IN BRIEF

The Role of Intraarticular Injections of Hyaluronic Acid and Platelet Rich Plasma for the Treatment of Articular Pain in Knee Osteoarthritis

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Abstract

The purpose of this in brief article was to determine the current role of intraarticular injections of hyaluronic acid (HA) and platelet-rich plasma (PRP) for the treatment of painful KOA. It has been reported that the average duration of effectiveness (pain relief) of one injection of extended-release HA is around one year. Kellgren-Lawrence grade (I-II versus III-IV), male gender, and older age are associated with a longer duration of effectiveness. Cartilage degeneration might be improved with a higher number of injections of HA. Intraarticular injections of HA alleviate pain, function, and diminish non-steroidal anti-inflammatory drugs (NSAIDs) consumption. In addition, several studies have indicated that the combination of HA and PRP is more effective than HA alone. Finally, other studies seemed to demonstrate that PRP was more effective than HA.

Level of evidence: III

Keywords: Efficacy, Hyaluronic acid, Intraarticular injections, Knee osteoarthritis, Platelet-rich plasma

Introduction

According to Langworthy et al (2024) osteoarthritis (OA) is a widespread disease that affects almost 528 million people worldwide, including 23% of the global population aged ⩾40, and is defined by advancing damage to articular cartilage, which frequenly causes severe pain, stiffness, and reduced mobility for affected individuals. Pain related to OA is an obstacle to keeping physical activity and a principal source of disability, accounting for 2.4% of all years lived with disability globally, diminishing the capability to work in 66% of USA individuals with OA and increasing absenteeism in 21% of USA individuals with OA. The joint most frequently affected in OA is the knee, which is involved in approximately 60%-85% of all OA cases.[1]

According to Kang et al, in 2019, the global age-standardized frequency percentage of knee osteoarthritis (KOA) escalated by 7.5% compared with 1990, and the age-standardized frequency percentage escalated by approximately 6.2%; the age-standardized YLDs (years of healthy life lost due to disability) percentage escalated by around 7.8%. The age-standardized YLDs frequency escalated by approximately 7.8%.[2]

The objective of this in brief article was to determine the current role of intraarticular injections of hyaluronic acid (HA) and platelet-rich plasma (PRP) for the treatment of painful knee osteoarthritis (KOA).

Main body

On October 1, 2024, a literature search was performed in PubMed using two sets of keywords: "Hyaluronic acid AND knee osteoarthritis" (932 articles were found) and "PRP AND knee osteoarthritis" (650 articles were found). Of the 1582 articles found in total, 27 were selected as being of greater interest with respect to the title of this article (the role of intraarticular injections of HA and PRP for the treatment of articular pain in KOA).

Efficacy of hyaluronic acid (HA)

Many articles have been published that have assessed the efficacy of intraarticular injections of HA in patients with KOA, the results of which are shown in [Table 1].[3-13] EUROVISCO (European Viscosupplementation Consensus Group) gave a series of recommendations that are shown in [Table 2].[13]

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Efficacy of platelet-rich plasma (PRP)

In 2019 Mousaei Ghasroldasht et al evaluated the effects of PRP injection on KOA, based on gene expression analysis. They analyzed 30 individuals who experienced intraarticular injections of PRP. It was found that PRP injections eased the pain, diminished the stiffness, and improve quality of life through the promotion of *IGF-1* (Insulin-like growth factor 1) expression. The individuals were assessed before and 1 month after the injection, utilizing questionnaires of Knee injury and osteoarthritis outcome scores (KOOS) and the intermittent and constant pain score (ICOAP).[14]

Prost et al evidenced the efficacy of a standardized high or very high-volume injection of very pure PRP in individuals with KOA, including those with a severe grade.[15] in a systematic review positive results were observed. Besides, it was stated that improved clinical results from PRP injections for KOA may be related to a greater platelet dose.[16] Zhuang et al recommended three injections of PRP in individuals with KOA of Kellgren-Lawrence (K-L) grade I-III.[17]

Table 1. Efficacy of intraarticular injections of hyaluronic acid (HA) on pain relief in painful knee osteoarthritis (KOA-3-13)

AUTHORS [REFERENCE]	YEAR	TYPE OF STUDY GRADE OF RECOMMENDATION LEVEL OF EVIDENCE	RESULTS
Hummer et al [3]	2020	Network meta-analysis. A 1a	These authors assessed the effectiveness of viscosupplementation in KOA based on molecular weight. It was found that in contrast to low molecular weight viscosupplementation (less than 750 kDa), high molecular weight viscosupplementation (≥6000 kDa) surpassed the minimal clinically important improvement threshold for pain alleviation.
Bahrami et al [4]	2020	Single-blinded randomized controlled trial. B 2a	At 2 and 6 months follow-up a single high molecular weight HA injection was as efficacious as three weekly injections of low molecular weight HA.
Ikuta et al [5]	2021	These authors analyzed 60 individuals with KOA by magnetic resonance imaging (MRI) T1ρ mapping to assess whether long-run repeated administration of viscosupplementation impacted cartilage degeneration. C 4	Body mass index and the number of intraarticular injections of HA were substantial factors causing change in the zone of degeneration with no relation to age, gender, and Kellgren-Lawrence grade.
Park et al [6]	2021	Double-blind, randomized, phase III clinical trial. to evaluate the effectiveness and safety of a single injection of divinyl sulfone cross-linked hyaluronate (YYD302) compared with a single injection of 1,4-0 diglycidyl ether cross-linked hyaluronate (Synovian) in 184 individuals with KOA (Kellgren-Lawrence grade I-III). They were randomized to one of two study cohorts (YYD302 cohorts, 95 individuals; Synovian cohort, 87 individuals). B 2a	No substantial difference was found between the two cohorts after 36 weeks.
Webner et al [7]	2021	In a systematic review of the literature these authors analyzed intraarticular injections of HA formulations approved in the United States for the management of KOA. A 1b	It was found that Hylan G-F 20 had been the most extensively studied formulation, with consistent outcomes confirming effectiveness in placebo-controlled studies. Supartz, Monovisc, and Euflexxa were also effective. However, Hyalgan, Orthovisc, and Durolane were not effective. The conclusion was that viscosupplementation effectiveness varied widely across formulations.
Miller et al [8]	2021	Systematic review and meta-analysis to evaluate the safety of viscosupplementation in individuals with painful KOA. A 1a	Comparing viscosupplementation with intraarticular saline over a median of 6 months follow-up, this study found no differences in rate of serious complications unrelated to the treatment itself (2% versus 1%). Local complications (transient local reactions such as injection site pain, arthralgia, joint swelling, and joint effusion), all of which were nonserious, were more frequent with intraarticular injections of hyaluronic acid versus intraarticular saline (14% versus 12%) and resolved within 2-3 days in most instances. Viscosupplementation was demonstrated to be safe for utilization in individuals with painful KOA.

Table 1. Continued

Onuma et al [9]	2022	This study compared the effectiveness of two intraarticular HA products, with average molecular weights of 900,000 (HA90) and 1.9 million (HA190), for 49 individuals (54 knees) with KOA (Kellgren-Lawrence grades I to III). Twenty-seven patients received both HA90 and HA190 injections. The assigned HA product was injected into the joints of individuals once a week, for 5 weeks. B 3b	Both HA formulations relieved walking pain for 6 months.
Lee et al [10]	2022	Prospective clinical trial of 56 individuals with KOA. B 3b	This study found significant improvement at 3- and 6-month follow-ups on cartilage by ultrasonography after intraarticular injection with HYAJOINT Plus (a biofermentation-derived, high-molecular weight HA).
Kim JG et al [11]	2023	This study assessed the results of one or two injections of highly cross-linked HA-LBSA0103 in a series of 3,140 patients. The mean follow-up was around 1 year. B 3b	Mild complications occurred in 10% of individuals. Ha-LBSA0103 was efficacious in alleviating pain in KOA individuals. Pain in more than 80% of the individuals was deemed to be improved. Highly cross-linked HA-LBSA0103 substantially reduced the mean visual analog scale (VAS) score at 12 weeks after the first and second injections.
Perruchet et al [12]	2023	In a case series these authors analyzed the radiological features associated with duration of effectiveness of viscosupplementation in 51 individuals (76 knees) with KOA treated with a single injection of extended-release HA (HANOX-M-XL) B 3b	It was found that even the individuals with more advanced KOA benefited from HANOX-M-XL injection for an average duration of about 1 year.
Conrozier et al [13]	2023	EUROVISCO good practice recommendations for a first viscosupplementation in patients with KOA. C 4	Viscosupplementation with HA is widely employed in the treatment of KOA. However, there is no clear recommendation on the decision-making to accomplish viscosupplementation. That is why EUROVISCO (European Viscosupplementation Consensus Group) gave a series of recommendations.

GRADES OF RECOMMENDATION (A-B-C-D) AND LEVELS OF EVIDENCE from high to low (1a-1b-2a-2b-3a-3b-4-5): A / 1a [Systematic review of (homogeneous) randomized controlled trials]; A / 1 b [Individual randomized controlled trials (with narrow confidence intervals)]; B / 2a [Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects]; B / 2b (Individual cohort study / low-quality randomized control studies); B / 3a (Systematic review of (homogeneous) case-control studies); B / 3b (Individual case-control studies); C / 4 (Case series, low-quality cohort or case-control studies); D / 5 (Expert opinions based on non-systematic reviews of results or mechanistic studies).

Table 2. Recommendations given by EUROVISCO (European Viscosupplementation Consensus Group) regarding viscosupplementation (VS) with intraarticular injections of hyaluronic acid (HA) in individuals with knee osteoarthritis (KOA).[13]

Evaluate pain on a visual or 10-point numeric before considering VS
VS can be deemed for individuals with pain scores between 3 and 8.
A standard x-ray must be taken prior to the decision of VS.
If the x-ray is normal, KOA must be confirmed by MRI or CT arthrogram before considering VS.
The aims of VS are alleviating pain, improving function, and diminishing NSAIDs consumption.
The use of VS must not be deemed for managing a KOA flare.
VS can be envisaged as a first-line pharmacological treatment in individuals having a contraindication to NSAIDs or analgesics.
VS can be deemed in individuals with contraindications to arthroplasty.
In the case of severe comorbidities (diabetes, hypertension, gastrointestinal disorders, renal failure), VS can avert the utilization of potentially dangerous treatments.
VS can be deemed in individuals receiving antiplatelet drugs, vitamin K antagonists, and direct factor Xa or thrombin inhibitors.
MRI, magnetic resonance imaging; CT, computed tomography; NSAIDs, non-steroidal anti-inflammatory drugs.

According to The ESSKA (European Society of Sports Traumatology, Knee Surgery, and Arthroscopy)-ICRS (International Cartilage Regeneration and Joint Preservation Society) consensus, PRP injections are appropriate in individuals aged ≤80 years with knee K-L 0-III KOA grade after failed conservative non-injective or injective treatments, while they are not appropriate as first treatment in K-L IV KOA grade.[18] Main data and results on the use of PRP for the treatment of painful KOA are shown in [Table 3].

Table 3. Efficacy of intraarticular injections of platelet-rich plasma (PRP) on pain relief in painful knee osteoarthritis (KOA).[14-18]

AUTHORS [REFERENCE]	YEAR	TYPE OF STUDY GRADE OF RECOMMENDATION LEVEL OF EVIDENCE	RESULTS
Mousaei Ghasroldasht et al [14]	2019	Prospective study of 30 individuals. B 3b	Intraarticular injections of PRP were found to ease the pain, decrease the stiffness, and improve quality of life through the promotion of IGF-1 (Insulin-like growth factor 1) expression.
Prost et al [15]	2024	Retrospective analysis of patients optimally managed in dedicated centers B 3b	PRP induced a significant decrease of WOMAC (The Western Ontario and McMaster Universities Arthritis Index) score at all follow up endpoints (3 months and 12 months). Similar results were observed for pain Visual Analog Scale-VAS (at 3 months and at 12 months, compared to at baseline).
Berrigan et al [16]	2024	Systematic review. B 3a	After exclusion criteria were applied, 29 studies were analyzed. Of the 29, there were 31 arms that used PRP as a treatment method, of which 28 had statistically significant positive outcomes at 6 months compared with the control group. There were 18 studies with 12-month outcomes, with 16 of 18 having positive outcomes. Improved clinical outcomes from PRP injections for knee OA may be related to a greater platelet dose.
Zhuang et al [17]	2024	One hundred twenty patients with grade I-III KOA were randomly assigned to three groups: PRP1 group, who received a single injection of PRP; PRP3 group, who received three PRP injections one week apart; PRP5 group, who received five PRP injections one week apart. C 4	The administration of three or five injections of PRP is safe, substantially more effective than single injections, and leads to remarkable clinical improvement by significantly reducing knee pain, improving joint stiffness, and enhancing physical function in individuals with grade I-III KOA. Furthermore, no significant difference was observed in the efficacy of three or five injections.
Kon et al [18]	2024	The ESSKA-ICRS consensus: European Society of Sports Traumatology, Knee Surgery, and Arthroscopy (ESSKA), as well as the International Cartilage Regeneration and Joint Preservation Society (ICRS) D 5	PRP injections were considered appropriate in patients aged ≤80 years with knee Kellgren-Lawrence (K-L) 0-III KOA grade after failed conservative non-injective or injective treatments, while they are not considered appropriate as first treatment nor in K-L IV KOA grade.

GRADES OF RECOMMENDATION (A-B-C-D) AND LEVELS OF EVIDENCE from high to low (1a-1b-2a-2b-3a-3b-4-5): A / 1a [Systematic review of (homogeneous) randomized controlled trials]; A / 1 b [Individual randomized controlled trials (with narrow confidence intervals)]; B / 2a [Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects]; B / 2b (Individual cohort study / low-quality randomized control studies); B / 3a (Systematic review of (homogeneous) case-control studies); B / 3b (Individual case-control studies); C / 4 (Case series, low-quality cohort or case-control studies); D / 5 (Expert opinions based on non-systematic reviews of results or mechanistic studies).

Efficacy of combined therapy of hyaluronic acid (HA) and other drugs

Stagni et al demonstrated that a brief cycle of intraarticular therapy with polynucleotides in combination with high molecular weight HA was more efficacious in alleviating pain than HA alone.[19] Karasavvidis et al reported that at 1-year follow-up, a combination of PRP and HA alleviated pain more than HA injections alone.[20] In 2023 Ciapini et al found that the combination of PRP and HA was efficacious in the management of K-L grade II-III KOA in a short-to-mid-run follow-up.[21] Main data and results on the combined use of HA and other drugs for the treatment of painful KOA are shown in [Table 4].

Comparative studies of hyaluronic acid (HA) versus other drugs

In 2021 Jalali Jivan et al found that intraarticular injection of PRP or HA alleviated symptoms and pain and improved functionality and physical examinations in individuals with KOA. However, PRP therapy produced greater and longer-lasting improvements in most of the outcome parameters

compared to HA. In this phase I open-label clinical trial, 10 individuals experienced intraarticular PRP injection and 10 others received HA injection. At baseline (pre-injection) visit and 1, 3, 6, and 12 months post-injection, clinical evaluations were carried out utilizing visual analogue scale (VAS) and KOOS questionnaire. Physical examinations of the knee, including crepitation and range of motion (ROM) were performed at each visit. The follow-up responses were compared with the baseline visit.[22]

Table 4. Results of combined therapy of hyaluronic acid (HA) and other drugs for the treatment of articular pain in knee osteoarthritis (KOA.18-20). PRP = Platelet-rich plasma

AUTHORS [REFERENCE]	YEAR	COMBINED THERAPY	TYPE OF STUDY GRADE OF RECOMMENDATION LEVEL OF EVIDENCE	RESULTS
Stagni et al [18]	2021	Polynucleotides in combination with high molecular weight HA	Randomized, double-blind, HA-controlled clinical trial A 1b	A brief cycle of intraarticular therapy (3 weekly double-blind injections) with polynucleotides in combination with high molecular weight HA was more efficacious in alleviating pain than HA alone.
Karasavvidis et al [19]	2021	Combination of HA and PRP	Meta-analysis of randomized and non-randomized comparative trials A 1b	At 1-year follow-up, a combination of PRP and HA alleviated pain more than HA injections alone.
Ciapini et al [20]	2023	Combination of HA and PRP	Case series B 3b	The combination of PRP and HA was efficacious in the management of Kellgren-Lawrence grade II-III KOA in a short-to-mid-run follow-up.

GRADES OF RECOMMENDATION (A-B-C-D) AND LEVELS OF EVIDENCE from high to low (1a-1b-2a-2b-3a-3b-4-5): A / 1a [Systematic review of (homogeneous) randomized controlled trials]; A / 1 b [Individual randomized controlled trials (with narrow confidence intervals)]; B / 2a [Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects]; B / 2b (Individual cohort study / low-quality randomized control studies); B / 3a (Systematic review of (homogeneous) case-control studies); B / 3b (Individual case-control studies); C / 4 (Case series, low-quality cohort or case-control studies); D / 5 (Expert opinions based on non-systematic reviews of results or mechanistic studies).

Huang et al reported that Hylan G-F 20 considerably reduced pain compared to arthrocentesis.[23] TW Kim et al found that polynucleotide injection had comparable efficacy to intraarticular high molecular weight HA at 3 times injection with an interval of 1 week.[24] Belk et al observed that individuals undergoing treatment with PRP achieved better clinical results than individuals who received HA.[25] JH Kim et al encountered that intraarticular injection of PRP alleviated pain in individuals with KOA for up to 1 year. Besides, PRP was better than HA.[26] Gobbi et al reported that at two-year follow-up autologous microfragmented adipose tissue (AMAT) did not demonstrate substantial superior clinical improvement compared with three leukocyte poor PRP (LP-PRP) combined with HA injections.[27] Main data and results of studies comparing the efficacy of intraarticular injections of HA versus the efficacy of other drugs are shown in [Table 5].

Table 5. Comparative studies of hyaluronic acid (HA) versus other drugs for the treatment of articular pain in knee osteoarthritis (KOA).[22-27]

AUTHORS [REFERENCE]	YEAR	COMPARISON	TYPE OF STUDY GRADE OF RECOMMENDATION LEVEL OF EVIDENCE	RESULTS
Jalali Jivan et al [22]	2021	HA versus Platelet-rich Plasma	Phase I open-label clinical trial B 2b	Intraarticular injection of PRP or HA alleviated pain. However, PRP therapy produced greater and longer-lasting improvements in most of the outcome parameters compared to HA.
Huang et al [23]	2023	Hylan G-F 20 versus arthrocentesis	Multicenter, evaluator- and patient blinded randomized controlled trial (RCT) A 1b	Hylan G-F 20 considerably reduced pain compared to arthrocentesis in flare individuals. A duplicate of Hylan G-F 20 was found to be efficacious.

Table 5. Continued

Kim TW et al [24]	2023	High molecular weight HA versus polynucleotide	RCT A 1b	Polynucleotide injection had comparable efficacy and safety to intraarticular high molecular weight HA at 3 times injection with an interval of 1 week.
Belk et al [25]	2023	HA versus PRP	Meta-analysis of level 1 studies A 1a	PRP gave better clinical results than HA.
Kim JH et al [26]	2023	HA versus PRP	Meta-analysis of level 1 studies A 1a	For up to 1 year PRP was more effective than HA.
Gobbi et al [27]	2023	HA plus LP-PRP versus AMAT	Prospective RCT A 1b	At two-year follow-up AMAT did not demonstrate substantial superior clinical improvement compared with three leukocyte poor PRP combined with HA injections.

GRADES OF RECOMMENDATION (A-B-C-D) AND LEVELS OF EVIDENCE from high to low (1a-1b-2a-2b-3a-3b-4-5): A / 1a [Systematic review of (homogeneous) randomized controlled trials]; A / 1 b [Individual randomized controlled trials (with narrow confidence intervals)]; B / 2a [Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects]; B / 2b (Individual cohort study / low-quality randomized control studies); B / 3a (Systematic review of (homogeneous) case-control studies); B / 3b (Individual case-control studies); C / 4 (Case series, low-quality cohort or case-control studies); D / 5 (Expert opinions based on non-systematic reviews of results or mechanistic studies). LP = leukocyte poor; AMAT = autologous microfragmented adipose tissue.

Several studies have observed clinical improvement of knee pain after HA injections in patients with KOA.[3,4,7,10,11] It has also been found that high molecular weight HA (≥6000 kDa) is more effective than low molecular weight HA (less than 750 kDa). One study observed that a single injection of high molecular weight HA was as effective as three injections of low molecular weight HA at 2 and 6 months follow-up.[4] Other authors found that the efficacy of HA injections varied greatly across formulations.[7] A study using ultrasonography showed a significant improvement of the articular cartilage at 3 and 6 months after HA injection.

However, it should not be forgotten that HA injections can cause nonserious local complications (transient local reactions such as injection site pain, arthralgia, joint swelling, and joint effusion) that resolve within 2-3 days in most instances.[8]

Therefore, although HA is widely used for the treatment of KOA there is no clear recommendation on the decision-making. That is why EUROVISCO (European Viscosupplementation Consensus Group) gave a series of recommendations.[13]

Several studies have also observed an improvement of knee pain in patients with KOA at 3 and 12 months with PRP injections.[14,15,17,18] Some authors have published that 3-5 PRP injections are more effective than a single injection, although they found no difference between 3 injections and 5 injections.[17] The ESSKA-IRCS consensus considers that PRP injections are not suitable as a first treatment even in individuals with K-L KOA grade IV. But they are suitable in individuals younger than 80 years with knee K-L 0-III KOA grade after failed conservative non-injective or injective treatments.[18]

Regarding the combination of HA and PRP, one study observed a greater efficacy in terms of knee pain relief of the combination of HA and PRP versus HA alone at 1-year follow-up.[20] Regarding the comparison of HA and PRP, some authors found that at 1-year follow-up PRP was more effective than HA in relieving knee pain.[26]

Conclusion

Several studies have indicated that the HA plus PRP combination is more effective than HA alone. Finally, other studies seemed to show that PRP is more effective than intraarticular injections of HA.

Despite all the existing information on intra-articular HA and PRP injections, alone or in combination, there are still some questions to be clarified, given the great heterogeneity of the studies published on the subject. Until these doubts are clarified, logic seems to indicate that we should follow the recommendations of EUROVISCO regarding HA and of the ESSKA-ICRS regarding PRP.

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Authors Contribution:

ECR-M conceived and designed the analysis, collected the data, contributed data or analysis tools, performed the analysis, and wrote the paper. HDlC-R collected the data, contributed data or analysis tools, performed the analysis, and wrote the paper.

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