Intra-articular sodium hyaluronate 2 mL versus physiological saline 20 mL versus physiological saline 2 mL for painful knee osteoarthritis: a randomized clinical trial

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Objective: Methodological constraints weaken previous evidence on intra-articular viscosupplementation and physiological saline distention for osteoarthritis. We conducted a randomized, patient- and observer-blind trial to evaluate these interventions in patients with painful knee osteoarthritis.

Methods: We centrally randomized 251 patients with knee osteoarthritis to four weekly intra-articular injections of sodium hyaluronate 2 mL (Hyalgan® 10.3 mg/mL) versus physiological saline 20 mL (distention) versus physiological saline 2 mL (placebo) and followed patients for 26 weeks. Inclusion criteria were age over 59 years and daily knee pain more than 20 mm on a 100-mm visual analogue scale (VAS) without satisfactory response to analgesics. During the trial, rescue analgesic were allowed. The primary outcome was pain on movement. The secondary outcomes were pain at rest, pain during the night, Knee Injury and Osteoarthritis Outcome Score (KOOS), Osteoarthritis Research Society International (OARSI) criteria, and global assessment of the patient's condition.

Results: The mean age of the patients was 69.4 years; 55% were women. The effects of hyaluronate 2 mL, physiological saline 20 mL, and physiological saline 2 mL did not differ significantly in reducing knee pain, knee function, or consumption of analgesics. Using OARSI criteria, no significant differences were found. The VAS and KOOS outcomes all improved significantly over time ($p < 0.0005$), regardless of intervention group. No adverse events were reported.

Conclusions: Intra-articular hyaluronate or distention with physiological saline did not significantly reduce pain compared with physiological saline placebo in patients with osteoarthritis of the knee. (ClinicalTrials.gov number, NCT00144820)

Osteoarthritis is the most common form of arthritis and one of the most common causes of long-term disability among adults (1, 2). Especially common is osteoarthritis of the knee, causing personal suffering and requiring extensive utilization of health-care resources (3). In 2001, a review of knee osteoarthritis in the UK and the Netherlands found that approximately 25% of persons over 54 years of age had had knee pain on most days in a month during the past year (4).

Treatment options of patients with osteoarthritis include, initially, non-pharmacological modalities, primarily exercise, physical therapy, and weight loss if overweight (5–8). The next step is pharmacological therapy, which encompasses many options. In patients whose symptoms are not adequately controlled by these interventions, surgery should be considered (9). Surgery, however, carries the risk of seldom, but severe, adverse events and is expensive (10, 11). The pharmacological approaches do have some disadvantages, especially the use of non-steroidal anti-inflammatory drugs (NSAIDs) (non-selective and cyclooxygenase (COX)-2 selective), and particularly in elderly people (12–15). Recent trials show that the dietary supplements glucosamine and chondroitin sulfate alone or in combination do not reduce knee osteoarthritis pain (16). The combination may be effective in the subgroup of patients with moderate to severe knee pain (16). Recent investigations in human cartilage suggest an anabolic effect of low-intensity ultrasound (LIUS) in vitro (17) and new mechanisms of effect (NO-inhibition) from the well-known disease-modifying anti-rheumatic drugs (DMARDs) aurothiomalate and hydroxychloroquine (18). There are

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therefore good reasons to explore the effects of other pharmacological and mechanical interventions.

Viscosupplementation by intra-articular injection of hyaluronate and other substances has been supported by a number of randomized trials conducted during the past 20 years. Meta-analyses and systematic reviews of these trials point to several weaknesses in the primary trials and have reached conflicting results (19–25). Patients with osteoarthritis of the knee seem to display large placebo effects (19–21). Furthermore, several meta-analyses suggest that the beneficial effects of hyaluronate are insufficiently backed by evidence (20, 22, 23). A review published in the Cochrane Database of Systematic Reviews concludes that viscosupplementation compared with saline injection beneficially affects pain, function, and patients' global assessment (21). However, this review is supported by and edited by the industry producing viscosupplementation (21). Furthermore, the review did not consider bias risk of the included trials when assessing intervention effects (21). These aspects may weaken the conclusions drawn.

Saline washout, closed needle joint lavage, and saline injection without lavage have been reported to diminish knee osteoarthritis symptoms (26, 27). Lavage may remove debris from the joint, may dilute cytokines and degradative enzymes, and may reduce the distention of the joint capsule (26–28). Isotonic saline distention of osteoarthritic hip joints resulted in significant pain relief for at least 12 weeks in approximately half of the patients (28). A placebo effect is also possible (29).

We conducted a randomized three-armed, single-centre trial with 26 weeks follow-up and blinded outcome assessment comparing hyaluronate 2 mL (Hyalgan® 10.3 mg/mL) versus physiological saline 20 mL (distention) versus physiological saline 2 mL (placebo) in elderly patients with osteoarthritic knee pain resistant to analgesics.

Materials and methods

Eligible patients were over 59 years of age with daily knee pain above 20 mm on a 100-mm visual analogue scale (VAS-movement) that did not respond satisfactorily to analgesics. Based on radiographic findings, OA patients were classified into mild (Kellgren–Lawrence grade 1 or 2) or severe (Kellgren–Lawrence grade 3 or 4) (30). Patients were excluded if they had rheumatoid arthritis or other inflammatory arthritis as diagnosed by the American College of Rheumatology (31), intra-articular steroid injections within the previous 2 months, invasive knee procedures within the past 6 months, contraindications to hyaluronate (e.g. allergy), contraindications to injections into the knee (e.g. local dermatological disease), medications that could interfere with the planned interventions, or coexisting diseases (e.g. psychosis, dementia) that could interfere with the investigation. Routine blood (including immunoglobulin M rheumatoid factor) and urine laboratory values were examined before entry into the trial. Knee effusion, if present, underwent crystal analysis, white blood cell count, and culture. If crystals or signs of infection were found, the patient was excluded. The local ethics committee of Copenhagen County and the Danish Medicines Agency approved the trial. The Helsinki Declaration was adhered to, and all patients gave written informed consent.

Study design

Two hundred and fifty-one patients were randomized to one of three interventions: four weekly injections of sodium hyaluronate 2 mL (Hyalgan® 10.3 mg/mL), isotonic saline 20 mL (distention), or isotonic saline 2 mL (placebo). The injections were given to the knee joint that was causing the patient the most pain. The patients were positioned sitting with the legs flexed. The knee was disinfected with an iodine solution twice. A cannula 21 G (diameter 0.8 mm) was adapted to a 5 mL syringe and inserted into the knee joint through the lateral midpatellar portal. Before treatment, any accumulation in the knee was withdrawn through aspiration. The cannula was left in situ and the syringe removed. Then the allocated intervention added in a syringe was injected intra-articularly. The syringe and cannula were removed and the injection site covered with sterile gauze.

The Central Hospital Pharmacy, the County of Copenhagen, conducted the computer-generated, centralized randomization in blocks of 15 patients (1:1:1) and packed the interventions in identical, consecutively numbered packages. When an eligible patient was identified, the patient received the next package in line. All data management and analyses were conducted under code blinded to intervention arm. No-one had access to the coded list (unless in case of emergencies, which did not occur) until statistical analyses were finished and the main conclusions drawn.

All patients were permitted analgesics of the acetaminophen, aspirin, NSAID (inclusive COX-2 selective inhibitors), codeine, and tramadol groups. The trial was blinded, with injections performed by one of only two physicians who did not otherwise participate in the examination or follow-up of the patients. Patients were blinded by blocking their sight to the knee by a curtain so they did not see the viscosity or volume being injected.

Just prior to start of treatment the following baseline quantities were recorded: age, sex, body

mass index (BMI), smoking habits (smokers versus non-smokers), alcohol consumption (proportion drinking two drinks or less per day for women and three drinks or less per day for men), activity level (in work, sick leave, out of work, on pension), disease classification (radiological according to Kellgren), duration of pain (years), and daily consumption of analgesics.

Outcome measures

Baseline values of all outcome measures were measured just prior to the first injection. The patients were evaluated at weeks 1, 2, 3, 8, 12, 16, and 26 after randomization. These evaluations were conducted before any new intervention was administrated. The primary outcome measure was pain on movement on a 100-mm visual analogue scale (VAS-movement). Secondary outcome measures were pain at rest (VAS-rest) and during the night (VAS-night), the quadriceps circumference (cm), ability to bend (degrees flexion) and stretch (degrees extension), and the knee injury and osteoarthritis outcome score (KOOS) (32) of symptoms, rigidity, pain, daily functions during sport and leisure time, quality of life (all questions from the Western Ontario and McMaster Universities Osteoarthritis Index, WOMAC (33), and sport function. In the KOOS scale zero represents extreme knee problems and 100 no knee problems. The response according to the Osteoarthritis Research Society International (OARSI) criteria (34) was measured in all but 41 patients (see statistical methods).

At each follow-up the global assessment of the patient's condition as compared to that of the previous visit was recorded by the patient and the physician independently, and scored as greatly improved, improved, unchanged, deteriorated, or much deteriorated. The results were coded as 2, 1, 0, −1, and −2, respectively. It was assumed that the results could be meaningfully analysed within patients, but not between patients. Consequently, the scores were added within each patient and the results recoded as 1, 0, and −1 if the sum was positive, zero, or negative, respectively. The consumption of analgesics was scored at each visit as increased, unchanged, or decreased as compared to that observed on the previous visit. The scores were added within patients, and positive, zero, or negative sums transformed to 1, 0, and −1, respectively. BMI and quadriceps circumference were only measured at the last follow-up visit.

Adverse events

Adverse events and serious adverse events were assessed by the investigators at each follow-up visit or if the patient had complaints.

Sample size and power

The primary outcome measure, pain on movement on a 100-mm VAS (VAS-movement), has a standard deviation of 26 mm (35). Based on $\alpha=0.05$ and $\beta=0.05$ and a minimal relevant difference of 15 mm, we estimated that at least 80 patients were needed in each group, making a total of 240 patients. After 251 patients had been randomized, we stopped inclusion.

Statistical analysis

We conducted intention-to-treat analyses. The relationship between each continuous outcome measure and time of measurement (number of weeks following start of treatment) and intervention group was assessed using the linear mixed model (SPSS version 13.1 for Windows) with fixed effect only. To compensate for differences between baseline values, the variable measured at baseline was included as a covariate. The variance covariance matrices of the participants were assumed to be identical and distribution of the effect measure within each time group combination to be normal. The approximate validity of the latter assumption was assessed using probability plots. Using a likelihood ratio test, we then tested whether a repeated measures model with compound symmetry covariance structure differed significantly from one with an unstructured covariance matrix ($p<0.05$). If this was the case, no assumptions were made regarding the structure. Finally, we tested whether the main effects of time and groups and their interaction differed significantly from zero ($p<0.05$). Observed data maximum likelihood estimates were used. To assess the main effect of intervention group, we compared the means of the outcomes assessed at the seven follow-ups across the three intervention groups. To assess the main effect of time, we compared the means of the outcomes of the three intervention groups between the seven follow-ups. We assessed the interaction between intervention group and time by examining whether or not the time curves of the three interventions were parallel. The global assessment scores and analgesics scores were compared between the three intervention groups using the Kruskal–Wallis test ($p<0.05$). As the patient global assessment score was not recorded using a VAS, 41 patients whose classification depended on the magnitude of improvement in patient global assessment could not be classified using the OARSI criteria. Therefore, we conducted two analyses in which the 41 patients were classified as responders and non-responders, respectively. In each analysis a logistic regression analysis was performed with the binary variable, response, as the outcome, and one covariate, intervention group, and we tested whether 'intervention group' had a significant ($p<0.05$) effect on the outcome.

Results

Characteristics of the patients at baseline

Recruitment began in May 1999 and ended in November 2001. Three hundred and eight consecutive patients enrolled from orthopaedic departments or from general practitioners in Zealand, Denmark, were assessed for eligibility. Of these, 57 were excluded (Figure 1), leaving 251 (113 men, 138 women) who were eligible and underwent randomization. Eight patients withdrew after randomization primarily because they were offered a standby knee replacement operation (Figure 1). Of these, three did not have any follow-up visits whereas the remaining five had one or more missing values.

Table 1 shows the entry mean values with 95% confidence intervals (CIs) (for continuous variables) or number and percentage (for categorical variables) of each of the three intervention groups for the demographic data (age, sex, BMI), the lifestyle data (smoking, drinking habits), the aetiological classification, the classification of radiologically verified osteoarthritis, patients' activity level, duration of pain, and baseline values of the outcome measures. The three groups did not demonstrate any major differences.

Benefits and harms

No significant interaction between time and group was observed (the range of p-values was 0.13–0.91). Thus, the time curves of the three intervention groups were parallel except for random variation. The model was therefore simplified to include only main effects of time and of group, that is only differences between mean levels.

Tables 2 and 3 shows the mean difference from the reference group (physiological saline 2%) of the primary and secondary outcome measures in each intervention group during and after intervention. p-values of the statistical analyses are presented. Table 3 includes assessment by OARSI criteria.

The mean levels of the primary and secondary outcome measures did not differ significantly

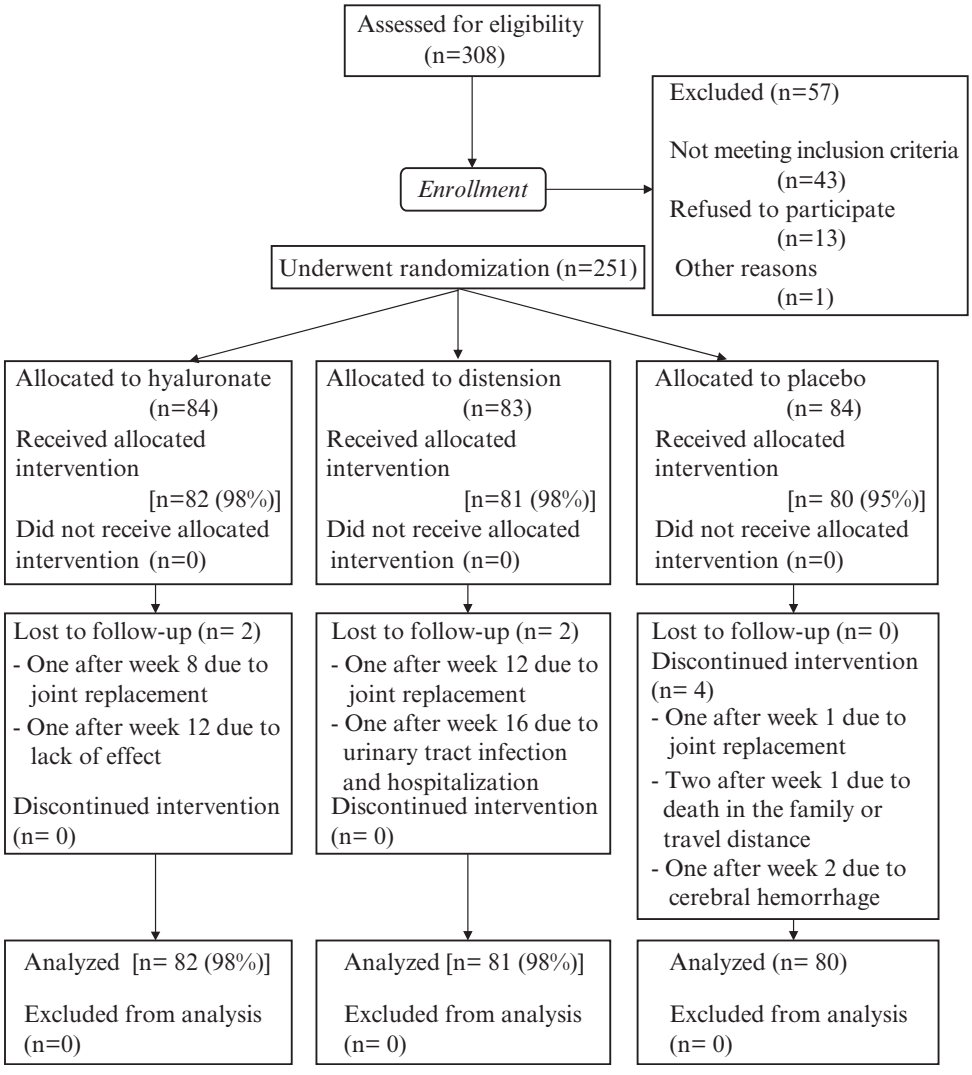

Figure 1. Participant flow through the trial.

Table 1. Baseline characteristics of the patients.

Characteristic	Hyaluronate 2 mL (n=84)	Physiological saline 20 mL (n=83)	Physiological saline 2 mL (n=84)
Age (years)	68.8 (6.27)	69.8 (6.80)	69.6 (7.27)
Female sex	48 (57.1)	46 (55.4)	44 (52.4)
Body mass index (kg/m^2)	29.6 (4.28)	29.2 (4.89)	29.3 (4.26)
Drinking habits			
Never	37 (44.0)	29 (34.9)	37 (44.0)
Below maximum level*	4 (4.8)	6 (7.2)	8 (9.5)
Above or equal to maximum level*	43 (51.2)	48 (57.8)	37 (44.0)
Smokers	20 (23.8)	11 (13.3)	18 (21.7)
Kellgren and Lawrence radiographic reading			
Grade 1	9 (10.7)	11 (13.3)	9 (11.3)
Grade 2	13 (15.5)	11 (13.3)	10 (12.5)
Grade 3	31 (36.9)	34 (41.0)	30 (37.5)
Grade 4	31 (36.9)	27 (32.5)	31 (38.8)
Activity			
At work	1 (1.2)	1 (1.2)	0 (0.0)
Sick leave	1 (1.2)	0 (0.0)	1 (1.2)
On pension	74 (88.1)	73 (88.0)	69 (82.1)
Out of work	8 (9.5)	9 (10.8)	14 (16.7)
Idiopathic arthrosis	75 (89.3)	77 (92.8)	81 (96.4)
Duration of pain (years)	7.8 (7.1)	7.03 (8.52)	8.27 (7.21)
VAS pain at movement (0–100 mm)	54.4 (18.3)	54.7 (16.5)	57.1 (19.5)
VAS pain at rest (0–100 mm)	24.6 (19.8)	22.1 (14.9)	23.5 (19.8)
VAS pain at night (0–100 mm)	26.0 (24.4)	26.7 (23.6)	23.1 (24.1)
KOOS symptoms (100–0)	55.7 (17.0)	56.4 (19.7)	56.7 (17.8)
KOOS activities (100–0)	55.6 (17.0)	55.8 (16.9)	53.0 (17.9)
KOOS pain (100–0)	53.0 (14.8)	53.5 (14.2)	52.3 (14.3)
KOOS sports (100–0)	24.6 (20.1)	27.5 (20.9)	24.1 (21.1)
KOOS quality of life (100–0)	36.6 (16.5)	34.9 (13.8)	33.6 (16.9)
Quadriceps circumferences (cm)	47.5 (5.32)	47.0 (5.27)	46.8 (4.74)
Extension gap (deg)	11.8 (7.50)	12.8 (7.14)	11.7 (6.82)
Flexion (deg)	120.2 (9.34)	122.2 (12.5)	122.4 (12.3)

Values are given as n (%) or, for continuous quantities, mean (standard deviation). *Maximum level more than three drinks per day for males and more than two drinks per day for females.

Table 2. Outcomes, mixed model analyses.

	Hyaluronate 2 mL	Physiological saline 20 mL	Physiological saline 2 mL	p of group main effect	p of time main effect
Primary outcome					
VAS-pain at movement (mm)	5.46 (−0.08 to 11.0)	3.87 (−1.69 to 9.44)	0.0	0.37	<0.0005
Secondary outcomes					
VAS pain at rest (mm)	0.75 (−3.54 to 5.04)	1.25 (−3.06 to 5.55)	0.0	0.72	<0.0005
VAS pain at night (mm)	−1.80 (−7.36 to 3.76)	0.39 (−5.19 to 5.97)	0.0	0.42	0.011
KOOS symptoms	−3.12 (−6.14 to 1.79)	−1.25 (−4.29 to 1.79)	0.0	0.40	<0.0005
KOOS activities	−3.67 (−8.54 to 1.20)	−3.45 (−8.33 to 1.43)	0.0	0.52	<0.0005
KOOS pain	−1.41 (−5.79 to 2.97)	−1.59 (−5.98 to 2.80)	0.0	0.63	<0.0005
KOOS sports	−1.31 (−7.13 to 4.50)	−4.19 (−10.0 to 1.64)	0.0	0.84	<0.0005
KOOS quality of life	−2.72 (−7.31 to 1.87)	−2.06 (−6.66 to 2.55)	0.0	0.72	<0.0005
Extension gap (deg)	0.844 (−0.59 to 2.28)	1.88 (0.44–3.31)	0.0	0.038	0.40
Flexion (deg)	−1.27 (−4.33 to 1.79)	−1.57 (−4.65 to 1.50)	0.0	0.10	0.91

The value shown for outcome is the group mean difference from the reference group (physiological saline 2 mL) and the corresponding 95% confidence interval. The p-values are based on the results of an analysis only including the main effects of intervention group and time.

Table 3. Secondary outcomes.

Secondary outcomes	Hyaluronate 2 mL	Physiological saline 20 mL	Physiological saline 2 mL	p-value
				Rank differences between groups
Global assessment by patient				
Improvement	57 (67.9)	52 (62.7)	42 (51.9)	0.070
Deterioration	19 (22.6)	17 (20.5)	29 (35.8)	
Global assessment by physician				
Improvement	68 (81.0)	56 (67.5)	47 (58.0)	0.010
Deterioration	13 (15.5)	17 (20.5)	29 (35.8)	
Consumption of analgesics				
Decreased	30 (35.7)	23 (27.7)	17 (21.0)	0.29
Increased	22 (26.2)	18 (21.7)	23 (28.4)	
				Group effect by logistic regression
Assessment by OARSI criteria				
Class-1 responders*	50 (61.0)	42 (51.9)	33 (41.8)	0.053
Odds ratio (95% CI)	2.18 (1.15–4.14)	1.51 (0.79–2.83)	reference	
Class-2 responders**	30 (36.6)	27 (33.3)	27 (34.2)	0.90
Odds ratio (95% CI)	1.12 (0.58–2.16)	0.96 (0.49–1.88)	reference	
				Main effect of groups
Quadriceps circumference (cm)	47.3 (46.2–48.5)	47.0 (45.9–48.2)	46.5 (45.4–47.6)	0.36
Body mass index (kg/m^2)	29.4 (28.5–30.4)	29.0 (27.9–30.1)	29.3 (28.3–30.3)	0.69

Values are given as n (%) or, for continuous quantities, mean (95% confidence interval). *Class-1 responders are patients who responded according to the OARSIS criteria. If this response could not be determined because of insufficient information on global assessment, the patient was classified as a responder. **Class-2 responders are patients who responded according to the OARSIS criteria. If this response could not be determined because of insufficient information on global assessment, the patient was classified as a non-responder.

between the three intervention groups except for extension gap, where a difference in borderline significance was noted. Pairwise comparisons revealed that only the difference between the 20 mL vs. the 2 mL physiological saline groups was significant (p=0.033). Figure 2 shows the mean scores and 95% CIs for each intervention group and each of the KOOS and VAS outcome measures.

For all KOOS and VAS outcome measures there was a highly significant main effect of time. The mean of the primary outcome measure pain of movement versus time is typical of the effect (Figure 3). There were no significant differences between the three intervention groups. All three groups showed initial improvement, which later declined somewhat.

The investigators' global assessment differed significantly between the three groups. The highest proportion with improvement was found in the hyaluronate group. In the 20 mL saline group the percentage improvement was intermediate. The smallest proportion was found in the placebo group.

The outcome as assessed using the OARSI criteria did not differ significantly between the three intervention groups either when the 41 patients without data were classified as responders (p=0.053) or when

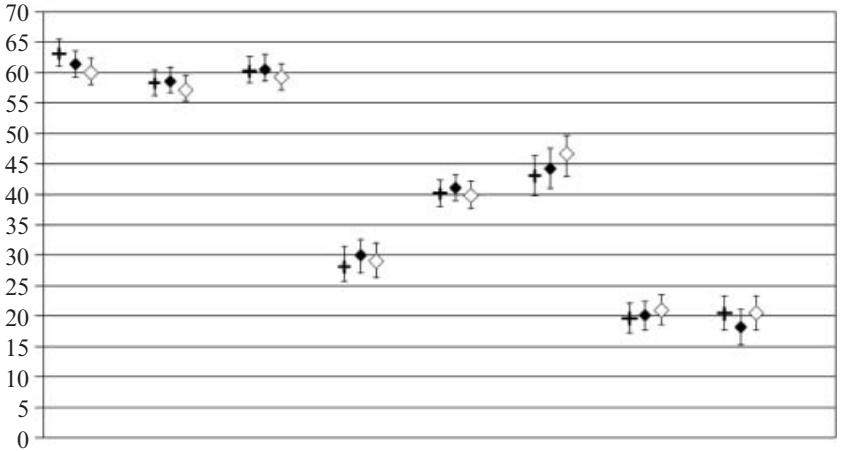

Figure 2. Means and 95% confidence intervals of the three intervention groups for the primary outcome and the secondary outcomes. +, hyaluronate 2 mL; ♦, saline 20 mL; ◇, saline 2 mL. The y-axis depicts for each of the intervention groups the mean score and 95% confidence interval of all values obtained after start of intervention (eight assessments) (theoretically ranging between 0 and 100). 1, KOOS-symptoms; 2, KOOS-pain; 3, KOOS-activities; 4, KOOS-sports; 5, KOOS-quality of life; 6, VAS-pain at movement; 7, VAS-pain at rest; 8, VAS-pain at night.

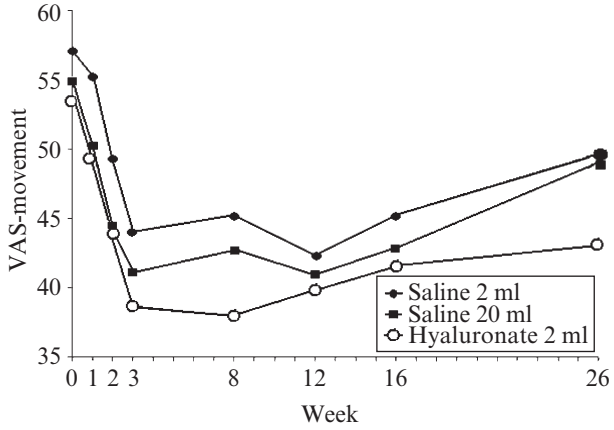

Figure 3. The mean of VAS-movement as a function of number of weeks elapsed since entry into the trial for each of the three intervention groups.

they were classified as non-responders (p=0.90). The odds of responding according to the OARSI criteria in the hyaluronate group relative to the control group was 2.18 (95% CI 1.15–4.14) if, and only if, patients without global assessment were classified as responders (Table 3).

No serious or non-serious adverse events were reported, thus no local reactions at the injection site with pain, tenderness, and erythema were seen. No post-injection 'flares' were reported.

Discussion

Osteoarthritis is the most common form of arthritis and the second most common cause of long-term disability among adults in the USA (36). There is no cure. Current therapeutic strategies are aimed primarily at reducing pain and improving joint function (37).

The analysis of the primary outcome measure of VAS-movement in this trial demonstrated no significant differences between the three intervention groups. In all of the intervention groups a significant improvement was demonstrated during the intervention compared with baseline. This confirms the well-known high placebo response in intra-articular interventions on patients with osteoarthrosis (19–21, 36, 37). We observed no local adverse events after injection, possibly because of the injection technique (38).

The intervention groups did not differ significantly in terms of any of the secondary outcome measures except for a difference of borderline significance in lack of extension and a significant difference in investigators' global assessment of the patients. The magnitude of the former effect is considered clinically unimportant. Furthermore, there was a small beneficial effect of hyaluronate in a sensitivity analysis using the OARSI criteria as outcome. This effect did not reach the usual criteria for significance (p=0.053) and required that all patients without OARSI score were classified as responders. This, however, is fairly unlikely. From an additional statistical point of view, the large number of significance tests carried out ought to be considered. Hence, we think the result can be ignored.

The investigators' global assessment of the response to treatment differed significantly between the groups, with the hyaluronate group receiving a better assessment than the distension group, which in turn received a better assessment than the placebo group. Similar results, but of borderline significance, were observed for the patients' global assessment in the hyaluronate group. These findings may suggest either a subtle effect not measurable by the other outcome measures or a break in the blinding, creating a wish bias (39, 40). The break in the blinding might originate from the physicochemical differences between the interventions, causing different local sensations in the knee.

The present trial offers a number of strengths. First, it uses central randomization, which reduces the risks of allocation bias (39, 40). Second, it uses a blinded outcome assessment, which reduces the risk of assessment bias (39, 40). Third, data management and statistical analyses were conducted blinded to intervention, which reduces the risks of bias introduced during these stages of the trial. Fourth, the trial was investigator initiated and driven, which reduces the bias risks that industrial affiliation may create (41–45). Fifth, the drop-out rate was low, which reduces the risk of attrition bias. Sixth, because of the three-armed design we were able to examine two interventions versus the same placebo. Seventh, and finally, because of the lack of significant changes in consumption of analgesics, we are reasonably confident that that the lack of significant differences between the three interventions was not confounded by analgesic consumption.

We are also aware of some of the potential weaknesses of our trial. First, it is a single-centre trial, which may reduce the external validity of our results. However, as our results come out without significant differences this may also be seen as a strength. Single-centre trial designs usually reduce random variation and hence give the best opportunity to detect differences if they exist. Second, we only examined one dose and form of viscosupplementation (Hyalgan® 2 mL) and one dose and form of distention (physiological saline 20 mL). Accordingly, we are unable to exclude the possibility that other preparations, concentrations, and volumes could have reached other results. Third, we cannot exclude the possibility that a break in the blinding between the investigator giving the intervention and the patient is the cause for the differences observed between intervention groups regarding global assessment. We did not examine whether a break had

occurred by asking the patients and the investigators about their assessment of the likely intervention. Fourth, we used physiological saline 2 mL as our placebo. We cannot exclude the fact that this intervention may have exerted beneficial effects. However, this volume of physiological saline is routinely used as comparator in viscosupplementation trials (21). Fifth, the number of patients included was moderate, and therefore risk of type 2 errors must be considered. However, we performed a number of statistical comparisons in a three-armed trial without adjusting our p-value. Accordingly, any statistical significant difference or trend towards significance should be interpreted conservatively.

The estimated annual sales of hyaluronate in the USA were USD 235 million in 2001 and the global market value is USD 564 million (46). Several meta-analyses have evaluated the efficacy of hyaluronate (19–24). Some have demonstrated efficacy, others no effects at all compared with placebo. In particular, the magnitude and duration of the placebo response to intra-articular injections is large and may be sustained for 6 months or longer, making evaluation of any intra-articular interventions difficult. Studies supported by industry are often biased compared to corresponding studies conducted by independent parties (41–45). Therefore, the present trial was justified. The results of our trial, combined with the sparse number of industry-independent studies conducted so far, support the contention that the question of whether hyaluronate has in fact any effect should be studied further. These trials should be conducted without interference from industry. Until independent and indisputable evidence of an effect is presented, the widespread and costly use of hyaluronate should be put on standby. Distention with a small volume of physiological saline seems to offer the same benefits as a 10 times larger volume. Whether this is simply a placebo effect could be studied in randomized trials comparing 2 mL of physiological saline with sham injection.

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