis)
- non-ambulatory or bedridden patients
- patients who stated their intention to change their level of physical activity during the study
- probable surgical treatment of the arthritic joint in the near future
- intra-articular corticosteroid treatment of the arthritic joint within the past 2 months
- low-grade pain (<25 mm on the 100 mm visual analog scale)
- a history of allergic reactions to Zeel® compositum or Hyalart®
- serious liver or kidney disease
- long-term treatment with immunosuppressives during the last month
- ongoing concomitant therapy with analgesics/anti-inflammatories

Random assignment to one of the two treatment groups was accomplished with the help of a special EDP program (Rancode, IDV), which also sorted the patients into subgroups on the basis of pain intensity during active movement of the arthritic joint. Less severe pain was defined as 25-60 mm on the VAS-SB, severe pain as 61-100 mm. Treatment proceeded according to the manufacturers' recommendations. Over the five-week course of the study, each patient received either 10 injections of Zeel® compositum (two 2 ml intra-articular injections per week) or 5 injections of Hyalart® (one 2 ml intra-articular injection per week). To ensure that the patients did not know which medication they were receiving, the physicians were requested to prepare and administer the injections in such a way that the patients could not see the packaging and to make sure that participants in the study were not in the same room at the same time.

Primary parameters were:

- subjective experience of pain in the arthritic knee joint during active movement, measured on a standardized visual analog scale (VAS) 100 mm in length (0 mm = pain-free, 100 mm = worst pain to date)
- the patients' final assessment of tolerance at the end of five weeks of treatment, measured on the 100 mm VAS (0 = extremely poorly tolerated, 100 = extremely well tolerated)

Secondary parameters were:

- pain in the arthritic knee joint during the night, measured on the 100 mm VAS (0 mm = pain-free, 100 mm = worst pain to date)
- duration of morning stiffness (in minutes)
- maximum distance the patient was capable of walking (as a functional criterion for assessing the severity of the arthritis)
- time required (in seconds) to walk up and down a standard series (one flight) of stairs (relative change)
- final assessment of efficacy by physician and patient at the end of five weeks of treatment, measured on the 100 mm VAS (0 mm = no improvement, 100 mm = extreme improvement)
- final assessment of tolerance by physician and patient at the end of five weeks of treatment, measured on the 100 mm VAS (0 mm = extremely poorly tolerated, 100 = extremely well tolerated)
- drop-out rate in both groups resulting from inadequate product efficacy
- reporting of undesired side effects during treatment (recorded weekly)

All of the compiled data were recorded on standardized questionnaires. The study was conducted in accordance with the European Union's Good Clinical Practice guidelines and German and Austrian national laws.

Data Preparation and Statistical Analysis

A two-tailed Wilcoxon's rank-sum test (= 0.05 and = 0.20) was used to analyze the differences between the treatment groups with regard to efficacy and tolerance. In calculating required sample size, the efficacy or tolerance of the two forms of treatment was assumed to be therapeutically equivalent if the absolute difference in therapeutic efficacy (defined as reduction in pain during active movement after five weeks of treatment, as measured on the VAS) or tolerance (defined as final assessment after five weeks of treatment, as measured on the VAS) between Zeel® compositum and Hyalart® was no greater than 33%. Minimum group size was calculated at n1 = n2 = 51, without including drop-outs amounting to approximately 10%. Comparability of treatment groups with regard to baseline characteristics was tested by means of either the Wilcoxon test (pain during active movement or during the night when the study began) or the chi-square test (number of affected knee joints); the difference in frequency of side effects was tested by means of the chi-square test. Taking into account the patients' subjective experience of pain intensity during active movement when the study began (as per VAS-SB), therapeutic efficacy and tolerance in each treatment group were compared by means of either covariance analysis or the Wilcoxon test (patients with more or less severe pain were assigned to subgroups). A descriptive statistical analysis of baseline characteristics and all secondary parameters was performed with a chosen level of significance of = 0.05.

Results

In accordance with the intent-to-treat principle, all available analyzable data on 114 patients, including drop-outs and protocol violators, were used in analyzing efficacy and tolerance. Of a total of 121 randomly selected patients, three did not meet the minimum pain requirement (at least 25 mm on the VAS-SB). Four patients who had been mistakenly treated with both products (in different knees) were studied only with respect to undesired incidents and excluded from the analysis of efficacy, resulting in 114 assessable patients (Table 1). The two treatment groups (n = 57) were comparable both with regard to all baseline characteristics (age, gender, height and weight, concomitant illnesses and medications) and with regard to anamnestic

data on the arthritis (duration of illness, intensity of pain, and morning stiffness at the inception of the study, Table 2). In accordance with the exclusion criteria, concomitant use of analgesics and anti-inflammatories was prohibited. Protocol violations on this count occurred in one patient receiving Zeel® compositum and in three receiving Hyalart®. Other protocol violations were premature termination of therapy for non-medical reasons (one patient), failure to adhere to treatment schedule (one patient), and premature termination of therapy because of inadequate improvement (two patients receiving Zeel® compositum and one receiving Hyalart®).

a) Therapeutic Efficacy

The patients' arthritic symptoms clearly decreased both under treatment with Zeel® compositum and under treatment with Hyalart.® In both treatment groups there was a roughly linear decrease in pain due to active movement of the arthritic joint. This decrease averaged 36 mm for Zeel® compositum (from 67 mm to 31 mm) and 37 mm for Hyalart® (from 63 mm to 26 mm). The reduction in nocturnal joint pain followed a similar pattern, with a linear decrease during treatment (from 33 mm to 9 mm for Zeel® compositum and from 35 mm to 7 mm for Hyalart®). Duration of morning stiffness in the arthritic joint was reduced from 5 minutes to 2 minutes for Zeel® compositum and to 1 minute for Hyalart® (Table 3).

According to analysis of the difference in therapeutic efficacy between Zeel® compositum and Hyalart® by means of a two-tailed Wilcoxon's rank-sum test, these two forms of treatment can be seen as therapeutically equivalent (pain during movement: $p = 0.4298$; pain during the night: $p = 0.3077$; duration of morning stiffness: $p = 0.9211$). An increase in functional ability was associated with pain reduction during treatment. After five weeks of treatment, the percentage of patients who were able to walk more than 1 km increased from 55% to 67% for Zeel® compositum and from 68% to 79% for Hyalart®. In 3 out of 5 patients in the Zeel® compositum group and 1 out of 3 patients in the Hyalart® group, symptoms improved so much that they were able to do without the cane they had needed when treatment began. The time needed to climb one flight of stairs also decreased by an average of 18% for patients treated with Zeel® compositum

Criteria	Number of patients
number of randomly selected patients	121
number of patients with pain <25 mm VAS-SB	-3
number of patients mistakenly treated with both Zeel® compositum and Hyalart®	-4
number of analyzable cases (in accordance with intent-to-treat)	114
number of patients terminating therapy prematurely	-5
number of patients terminating therapy after 5 weeks	109
number of patients with protocol violations	-6
number of patients completing the study as per protocol	103

Table 1: Size of the different subgroups

Criteria		Zeel® compositum	Hyalart®
age (in years)	n	57	57
	mean	67	66
	S.D.	10	10
	min	37	38
	max	83	84
gender	male	12	11
	female	45	46
height in cm	n	56	57
	mean	164	166
	S.D.	8	8
weight in kg	n	56	57
	mean	78	76
	S.D.	13	11
concomitant illness	yes	20	24
	no/not indicated	37	33
concomitant medication	yes	32	31
	no/not indicated	25	26
duration of arthritis in years	<1	39	39
	>1-<2	7	5
	>2	11	11
	not indicated	0	2
knee joint(s) affected	both sides	42	27
	one side	15	28
	not indicated	0	2
pain in arthritic joint during movement, as per VAS in mm, at inception of treatment	median	67	63
	25th percentile	49	44
	75th percentile	80	79
nocturnal pain in arthritic joint at inception of treatment, as per VAS in mm	median	33	35
	25th percentile	13	20
	75th	50	58
morning stiffness at inception of treatment, in min	median	5	5
	25th percentile	3	1
	75th percentile	10	10

Table 2: Demographic and anamnestic data on the two treatment groups. Numbers not otherwise identified refer to number of individuals.

Criteria		Visit 1		Visit 2		Visit 3		Visit 4		Visit 5		Visit 6	
		Zeel®	Hyalart®	Zeel®	Hyalart®	Zeel®	Hyalart®	Zeel®	Hyalart®	Zeel®	Hyalart®	Zeel®	Hyalart®
joint pain	n	57	57	56	56	55	54	55	54	55	54	54	54
during movement	median	67	63	59	53	52	61	46	44	42	31	31	26
(in mm)	min	29	21	15	10	10	3	4	0	2	2	1	0
	max	98	98	92	100	95	98	90	94	92	95	94	79
joint pain	n	57	57	56	56	55	54	55	54	55	54	54	54
during the night	median	33	35	21	23	18	26	19	18	12	12	9	7
(in mm)	min	0	0	0	0	0	0	0	0	0	0	0	0
	max	95	99	94	100	91	87	86	85	97	90	95	77
duration of	n	57	57	56	54	55	54	55	54	55	54	55	53
morning stiffness	median	5	5	5	3	5	3	5	2	4	2	2	1
(in mm)	min	0	0	0	0	0	0	0	0	0	0	0	0
	max	120	75	120	120	120	60	120	60	120	50	120	50

Table 3: Change in pain intensity and duration of morning stiffness under treatment with Zeel® compositum and Hyalart® (pain data as per VAS: 0mm = pain-free, 100mm = worst pain to date)

and by an average of 9% for those treated with Hyalart®.

The results of the final assessment confirmed the comparable therapeutic efficacy of the two products (Table 4). Noticeable improvement in symptoms was reported for 87.3% of the patients treated with Zeel® compositum and 93.0% of those treated with Hyalart®. In both treatment groups, the patients' subjective assessment was slightly more favorable than that of the physicians who treated them. VAS values assigned by patients were 2 mm greater for Zeel® compositum and 4 mm greater for Hyalart® than the values assigned by the physicians. In both treatment groups, co-variance analysis reveals that the success of treatment depends significantly on pain intensity at the inception of the study (p = 0.0060). When initial pain was considered as a co-variable, no significant difference between Zeel® compositum and Hyalart® with regard to therapeutic success could be determined (p = 0.7555). This means that the efficacy of Zeel® compositum must be seen as equivalent to that of Hyalart® both in patients with less severe pain (25 to 60 mm as per VAS) and in cases of more severe pain (61 to 100 mm as per VAS). The fundamental character of the results is not changed if, instead of conducting the assessment according to the intent-to-treat principle, the analysis comprises only the data on the 103 patients who completed the study according to plan.

Efficacy		Zeel® compositum	Hyalart®
physician	n	55 patients	57 patients
	median	57 mm	59 mm
	min	00 mm	00 mm
	max	96 mm	98 mm
patient	n	55 patients	57 patients
	median	59 mm	63 mm
	min	00 mm	00 mm
	max	97 mm	100 mm
Tolerance		**Zeel® compositum**	**Hyalart®**
physician	n	55 patients	57 patients
	median	96 mm	95 mm
	min	1 mm	12 mm
	max	100 mm	100 mm
patient	n	55 patients	57 patients
	median	94 mm	97 mm
	min	13 mm	36 mm
	max	100 mm	100 mm

Table 4: Final assessment (efficacy/tolerance) by patients and physicians as per VAS (efficacy: 0mm = no improvement, 100 = extreme improvement) (tolerance: 0mm = extremely poorly tolerated, 100mm = extremely well tolerated)

b) Tolerance

In terms of tolerance, the trend favored Zeel® compositum. A total of 6 patients (11%) treated with Zeel® compositum and 13 patients (23%) treated with Hyalart® developed undesirable side effects (chi-square test: p = 0.079). While receiving twice-weekly injections of Zeel® compositum 3 patients developed low-grade joint effusions that had to be tapped. Renewed applications of Zeel® compositum induced new effusions in 2 of these 3 patients, and as a result treatment was prematurely terminated (after 9 injections) in one case. The two other patients completed the study according to plan in spite of intermittent joint effusions. One patient reported a temporary sensation of heaviness in the leg after the first injection of Zeel® compositum Another Zeel® com-

positum patient terminated treatment prematurely after two weeks because of headaches and insomnia. Two patients from the Zeel® compositum group and 9 from the Hyalart® group complained of increased pain in the knee joint after the intra-articular injections; the pain lasted from 3 to 7 days. One patient from the Hyalart® group had to terminate therapy after the first injection because of an allergic reaction (pain, swelling, and redness from the knee to the mid thigh). In contrast to Zeel® compositum, no joint effusions were observed in the Hyalart® group, but one patient complained of a hot burning sensation in the knee joint that appeared 24 hours after each of the first two Hyalart® injections and lasted approximately 24 hours. Another Hyalart® patient reported a mild sensation of pressure and fullness in the joint for about 15 minutes after the third injection. In one patient, nausea and repeated vertigo were experienced after intra-articular applications of Hyalart®. The physicians of two additional patients from the Hyalart® group reported that side effects had appeared but they failed to specify further. In all of these cases, the side effects subsided without medication during the course of the study.

The final assessment of tolerance (as per VAS) upon conclusion of treatment indicated very good tolerance of both tested products without significant differences between the two treatment groups. According to the Wilcoxon test: patients' assessment of tolerance $p = 0.1213$; physicians' assessment $p = 0.7287$; in the great majority of cases, the physicians' assessments coincided with those of their patients. (The difference between physician and patient assessments was 2 mm for both treatment groups; Table 4).

Discussion

Many studies restrict themselves to statistically substantiating improvement over the course of therapy in comparison to the starting point (pre-post comparison). However, since symptom patterns do not remain constant over the course of an illness, patients generally tend to see a physician only when the pain has already increased. As a result, there is a high degree of probability that the pain will revert spontaneously to its previous level. This is also known as 'regression to the mean.'[7] Thus analyses based on pre-post comparisons are not always reliable because, taken by themselves, they cannot separate spontaneous improvement from strictly therapeutic effects. A different route was chosen in the context of this present study, namely comparison of improvement in the two treatment groups at the end of a predefined course of therapy (post-post comparison). The definition of therapeutic equivalence that was used here was not purely statistical but primarily clinical, namely a certain range within which the improvement in one group would be considered equivalent to that in the other. In this study, equivalence was assumed if the maximum difference in decrease in pain between the two groups was no more than 33% (pain at inception of study = 100%). In fact, this investigation showed the difference to be only five percentage points (59% for Hyalart® vs. 54% for Zeel® compositum), meaning that with regard to therapeutic efficacy, Zeel® compositum and Hyalart® are equivalent.

There is a linear correlation between improvement in pain and duration of treatment. The criterion 'pain during movement' yields a coefficient of $r = -0.80$ while the criterion 'pain during the night' yields a coefficient of $r = -0.69$. A similarly linear relationship was also found in a recently completed prospective study in which 446 patients with knee arthritis were treated with Zeel® compositum.[8]

In addition, it is especially interesting to note that the therapeutic efficacy of Zeel® compositum was found to be equivalent to that of Hyalart® not only in the subgroup with less severe pain but also in the group with more severe pain. Analysis of the assessments of therapy resulted in a therapeutic success rate of 87.3% for Zeel® compositum when the criterion for success was set at a reduction of at least 10 mm on the 100 mm visual analog scale. Treatment with either Zeel® compositum or Hyalart® led to an increased sense of well-being as a result of pain reduction and to an increase in functional capacity (climbing stairs, distance patients were able to walk) that also contributed to improving the patients' quality of life.

In this trial, a trend in favor of Zeel® compositum was noted with regard to tolerance. Although Zeel® compositum was injected twice as often as Hyalart® and the probability of complications was therefore greater, Zeel® compositum had only half as many undesired incidents. While one patient terminated treatment prematurely because of a suspected allergic reaction after being injected with Hyalart®, no allergic reactions of any kind appeared in the Zeel® compositum group.

The results of this clinical study and of the prospective study of Zeel® compositum confirm the favorable empirical reports of this homeopathic preparation that have accumulated over the years. A 1992 prospective study of Zeel® P (which has 10 more ingredients than Zeel® compositum) involved 1845 patients with osteoarthritis of the knee. That study also documented a significant linear decrease in pain symptoms.[9] Like Zeel® compositum, Zeel® P was also found to be therapeutically effective for mild, moderate, and severe symptoms, with 93.1% of the patients rating the therapeutic success as positive, i.e. satisfactory to very good.

References

(1) Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee arthritis in women. *Ann Int Med* 116 (1992):535-39.

(2) Hadler NM. Knee pain is the malady - not osteoarthritis. *Ann Int Med* 116 (1992) 598-99.

(3) Bragantini A, Cassini M, DeBastiani G, Perbellini A. Controlled single-blind trial of intra-articularly injected hyaluronic acid in osteoarthritis of the knee. *Clin Trial J* 24 (1987) 333-40.

(4) Carraba M, Paresce E, Angelini M, Zamboni AM, Bragantini A, Paissan A, Molinaroli F, Perbellini A. The intra-

articular treatment of osteoarthritis of the knee. A comparative study between hyaluronic acid and orgotein. *Eur J Rheumatol Inflam* 12 (1992) 47-57.

(5) Dixon ASJ, Jacoby RK, Berry H, Hamilton EBD. Clinical trial of intra-articular injection of sodium hyaluronate in patients with osteoarthritis of the knee. *Current Med Res and Opinion* 11 (1988) 205-13.

(6) Pietrogrande VPL, Melanotte D, Agnolo B, Ulivi M, Benigni GA, Turchetto L, Plerfederici P, Perbellini A. Hyaluronic acid versus methylprednisilone intra-articularly injected for treatment of osteoarthritis of the knee. *Current Ther Res* 50 (1991) 691-701.

(7) Nahler G. *Dictionary of Pharmaceutical Medicine.* Springer Verlag. Wien, New York. 1994.

(8) Weiser M. Metelmann H. Intraartikulare Behandlung der Gonarthrose mit Zeel® comp. Ergebnisse einer Anwendsungsbeob-achtung (Publikation in vorbereitung)

(9) Weser M, Metelmann H. Behandlung der Gonarthrose mit Zeel®P injektionslosung - Ergebnisse einer Anwendsungsbeobachtung. *Biol Med* Heft 4 (1993) 193-201.

For the authors:

H. Metelmann
Biologische Heilmittel Heel GmbH
Scientific Department
Dr. Reckeweg Str. 2-4
D-76532 Baden-Baden
Germany