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Hyaluronic Acid Intra-articular Injection and Exercise Therapy: Effects on Pain and Disability in Subjects Affected by Lower Limb Joints Osteoarthritis. The Italian Society of Physical and Rehabilitation Medicine (SIMFER) systematic review.

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Hyaluronic Acid Intra-articular Injection and Exercise Therapy: Effects on Pain and Disability in Subjects Affected by Lower Limb Joints Osteoarthritis.

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ABSTRACT

Background. It is debated whether intra-articular viscosupplementation with hyaluronic acid (HA) can lead to improvements in subjects with osteoarthritis (OA) undergoing physical and rehabilitative interventions.

Aim. To assess the effects of intra-articular viscosupplementation on disability in subjects with OA undergoing physical and rehabilitative interventions. Information on pain and quality of life were also collected.

Methods. The databases of PubMed, Medline, EMbase and CINAHL were searched for English language full-text randomized controlled trials comparing intra-articular

viscosupplementation alone or associated with physical and rehabilitative interventions to viscosupplementation alone, shame treatment, waiting lists, and any type of rehabilitative interventions. Methodological quality of each study was assessed by using the Physiotherapy Evidence Database scale (PEDro).

Results. A total of 115 references were retrieved, and 8 studies were selected. Three trials compared HA injection and physical therapy in knee OA, with disability and pain improvements in all studies, and between-group differences in favor of physical therapy in two studies; two trials compared HA injection and home exercises in knee OA, with improvements in pain, disability and quality of life in all studies, without between-group differences; two trials compared HA injection plus physical therapy agents and exercises to exercises plus physical therapy agents in knee OA, with improvements in disability and pain in both studies, and between-group differences in favor of the inclusion HA in one study; one trial compared HA injection and home exercises in ankle OA, with improvements in disability and pain in both arms without between-group differences.

Conclusion. Physical therapy agents seemed have greater effects than intra-articular viscosupplementation on disability and pain. In the other cases both intra-articular viscosupplementation and physical and rehabilitative interventions seemed to be equally effective in improving disability, pain, and quality of life in subjects with knee and ankle OA.

Keywords: osteoarthritis, rehabilitation, exercises, physical therapy agents, hyaluronic intra-articular injection, systematic review.

INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and constitutes one of the main causes of disability in the elderly [1]. It is considered a multifactorial disease affecting

cartilage, subchondral bone and synovium, characterized by increasing pain and loss of physical function [2]. OA is considered as a dynamic process in which the mechanical stimulation determines a biochemical activation of inflammatory mediators released by cartilage, subchondral bone and synovial tissue [3-9].

In OA viscoelastic properties of synovial fluid are compromised as a result of decrease of both the concentration and the molecular weight of hyaluronic acid (HA) in the synovial fluid [10,11]. HA has a variety of biological properties and it is actively synthesized by type B synoviocytes, fibroblasts and chondrocytes [12]. OA pathogenic process leads to alterations in the metabolism of type B synoviocytes that begin to produce pathologic HA [13]. The increased mechanical strains due to reduction of lubricating capacity of synovial fluid stimulate nociceptors causing pain [14,15]. It was observed that joint movement is coupled with active HA secretion and the magnitude of secretion depends on the frequency and duration of joint movement, suggesting a possible biochemical mechanism supporting exercise therapy [16,17].

In the 70s, Balazs introduced the term “viscosupplementation” to indicate a particular treatment consisting of intra-articular HA injections to reduce pain and improve joint mobility in knee osteoarthritis [18]. This therapy was practiced for more than 15 years in many countries around the world for its efficacy and tolerability in patients who do not respond to conservative non-pharmacological and pharmacological treatment [19]. The in vivo and in vitro effect of viscosupplementation are not just due to the simple replacement of pathologic synovial fluid with the healthy one or to stimulation of the endogenous hyaluronic acid production, but are regulated by the interaction between the molecule and its membrane and intracellular receptors, expressed by different types of cells [20].

Intra-articular viscosupplementation with HA was effective as a symptom-modifying drug and there are evidences about potential disease-modifying effects [20]. HA interacts with its receptors CD44, ICAM-1 and RHAMM [21-23], that are over expressed in OA, inhibiting

the expression of IL-1 [24], IL-6, IL-8 [25] PGE2 [26,27] and proteases [28,29], stimulating the production of endogenous hyaluronic acid [30-32] and other matrix components (PGs and collagen) [33] and decreasing apopthosis mediated by NO and Fas-Fas ligand [34,35]. The majority of clinical trials performed in humans found benefits on pain control and physical function particularly in knee OA, although there were differences in results due to some variables such as methods used, patients included, scales used to evaluate outcomes, molecular weight of HA, inclusion criteria and observational period durations. It was suggested that analgesic action depends on the increasing of elastoviscosity of extracellular matrix inducing modification of rheological proprieties of synovial fluid and reducing forces transmitted to sensory nerve afferents [36]. Moreover, analgesic action depends on the decreasing of inflammatory mediators, such as PGE2 and bradikinin, involved in nociceptive transmission [14,15,36].

However, it is still debated whether intra-articular viscosupplementation with HA can actually lead to clinically meaningful changes in disability of life in subjects with OA undergoing physical and rehabilitative interventions. Moreover the role of a chronic intra-articular therapy with HA should be better studied, considering the fact that OA is a chronic disease. The main aim of these interventions should not be targeted only at treating pain but should also attempt at modifying physical dysfunction, that is considered the most relevant barrier to recovery.

Hence, our aim is to assess by means of a systematic review the effects of intra-articular viscosupplementation on disability (primary endpoint), pain, quality of life, return to work and satisfaction with treatment (secondary endpoints) in subjects with OA undergoing physical and rehabilitative interventions.

METHODS

The PRISMA checklist and flow diagram were adopted in the revision of our SR [37,38].

Search strategy

The databases of PubMed, Medline, EMbase and CINAHL were searched for full-text articles published up to March 2015 using combination of the following key-words: “viscosupplementation”, “viscoinduction”, “intra-articular injection”, “intra-articular infiltration”, “hyaluron*”, “condroprotection”, “cartilage preservation”, “cartilage deterioration”, “physical therapy”, “electrophysical therapy”, “exercise”, “rehabilitation”, “placebo”, “shame treatment”, “waiting lists”, “osteoarthritis” (see Appendix 1 for the full search strategy). Database searching were supplemented by screening reference lists and citation tracking included in trials to identify additional studies.

Study selection criteria

In order to be included in our systematic review, the articles had to meet the following criteria, formulated based on a PICO model [37,38].

Patients with a diagnosis of primary or secondary osteoarthritis were considered eligible. No limitations were applied concerning the technique used in order to obtain the diagnosis, the stage of OA and the lower extremity joint under investigation.

Studies were eligible for the review whether they compared intra-articular viscosupplementation associated with physical and rehabilitative interventions versus viscosupplementation alone, shame treatment (placebo) or waiting lists. Studies were eligible also if they compared intra-articular viscosupplementation, alone or associated with physical and rehabilitative interventions, to any type of rehabilitative interventions. Any type of hyaluronic acid intra-articular joint infiltration as well as any kind of physical and rehabilitative intervention such as electro-physical therapy, physical therapy or exercises were eligible.

All studies included in the review necessarily had to report at least a measure evaluating our primary endpoint (disability). The absence of one or more secondary outcomes (pain, quality of life, return to work and satisfaction with treatment) was not considered an exclusion criterion in our work.

Only Randomized Controlled Trials, published in English, were included.

Selection of trials

The search yield was initially screened by two assessors (CN, VL) in order to remove duplicates and to independently assess titles and abstracts of potentially relevant articles retrieved by literature search by using the mentioned criteria. A full-text article was retrieved when the title or abstract revealed insufficient information to determine inclusion. In case of disagreement, a discussion to reach consensus was conducted, and if necessary, a third reviewer (MM) made the decision regarding inclusion.

If sufficient homogeneity existed between at least two studies in the pre-defined comparisons, a meta-analysis was performed.

Data collection and quality assessment

Demographic characteristics of the sample (average age, sex, and disease severity), trial characteristics (comparison treatments, duration) and study outcomes (disability, pain, quality of life, return to work and satisfaction with treatment) of each trial were collected by two independent reviewers into a standardised data extraction form designed and tested before being used.

The two independent reviewers also completed the quality and risk of bias assessment by applying the Physiotherapy Evidence Database (PEDro) scale. In case of disagreement,

there was discussion in order to reach consensus, and if necessary, a third reviewer made the decision. PEDro scale is based on the Delphi list [39] and it is developed to evaluate the methodological quality of physical therapy RCTs. This scale consists of 11 items rating internal validity (10 items) and external validity (1 item) of a clinical trial; the last item does not influence internal validity of the trial and, in general, it is not considered to calculate the PEDro scale total score. Each adequately fulfilled item, with the exception of item 1, receives one point and contributes to the score which has a maximum of 10 points; higher PEDro scores correspond to higher methodological quality.

Consistent with the PEDro scale, we only considered the internal validity (10 items) to assess risk of bias.

Institutional Review Board approval

The Institutional Review Board of the Salvatore Maugeri Foundation's Scientific Institute in Lissone (Monza Brianza, Italy) approved the study.

RESULTS

The search strategy identified 298 articles, 183 of which were excluded because irrelevant. 10 articles of 115 were selected on the basis of their titles and abstracts. The subsequent full text assessment excluded 2 articles, and this systematic review was based on 8 articles (Figure 1) [40-47]. Seven articles dealt with knee osteoarthritis [40-46], one article with ankle osteoarthritis [47].

Patient demographic and disease characteristics were described in Table I. The average age of patients in the 7 trials on knee osteoarthritis ranged from 54 to 71 years old. Overall, there were 435 women and 73 men included in 6 studies; demographic characteristics (gender) of patients of one trial [42] were not available. All patients reported a diagnosis of osteoarthritis based on radiographic findings: 4 studies used the Kellgren

and Lawrence classification (grade II to IV) [40,42,43,45], 1 study referred to the Altman classification (grade II) [44], 1 study classified the degree of OA according to radiographic Joint Space Width (grade early or advance) [41], whereas the remaining study did not specify the classification used in the inclusion criteria [46].

Only a single study focusing on ankle OA was available: the average age of patients ranged from 52 to 58 years old, 70% of patients were women and 30% men. Patients suffered from primary or secondary OA classified with the Kellgren and Lawrence classification (grade III) [47].

Six studies compared the effect of hyaluronic acid injections to a physical and rehabilitative intervention: Transcutaneous Electrical Nerve Stimulation (TENS) [40,42], diathermy and interferential therapy [43] and home exercise programs [41,45,47] which mainly consisted of range of motion and strength exercises. Two studies compared the efficacy of hyaluronic acid injections, associated with a rehabilitative intervention composed of both electrophysical therapies and exercises, versus rehabilitation alone [44,46]. Different type of hyaluronic acid injections were tested in the trials: hyaluronic acid [45,47], sodium hyaluronate [40,41,43], hyaluronan [44,46], hylan G-F 20 [42,43,46]. In two studies, the group undergoing viscosupplementation was split up in two smaller subgroups [43,46]. Three studies performed 3 intra-articular injections every week [42,45-47], two trials carried out 5 intra-articular injection weekly [40,44], whereas 2 studies preferred a bigger number of infiltration on a wider period of time [41,43]. Additional details including group characteristics and type of interventions are fully displayed in Table I.

The PEDro scale score ranged from 5 to 7 (mean 5.87; median 6). Most of the studies (n=5, 62.5%) scored 6 or higher [41,44-47], whereas the minority (n=3, 37.5%) scored 5 [40,42,43]. The criterion “blinding therapists” and “blinding subjects” were never satisfied, while the criterion “blinding assessor” was reported in all of the studies but one (87.5%) [43]. However, all of the studies satisfied the criterion “random allocation of participants”

and “results of between-group statistical comparison reported for at least one key outcome”. All of the studies but one [44] reported less than 15% dropouts (87.5%). Three studies performed an “intention-to-treat analysis” (37.5%) [41,45,47]; the criterion “allocation was concealed” was satisfied in only two studies (25%) [42,44], while the criterion “groups similar at baseline” was not achieved by 3 studies (37.5%) [40,42,47]. The quality assessment of the included trials is fully shown in Table II.

The primary endpoint of our systematic review (i.e. the effects of intra-articular viscosupplementation on disability) was assessed in all of the studies included. The outcome measures used to assess disability were the Lequesne Disease Severity Index [40,42,44,46], the WOMAC scale [43], the Outcome Measure in Rheumatology Clinical Trials and Osteaoarthritis Research Society International Criteria [41], the Hospital for Special Surgery Knee Score [45] and the American Orthopaedic Foot and Ankle Society [47]. As far as secondary outcomes were concerned, five studies evaluated pain [40,41,43-45,47] and most of them used the Visual Analogue Scale [40,41,44,47]. Four studies assessed quality of life [40-43], two of them by using the Short Form 36 Health Survey [42,43], whereas none reported return to work and satisfaction with treatment. Outcome measures, time assessments and main findings of all of the studies were fully reported in Table III.

Owing to the scarce availability of studies and heterogeneity among interventions, especially the Physical Therapy Agents used in the trials, follow-up periods for each study and different degree of OA, meta-analysis could not be performed.

Results per type of trial comparison are reported below.

Trials comparing HA injection and Physical Therapy Agents (PTA) in knee OA

Three trials examined the effects of HA injection versus PTA: Chen et al and Paker et al [40,42] compared viscosupplementation to TENS, while Atamaz et al [43] to diathermy and

interferential therapy. Disability and pain scores showed a significant improvement in both injection and PTA groups in all studies comparing follow-up scores to baseline. Between-group comparison reported better disability scores in favour of TENS group in Chen et al study at baseline, post-treatment and 3 months follow-up [40], and in Paker et al at post-treatment assessment [42]. Between-group analysis of pain results was significant in Chen et al study at post-treatment evaluation in favour of TENS group [40] and in Atamaz et al at 1 month, 3 and 6 months in favour of PTA group. Quality of life scores showed conflicting results in intra-group comparison: Chen et al [40] and Atamaz et al. [43] reported a significant improvement from baseline to follow-up assessment in both groups, while no differences in scores were found in Paker et al study [42].

A meta-analysis was not conducted since the three studies evaluated three different interventions; the only two comparable studies [40,42] differed in the follow-up periods and TENS technique adopted.

Trials comparing HA injection and Home Exercises in knee OA

Two studies opposed the effects of HA injection to home exercises [41,45]. Both studies evaluated disability and pain; Kawasaki et al [41] assessed also quality of life. Disability and pain showed significant improvements after treatment compared to baseline values [41,45]. No differences in between-group comparison were reported for these outcome measures [41,45]. Quality of life scores significantly improved at the last follow-up evaluation (18 months), compared to baseline in both groups without reporting between-group differences comparison [41].

A meta-analysis was not conducted since the two available studies had no outcomes in common.

Trials comparing HA injection plus PTA and Exercises versus Exercises plus PTA in knee OA

Two studies compared the efficacy of intra-articular injection associated with exercises and PTA programs to exercises and PTA alone. Huang et al [44] performed ultrasound therapy, while Bayramoğlu et al [46] performed short wave diathermy and TENS as PTA program. Disability improved significantly in all groups after treatment in both trials [44,46], and between-group differences were seen only in Huang et al [44] in favour of HA+Exercise+US group at 1 year follow-up. No differences in between-group comparison were reported in Bayramoğlu et al. [46]. Pain was evaluated only in Huang's study [44] and reported a significant improvement in VAS score in all groups after treatment, this improvement continued in two treated groups (HA+Exercise+US and Exercise+US) at 1 year follow-up.

A meta-analysis was not conducted since the studies evaluated two different interventions PTA: ultrasound [44] and Short wave diathermy plus TENS [46].

Trials comparing HA injection and Home Exercises in ankle OA

A single study assessed the efficacy of intra-articular viscosupplementation compared to a home exercises in primary and secondary ankle OA [47]. Both disability and pain outcome measures significantly improved at last follow-up evaluation (12 months), compared to baseline in both groups without reporting between-group differences comparison.

DISCUSSION

The aim of this systematic review was to investigate the effects on disability of intra-articular viscosupplementation in subjects with OA undergoing physical and rehabilitative interventions. Data on secondary outcomes such as pain and quality of life were also collected whenever available.

Intra-articular HA in osteoarthritis has been widely studied in large joints as a symptom-modifying treatment [48-51]. Although some authors showed a lack of efficacy of HA

injections [52], other studies and 2 high-quality no-sponsored meta-analyses confirm its efficacy and safety for the treatment of OA, especially comparing the efficacy and safety of intra-articular injections of HA versus CS and placebo [19,53-56].

Based on the findings of this systematic review, three studies compared intra-articular viscosupplementation alone to physical therapy agents in subjects with knee OA. Chen et al reported TENS as more efficient than HA injections on disability and pain; reasons of these findings might be ascribed to the different type of electrodes used (silver spike point electrodes versus conventional electrodes) and their specific placement following acupuncture points [40]. TENS and other physical therapy agents such as diathermy and interferential therapy also led to greater benefits on disability [40] and pain [40-43] than intra-articular viscosupplementation in the short period [40]; this was in line with other reviews evaluating the effect of TENS on knee OA [57-59], suggesting that physical therapy agents may represent a useful first-aid approach to reduce pain, to increase knee function and the level of activity in the short-term.

Three studies compared intra-articular viscosupplementation alone to exercises carried on individually at home in knee and ankle OA. No differences on disability and pain at short and at long follow-ups were found, leaving a gap to evidence and to clinicians choices [41,45,47]. However, based on the chronic nature of OA and the need for long-term care, learning specific exercises on a outpatient basis and then performing them at home without the supervision of a physiotherapist could be initially suggested as this would help national health system policy managers to reduce costs for outpatient services and redirect limited resources to areas of greater need. Intra-articular viscosupplementation could be suggested subsequently, given the fact it is a semi-invasive procedure, the rates of infiltrations required (up to 3-6) and the local adverse effects usually reported (up to 1-4% per injections) such as mild pain, swelling, effusion, warmth, and redness [60-62].

Two studies conducted in knee OA compared intra-articular viscosupplementation associated to exercises and physical therapy agents to exercises and physical therapy agents alone [44,46]. The first study showed between-group differences on disability at long-term when also intra-articular viscosupplementation was included while the second did not. However, differences may depend on to the different interventions delivered: the first study proposed isokinetic muscular strengthening exercises together with ultrasound therapy [44], while the second study proposed progressive resistive exercises according to De Lorme's technique together with diathermy and TENS [46]. According to these results, the two studies cannot be fully compared and, despite promising, the association of intra-articular viscosupplementation to physical and rehabilitative interventions should be further investigated.

The inclusion of only RCTs and their high quality as demonstrated by the PEDro score scale varying from 5 to 7 can be considered two strengths of our work. The PEDro scale had been widely used as a tool to rate methodological quality of RCTs, as its 10 criteria assessed internal validity of a clinical trial. Even though validated cutoff scores for the PEDro scale had not been published yet, we consider our results as satisfactory as the most relevant criteria for a rehabilitative RCT were fulfilled.

Our systematic review has some limitations. The exclusion of studies written in languages other than English may have introduced a selection bias. Meta-analysis was not performed owing to the small number of trials available (7 dealing with knee OA, 1 concerning ankle OA). Finally, the limited number of subjects enrolled (less than 600), most of them females, might represent a limitation in the generalisability of results. OA affected 33.6% of adults aged 65 years and older in 2008 [63], so the sample size of our systematic review might not be faithfully representative of the real OA population.

CONCLUSION

In most cases both intra-articular viscosupplementation and physical and rehabilitative interventions seemed to be equally effective on disability due to knee and ankle OA at long-term. Physical therapy agents might have greater effects than intra-articular viscosupplementation on disability and pain only at short-term. Given the lack of evidence, the choice on these therapeutic options is left to clinicians who make decisions upon hospital setting availability as well as patients' impairment and needs. Moreover, it has to be considered that Hyaluronic Acid is proposed in different formulations, and there are not, to our knowledge, studies reporting data on comparisons among different molecular weight. Considering the fact that OA is a chronic and progressive multifactorial joint affection, it should be also interesting to evaluate the effect of HA injection on OA progression depending on the pathologic stadium considering HA injection as a chronic therapy. A treatment model associating intra-articular viscosupplementation to physical and rehabilitative interventions seems promising but more high quality RCTs are needed before it can be suggested.

CONFLICT OF INTEREST

All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) the work.

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Appendix A – Full search strategy used in Pubmed database

(((viscosupplementation OR intra-articular injection OR intra-articular infiltration OR hyaluron* OR viscoinduction OR disease modifying disease OR cartilage deterioration OR joint homeostasis OR condroprotection) AND (physical therapy OR electrophysical therapy OR exercise OR rehabilitation)) AND (osteoarthritis)) OR ((((viscosupplementation OR intra-articular injection OR intra-articular infiltration OR hyaluron* OR viscoinduction OR disease modifying disease OR cartilage deterioration OR joint homeostasis OR condroprotection) AND (physical therapy OR electrophysical therapy OR exercise OR rehabilitation)) AND (physical therapy OR electrophysical therapy OR exercise OR rehabilitation))) AND (osteoarthritis) OR ((((viscosupplementation OR intra-articular injection OR intra-articular infiltration OR hyaluron* OR viscoinduction OR disease modifying disease OR cartilage deterioration OR joint homeostasis OR condroprotection) AND (physical therapy OR electrophysical therapy OR exercise OR rehabilitation)) AND (viscosupplementation OR intra-articular injection OR intra-articular infiltration OR hyaluron* OR viscoinduction OR disease modifying disease OR cartilage deterioration OR joint homeostasis OR condroprotection))) AND (osteoarthritis) OR ((((viscosupplementation OR intra-articular injection OR intra-articular infiltration OR hyaluron* OR viscoinduction OR disease modifying disease OR cartilage deterioration OR joint homeostasis OR condroprotection) AND (physical therapy OR electrophysical therapy OR exercise OR rehabilitation)) AND (placebo OR **shame** treatment))) AND (osteoarthritis)

Filters: RCT, HUMANS

Table I. Descriptions of patient demographic and clinical characteristics, type of interventions of the studies included in the SR

Joint interested	Disease	Study	Population	Participants HA group	Participants PT/exercise group	Intervention HA group	Intervention PT/exercise group
Knee	Osteoarthritis	Chen et al. [39]	OA outpatients Kellgren and Lawrence grading II to IV	**HA group** n = 27 F = 23, M = 4 67.96 y [±9.94]	**TENS group** n = 23 F = 20, M = 3 66.52 y [±7.20]	**HA group** 1 sodium hyaluronate injection/week, 5 weeks	**TENS group** 20'/day, 3 times/week,4 weeks silver spike point electrodes
		Kawasaki et al. [40]	OA outpatients Grade early or advance (radiographic stage according to Joint Space Width)	**HA group** n = 42 F = 42, M = 0 69.50 y [±8.40]	**Home exercise group** n = 45 F = 45, M = 0 71.20 y [±7.10]	**HA group** 1 sodium hyaluronate injection/week, 5 weeks + 1 sodium hyaluronate injection/month until 24 weeks	**Home exercise group** isometric muscle exercises and range of motion exercises bilaterally 2 times/day, 24 weeks
		Paker et al. [41]	OA outpatients Kellgren and Lawrence grading II to III	**HA group** n = 25 F = NA, M = NA 64.04 y [±8.62]	**TENS group** n = 27 F = NA, M = NA 54.18 y [±8.19]	**HA group** 1 hylan G-F 20 injection/week, 3 weeks	**TENS group** 20'/day, 5 times/week, 3 weeks conventional electrodes
		Atamaz et al. [42]	OA outpatients Kellgren and Lawrence grading II to III	**NaHA group** n = 20 F = 18, M = 2 62.40 y [±9.00] **HL group** n = 20 F = 15, M = 5 60.40 y [±9.30]	**PTA group** n = 42 F = 34, M = 6 58.70 y [±8.30]	**NaHA and HL group** 1 sodium hyaluronate/hylan G-F 20 injection/week, 3 weeks + 4 injections in the next 6 months	**PTA group** diathermy and interferential therapy 60'/day, 2 times/week, 3 weeks
		Huang et al. [43]	OA outpatients Altman grade II n = 140 F = 113, M = 27 65.00 y [±6.40]	**HA + Exercise + US group** n = 32 F = NA, M = NA Age NA	**Exercise group** n = 26 F = NA, M = NA Age NA **Exercise + US group** n = 29 F = NA, M = NA Age NA	**HA + Exercise + US group** 1 hyaluronan injection/week, 5 weeks +20' warmup exercises + isokinetic muscular strengthening exercises + ultrasound 3 times/week, 8	**Exercise group** 20' warm-up exercises + isokinetic muscular strengthening exercises, 3 times/week, 8 weeks + 15' stationary bicycle at home after 8 weeks treatment **Exercise + US group** 20' warm-up exercises +

					Control group n = 31 F = NA, M = NA Age NA	weeks + 15' stationary bicycle at home after 8 weeks treatment	isokinetic muscular strenghting exercises + ultrasound 3 times/week, 8 weeks + 15' stationary bicycle at home after 8 weeks treatment **Control group** 20' warm-up exercises
		Karatosun et al. [44]	OA outpatients Kellgren and Lawrence grading III	**HA group** n = 52 F = 44, M = 8 57.80 y [±12.10]	**Home Exercise group** n = 53 F = 46, M = 7 55.30 y [±13.60]	**HA group** 1 hyaluronic acid injection/week, 3 weeks	**Home Exercise group** Home-based range of motion and progressive resistance exercises, 6 weeks
		Bayramoğlu et al. [45]	OA outpatients n = 37 F = 35, M = 2	**HN + PT group** n = 16 F = NA, M = NA 62.60 y [±10.20] **HL + PT group** n = 12 F = NA, M = NA 61.50 y [±10.90]	**PT group** n = 9 F = NA, M = NA 60.70 y [±8.50]	**HN + PT or HL + PT group** 1 hyaluronan/hylan G-F 20 week, 3 weeks + Short wave diathermy (20'), TENS (30'), progressive resistive exercises (De Lorme's technique)	**PT group** Short wave diathermy (20'), TENS (30'), progressive resistive exercises (De Lorme's technique)
Ankle	Osteoarthritis	Karatosun et al. [46]	Primary and secondary OA outpatients Kellgren and Lawrence grading III Primary OA n = 17 (26 ankles) Secondary OA n = 13 (17 ankles)	**HA group** n = 15 (19 ankles) F = 9, M = 6 52.10 y [±11.30]	**Home Exercise group** n = 15 (24 ankles) F = 12, M = 3 58.10 y [±12.10]	**HA group** 1 hyaluronic acid injection/week, 3 weeks	**Home Exercise group** Home-based range of motion and progressive resistance (isometric and isotonic), proprioceptive and closed kinetic chain exercises, 6 weeks

OA means osteoarthritis; HA means hyaluronic acid; NaHA means sodium hyaluronate; HL means hylan G-F 20; HN means hyaluronan; TENS means transcutaneous electrical nerve stimulation; PTA means physical therapy agents; PT means physical therapies; US means ultrasound; M means male; F means female; y means years of age with [standard deviation] or [range] as available; NA means not available.

Table II. Quality assessment - PEDro scores of included trials [39-46]

PEDro criteria	Knee Osteoarthritis							Ankle Osteoarthritis
	Chen et al. [39]	Kawasaki et al. [40]	Paker et al. [41]	Atamaz et al. [42]	Huang et al. [43]	Karatosun et al. [44]	Bayramoğlu et al. [45]	Karatosun et al. [46]
1. Eligibility criteria were specified	Y	N	Y	Y	N	Y	Y	Y
2. Random allocation of subjects	Y	Y	Y	Y	Y	Y	Y	Y
3. Allocation was concealed	N	N	Y	N	Y	N	N	N
4. Groups similar at baseline	N	Y	N	Y	Y	Y	Y	N
5. Blinding of all subjects	N	N	N	N	N	N	N	N
6. Blinding of all therapists	N	N	N	N	N	N	N	N
7. Blinding of all assessors	Y	Y	Y	N	Y	Y	Y	Y
8. ≤ 15% dropouts	Y	Y	Y	Y	N	Y	Y	Y
9. Intention-to-treat analysis	N	Y	N	N	N	Y	N	Y
10. Between-group differences reported (≥ 1 key outcome)	Y	Y	Y	Y	Y	Y	Y	Y
11. Point estimate and variability reported	Y	Y	N	Y	Y	Y	Y	Y
Total score	5/10	7/10	5/10	5/10	6/10	7/10	6/10	6/10

Item one is not included as part of the 10 point PEDro scoring.

Table III. Descriptions of outcomes, time assessments and main findings of the studies included in the SR

Joint interested	Study	Primary outcome measures	Secondary outcome measures	Time assessments	Main findings
Knee	Chen et al. [40]	- Lequesne Disease severity Index [a] - VAS [b]	- Disability in ADL [a] - Patient global assessment [c] - Measurement of ROM (extension / flexion) - Walking time - Pain threshold	T0: pre-treatment T1: post-treatment (2 weeks) T2: follow-up (2 months) T3: follow-up (3 months)	Both groups improve in VAS, Lequesne Index and patient global assessment at all time evaluations compared to baseline. Between-group differences for VAS score at T1 and in Lequesne Index at T0, T1, T3 in favour of TENS group.
	Kawasaki et al. [41]	- Outcome Measures in Rheumatology Clinical Trials and Osteoarthritis Research Society International Criteria (OMERACT-OARSI) [a] - VAS [b] - Japanese Knee Osteoarthritis Measure (JKOM) [c]	- Age - BMI - ROM - Swelling - Joint deformation (JSW) - Urinary markers (U-NTX, uCTX-II, s-HA, s-hsCRP)	T0: pre-treatment T1: 24 weeks	Both groups significantly improve in VAS and JKOM after treatment. No differences in between-group comparison in all primary outcomes.
	Paker et al. [42]	- WOMAC (pain, stiffness, function) [a] - Lequesne Disease severity Index [a] - SF-36 [c]		T0: pre-treatment T1: post-treatment (1 month) T2: follow-up (3 months) T3: follow-up (6 months)	No improvement in SF-36 in both groups after treatment. Lequesne Index improves in both groups at 6 months compared to baseline (significantly better TENS group at T1). No significant differences between-group. WOMAC pain decreases within the first month and improvement continues during the follow-up period in both groups, without differences between groups.
	Atamaz et al. [43]	- WOMAC (pain, stiffness, function) [a] - VAS [b] - Pain (at night, at rest, on movement, on touch) [b] - SF-36 [c] - Measurement of ROM (extension / flexion)		T0: pre-treatment T1: post-treatment (1 month) T2: follow-up (3 months) T3: follow-up (6 months) T4: follow-up (9 months) T5: follow-up (12 months)	WOMAC, VAS, SF-36 significantly improve from the baseline for both groups, without between-group differences except for pain at rest and on touch at 1 month, 3 and 6 months follow-up in favour of PTA group.

		- Walking time 15 meters - Swelling			
	Huang et al. [44]	- Lequesne Disease severity Index [a] - VAS [b] - Measurement of ROM (extension / flexion) - Ambulation speed - Muscle peak torque (flexion / extension)		T0: pre-treatment T1: post-treatment (8 weeks) T2: follow-up (1 year)	Compared to baseline, VAS and Lequesne Index decrease in all groups after treatment, significantly lower in treated groups. Significant improvement in VAS score at 1 year follow-up in HA+Exercise+US and in Exercise+US groups (control group shows greater VAS score and Lequesne Index than baseline). Between-group differences in favour of HA+Exercise+US group at 1 year follow-up on pain and disability.
	Karatosun et al. [45]	- Hospital for Special Surgery (HSS) Knee Score [a]	- Pain during activity - Pain at rest - Pain during climbing stairs - Pain during transfer activity - Walking distance - Range of motion	T0: pre-treatment T1: 1 week T2: 2 weeks T3: 3 weeks (HA post-treatment) T4: 6 weeks (E.G. post-treatment) T5: follow-up (3 months) T6: follow-up (6 months) T7: follow-up (12 months) T8: follow-up (18 months)	HSS and all pain scores significantly improve at 18 months follow-up compared to baseline. No differences in between-group comparison.
	Bayramoğlu et al. [46]	- Lequesne Disease severity Index [a] - Isokinetic strength (flexor / extensor muscle strength 60° and 90° of knee flexion)		T0: pre-treatment T1: post-treatment (3 weeks) T2: follow-up (3 months)	Significant improvement at T1 and T2 evaluations in the Lequesne Index in all groups. No differences in between-group comparison.
Ankle	Karatosun et al. [47]	- American Orthopaedic Foot and Ankle Society (AOFAS) [a] - VAS (at rest and during activity) [b]		T0: pre-treatment T1: 1 week T2: 2 weeks T3: 3 weeks (HA post-treatment)	Significant improvement at 12 months compared to baseline in AOFAS and VAS in both groups. No differences in between-group comparison.

				T4: follow-up (2 months) T5: follow-up (3 months) T6: follow-up (6 months) T7: follow-up (12 months)	

VAS means Visual Analog Scale; ROM means Range of Motion; BMI means Body Mass Index; SF-36 means Short Form 36; JSW means Joint Space Width; WOMAC means Western Ontario and McMaster Universities Arthritis Index.

[a] outcome measures which assess disability, [b] outcome measures which evaluate pain, [c] outcome measures which assess quality of life.

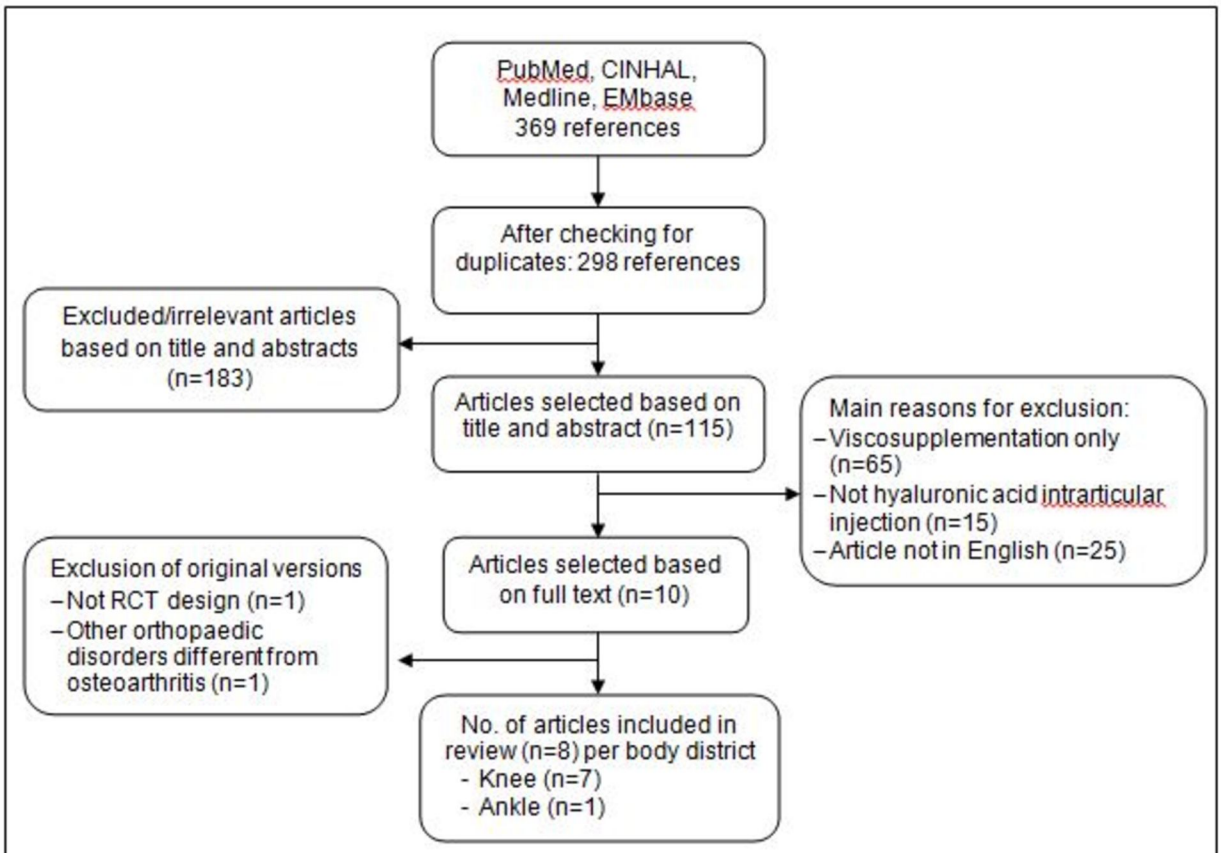

Figure 1. Flowchart search and selection.