*Review article*

# Effectiveness of ultrasound-guided hip injections on pain and functioning in patients with hip osteoarthritis: A systematic review

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## Abstract

**Background:** Osteoarthritis is the most common form of arthritis, causing pain, functional disability, and a reduction in terms of quality of life. Minimally invasive treatments like intra-articular hip injections are a therapeutic option and ultrasound guidance might improve the results of these injections.

**Objective:** To summarize the evidence about the effectiveness of ultrasound-guided hip injections in terms of pain and functioning in patients affected by hip osteoarthritis.

**Methods:** A systematic search of the literature was performed on three electronic databases: PubMed, Cochrane and PEDro, using a specific search strategy. We evaluated for inclusion all articles according to the following participants, intervention, comparison, and outcomes (PICO) model: P) Population: human patients affected by hip osteoarthritis; I) Intervention: intra-articular hip injections performed with a ultrasound-guidance; C) Comparator: sham therapy or every other conservative or oral, non-invasive, minimally invasive or surgical technique; O) Outcome measures: pain assessed by Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS); functional outcomes.

**Results:** At the end of the search, 43 articles were included in the review. Several drugs have been considered in the included studies: hyaluronic acid, platelet-rich plasma, corticosteroids, micro-fragmented adipose tissue, bone marrow concentrates, amniotic suspension allograft.

**Conclusion:** Ultrasound-guided injections of hyaluronic acid might be effective on pain relief and functioning in patients affected by hip osteoarthritis. Also, other rehabilitative infiltrative techniques (i.e., corticosteroids and platelet-rich plasma) showed a positive effect in the short-term period.

## Keywords

Hip osteoarthritis, hyaluronic acid, intra-articular injections, ultrasonography

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## Introduction

Osteoarthritis (OA) is the most common form of arthritis affecting approximately 250 millions of people. In this context, hip osteoarthritis is a disabling form of osteoarthritis that might cause pain, functional disability, and a reduction in terms of quality of life in the affected subjects.[1]

Several therapeutic approaches are possible for OA: pharmacological treatments (i.e., corticosteroids and hyaluronic acid, HA), non-pharmacological conservative measures (e.g., physical exercise, oxygen-ozone therapy, physical agent modalities), nutraceuticals, Symptomatic Slow-Acting

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Drugs (SYSADOA), and surgical interventions, depending on the stage, the comorbidities, and the characteristics of the patients.[2–8]

Several drugs have been injected in the hip for a resolution of the pain and functional improvements, and several guidelines have been drafted by different societies, following the increasing literature on the argument.[9,10] However, due to the increasing number of studies and to the different publication date, guidelines give no unique indications.

The HA is a naturally occurring polysaccharide that is abundantly found in several tissues. that has been recently demonstrated to have different characteristics, including the suppression of pro-inflammatory mediators, and pain relief, improving joint function, and potentially slowing hip OA onset.[3,4,11,12]

Ultrasound (US) guidance might improve the results in several musculoskeletal interventions, as it showed to reach a success rate of 90–100% for injective procedures.[9,10] It also does not expose patients to radiation. Furthermore, it should be noted that US guidance is also strongly recommended for injection into hip joints by American College of Rheumatology (ACR) guidelines for the management of osteoarthritis of the hip.[10] US-guided procedures might have an impact on the effects of the drugs injected in the hip in patients with hip OA, albeit to date, there is no scientific consensus on this topic.

Therefore, the aim of this systematic review was to summarize the evidence about the effectiveness of US-guided intra-articular (IA) hip injections in terms of pain and functioning in patients affected by hip OA.

## Materials and methods

### Search strategy

A systematic literature search was performed in three electronic databases: PubMed, Cochrane and PEDro, from their inception to February 28th 2024. The reference lists of all articles included in the review were also screened for further reports that met the inclusion criteria. A specific search strategy (further details in Supplementary Table 1) was used, which consisted of linking free-text terms and MeSH terms using various Boolean operators. The search was restricted to articles published in English language, with no restriction on publication date.

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement guidelines were followed for the reporting of this review. The protocol of this systematic review protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO): PROSPERO registration number CRD42023484956.

### Selection criteria

Among the retrieved studies, those that answered the following questions according to the Participants, Intervention, Comparison, and Outcomes (PICO) model were considered eligible for inclusion:

1. P) Population: human patients with hip osteoarthritis, so defined by the authors of the articles. No specific restrictions on the degree of osteoarthritis.
2. I) Intervention: intra-articular hip injections performed under US-guidance. No specific restrictions on the type of the drug administered or on the administration protocol. Articles were manually screened to confirm the US-guidance.
3. C) Comparator: no treatment, sham therapy or any other conservative or oral, non-invasive, minimally invasive or surgical technique.
4. O) Outcome measures: the effectiveness of the drug injections was assessed on the basis of pain and/or functional measurable outcomes. Any measurable pain scale was considered eligible (i.e., pain assessed by Visual Analogue Scale (VAS) or Numerical Rating Scale (NRS) or any other measurable scale). Any measurable scale or tool to assess functional outcome was considered eligible, such as the Harris Hip Score (HHS), Lequesne Index, 6-min walking test (6MWT), Oxford Hip Score (OHS), Western Ontario and McMaster Universities Arthritis Index (WOMAC). Data on any other functional outcome were also collected and reported. For a more comprehensive analysis, all follow-ups (at short-, medium- and long-term periods) were included. Adverse events related to the injection therapy were also collected, if available.

Articles were excluded if they did not meet our inclusion criteria, regarding methodology and main topics. Concerning the methodology of the evaluated studies, we did not include:

1. Reviews, systematic reviews, meta-analyses and umbrella reviews focusing on the same topic.
2. Protocols, comments on articles, surveys, letters to editor, editorials, case reports or incomplete studies.
3. Studies in languages other than English.

Concerning the main topics of the studies evaluated, we excluded all articles that:

1. Performed a multi-district intervention (for hip OA together with OA of other districts).
2. Used the ultrasound guidance together with anatomical, fluoroscopic, or other types of guidance. Articles that did not specify the guidance used were also excluded.

3. Did not report results on the effectiveness of treatments, although they did report data on the pharmacology or pathophysiology of IA hip injections.

### Data screening and extraction

Two different reviewers independently screened the list of reports for eligibility by title and abstract. Duplicates were excluded. The full text of the articles considered eligible by both reviewers was obtained and the articles were manually screened to assess the US-guidance for the IA injection therapy. If US-guidance was not specified, articles were not included in the review. In case of disagreement between the reviewers, the opinion of a third reviewer was taken into account.

The same reviewers independently performed the data extraction using a predesigned form. The data of interest were entered into an Excel spreadsheet. When available, the following characteristics of the included studies were collected: name of the first author, publication date, population characteristics, inclusion criteria, description of the US-guidance technique, type of interventions, outcomes of interest and follow-up time points.

## Results

At the end of the search, 569 studies were identified. A total of 90 articles were duplicates and were excluded. Thirty-six articles were not in English language and were excluded. Of the remaining 443 articles, after a first screening of title and abstract, 219 articles were selected for full text assessment. Ten articles could not be retrieved and were excluded from the search. The articles were then screened manually to check the inclusion criteria. Forty articles were excluded because they did not specify the US-guidance or reported fluoroscopic, anatomical or other different guides. Sixty-two articles were excluded because they were focused on a different topic. Sixty-six articles were excluded because they did not meet the methodological inclusion criteria (reviews, systematic reviews or other primary and secondary studies as specified in the "Selection Criteria" section).

Prior to submission, the electronic databases were re-searched with the same search strategy and a total of 23 new articles were identified. After an initial screening of titles and abstracts, three of these were found to be duplicates and were excluded; ten articles were excluded because they had a different topic; six articles did not meet the inclusion criteria because of the type of publication; two articles were not human studies. Two final studies were considered eligible for full text assessment and were then included. Thus, 43 articles were included in the review, as shown in the PRISMA flowchart in Figure 1.

The main data from the articles, including data on the population, interventions, comparisons, outcomes and a synthesis of the main findings are presented in Table 1. A qualitative synthesis of the outcomes evaluated is reported below, reporting the main findings for each of the different drugs provided.

### Hyaluronic acid

Thirty-one articles focused on the effectiveness of US-guided IA injections of HA in patients with hip OA.[15,19–21,23,25,26,28–31,33–43,45,46,48–54] Eleven of them have been published in the last five years, twenty-one in the last decade, with an increasing trend between the included studies. Specifically, seventeen articles[20,23,25,26,28,29,31,35,36,40,43,45,49,50,52–54] evaluated the effectiveness of HA injections in trials or observational studies without any comparisons (one of them[26] considered a specific formulation with the adjunct of chondroitin non-sulphate). One article[41] mainly focused on the safety of HA injections. Four articles compared the effectiveness of two different HA formulations.[21,30,33,37] Six articles performed comparisons with platelet-rich-plasma (PRP): in particular, three articles[34,38,42] considered two groups (one treated with HA, the second with PRP); two articles[15,39] considered three groups (one treated with HA injections, the second with PRP injections and the third PRP + HA injections); one article[24] compared PRP injections with PRP + HA injections and will be discussed in "PRP" section. One article[19] compared HA injections with a standard of care comprising Non-steroidal Anti-Inflammatory Drugs (NSAIDs), pain killers, (SYSADOA); another one[48] compared HA injections with mepivacaine. Two studies[46,51] performed multiple comparisons.

*Hyaluronic acid – pain assessment.* Twenty-six studies reported improvements in pain.[15,19–21,26,28–30,33–40,42,43,45,48–50,52–54] Pain was most frequently assessed with VAS scale.[15,19,20,26,28–30,33–38,40,42,43,45,48–54] Three studies[21,39,46] reported evaluation of pain at NRS scale. Two studies[46,51] could not find demonstrable improvements from the injection of a high molecular weight hyaluronan.

When performed without any comparison, HA injections have been judged as effective on pain relief.[20,26,28,31,35,36,40,45,49,50,52–54] Despite the majority of the included studies considered a short- or medium-term follow up, effectiveness on pain relief has been evaluated with retrospective observational studies up to 84 months.[36] Pain reduction has been reported since the first follow up periods, though a possible progression in the beneficial effects of the treatment during time has been supposed.[45] However, when considering a long-term period, Schiavi et al.[28] found that the effects on pain might be higher at one year. Despite similar results at 1-month follow-up, at one-year follow-up the effectiveness of this treatment on pain relief is different between primary OA

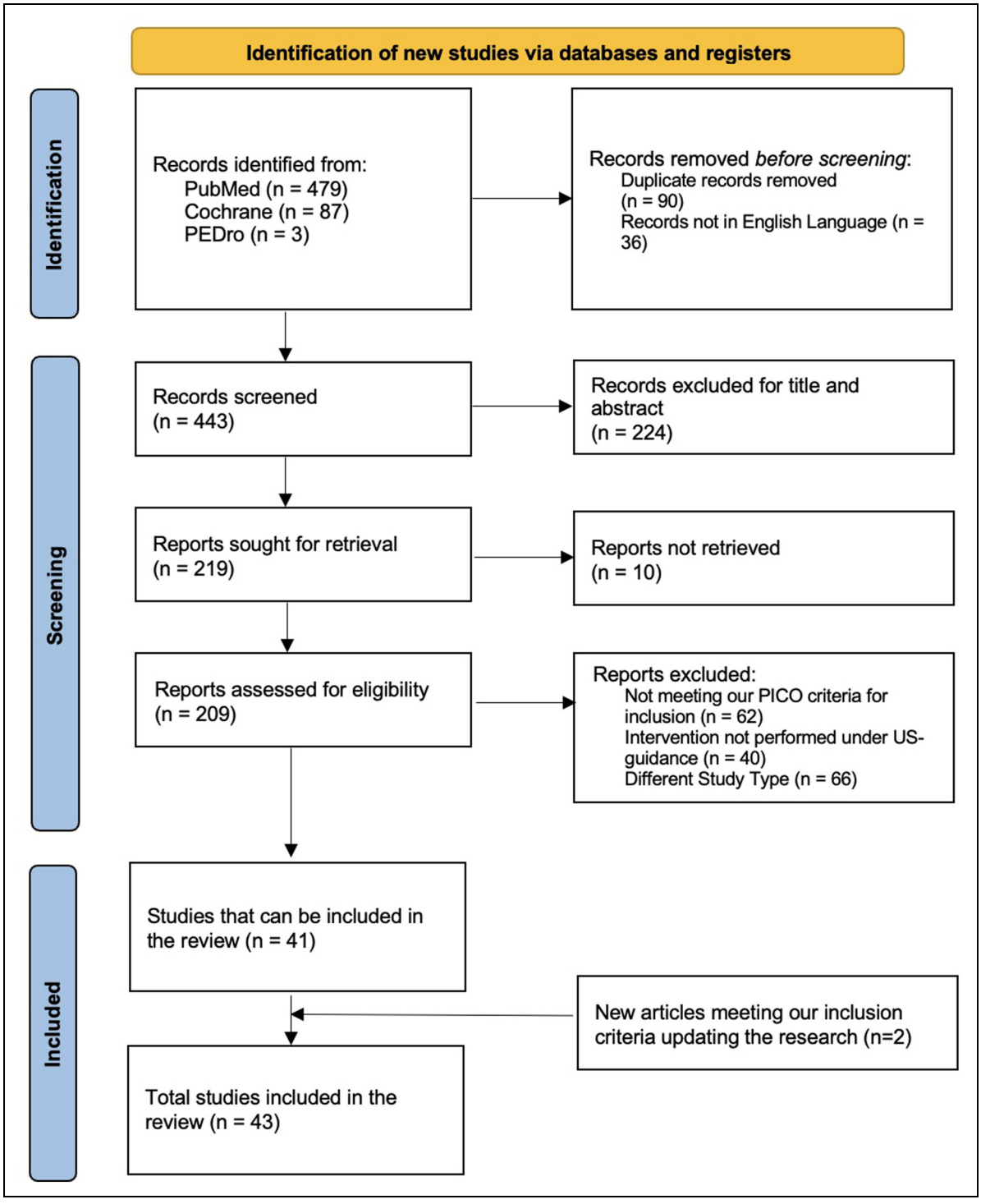


**Figure 1.** PRISMA flow diagram.

and OA related to juvenile idiopathic arthritis.[20] The combination of HA injections and exercise therapy has been considered effective on pain relief up to 105 days.[35] Papalia et al.[26] reported the effectiveness of a specific HA formulation with the adjunct of sodium chondroitin non-sulphate.

When compared to PRP injections, findings are not conclusive. Three clinical trials[34,38,42] directly compared the effectiveness on pain relief of HA injections with PRP injections. Two of them[34,42] reported similar results on VAS score for both treatments at 6- and 12-months follow up, with one[42] specifying that the best results were

**Table 1.** Synthesis of the PICO, study type and main results of the included studies.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| Natali et al. (2022)[13] | Retrospective Study | Inclusion: patients with hip pain for at least 4 months, resistant to NSAIDs; functional limitations; previous treatments failure. Participants: n = 55 | US-guidance not better specified. One (or more) injections of 4 mL of autologous MFAT. Four groups based on OHS: 1) Early OA (OHS 40–48); 2) Moderate (30–39); 3) Moderate to severe (20–29); Severe (0–19) | VAS, Radiological evaluation, based on K-L classification; new treatments needed. Follow up period: 35 ± 6 months. | VAS: no worsening Radiological follow up: no improvements; eight patients worsened. New treatments:28 patients did not undergo new treatments; 10 patients underwent a new injection; 17 underwent a total hip replacement. AEs: one patient reported a deep bruise resolved over a few months. Authors support the safety and efficacy in the long term of MFAT injections in patients with early to moderate OA (based on OHS). |
| Kose et al. (2022)[14] | Prospective RCT | Inclusion: unilateral symptomatic hip OA not responsive to conservative treatments. Hip pain score NRS ≥4; K-L II-III; no laboratory abnormalities. Participants: n = 60. | Group 1: US-guided Pericapsular nerve group (PENG) block. 30 participants. Group 2: US-guided IA injections if 13 mL bupivacaine 0,25% (11 mL) and dexamethasone 8 mg (2 mL). 30 participants. US-guidance for IA injections: probe parallel to the femoral neck in the anterior oblique sagittal plane. Needle in the joint capsule. | Primary outcome: NRS at 1 month. Secondary outcomes: NRS at day 1, week 1, week 8; WOMAC and HHS at 4 and 8 weeks; Patients' satisfaction and pain medication consumption at week 8. | NRS: Both groups achieved lower NRS scores than baseline at 1 week, 4 weeks and 8 weeks. IA injection group had significantly better results at 4 weeks and 8 weeks follow up. WOMAC score showed improvements in both groups at 8 week follow up. The effect size was larger in IA injections group than PENG group. HHS improved in both groups at each follow up period than baseline. IA injection group had greater results at week 4 and 8. Patients' satisfaction showed no differences between the two groups and pain medication consumption was reduced in both groups. |
| Nouri et al. (2022)[15] | RCT | Inclusion: patients aged 50–70; symptoms from more than 3 months; K-L grade 2–3. | US-guidance, "classic" approach. Two injections for all groups (2 weeks apart). | WOMAC total score; VAS, Lequesne questionnaire and patient satisfaction (Likert scale). | All outcomes improved in all groups compared to baseline at 2 and 6 months after. Effects of PRP and PRP + HA |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | Participants: n = 105 (35 HA, 35 PRP, 35 HA + PRP) | Three groups: 1) 5 ml of autologous PRP; 2) 2,5 ml of high molecular weight HA; 3) 5 ml of PRP + 2,5 ml of HA. | Evaluation at baseline, 2 months, 6 months. | were superior to HA alone in the long term. |
| Meadows et al. (2022)[16] | Pilot Study | Inclusion: age between 18 and 70, radiographic assessment of moderate hip OA (grade 1–2 at Tonnis grading), ≥ 2 at Tegner activity scale, body mass index ≤ 40, a 7-day average pain score ≥ 4. Participants: n = 9 | US-guidance not better specified. A total of 4 ml of Amniotic Suspension Allograft (ASA) (2 ml of ASA combined with 0.9% saline solution). | Patient reported outcomes: modified HHS, SF-12, VAS, Single Assessment Numerical Evaluation (SANE), 12-item International Hip Outcome Tool (iHOT-12) at 1 week, 2, 3, 6 and 12 months. Safety assessed at physical evaluation and laboratory exams at 2, 6, 12 months. | Authors reported improvements in pain and function at different patient-rated outcomes, by one-month post-treatment and maintained at 1 year follow up. Authors report no severe AE. |
| Paskins et al. (2022)[17] | RCT | Inclusion: age ≥ 40 years, moderate to severe pain for at least 6 weeks and occurring on most days in the past month. Participants: n = 199. Three groups: 1) BCT = 67; 2) BCT + US-triamcinolone-lidocaine = 66; BCT + US-lidocaine = 66 | US-guidance, detecting the anterior capsule. Three groups of treatment: 1) Best current treatment (BCT); 2) BCT + single US-guided triamcinolone + lidocaine injection; 3) BCT + US-guided lidocaine injection | Primary outcome: NRS scale (at 2 weeks, 2, 4, 6 months). Secondary outcomes: pain and function with WOMAC score, self-reported impressions and QoL (with SF-12 and EuroQoL Q-5D-5L), sleep disturbance, return to desired activities, participants' satisfaction and work status | BCT + US-triamcinolone-lidocaine led to greater pain reduction and functional improvements in the months period. Improvements in BCT + US-lidocaine group was lower than the double injection but was still more effective than BCT only. Effects of the three treatments were similar at 6 months follow up. Authors reported only known AE, including one death from subacute bacterial endocarditis, which was deemed possibly related to the treatment. |
| Mazzotta et al. (2022)[18] | Randomized Clinical Trial | Inclusion: age between 18 and 65; unilateral hip pain from at least 4 months (VAS ≥2); BMI <35; failure of conservative treatments. Participants: n = 100 (50 autologous, 50 umbilical cord PRP) | US-guidance: probe in line with femoral neck, needle at 45° reaching the head-neck passage. Group 1: 3 weekly IA injections of 5 mL autologous PRP; Group 2: 3 weekly IA injections of 5 mL umbilical cord PRP | HHS, WOMAC and VAS pain scores at baseline, 2, 6 and 12 months follow up. AEs were also evaluated. | No major adverse events in both treatments. Five participants in group 1 and 2 participants in group 2 reported mild adverse events. Both groups reported a non-statistically significant improvement from baseline to all follow-ups for the outcomes assessed. Statistically significant |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | | | improvements were found at 2 months follow up in group 2 for VAS and HHS, but was not confirmed at 6 and 12 months follow up. OA severity based on the Tonnis classification influenced the clinical outcomes for both groups. |
| Micu et al. (2022)[19] | Retrospective case-control study | Inclusion: Patients with hip OA not responding to conventional treatments (NSAIDs, pain killers, SYSADOAs) $\geq$ 3 months. Participants: n = 32 (case group = 15, control group = 17) | US-guidance not better specified. Case group: three weekly doses of US-guided intra-articular injections (USGIAI) of HA Control group: conventional treatments (NSAIDs, pain killers, SYSADOAs) | Primary outcomes: VAS score, WOMAC score at baseline, 3 months and 6 months. Secondary outcomes: NSAIDs intake | Authors reported improvements in pain and function at VAS and WOMAC scores at 3 and 6 months in case group. They also highlighted the reduction of NSAIDs intake in case group at 3 months. All these results were not seen in the control group. Authors support the use of HA injections, also reporting no drug-related or injection-dependant AE during the follow-up. |
| De Lucia et al. (2022)[20] | Observational cohort study | Inclusion. Two groups: 1) Primary OA: age $\geq$ 18 and $\leq$ 50; symptomatic hip OA according ACR criteria; radiological OA (grade 2–3 K-L) 6 months preceding baseline; hip pain $\geq$ 1 year. 2) Secondary OA: diagnosis of Juvenile Idiopathic Arthritis (JIA) according to ILAR classification. Participants: n = 40 (primary OA = 26, secondary OA = 14) | Anterior parasagittal projection, lateral to femoral vessels for US-guidance. Needle inserted with an antero-inferior approach. Hylan G-F 20 2 ml once a month for 3 consecutive months; 6-monthly IA injections for 2 years as maintenance treatment | VAS score, WOMAC score, use of NASIDs/analgesics at baseline and during a total 2-year follow-up (baseline, 1, 6, 12, 24 months) | Authors concluded that the effectiveness of intra-articular HA is similar in both two groups in the first phase in terms of VAS and WOMAC. After the first period, VAS and WOMAC scores begin to worsen in the JIA group, almost returning to basal values. |
| Scaturro et al. (2022)[21] | Randomized single-center, case-control clinical study | Inclusion: age $\geq$ 30; BMI $\geq$ 25 kg/m$^2$; hip OA (grade 2–3 at K-L scale); no previous infiltrative treatment in the previous 6 months; consent for participation. Participants: n = 80 (43 group A, 37 group B) | Anterior-parasagittal approach for US-guidance. Needle inserted with an antero-superior approach. Group1 (Treatment group): two injections of hybrid HA complexes (64 mg/2 ml) 2 weeks apart; | Primary outcomes: pain (NRS scale), function (6MWT); Lequesne index. Secondary outcomes: QoL (SF-12), percentage of fat and lean mass; analgesics taken, AE. | Pain and function improved at both follow up periods. The major improvements were seen at 3 months follow up. Group 1 had better improvements at 3 months follow up; differences between groups were lower at 6 months. No differences were |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | Group 2 (Control group): single medium-high molecular weight HA(1500 kDa) (60 mg/ 4 ml) | All outcomes were evaluated at baseline, 3 and 6 months. | found at secondary outcomes. A total of 8 patients experienced mild and transient AE (local pain and sensation of joint encumbrance) |
| Heidari et al. (2022)[22] | Prospective observational, intention-to-treat study | Inclusion: Hip OA as diagnosed at X-ray and/or MRI. Participants: n = 147 (57 MFAT, 90 MFAT + PRP) | US-guidance not better specified. Two groups: 1) 6 ml of MFAT; 2) 4 ml of MFAT + 2 ml of PRP | VAS, OHS administered at baseline, 3 months, 6 months and 1 year after treatment. | Hip pain and hip joint function were improved at 6–12 months follow up compared to baseline in both groups. No statistically differences were found between groups. |
| Long et al. (2021)[23] | Case series | Inclusion: > 18 yo; K-L grade 2–3. Participants: n = 87 | Antero-lateral approach under direct in-plane US guidance. Singe injection of HA | Modified HHS, at baseline and 6 weeks post injection. Number of AE. | Modified HHS improvement was statistically significant and greater than MCID. No severe/mild AE reported. |
| Palco et al. (2021)[24] | Retrospective, comparative study | Inclusion: mild-moderate hip OA (K-L grade 2–3); physiological hematocrit and coagulation profile; no response to NSAIDs. Participants: n = 52 (26 L-PRP, 26 PRP + HA) | In-plane US-guidance, needle near the anterolater surface of the femoral neck. Two groups: 1) PRP with high concentration of platelets and leukocites (L-PRP); 2) PRP + HA. Two injections for both groups (2 weeks apart) | HHS and VAS, administered at baseline, 3 months and 12 months evaluation. | Authors report analgesic effect, major at three months follow up, still present at 1 year follow up (L-PRP more than PRP + HA, with no statistical differences). No statistically significant improvements in hip function. Authors report no relevant AE. |
| Rando et al. (2021)[25] | Retrospective cohort study | Inclusion: male aged 40–65; tennis or cycling two times/week for no less than 10 years; hip pain for at least 3 months; grade 2–3 at K-L scale Participants: n = 30 (16 cyclists, 14 tennis players) | US-guidance not better specified. Cycles of two (24 mg/3 ml) Hymovis intra-articular injections (2 weeks apart), repeated every 3/4 months as required | Primary outcome: Heidelberg Sports Activity Score (HAS). Secondary outcomes: subjects' symptoms, activity limitations, participation restrictions and QoL by Copenhagen Hip and Groin Outcome Score (HAGOS); MRI Clinical signs at Hip OA MRI Scoring System (HOAMS). HAGOS at baseline, 4 months and 24 months; HOAMS at baseline and 24 months | Authors reported self-perceived clinical benefit of injections in both groups, peaking at 12 months. Improvements are also reported in single subscores of HAGOS score on a medium-term period (24 months). Authors report no severe AE. |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| Papalia et al. (2021)[26] | Pilot Study | Inclusion: age ≥ 40 years, moderate-severe pain (VAS > 40 mm), hip OA confirmed at X-ray within six months, no response to analgesics<br>Participants: n = 48 | Anterior parasagittal approach, lateral to femoral vessels. Needle inserted using an antero-superior approach.<br>Drug used: single injection of 3 ml of high molecular Sodium Hyaluronate 2,4% with sodium chondroitin non-sulphated 1,6%. | Primary outcome: safety assessment evaluating AE and adverse device events (ADE)<br>Secondary outcome: efficacy in terms of VAS score, Lequesne Index, analgesic treatments | None of the participants experienced severe AE and tolerability was rated as excellent or good by the majority of participants. Improvements on pain were rapid (at 7 days) and sustained up to 6 months. |
| Whitney et al. (2020)[27] | Case Series | Inclusion: age between 18 and 80. A ≤ 2 mm of joint space on AP rediograph, anterior groin pain, a minimum of 6/10 at NRS for pain with activity<br>Participants: n = 24 | US-guidance not better specified.<br>A single injection of 6–12 ml of Bone Marrow Concentrate (BMC) | Outcomes evaluated at baseline, 6 weeks, 3 and 6 months: NRS, modified HHS, Hip Outcome Score-ADL, SF-12, WOMAC, Mental Component Summary (MCS) | Authors concluded that BMC injection can improve subjective and function scores up to 6 months in patients with hip OA. Authors report no severe AE. |
| Schiavi et al. (2020)[28] | Cross-sectional Study | Inclusion: age ≥40 years, K-L ≤ 3 at X-ray, hip disease from at least 3 months, good/full hip mobility<br>Participants: n = 183 | US-guidance not better specified.<br>Intra-articular injections of high weight HA (2500 kDa) sodium hyaluronate (60 mg/4 ml). Seventy-two participants underwent a second injection, 30 subjects a third. | Outcomes analyzed were HHS and VAS. All outcomes were evaluated every year for four years | Authors conclude that US-guided intra-articular injections are safe and effective from the first administration, with the higher effect in the first year after injection. |
| Migliore et al. (2020)[29] | Retrospective cohort study | Inclusion: ≥ 40 years, BMI < 30, mild to moderate hip OA (K-L grade ≤ 3), VAS score between 40 to 80 mm | Anterosuperior approach: anterior parasagittal scanning, lateral to femoral vessels. Single intra-articular injection of HYMOVIS ONE | Outcomes on study were VAS score, Lequesne index, NSAIDs consumption. Outcomes were studied at baseline, 6 and 12 months. | Authors reported the safety and effectiveness of the treatment on the outcomes on study. |
| De Lucia et al. (2019)[30] | Retrospective, observational cohort study | Inclusion: symptomatic hip OA according to the ACR criteria; K-L grades II, III, and IV at X-Rays not older than 6 months before baseline; and hip pain for at least 1 year.<br>Participants: n = 142 (122 viscosupplementation, 20 controls only NSAIDS) | US-guidance: anterior parasagittal scan, lateral to femoral vessels. Needle inserted with an antero-inferior approach.<br>Group 1: HA 1500–3200 kDa 2 ml (Hyalubrix)<br>Group 2: Hylan G-F 20 2 ml (Synvisc) | VAS, WOMAC, NSAIDs consumption<br>Follow up time points at 1, 6, 12, 24 months. | VAS score significantly improved since the first months in patients treated with both hyaluronic acids. Statistical significance was reached at 12 months follow up. NSAIDs did not show any effect at any time point.<br>Both HAs improved WOMAC since the first month |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | Group 3: controls, only NSAIDs<br>Group 1 and 2 underwent three monthly injections and then one injection every 6 months for 2 years. | | post-treatment. A further significant variation was found at 12 months follow up. NSAIDs did not show any effect at any time point.<br>The overall effectiveness over 2 years follow up was similar between Group1 and Group 2.<br>A reduction in NSAIDs intake is reported in the two groups treated with HA injections. |
| Pogliacomi et al. (2018)[31] | Trial | Inclusion: age > 40 years, hip pain from at least 3 months, X-ray proof of a partially preserved joint space (K-L grade 1–2–3), good or full joint mobility.<br>Participants: n = 226 | US-guidance: antero-sagittal approach.<br>Single injection of 2,5% sodium hyaluronate (60 mg/4 mL, high molecular weight - 2500 kDa) | WOMAC and HHS, AEs.<br>Follow up periods: Baseline, 3, 6, 12 months. | Authors found statistically significant improvements of WOMAC and HHS scores at each follow-up period compared to baseline.<br>No AEs are reported.<br>Authors suggest US-guided IA injections as possible treatment in symptomatic hip OA. Patients with moderate hip OA might have the best results. |
| Darrow et al. (2018)[32] | Case series | Inclusion: hip OA. Inclusion criteria not better specified.<br>Participants: n = 4 patients | US-guidance: anterior approach.<br>Treatment: four injections of Bone Marrow Concentrates (BMC), 14 days apart from each other. | Pain at NRS scale, overall improvement (percentage scale) and joint function at "Lower extremity Functional Scale".<br>Follow up period: different for each patient (3.5 months average) | Resting and active pain decreased and a mean of 72,4% total overall improvement was found compared with baseline. Patients reported less difficult in performing activities of daily living (ADLs) |
| Clementi et al. (2017)[33] | RCT | Inclusions: hip OA; K-L grade 3; age > 40<br>Participants: n = 54 patients | US-guidance: Anterosuperior approach. Needle into the anterior capsule.<br>Group 1: Two injections of medium molecular weight HA (at baseline and 3–4 weeks)<br>Group 2: One injection of ultra-high molecular weight HA (Fermathron S) | Primary outcome: Lequesne Index, VAS, WOMAC<br>Follow up periods: 1, 3, 6, 12 months | A clinical improvement is reported in both groups starting from 1 month follow up. At 12 months follow up, all outcomes improved. No significant differences between the two groups were found in the clinical outcomes. |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| Doria et al. (2017)[34] | Prospective, double-blinded RCT | Inclusions: Symptomatic hip OA documented by X-ray; K-L grade 0–2; age 40–72<br>Participants: n = 80 (40 PRP + 40 HA) | US-guidance: anterosuperior, parasagittal approach, injection at the base of the femoral neck<br>Group 1: three weekly IA injections of PRP (5 ml per each injection)<br>Group 2: three weekly IA injections of Hyalubrix (15 mg/mL) | Primary outcomes: VAS, WOMAC subscale for pain intensity and domain of pain of HHS.<br>Secondary outcomes: function at HHS and WOMAC.<br>AEs.<br>Follow up period: 6–12 months | Pain and functional outcomes improved in both groups at both two follow up periods.<br>AEs: pain was more frequent in group 1.<br>Authors conclude that PRP did not offer better results compared with HA. |
| Mauro et al. (2017)[35] | Single site, open-label, investigator-initiated prospective study | Inclusion age between 35 and 85; K-L grade > 1 | US-guidance: Anterior approach<br>Three injections of Hyalubrix (at 45 days interval).<br>Every patient started physical activity (one week after the first injection) for 10 weeks (3 sessions/week) consisting in: proprioceptive rehabilitation of the lower limbs, gait and balance training | Pain: VAS reduction,<br>Disability: Range of motion (ROM), Lequesne Index, NSAIDs intake, safety.<br>Follow up period: baseline, 45, 90, 135 and 150 days. | Pain: a reduction is visible at all follow up times, both at rest and during activity.<br>Function: ROM improved during the study.<br>Lequesne Index decreased during the study.<br>NSAIDs intake reduced during the study.<br>Safety: well tolerated.<br>Authors support the use of Hyalubrix injections plus exercise therapy in patients for hip OA treatment. |
| Migliore et al. (2017)[36] | Prospective cohort study | Inclusions: age ≥ 18 years, symptomatic hip OA (from at least one year) diagnosed according to the ACR criteria, and up to 84 months of follow-up<br>Participants: n = 1022 | US-guidance: not better specified.<br>Single IA injection of 4 ml (60 mg) of HyalOne (Hyalubrix 60) every 6 months. (2 injections per year)<br>If clinically requested a maximum of 4 injections per year was possible. | VAS score, Laquesne index reduction, NSAIDs consumption reduction, Global patient assessment (GPA) reduction, Global medical assessment (GMA) reduction, Safety<br>Follow up period: every 3 months, up to 84 months. | All outcomes had a statistically significant improvement at all follow-up periods compared to baseline.<br>Age and body mass index (BMI) might influence the range of efficacy of the injections.<br>Safety: no systemic o severe local AEs were reported.<br>Authors support the efficacy, safety, and reproducibility of the treatments: a statistically significant improvement is achieved in the first six months, and the repetition of successive injections (at least 2 times/year) |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | | | keeps the level of benefit achieved without loss of efficacy. |
| Abate et al. (2017)[37] | Retrospective study | Inclusion: K-L grade II-IV; symptomatic 3 mo+<br>Participants: n = 40. | US guidance: antero-inferior approach, needle at the base of the femoral neck.<br>Group 1: One injection of 2 mL of a hybrid high + low molecular weight (MW) (3.2%, 32 mg high WM and 32 mg low MW, not cross-linked) + 1 more injection after 40 days<br>Group 2: One injection of 2,5 mL high MW HA (2%, 50 mg) not cross-linked, MW 800–1200 kDa) | VAS reduction, Disability reduction, HHS<br>Follow up periods: 3 and 6 months | All outcomes showed improvements at 3 and 6 months follow up.<br>Pain reduction and function improved more in the group treated with the hybrid high-low MW hyaluronic acid.<br>Authors conclude that the hybrid HA is effective and safe in mild-moderate hip OA. |
| Di Sante et al. (2016)[38] | Randomized controlled trial | Inclusion: Patients with hip OA according to ACR criteria. K-L grade II, III.<br>Participants: n = 43 (22 HA + 21 PRP) | US-guidance: probe aligned with the long axis of the femoral neck, needle into the anterior synovial recess between femoral head and neck.<br>Group 1: Na-HA (30 mg/ 2 ml of HA with molecular weight 1000 to 2900 kDa)<br>Group 2: PRP (3 ml) injections (3 injections, one per week) | Primary outcome: pain intensity at VAS score<br>Secondary outcomes: pain and function at WOMAC index.<br>Follow up time: baseline, 4 and 16 weeks (total) | PRP: VAS had significantly improvements at T1 (not at T2) compared to baseline. WOMAC pain subscore did not reach statistical significance.<br>HA: VAS and WOMAC subscores improvements reached statistical significance only at T2 compared to baseline.<br>Function assessed at WOMAC score significantly improve in T2 compared to baseline.<br>Authors suggest that PRP might have early effects on joint pain though might have HA long-term effects. |
| Dallari et al. (2016)[39] | Randomized controlled trial | Inclusion: hip OA, K-L grades 1 to 4; RX not more than 1 month before inclusion; age >18 and <65 years. VAS at baseline >20/100.<br>Participants: n = 111 | US-guidance: transducer aligned with femoral neck. Needle in the anterior capsular recess at the base of femoral neck.<br>All patients underwent 3 injections (one week apart) of:<br>Group 1: 5 mL autologous | VAS, WOMAC, HHS<br>Follow up period: baseline, 2, 6 and 12 months. | VAS: PRP had the lowest VAS scores at all follow ups.<br>WOMAC: PRP had the best results at 2 and 6 months follow up.<br>Authors conclude that PRP alone had better results than HA alone or PRP + HA. |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | PRP<br>Group 2: 2 mL of HA (Hyalubrix)<br>Group 3: 7 mL of PRP + HA (PRP: HA = 5:2 mL) | | |
| Migliore et al. (2014)[40] | Prospective Pilot Study | Inclusion: age ≥ 40, symptomatic hip OA according to ARA criteria for at least 6 months, K-L II or III. | Anterior parasagittal approach, lateral to the femoral vessels. Needle inserted via an anterosuperior approach into the anterior capsular recess.<br>Single US injection of with 2 syringes of Synolis V-A (a product made by a high concentration 20 mg/mL of 2 mDa HA with a high concentration of sorbitol (40 mg/mL) | Primary Endpoint:<br>- Lequesne index<br>Secondary Endpoints:<br>VAS, Health Assessment Questionnaire (HAQ), Global Patient Assessment (GPA), Global Medical Assessment (GMA), Consumption of Colecoxib, AEs.<br>Follow up periods: 3, 6, 9, 12 months. | Lequesne index mean scores significantly improved than baseline mean values at all follow up points.<br>VAS, HAQ, GPA, GMA significantly improved at all follow up points.<br>No systemic AEs were reported. Two patients reported a discomfort in the injection area for 1–3 days after the injection. |
| Migliore et al. (2013)[41] | Multicentric Retrospective Study | Inclusion: mono-/bilateral hip OA according to ARA criteria, K-L II, III or IV, refractory to therapy.<br>Participants: n = 1906. | Anterior parasagittal approach, lateral to femoral vessels. Needle at the anterior or capsular recess at the level of femoral head with an antero-superior approach.<br>One or two injections every six months (according to clinical conditions). One vial of 2 mL of HMW HA; two ampules of 2 mL with LMW or MMW HA. | Primary outcome: Adverse effects, recorded at baseline and at each control visit, performed every 3 months. | No systemic side effects or infections were observed. A transient heaviness or pain lasting 1–4 days was reported. Modest ecchymosis was reported by 6,3% of the injections. Four patients reported a rapid worsening with evidence of bone oedema at a subsequent MRI, with remission of symptoms after intra-muscular Clodronate injections. |
| Battaglia et al. (2013)[42] | Prospective Randomized Controlled Trial | Inclusion: Chronic unilateral hip pain lasting between 6–24 months. Previous injections more than 12 months from study enrolment.<br>Participants: n = 104 | Anterior approach, lateral to femoral vessels. Needle at the level of femoral head-neck junction.<br>Two treatment groups: 1) Autologous PRP (5 mL); 2) | Primary outcome: HHS at 12 months between the 2 groups. Other outcomes: VAS pain score. Adverse events were also collected. | Authors report that IA injections of PRP and HA both improve VAS and HHS in patients with Hip OA. The best results were registered at 1- and 3- months follow-up. Results up to 12- |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | A vial (30 mL/2 mg) of HMW HA (1500 kDa). Three consecutive (once every 3 weeks) IA injections per group. | | months follow-up were still better than baseline and similar between group, but were worse than at 1- and 3- months. Side effects: 1 superficial hematoma, no other major peri-/post-treatment complications. |
| Migliore et al. (2012)[43] | Retrospective, single cohort study with historical follow up | Inclusion: age ≥18 years; symptomatic OA according to ACR criteria from at least 1-year; 18 months follow up Participants: n = 176 | US guidance not better specified. Single IA injection of 4 mL of HyalOne (1500–2000 kDa). Injection repeatable every 6 months (up to 2 additional injections per year, with a maximum of 1 injection every 3 months). | Patients were divided in three groups by the concordance among six orthopaedists for total hip replacement eligibility. VAS pain score, Lequesne index, NSAIDs intake were also collected. Data on AEs were also collected. | Improvements in pain and functional scales were seen and authors concluded that IA US-guided injections of HA seem to delay total hip replacement. AEs: during the 48 months follow up no systemic or severe AEs were recorded. |
| Sánchez et al. (2012)[44] | Prospective case series study | Inclusion: hip OA based on ACR criteria, VAS >20/100 mm. Participants: n = 40 | US-guidance: anterior, parasagittal approach. Probe aligned with the long axis of the femoral neck. Needle inserted at the base of the femoral neck Treatment: Three injections of 8 cc of PRP. Interval between each injection: one or two weeks. | Primary outcome: pain at VAS and WOMAC subscale. Secondary outcomes: WOMAC, HHS, proportion of responders, AEs. Follow up periods: 6–7 weeks and 6 months. | Primary outcomes: both VAS and WOMAC subscore significantly improved in both follow up periods compared to baseline. Secondary outcomes: HHS and WOMAC significantly improved in both follow up periods compared to baseline. Twenty-three patients (57,5%) reported relevant reduction of pain. Authors defined AEs as negligible. |
| Migliore et al. (2011)[45] | Observational, cohort study | Inclusion: symptomatic hip OA (from at least one year) according to ACR criteria; age ≥ 40; K-L grade I, II, III, IV (at X-rays taken no more than 2 months before) Participants: n = 120 | US-guidance: probe scan with an anterior parasagittal approach, lateral to the femoral neck. Needle inserted via an anterosuperior approach. Single (60 mg/4 mL) injections of HyalOne, every 6 months, with a | Lequesne Index, VAS score, NSAIDs intake, AEs. Follow up periods: 3, 6, 9, 12, 15, 18 months. | Lequesne Index: Statistically significant improvements at all study points compared to baseline. VAS: significant VAS decrease was found at all follow up points compared to baseline. Statistically significant reduction at month 18 compared to the third month's VAS. |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | possible additional injection at 3 months. | | NSAIDs intake: a progressive reduction was found from the first injection to month 18.<br>No systemic or septic AEs were reported. |
| Atchia et al. (2011)[46] | Prospective RCT | Inclusion: unilateral hip OA, pain from more than one month, listed for total hip arthroplasty (THR) or warranting consideration for THR.<br>Participants: n = 77 | US-guidance: not better specified.<br>Group 1: standard care (non-injection group);<br>Group 2: single injection of normal saline (3 mL);<br>Group 3: single injection of non-animal stablished HA (durolane, 3 mL/60 mg);<br>Group 4: single injection of 40 mL of methylprednisolone acetate (depomedrone, 3 mL/ 120 mg) | Primary outcome: NRS for worst pain.<br>Secondary outcomes: WOMAC, patient global assessment and Outcome Measure in Rheumatoid Arthritis Clinical Trials (OMERTAC-OARSI), AEs.<br>Follow up periods: baseline, 1, 4, 8, 16 weeks. | Steroid group: all outcomes improved on study improved.<br>Magnitude and duration of effect was limited with a single injection.<br>High molecular weight HA: no demonstrable improvements.<br>Normal saline: Improvements at week 1 is in accordance with data published on placebo effect.<br>AEs: one femoral head collapse in non-injection group; one confirmed infection in HA group. |
| Micu et al. (2010)[47] | Trial | Inclusion: hip OA according to ACR criteria. Chronic hip pain, refractory to daily conventional therapy in the previous 2 months.<br>Participants: n = 61 (40 injection; 21 control) | US-guidance: anterior longitudinal approach.<br>Needle target: head-neck junction.<br>Treatment group: one injection of betamethasone 8 mg, lidocaine 1% 2 mL and 0,5 mL air.<br>Control group: patients who refused the CS injection (no treatment). | Walking pain VAS, Lequesne Index, US check for synovitis, AEs.<br>Follow up period: baseline, 1 month, 3 months. | Walking pain VAS: statistically significant reduction in treatment group, not in control group.<br>Lequesne Index: reduction in treatment group correlated to VAS reduction. In control group no significant changes at 3 months.<br>Synovitis: reduction found in treatment group, not in control group.<br>No side effects reported. |
| Migliore et al. (2009)[48] | Prospective RCT | Inclusion: age >40 years; ambulant without assistance; hip OA according to ACR criteria; baseline VAS $\geq$ 4 cm; hip pain for at least 1 month.<br>Participants: n = 42. | US-guidance: antero parasagittal approach, aligned with the long axis of the femoral neck. Needle in the anterior capsular recess.<br>Two treatment sessione (once per month) of:<br>Group 1: Hyalubrix: HA 4 mL (two syringes, 60 mg); | Primary outcome: Lequesne Index at 26 weeks.<br>Secondary outcomes: VAS, NSAIDs consumption, patient's global assessment, demographic correlation to response, AEs.<br>Follow up periods: baseline, 3, 6 months. | VAS: both groups improved at both follow up periods (HA group was statistically superior to mepivacaine).<br>NSAIDs intake and Global assessment: both group improved at both follow up (no statistical differences between groups). |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | Group 2: Mepivacaine 2%, manufactured with mepivacaine hydrochloride 20 mg/mL. | | AEs: two patients reported pain. No serious AEs reported. |
| Migliore et al. (2008)[49] | Prospective observational study | Inclusion: symptomatic hip OA diagnosed according to ACR criteria, K-L grade II, III, age $\geq$ 40, pain > 1 year.<br>Participants: n = 250. | US-guidance: anterior parasagittal approach, lateral to femoral vessels. Probe aligned with the long axis of the femur. Needle inserted via an anterosuperior approach. Single 2 mL injection of Hylan G-F 20 with optional injection at 3 months | Lequesne index, VAS, NSAIDs intake, patient global assessment, physician global assessment, AEs.<br>Follow up periods: baseline, 3, 6, 9, 12 months. | All outcome measures showed a statistically significant improvement at all follow up points.<br>No systemic AEs were reported. Mild or local pain was the most frequent AEs. |
| Migliore et al. (2006)[50] | Prospective study | Inclusion: symptomatic hip OA according to ACR criteria; K-L grade I, II, III; age $\geq$ 40; no previous injections.<br>Participants: n = 30. | US-guidance: anterior parasagittal approach, lateral to femoral vessels. Transducer aligned with the femoral neck. Needle inserted via an anterior-superior approach. One, two or three injections of 2 mL of Hylan G-F 20. | Lequesne Index, VAS, NSAIDs consumption, AEs.<br>Follow up periods: baseline, 2, 6 months. | Lequesne Index, VAS: a statistically significant reduction was found at 2 and 6 months compared to baseline.<br>NSAIDs consumption reduced by 47,7% at the 2$^{nd}$ month, by 69,9% at 6$^{th}$ month.<br>AEs: no systemic AEs were reported. |
| Qvistgaard (2006)[51] | Prospective randomized controlled trial | Inclusion: hip OA as defined by the ACR criteria; radiographic signs of OA; age $\geq$ 18 years; stable medication for at least 3 weeks before inclusion.<br>Participants: n = 101. | US-guidance: anterior approach, 8–10 cm under the inguinal ligament towards tha anterior/ inferior capsule.<br>Group 1: one injection with 1 mL (40 mg Depo-medrol) methylprednisolone + 2 sham injections;<br>Group 2: three injections of 2 mL HA (Hyalgan);<br>Group 3: three injections of 2 mL saline solution.<br>In all injections 1 mL of 1% lidocaine was added. Fourteen days interval between injections. | Primary outcome: VAS pain on walking.<br>Secondary outcomes: VAS pain at rest; Lequesne Index; WOMAC; patient global assessment, AEs.<br>Follow up periods: baseline, 14, 28, 90 days. | VAS on walking: all groups significantly improved pain. Corticosteroids statistically better than saline solution at 14 and 28 days. HA better results than saline at the first 2 follow up times (statistically significance only at 14 days).<br>Secondary outcomes: no significant effects related to the treatment.<br>AEs: no infections or severe AEs reported.<br>Corticosteroids had an effect size indicating a moderate clinical effect. Similar effects related to treatment with HA |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| | | | | | could not be shown, the effect size indicated a small clinical improvement. |
| Pourbagher et al. (2005)[52] | Prospective study | Inclusion: unilateral hip OA; Hartofilakidis type I or two according to clinical and radiological findings. | US guidance: parasagittal approach. Needle inserted lateral to the femoral vessels. Injection of 1 mL of nonionic contrast material (to correctly locate the needle), followed by the injection of sodium hyaluronate. Treatment: Three injections (one per week) of 2 mL of low molecular weight sodium hyaluronate. | VAS, WOMAC and AEs. Follow up periods: baseline, 2, 4, 6 months after the third injection. | Statistically significant improvements were found both at all follow up points. AEs: no complications at the injection site and no hip or systemic infections. |
| Migliore et al. (2005)[53] | Pilot study | Inclusion: age $\geq$ 40; symptomatic hip OA according to ACR criteria; K-L grade II-III (X-Rays taken not earlier than 2 months before enrolment); no previous injections. Participants: n = 12. | US-guidance: anterior parasagittal approach, lateral to femoral vessels. Probe aligned with the long axis of the femoral neck. Needle inserted via an anterosuperior approach into the anterior capsular recess. Treatment: one injection of 2 mL Hylan G-F 20. | VAS, Lequesne Index, NSAIDs consumption, AEs. Follow up periods: baseline, 1, 3 months after injection. | Lequesne Index: 8 patients out of 12 had sustained improvements for more than 3 months (statistically significant results). VAS: a statistically significant improvement was found at each follow up time point compared to baseline. NSAIDs consumption: reduced by 65,6% at 1 month follow up, by 56,1% at 3 months follow up No systemic AEs reported. |

(continued)

**Table 1.** Continued.

| Study | Type of study | Participants | Intervention | Outcome | Results |
|---|---|---|---|---|---|
| Caglar-Yagci et al. (2005)[54] | Pilot study | Inclusion: hip OA diagnosis according to ACR criteria, K-L grade II- III, Lequesne Index ≥ 8, NSAIDs consumption for > 1 month, no previous surgery for hip OA. Participants: n = 14. | US-guidance: transducer parallel to the femoral neck. One cm proximal to the great trochanter a needle was inserted vertically by a lateral approach. Three weekly injections of 2 mL Hylan G-F | VAS, Lequesne Index, 15-meter walking time, patient's satisfaction, NSAIDs consumption, AEs. Follow up periods: baseline, 30, 90 days post-injection. | VAS, Lequesne Index, 15-meter walking time: statistically significant improvements at the follow up points compared to baseline. All patients need NSAIDs consumption before the injection; six at 30th day, two at 90th day after injection. Patients' satisfaction: 5 completely satisfied, 5 almost completely, 4 moderately satisfied. AEs: no severe complications were reported. |

6MVT: Six-Minute-Walking-Test; ACR: American College of Rheumatology; AE: Adverse Events; HA: Hyaluronic Acid; HHS: Harris Hip Score; IA: Intra-articular; K-L: Kellgren-Lawrence; MCID: Minimal Clinically Important Difference; MFAT: Micro-fragmented adipose tissue; NRS: Numerical Rating Scale; NSAIDs: Non-Steroideal Anti-Inflammatory Drugs; OA: Osteoarthritis; OHS: Oxford hip score; PRP: Platelet-rich plasma; QoL: Quality of Life; RCT: Randomized Clinical Trial; SF-12: Short Form – 12; US: ultrasound; SYSADOAs: Symptomatic Slow Acting Drugs in Osteoarthritis); WOMAC: Western Ontarioand McMaster Universities Arthritis Index; AP: Antero-Posterior.

reached at 3 months. The other one[38] considered a 16-weeks follow up, reporting better results for PRP at 4-week follow up, with statistically significant better results for HA at 16-weeks follow up. Two randomized controlled studies[15,39] considered three treatment groups: one treated with HA injections; the second treated with PRP injections; the third treated with PRP + HA injections. In these two studies, all three groups achieved pain relief with the best results at 6-months follow up, with Nouri et al.[15] reporting the lower improvements for HA group and Dallari et al.[39] reporting the best results for PRP group.

Three trials[21,33,37] and one observational study[30] compared the effectiveness of two different HA formulations. One trial[33] did not report differences between ultra-high molecular weight HA and medium weight HA injections up to 12-months follow up. These results are supported by the observational study,[30] which did not find differences between high and medium weight HA. Hybrid HA (combining low and high molecular weight HA) could be more effective than high molecular weight HA on patients with hip OA,[37] especially on obese/overweight patients.[21]

HA injections have been reported as more effective than NSAIDs and SYSADOAs,[19] and local anaesthetic (mepivacaine) injections[48] at 3- and 6-months follow up.

Two studies[46,51] performed multiple comparisons on pain and functional outcomes between three groups, treated one with saline solution, the second with HA, the third with methylprednisolone acetate. Atchia et al.[46] considered a fourth non-injective group. Both authors report the effectiveness of corticosteroid (CS) injections in a short-term follow-up period (one[46] reported a partial reduction in the effectiveness over 8 weeks): Qvistgaard et al.[51] reported that HA and CS injections were both superior to saline solution (CS reached a statistical significance and had a higher effect size than HA, which did not reach statistical significance and showed a smaller effect size). Atchia et al.[46] reported no demonstrable improvements from the injection of a high molecular weight hyaluronan, and a response from the injection of saline solution in accordance with a placebo effect.

*Hyaluronic acid – functional evaluation.* Twenty-eight studies reported improvements in the functional evaluation.[15,19–21,23,26,28–31,33–40,42,43,45,48–54] Two studies[46,51] reported no improvements in functional outcomes.

The majority of the included studies administered functional questionnaires or scales: six studies administered the Harris Hip scale (HHS),[23,28,31,34,37,42] twelve studies used the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[15,19,20,30,31,33,34,38,39,46,51,52]; fifteen studies used the Lequesne scale[15,21,26,29,33,35,36,43,45,48–51,53,54]; other scales (such as Heidelberg Sports Activity Scale – HSAS, Global Patient Assessment – GPA) were also singularly used.[21,25,40,46,48]

When injective treatment has been performed without any other comparison or when compared two different HA formulations, similar results have been depicted for functional outcomes such as for pain relief. Long et al.[23] reported that the functional improvements were greater than the MCID stated for hip OA. In addition, Rando et al.[25] supported the effectiveness of these injective treatments in sportsmen. One study[35] evaluated functional improvements by considering range of motion changes and reported the effectiveness of HA injections associated with physical activity.

When compared with PRP injections, three studies[34,39,42] reported similar results for HA and PRP on functional scales at 6- and 12-months follow up, one[38] reported amelioration only at 16 week follow up only for HA injections (not for PRP injections), another one[15] reported that HA had the lower improvements at 6 months compared with PRP and PRP + HA.

Two studies support the superiority of HA injections to NSAIDs and SYSADOAs[19] and to local anaesthetic (mepivacaine) injections[48] on functional outcomes at 3- and 6-months follow up.

Two studies[46,51] performed multiple comparisons between CS, HA and saline solution on pain and functional outcomes. Conclusions by the authors on functional outcomes are similar to these reported in "pain assessment" section.

*Hyaluronic acid – adverse events.* Adverse events (AE) were analysed in twenty-two articles.[19,21,23,25,26,29,31,34,38,40–43,45,46,48,50–54] One study by Migliore et al.[41] specifically focused on the adverse effects: on a collected sample of 1906 patients (4002 injections), they did not report any systemic side effect or infection, with no differences observed when comparing the side effects rate of different HA products. Local adverse events were frequently reported. Scaturro et al.[21] reported mild and transient pain and sensation of joint encumbrance as the most frequent AE. Superficial hematomas are also possible.[42] When compared with PRP and PRP + HA injections,[15] pain was lower in the group treated with only HA. Papalia et al.[26] reported one serious adverse event (atrial fibrillation and cardiac failure) not related to the injective treatment, when HA was injected in association with sodium chondroitin non-sulphated.

## Platelet-Rich plasma – PRP

Nine articles focused on the use of US-guided PRP injections in patients with hip OA.[15,18,22,24,34,38,39,42,44] Specifically, one study[44] evaluated the effectiveness of PRP injections with no comparisons. Two studies[18,24] compared two different types of PRP: one[18] compared autologous PRP versus umbilical cord PRP; the other[24] compared plasma with a high concentration of platelets and leukocytes (L-PRP) with PRP plus HA. Three articles[34,38,42] compared two groups: one treated with PRP injections, the other one treated with HA injections with different formulations. Two articles[15,39] split their patients in 3 groups: one treated with PRP injections alone, the second one with HA injections and the third with PRP together with HA injections. Heidari et al.[22] used PRP only in association with micro-fragmented adipose tissue (MFAT), compared to MFAT injections only and will be discussed in "MFAT" section.

*PRP – pain assessment.* Pain reduction has been evaluated in all included studies.[15,18,22,24,34,38,39,42,44] Visual Analogue Scale (VAS) was used to assess pain in all studies, with 4 studies[24,34,38] specifically assessing pain also with subscales of other questionnaires: WOMAC pain subscale[34,38,44] or Harris Hip Score (HHS) pain subscale.[24,34] Several of the included studies reported a reduction in VAS score (or in the other sub scores) with pain improvements,[15,22,24,34.39,42,44] with Di Sante et al.[38] reporting statistically significant results on pain only at a very early follow up (4 weeks post-injection) and one article[18] reporting pain improvements only in specific follow ups.

When performed without any comparison,[44] beneficial effects on pain were reported since 6 weeks post-injection (up to 6 months post-injection).

When two different PRP formulations (autologous vs umbilical cord PRP) were compared, Mazzotta et al.[18] reported improvements in both pain and functional outcomes that did not reach a statistical significance in both autologous and umbilical cord PRP. Only VAS and HHS at 2 months follow up in the second group reached a statistical significance. Palco et al.[24] reported improvements in VAS score in both L-PRP and PRP + HA groups, showing the best results at 3 months follow-up, with L-PRP superiority at 1-year follow up.

When compared to HA injections, findings are not conclusive. Three clinical trials[34,38,42] directly compared the effectiveness on pain relief of HA injections with PRP injections; two randomized controlled studies[15,39] considered three treatment groups and the results of all these articles have been synthesized in "HA - Pain Assessment" section.

*PRP – functional assessment.* A functional evaluation was performed as secondary outcome in all included studies.[15,18,22,24,34,38,39,42,44] Function was assessed with different scales: in particular, WOMAC,[15,18,34,38,39,44] HHS,[18,24,34,39,42,44] OHS,[22] Lequesne.[15] Benefits on function are not clear, since six articles reported functional improvements,[15,22,34,39,42,44] though all/several follow up points could not demonstrate statistically significant improvements in three articles.[18,24,38]

When performed without any comparison,[44] improvements in functional evaluation (at WOMAC and HHS) were found at 6-week and 6-months follow up.

When two different PRP formulations (autologous vs umbilical cord PRP) were compared,[18] authors found a statistically significant improvement only at HHS at 2 months follow-up for the umbilical cord PRP group (despite a 12-month evaluation of WOMAC and HHS scores). Palco et al.[24] could not find statistically significant improvements in both plasma rich in platelets and leukocytes and PRP + HA injections.

When directly compared to HA injections,[34,38,42] two studies[34,42] reported similar results on functional outcomes up to 12 months for both PRP and HA injections, with the best results at 3 months;[42] one study[38] did not report any effectiveness by PRP injections on WOMAC disability subscale during a 16-week period. When three groups were considered (PRP injections in one group, HA in a second group, PRP + HA in a third group),[15,39] Nouri et al.[15] reported improvements in functional outcomes in all three treated groups, with PRP and combined injections of PRP + HA showing a long-term superiority than HA injections alone; Dallari et al.[39] reported statistically significant amelioration in WOMAC score up to 6 months in the group treated with PRP, though HHS amelioration did not reach a significance; WOMAC results at 12 months follow up lost the significance.

*PRP – adverse events.* None of the studies collecting data on the topic reported major adverse effects.[18,24,34,42] The most reported adverse effects were sporadic and transient pain, burning or swelling sensation in the injection site. Battaglia et al.[42] reported the possibility of hematomas due to the abnormal course of the vessels. In a study conducted by Doria et al.[34] pain was more frequent in patients treated with PRP injections than in patients treated with HA injections.

## Corticosteroids

Five studies included in our review focused on the effectiveness of US-guided intraarticular steroid injections in patients with hip OA.[14,17,46,47,51] Specifically, one article[47] compared the effectiveness of an injective treatment with betamethasone plus lidocaine to a non-intervention group (patients who refused the injective therapy). One article[14] compared the effectiveness of dexamethasone plus bupivacaine injections with a pericapsular nerve group block – PENG. One article[17] divided their patients in 3 treatment groups, with one undergoing best current treatment – BCT (educational indication plus advice for physiotherapy exercises), the second undergoing BCT plus lidocaine and the third BCT plus triamcinolone and lidocaine. Two studies[46,51] performed multiple comparisons on pain and functional outcomes between three groups: one treated with saline solution, the second with HA, the third with methylprednisolone acetate. Atchia et al.[46] considered a fourth non-injective group.

*Corticosteroids – pain assessment.* Effects on pain were evaluated in five articles.[14,17,46,47,51] Pain was evaluated at VAS[47,51] and NRS.[14,17,46] When compared to a non-treatment group[47] CS injections reported statistically significant improvements in pain up to three months. Corticosteroid injections[17] improved pain up to 6 months also when compared to a non-injective group or to a group injected with local anaesthetic, with a statistically significant difference found between the CS injective group and the non-injective group. Both CS injections and PENG[14] were effective on pain reduction, with corticosteroids having statistically significant higher improvements in terms of pain amelioration at 4 weeks compared to PENG. Qvistgaard et al.[51] reported that CS injections were effective on pain reduction during the 3 months after the treatment; these results were superior to comparisons only in the first month post-treatment. Atchia et al.[46] evaluated pain at NRS, reporting statistically significant results in patients treated with corticosteroids up to 8 week follow up, when compared to the other treatments.

*Corticosteroids – functional assessment.* Function was evaluated in four articles.[14,17,46,47] When compared to a non-treatment group,[47] Lequesne algo-functional index was significantly ameliorated in corticosteroids group, with no improvements in the untreated group. Paskins et al.[17] evaluated function at WOMAC score and other different scales (SF-12): higher improvements were found in patients treated with best current treatment plus triamcinolone, with better results at earlier follow up points. Corticosteroids injections and PENG[14] were both effective for functional improvements, with patients treated with corticosteroids experiencing better results. Atchia et al.[46] reported WOMAC results, reporting statistically significant functional amelioration up to 8-week post treatment in CS group.

*Corticosteroids – adverse effects.* Data on adverse events were specifically collected in two studies.[17,51] One did not report any severe adverse event.[51] Paskins et al.[17] reported that in the group treated with triamcinolone plus lidocaine, by 66 patients included, four reported whitening of the skin, four reported hot flushes, and a participant with a bioprosthetic aortic valve died from subacute bacterial endocarditis four months after receiving the injective treatment (authors and the trial committee could not exclude a possible link with the treatment).

### Micro-fragmented adipose tissue – MFAT

Two studies[13,22] analysed the effectiveness of US-guided intraarticular MFAT injections in patients with hip OA. In particular, Natali et al.[13] evaluated the safety and the effectiveness of autologous MFAT injections in patients with early to moderate hip OA. They reported that 28 out of 55 patients did not need any further injective treatment in a follow-up period of 1 year. They also reported the presence of deep bruise near the harvest site as adverse event.

Heidari et al.[22] evaluated the effectiveness of MFAT or MFAT + PRP injections in patients with hip OA: the outcomes evaluated were VAS changes and improvements in Oxford hip score – OHS - at 12 months follow up. They reported improvements in OHS score up to 1 year, with the adjunct of PRP to MFAT injection not ameliorating the functional outcomes. Concerning VAS changes, they reported VAS improvements in both treatment groups, with similar results. They also reported no severe complications or thromboembolic events.

### Bone marrow concentrate – BMC

One pilot study[27] and one case series[32] evaluated the effectiveness of US-guided intraarticular injections of BMC in patients with hip OA. Whitney et al.[27] found that a single BMC injection can improve both pain and functional scores up to 6 months in patients with hip OA with no severe adverse effects (two patients out of 18 underwent total hip arthroplasty in the 6-months follow up period).

Darrow et al.[32] synthesized their experience of 4 cases, reporting that 4 BMC injections decrease resting and active pain, improving hip functioning overall, also hypothesizing that BMC injections could stimulate hip cartilage repair.

### Amniotic suspension allograft – ASA

Meadows et al.[16] evaluated in a pilot study the effectiveness of intra-articular ASA injection in patients with symptomatic hip OA. They reported at 1 year follow up improvements in pain (VAS score for maximal pain) and functional outcomes (modified HHS, international hip outcome tool – iHOT, single assessment numerical evaluation – SANE), with iHOT and modified HHS improvements exceeding the minimal clinically important difference.

## Discussion

Intra-articular injections of the hip have been studied in the recent years, with different guidelines leading to different considerations.[55] In recent decades, a large number of studies have been conducted to evaluate the effectiveness of HA, PRP, corticosteroids, Non-Steroidal anti-inflammatory Drugs (NSAIDs), and also saline solution (SS), Mesenchymal Stem Cells (MSCs) and other novel drugs.[56]

The use of an ultrasound guidance has recently been advocated and the common procedure consists of placing the probe (usually a convex probe) to visualize the femoral head-neck junction in the long axis, inserting an appropriate length needle via an anterior or lateral approach, avoiding the femoral vessels. However, there is no standardization of the procedure (see Table 1 for a summary of the injection procedures). This should be taken into account as different approaches may affect the pain during and immediately after the procedure, which was reported as a common adverse effect. In addition, in several cases the authors of the studies did not adequately describe the injection technique, reporting only that the treatment was performed under ultrasound guidance.

Hyaluronic acid is by far the drug with the highest number of included studies. This high number of studies underlines the focus on this drug in the recent years. HA belongs to the family of glycosaminoglycans (GAGs). It is a common component of cartilage, connective tissues, and synovial fluid. It is composed by a long chain of repeating units of disaccharides, the length of which influences the molecular weight of HA.[57] The molecular weight of HA influences the rheological and structural properties of this drug, which has been studied in several articles.[58] The results of this study show that there is also no agreement on which type of HA should be injected. Different formulations have been studied (a summary of these formulations has been reported in Table 2).

ACR guidelines[10] strongly recommend against the use of HA injections in hip osteoarthritis, due to the lack of benefit; OARSI guidelines[9] do not recommend HA injections, as strong evidence does not support its benefits on function, stiffness, and pain.[59]

Nevertheless, several of the included studies support the beneficial effects of HA injections on pain relief.[15,19–21,26,28–30,33–40,42,43,45,48–50,52–54] However, there are some critical issues to consider: eighteen articles assessing the effectiveness of HA have been conducted without a comparison, focusing only on the effectiveness of this treatment over time, which may have increased the risk of bias of the included articles. In addition, ten studies[29,36,40,41,43–50,53] have been conducted by a specific group of researchers, with trained operators. This could have had an impact on the results, as highly specialised centres with a long experience in the use of US-guided IA injections may be able to select patients better and achieve better results with a lower rate of adverse effects.

Several articles[19,20,25,29,30,35,36,43,45,48–50,53,54] evaluated the reduction in NSAIDs consumption as an indirect measure of effectiveness. This should be considered, as NSAIDs are known to increase the risk of gastrointestinal or cardiovascular adverse events,[60] and the reduction in

**Table 2.** Different formulations of Hyaluronic Acid used for injection.

| Study | Hyaluronic Acid formulations used |
|---|---|
| Nouri et al. (2022)[15] | Viscor 50 mg/2,5 mL (2500–3000 kDa, Nitka, Iran): A vial of 2,5 mL containing 50 mg linear fermentation source high molecular weight HA was used alone in one group; immediately afterwards a 5 mL injection of PRP in another group |
| Micu et al. (2022)[19] | Hyalgan, Fidia Farmaceutici, Italy |
| De Lucia (2022)[20] | Hylan G-F 20, 2 mL |
| Scaturro et al. (2022)[21] | Treatment group: Sinovial HL by IBSA, a viscosupplementation made up of hybrid complexes produced by a thermal process from a combination of high and low molecular weight hyaluronans, without 1,4-butanediol-dyglycidyl ether or other chemicals. High concentration (64 mg in 2 mL), low viscosity and durability comparable to a weakly cross-linked gel.<br>Control group: medium-high molecular weight hyaluronic acid (60 mg/ 4 mL) (1500–2000 kDa) |
| Long et al. (2021)[23] | Durolane (Bioventus Global LL, Netherlands), 3 mL preparation: non-animal derived, stablished HA (NASHA) with molecular weight of > 3000 kilodaltons |
| Rando et al. (2021)[25] | Hymovis (HYADD-4, Fidia Farmaceutici, Italy), a hexadecyl derivative of HA. Two consecutive injections of Hymovis (24 mg/3 mL) |
| Papalia et al. (2021)[26] | Hybrid cooperative complex of sodium hyaluronate and sodium chondroitin. Injections of a 3 mL syringe containing sodium hyaluronate 2,4% (72 mg of sodium hyaluronate) and sodium chondroitin non-sulphated 1,6% (48 mg of sodium chondroitin) of biotechnical origin. |
| Schiavi et al. (2020)[28] | High weight HA (2500 kDa). Injections (60 mg/ 4 mL) of 2,5% sodium hyaluronate |
| Migliore et al. (2020)[29] | Single (32 mg/ 4 mL) injection of Hymovis One (HYADD 4-G, Fidia Farmaceutici, Italy): a HA alkyl-derivative, non-chemically cross-linked-based formulation, whose reological properties are derived from the presence of hexadecyl hydrophobic chains. |
| De Lucia et al. (2019)[30] | Group 1: HA 1500–3200 kDa 2 mL (Hyalubrix, Fidia Farmaceutici, Italy) a sterile non-pyrigenic sodium hyaluronate salt (15 mg/mL sodium salt) with medium molecular weight (1500–3200 kDa).<br>Group 2: Hylan G-F 20 2 mL (Synvisc, Sanofi, France) a sterile non-pyrogenic solution of cross-linked hyaluronans ranging between 4000 and 6000 kDa termed hylans (hylan A soluble + hylan B insoluble gel). |
| Pogliacomi et al. (2018)[31] | Single injection of 2,5% sodium hyaluronate (60 mg/4 mL, high molecular weight - 2500 kDa) |
| Clementi et al. (2017)[33] | Group 1: Two injections (60 mg/4 mL per injection) of medium molecular weight hyaluronic acid (Hyalubrix 60), a linear hyaluronic acid (1,3–3,6 MDa) obtained by bacterial fermentation from a fraction of high molecular weight HA.<br>Group 2: One injection (69 mg/ 3 mL) of ultra-high molecular weight hyaluronic acid (Fermathron S), made up by several folded chains of sodium hyaluronate molecules cross-linked to one another with ether links. Its molecular weight is not quantificable. |
| Doria et al. (2017)[34] | Hyalubrix 15 mg/mL (Fidia Farmaceutici, Italy) |
| Migliore et al. (2017)[36] | HyalOne (Hyalubrix 60 Italian Brand), a hyaluronic acid sodium salt produced by bacterial fermentation from a fraction of high molecular weight (1500–2000 kDa). Single injection of 4 mL (60 mg) into the affected hip |
| Mauro et al. (2017)[35] | Hyalubrix, a sterile, non-pyrogenic, viscoelastic solution produced by bacterial fermentation from a fraction of high molecular weight hyaluronic acid. |
| Abate et al. (2016)[37] | Group 1: 2 mL hyaluronic acid (3,2%, 32 mg high molecular weight and 32 mg low molecular weight, not cross-linked)<br>Group 2: 2,5 mL high molecular weight hyaluronic acid (2%, 50 mg; not cross-linked, molecular weight 800–1200 kDa) |
| Di Sante et al. (2016)[38] | Sodium Hyaluronate (30 mg/2 mL of HA with molecular weight of 1000–2900 kDa). |
| Dallari et al. (2016)[39] | Group 1: PRP<br>Group 2: 2 mL of HA (Hyalubrix)<br>Group 3: 7 mL of PRP + HA (PRP:HA = 5:2 mL) |
| Migliore et al. (2014)[40] | SynolisV-A (ANTI-OX-VS) a compound for viscosupplementation produced from high concentration (20 mg/ml) of a 2mDa HA of non-animal origin, combined with high concentration of sorbitol (40 mg/ml) |
| Migliore et al. (2013)[41] | One ampule containing 2 mL of high molecular weight hyaluronic acid (e.g., Synovisc and Euflexxa) or two 2 mL ampules containing low or medium molecular weight hyaluronic acid (e.g., Hyalgan, Hyalubrix, Jointex, Ortoial). The characteristics of each viscosupplemantation are reported in Table 2 of the article. |
| Battaglia et al. (2013)[42] | A vial (30 mg/ 2 mL) of Hyalubrix, (Fidia Famaceutici, Italy), a high molecular weight (1500 kDa) hyaluronic acid). |
| Migliore et al. (2012)[43] | Single injection of 4 mL (60 mg) of HyalOne (Hyalubrix 60 Italian brand name), a steril, non-pyrogenic solution with hyaluronic acid sodium salt, produced by fermentation from a fraction of high molecular weight with a range of 1500–2000kDa |

(continued)

**Table 2.** Continued.

| Study | Hyaluronic Acid formulations used |
|---|---|
| Migliore et al. (2011)[45] | Injections of 4 mL of HyalOne (Hyalubrix 60 Italian brand name), a hyaluronic acid sodium salt, obtained by bacterial fermentation from a fraction of high molecular weight (1500–2000 kDa) |
| Atchia et al. (2010)[46] | Group 2: non-animal stablished hyaluronic acid (durolane, 3 mL/60 mg licensed for single injection) |
| Migliore et al. (2009)[48] | Hyalubrix, HA 4 mL (two syringes, 60 mg), a nonpyrogenic viscoelastic solution of hyaluronic acid sodium salt obtained by bacterial fermentation from a fraction of high molecular weight (>1500 kDa). |
| Migliore et al. (2008)[49] | Single or multiple injections of syringes of 2 mL of Hylan G-F 20 (Synvisc, Genzyme Corporation, USA), a high molecular weight (6 MDa), a cross-linked derivative hyaluronic acid. |
| Migliore et al. (2006)[50] | Single or multiple (up to three, one month apart from each other) of 2 mL of Hylan G-F 20 (an average molecular weight, cross-linked hyaluronan derivative of 6 million Da) |
| Qvistgaard et al. (2006)[51] | Group 1: three injections of methylprednisolone<br>Group 2: three injections of 2 mL HA (Hyalgan)<br>Group 3: three injections of saline solution |
| Pourbagher et al. (2005)[52] | Three injections (one per week) of 2 mL of low molecular weight sodium hyaluronate (Ostenil, TRB Chemedica Ltd, England). |
| Migliore et al. (2005)[53] | One injection of 2 mL of Hylan G-F 20 (Synvisc, Genzyme Biosurgery, USA), an average molecular weight, cross-linked hyaluronan derivative (6 million Da) |
| Caglar-Yagci et al. (2004)[54] | Injections of 2 mL of Hylan G-F |

NSAIDs consumption might be also useful in directly or indirectly reducing healthcare costs.[61] One study by Migliore et al.[43] also suggested that the treatment with US-guided IA injections of HA could delay total hip arthroplasty. This should be taken into consideration, as it could be considered and indirect benefit of this treatment.

Another important point to consider is the age of the patients treated, which may predict differences in the outcomes:[36] in particular, several articles[16,18,20,23,27,36,39,43,51] included patients older than 18 years. The inclusion of a large number of young patients could bias the results of the analysis, as young patients have a better prognosis. However, only one study[20] reported a median age of above 40 years and this was due to the inclusion of participants with juvenile idiopathic arthritis. The presence of certain pathologies, such as juvenile idiopathic arthritis, might also affect the long-term effectiveness of the IA injections of HA.[20]

Autologous PRP is the processed liquid fraction of autologous peripheral blood with highly concentrated platelets, cytokines and grow factors.[62] To produce PRP, a venous blood sample is collected and centrifugated, obtaining millilitres (mL) of a blood compound with an increased platelet count per mL (from 100% to 600% compared to whole blood values).[63] Several studies have shown that US-guided injections of PRP influence inflammation, angiogenesis, and tissue repair, with several biochemical effects.[64,65]

The ACR guidelines[10] strongly recommend against the use of PRP, and other guidelines do not support the use of PRP intra-articular injections due to the lack of standardization of the technique.[55] In fact, different protocols result in blood-derived samples with distinctive properties and bioformulations[64] What emerges from our review is that in most cases the authors of the included studies adequately describe the method used to obtain the final product (a summary of the injected bioformulations can be seen in Table 3), but there is no standardization of the technique, as it has been suggested by the guidelines.

The studies included support the effectiveness of this treatment for pain[15,24,34,39,42,44] at different follow-ups, although two studies[18,38] assessed its effectiveness only at a specific follow-up[38] and only for specific formulations.[18] Moreover, two trials found improvements in pain but not in functional outcomes,[24,38] and another reported improvements only in certain functional outcomes.[39] The authors of the included studies do not agree on the duration of the beneficial effects of PRP, with two studies reporting a reduction in the effectiveness at one year.[39,42] As reported in the "Results" section, when the articles compared the effectiveness of HA versus PRP injections, the results were inconclusive and did not uniformly support the superiority of one treatment over the other.

Corticosteroids are used to treat peripheral joint disease. Methylprednisolone and triamcinolone have been the most studied CS, due to their low water solubility.[7] The CS formulations have been synthesised in Table 4. Although corticosteroids were one of the first drugs to be used for injection, only a small number of studies have been conducted under US-guidance. Corticosteroid injections are strongly recommended by ACR guidelines[10] but are not recommended by OARSI guidelines.[9]

The included studies all had a short- or medium-term follow-up: in particular, one considered a period of 6 months,[15] though the others had a shorter follow-up period. All included articles supported the short-term

**Table 3.** Platelet-rich Plasma (PRP) formulations used.

| Study | PRP formulations used |
|---|---|
| Nouri et al. (2022)[15] | 35 ml of venous blood sample. 5 ml of acid citrate dextrose solution containing 2.20-g sodium citrate dehydrate, 0.73-g sodium citrate anhydrousand 2.45-g dextrose monohydrate was added. 1 ml is sent to laboratory for testing.<br>Compound divided into 4 test-tubes and centrifuged at 1600 rpm (400 g) for 12 min. Plasma containing PLT was aspirated and divided again into 2 test-tubes to be centrifuged again at 3500 rpm (1900 g) for 7 min. Platelet poor plasma is removed. A sample of PRP is sent to laboratory for platelet and white blood cells counting. 2 test-tubes with 3 ml of PRP with a platelet count at least 4 times higher than whole blood values are approved for injection. Before injections, PRP test-tubes were shaken with a standard tube shaker. The storage of the samples was normal room light and temperature for the whole process. |
| Mazzotta et al. (2022)[18] | Group 1: autologous-PRP (A-PRP)150 mL of autologous blood was taken and centrifuged at 1800 rpm for 15 min. Plasma and buffy coat were transferred to a second bag and red blood cells were removed. This bag was centrifuged at 3500 rpm for 10 min. The supernatant was removed and 20 mL of PRP produced. PRP was divided into three quotes of 5 mL each and stored at −30° C. One more sample was used for testing Before the injection, the samples were thawed in a dry thermostat at 37 °C for 30 min and transferred from the transfusion unit to the patient room using a thermal bag and avoiding exposure to light. In order to activate platelets 10% of Ca-gluconate was added to PRP concentrate.<br>Group 2: umbilical cord PRP (C -PRP): The umbilical vein was punctured with a sterile system (Cord blood collection set, JMS, Singapore) to obtain cord blood (CB), while the placenta was still in utero. CB was put in a bag containing 20 mL citrate-phosphate-dextrose and was collected from spontaneous term births (with no complications) and from Caesarean births (≥37 week of pregnancy). Units were tested to establish the absence of infective diseases. CB units were processed within 48 h. CB pools consisting of 4–5 homogroup units (final weight of 300–410 g) were prepared: each bag is made to flow using a sterile connection into a single collection bag of the separation kit (Fresenius, Terumo). A Heraeus Cryofuge 6000i was used to centrifuge CB pools at 799 g for 4 min. Compomat G4 automatic separators (Fresenius Kabi company) were used to separate PRP from concentrated red blood cells and leukocytes. Doing this, PRP is pushed into the second bag of the kit, after the filtration of the leukocytes. PRP was centrifuged again at 3845 g for 6 min and the excess of plasma was transferred into a sterile connected bag by manual crushing of the first one. PRP was divided in 5 mL quotes and frozen at −80 °C. 10% calcium gluconate was added to activate C-PRP. For each preparation microbiological tests were performed (Bact Alert Biomerieux). All steps were performed by Emilia Romagna Cord Blood Bank (ERCB) according to the Foundation for the accreditation of cellular therapy (FACT) guidelines and the Italian regulation.<br>Both PRP were produced via a manual method without the use of a commercial kit. |
| Heidari et al. (2022)[22] | *Endoret®(prgf®)* Technology (BTI System IV/V; BTI Biotechnology Institute, Vitoria, Spain) used to prepare PRP. Two 9 mL samples of venous blood were taken using tubes containing 3.8% (*w*/*v*) sodium citrate. Each tube was centrifuged at room temperature for 8 min at 580 G (1902 rpm) and the plasma located above the buffy coat was taken, obtaining 4 mL of PRP per patient (2 mL from each tube). Calcium chloride (10% *w*/*v*) was added to activate PRP. The compound was enriched in platelets and reduced in leucocytes. |
| Palco et al. (2021)[24] | 8 mL of venous blood was taken for each preparation.<br>Group 1: L-PRP was obtained with RegenKit®-THT-3/RegenCell® (Regen Lab SA, En Budron B2, 1052 Mont-sur-Lausanne, Switzerland), centrifuging blood for 9 min at 3400 rpm/1500 *g*. Injected 5 ml of comound. On average, L-PRP contained 3600–4000 leukocytes/$mm^3$ and 340.000–370.000 platelets/$mm^3$.<br>Group 2: PRP + HA was obtained with Cellular Matrix A-CP-HA, centrifuging blood for 5 min at 3400 rpm/1500 *g*. Injected 3 ml of PRP and 2 ml of HA.<br>On average, PRP + HA contained 800–1000 leukocytes/$mm^3$ and 290.000–310.000 platelets/$mm^3$ |
| Doria et al. (2017)[34] | 150 mL of venous blood were taken and centrifuged two times: first for 6 min at 1480 rpm in order to separate erythrocytes and then for 15 min at 3400 rpm to concentrate platelets. 20 mL of PRP was produced and divided into four smaller units of 5 mL. Three of these were stored at −30 C and one was sent to the laboratory to analize platelet concentration and for quality test. |
| Di Sante et al. (2016)[38] | 8 ml of venous blood was taken and then centrifuged two times for 9 min at 3100 rpm to obtain 4 ml of PRP. The test-tubes were turned upside down multiple times to distribute the mixture evenly, then the content was aspirated.<br>One PRP sample chosen at random was sent to the laboratory for platelet count and bacteriological test. The mean increase of platelets/ml in the PRP without leukocytes was 100–150% in comparisong with whole blood. Regen Kit® was used to prepare PRP. |
| Dallari et al. (2016)[39] | Before starting the PRP production procedure the limit of acceptable hemoglobin for both sexes was set at |

(continued)

**Table 3.** Continued.

| Study | PRP formulations used |
|---|---|
| | 11 mg/dL, and the platelet count was 150,000/mm3 in excess.<br>150 ml of peripheral blood were sampled for patients with unilateral degenerative disease and 300 for those who had a bilateral one. Samples were centrifuged first at 140 rpm for 6 min to separate erythrocytes from platelets and then again at 3400 rpm for 15 min to concentrate them. PRP was then divided into smaller units of 5 ml each: 4 total units for patients with unilateral disease and 7 total units if they had a bilateral disease. Units were stored at -30 C and thawed putting them for 30 min in a thermostat at 37 C. 1 ml of calcium chloride (10%) was used as platelet activator.<br>Samples chosen at random from at least 25% of patients from each group were sent to the laboratory to be analyzed for proinflammatory and anti-inflammatory markers (IL-6, TNFa, IL-1RA, IL-10, TIMP1, TGF-b1, VEGF) using immunosorbent assay kits (Boster Immunoleader) using an Imark microplate reader (Bio-Rad Laboratories). |
| Sanchez et al. (2012)[44] | 40 ml of peripheral venous blood was taken and put into 9 ml tubes containing a solution 3.8% sodium citrate. This was centrifuged for 8 min at 580 g at room temperature (PRGF, Vitoria, Spain). 2 ml of plasma fraction and the buffy coat were collected in a sterile tube under vertical air flow conditions. Before the injection of PRP (8 ml each), calcium chloride (10%) was added at a final concentration of 22.8 mM |

**Table 4.** Corticosteroids (CSs) formulations used.

| Study | Corticosteroids formulations used |
|---|---|
| Kose et al. (2022)[14] | One injection comprising 13 mL of bupivacaine 0,25% (11 mL) and dexamethasone 8 mg (2 mL) |
| Paskins et al. (2022)[17] | One injection of Triamcinolone acetonide 40 mg/mL sterile, aqueous solution and 4 mL 1% lidocaine hydrocloride |
| Atchia et al. (2011)[46] | Injections of 5 mL of methylprednisolone acetate (depomedrone, 3 mL/120 mg) |
| Micu et al. (2010)[47] | Bethametasone 8 mg, lidocaine 1% 2 mg and 0,5 mL air |
| Qvistgaard et al. (2006)[51] | One injection with 1 mL of methylprednisolone (40 mg Depomedrol) followed by 2 sham injections |

**Table 5.** Micro-fragmented adipose tissue (MFAT) formulations used.

| Study | MFAT formulations used |
|---|---|
| Natali et al. (2022)[13] | Lipogems® ortho kit (Lipogems International SpA, Milan, Italy) was used to obtain MFAT. Patients were injected with 4 mL of autologous MFAT. |
| Heidari et al. (2022)[22] | Klein sterile solution (saline, Lignocaine, and epinephrine) was injected into the subcutaneous fat. A 13 G blunt cannula connected to a Vaclock 20 mL syringe was used to harvest adipose tissue. Lipogems® system was used to inject and process the lipoaspirate. The size of clusters of adipose tissue were mechanically fragmented and reduced from 1–3.5 mm to 0.2–0.8 mm agitating the stainless steel ball of the device, which is prefilled with saline. Saline was used to wash out impurities from the chamber and the resulting product was filtered through a 500 micron filter. |

effectiveness of CS injections, which is known in the literature, as CS injections are the only one supported by several international guidelines.[55,59] Synovitis is considered to be a major cause of pain in hip OA; corticosteroids may be effective against pain as they act as local anti-inflammatory drugs, downregulating the expression of several pro-inflammatory proteins.[7] However, concerns about the adverse effects associated with the treatment have been raised over the years, with a recent article assessing the risk of rapidly progressive idiopathic osteoarthritis showing a rate of 0,6%.[66]

Other treatments have been also experimented in five studies. Two pilot studies, two observational studies and one case series were conducted to evaluate the effectiveness of MFAT, BMC and ASA. Micro-fragmented adipose tissue (MFAT)[13,22] is derived from adipose tissue processing and is rich in stem cells, growth factors, and release factors (e.g., cytokines and chemokines).[13] Bone marrow concentrates[27,32] consist of a harvest of bone marrow that is centrifuged and processed with other substances to produce an injectable compound. Different protocols can be used to produce BMC. Amniotic Suspension Allograft

**Table 6.** Bone Marrow Concentrates (BMC) formulations used.

| Study | BMC formulations used |
|---|---|
| Whitney et al. (2020)[27] | To harvest the bone marrow aspirate (BMA) the patients were placed in the prone position and the harvest site were sterilized. Bony landmarks of the posterior superior iliac crest (PSIC) were located and local anesthetics were injected. An 11 G ported aspiration needle was inserted until reaching the posterior superior iliac crest (PSIC) and inserted into the medullary cavity using a sterirely drapped aspiration drill (Arrow OnControl). 1 mL of a citrate dextrose solution formula A (ACD-A) was injected into the site as anticoagulant. 60–120 mL of BMA was collected in 30 mL syringes containing 5 mL of ACD-A. Every 5–10 mL of BMA the trocar needle was rotated. BMA samples were sent to a laboratory for processing, where were divived into 50 mL conical tubes. 0.8 mL was transferred into a microcentrifuge tube for analysis. An IEC Centra-CL2 benchtop centrifuge (ThermoIEC) was used to centrifuge BMA at 2400 rpm for 10 min. The buffy coat leukocyte layer and a small volume of the platelet-poor plasma layer were extracted and combined into one 50 mL conical tube to be centrifuged at 3400 rpm for 6 min. The white blood cells layer and a small volume of plasma were extracted and transferred to a conical tube. 6–12 mL of BMC was produced and 0.8 mL was used for analysis. Activation and storing products were not used.<br>All samples were processed and reinjected in a liquid state at room temperature within 4 h of the BMA harvest. A CellDyn Ruby (multiparameter automated hematology analyzer, Abbott Diagnostic Division) was used to count platelets, red blood cells, white blood cells, neutrophils, lymphocytes, monocytes, eosinophils and basophils from all BMA samples and BMC final products. A BMA kit (Arrow OnControl; Teleflex) was used for the preparation of every BMA sample. |
| Darrow et al. (2018)[32] | Patients were placed in the prone position and the skin above the posterior superior iliac spine (PSIS) were sterilized with 10% Povidone-Iodine and then with 4% chlorhexidine gluconate (Hibiclens). 10 ml of 1% lidocaine and 2 ml of 8.4% sodium bicarbonate was injected to anesthetize the patient. A fenestrated 11 G, 4 in needle was used to penetrate the PSIS and a 20 ml syringe containing 1 ml of heparin (1000 USP units/mL) was used to extract 19 ml of BMC. The compound was centrifuged and the portion without visible red cells was isolated. 5 ml of centrifuged BMC was injected with 1 ml of ropivacaine. |

**Table 7.** Amniotic suspension allograft (ASA) formulations used.

| Study | Amniotic suspension allograft formulations used |
|---|---|
| Meadows et al. (2022)[16] | Amniotic tissue components were obtained during cesarean section and then frozen. Thawed before using. 4 ml of solution injected (2 ml of ASA and with 2 ml of 0.9% saline). |

(ASA)[16] is a cryogenically preserved compound made of micronized human amniotic membrane and amniotic fluid cells that come from the same donor. The specific formulations of these drugs have been synthesized at Tables 5, 6 and 7. Despite the promising results of all studies suggesting the effectiveness and the safety of these treatments, no RCTs of these drugs could be found. Regarding comparisons, only one[22] included a control group (treated with PRP + MFAT), but it did not consider any other conservative/more invasive treatment. The authors aim for further trials to evaluate the effectiveness of these drugs.

### *Study limitations*

We are aware that this systematic review is not free from limitations. Firstly, the lack of studies comparing US-guided IA hip injections with non-US-guided IA hip injections. Secondly, the lack of a risk of bias assessment. Thirdly, a meta-analysis could not be performed because of the lack of standardised consensus on the US-guided injections, with large differences between the included studies. Specifically, there is a high heterogeneity of hyaluronic acids used in our paper and the high heterogeneity in terms of timing (different time-points of the evaluations after the injections).

## Conclusions

Taken together, the results of this systematic review showed that most of the included studies reported the effectiveness of US-guided HA injections on pain relief and function in patients with hip OA. However, studies evaluating other rehabilitative infiltrative techniques (i.e., corticosteroids and PRP) have also reported positive effects in the short-term period, although the comparisons between the drugs are not conclusive. A small number of observational studies or pilot studies also supported the use of other novel drugs (MFAT, BMC, ASA). Albeit there is still a lack of studies comparing US-guided with not US-guided IA hip injections, we retain that it is mandatory for physicians to perform their infiltrative clinical practice both in the present and in the next future using the US. More research is needed to better define the role of the novel drugs.

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## Statements and declarations

### Data availability statement

The dataset is available from the corresponding author on request.

### Author contributions

Study Design and Conceptualisation: AB, FA, and AdS; Methodology: AB and AdS; Investigation: FA, NF, and FDB; Data analysis: AB, FA, and AdS; Writing - Original Draft Preparation: AB, FA, and NF; Writing—Review and Editing: MP and AdS; Visualisation: MDB, MM, and AA; Supervision: AB and AdS. All authors have read and agreed to the published version of the manuscript.

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## Supplemental material

Supplemental material for this article is available online.

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