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Intra-articular treatment of hip osteoarthritis: a randomized trial of hyaluronic acid, corticosteroid, and isotonic saline

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Summary

Objective: Hyaluronic acid (HA) and corticosteroids are both widely used for intra-articular treatment of knee osteoarthritis (OA). We examined the effect of both drugs in intra-articular treatment for hip OA.

Methods: One hundred and one patients with hip OA were included in a prospective double blind study, using a randomized controlled trial with a three-armed parallel-group design. Three ultrasound-guided, intra-articular injections were given at 14 days interval. The primary outcome measure was 'pain on walking', registered on a visual analogue scale (VAS). Evaluation was performed at baseline and after 14, 28 and 90 days. The study adhered to the Consolidated Standards of Reporting Trials. All analyses were based on intention-to-treat analyses, and used 'mixed-procedures' with the baseline-observation as covariate.

Results: There were no significant interactions with respect to Treatment × Time for any of the analyzed outcome measures. There was a significant treatment effect for 'pain on walking' ($P = 0.044$) due to a significant improvement following corticosteroid compared to saline with an effect-size of 0.6 (95% confidence interval: 0.1–1.1, $P = 0.021$). By contrast, HA compared to saline had an effect size of 0.4 (−0.1 to 0.9; $P = 0.13$). The peak-effect was obtained after 2 weeks. There was no difference between the treatment groups at endpoint. No significant side effects of the injections were observed.

Conclusions: Patients treated with corticosteroids experienced significant improvement during the 3 months of intervention, with an effect size indicating a moderate clinical effect. Although a similar significant result following treatment with HA could not be shown, the effect size indicated a small clinical improvement. A higher number of patients in future HA studies would serve to clarify this point.

Key words: Hyaluronic acid, Glucocorticosteroid, Intra-articular, Injection, Hip joint, Osteoarthritis, CONSORT.

There has been no indication of any change in the age-standardized incidence rate of OA over the last four decades[1–3]. In spite of this, the socioeconomic costs of OA have increased by 80% in the last 10 years[4]. Pharmacological interventions are of interest in this context, both as basic agents of relief and for flares of pain in more acute situations. They may also have the effect of postponing surgical interventions, by improving the patient's perceived quality of life[5].

Nonetheless, the non-operative therapeutic armamentarium recommended for reducing pain and maintaining mobility in the hip is still very limited with regard to OA[6]. Some supplementary therapies recommended for knee OA may, however, also be considered for use in hip OA.

One of these, hyaluronic acid (HA), is well established for intra-articular treatment of OA of the knee and is included in the guidelines for treatment of OA with this localization[7]. Some controversy exists over the benefit of the treatments[8–10]. In one large controlled study, saline has proven to be as efficacious as HA for treatment of knee OA[11].

Similarly, corticosteroid injections are very commonly prescribed in knee OA, even though the results of clinical trials with these compounds are varied[12,13]. The relationship between HA and corticosteroid and their comparability with regard to effect in knee OA still need to be clarified[14,15].

Injection therapy for OA of the hip has not been extensively used, presumably due to the fact that access to the joint is fairly difficult[16]. Until now, only casuistic evidence pointing to an effect of HA in the hip has been presented[17–20]. The use of corticosteroid injections in hip OA has been advocated[16], and this pain relief has been supported by controlled studies[21,22]. Corticosteroid treatment, however, remains controversial due to a rather short-lived effect and some reports of adverse events following the injections[21,23].

The former reluctance to injection therapy in the hip may partly be overcome by the use of ultrasound[24] and as a result, injections are now being used more extensively[18,25,26]. The ultrasound method also allows a precise demonstration of the correct placement of the injections into the hip joint[27].

The aim of this study was to compare in a randomized, controlled, double blind design, and in accordance with the '*Consolidated Standards of Reporting Trials*' (CONSORT)[28] the effect of injections with HA, corticosteroid, or isotonic saline into hip joints with OA.

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Materials and methods

DESIGN

Prospective double blind study, using a randomized controlled trial with a three-armed parallel-group design.

INTERVENTION

Patients were randomized to (1) one injection with 1 mL (40 mg Depo-medrol®) methylprednisolone corticosteroid followed by two sham injections, (2) three injections of 2 mL HA (Hyalgan®), or (3) three intra-articular injections of 2 mL saline water. In all cases, including the sham injections, 1 mL of 1% lidocaine was added to the syringe. The three intra-articular injections were given at 14 days interval. The primary endpoint status was carried out after 3 months without any interim analyses.

No bed rest was required after the injection. A low level of physical activity, however, was recommended for the rest of the day.

BLINDING

The primary investigator placed the needle, aspirated any joint fluid from the hip joint and ascertained the correct placement of the needle with the aid of a small injection of air as previously described[27]. During these administrations the investigator was blinded from the ultrasound screen and an assistant performed the actual injection using a masked syringe. The assistant did not otherwise participate in the treatment or follow-up of the patients.

PATIENT MATERIAL

General practitioners and specialists in rheumatology were asked to refer patients with hip OA. One hundred and eighty-five consecutive patients with hip OA referred to the Department of Rheumatology for the study were evaluated in terms of their suitability for participation. Demographics and clinical characteristics of the patients included are given in Table I.

Inclusion criteria were hip OA as defined by the ACR criteria[29], radiographic changes of hip OA[30], age above 18 years, stable medication for at least 3 weeks before inclusion, and written informed consent.

Exclusion criteria were radiographic signs of osteonecrosis of the hip, pain demanding morphine or incompatibility with long-term observation, pain-free at randomization, participation in other medical trials, previous intra-articular injection in the hip joint within the last 3 months, defects or other skin changes in the injection area with resultant increased risk of infection, inflammatory or neurological diseases, poultry allergy, anticoagulation treatment, pregnancy, language or intellectual problems, or suspected potential noncompliance with protocol. Radiograms taken within 6 months prior to the study were accepted.

Patients were asked to continue their usual analgesic consumption throughout the study. If the pain demanded change in therapy, the patient was secondarily excluded.

OUTCOME MEASURES

The primary outcome measure was 'pain on walking' registered on a 100 mm visual analogue scale (VAS).

Secondary outcome measures were 'pain at rest' on a VAS, Lequesne score, the Western Ontario and McMaster Universities (WOMAC) total osteoarthritis index, and 'patient global assessment' on a VAS.

PATIENT MATERIAL

A flow diagram of the study is shown in Fig. 1. In the study period, 185 patients were referred to the department for this study. Of these, 81 patients were not included in the study: 25 patients did not want to participate after information on the study, 12 were pain free, 12 had too much pain to participate and were mostly referred for surgery, 9 had significant medical diseases, 7 had normal radiograms, and 16 were excluded for other reasons (participation in other medical trials, treatment with anticoagulants, and skin defects). One hundred and four patients were allocated to trial intervention through a six-envelope (2×3 treatments) block randomization. Three patients subsequently withdrew their consent and were not treated. Thus the study included a total of 101 patients receiving their allocated intervention. One patient was included with a radiogram showing OA, Kellgren–Lawrence score II. However, a new radiogram was run after the second injection since the patient reported the onset of leg shortening after the first radiogram. The second radiogram showed osteonecrosis of the hip and the patient was subsequently excluded. This patient was included in all calculations in his group.

Table I
Baseline characteristics of participants by randomization group. No significant differences between groups were observed

	HA ($n = 33$)	Saline ($n = 36$)	Corticosteroid ($n = 32$)	Total ($n = 101$)
Age (years)	65 ± 14	64 ± 11	69 ± 9	66 ± 12
[range]	[33–88]	[32–80]	[28–81]	[28–88]
Females (%)	61	61	72	64
Pain on walking (mm VAS)	49.2 ± 24.8	42.4 ± 19.7	44.0 ± 19.7	45.1 ± 21.7
Pain at rest (mm VAS)	25.4 ± 19.9	29.4 ± 21.3	20.4 ± 15.2	25.2 ± 19.3
Lequesne index (score: 1–24)	10.0 ± 4.0	9.5 ± 3.8	8.6 ± 3.1	9.4 ± 3.7
WOMAC-total (score: 0–96)	38.7 ± 14.8	41.2 ± 14.6	37.3 ± 15.4	39.2 ± 14.9
Patient global evaluation (mm VAS)	51.1 ± 22.2	49.0 ± 20.2	40.1 ± 20.2	46.9 ± 20.8
Kellgren grade I–II (%)	50	65	54	57
Kellgren grade III–IV (%)	50	35	46	43
No intra-articular effusion (%)	88	72	78	79
Intra-articular effusion (%)	12	28	22	21

Values are mean ± SD.

Methods

CLINICAL EVALUATION

At baseline and each time during follow-up (14, 28 and 90 days), the following measurements were obtained: pain (on walking and at rest), the 'patient global assessment' using 100 mm VAS, Lequesne score[31] and WOMAC[32]. 'The OARSI Standing Committee for Clinical Trials Response Criteria' were applied and calculated on the basis of the various VAS values[33].

ULTRASOUND EXAMINATION

An Acuson, Sequoia® Mountainview, CA, USA was used for the procedure. The examination of the hip joint was performed with a linear transducer with a center frequency of 14 MHz. The scan was performed with the patient in supine position and the leg in neutral position.

INJECTION

Non-touch technique was applied. With the patient in supine position and after triple skin disinfection, a needle (gauge 21, 0.8 × 80 mm) was inserted anteriorly 8–10 cm under the inguinal ligament towards the anterior/inferior capsule below the femoral head with free hand technique (Fig. 2). Guided by ultrasound, the needle was traced from 1 cm below the skin surface all the way to the joint. Joint fluid was aspirated if present. Thereafter, a small amount, 0.3–0.5 mL of air was injected into the joint in order to confirm correct needle placement[27]. The ultrasound pictures of both the aspiration and the injection of air were recorded as evidence of the placement.

ETHICS

The study protocol was approved by the local ethical committee (KF 02-013/00), and all patients signed informed consent before entering the study.

STATISTICAL METHODS

Owing to the relative invasiveness of the investigated treatments, the effect size (ES) was chosen to demonstrate a "moderate to large" clinical effect.

Thirty patients per group were required to complete the 3-month study period, which corresponds to a statistically significant change (two-tailed, $\alpha = 5\%$) and an ES[34,35] of more than 0.7 with a power ($1 - \beta$) of 80%[36]. The study aimed at enrolling 36 patients per group, allowing a drop-out rate of 10%. The *SAS*® statistical package (version 8; SAS institute Inc., Cary, NC, USA) was used for all statistical analyses. The primary analyses were based on intention-to-treat (ITT) and involved all the patients who received treatment at baseline using the last-observation carried forward technique. These patients are subsequently referred to as the ITT population. When considering the longitudinal part of the randomized trials, a linear approach was used for repeated measurements using the model proposed by PJ Diggle[37], which may be fitted in *SAS*® using the procedure

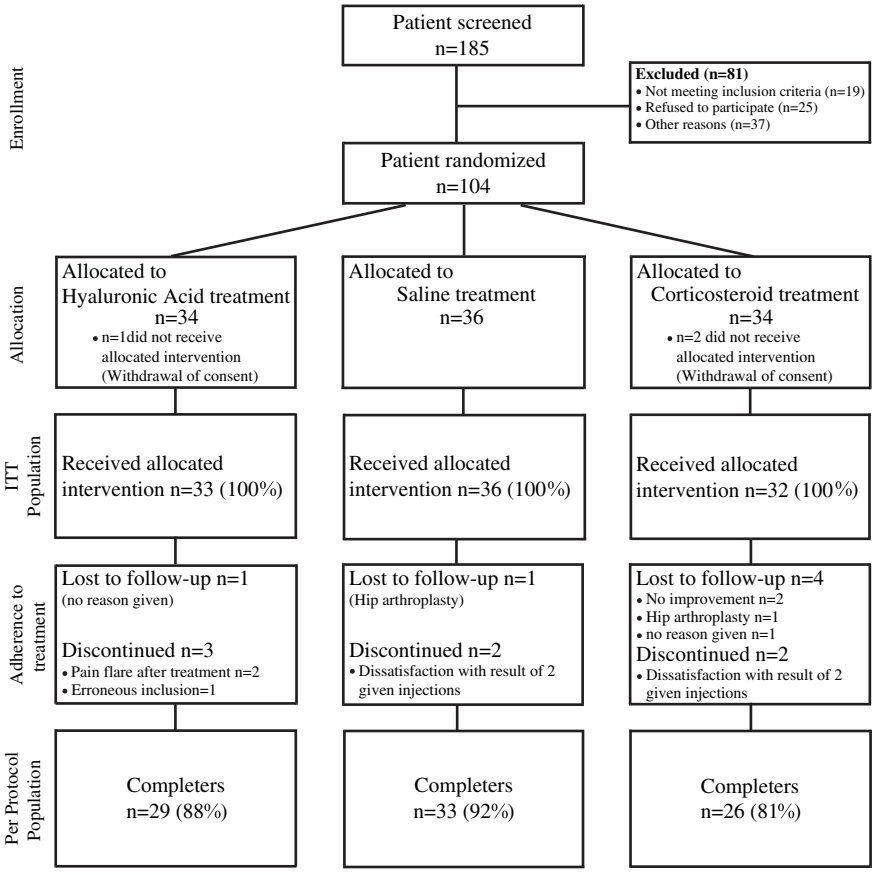

Fig. 1. Flow diagram of the study population according to the CONSORT statement. Drop-outs were for HA: at 14 days, 1 patient (pt); 28 days, 1 pt.; 90 days, 2 pt. Drop-outs for saline were: 28 days, 1 pt.; 90 days, 2 pt.; and for corticosteroid: 28 days, 2 pt.; 90 days, 4 pt.

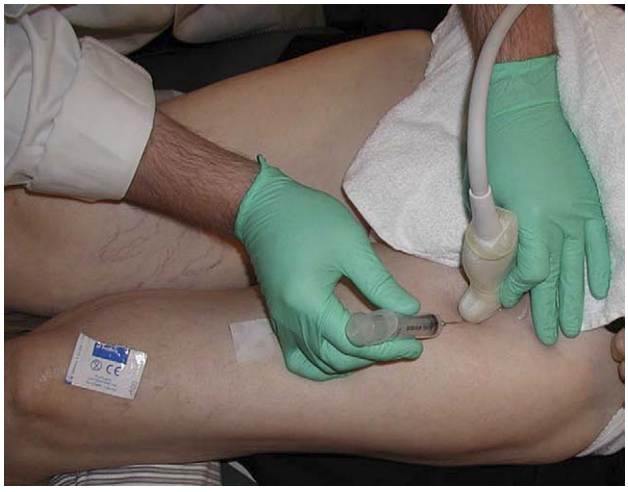

Fig. 2. The injection procedure. Note the antero-lateral approach, which was used in all cases in the present study after triple skin disinfection and by applying non-touch technique.

'*PROC MIXED*' based on maximum likelihood estimates of the parameters. The factor [*Subject*] was considered as a random effects factor. The assessment of the treatment and time effects was of interest in testing for a possible interaction and both treatment and time were considered as systematic factors − using the baseline value as covariate to reduce the random variation[38] and increase power[39]. To report the overall treatment effect following the 3-month time course, the average ES was calculated for each of the reported outcome measures; clinically, ES = 0.2 is considered small, ES = 0.5 is moderate, and ES > 0.8 is large[35], with standardized mean differences (SMD) analyzed as recommended by the Cochrane Collaboration[40], making the results more applicable to general practice. All analyses were based on the above-mentioned random subject (intercept) model, as several measurements were available on the same patient[41]. Unless stated otherwise, all results are presented explicitly by treatment group as mean (95% confidence interval, CI), as recommended in the CONSORT statement[42].

Results

STUDY ADHERENCE

The secondary drop-out rate was similar in the three study groups and 87% of the patients were evaluable at 3-month follow-up (Fig. 1).

The demographics of the patients are presented in Table I; there were no significant differences between the three treatment groups at baseline.

The primary outcome measure of this study, 'pain on walking', showed no significant interaction with respect to Treatment × Time ($P = 0.14$), indicating that there was no difference between the treatment patterns during the 3 months of treatment [presented in Fig. 3(a)]. Despite that fact, there was a significant treatment effect across all time-points ($P = 0.044$), due to a significant improvement following corticosteroid compared to saline, $SMD_{Steroid} = 0.6$ (95% CI: 0.1−1.1, $P = 0.021$) whereas HA compared to saline was $SMD_{HA} = 0.4$ (−0.1 to 0.9; $P = 0.13$). The difference between placebo (saline) and corticosteroid was significant at 14 and 28 days but vanished after 3 months ($P_{14\ days} = 0.006$; $P_{28\ days} = 0.006$; $P_{3\ months} = 0.58$). With regard to HA vs placebo, the difference was most substantial at 14 and 28 days but vanished after 3 months ($P_{14\ days} = 0.069$; $P_{28\ days} = 0.14$; $P_{3\ months} = 0.57$). There were no significant differences between HA and corticosteroid at any time-point ($P > 0.21$). The mean within-group difference in mm VAS (Δ'Pain on walking') for HA after 14, 28 and 90 days was −10 (95% CI: −18 to −2); −11 (−19 to −3) and −11 (−19 to −3), respectively. For corticosteroid it was −12 (−20 to −4); −15 (−23 to −7) and −9 (−16 to −1), respectively. By contrast, there were no significant changes for saline: 2 (−5 to 9); −1 (−8 to 7) and −5 (−13 to 2), at any time-point.

Secondary outcome 'Pain at rest', showed no significant interaction in relation to Treatment × Time ($P = 0.43$). Nor was there any effect of the treatment when evaluating data across all time-points [$P = 0.30$; data are presented in Fig. 3(b); $SMD_{Steroid} = 0.4$ (−0.1 to 0.9, $P = 0.13$); $SMD_{HA} = 0.1$ (−0.3 to 0.6; $P = 0.56$)].

Similar results were obtained regarding the Lequesne index [Treatment × Time ($P = 0.58$); treatment effect across all time-points ($P = 0.44$); $SMD_{Steroid} = 0.3$ (−0.2 to 0.8; $P = 0.22$); $SMD_{HA} = 0.2$ (−0.3 to 0.7; $P = 0.47$)] [Fig. 4(a)] and WOMAC index [Treatment × Time ($P = 0.29$); treatment effect ($P = 0.14$); $SMD_{Steroid} = 0.5$ (−0.0 to 1.0; $P = 0.059$); $SMD_{HA} = 0.3$ (−0.2 to 0.7; $P = 0.28$)] [Fig. 4(b)].

Finally, the effects following 3 months of therapy were evaluated using the 'patient global assessment' VAS (Fig. 5). These data showed no interaction with respect to Treatment × Time ($P = 0.073$), and no indication of

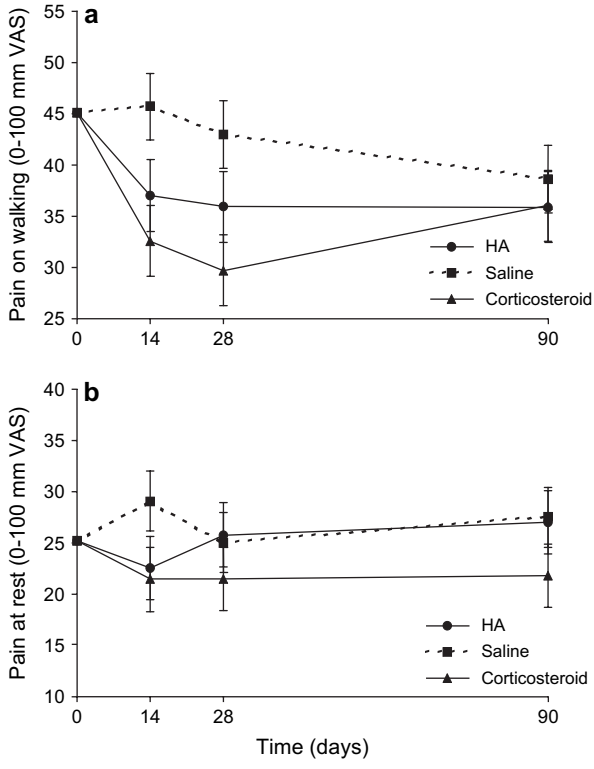

Fig. 3. Values are mean ± SE following 3 months of intervention in 101 patients with hip OA treated with injections of hyaluronic acid (HA, $n = 33$), corticosteroid ($n = 32$), or placebo (saline, $n = 36$). (a) For the primary outcome 'Pain on walking'. (b) For the outcome 'Pain at rest'.

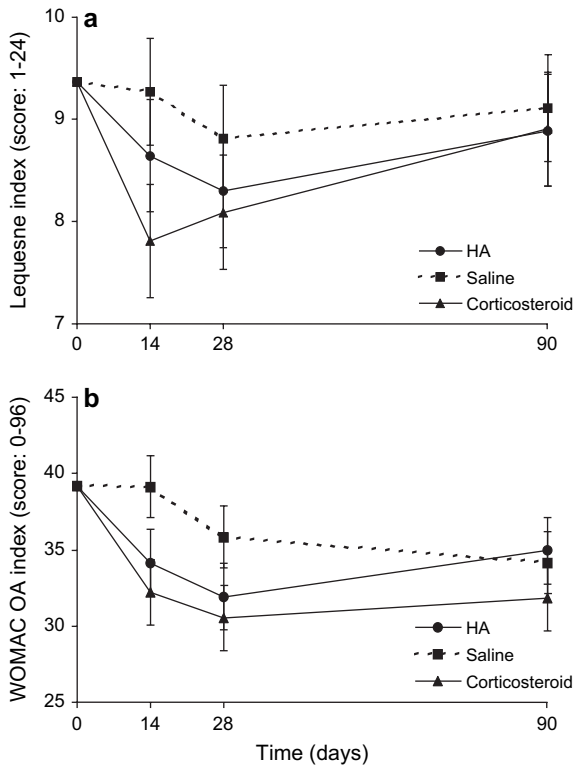

Fig. 4. Values of (a) The Lequesne index and (b) The WOMAC scores given as mean ± SE.

treatment effect overall ($P = 0.29$); $SMD_{Steroid} = 0.3$ (−0.1 to 0.8; $P = 0.17$); $SMD_{HA} = -0.0$ (−0.5 to 0.5; $P = 0.97$).

To explore whether there was any hidden, additional information, we applied two subgroup analyses on the primary outcome measure to test for potential interactions with the degree of OA [Fig. 6(a)], and to ascertain to what extent effusion interfered with any treatment effect [Fig. 6(b)]. There was no significant interaction with the dichotomized Kellgren grading ([I−II]/[III−IV]) when the change (Δ) in 'Pain on walking' was analyzed: Treatment × Time × Kellgren, $P = 0.13$; Treatment × Kellgren, $P = 0.82$. The average Treatment × Kellgren (95% CI) Δ'Pain on walking' (in mm VAS, by group × Kellgren) was HA[I−II] = −9 (−17 to 0, $P = 0.055$); HA[III−IV] = −1 (−11 to 8, $P = 0.75$); Corticosteroid[I−II] = −13 (−21 to −5, $P = 0.001$); Corticosteroid[III−IV] = −8 (−16 to 1, $P = 0.069$); Saline[I−II] = −3 (−10 to 4, $P = 0.36$); Saline[III−IV] = −1 (−11 to 8, $P = 0.76$).

There was no significant interaction with the dichotomous effusion in joint ([no]/[yes]) when the change (Δ) in 'Pain on walking' was analyzed: Treatment × Time × Effusion, $P = 0.26$; Treatment × Effusion, $P = 0.15$. The average Treatment × Effusion (95% CI) Δ'Pain on walking' (in mm VAS, by group × Effusion) was HA[no] = −11 (−17 to −5, $P = 0.0003$); HA[yes] = 7 (−9 to 22, $P = 0.40$); Corticosteroid[no] = −12 (−18 to −5, $P = 0.0003$); Corticosteroid[yes] = −15 (−27 to −3, $P = 0.012$); Saline[no] = −4 (−10 to 2, $P = 0.22$); Saline[yes] = 0 (−10 to 10, $P = 0.98$). Subgroup analysis for patients below and above the median age (66 years in our ITT-population) did not reveal any significant treatment differences (data not presented).

Using the OARSI outcome measures[33], at 14 days 53% (95% CI: 36−70%) responded to HA, 56% (39−73%) to corticosteroid, and 33% (18−49%) to placebo. At 28 days the results were 53% (36−70%) response to HA, 66% (49−82%) to corticosteroid, and 44% (28−61%) to placebo.

SAFETY

No hip-infections or other serious adverse events were encountered during the study period. Thus, all patients

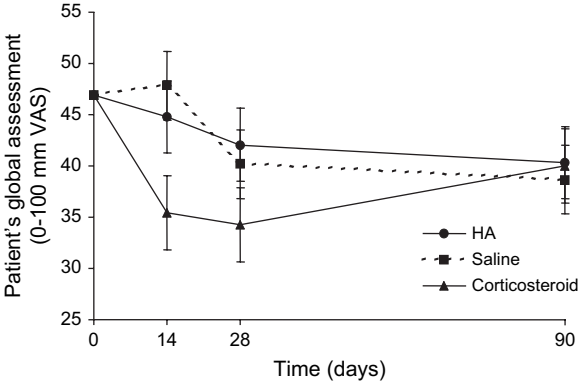

Fig. 5. Patient's global assessments given as mean ± SE.

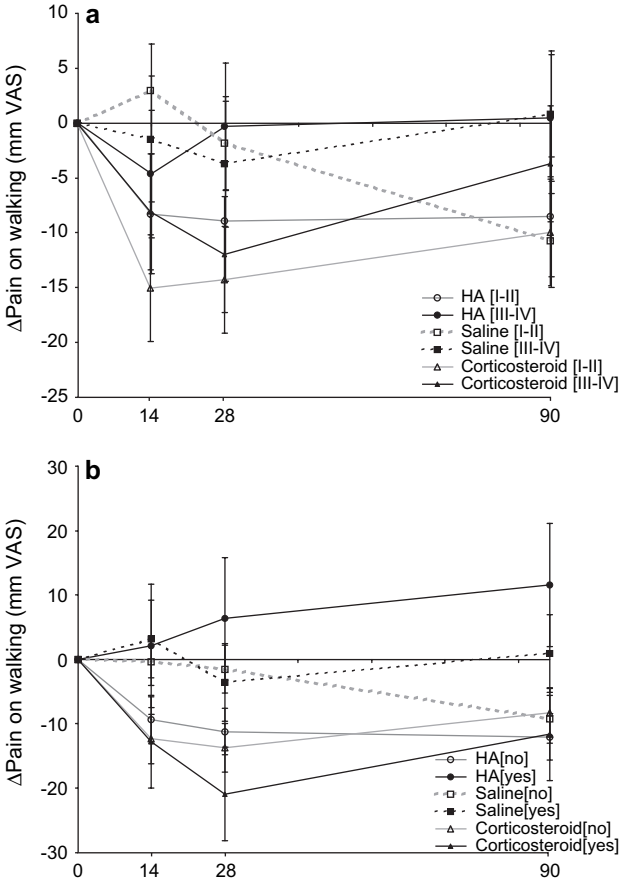

Fig. 6. Values are mean ± SE for the change (Δ) in 'Pain on walking'. (a) Dichotomized according to Kellgren grade ([I−II]/[III−IV]). (b) Dichotomized according to effusion in joint ([no]/[yes]).

could be treated throughout the study in the outpatients' clinic and no admissions to the hospital were necessary. The procedure, including both aspiration and injection of the hip, was basically tolerated without problems except for inevitable minor discomfort due to the sting of the needle. In some patients, the needling caused local pain and had to be repeated a second time via another route of access. One patient had a flare of pain on the primary needling before any injection could be performed. However, this patient was treated without problems the following day. Three patients developed an adverse reaction with a flare of hip pain varying between hours to days after the injection. In all these cases, the event passed without further sequels. None of the patients who quit the study reported pain on injection as a reason.

Discussion

The present study is, to our knowledge, the first randomized, placebo-controlled trial of HA injections in the hip joint. Numerous open-labeled, uncontrolled studies have indicated an effect of HA in knee OA and the same effect has been reported in hip OA[20]. In our study, the data handling and analyses adhered strictly to the CONSORT statement[28] and employed intention-to-treat statistics. As none of the interventions studied has been properly evaluated before, it was necessary to include a placebo group. The ES and thereby the power of our study was chosen in the moderate to high level with regard to the invasiveness and feasibility of the intervention. If hip injections were to be included in daily practice, the tediousness of the procedure as well as the costs of medication etc. must be matched by a considerable benefit. There was no statistically significant effect of HA on any outcome measure including the primary outcome measure, i.e., 'Pain on walking', during the 3 months of intervention. The group of patients treated with corticosteroids experienced a significant, but short lasting improvement with an effect size indicating a moderate clinical effect (ES = 0.6). In none of the groups any tendency of effect was observed at the 3-month follow-up. Our results are in agreement with the general impression of joint injections as a remedy in acute flares of activity in both rheumatoid arthritis[43] and OA[44]. This *à priori* assumption led us to search for a high degree of acute effect and to limit the follow-up time to 3 months. The present results confirmed the notion of an immediate rather than a long-lasting effect of injection, whatever the substance used.

Although the effect following HA was not significant, it can be calculated that an ES of 0.4 (small to moderate clinical effect) would require 100 patients per group to achieve statistical significance with a power of 80%[36]; the actual power in this trial in terms of HA vs saline was approximately 40%. In comparison, using data from the meta-analysis by Lo *et al.*[10] and weighted for the number of patients analyzed, we calculated the overall (arithmetic mean) ES of light-weighted hyaluronan (Hyalgan®) in knees to be 0.23[10]. Whether HA of higher molecular weight might be of larger value in hip joints remains to be studied. Subgroup analysis was predestined in the protocol and the material dichotomized according to the median age due to former indications of a positive effect for elderly patients in a similar study of HA treatment of knee OA[11]. In our hip patients no age-related treatment differences were observed. Earlier experience from large open-labeled studies has suggested a difference for HA on knee OA according to the degree of radiographic changes, with a larger effect being observed on lightly affected knees[45]. Our results seemed to indicate a similar tendency towards a relatively large effect of HA on patients with lowish Kellgren gradings on hip radiograms. The size of our material only allowed a dichotomization of the radiographic scores.

Given the possibility that corticosteroid might have a more pronounced effect in patients with signs of inflammation, e.g., joint effusion, a further subgroup analysis based on presence or absence of effusion in the hip joint at baseline was performed in our study. An effusion was only present in 21 patients (Table I). However, HA had a considerable effect on patients without effusion. In contrast, there was no effect from HA on patients with effusion. Corticosteroid, on the other hand, had an effect on both patients with and without effusion. The effect of HA in patients without effusion was comparable to the one observed following corticosteroids in the same subgroup of patients.

The intra-articular injections in the hip in all three treatment groups were well tolerated by the OA patients and easy to perform when guided by ultrasound. With this method, no radiation is given to the patient and the placement of the needle can be verified before the injection is given[27].

The experience with HA therapy in OA is based mostly on data from studies of knee injections. Knee OA seems to respond to these treatments to a varying degree[46], although there has been some indication of a publication bias and a relative lack of negative studies in the literature[10]. The effect in knee OA seems to be obtained within 3 months corresponding to our observation period[46]. The number and interval of HA injections could have influenced the effect. The 14 days interval between HA injection was opted in regard to patient security, as this period would be long enough to diagnose a joint infection and differentiate this from soft tissue irritation.

There was a definite, though short-lived effect of a corticosteroid injection and our results indicate that corticosteroids may have some use in the treatment of hip OA in need of an acute pain relief.

A similar course after corticosteroid injection of the knee in OA has been indicated in earlier publications[12]. This has led to the recommendation of corticosteroid therapy in selected cases of knee OA, which is now, considering the results of the present RCT, evident for hip OA as well (category 1b evidence[47]).

In accordance with observations in open-labeled studies of corticosteroid injections in knee OA[48], the presence of effusion in the hip joint in our material seemed to be associated with a good clinical response.

Although the effusion was aspirated in all groups, a recurrence of the effusion was observed in some of the patients. However, in no cases did the amount of effusion exceed more than a few milliliters.

It has previously been reported that the pain in hip OA could be relieved by injection of large quantities of saline[49]. A similar effect would not be expected with the use of a mere 2 mL of saline, as in our study, and we regard the saline-treated group as a proper placebo control. An effect of saline has been reported in knee OA[11]. However, a lavage effect would not be expected with these small quantities[50].

In this study, numerous needle aspirations and injections of the hip were given without serious adverse events and, in general, this procedure may be regarded as innocuous and safe[16]. At present, such injections should, however, be performed without use of radiation[26,27]. Whether efficient or not, injection of HA seems to be safe when given with the aid of ultrasound guidance[51].

Cost–benefit analysis is only partly possible in relation to the present study. With market prices in DK, three doses of HA cost 24 times as much as one dose of methylprednisolone (about $US263 vs $US11). To this should be added the costs of extra consultations.

In agreement with the results in knee OA44 corticosteroid seems to have a definite, albeit short-lived effect in hip OA, regardless of subgrouping. It is not, however, expected that any of the medications tested will have an effect of longer duration or significance at a clinically applicable level of effect size 33, 35. Based on the effect sizes calculated in the present study, future controlled studies of hip injections with these substances in parallel groups should include a minimum of 100 patients in each group. In conclusion, this controlled study could not demonstrate a 3-month effect on hip OA using HA. Nevertheless, the treatment was quite harmless. Future studies should seek to clarify a possible importance of injections in subgroups of patients with hip OA. Considering the costs and invasiveness of the procedures, injections cannot be recommended as standard therapy in hip OA for wider populations, and therefore the indications remain a highly individualized matter.

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