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SFR

Reprinted from
2015;82:116-121

85389

Joint Bone Spine 82 (2015) 116–121

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Comparative efficacy of intra-articular hyaluronic acid and corticoid injections in osteoarthritis of the first carpometacarpal joint: Results of a 6-month single-masked randomized study

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ARTICLE INFO

Article history:
Accepted 22 August 2014
Available online 11 October 2014

Keywords:
Rhizarthrosis
Corticosteroids
Hyaluronic acid
Ultrasound-guided
Intra-articular injections

ABSTRACT

Objective: The study aim was to compare the efficacy and safety of ultrasound-guided intra-articular injections of hyaluronic acid and betamethasone in the management of patients with osteoarthritis of the thumb.

Methods: Eighty-eight evaluable patients diagnosed with osteoarthritis of the thumb (Kellgren-Lawrence grade II-III) received ultrasound-guided intra-articular treatment with hyaluronic acid (48) or betamethasone (40). In total, 3 local injections were scheduled at 7-day intervals. Assessments were performed at baseline and at 7, 14, 30, 90, and 180 days.

Results: In both study groups, the pain Visual Analogue Scale and Functional Index for Hand Osteoarthritis scores decreased significantly during follow-up compared to baseline. There were no significant differences between the groups. However, at 90 days, the functional score showed a trend towards greater clinical improvement in the hyaluronic acid group (P 0.071). A subanalysis of patients with Functional Index score ≥ 5 and Visual Analogue Scale score ≥ 3 at baseline showed a significantly higher median functionality score in the hyaluronic acid group (P 0.005 at 90 days and P 0.020 at 180 days). Further limiting analysis to a baseline pain score ≥ 5 showed significantly greater improvement in functionality score (P 0.004 at 180 days), which was already apparent after the second intra-articular injection at 14 days (P 0.028). In this patient subset, the mean pain score also improved significantly at 180 days (P 0.02).

Conclusions: Both hyaluronic acid and betamethasone were effective and well-tolerated for the management of rhizarthrosis. Hyaluronic acid was more effective over time and more efficiently improved functionality and pain in patients with more severe symptoms.

1. Introduction

Osteoarthritis (OA) of the trapeziometacarpal or thumb carpometacarpal (CMC) joint, also called rhizarthrosis, most commonly occurs in women over 50 years of age and is often bilateral. The age-adjusted prevalence of radiographic OA of the first CMC joint has been reported to be 7% for men and 15% for women [1]. Among men and women older than 40 years, the radiological prevalence is 21% [2] and as high as 35% among post-menopausal women [3]. In some patients, the evolution of the disease is painless and is likely to be underdiagnosed in clinical practice; in others, the progression in episodes results in the stiffening and deformity of the thumb, with considerable functional disability and pain [4]. If the condition is not treated, a severe adduction contraction of the thumb and subluxation of the CMC joint can develop [5]. Thumb CMC OA is classified radiologically using either the Kellgren-Lawrence I–IV or Eaton and Glickel I–IV scale.

Although there are numerous surgical procedures to treat resistant cases and severe disabling forms of CMC [6], most patients are initially managed conservatively. Conservative options, reported to

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http://dx.doi.org/10.1016/j.jbspin.2014.08.008
1297-319X/

be of moderate benefit [7], include both nonpharmacological therapies (such as splinting, hand therapy, or extensive advice on how to accommodate activities of daily living) and pharmacological treatment (primarily nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroid injection into the thumb CMC joint [8,9]). However, in a double-blind, randomized, controlled trial, no clinical benefit was gained from intra-articular corticosteroid injections in moderate to severe OA of the CMC as compared with placebo [10], exposing a problem with disease management.

Hyaluronic acid (HA) is a macromolecular component of the normal synovial fluid. In OA, there is a lower concentration of this compound. The effect of HA on joint lubrication and prevention of articular cartilage degradation has been extensively studied [11–13]. Viscosupplementation with HA injections has been shown to relieve pain and improve function in the management of knee OA [14,15]. The usefulness of intra-articular HA for treating symptomatic OA pain in other joints has also been reported [16–18], including the hip, ankle, temporomandibular joint, hand, spine, and foot. The experience with the use of intra-articular HA injections for trapeziometacarpal OA is limited but has produced promising results [16,19–21]. However, the superiority of HA injections as an alternative to corticoid injections for the treatment of rhizarthrosis is unclear and the available evidence derived from small, randomized, controlled studies is inconclusive [22–25].

Therefore, a randomized controlled study was designed to determine the efficacy and safety of intra-articular injections of low-molecular-weight HA into the osteoarthritic thumb CMC joint in comparison with corticoid injections.

2. Methods

2.1. Study design and participants

This single-center, randomized, prospective, active-controlled, and single-masked study was conducted to assess whether the efficacy of intra-articular HA injection was superior to corticoid injections for the treatment of rhizarthrosis. Tolerability of the study medication was also assessed. The study was carried out at the outpatient clinics of the Rheumatology Department, Parc de Salut Mar (an acute-care, 450-bed, university-affiliated hospital in the city of Barcelona, Spain, serving a population of ~340,000 people). The study protocol was approved by the hospital's Ethical Review Board and the study was conducted in accordance with the principles of the Declaration of Helsinki and its amendments. All patients were fully informed of the characteristics of the study and gave written informed consent.

All male and female patients aged 18 years or older who received a diagnosis of thumb CMC joint OA between January 2005 and December 2009, as defined by criteria of the American College of Rheumatology [26], were eligible, provided that they had clinical symptoms in the affected thumb for at least the 90 days prior to the start of the study, required treatment with analgesics or NSAIDs on a routine basis, had an available confirmatory X-ray diagnosis (Kellgren–Lawrence grade I–III) [27] within the previous 6 months, gave written informed consent, and were able to understand and follow the study procedures. Negative pregnancy test and appropriate use of a safe contraceptive method were required for women of childbearing age.

Exclusion criteria included the following: pregnant or lactating women; liver dysfunction (serum aminotransferases > 3 times the upper limit of normal); hemodialysis or renal dysfunction (serum creatinine concentration > 1.5 mg/dL); physical therapy performed by a physiotherapist at home or in a specialized center; history of any surgical procedure in the trapeziometacarpal joint; diagnosis of OA of the trapezioscaphoid joint or microcrystalline arthritis; participation in a clinical trial in the previous three months; and presence of any medical condition judged by the investigator to preclude the patient's inclusion in the study. Patients were also excluded for a known allergy to corticoids, paracetamol, or low-molecular-weight HA; concomitant treatment with antiepileptic drugs, oral anticoagulants, acetylsalicylic acid > 325 mg/day, lithium, potassium-sparing diuretics, digoxin, minocycline, metalloprotease inhibitors, methotrexate, or regular use of analgesic and/or NSAIDs; treatment with chondroitin sulphate, glucosamine sulphate, diacerein, oral or parenteral corticosteroids, or corticosteroid injection in any other joint during the previous 3 months.

2.2. Treatment and patient evaluation

Study participants attended a screening visit (visit 1), which included the following: medical history, physical examination, standard radiography, laboratory tests (blood cell count, biochemical profile, and pregnancy test in women of reproductive age), a 10-point visual analogue scale (VAS) for pain (with 0 being no pain and 10 being the worst pain imaginable, and the algofunctional index for hand OA (FIHOA) [28]. FIHOA is based on a physician-administered questionnaire on 10 daily activities involving the hands. Patients are asked to answer each item using a 4-point verbal scale, from 'possible without difficulty' (0) to 'impossible' (3 points); thus, total scores range from 0 to 30 and the highest values correspond to worst functionality.

Patients were fully informed of the purpose of the study and signed the informed consent. They were instructed to discontinue or taper off gradually any systemic or topical treatment in accordance with eligibility criteria and were scheduled to return to the study center in 7 days for the baseline/randomization visit (visit 2). Medications used within 30 days before screening and throughout the study period, including paracetamol (maximum 3 g/day) as rescue medication, were recorded in a diary card.

At baseline (visit 2, day 0), the following procedures were performed: physical examination, assessment of concomitant medication, randomization, provision of rescue medication, intra-articular injection of the study medication under echographic control, and VAS and FIHOA scores. Patients were instructed to complete the Short Form-36 (SF-36) quality of life questionnaire, using a Spanish validated version [29]. SF-36 questionnaire has mental and physical component summary (MCS-36, and PCS-36, respectively), and both scores range from 0 to 100, where 0 indicates the worst possible perceived mental and physical health, and 100 the best. The patient's general condition was assessed by the patients and investigators from 'very bad' to 'very good' on a 5-point Likert scale. The same procedures were repeated at visits 3 (day 7) and 4 (day 14), except for the administration of the SF-36 questionnaire.

All eligible participants were assigned a sequential number, according to the order in which the initial visit was conducted. Treatment randomization list was generated using the procPlan of SAS System (version 9.2, SAS Institute Inc., Cary, NC, USA http://www.sas.com/) software. Patient were assigned to one of the two treatment products (HA or betamethasone) following a 1:1 pattern. Subjects, and post-randomization dropouts were not substituted (randomization numbers were not re-assigned).

Patients underwent one cycle of three injections (one per week, visits 2, 3 and 4) of 0.5 cm^3 of HA (5 mg) (Suplasyn®, Mylan Institutional, Galway, Ireland (between 500-1′000 kDa, with a high degree of purity, produced by fermentation of Streptoccus spp. Bacteria)) or 0.5 cm^3 of betamethasone disodium phosphate 1.5 mg and betamethasone acetate 1.5 mg. To receive the treatment, patients sat with the affected hand in a semi-prone position on a table. The intercarpometacarpal space was identified by palpation, the

needle tip inserted lateral to the abductor pollicis longus tendon and the injection carried out under echographic control using a high-resolution GE Logiq-5 Expert Ultrasound System, L-12 liner transducer and 10 MHz frequency, with the probe placed transversally for better needle visibility. To avoid bias from different treatment techniques, all ultrasound studies and injections with the study products were administered by the same investigator according to the randomization list.

Assessments were performed at 30 days (visit 5), 90 days (visit 6), and 180 days (visit 7, final visit) after initiation of the treatment, by an investigator who was blind to the treatment administered (patients were instructed not to disclose the treatment received). At follow-up visits, the same procedures as described for the baseline visit were performed, except the SF-36 quality of life assessment, which was repeated only at visits 6 and 7. Adverse events were recorded at each follow-up visit and a final laboratory test was performed as a safety index.

2.3. Efficacy and safety parameters

The primary efficacy endpoint was the clinical improvement determined by the FIHOA score at the end of treatment as compared with baseline. Secondary efficacy parameters included pain relief, changes in the physical component summary (PCS-36) and mental component summary (MCS-36) of the SF-36 questionnaire, and assessment of the overall condition by patients and investigators. Tolerability and safety parameters were the incidence and severity of adverse events reported throughout the study and changes in heart rate, blood pressure, and laboratory tests during the study.

2.4. Statistical analysis

The sample size calculation was estimated according to data from a previous study of intra-articular HA injection in knee OA [30], in which a mean score of the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) at baseline was 38.8 (standard deviation, SD 15.5), with a correlation of 0.362 between the first measurement and the second, three months later. A sample size of 50 patients in each group provided 80% power at a two-sided alpha level of 0.05 to detect a difference greater than 30% between both groups in changes of the FIHOA score between baseline and at three months. The study was based on an intention to treat, which means that all randomized patients who fulfilled inclusion criteria and received at least one intra-articular injection were included in the data set.

Differences between the study groups in FIHOA, VAS, PCS-36, and MCS-36 scores were analyzed for the overall study population and for the subsets of patients with FIHOA ≥ 5 and pain levels ≥ 30 and ≥ 50 at baseline. Data are expressed as mean and standard deviation (SD) for normally distributed data or as median and interquartile range (IQR) (25th–75th percentile) for data with non-normal distribution. Categorical variables are expressed as frequency and percentages. Continuous variables were analyzed with the Student t or Mann-Whitney U test, and categorical variables with chi-square (χ^2) or Fisher exact test. Statistical significance was set at $P < 0.05$. The Statistical Package for Social Sciences (SPSS) (version 15.0) for Windows was used for data analysis.

3. Results

One hundred patients were randomized to treatment with HA or betamethasone (1:1), although only 88 of them (HA = 48; betamethasone = 40) were finally evaluable: 5 of them did not carry out the washout period due to they were taking AINEs, 3 of them were asymptomatic, and the remaining 4 did not fulfil radiological criteria. The final sample was composed of 11 men and 77 women, mean (SD) age 62.8 (8.7) years (range 45–92). No differences were observed between the study groups in sex and age distribution.

Table 1
Changes from the baseline in the study variables throughout the study period in both treatment groups.

	HA	Betamethasone
FIHOA[¬]		
D7	0 (−3 and −1)	−1 (−2 and −1)
D14	−2 (−5 and −0)	−1 (−4 and −0)
D30	−3 (−6.7 and −0)	−3 (−7.5 and −0)
D90[***]	−4 (−8 and −1)	−1 (−3 and −1)
D180	−3 (−8.7 and −1)	−1 (−3 and −3)
VAS[†]		
D7	−0.71 (1.66)	−0.95 (1.60)
D14	−1.42 (2.23)	−2.01 (1.84)
D30	−1.97 (2.62)	−2.53 (2.26)
D90	−1.61 (2.53)	−1.55 (2.14)
D180	−1.97 (2.73)	−1.42 (2.35)
PCS-36[†]		
D90	0.51 (7.02)	1.70 (9.32)
D180	−1.66 (9.60)	1.31 (9.42)
MCS-36[†]		
D90	−0.46 (6.77)	1.73 (10.75)
D180	2.79 (11.78)	2.17 (9.64)

HA: hyaluronic acid; FIHOA: Functional Index for Hand Osteoarthritis score; D: day; VAS: Visual Analogue Scale score; PCS-36: physical component summary of the SF-36 questionnaire; MCS-36: mental component summary of the SF-36 questionnaire; [¬]: median and interquartile range (25th and 75th percentiles); [†]: mean and standard deviation (SD).
[***] $P = 0.071$.

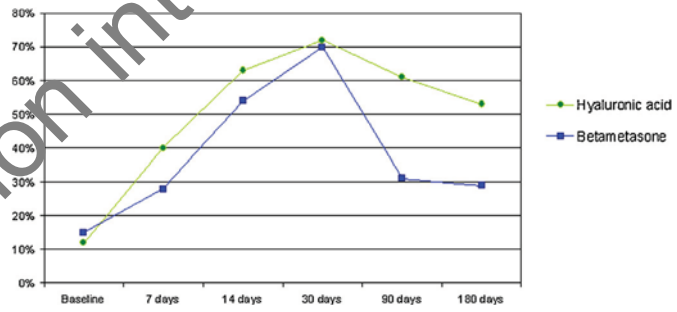

Fig. 1. Percentage of patients whose general condition was rated as "good" or "very good" by the investigator throughout the study period.

At baseline, scores on the study variables were similar in the HA and betamethasone groups (median FIHOA score 11.0 [IQR 7 – 14.7] vs 11.5 [8–14], P 0.814; mean VAS score 6.0 [1.8] vs 6.4 [1.3], P 0.171; PCS-36 38.9 [8.1] vs 37.7 [10.3], P 0.553; and MCS-36 45.4 [12.3] vs 48.9 [10.8], P 0.178, respectively). The FIHOA and VAS scores decreased significantly for both groups after treatment. Values obtained for these two indexes at follow-up visits were all below baseline values; neither PCS-36 nor MCS-36 showed any statistically significant trend.

Changes in these variables during the study period were not significantly different between the study groups; however, the median difference of FIHOA scores was greater in the HA arm than in the betamethasone arm (Table 1). Changes from baseline were −4.0 and −3.0 in the HA group in the assessments carried out at 90 and 180 days, respectively, whereas the median difference was −1.0 at each of these visits in the betamethasone group (P0.071 at day 90).

As shown in Fig. 1, the percentage of patients rated by the investigator as being in 'good' or 'very good' general condition was higher for the HA group than for the betamethasone group, with differences especially remarkable at 90 days (61.6% vs 30.8%) and 180 days (53.4% vs 28.6%). Differences between the study groups in the categories of 'good' and 'very good' were also more favorable for

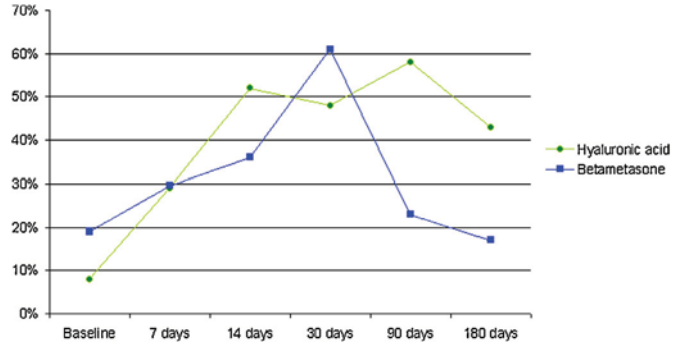

Fig. 2. Percentage of patients who rated their own general condition as "good" or "very good" throughout the study period.

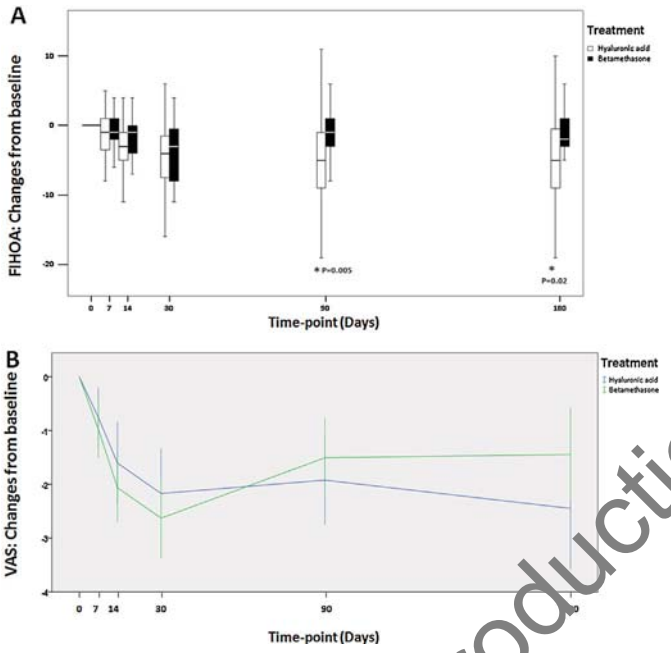

Fig. 3. Changes from baseline in a subset of patients with FIHOA score ≥ 5 and VAS score ≥ 3 at entry. A. Changes from baseline in Functional Index for Hand Osteoarthritis score. Median, interquartile range (25th and 75th percentiles) and maximum and minimum values are shown. B. Changes from baseline in Visual Analogue Scale score. Mean and 95 percent confidence interval are shown.

the HA arm at follow-up when the patients themselves rated their general condition (Fig. 2). No significant differences in use of rescue medication were observed between study groups.

The subset of patients with FIHOA score ≥ 5 and VAS score ≥ 3 at entry included 77 patients (9 men, 68 women; mean age of 62.7 [9.0] years), 39 of whom were randomized to treatment with HA and 38 to treatment with betamethasone. At baseline, there were no significant differences in demographics or FIHOA, VAS, PCS-36, and MCS-36 scores between both treatment groups. However, patients treated with HA showed significantly higher differences between the median FIHOA scores at baseline and follow-up than the patients treated with betamethasone (Table S1, Supplementary data), both at 90 days (−5.0 [IQR −9 and −0.75] vs −1.0 [IQR −3.0 and 1.25]; *P* 0.005) and 180 days (−5.0 [IQR −9 and 0] vs −2.0 [IQR −3.0 and 2.0]; *P* 0.020) (Fig. 3). Differences in the remaining study variables were not observed.

The subgroup of patients with FIHOA score ≥ 5 and VAS score ≥ 5 at baseline included 65 patients (8 men, 57 women; mean age of 62.9 [9.2] years). Thirty-two patients were treated with HA and 33 with corticoid injection. Baseline characteristics of patients in

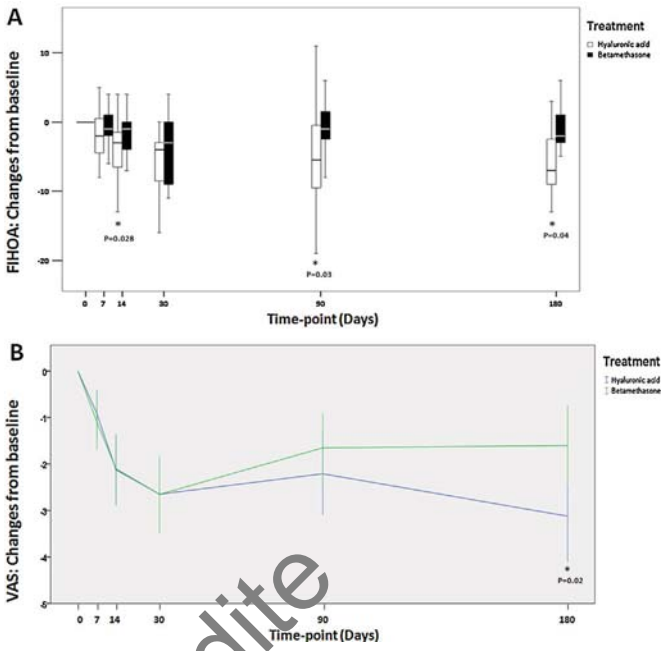

Fig. 4. Changes from baseline in a subset of patients with FIHOA score ≥ 5 and VAS score ≥ 5 at entry. A. Changes from baseline in Functional Index for Hand Osteoarthritis score. Median, interquartile range (25th and 75th percentiles) and maximum and minimum values are shown. B. Changes from baseline in Visual Analogue Scale score. Mean and 95 percent confidence interval are shown.

Table 2
Changes in the study variables throughout the study period as compared with baseline in patients with FIHOA score ≥ 5 and VAS score ≥ 5 at entry.

	HA	Betamethasone
FIHOA[T]		
D7	−2 (−4.75 and 0.75)	−1 (−2 – 1)
D14[**]	−3 (−6.75 and −1.25)	−1 (−4 – 0)
D30	−4 (−8.75 and −3)	−3 (−9 – 0)
D90[*]	−5.5 (−9.75 and −0.25)	−1 (−3 – 2)
D180[*]	−7 (−9 and −2)	−2 (−3 – 1)
VAS[†]		
D7	−0.92 (1.44)	−1.10 (1.70)
D14	−2.12 (2.13)	−2.10 (1.81)
D30	−2.65 (2.29)	−2.65 (2.33)
D90	−2.21 (2.29)	−1.65 (1.98)
D180[**]	−3.12 (2.33)	−1.60 (2.29)

HA: hyaluronic acid; FIHOA: Functional Index for Hand Osteoarthritis score; D: day; VAS: Visual Analogue Scale score; [T]: median and interquartile range (25th and 75th percentiles); [†]: mean and standard deviation (SD).
[*] $P < 0.005$.
[**] $P < 0.05$.

both treatment arms were similar. Treatment with HA was superior to betamethasone, as shown by significantly greater differences in FIHOA scores as compared with baseline, which were already apparent after the first intra-articular injection (Fig. 4 and Table 2). Moreover, significant differences in mean changes of VAS score were also observed at the final assessment (*P*0.02). Changes in PMS-36 and MCS-36 during the study period were similar in both groups.

The mean difference of Kellgren-Lawrence grade was not significant between study groups in either of three analyses.

Treatment was well-tolerated and no severe adverse events were reported during the study, only 10 patients (5 of Bethametasone group and 5 of the HA group) shown minor or moderate local pain after intra-articular injection (5 of them including swelling (2 of the Bethametasone group and 3 of the HA)), which have

disappeared at the following visit. No significant changes were observed in vital signs and laboratory test results.

4. Discussion

The evaluation of a drug in OA focuses on the exploration of two important areas: pain and function. Although there are many evaluation approaches [31], this is not always an easy task due to the subjectivity of the assessment techniques used.

Rhizarthrosis can involve a high degree of pain and functional disability, which is especially reflected in performing activities of daily living [32]. Despite many trials focused on evaluating observable and objective aspects of manual functionality, such as pinch or grip strength [22–24], questionnaires such as FIHOA that evaluate functionality in daily life situations can be a useful tool with great ecological validity because it provides an index of actual limitation.

On the other hand, the management of the disease remains controversial. Existing treatments are purely symptomatic and often fail to significantly restore function and reduce pain.

In our study, although the analysis of the overall series of patients encountered no statistically significant differences between the study groups, patients in the HA group experienced a functional improvement of greater magnitude than the patients treated with betamethasone. Moreover, these findings were more evident, and reached statistical significance, when patients selected for analysis had a FIHOA score of at least 5 and a VAS score of 50 or more. According to these findings, HA injection seems to be an equivalent and possibly better alternative to corticoid injection in the treatment of thumb CMC joint OA, particularly in patients with functional repercussions and moderate-severe pain level.

Unlike steroids, shown to be effective for reducing acute pain, improvement due to injections of HA was more gradual but more prolonged over time. These results are consistent with the widely accepted idea that corticosteroids could be more effective in reducing inflammation and ameliorating pain in its earliest form, while the regeneration of the viscoelasticity of the sinovial fluid achieved by HA could improve the homeostasis of the joint, contributing to more long-lasting improvement of both function and pain.

The results of this study suggest that HA injections may be a better patient management option than betamethasone. In addition to the extended improvement observed in patient well-being, this therapy could decrease both the consumption of symptomatic analgesics or anti-inflammatory drugs and their potential secondary effects, as has been seen in knee OA [33]. Moreover, it could also reduce the care burden on the health system by helping to decrease office visits, pharmacology costs, and replacement surgeries [34].

So far, only a few studies have evaluated the effectiveness of both HA and betamethasone for the treatment of rhizarthrosis [22–24]; trials with more rigorous methodologies and larger samples are obviously needed. In our case, the ultrasound-guided injection method avoided possible biases that were not previously taken into account [22–24]; this technique improves performance by facilitating proper intra-articular administration [35]. Moreover, unlike Fuchs et al. and Stahl et al., in this study, the treatment was delivered by the same investigator to prevent a possible operator bias, and clinical assessments were performed by a single investigator who was blind to the patients' study arm assignment.

Furthermore, the amount of substance administered in both groups was the same and both received one cycle of three injections, the dose recommended by the technical data sheet of both products and commonly used in previous trials with OA of the small sinovial joints [22,36]. This methodology avoids potential biases due to differences in the procedure, an aspect not taken into account either by Bahadir et al. or by Stahl et al.

On the other hand, statistical analysis of subgroups with a greater degree of pain and dysfunction has proven to be a useful strategy in defining a subgroup of patients who could obtain better outcomes from this treatment. In this sense, the HA could be a good alternative for those cases where conventional conservative strategies fail and it is necessary to consider a surgical intervention [19–21].

However, we are aware that, like all studies, ours also has some limitations. Perhaps the most obvious is the absence of a placebo group. Some studies have confirmed a strong placebo effect linked to the complexity of the treatment [37,38]. Intra-articular injection appears to be a technique that, due to its complexity, could increase patient expectations of clinical improvement; therefore, it would have been interesting to control for this effect. Moreover, it was not possible to assess patients for longer than 6 months, and others [22] have suggested that a long-term follow-up would be of great interest in order to establish the duration of the treatment effect. In the case of knee OA, for instance, studies have demonstrated that the effect of HA infiltration may extend beyond 6 months [39].

Despite these limitations, the results of this single-center, randomized, prospective, active-controlled and single-masked study show that intra-articular low-molecular-weight HA injections into the thumb CMC joint in OA are more efficient than corticosteroids in improving functionality and pain, with persistent effects after 6 months. Treatment with HA is particularly relevant for patients with more severe symptoms. This is a significant finding for the future management of the disease. Although both treatments are symptomatic, HA has a better safety profile and greater tolerance [40]. Still, much remains to be discovered and it is becoming increasingly clear that future research lines should seek treatments that modify the course of the disease rather than focusing on alleviation of symptoms.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgements

We would like to acknowledge and thank Elaine M. Lilly for her correction work and patience and Laura Tio for her logistical support.

Appendix A. Supplementary data

Supplementary material (Table S1) associated with this article can be found at http://www.sciencedirect.com, in the online version, at http://dx.doi.org/10.1016/j.jbspin.2014.08.008.

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