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

Jordi Monfort[a,b,*], Delfin Rotés-Sala[a], Nuria Segalés[c], Francisco-Jose Montañes[a], Cristobal Orellana[d], Jone Llorente-Onaindia[b], Sergi Mojal[e], Isabel Padró[a], Pere Benito[a,b]

[a] Servei de Reumatologia, Hospital del Mar, Parc de Salut Mar, Passeig Marítim 25–29, 08003 Barcelona, Spain
[b] Unitat de Recerca en Inflamació i Cartílag, Institut Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain
[c] Servei de Reumatologia, Consorci Sanitari del Maresme, Mataró, Spain
[d] Servei de Reumatologia. Hospital Parc Taulí, Sabadell, Spain
[e] Servei d'Assessorament Metodològic en Investigació Biomèdica (AMIB), Institut Mar d'Investigacions Mèdiques (IMIM), Barcelona, Spain

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 $\geq 5$ and Visual Analogue Scale score $\geq 3$ 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 $\geq 5$ 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

* Corresponding author at: Servei de Reumatologia, Hospital del Mar, Parc de Salut Mar, Passeig Marítim 25–29, 08003 Barcelona, Spain. Tel.: +3 4932483345; fax: +3 4932483259.
*E-mail address:* JMonfort@parcdesalutmar.cat (J. Monfort).

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