

Hyaluronic Acid and Platelet-rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review

Mohammad Hassan Jokar¹ (MD); Mohammad Reza Hatef¹ (MD); Seyedeh Zahra Mirfeyzi¹ (MD); Hamzeh Zarei^{1*} (MD); Kamila Hashem Zade¹ (MD)

¹: Rheumatic Diseases Research Center, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

ARTICLE INFO	ABSTRACT
<p>Article type: Review Article</p> <hr/> <p>Article history: Received: 10-Aug-2015 Accepted: 31-Aug-2015</p> <hr/> <p>Keywords: Hyaluronic acid Knee Osteoarthritis</p>	<p>Introduction: Due to loss of function and intolerable pain associated with Osteoarthritis (OA), this condition is regarded as one of the major causes of disability, worldwide. Aging and obesity are regarded as two fundamental causes of knee OA. The aim of this study was to review the literature on the efficacy of hyaluronic acid in compression in patients with knee OA.</p> <p>Materials and Methods: A systematic web-based search was conducted in Cochrane Library and MEDLINE to identify articles published before December 2014. English articles with available abstracts, relevant to the subject of the study, were retrieved. Moreover, manual search was performed in reference lists of the articles. Two commentators independently reviewed and assessed the inclusion criteria, evaluated the quality of articles and extracted the data.</p> <p>Results: The evaluated articles were published during 2011-2014. All studies were conducted on adult patients with knee OA. Overall, 745 patients were evaluated in five studies. More than 100 participants were enrolled in four studies and 90 patients were included in only one study.</p> <p>Conclusion: Based on the findings, the application of single-dose platelet-rich plasma is safe, useful and cost-effective in patients with knee OA.</p>

► **Please cite this paper as:**

Jokar MH, Hatef MR, Mirfeyzi S.Z, Zarei H, Hashem Zade K. Hyaluronic Acid and Platelet-rich Plasma in the Treatment of Knee Osteoarthritis: A Systematic Review. *Patient Saf Qual Improv.* 2015; 3(4): 304-307.

Introduction

Osteoarthritis (OA) is a degenerative joint disease with a multifactorial etiology. OA might present with articular cartilage damage, bone remodeling, osteophyte formation and inflammation (1). Knee OA might occur in various parts of the knee such as the patellofemoral joint, tibiofemoral joint or both.

There is some evidence on the role of patellofemoral joint damage in causing pain in the anterior part of the knee and inducing pain while performing activities which require knee flexion (2, 3).

Degenerative knee OA is a major source of knee pain, affecting 35% of individuals older than 65 years of age (4). Non-invasive treatment is commonly indicated in the early radiological phases of OA by means of relative rests, oral anti-inflammatory drugs, oral analgesics and physical therapy. In case of pain persistence, intra-articular injection of a number of agents may be indicated before surgical treatment.

These drugs typically include Hyaluronic Acid (HA), corticosteroids and Platelet-Rich Plasma (PRP) (5, 6).

Due to the loss of function and intolerable pain associated with OA, this condition is regarded as one of the main causes of disability, worldwide. Aging and obesity have been introduced as two fundamental causes of knee OA (7). Various conservative treatment modalities have been proposed for the treatment of knee OA (5). Exercise, weight management programs, walking support and braces, local cooling/heating, acupuncture and electromagnetic therapy are some of the non-pharmacological modalities (6-8).

Pharmacological approaches for OA are categorized into orally administered drugs and intra-articular injections. Analgesics such as non-steroidal, anti-inflammatory drugs and opioids are extensively used by OA patients.

Corticosteroids, HA, viscosupplements and blood-derived agents such as PRP have been used for intra-articular injections (9, 10). Intra-articular injection is contraindicated in septic arthritis and is associated with iatrogenic damage (11). The aim of this study was to

review the literature on the efficacy of HA in compression in patients with knee OA.

Materials and Methods

Articles were retrieved by searching the Cochrane Library and MEDLINE to identify articles published before December 2014. The used keywords and Medical Subject Headings (MESH) included broad terms such as "hyaluronic acid" AND "platelet-rich plasma" AND "knee osteoarthritis". The studies were assessed to identify additional relevant articles from the reference lists of the articles. English articles with available abstracts and full texts, designed as human clinical trials, were included in our analysis. Moreover, manual search was conducted in the reference lists of the articles.

Critical appraisal

Firstly, the retrieved abstracts were reviewed by two independent researchers. Finally, 33 abstracts were assessed twice in terms of relevance. Overall, 19 articles were excluded from our evaluation, based on the type of the article (11 reviews and 8 case reports). Moreover, eight full text articles were excluded due to irrelevance. The remaining six full-text articles were fully assessed by our two reviewers. We used the CONSOLIDATED Standards of Reporting Trials (CONSORT) quality appraisal from reference (12) to assess the quality of the included studies. Two reviewers independently scored the quality criteria for each included study and a third reviewer resolved the discrepancies. We used a structural data extraction tool. However, due to heterogeneity in the main outcomes, no meta-analysis was performed.

Results

The flow diagram of literature search is shown in Figure1.

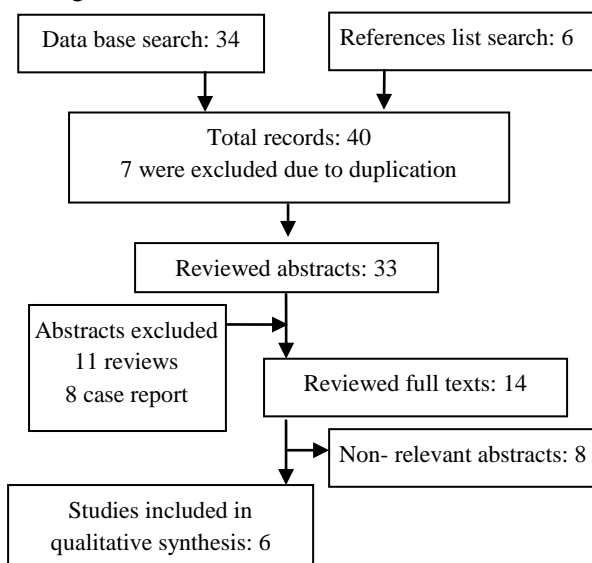


Figure: Flow diagram of the literature search and study selection.

The oldest study was published in 2011 and the most recent one in 2014. All studies have been conducted on adult patients with knee OA. Table1 shows the general characteristics of the included studies. 745 patients were evaluated in 5 studies. 4 studies had participants more than 100 and only one study was enrolled on 90 patients.

Table1: Summary of the 5 studies included in the review

Reference NO.	year	Target population	Drugs	Sample size	The main microbiology
13	2013	Adults	HA/ (PRP)	90	PRP is more effective than HA
14	2013	Adults	HA/ (PRP)	100	PRP is more effective than HA
15	2012	Adults	HA/ (PRP)	109	PRP is more effective than HA
16	2012	Adults	HA/ (PRP)	176	PRP is more effective than HA
17	2012	Adults	HA/ (PRP)	120	PRP is more effective than HA
18	2011	Adults	HA/ (PRP)	150	PRP is more effective than HA

The results of these studies have shown the application of single dose PRP is safe, effective and low-cost in patients with knee OA (13-18). Current research is investigating new methods for stimulating repair or replacing damaged cartilage. In particular, the most recent knowledge about tissue biology concerns a complex regulation of Growth Factors (GFs) for the normal tissue structure and its reaction to damage. The influence of GFs on cartilage repair has been investigated in vitro and in vivo (9), and Platelet Rich Plasma (PRP) is a simple, low- cost and minimally-invasive method that provides a natural concentrate of autologous GFs from the blood (14). This method is now being increasingly applied in clinical practice to treat knee degenerative pathology, such as chondropathy and early OA (7-10).

In OA, a deleterious fluidic microenvironment is established, with presence of HA fragments, catabolic enzymes and inflammatory molecules. The central concept underlying intra-articular injection is to modify deleterious fluidic microenvironments. PRP administration has shown pain remission and function improvement, but less than half of the patients showed clinically significant improvement. PRP exceeds HA, the comparator used in PRP clinical trials, albeit both HA and PRP alleviate symptoms in mild-to-moderate OA patients. Combining PRP and HA may benefit from their dissimilar biological mechanisms and help in

controlling delivery and presentation of signaling molecules. Three armed randomized studies, using both HA and PRP as comparators, will provide information about the impact of this approach (19-21). Although beneficial effects on pain, function and patient global assessment have been documented, the real entity of improvement and which of the many available HA products can offer the best results is not clear (17).

Discussion & Conclusion

Osteoarthritis (OA) is the most common type of arthritis found in the United States population and is also the most common disease of joints in adults throughout the world (3). The knee joint is the most frequently affected of all joints per epidemiological studies with estimates of 37% of United States' adults ≥ 60 years of age having radiographic evidence of knee OA and 12% having symptoms related to knee OA accompanying radiographic findings (5). Symptomatic knee OA has also been highly associated with self-reported activity limitations, need for assistive walking devices, and increased use of prescription medications for pain relief (7). While the synovium, bone, and cartilage are recognized as the main structures being destroyed during disease progression, further research in the field is revealing that OA is not simply a biomechanical process placing excess load on the

References

- 1- Fibel KH, Hillstrom HJ, Halpern BC. State-of-the-Art management of knee osteoarthritis. *World journal of clinical cases*. 2015 Feb 16;3(2):89-101.
- 2- Colen S, Geervliet P, Haverkamp D, Van Den Bekerom MP. Intra-articular infiltration therapy for patients with glenohumeral osteoarthritis: A systematic review of the literature. *International journal of shoulder surgery*. 2014 Oct;8(4):114-21..
- 3- Jokar M, Mirfeizi Z, Keyvanpajouh K. The effect of hydroxychloroquine on symptoms of knee osteoarthritis: a double-blind randomized controlled clinical trial. *Iranian journal of medical sciences*. 2013 Sep;38(3):221-6.
- 4- Ayhan E, Kesmezacar H, Akgun I. Intraarticular injections (corticosteroid, hyaluronic acid, platelet rich plasma) for the knee osteoarthritis. *World journal of orthopedics*. 2014 Jul 18;5(3):351-61.
- 5- Rodriguez-Merchan EC. Intra-articular Injections of Hyaluronic Acid and Other Drugs in the Knee Joint. *HSS journal: the musculoskeletal journal of Hospital for Special Surgery*. 2013 Jul;9(2):180-2..
- 6- Roque V, Agre M, Barroso J, Brito I. Managing knee osteoarthritis: efficacy of hyaluronic acid injections. *Acta reumatologica portuguesa*. 2013 Jul-Sep;38(3):154-61.
- 7- Van Jonbergen HP, Poolman RW, van Kampen A. Isolated patellofemoral osteoarthritis. *Acta orthopaedica*. 2010 Apr;81(2):199-205.
- 8- Bannuru RR, Natov NS, Obadan IE, Price LL, Schmid CH, McAlindon TE. Therapeutic trajectory of affected joint but contributions from catabolic cytokine cascades and production of inflammatory mediators also play a significant role and should be targets for intervention (9-11).
- 9- Simopoulou T, Malizos KN, Poultsides L, Tsezou A. Protective effect of atorvastatin in cultured osteoarthritic chondrocytes. *Journal of orthopaedic research: official publication of the Orthopaedic Research Society*. 2010 Jan;28(1):110-5.
- 10- Pathak NN, Lingaraju MC, Balaganur V, Kant V, More AS, Kumar D, et al. Anti-inflammatory and chondroprotective effects of atorvastatin in a cartilage explant model of osteoarthritis. *Inflammation research: official journal of the European Histamine Research Society [et al]*. 2015 Apr;64(3-4):161-9.
- 11- Hatef MR, Mirfeizi Z, Sahebari M, Jokar MH, Mirheydari M. Superiority of laterally elevated wedged insoles to neutrally wedged insoles in medial knee osteoarthritis symptom relief. *International journal of rheumatic diseases*. 2014 Jan;17(1):84-8.
- 12- Habib Agahi R, Navabi N, Shahravan A, Ghassemi A. Critical appraisal of reporting randomized clinical trials published in Iranian dental journals during 2003-2010. *Journal of dentistry (Tehran, Iran)*. 2014 May;11(3):310-8.
- 13- Say F, Gurler D, Yener K, Bulbul M, Malkoc M. Platelet-rich plasma injection is more effective than hyaluronic acid in the treatment of knee osteoarthritis. *Acta chirurgiae orthopaedicae et traumatologiae Cechoslovaca*. 2013;80(4):278-83.

affected joint but contributions from catabolic cytokine cascades and production of inflammatory mediators also play a significant role and should be targets for intervention (9-11).

In conclusion, despite PRP widespread application, there is a lack of high level studies in the literature to demonstrate the real efficacy of PRP. We believe that it is important to have scientifically robust studies to clearly prove the real potential of this biological approach in order to guide its clinical use and avoid an indiscriminate clinical application, and therefore a high level study was designed. Due to similarity in the current treatment indications and the widespread use of viscosupplementation, this was chosen as a control group, whereas for ethical reasons a placebo group was avoided. Viscosupplementation involves the use of intra-articular injections of hyaluronic acid (HA), a glycosaminoglycan that provides joint lubrication, shock absorbency, and acts as the backbone for the proteoglycans of the extracellular matrix.

Acknowledgement

The authors thank the research chancellor of Mashhad University of medical sciences, Mashhad, Iran, for their assistance and support of this study.

- 14- Vaquerizo V, Plasencia MA, Arribas I, Seijas R, Padilla S, Orive G, et al. Comparison of intra-articular injections of plasma rich in growth factors (PRGF-Endoret) versus Durolane hyaluronic acid in the treatment of patients with symptomatic osteoarthritis: a randomized controlled trial. *Arthroscopy: the journal of arthroscopic & related surgery: official publication of the Arthroscopy Association of North America and the International Arthroscopy Association*. 2013 Oct;29(10):1635-43.
- 15- Filardo G, Kon E, Di Martino A, Di Matteo B, Merli ML, Cenacchi A, et al. Platelet-rich plasma vs hyaluronic acid to treat knee degenerative pathology: study design and preliminary results of a randomized controlled trial. *BMC musculoskeletal disorders*. 2012;13:229.
- 16- Cerza F, Carni S, Carcangiu A, Di Vavo I, Schiavilla V, Pecora A, et al. Comparison between hyaluronic acid and platelet-rich plasma, intra-articular infiltration in the treatment of gonarthrosis. *The American journal of sports medicine*. 2012 Dec;40(12):2822-7.
- 17- Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists*. 2012 May;91(5):411-7.
- 18- Kon E, Mandelbaum B, Buda R, Filardo G, Delcogliano M, Timoncini A, et al. Platelet-rich plasma intra-articular injection versus hyaluronic acid viscosupplementation as treatments for cartilage pathology: from early degeneration to osteoarthritis. *Arthroscopy: the journal of arthroscopic & related surgery: official publication of the Arthroscopy Association of North America and the International Arthroscopy Association*. 2011 Nov;27(11):1490-501.
- 19- Peeters G, Tett SE, Conaghan PG, Mishra GD, Dobson AJ. Is statin use associated with new joint-related symptoms, physical function, and quality of life? Results from two population-based cohorts of women. *Arthritis care & research*. 2015 Jan;67(1):13-20.
- 20- Gierman LM, Kuhnast S, Koudijs A, Pieterman EJ, Kloppenburg M, van Osch GJ, et al. Osteoarthritis development is induced by increased dietary cholesterol and can be inhibited by atorvastatin in APOE*3Leiden.CETP mice--a translational model for atherosclerosis. *Annals of the rheumatic diseases*. 2014 May;73(5):921-7.
- 21- Connor AM, Berger S, Narendran A, Keystone EC. Inhibition of protein geranylgeranylation induces apoptosis in synovial fibroblasts. *Arthritis research & therapy*. 2006;8(4):R94.