Intraarticular Hyaluronic Acid versus Glucocorticoid Injections for Nonradicular Pain in the Lumbar Spine

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PURPOSE: To investigate the efficacy and safety of intraarticular sodium hyaluronate (SH) compared with intraarticular glucocorticoids (triamcinolone acetonide; TA) in the treatment of chronic nonradicular lumbar pain.

MATERIALS AND METHODS: Sixty patients were included in this randomized, controlled, blind-observer clinical study and randomly assigned to two groups to receive 10 mg SH or 10 mg TA per facet joint. The facet joints on both sides at levels S1–L5, L5–L4, and L4–L3 were treated once per week under computed tomographic guidance. The study visits were timed to permit assessment of the immediate effect as well as possible carryover effects at 3 and 6 months after completion of treatment. Changes in pain were assessed with a visual analog scale (VAS) and changes in function and quality of life were assessed by the Roland Morris Questionnaire (RMQ), the Oswestry Disability Questionnaire (ODQ), the Low Back Outcome Score (LBOS), and the Short Form 36 (SF-36) questionnaire.

RESULTS: Patients reported lasting pain relief, better function, and improved quality of life with both treatments. Mann-Whitney analyses of the patient questionnaires (RMQ, ODQ, and LBOS) very consistently showed that SH is not inferior to TA. In addition, the efficacy of SH was largely comparable with that of TA on the VAS and SF-36. No adverse effects were reported after administration of the test products. The intraarticular treatment of facet joints (levels S1–L5, L5–L4, and L4–L3) with SH in patients with chronic nonradicular pain in the lumbar spine resulted in a marked reduction in pain with improved function and better quality of life, which was at least equal to the effect of a course of TA injections. SH-treated patients showed greater benefits in the long term.

CONCLUSION: Intraarticular SH is a very promising new option for the treatment of patients with chronic nonradicular lumbar symptoms.

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Abbreviations: LBOS = Low Back Outcome Score, OA = osteoarthritis, ODQ = Oswestry Disability Questionnaire, RMQ = Roland Morris Questionnaire, SF-36 = Short Form 36 (questionnaire), SH = sodium hyaluronate, TA = triamcinolone acetonide, VAS = visual analog scale

THE facet joints of the vertebral column are surrounded by a synovial (ie, articular) capsule. Degenerative changes of the facet joints are commonly caused by thinning of the intervertebral discs as a result of absorptive processes in the lumbar spine. This may result in osteoarthritic changes in the facet joints (1). The clinical symptom of facet joint osteoarthritis (OA) is chronic back pain that typically occurs when starting movement and at rest. Apart from generalized measures, pharmacologic treatment consists of direct infiltration of a product into the joints, usually under fluoroscopic or computed tomographic (CT) guidance. The injections traditionally contain local anesthetics and/or glucocorticoids (2–4).

Hyaluronic acid is a linear polysaccharide consisting of glucuronic acid and n-acetyl glucosamine. It is synthesized in the joints by the chondrocytes in articular cartilage and fibroblasts in the synovial intima. Clinical studies have shown that intraarticular hyaluronic acid restores rheologic homeostasis in joints with OA by improving the viscoelastic properties of defective synovial fluid (5). The term "viscosupplementation" has been used to describe this concept (6). The international literature contains a host of publications on the treatment of OA of the large joints with intraarticular hyaluronic acid. These have confirmed the favorable effect of sodium hyaluronate (SH) on pain and restricted joint mobility in patients with knee OA (7).

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Table 1
Examinations and Treatment Over Time

Visit	Appointments	Examinations
1	Baseline	Clinical and radiologic findings before treatment, inclusion and exclusion criteria, randomization to treatment group, Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
2	7 d ± 1 after visit 1	First injection (S1–L5) Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
3	7 d ± 1 after visit 2	Second injection (L5–L4) Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
4	7 d ± 1 after visit 3	Third injection (L4–L3) Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
5	7 d ± 1 after visit 4	Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
6	90 d ± 3 after visit 4	Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36
7	180 d ± 3 after visit 4	Efficacy and tolerability Patient questionnaires: VAS, RMQ, ODQ, LBOS, SF-36

Table 2
Demographic Data and Severity of Osteoarthritis

Category	Value	
	SH group	TA group
Age (y)	64.97 ± 8.31	65.87 ± 9.79
Height (cm)	168.97 ± 7.90	166.68 ± 7.76
Weight (kg)	74.31 ± 12.40	72.89 ± 12.57
Sex (M/F)	18/12	24/6
Severity of Osteoarthritis (Kellgren)		
L3 right	2.41 ± 0.82	2.57 ± 0.74
L3 left	2.28 ± 0.75	2.57 ± 0.74
L4 right	2.90 ± 0.90	2.96 ± 0.75
L4 left	2.90 ± 0.82	3.04 ± 0.85
L5 right	3.21 ± 0.69	3.36 ± 0.76
L5 left	3.21 ± 0.79	3.29 ± 0.79

Note.—Values are presented as means SD unless specified otherwise.

The present study was undertaken to investigate the efficacy and safety of intraarticular SH compared with intraarticular glucocorticoids applied under CT guidance to the facet joints in the treatment of chronic nonradicular lumbar pain.

PATIENTS AND METHODS

Patient Groups

Sixty patients with chronic nonradicular low back pain were admitted to this single-center, controlled, randomized, masked-observer study. Patient treatment was performed in Coesfeld, Germany, under the scientific guidance of Münster University.

The inclusion criteria were persistent pain in the lumbar spine for at least 3 months before the study, radiologic confirmation of facet joint OA of Kellgren grade 2/3, and good general and nutritive condition. The radiologic score according to Kellgren and Lawrence was used (8). This score classifies the radiologic features of OA such as osteophytes, joint space impairment, and subchondral sclerosis. It specifies scores 0 for no radiologic features of OA, 1 for minute osteophyte formation with doubtful significance, 2 for definite osteophyte formation and an unimpaired joint space, 3 for moderate diminution of the joint space, and 4 for a greatly impaired joint space with sclerosis of the subchondral bone.

Institutional review board approval was obtained from the international ethics commission of Freiburg in 2000. Patients had to provide written informed consent to participate in the study. Patients with a history of hypersensitivity or contraindication to the test products or one of their constituents, contraindication to intraarticular treatment, a current regimen of anticoagulants, or radicular pain or other conditions that could interfere with the findings of nonradicular low back pain were excluded after clinical examination or CT scan, which was performed in each patient.

Technique

The test products were SH (Ostenil mini; TRB Chemedica, Haar, Germany) and a commercially available drug containing the active constituent triamcinolone acetonide (TA). Ostenil mini is a viscous solution containing 10 mg of highly purified SH of fermentation origin in a 1-mL buffer solution and is supplied in an autoclaved ready-to-use syringe. TA, which was presented in vials containing 10 mg in 1 mL crystalline suspension, was drawn into suitable syringes. The recruited patients were randomized in blocks of six (computer generated by Rancode, idv Gauting, Germany) to one of the two treatment regimens in the order of their admission into the study.

At each visit, patients received one injection of the assigned test product into both facet joints at the relevant spinal level. To avoid bias, the same investigator made all the intraarticular injections. Because it is most important, in the interest of optimizing the effect, to inject the product reliably into the small articular capsule, the intraarticular injections were given under CT guidance to make sure that the injections were all strictly intraarticular. The facet joints at three levels in the lower lumbar spine (S1–L5, L5–L4, and L4–L3) presumably most affected by degenerative changes were treated at weekly intervals. Therefore,

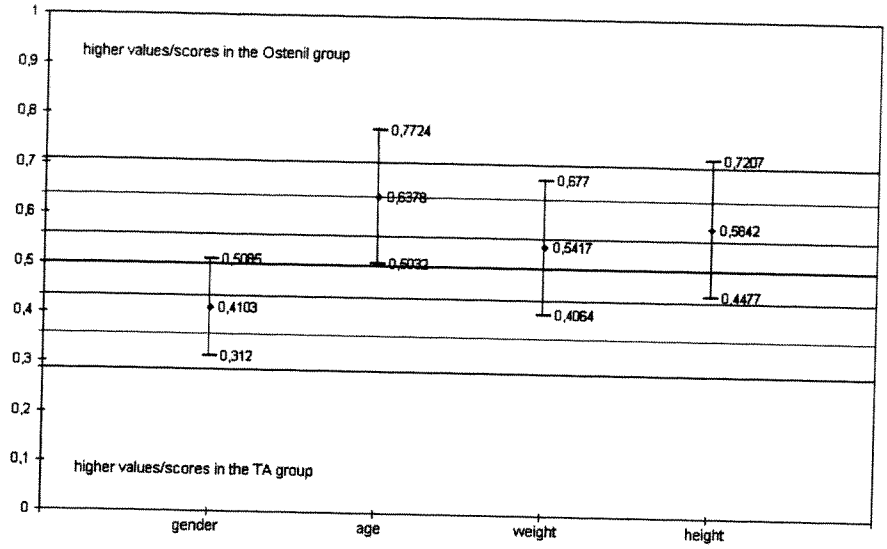

Figure 1. Homogeneity analysis of demographic data. Inhomogeneity is indicated if the estimator (dot) is outside the dashed lines.

each patient ultimately received six injections of the assigned test product.

Study Endpoints

Efficacy data were obtained with use of validated scales and patient questionnaires. The patients were assessed by another investigator who had no idea about the treatment received.

Pain intensity was recorded on the 100-mm Huskisson visual analogue scale (VAS) for pain (0 mm = "no pain" and 100 mm = "intolerable pain") (9). The Roland Morris Questionnaire (RMQ), a patient questionnaire, lists 24 daily activities that could be affected by low back pain (10). The patient reports which daily activities (s)he was unable to pursue on account of low back pain. A total score of 0 means there are no restrictions whatsoever whereas 24 points signify the maximum possible impediment. In the Oswestry Disability Questionnaire (ODQ), the patient records the degree of impairment from pain during everyday activities (eg, personal care, walking, sitting, standing, sleeping) on an ordinal scale. The scale contains 10 items with a maximum score of 50, which signals the most severe impairment (11). The Low Back Outcome Score (LBOS) assesses the patient's physical function (12). The 10 ordinal scales give a total score of 0 for the most severe handicap and a maximum score of 75 for the least possible impairment. The German version of the Short Form 36 (SF-36), a questionnaire for surveying general state of health, was used for assessing the quality of life of the patients (13). The SF-36 consists of a total of eight items with a maximum possible score of 100. Higher values denote minor impairment, better function, or less pain.

Table 1 describes the timing of the interviews/examinations and injections. Accordingly, the findings from visits 1 to 5 reflect the baseline values and the immediate effects of treatment, whereas the findings at visits 6 and 7 assess a possible carryover effect at 3 and 6 months after the end of treatment.

Statistical Analysis

Because the literature describes intraarticular TA as an effective form of treatment for facet OA, we investigated whether it was possible to show that the test product SH was not inferior to TA.

The study was started in August 2000 and completed in June 2001 after all 60 patients had been treated according to the protocol. Data from all the patients were considered for the safety evaluation. One patient in the SH group was not included in the efficacy evaluation because an exclusion criterion was met. Therefore, 29 patients in the SH group and the 30 in the TA group were included in the intent-to-treat data set for the primary analysis. The primary efficacy endpoint was pain (scored with the VAS).

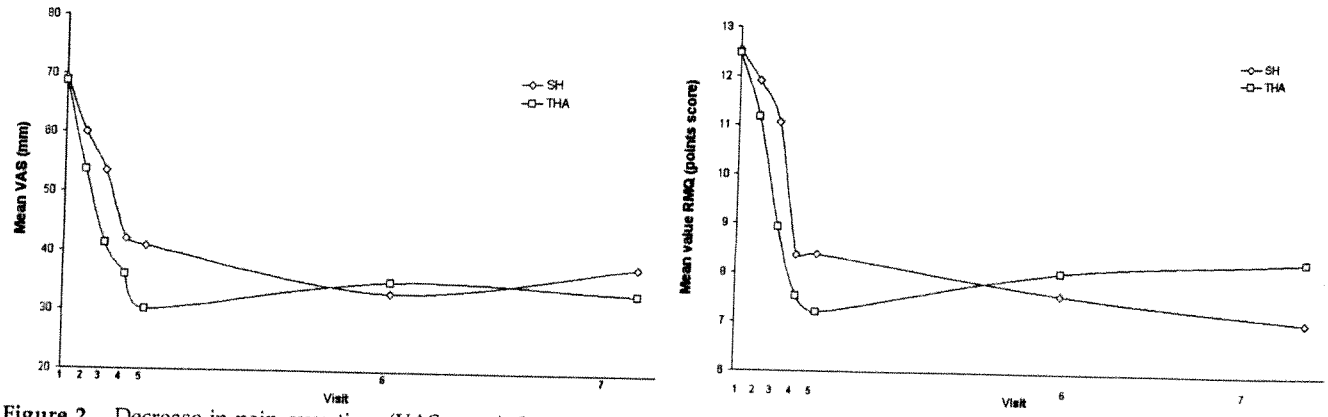

Figure 2. Decrease in pain over time (VAS score). Increase in physical function according to the RMQ.

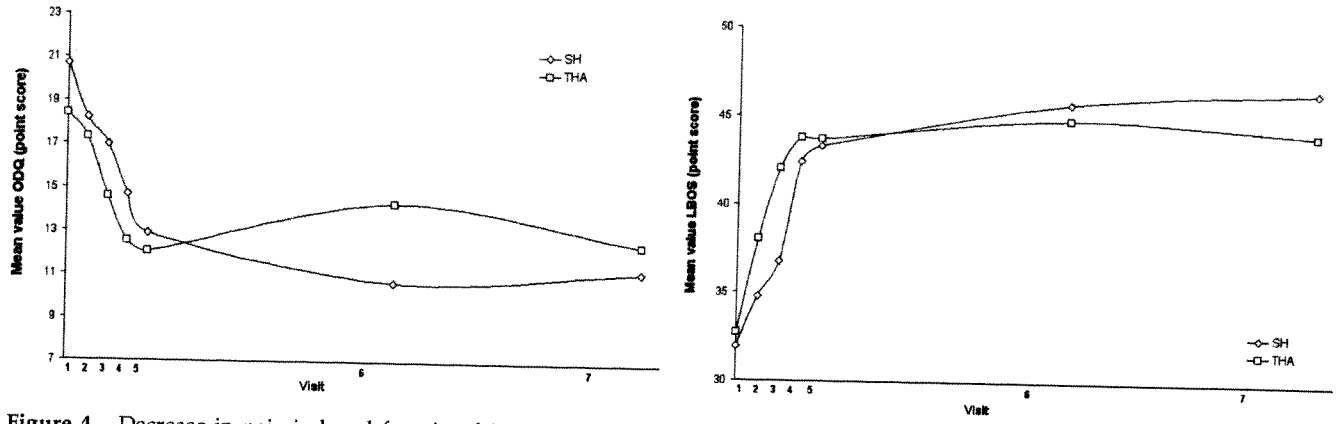

Figure 4. Decrease in pain-induced functional impairment as measured by the ODQ. Increased physical function according to the LBOS.

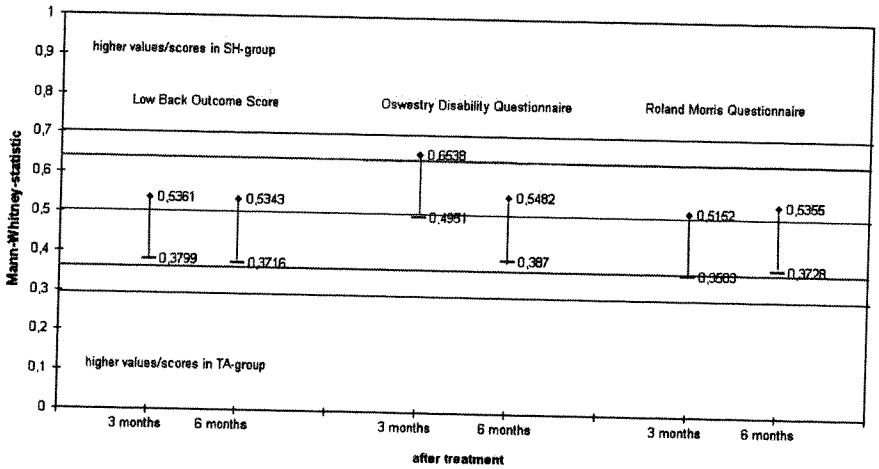

Figure 6. Exploratory statistical analyses for LBOS, ODQ, and RMQ at visits 6 and 7. On the LBOS, superiority of SH and proven noninferiority of SH at visits 6 and 7 are shown. On the ODQ, observed middle (relevant) superiority and proven superiority of SH at visit 6 and observed superiority and proven noninferiority of SH at visit 7 are shown. On the RMQ, observed superiority of SH and proven noninferiority of SH at visits 6 and 7 are shown.

The secondary efficacy endpoints included the aforementioned patient questionnaires mentioned (RMQ, ODQ, and LBOS). The data from the SF-36 are shown only descriptively.

The hypothesis tested in the statistical analysis was that the effectiveness of the test product SH was not inferior to that of the established drug TA (14). The hypothesis was tested with use of the measure of relevance. The standardized difference was used in the case of the primary efficacy endpoint (pain score on VAS), whereas the secondary parameters were analyzed according to Mann-Whitney scores. The mean inferiority according to Cohen was selected as the threshold for noninferiority, and equality according to Cohen was selected as the threshold for superiority (15,16). Homogeneity of demographic data and Kellgren scores between the two treatment groups was tested with use of a two-sided Wilcoxon/Mann-Whitney test with 90% confidence intervals. (14).

RESULTS

The demographic data of the patients are shown in **Table 2**. The two treatment groups showed homogeneity in sex, age, weight, and height (**Fig 1**). The mean values for the radiologic findings of the individual facet joints according to Kellgren are listed in **Table 2**. There were no differences in the single spinal levels between the two treatment groups (Mann-Whitney statistics for all levels, $P > .36$ and $P < .64$). Descriptive data analysis showed that the L5 joints had higher scores compared with the L3 joints in both treatment groups, indicating that the lower joints presented more severe degeneration. During the study, the mean intensity of pain on the VAS scale in the SH group decreased by 40.1% from a mean baseline value of 69.2 mm ± 14.2 to 40.8 mm ± 25.6 (visit 5–visit 1 immediate effect) and by 45.1% to 38.0 mm ± 26.5 at the end of the study (visit 7–visit 1 carryover effect). In the TA group the pain intensity decreased by 56.2% from a mean baseline value of 68.7 mm ± 11.5 to 30.1 mm ± 23.3 mm (visit 5–visit 1 immediate effect) and by 51.7% to 33.4 mm ± 20.7 at the end of the study (visit 7–visit 1 carryover effect). The greatest decreases in pain (50.5%) were observed at V6 in the SH group and at V5 (55.5%) in the TA group. The evolution of pain over time for each treatment is shown in **Figure 2**. The figures show that both treatments caused a marked decrease in the initial severity of pain. Statistical analysis of the VAS scores for pain did not show any noninferiority of SH versus TA.

The RMQ showed that both treatments caused a reduction of impairment in everyday activities (**Fig 3**). In the SH group, the mean baseline score

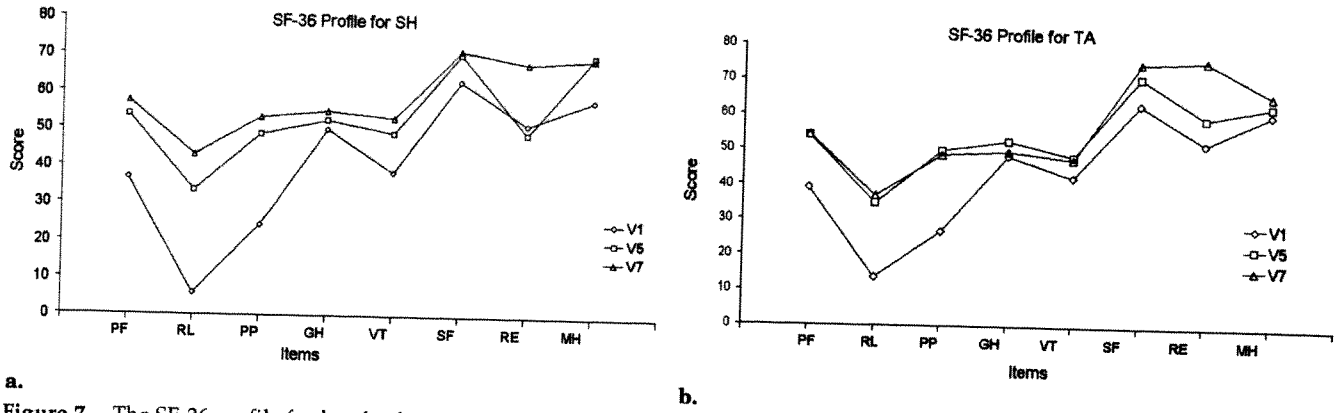

Figure 7. The SF-36 profile for low back pain shows that the impairments as measured by the items physical function (*PF*), functional limitation caused by physical problems (*RL*), physical pain (*PP*), and functional limitations caused by emotional problems (*RE*) responded particularly well to therapy in both groups.

of 12.5 points ± 4.9 decreased by 32.8% to 8.4 points ± 5.4 (immediate effect to visit 5 from visit 1) and by 43.2% to 7.1 points ± 5.4 at the end of the study (carryover effect to visit 7 from visit 1). The TA group showed a reduction from 12.5 points ± 4.4 to 7.2 points ± 5.1 (visit 5–visit 1, 42.4%) and finally to 8.32 points ± 4.8 (visit 7–visit 1, 33.4%), respectively. Therefore, the carryover effect was somewhat greater with SH than with TA.

The ODQ data showed that the degree of impairment during the observation period also decreased sharply in both groups (**Fig 4**). In the SH group, it decreased from the baseline score of 20.7 points ± 8.5 to 14.2 points ± 10.7 (31.2%, visit 5–visit 1) and to 12.6 points ± 9.7 at the end of the study (39.1%, visit 7–visit 1). In the TA group, the corresponding scores were 18.4 points ± 6.2 at baseline and 12.3 points ± 7.5 at visit 5, with an improvement of 32.3% (visit 5–visit 1), which reached 13.0 points ± 7.1 at the end of the study (29.5%, visit 7–visit 1). The carryover effect for SH was slightly greater than that for TA.

The LBOS takes into account a particularly broad spectrum of activities and, in contrast to the previously described patient questionnaires, a high score signifies a lesser degree of impairment **Figure 5**. The scores for the SH group improved from 31.9 points ± 11.4 at baseline to 43.3 points ± 15.5 at visit 5 (35.5% improvement at visit 5 versus visit 1) and 46.0 points ± 16.5 at visit 7 (43.9% improvement at visit 7 versus visit 1). Scores for the TA group were 32.7 points ± 11.4 at baseline, 43.7 points ± 13.3 at visit 5 (33.6% improvement at visit 5 versus visit 1), and 44.1 points ± 14.0 at the end of the study (34.8% improvement at visit 7 versus visit 1). The carryover effect of SH is more pronounced than that of TA.

Figure 6 illustrates the results of the exploratory statistical analysis for RMQ, ODQ, and LBOS. Noninferiority of SH versus TA could be shown for visits 6 and 7.

One week after treatment completion, seven of the eight items of the quality of life questionnaire SF-36 showed an improvement in the SH group. The clearest improvements were observed for the items for physical function, functional limitation as a result of physical problems, and physical pain. At visit 7, the item functional limitation of activity resulting from emotional problems also showed a marked improvement. Similar improvements were observed in the TA treatment group at 1 week after treatment completion and at visit 7 (**Fig 7**).

DISCUSSION

Intraarticular treatment of OA with exogenous SH has been described in numerous publications. Several medical societies including the American College of Rheumatology now recommend SH as standard therapy for OA of the knee (17). The first reports on the treatment of OA of small joints, such as the temporomandibular joint (18,19) and the carpometacarpal joint (20), with intraarticular SH have now been published. However, although infiltration of the facet joints with local anesthetic agents and/or corticosteroids is one of the established forms of treatment for chronic low back pain (2–4), little is known about the benefits and safety of intraarticular SH in the symptomatic treatment of osteoarthritic changes in the vertebral facet joints. Lynch and Taylor (21) reported that patients with chronic nonradicular lumbar pain benefited from intraarticular injections of methylprednisolone only if the injection into the joint capsule had been confirmed under an image converter after administration of a contrast agent. Accidental periarticular infiltration had no notable effect.

Distension of the capsule as a result of the injection of relatively high volumes of fluid into the joint capsule may provoke typical pain in patients. In addition, injection of larger volumes of fluid into the facet joints may cause capsule rupture, with leakage of the injected SH probably leading to a loss of efficacy. Therefore, we decided to inject no more than 1 mL of fluid into this type of joint.

In the present study, the correct position of the needle in the joint capsule was confirmed by CT and the maximum volume of test product injected into the joints did not exceed 1 mL. Therefore, it may be assumed that the results obtained reflect the effects of the respective test product. Pain relief and restored function are shown very consistently for both treatments on the

VAS and patient questionnaires. As expected, TA treatment showed a more rapid onset of effect compared with SH. However, the effect of SH was not inferior to that of TA and SH had a more pronounced carryover effect. When designing clinical studies, and in particular when defining efficacy endpoints, it may be of interest to demonstrate a marked improvement in function and quality of life for the patient, even if the pain does not improve to the same degree under treatment. The radiologic signs of OA in this study cohort were most pronounced at level L5 and least marked at L3. Because each joint was injected only once, it remains to be seen whether more than one injection per joint (perhaps at level L5) would induce an even greater improvement in the facet symptoms. Future studies should also investigate whether simpler methods than CT such as the use of image converters or ultrasonography would be adequate for reliable intraarticular delivery of the test products.

Although the positive effects of intraarticular SH can be primarily attributed to the aforementioned improvement of the synovial fluid in the facet joints as well as the antiinflammatory effects of SH, the results published by Gotoh et al (22) must also be mentioned at this point. These experimental investigations found that bradykinin-induced joint pain was exacerbated by hyaluronidase, which breaks down SH, and that such pain was reduced by intraarticular injections of the type of exogenous SH contained in Ostenil mini (TRB Chemedica). Because the experimental design rules out classical competitive suppression at the bradykinin receptors, it may be assumed that SH achieves its analgesic effect more by coating or masking the synovial intima that contains the nociceptors.

No significant adverse events caused by the test products were reported during the study. This does not alter the fact that the list of contraindications, possible side effects, and interactions considerably restricts or prevents the use of glucocorticoids, and that many patients reject this form of treatment on the basis of their somewhat justified "corticoid phobia." In contrast, the only contraindication for intraarticular SH is the mode of administration itself, which also applies to corticosteroids. Adverse effects occur infrequently with administration of intraarticular SH and those that occur are local and mild and generally resolve spontaneously. Therefore, a comparative benefit/risk analysis is in favor of the administration of intraarticular SH in the treatment of facet joint OA. Further studies should be conducted to confirm the positive findings of this study with respect to the effectiveness and safety of intraarticular SH in the treatment of chronic nonradicular low back pain.

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