Impact of hyaluronic acid treatment on rhizarthrosis: a systematic review.

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Abstract

Objetive: Trapeziometacarpal (TMC) joint osteoarthritis (OA) is a common disabling condition. Current treatments do not have a significant impact on symptom relief or disease progression and the benefit of visco-supplementation remains uncertain. We aim to evaluate the efficacy of hyaluronic acid (HA) intra-articular injection in rhizarthrosis.

Methods: A systematic review of the literature addressing the efficacy of HA on pain reduction, functional capacity or pinch strength in patients with rhizarthrosis was performed. Pain at rest, functional capacity and pinch strength were assessed at baseline, 4th, 12th and 24th weeks

Results: Sixteen trials were included with a total of 587 patients treated with HA injections (9 randomized controlled trials (RCTs), 5 single-arm studies and 2 non-randomized comparative trials). Despite important heterogeneity among trials, HA injections lead to a reduction in pain at rest (decrease of 0.65-3.5 points and 0.8-4.03 points on Visual Analogue Score after 4th and 24th weeks respectively, compared to baseline). Regarding disability, as assessed by functional scales, all studies reported improvement on functionality. An increase in pinch strength of 0.1-1.4 kg and 0.4-2kg was also reported at 4th and 24th weeks respectively.

Conclusion: HA injections can be a valid therapeutic option for reducing pain as well as to improve functionality and strength in patients suffering from TMC joint OA.

Keywords: Hand; Osteoarthritis; Systematic review

INTRODUCTION

First carpometacarpal (CMC) osteoarthritis, also known as rhizarthrosis, terms the degenerative process involving the first trapeziometacarpal (TMC) joint. Rhizarthrosis affects 5-7% of people aged over 50 years [1], most commonly post-menopausal women. [2] Clinical presentation is usually pain or deformity and impacts significantly on daily activities, such as writing or fingering of small objects.

Diagnosis of rhizarthrosis is based on the identification, upon clinical examination, of a hard tissue enlargement of the joint causing deformity[3]. Nonetheless, radiographic findings are commonly used in the classification of the disease stage[4].

Management of rhizarthrosis should include both non-pharmacological measures, such as the utilization of orthoses, and pharmacological treatments, mainly based on the use of non-steroidal anti-inflammatory drugs (NSAIDs) topical agents[5]. The utilization of intra-articular corticosteroids is still a matter of debate, with different views proposed by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR)[5,6] However, none of the currently used treatments have a significant impact on preventdisease progression[7].

Hyaluronic acid (HA) is an important component of the normal synovial fluid, ensuring its viscoelastic properties, providing lubrication and absorbing shock [8,9]. Decreased levels of HA play a crucial role in the pathophysiology of this process[10] and research data seems to indicate that HA intra-articular administration has chondroprotective[11,12] and immunosuppressive effects[13,14]. However, visco-supplementation of OA with HA derivatives is still a subject for discussion. Although effective in reducing pain and improving functional capacity associated with both knee and hip osteoarthritis [8] the benefits of its utilization in TMC joint OA remain uncertain.

By performing a systematic review of contemporary literature, we aim to assess the efficacy of intra-articular injection of HA on pain reduction, functional improvement and pinch strength, in patients with rhizarthrosis.

METHODS

Search Strategy

A systematic review was conducted according to the recommendations of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. The literature search was last updated in February 2022.

Two databases were reviewed: MEDLINE (via Pubmed) and Web of Science. The search was performed, without limitation of year of publication or journal, using the following keywords: "thumb", “trapeziometacarpal”, “carpo-metacarpal”, "osteoarthritis", “rhizarthrosis”, “hyaluronic acid”, “hyaluronic”, “hyaluronan” and “hyaluronate”. The controlled specific vocabulary of each database was also used (e.g., MESH in MEDLINE). Studies were initially selected on their title and abstract by one author. All papers that could potentially match the inclusion criteria were then critically read and data was extracted using purpose-made data-extraction tables. Articles were not blinded for author, affiliation or source.

The minimum criteria for inclusion of the trial was the adequate reporting of at least one of the defined outcome variables: pain, functional capacity and pinch strength. The efficacy of HA intra-articular injections was assessed by the change in these variables between baseline and week 4, week 12 and week 24.

Exclusion criteria were: ineligible publications (book chapters, reviews, editorials, comments, conference proceedings, meeting abstracts), non-human studies (e.g., in vitro or animal research), non-Portuguese, English or Spanish languages, case reports, studies concerning osteoarthritis in other joints (e.g., knee), studies merely describing HA administration technique.

Data Extraction

Two authors (IP; CD) working independently determined eligibility and extracted data from included studies using a standard form. Disagreements were discussed with a third author (FV).

Aim and Outcome Assessment

The goal was to review the existing evidence on the efficacy of HA in the treatment of TMC joint AO.

Rhizarthrosis diagnosis was established according to clinical assessment and/or radiography findings, following the Kellgren-Lawrence [4] or the Eaton-Litter scores [15], with all degrees of severity of osteoarthritis included.

Pain was assessed during resting periods, using either the Visual Analog Scale (VAS), or Visual Numeric Scale (VNS)[16]. When using VAS, patient's perceived pain was rated along a 100mm horizontal line, while when using VNS patients were asked to circle the number between 0 and 10, 0 and 20 or 0 and 100 that fits best to their pain intensity. In both VAS and VNS, endpoints define extreme limits such as "no pain at all" and "pain as bad as it could be"

Functional capacity was extracted, as available, by the following scores: Disabilities of the Arm, Shoulder and Hand (DASH) - a 30-item scale covering the patients' physical impairment, severity of symptoms and their impact on social and professional activities, where 0 indicated no

disability and 100 most severe disability [17]; Functional Index for Hand OsteoArthritis (FIHOA), - a 10-item questionnaire assessing hand OA-related functional impairment, scoring from 0 (no functional impairment) to 30 points (maximal impairment)[18–20]; and/or the Duruöz Hand Index (DHI) - a 18-item scale that assesses hand functional handicap in activities such as kitchen, dressing, personal hygiene or office tasks, ranging from 0 to 90, with higher scores indicating severe impairment[21,22]. Disability was also assessed by pinch strength, extracted by dynamometer measure.

Information regarding either other outcomes or outcomes assessed by other tools was extracted and analyzed, when feasible, but was not included in this analysis.

Quality assessment

RCTs were analyzed using the Cochrane Assessment Tool[23] and non-randomized trials were assessed for the risk of bias using the Newcastle Ottawa Quality Assessment Scale [24] (Table I).

RESULTS

Literature search results and trial characteristics

Initially, 278 potentially relevant non-duplicated articles were screened; 239 were excluded after reading the title and abstract. Of the 39 papers assessed by reading the full text, 16 papers were included in this systematic review (Figure 1) [9,25–39]. Those comprise 9 RCT [25,26,29–32,34,35,37], 4 single-arm prospective clinical trials [27,28,38,39], 2 retrospective case-control studies [9,33] and 1 single-arm retrospective clinical trial [36], published between 2005 and 2020. Outcome variables were not all available in every considered article. Additionally, in some of the included papers [26,30,35,37], data was only graphically presented and, therefore, impossible to extract.

A total of 893 participants were included, 587 of which were treated with intra-articular hyaluronic acid injections (65.7%). Most patients were females (n = 692, 77.5%) and mean age ranged from 52 to 68 years. A further description of trials' characteristics is depicted in table II.

HA formulations of different molecular weights were used (Hyalgan®, Ostenil®, HappyMini®; Synvisc®, Hyalubrix®, Sinovial mini®, OrthoVisc®; Suplasyn®; Durolane®) and injection was guided by different techniques (7 studies used anatomic references, 5 studies were guided by ultrasound, 2 studies by fluoroscopy, 1 study by fluoroscopy and ultrasound and 1 study by anatomic references and X-ray). There was great heterogeneity among included articles regarding HA dosing, number of injections administered and the time interval between each one (Table II).

Pain at rest

Pain at rest was evaluated in all considered articles. At 4 weeks after HA intra-articular administration, pain at rest was evaluated in eight papers (n = 316) with VAS, with pain relief ranging between 0.65 to 3.5 compared to baseline evaluation [9,25,29,31,32,34,36,38]. Similar results were found at 24 weeks past HA injection, (n=311 in nine of the included papers) with a pain relief measured ranging between 0.8 to 4.03 points on VAS [9,25,27,29–31,33,36,38]. Two studies have shown a greater reduction early (at 4 weeks) compared to the 24th week evaluation [25,36]. Conversely, two other papers presented sustained pain reduction throughout the follow-up period [9,29] – Table III.

The graphic data presented by Dauvissat et al. also shows a reduction in pain 90 days after a one single dose HA injection. [28] Velasco et al. demonstrated a decrease of 28% in pain , measured by VAS, after a single injection of 1mL HA. [38]

Functional capacity

Functional capacity was assessed in eleven articles by at least one of the above described disability scales (DASH/QuickDASH, FIHOA and DHI).

An improvement in functional capacity was observed by Roux et al. and Monfort et al. (n=90) 4 weeks after HA administration. These studies reported a reduction of 6 and 3 points, respectively, on FIHOA scale, sustained throughout the follow-up period. Concerning disability, Roux et al. also evaluated the benefit of performing this procedure twice or thrice when compared to one intervention only, in 42 patients, during a 3-month period. Similar results were found regardless of the number of injections[29,32]. Figen et al. also suggested that single-injection of hyaluronan is enough for improvement of both pain and functional capacity.[37]

Three other papers (n=105) also reported an improvement at 24 weeks after HA administration, with reductions of 1 to 7.7 points in disability measured by the FIHOA score [27,29,33].

Badahir et al. (n=20) assessed a decrease in disability 4 and 24 weeks after HA administration, reporting 3.9 and 5.8 point reduction in the DHI score, respectively. [25] Koh et al. as well as Velasco et al. (n=71) reported a decrease on disability 4 [th] and 24 [th] weeks of HA administration, with a 8.11 to 8.6 point reduction and a 12.74 to 13.5 point reduction on DASH|QuickDAHS score, respectively. [9,38]

Pinch strength

Pinch strength was evaluated using a dynamometer in nine of the included articles. Three studies (n=92) reported an increase in pinch strength of 0.1 to 1.4 kg, after 4 weeks of HA administration [25,31,38]. Similarly, four articles (n=112) assessed this variable at 24 weeks, finding an improvement of 0.4 to 2kg [25,30,31,38] - Table III.

DISCUSSION

The present systematic review found great heterogeneity in the results. Howeverm the analysis of included articles supports that HA can be useful in OA of the thumb, mainly to reduce pain and improve functional capacity.

Regarding pain, homogeneity of results was observed across included articles, revealing a reduction of pain at rest, 4 and 12 weeks post injection. Additionally, similar results were found among patients receiving 1, 2 or 3 injections, which indicates that HA efficacy does not appear to be dose-dependent [30,32,37].

Studies also show that the effect of this procedure on pain relief is sustained. Reduction in pain does not only occur in an initial phase (4 weeks) but also it extends throughout a 12 and 24 weeks period. Ioppolo et al. found that HA injection produced a significant decrease in pain between baseline and the 3rd and 6th month of follow-up [30]. The same finding was observed by Koh et al. and Dauvissat et al. with a significant decrease in the mean VNS score in patients receiving HA, 3 and 6 months post-injection, providing reassurance about procedure durability [9,28].

However, two studies suggested that pain reduction waned-off at 24 weeks[25,36].

Hand performance, as evaluated by DHI, FIHOA, DASH/QuickDASH scales, improved after HA injection across all studies. Despite being homogeneous regarding this outcome, results were not always statistically significant.

Because of the important pain and characteristic deformities resulting from first CMC joint osteoarthritis, pinch strength is known to decrease as soon as the degenerative process begins[40]. The pinch strength test shows significant improvements over follow-up time in four reviewed

articles[31,35,37,38]. Nevertheless, three studies reported no significant improvement in pinch strength on patients treated with intra-articular hyaluronate[25,32,36]. These different results might be either due to the inclusion of patients with a more severe disease stage in these later trials or to the utilization of distinct measuring techniques. Schumacher et al. showed a reduction in pinch strength at 12 weeks, which reversed at 20 weeks [39]. Accordingly, we suggest that even if pain relief can be expected after HA, this is not enough to restore good hand function, with a functional impairment of the thumb at extreme load when compared with fine activities. Moreover, intra- or inter-rater reliability of pinch strength measurements using a pinch gauge have not been evaluated.

Despite the high prevalence of hand OA, randomized controlled trials addressing clinical impact of HA on rhizarthrosis lacks in the literature. Furthermore, those available have a small sample of patients. The utilization of different molecular weight compounds also poses a challenge for the interpretation of results. In fact, some authors have suggested that low weight HA might be more effective when compared to higher size compounds, especially in such a small articulation, with an important role on fine movements [10,41] Importantly, the majority of the studies included in this review presented a moderate to low quality, highlighting the difficulties inherent to study design for injections trials.

In conclusion, intra-articular HA injection could represent a complementary strategy to be considered in the therapeutic approach to patients diagnosed with rhizarthrosis. Future trials, including larger cohorts and good quality, are required to define intra-articular HA injections recommendation and to analyze its long-term cost–benefit in rhizarthrosis.

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Figures and Tables

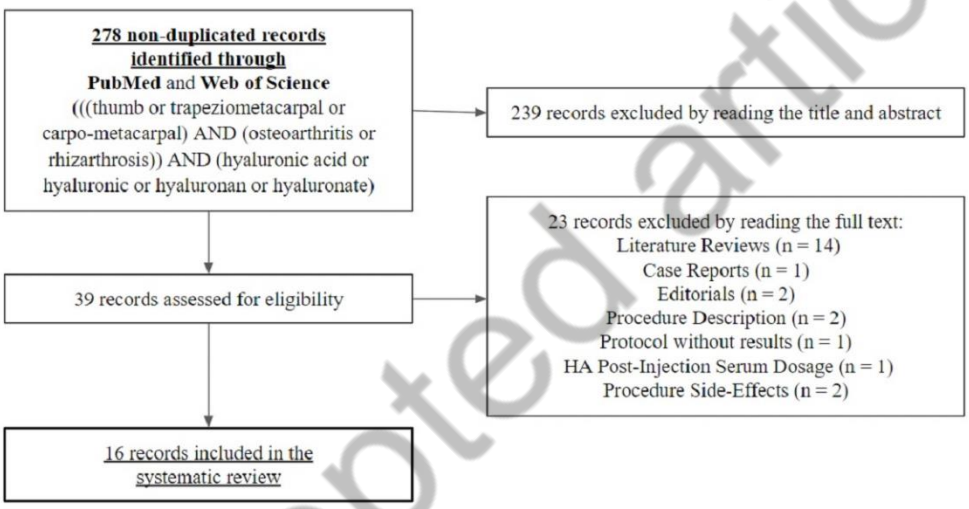

Fig. 1. PRISMA flow-chart diagram.

Table I: Studies Quality Assessment

		Cochrane Risk of Bias Tool							Newcastle-Ottawa Scale		
	Design Study	**Random sequence generation**	**Allocation concealment**	**Blinding (participants and personnel)**	**Blinding (outcome assessment)**	**Incomplete outcome data**	**Selective reporting**	**Other sources of bias**	**Selection**	**Comparability**	**Outcome**
Sabah et al. (2020)	RCT	⊕	?	?	?	?	?	?	NA		
Badahir et al. (2009)	RCT	⊕	?	?	?	?	?	⊕	NA		
Dauvissat et al. (2018)	Single arm prospective clinical trial	NA									
Frizziero et al. (2014)	Single arm retrospective clinical trial	NA									
Ayhan et al. (2009)	RCT	⊕	⊕	?	⊕	⊕	?	?	NA		
Fuchs et al. (2006)	RCT	?	?	⊕	⊕	⊕	?	⊕	NA		
Heyworth et al. (2008)	RCT	⊕	⊕	⊕	⊕	?	?	?	NA		
Ingegnoli et al (2011)	Single arm prospective clinical trial	NA									
Ioppolo et al. (2018)	RCT	⊕	⊕	-	-	?	?	⊕	NA		
Koh et al. (2019)	Retrospective case-control/comparative study	NA							****	--	*
Monfort et al. (2014)	RCT	⊕	?	⊕	⊕	⊕	?	⊕	NA		
Roux et al. (2006)	RCT	?	?	-	?	⊕	?	?	NA		
Stahl et al. (2005)	RCT	⊕	?	?	?	?	?	?	NA		
Tenti et al. (2017)	Retrospective case-control/comparative study	NA							****	--	*
Velasco et al. (2017)	Single arm prospective clinical trial	NA									
Schumacher el al (2004)	Single arm prospective clinical trial	NA									

Legend: Randomized Controlled Trial (RCT) studies assessed using the Cochrane risk of bias tool and non-randomized trials assessed by Newcastle Ottawa Scale
Cochrane risk of bias tool: ⊕ indicates that the study has met the domain criterion; **-** indicates that the study hasn't met the domain criterion**;** an **?** indicates that it is unclear whether the domain criterion has been met
Newcastle Ottawa Scale: Asterisks (*) indicate the star rating according to the Newcastle-Ottawa Scale for cohort studies. A study can be awarded a maximum of 4 stars for selection, 2 stars for comparability, and 3 stars for outcome.
NA: not applicable

Table II: Baseline characteristics of patients treated with intra-articular injections in rizarthrosis

Study, publication year	Design and Follow-up duration	Sample size (n)	Mean age ± SD or (min–max) (years)	Study population	Intervention groups	HA brand	Follow-up (weeks)	Injection guidance	Oral analgesics allowed
Sabah et al. (2020)	Three armed parallel-group design 12 weeks	45 (6 male; 38 female)	52.45 ± 8.25	Patients diagnosed with thumb CMC OA according to clinical assessment	Group 1: (n=15) received an injection of PRP Group 2: (n=15) received an injection of 1 ml of HA Group 3: (n=15) received an injection of 1ml betamethasone and 0.25ml local anaesthetic	Hyalgan®	4,12 weeks	Fluoroscopy guided	Not allowed
Badahir et al. (2009)	Double armed parallel-group design 12 months	40 (female)	60.8±7.3	Patients diagnosed with TMJO according to clinical and radiological findings	Group 1:(n=20) received an injection of 20 mg/0.5 ml of triamcinolone acetonide Group 2: (n=20) received three injections of 5 mg/0.5 ml of HA (1-week interval)	Ostenil®	1,3, 6,12 months	Anatomic references	Not allowed
Dauvissat et al. (2018)	Single arm 3 months	122 (29 male; 93 female)	average age 60 years	Patients with TMC OA according to clinical assessment	All patients received an injection of 1mL of HA (16mg/mL)	HappyMini®	3 months	Fluoroscopy or ultrasound guided	Allowed
Frizziero et al. (2014)	Single arm 6 months	58 (8 male; 50 female)	57.0±8.4	Patients suffering from TMC joint OA according to radiography findings	All patients received three injections of 0.8 mL of HA (10 mg/mL) (weekly)	Hyalgan®	1,3, 6 months	Anatomic references	Allowed
Fingen et al. (2009)	Double arm parallel-group design 6 months	33 (female)	62.6±6.4	Patients with bilateral clinical and radiological thumb base OA	Group 1: (n=33) received an injection of 1 mL of HA Group 2: (n=33) received an injection of 1mL saline solution (contra-lateral joint)	Synvisc™	6 weeks, 6 months	Anatomic references	Not allowed
Fuchs et al. (2006)	Double arm parallel-group design 27 weeks	56 (11 male; 45 female)	59.5±0.44	Patients with symptomatic OA of the CMC joint of the thumb associated with radiographic evidence	Group 1: (n=28) received three injections of 1mL of HA (10.0 mg/mL) Group 2: (n=28) received three injection of triamcinolone acetonide	Ostenil® mini	3, 14, 26 weeks	Anatomic references	Not allowed
Heyworth et al. (2008)	Double arm parallel-group design	60 (8 male; 52 female)	63 years (range 48 to 85 years)	Patients with	Group 1: (n=20) received two injections of 1mL of HA (0-1 week)	Synvisc®	2, 4, 12, 26 weeks	Anatomic references	Allowed

	27 weeks			symptomatic basal joint OA according to radiographic and clinical criteria	Group 2: (n=22) received an injection of 1mL of placebo solution and 1mL of betamethasone acetate 1 week later Group 3: (n=18) received two injections of 1mL of normal saline (0-1 week)				
Ingegnoli et al (2011)	Single arm 26 weeks	16 (1 male; 15 female)	62.46 years (range 43.5 to 79.4 years)	Patients with symptomatic thumb base OA according to radiographs and clinical criteria	All patients received three injections of 0.5mL of HA (1-week intervals)	Hyalubrix®	2, 24 weeks	Ultrasound guided	Not allowed
Ioppolo et al. (2018)	Double arm parallel-group design 6 months	56 (22 male; 34 female)	66.67±8.06	Patients with diagnosis of first CMCJ OA defined by radiographic and clinical criteria	Group 1: (n=30) received na injection of 0.5mL HA injection (once a week for 3 weeks) Group 2: (n=28) received ESWT using a frequency of 4Hz and a energy flux density of 0.09mJ/mm^2	Sinovial® mini	3, 6 months	Ultrasound guided	Not allowed
Koh et al. (2019)	Double arm parallel-group design 6 months	74 (17 male; 57 female)	58.31±10.50	Patients with symptomatic OA of the CMCJ of the thumb	Group 1: (n=38) received an injection containing a mixture of 0.5 mL of HA and 0.5 mL of ketorolac 30mg/mL Group 2: (n=36) received an injection containing a mixture of 0.5 mL of HA and 0.5 mL of saline	NA	1, 3, 6 months	Ultrasound guided	Allowed
Monfort et al. (2014)	Double arm parallel-group design 6 months	88 (11 male; 77 female)	62.8±8.7	Patients with diagnosis of thumb CMC joint OA as defined by radiographic and clinical criteria	Group 1: (n=48) received three injections of 0.5 cm^3 of HA (5 mg) (7-day intervals) Group 2: (n=40) received three injections of 0.5cm^3 of betamethasone disodium phosphate 1.5mg and betamethasone acetate 1.5mg (7-day intervals)	Suplasyn®	7, 14, 30, 90, 180 days	Ultrasound guided	NA
Roux et al. (2006)	Triple arm parallel-group design 3 months	42 (4 male; 38 female)	64.8±8.0	Patients with OA of the CMC joint according to radiographs and clinical criteria	Group 1: (n=14) received a single injection of 1mL of HA Group 2: (n=14) received two injections of 1mLof HA	Sinovial®	1, 3 months	Anatomic references and standard X-ray	Allowed

					Group 3: (n=14) received three injection of 1mL of HA				
Stahl et al. (2005)	Triple arm parallel-group design 6 months	52 (4 male; 21 female)	62 (range, 37– 80 years)	Patients with symptomatic TMC joint arthritis diagnosed by clinical presentation and radiographic evaluation	Group 1: (n=27) received an injection of 1 mg of HA (15 mg/mL) Group 2: (n=25) received an injection of 4 mg methylprednisolone acetate	OrthoVisc®	1, 3, 6 months	Anatomic references	NA
Tenti et al. (2017)	Double arm parallel-group design 6 months	100 (69 female)	68.6 ± 9.4	Patients affected by monolateral or bilateral TMJ OA, according to radiographs and clinical criteria	Group 1: (n=41) received two injections of 1 ml of HA (16 mg/mL) (0-15 days apart) Group 2: (n=41) received two injections of 0.5 ml of triamcinolone acetonide (0 -15 days apart)	Sinovial®	1, 3, 6 months	Ultrasound guided	NA
Velasco et al. (2017)	Single-arm 6 months	35 (5 male; 30 female)	60.8 ± 8.3	Patients with rhizarthrosis according to radiographs and clinical criteria	All patients received five injections of 1mL HA (7-day intervals)	Durolane®	1, 3, 6 months	Fluoroscopy guided	Not allowed
Schumacher el al (2004)	Single-arm 6 months	16 (male)	NA	Patients OA at the first MC-C joint, according to radiographs and clinical criteria	All patients received five injections of 1mL of (HA 10 mg/mL) (weekly)	Hyalgan®	Anatomic references	3, 5 months	NA

RCT: Randomized Clinical Trial; TMC: trapeziometacarpal; ACR: American College of Rheumatology; OA: ostheoarthritis; HA: hyaluronic acid; TMJ: trapeziometacarpal joint; MC-C: metacarpal–carpal; CMCJ: carpometacarpal joint of the thumb; VAS: Visual Analogue Score; VNS: visual numeric scale DASH: Disability of the Arm, Shoulder and Hand; ESWT:extracorporeal shockwave therapy;Dreiser: Dreiser functional index ; DHI: Durüoz Hand Index; NA: not available

Table III: Results of patients treated with intra-articular injections in rizarthrosis.

Study, publication year	Type of injection	Nº of injection	Outcome measure	Baseline	Week 4	Week 12	Week 24
Sabah et al. (2020)	Hyalgan®	N = 1	Pain at rest (VAS) (cm)	7 (5-8)	4 (3-5)	3 (2-5)	NA
			Pinch strength (lateral) (Dynamometer - Camry, model: EH101)	NA	NA	NA	NA
Badahir et al. (2009)	Ostenil®	N = 3	Pain at rest (VAS) (cm)	6.5±2.0	4.7± 2.6	4.6± 2.7	5.7± 2.2
			Functional capacity (DHI)	27.9±11.4	24.0±12.4	22.2±13.2	22.1±12.5
			Pinch strength (tip) (Dynamometer - Baseline®, Hydraulic pinch gauge, Chattanooga Group Inc. Hixson, USA)	6.8±1.7	7.0±2.1	7.3±1.9	7.5±2.1
Dauvissat et al. (2018)	HappyMini ®	N = 1	Pain at rest (VAS) (cm)	6.5 ±1.6	NA	3.9 ±2.5	NA
Frizziero et al. (2014)	Hyalgan®	N = 3	Pain at rest (VAS) (cm)	8.2 ± 0.7	4.7 ± 2.2	5.3 ± 2.3	6.5 ± 1.9
			Pinch strength- (Dynamometer - Jamar Model 1 TEC, Clifton, NJ)	NA	NA	NA	NA
Ayhan et al. (2009)	Synvisc™	N = 1	Pain at rest (VAS) (cm)	4.7±3.3	NA	NA	NA
			Functional capacity (Dreiser's index)	10.1±8.4	NA	NA	NA
			Pinch strength (pulp) -Pound-force (Dynamometer -B&L Engineering, Santa Fe Springs, CA 90670 model no.PG-60 S/N B6F968)	9.8±3.6	NA	NA	NA
Fuchs et al. (2006)	Ostenil®	N = 3	Pain at rest (VAS)	NA	NA	NA	NA
Heyworth et al. (2008)	Synvisc®	N = 2	Pain at rest (VAS) (cm)	5 ± 1	NA	NA	NA
			Functional capacity (DASH)	37 ± 4	NA	NA	NA
			Pinch strength (lateral)- (Dynamometer - Jamar Northcoast Medical)	NA	NA	NA	NA
Ingegnoli et al (2011)	Hyalubrix®	N = 3	Pain at rest (VAS) (mm)	68.8 (50.5–80.0)	NA	NA	55 (45–70)
			Functional capacity (Dreiser's index)	9.0 (5.5–11.5)	NA	NA	8.0 (5.0–9.0)
Ioppolo et al. (2018)	Sinovial®	N = 3	Pain at rest (VAS) (cm)	7.62±1.34	NA	4.43	6.03
			Functional capacity (DHI)	51.56±14.04	NA	NA	NA
			Pinch strength- kg (Dynamometer - A853-4; Smith & Nephew, Germantown, WI, USA)	4.59±2.17	NA	5.34±2.06	5.97±1.75
Koh et al. (2019)	HA + Saline Solution	N = 1	Pain at rest (VNS) (cm)	6.37±1.04	3.39±2.01	2.83±1.72	2.82±1.62
			Functional capacity (DASH)	32.53±4.63	24.42±5.84	21.86±5.84	19.79±5.98
Monfort et al. (2014)	HA	N = 3	Pain at rest (VAS) (cm)	6.0 ± 1.8	−1.97 (2.62)**	−1.61 (2.53)**	−1.97 (2.73)**
			Functional capacity (FIHOA)	11.5 (8–14)	−3 (−6.7 and −0)**	−4 (−8 and −1)**	−3 (−8.7 and −1)**
Roux et al. (2006)	Sinovial®	N = 1	Pain at rest (VAS) (mm)	58.4 ± 16.2	46.2 ± 21.9	43.1 ± 22.8	NA
			Functional capacity (Dreiser's index)	12.1 ± 5.2	9.0 ± 5.1	9.7 ± 4.9	NA

		N = 2	Pain at rest (VAS) (mm)	54.6 ± 18.9	48.1 ± 27.9	39.5 ± 28.6	NA
			Functional capacity (Dreiser's index)	13.4 ± 5.9	10.7 ± 9.7	10.1 ± 7.9	NA
		N = 3	Pain at rest (VAS) (mm)	60.1 ± 17	28.4 ±20.8	29.8 ± 21.9	NA
			Functional capacity (Dreiser's index)	11.9 ± 6.6	5.9 ± 3.7	7.1 ± 4.6	NA
Stahl et al. (2005)	OrthoVisc®	N = 1	Pain at rest (VAS) (cm)	4.2	(-2.2) ± 2.0**	(-2.0) ± 2.0**	(- 2.2) ± 2.1**
			Pinch strength - kg (Dynamometer-(Jamar dynamometer; Asimov Engineering Co.)	3.4***	3.5***	3.6***	3.8***
Tenti et al. (2017)	Sinovial®	N = 2	Pain at rest (VAS) (mm)	58.5 ± 16.2	NA	NA	29.86 ± 20.13
			Functional capacity (FIHOA)	12.2 ± 4.3	NA	NA	4.44 ± 4.42
Velasco et al. (2017)	Durolane®	N = 5	Pain at rest (VAS) (cm)	7.2 ±1.8	5.4 ±2.5	5.3 ±2.7	5.0±2.7
			Functional capacity (QuickDASH)	58.0 ± 16.9	49.4 ± 18.4	49.1 ± 22.9	44.5 ±21.3
			Pinch strength (lateral) - kg (hand dynamometer – non specific)	3.1 ±3.4	4.5 ±8.1	3.0±3.1	5.1±5.0
Schumacher el al (2004)	Hyalgan®	N = 5	Pain at rest (VAS) (cm)	4.74 (0.6–8)*	NA	3.07 (0.6–7.5)*	NA
			Pinch strength - kg (dynamometer -TEC, Clifton, NJ)	16 (10–25)*	NA	14.91 (5–21)*	NA

VAS: Visual Analogue Score; VNS: visual numeric scale DASH: Disability of the Arm, Shoulder and Hand ; Dreiser: Dreiser functional index ; DHI: Durüoz Hand Index; NA: not available
* mean and standard deviation (SD)

**change in VAS score (average ± standard deviation) compared with Baseline

*** Average