HYADD 4 *versus* methylprednisolone acetate in symptomatic knee osteoarthritis: a single-centre single blind prospective randomised controlled clinical study with a 1-year follow-up

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Abstract

Objective

The aim of the present study was to compare the clinical results and the quality of life in patients with symptomatic knee osteoarthritis randomised to either a new HA (HYADD 4) or corticosteroid (CS). A separate rationale was to evaluate the safety profile of HYADD 4.

Methods

All the patients presenting for unilateral symptomatic primary knee osteoarthritis were prospectively randomly assigned to receive 2 injections of either HYADD 4 or CS, and were evaluated before the injections and at 6, 12, 26 and 52 weeks. Primary end point was WOMAC score at 26 weeks; secondary end points were WOMAC score, VAS for pain, and SF-36 score at any time point.

Results

There were 53 females and 22 males in the HYADD 4 group (mean age 71.5±10.6 years), and 50 females and 25 males in the CS group (mean age 68.6±9.9 years). The observed sided effects were mild and their incidence was similar in the two groups. Patients in the HYADD 4 group reported significantly better WOMAC scores at 26 weeks. The patients improved in all considered outcomes after the injections, with a peak of therapeutic effect between 6 and 12 weeks. Patients in the HYADD 4 group obtained significantly better scores than the CS group up to 26 weeks. At the 1-year follow-up no statistically significant differences between treatments were detected.

Conclusion

HYADD 4 did not have significantly higher side effects when compared to CS injections and provided better short-term (but not long-term) control of symptoms in patients with mild to moderate knee osteoarthritis. Patients with less pain and dysfunction at baseline may be the best candidates for HYADD 4 injections.

Key words

knee, osteoarthritis, hyaluronic acid, injection, HYADD 4

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Introduction

Osteoarthritis is the main joint disorder and represents one of the most common causes of pain, disability and loss of function, and at least 40% of people older than 65 suffer from osteoarthritis in the hips or knees (1). Hyaluronic acid (HA) is a large viscoelastic glycosaminoglycan that is naturally present in healthy joint fluid, but its molecular weight and concentration can be reduced during osteoarthritis (2-4). The result is a reduction in the viscoelasticity of the fluid, and an increased susceptibility of cartilage to breakdown.

Intra-articular injections are frequently used in the treatment of symptomatic osteoarthritis, especially in the knee. Long-acting corticosteroids (CS) and HA are the two most common substances injected into the knee joint; but multiple substances can be used (5). CS have potent anti-inflammatory effects reducing cytokine and metalloprotease expression (3, 6). The mechanism of HA injection is not clearly known, it seems it enhances endogenous HA synthesis, it stimulates chondrocyte metabolism and synthesis of cartilage matrix components, and it inhibits chondrodegenerative enzymes, reducing the inflammatory process (7, 8). Although guidelines from many international societies (1, 9-11) recommend CS as the gold standard in intra-articular therapy in patients with symptomatic knee osteoarthritis, many adverse events have been described, such as suppression of cartilage proteoglycan synthesis, worsening of cartilage lesions, or even degenerative lesions in normal cartilage (12, 13). There is increasing scientific evidence that viscosupplementation with intra-articular HA injections give the same, or even better, results avoiding the side effects observed with CS (14-22). International guidelines are controversial on this topic: some encourage HA use (1, 9, 11), and others recommend against (10, 23, 24).

Many different HA are commercially available, and they are classified according to their chemical structure (low molecular weight, high molecular weight, cross-linked, reticulated), having different biological and biomechanical activities. HYADD 4 (Fidia Farmaceutici Spa., Abano Terme, Italy) is a new reticulated HA with a very high biologic activity, provides elevated cushioning features, and has a long intra-articular residency time (up to 21 days) compared to previous molecules (25-28).

The aim of the present study was to compare the clinical results and the quality of life in patients with mild to moderate symptomatic knee osteoarthritis randomised to receive intra-articular injections of either HYADD 4 or 40 mg of 6-methylprednisolone acetate (Depo-Medrol 40 mg/ml, Pfizer, New York, NY, USA) (CS group). A separate rationale for performing the current study was that, despite extensive evidence on the contrary (14-22), the safety of intra-articular HA for knee osteoarthritis has recently been called into question (23). Thus, an evaluation of HYADD 4 safety is warranted.

Materials and methods

This is a single-centre single blind prospective randomised controlled clinical study. All the patients presenting for unilateral primary knee osteoarthritis (based on American College of Rheumatology criteria) to the authors' institution were prospectively scrutinised according to the following criteria. In the study were included male and female walking patients older than 45, with a single symptomatic knee. Patients were included if they had a Kellgren-Lawrence (29) grade 2–3 knee osteoarthritis and a VAS for pain ≥3. Two authors independently reviewed radiographs at baseline for determination of osteoarthritis grade, and disagreements were resolved by discussion. Patients were excluded in the case of grade 1 or 4 osteoarthritis according to Kellgren-Lawrence (29), symptoms in both knees, a varus or valgus deformity greater than 10 degrees, flexion contracture greater that 15 degrees, ligamentous instability, or meniscal tears, NSAIDSs used in the last 30 days, intra-articular injections in the last 12 months; septic, inflammatory or crystal arthritis, previous surgeries in the last 6 months, physical therapy in the last 30 days.

All the patients that fulfilled inclusion and exclusion criteria were invited to participate to the study after careful ex-

planation of aims and methods adopted. A centralised, computer-generated randomisation was conducted to assign patients in a 1:1 ratio to the HYADD 4 or CS group. Every patient received 2 injections in the index knee 7 days apart by the same physician. With the patient in the sitting position and the legs hanging out from the examination table, the skin was disinfected with Betadine. Using disposable gloves, a 18-Gauge needle was inserted through an antero-lateral parapatellar approach, and knee effusions were aspirated (if necessary) into a separate syringe. The same needle was left in place, and the syringe that had been prefilled with either HYADD 4 or CS was used for the injection. Patients were encouraged to refrain from strenuous activity for a day following the intra-articular injections. At the end of the first injection, every patient received a clinical diary to report side effects, and NSAIDs and acetaminophen consumption.

No formal physical therapy was prescribed after the injections; furthermore, NSAIDs and acetaminophen consumption were the only pain medications allowed.

Clinical evaluation

All the patients were evaluated before the injections and at 6, 12, 26 and 52 weeks after the first injection. Primary end point was WOMAC total score (30) at 26 weeks; secondary end points were WOMAC total score, VAS for pain, and SF-36 (31) score at any time point. Baseline and follow-up evaluations were performed by the same physician, who was not involved in injections and management of the patients (single blind toward the observer). Baseline data were collected in the clinic at the time the patients agreed to participate to the study, and all of the forms were given to them before the first injection. Follow-up data were collected through phone calls. No radiographs were collected at follow-up for evaluation of knee osteoarthritis. Failures were defined as any follow-up injections or indication to knee arthroplasty.

Sample sizing and statistical analysis

A review of the literature revealed that in a population similar to this study, WOMAC total scores are distributed normally with a standard deviation of 12 points, and the patients perceive as clinically significant a difference of at least 6 points. Considering an error alpha=5%, a power beta=80%, and potential dropout rate of 20% at follow-up, it was determined that 75 patients per group would be sufficient for this study. Our hypothesis was that HYADD 4 injections provide better WOMAC total scores at 26 weeks compared to CS (primary end point).

Descriptive statistics were used to summarise the characteristics of the study groups and sub-groups, including means and standard deviations of all continuous variables. An unpaired *t*-test was used to compare continuous variables. Categorical variables were compared using a Chi-square test or a Fisher exact test, as needed. Two-sided statistical significance was defined as $p<0.05$. Statistical analyses were performed with SPSS v. 15.0 (SPSS Inc., an IBM Company, Chicago, IL, USA).

This study conforms to the Declaration of Helsinki and subsequent modifications, and has been approved by the Institutional Review Board/Ethical Committee at the authors' institution. All the patients signed a written informed consent before being included in the study.

Table I. Summary of treatment-emergent adverse device effects by system organ class and preferred term (safety analysis set).

System organ class preferred term	HYADD 4 (n=75) n (%)	CS (n=75) n (%)	Overall (n=150) n (%)
Number of patients with at least one adverse or side effect	5 (6.6)	4 (5.3)	9 (6.0)
General disorders and administration site conditions	2 (2.7)	1 (1.3)	3 (2.0)
Injection site discomfort	1 (1.3)	1 (1.3)	2 (1.3)
Injection site erythema	0	0	0
Injection site pain	1 (1.3)	0	1 (1.3)
Musculoskeletal and connective tissue disorders	4 (3.3)	2 (2.7)	7 (4.7)
Arthralgia	2 (2.7)	2 (2.7)	5 (3.3)
Sensation of heaviness	1 (1.3)	0	1 (0.6)
Skin and subcutaneous tissue disorders	0	1 (1.3)	1 (1.3)
Pruritus	0	1 (1.3)	1 (1.3)

Results

One hundred and eighty-nine patients fulfilled inclusion and exclusion criteria and were invited to participate to the present study. Of these, 150 were enrolled (75 in each group). There were 53 females and 22 males in the HYADD 4 group with a mean age of 71.5±10.6 (range, 48–84) years; and 50 females and 25 males in the CS group with a mean age of 68.6±9.9 (range, 54–80) years. At the time of enrolment the two groups were homogeneous in terms of age, gender, WOMAC total score, VAS for pain, and SF-36 values. At the time of injections, no serious adverse events were recorded. The overall incidence of adverse and side effects was 6.6% in and 5.3% in HYADD 4 and CS groups, respectively ($p>0.05$), the two most common being pain or discomfort during the injection, and joint discomfort or arthralgia for about 2–3 days after the injection (Table I).

All the patients completed the evaluation at 6 and 12 weeks. Between 12 and 26 weeks, some patients came back to the clinic for a non-scheduled follow-up visit: 1 patient in HYADD 4 group and 2 patients in the CS group were indicated for total knee arthroplasty ($p>0.05$); 2 patients in HYADD 4 group and 9 patients in the CS group asked for a new injection cycle due to a significant reduction in the treatment effect ($p=0.02$). In the period between 26 and 52 weeks, 4 patients in each group came back to the clinic for a non-scheduled follow-up visit asking for a new injection cycle due to a significant reduction in the treatment effect ($p>0.05$). Repeated injections were done with either HA, CS or platelet-rich plasma (PRP) irrespectively of enrolment group. All these patients were considered treatment failures and were excluded from statistical analysis at 26

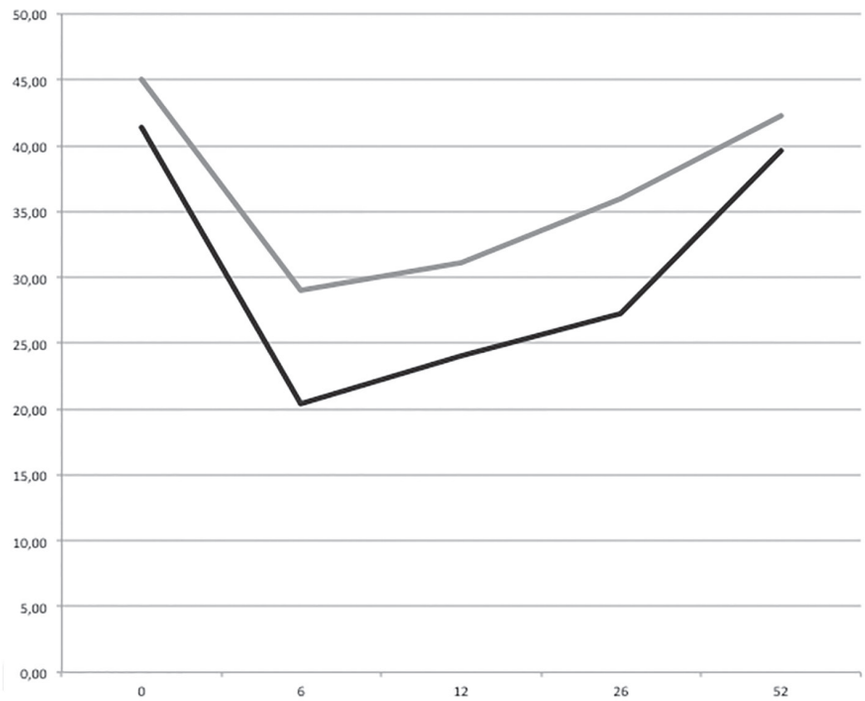

Fig. 1. At WOMAC evaluation, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in both groups. WOMAC scores progressively worsened at subsequent evaluations, even if patients in HYADD 4 group obtained significantly better scores than the CS group up to 26 weeks. At the 1-year follow-up both groups returned to their baseline scores, without statistically significant differences between treatments. Black line: HYADD 4 group, grey line: CS group.

Table II. WOMAC total scores at the different time points in HYADD 4 and corticosteroids (CS) groups. Stratified subgroup analysis showed that HYADD 4 had a prolonged effect over time compared to CS in patients with lower WOMAC total scores (<40 points) at baseline.

	Baseline	6 weeks	12 weeks	26 weeks	52 weeks
Total					
HYADD 4	41.4 ± 15.1	20.4 ± 11.5	24.0 ± 19.9	27.3 ± 10.8	39.6 ± 17.9
CS	45.0 ± 10.1	29.0 ± 9.0	31.1 ± 7.9	36.0 ± 7.1	42.3 ± 7.5
p-value	0.14	<0.0001	0.01	<0.0001	0.28
Lower WOMAC score at baseline (<40 points)					
HYADD 4	35.6 ± 6.9	15.3 ± 8.2	16.4 ± 12.3	18.6 ± 5.7	28.9 ± 6.9
CS	37.8 ± 8.3	21.7 ± 7.4	23.2 ± 7.4	28.8 ± 4.7	31.4 ± 8.3
p-value	0.10	<0.0001	0.0004	<0.0001	0.08
Higher WOMAC score at baseline (≥40 points)					
HYADD 4	50.3 ± 8.5	25.2 ± 10.1	31.9 ± 21.5	40.8 ± 12.5	50.3 ± 13.9
CS	53.2 ± 8.5	35.9 ± 6.5	39.1 ± 13.8	43.1 ± 10.3	53.2 ± 8.5
p-value	0.36	0.004	0.32	0.69	0.68

and 52 weeks, but were still followed-up for six months to make sure that no late adverse reactions took place, thus no patients were actually lost at follow-up. There were 72 patients (96%) in HYADD 4 group and 64 (85%) in the CS group at the 26-week evaluation, and 68 patients (90%) in the HYADD 4 group and 60 (80%) in the CS group at the 52-week evaluation.

Considering the WOMAC total score at 26 weeks (primary end point) patients in the HYADD 4 group reported significantly better results compared to the CS group (Fig. 1; Table II).

Considering the WOMAC total score at any time point, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in both groups. WOMAC total scores progressively worsened at subsequent evaluations, even if patients in the HYADD 4 group obtained significantly better scores than the CS group up to 26 weeks. At the 1-year follow-up both groups returned to their baseline scores, without statistically significant differences between treatments. Stratified subgroup analysis showed that HYADD 4 had a prolonged effect over time compared to CS in patients with lower WOMAC total scores (<40 points) at baseline (Fig. 1; Table II).

Considering VAS for pain, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in the CS group and at 12 weeks in the HYADD 4 group. At the 6-week evaluation no differences were noted between groups, but at 12 and 26 weeks patients in the HYADD 4 group obtained significantly better results, indicating that HYADD 4 has a greater therapeutic effect that is reached slowly over time. At the 1-year follow-up both groups returned to their baseline scores, without statistically significant differences between treatments. Stratified subgroup analysis showed that HYADD 4 provided prolonged pain relief overt time compared to CS in patients with lower VAS scores (3–6 points) at baseline (Fig. 2 and Table III).

Considering SF-36 scores, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in both groups. SF-36 scores remained quite stable in the HYADD 4 group up to 26 weeks; on the other hand, they progressively worsened at subsequent evaluations in the CS group. At the 1-year follow-up both groups returned to their baseline scores, without statistically significant differences between treatments (Fig. 3; Table IV).

Discussion

On the basis of the results of the study, the hypothesis was confirmed. In fact, patients in the HYADD 4 group obtained significantly better WOMAC total scores at 26 weeks. Furthermore, while patients in both groups obtained comparable results in the short term (6 weeks), patients in the HYADD 4 group obtained better results in terms of knee function, pain and quality of life at all subsequent time points up to

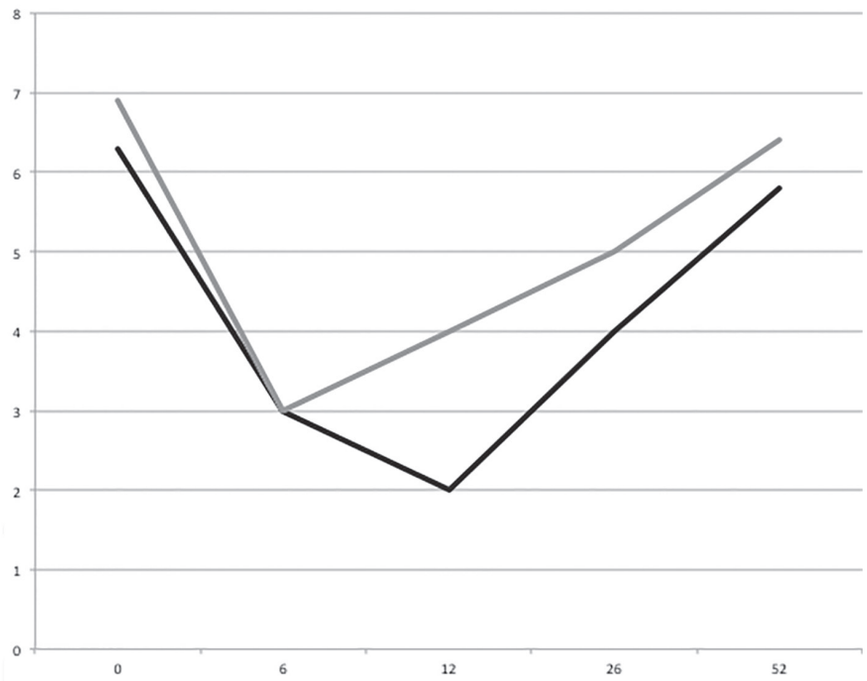

Fig. 2. At VAS for pain, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in the CS group and at 12 weeks in HYADD 4 group. At the 6-week evaluation no differences were noted between groups, but at 12 and 26 weeks patients in HYADD 4 group obtained significantly better results, indicating that HYADD 4 has a greater therapeutic effect that is reached slowly over time. At the 1-year follow-up both groups returned to their baseline scores, without statistically significant differences between treatments. Black line: HYADD 4 group, grey line: CS group.

Table III. VAS for pain scores at the different time points in HYADD 4 and corticosteroids (CS) groups. Stratified subgroup analysis showed that HYADD 4 had a prolonged pain relief over time compared to CS in patients with lower WOMAC scores (3-6 points) at baseline.

	Baseline	6 weeks	12 weeks	26 weeks	52 weeks
Total					
HYADD 4	6.3 ± 2.2	3.0 ± 2.0	2.0 ± 2.0	4.0 ± 2.0	5.8 ± 2.3
CS	6.9 ± 1.8	3.0 ± 1.0	4.0 ± 2.0	5.0 ± 1.0	6.4 ± 2.0
p-value	0.07	1	0.0001	0.0004	0.12
Lower VAS at baseline (3-6 points)					
HYADD 4	5.0 ± 1.2	2.2 ± 1.6	1.0 ± 1.7	2.1 ± 1.2	4.5 ± 2.0
CS	5.3 ± 0.9	2.0 ± 1.8	2.0 ± 1.5	4.0 ± 1.3	4.7 ± 2.3
p-value	0.12	0.52	0.0009	<0.0001	1
Higher VAS at baseline (>6 points)					
HYADD 4	8.0 ± 2.5	4 ± 1.5	3.2 ± 1.5	6.0 ± 1.6	7.3 ± 1.9
CS	8.7 ± 2.5	4 ± 1.1	6.0 ± 1.3	6.0 ± 1.5	7.9 ± 2.2
p-value	0.45	1	0.0001	1	0.62

26 weeks. At the 1-year follow-up both groups returned to their baseline scores in all considered outcomes, without statistically significant differences between treatments. Stratified subgroup analysis showed that HYADD 4 had a prolonged effect over time compared to CS in patients with less pain and dysfunction at baseline (Tables II-III), so this population may be the best candidate for HYADD 4.

The findings of the present study are in agreement with previously published data (18, 32-36) that reported on the superiority of CS, especially on pain control, in the short term (<1 month), and better results with HA at subsequent evaluations, but reporting only a moderate treatment effect of HA after 26 weeks. On the other hand, other studies reported a small effect (20, 37, 38); or inferred that HA is not more effective than saline as a placebo (15, 17, 39). Conrozier *et al*. (40) in their study of different regimens of HA reported that 24% of the patients were re-treated for lack of treatment effect at 24 weeks of follow-up. In our study, the withdrawal rate (patients who required further treatments) in the HYADD 4 group was 4% at 26 weeks and 10% at 1 year.

Adverse events after intra-articular injections have generally been reported as mild or moderate, the most common being injection site pain (41). The reported rate of those adverse events is very broad, ranging from 1.5% to 76%, according to the different methodologies adopted by different authors, but HA was generally considered to be safe when compared to CS or saline (34, 35, 40, 42, 43). HA demonstrated to be safe also after re-treatment after a previous course of injections (40). Recently, the safety profile of intra-articular HA injections has been questioned by Rutjes *et al*. (38). However, there were several important subtleties associated with their analysis. They did not relate serious adverse events to treatment, included unpublished and unverifiable data, and used incorrect statistical parameters. When correcting those issues, intra-articular HA demonstrated to be safe and effective (33). The adverse events of the current study were reported as per clinical diary given to the patients after the first injection, and their rate is low and in agreement with previously published data [(34, 35, 40, 42, 43), Timothy E. McAlindon, MD, MPH, personal communication]. Pain during injection and discomfort for a couple of days were observed at similar rates in both groups. Therefore, the safety profile of intra-articular HYADD 4 injections was demonstrated.

In agreement with the guidelines of some international societies (1, 9, 11), the current study supports the hypothesis that HA could be recommended in the management of patients with symptomatic knee osteoarthritis, because it is safe and effective. On the other hand, AAOS (23) recently recommended against its use. It has to be considered that these latter guidelines are biased by methodological errors, such as the number of publications included, the

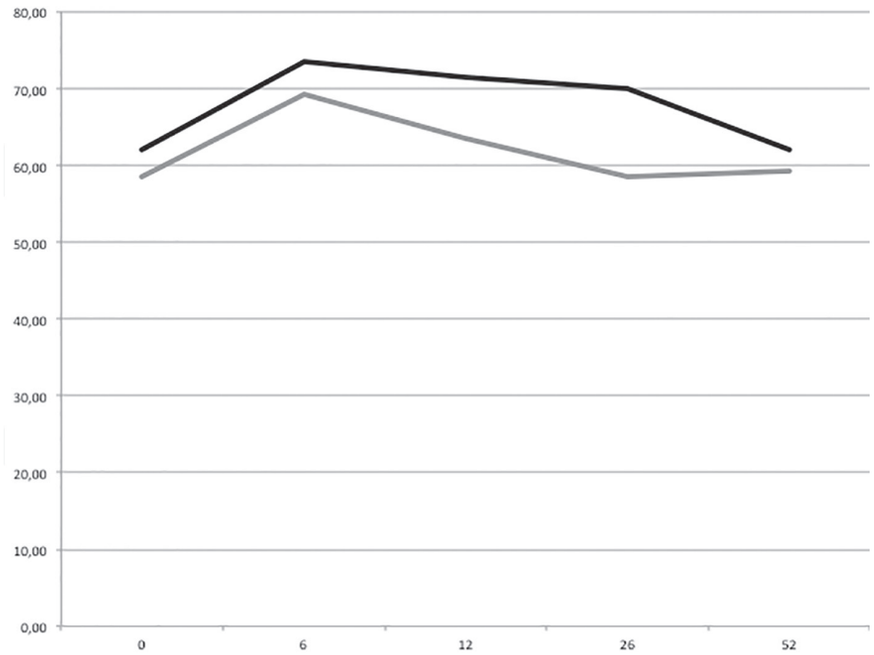

Fig. 3. At SF-36, patients significantly improved compared to baseline data, with a peak of therapeutic effect at 6 weeks from first injection in both groups. SF-36 scores remained quite stable in the HYADD 4 group up to 26 weeks; on the other hand, they progressively worsened at subsequent evaluations in the CS group. At the 1-year follow-up both groups returned to their baseline scores, without statistically the significant differences between treatments. Black line: HYADD 4 group, grey line: CS group.

Table IV. SF-36 scores at the different time points in HYADD 4 and corticosteroids (CS) groups.

SF-36 HYADD 4	62.0 ± 12.7	73.6 ± 12.2	71.5 ± 16.4	70.0 ± 13.3	62.0 ± 13.7
SF-36 CS	58.5 ± 11.5	69.2 ± 9.1	63.5 ± 12.1	58.6 ± 11.9	59.3 ± 11.7
p-value	0.12	0.03	0.003	< 0.0001	0.24

inclusion of non US-approved HA, and confusion on effect size interpretation (33, 44).

Strengths of the study

This is a single-centre prospective randomised controlled clinical study, all the injections were performed by the same physician (not involved in data collection and analysis), while another physician (blinded to the group randomisation) collected and analysed all the data. Furthermore, all injections were made in the same setting, with the same approach and using needles of the same size.

Limitations of the study

This is a single blind study (towards the observer) and the patients were aware which group they were assigned to, and which medication they received. This could have significantly biased the results of the study because patients in the HYADD 4 group could have reported better results knowing they were receiving a new medication. Side effects, discomfort and pain during and after the procedure were reported as per clinical diary given to the patients after first injection and were not assessed by a physician. A third group with a different HA was not enrolled; this could have provided useful information whether HYADD 4 is better than other HAs. A placebo group was not included for ethical reasons; in fact CS are considered the gold standard. No extension study was performed with the patients who failed the first course of injections and underwent a second course, so we do not know if repeated injections of HYADD 4 are effective. No histology samples were taken and analysed, and no radiographs were taken at follow-up because this is beyond the scopes of this clinically based study. BMI was not recorded and data were not stratified accordingly; it is possible that patients with higher BMIs could have obtained worse scores and higher pain levels, and had higher failure rates (45, 46). WOMAC sores were collected only as total scores, so sub-scores were not available in this study for further sub-group analysis. Moreover, data were not collected in the very short-term (<6 weeks). Signs of inflammation were not acquired, and their correlation to clinical outcome was not made (47).

Conclusions

HYADD 4 did not have significantly higher side effects when compared to CS injections and provided better short-term (but not long-term) control of symptoms in patients with mild to moderate knee osteoarthritis. Patients with less pain and dysfunction at baseline may be the best candidates for HYADD 4 injections.

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