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Hyaluronic acid in the treatment of osteoarthritis of the knee

E. C. Huskisson and S. Donnelly[1]

Department of Rheumatology, St Bartholomew's Hospital, West Smithfield, London and [1]Department of Rheumatology, Whipps Cross Hospital, London E11 1NR, UK

Abstract

Objectives. We examined the efficacy, safety and patient satisfaction of intra-articular hyaluronic acid (HA) in patients with osteoarthritis of the knee.

Methods. One hundred patients with mild to moderate osteoarthritis of the knee entered a randomized blind-observer trial of 6 months HA *vs* placebo. Primary efficacy criteria were pain on walking, measured with a visual analogue scale, and the Lequesne Index.

Results. For pain on walking, a significant difference in favour of HA was found for completed patients at week 5, the end of the course of injections, and at month 6, the end of the study ($P = 0.0087$ and $P = 0.0049$, respectively). Further analysis using the Last Observation Carried Forward (LOCF) also showed a significant benefit favouring HA at month 6 ($P = 0.0010$). For the Lequesne Index, a significant difference in favour of HA was found at week 5 ($P = 0.030$) and at month 2 ($P = 0.0431$), but this was only of borderline significance at month 4 ($P = 0.0528$). Patients' global assessment of efficacy favoured HA at month 6 ($P = 0.012$). Improvement in other secondary criteria was generally superior in the HA group compared to placebo both at week 5 and month 6. Adverse events, mainly local injection site reactions, occurred in both groups with equal frequency.

Conclusions. The study demonstrated that five weekly intra-articular injections of sodium hyaluronate (Hyalgan®) were superior to placebo and well tolerated in patients with osteoarthritis of the knee with a symptomatic benefit which persisted for 6 months.

KEY WORDS: HA, Sodium hyaluronate, Knee osteoarthritis, Intra-articular therapy.

Osteoarthritis (OA) of the knee is very common and very important. Population surveys have shown that radiographically determined OA of the knee is present in between 15 and 30% of subjects aged over 45 yr, and thereafter increases steadily with age [1, 2]. Current treatment is usually disappointing and most rheumatologists do not follow-up patients once the diagnosis is made. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of drug treatment in knee OA, as in other types of arthritis, but have obvious limitations. The elderly are most at risk from serious adverse effects of these drugs, particularly peptic ulceration, bleeding or perforation. Intra-articular steroids are used in OA, but their long-term efficacy is not well established.

Intra-articular sodium hyaluronate (hyaluronic acid; HA) offers the prospect of another approach to the treatment of OA. Studies have shown that a course of five injections of HA provides prolonged relief of symptoms in patients with OA of the knee [3–5]. This type of action is characteristic of a group of compounds called 'slow acting symptomatic drug for osteoarthritis' [6] to distinguish them from NSAIDs.

Hyalgan®, used in this study, is a highly purified, concentrated (10 mg/ml), viscous solution of natural HA with a molecular weight in the range of 500–730 kDa, extracted from rooster combs. In studies reported to date [3–5], Hyalgan® has been very well tolerated with no significant side-effects apart from the possibility of transient localized pain after the injection. While most studies have found Hyalgan® to be effective, Henderson *et al.* [7] failed to show a difference in a placebo-controlled study. This 6 month study of 91 patients had a high percentage of withdrawals (38%) and local adverse effects (pain and/or swelling: 47% in the HA group and 22% with placebo). This may have resulted in an insufficient power to detect a difference in the completed patients. The question, therefore, regarding the efficacy of Hyalgan® over placebo remains controversial and highly important. We have compared Hyalgan® and placebo in order to establish whether or not the compound is effective in OA of the knee.

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Correspondence to: S. Donnelly, Department of Rheumatology, Whipps Cross Hospital, London E11 1NR, UK.

Patients and methods

Patients

One hundred fully ambulant patients attending a hospital out-patient clinic with a diagnosis of OA of one or both of the knees according to the ARA criteria [8] were included. All patients had radiographic changes of OA equal to Kellgren and Lawrence grade II or III [9] on an X-ray taken within the 6 months prior to study entry. All patients had consistent pain for the 3 months prior to recruitment and moderate or severe pain on walking at both the initial screening visit and at the baseline visit.

Exclusion criteria included X-rays showing grade IV change on the Kellgren and Lawrence scale, serious functional impairment at the knee, associated OA of the hip of sufficient severity to interfere with assessment of the knee or OA of any other joint which might have hindered assessment of the knee, psoriasis, radiographic evidence of sacroiliitis or any other joint disease other than OA, known or suspected joint infection, poor general health or other conditions which would prevent regular hospital attendance, skin conditions overlying the joint which might make injection dangerous, painful knee conditions other than OA like Sudek's atrophy or Paget's disease, severe intercurrent hepatic or renal disease or major general medical conditions, and use of an intra-articular steroid or radiocolloid within the 3 months before the start of treatment.

The study was conducted in the Department of Rheumatology at St Bartholomew's Hospital, London, after approval of the ethics committee. Written informed consent was obtained from all patients.

Study design

This was a randomized, placebo-controlled, 'blind-observer', parallel group study with a 6 month follow-up period, comparing the efficacy of five weekly intra-articular injections of HA (20 mg/2 ml, Hyalgan®, Fidia, Abano Terme, Italy) with five weekly intra-articular injections of placebo (2 ml saline) in the treatment of knee OA. HA and placebo were both formulated in a buffered aqueous solution.

Because of the differences in viscosity between the drug and placebo, it was necessary to use a blind observer. The intra-articular injections were administered by a single physician (SD) who did not discuss the treatment with either patient or observer; the efficacy assessments were carried out by an experienced rheumatology nurse who was not aware of the treatment given.

Study procedure

Following initial screening, patients who fulfilled the entry criteria were admitted to the trial. The patients were re-examined 2 weeks later to verify the entry criteria, including pain severity. At this visit (baseline visit), patients were randomly assigned to receive either intra-articular HA or placebo in the affected knee joint. Patients received five weekly injections of HA or placebo using standard aseptic techniques after aspiration of any effusion present.

Clinical assessments were made at baseline, at weekly visits over 4 weeks, 1 week after the final injection (week 5), and at months 2, 4 and 6. During the treatment phase, the clinical assessments were carried out before each injection.

The primary efficacy criteria in the study were knee pain on walking as recorded by the patient on a 100 mm visual analogue scale (VAS) [10] and knee function as assessed by the Lequesne Functional Index [11].

Secondary efficacy parameters were knee pain at rest scored on a 100 mm VAS, joint tenderness and swelling assessed using a four-point nominal scale (none, mild, moderate or severe), morning stiffness and inactivity stiffness in minutes, patient's global impression of efficacy recorded on a four-point scale (excellent, fair, poor or useless), patient satisfaction with the treatment evaluated by a Satisfaction Index which assessed overall satisfaction, satisfaction based on perceived efficacy or adverse reactions on separate 100 mm VAS and satisfaction, pain relief, anti-inflammatory effect, therapeutic outcome and therapeutic preferences on separate five-point nominal scales [12, 13].

The occurrence of adverse events was assessed at all visits. Throughout the study, patients were permitted to continue with existing analgesic or anti-inflammatory therapy as considered appropriate by the referring physician. A record of all treatments was maintained at each visit.

Statistical methods

The pain on walking efficacy parameter was used to determine the number of patients to be recruited into the study, i.e. the sample size. The standard deviation calculated from changes in joint pain score on walking, as recorded on a 100 mm VAS, was expected to be $\sim$24 mm [14].

On this basis, a sample size of 50 patients for each group would give a power of around 90% for the detection of a mean treatment change of 15.4 mm in the pain on walking score, using a two-tailed test at the 5% significance level.

The principal analysis for the primary efficacy criteria was the analysis of covariance (ANCOVA) using the corresponding baseline (week 0) assessment as the covariate, performed at week 5 and month 6 using the data of all randomized patients who had the observations at 6 months. Where appropriate, additional analyses were carried out for these parameters at months 2 and 4. If there was evidence of statistically significant differences in the two groups at baseline ($P < 0.10$) for important prognostic factors, adjustment for these factors was made in the statistical analysis.

For the continuous secondary parameters, ANCOVA was also carried out, whereas categorical data were analysed by the χ^2 test. All statistical tests for efficacy parameters were performed using a two-tailed test, with a significance level of $\alpha = 0.05$.

All efficacy results are presented for patients who

TABLE 1. Patient characteristics at baseline

	Sex		Age (yr)	Involved knee		Kellgren–Lawrence (score)		Duration of pain (months)			
	Male	Female	Mean (S.D.)	Left	Right	II	III	0–6	7–12	13–24	>25
HA	12	38	65.8 (8.8)	23	27	30	20	12	14	10	14
Placebo	21	29	64.8 (9.3)	24	26	28	22	7	15	13	15

completed the 6 months follow-up. For the principal efficacy criteria (pain on walking), a 'Last Observation Carried Forward' (LOCF) analysis on all 100 randomized patients was performed as an intention-to-treat outcome.

The Statistical Analysis Systems (SAS) software was used in the statistical analyses (SAS Institute, Cary, NC, USA).

Results

A total of 100 patients, 33 males and 67 females, were recruited into the study and were assigned to one of the two treatment groups, 50 patients in each group. Baseline characteristics of the two groups (Table 1) were comparable except for sex distribution ($P = 0.056$).

Ninety-four patients completed the 5 week treatment course and 81 patients completed the 6 month follow-up. Of the 19 patients who withdrew from the study, six withdrew during the treatment period (week 0–4): four patients in the HA group, all for reasons unrelated to the treatment, and two patients in the placebo group, both for lack of efficacy. During the follow-up period, a further 13 patients withdrew from the study. Six withdrew from the HA group, two due to the onset of non-drug-related side-effects (removal of a calf ulcer in one, flare-up at month 4 in the other), two due to lack of efficacy and two who were lost to follow-up. Seven were withdrawn from the placebo group, six due to lack of efficacy and one for a non-drug-related side-event (a flare-up at month 4).

Primary efficacy criteria

Pain on walking. The results are shown in Table 2 and Fig. 1. A significant difference was found in the VAS score for pain on walking between the two treatment groups in favour of HA at week 5 and month 6 ($P = 0.0087$ and $P = 0.0049$, respectively). The analysis on all randomized patients, using the LOCF, also showed a significant result favouring HA ($P = 0.0010$).

Lequesne Functional Index. The results are shown in Table 3 and Fig. 2. At week 5, a significant difference in the Lequesne Functional Index for the knee was found between the two treatment groups in favour of HA ($P = 0.030$). This persisted to month 2 ($P = 0.0431$) and almost to month 4 ($P = 0.0528$), but the difference was not significant at month 6.

Secondary efficacy parameters

Analysis of pain at rest, at week 5 and month 6 compared with baseline showed differences between groups which favoured HA but were not significant. There were no differences between the groups in the nominal scores for joint tenderness, morning stiffness or inactivity stiffness at any time point. However, at week 5, 42.5% of the HA-treated patients compared with 29.3% of the placebo patients reported no morning stiffness ($P = 0.214$) and, at month 6, 35.9% of the patients in the HA group and 22.5% in the placebo group reported no inactivity stiffness ($P = 0.190$).

In the patient's global impression, a significant difference was found in favour of HA compared to placebo at month 6 ($P = 0.012$). At this time, 75% of the HA-treated patients rated the treatment as either excellent or fair compared with 47.5% of the placebo-treated patients.

In overall patient satisfaction, using the VAS, there was no difference at week 5 ($P = 0.276$), but, at month 6, there was a significant preference for HA ($P = 0.006$). Perceived treatment efficacy using VAS favoured HA, but was not significant. Using a five-point nominal scale, the only significant difference was in perceived efficacy at month 6 only in favour of HA ($P = 0.017$). There were no differences in perceived adverse effects between the groups.

In anti-inflammatory efficacy, using VAS, the difference significantly favoured HA only at month 6 ($P = 0.011$). In perceived disease progression, the response was significant in favour of HA at week 5 ($P = 0.006$), but not at month 6 ($P = 0.078$). In patient

TABLE 2. Pain on walking by VAS (completed patients)

	HA ($n = 39$)		Placebo ($n = 41$)	
Visit	Mean	S.D.	Mean	S.D.
Week 0	65.8	18.0	61.9	22.9
Week 5	27.5	22.7	40.6	29.4
Month 2	32.3	26.6	42.1	29.3
Month 4	33.0	29.2	48.3	31.6
Month 6	39.4	27.8	53.7	29.9

TABLE 3. Lequesne Functional Index (completed patients)

	HA ($n = 40$)		Placebo ($n = 41$)	
Visit	Mean	S.D.	Mean	S.D.
Week 0	13.4	3.4	14.0	2.7
Week 5	10.0	4.6	12.1	3.8
Month 2	9.9	4.8	12.0	4.0
Month 4	10.2	4.8	12.4	4.2
Month 6	11.2	4.4	12.6	4.8

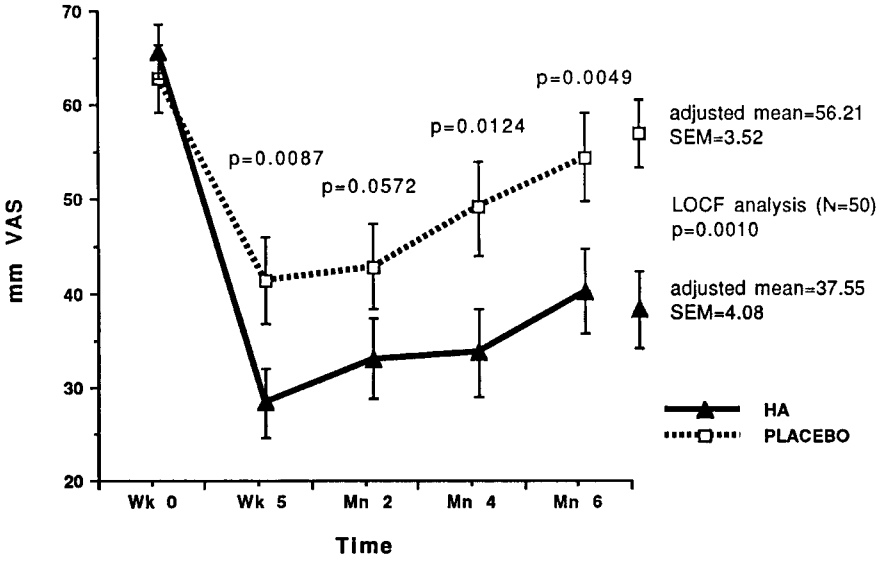

FIG. 1. Pain on walking as scored on a visual analogue scale (VAS) in the treatment groups. Mean values ± S.E.M. of the patients who completed the study and LOCF (Last Observation Carried Forward) analysis on all randomized patients.

acceptability, there was a significant benefit in favour of HA at month 6 ($P = 0.025$). For the other items of the questionnaire (perceived pain relief, duration of pain relief and patients' preferred treatment), although there were consistent trends in favour of HA at week 5 and month 6, these did not reach significance.

At baseline, the presence of an effusion was observed in 35 patients (14 placebo and 21 HA). Of the 14 patients in the placebo group with an effusion at baseline, nine (64.28%) did not have effusion at week 5; in the HA group, the number of patients without effusion at this time was 14 out of 19 (73.7%). At month 6, the percentages of patients with an effusion at baseline for whom the effusion disappeared were 58.3% (7/12) in the placebo group and 75.0% (12/16) in the HA group.

Concomitant medications

The consumption of anti-inflammatory drugs throughout the study was low. The number of patients who took NSAIDs was very similar in both groups during the treatment period (seven HA, four placebo) and during the 6 month follow-up (five HA, six placebo). Only one patient in the HA group took analgesics during the treatment period.

Adverse events

A total of 31 patients (14 from the placebo group and 17 from the HA group) reported adverse events during the study. The majority reported local reactions at the injection site during the treatment phase with no differences between placebo or active drug. Flare at the knee joint was recorded in seven patients in each group. Effusion was present in only one patient in the HA group compared with three patients in the placebo group.

Eleven patients in the HA group (five during the treatment, one during and after the treatment, and five during the follow-up) and five patients in the placebo

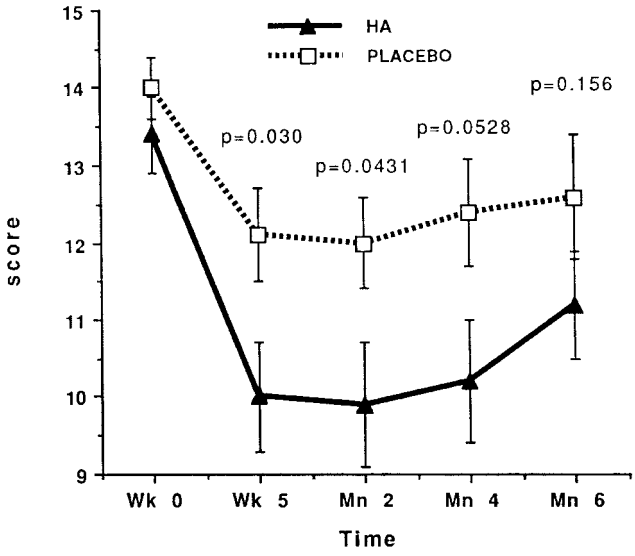

FIG. 2. Lequesne Functional Index in the treatment groups. Mean values ± S.E.M. of the patients who completed the study.

group (one during the treatment, one during and after the treatment, and three during the follow-up) reported adverse events which were not associated with local reactions in the knee joint area. Of these, one in the HA group was felt to be severe and possibly treatment related. The patient developed a cutaneous vasculitis progressively spreading from both legs to the abdomen and arms. The event occurred within the first week of treatment and progressed during the course of the study. The patient did not, however, interrupt the study. One other adverse event, which occurred in the HA group 8 days after the last injection, was considered severe and possibly drug related. This was a skin reaction characterized by peeling of the skin on the hands and toes, and

erythema which improved during the course of the study. At the 6 month follow-up, the reaction appeared milder than at its onset.

In the placebo group, there were no adverse events considered to be related to treatment. One patient in the placebo group experienced a myocardial infarction during the second week of the study.

Discussion

This study clearly demonstrates that a course of five weekly injections of HA (Hyalgan®) is effective, superior to placebo, and acceptable to patients with OA of the knee. It confirms many other studies which have demonstrated similar effects. Of particular relevance is a recent 6 month, US multicentre study [4] comparing a course of five weekly intra-articular injections of HA with five weekly intra-articular placebo injections and continuous oral naproxen. HA was superior to placebo and at least as effective as oral naproxen. There were significantly more premature terminations due to gastrointestinal side-effects in the naproxen group. Our study confirms these findings with respect to placebo, but, unlike the US study, we observed a gradual decline in patient efficacy in both the HA and placebo patients which may have resulted from a higher pain score at baseline in our patients: mean VAS 67.2 (HA) and 64.5 (placebo) in this study *vs* 52.7 (HA) and 49.3 (placebo) in the US study.

It is not surprising that pain relief was associated with improvement in function, demonstrated by changes in the Lequesne Index. There was a high degree of satisfaction with the treatment, superior to that produced by placebo in terms of efficacy and equal to that of placebo in terms of tolerance.

A course of injections of HA produced pain relief which continued for 6 months after the start of the treatment, a characteristic time course which is associated with symptomatic slow-acting drugs for OA. Courses repeated every 6 months have been shown to provide relief of symptoms over a 2 yr period [15]. A study comparing HA and triamcinolone hexacetonide [16] suggested that the steroid preparation had a brief advantage in the week after the injection, but that HA was superior in the ensuing 6 months.

HA is a naturally occurring substance found in synovial fluid and cartilage, in the eye and elsewhere. Synovial fluid depends upon HA for its viscoelasticity and therefore its lubricating properties, which deteriorate in OA. The mode of action of injected HA is unclear. It has a short half-life and restoration of viscosity is, therefore, unlikely to explain the prolonged symptomatic relief produced by a course of injections. Injected HA may, however, improve the quality of the material produced by the synovial B cells. It is more likely that HA works by influencing the presence and status of inflammatory cells and receptors [17].

HA was well tolerated, the only side-effect to occur with significant frequency being painful reactions at the injection site. Transient inflammatory flares have been reported after injections of HA, but in this study they were equally common in the placebo group. Cutaneous vasculitis has not been reported elsewhere in patients receiving HA, even though the product has been available in 20 countries for several years and widely used. In these circumstances, its relationship to the treatment must be regarded as unproven. The low incidence of side-effects and the safety of HA will make it particularly suitable for the treatment of OA in elderly patients who cannot tolerate NSAIDs or for whom they are contraindicated.

With its prolonged pain-relieving potential and avoiding the possible problems of anti-inflammatory drugs in the stomach, Hyalgan® has obvious potential in the management of OA of the knee in the elderly as well as in patients whose disease cannot easily be controlled in simpler ways. It is likely to be useful for other joints and its effects on the course and outcome of the disease remain to be explored. A novel approach to the treatment of such a common disease as OA is particularly welcome and is a reflection of the increasing interest in the disease process and in possible ways of modifying it.

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