Ivander G, Anggono Y. a comparison of intra-articular hyaluronic acid and platelet-rich plasma for knee osteoarthritis: a systematic review. *Orthopedic Reviews*. 2024;16. doi:10.52965/001c.94236

General

a comparison of intra-articular hyaluronic acid and platelet-rich plasma for knee osteoarthritis: a systematic review

Gian Ivander[1], Yovita Anggono[2]

[1] Orthopedic, Universitas Katolik Widya Mandala Surabaya, [2] Orthopaedic, Universitas Katolik Widya Mandala Surabaya

Keywords: Hyaluronic acid, Platelet-rich plasma, Knee osteoarthritis, Systemic review

https://doi.org/10.52965/001c.94236

Orthopedic Reviews

Vol. 16, 2024

Introduction

Knee osteoarthritis (KOA), the most common chronic degenerative condition in an older population, accounts for many disabilities around the world. One of the most popular treatments is intra-articular injection of hyaluronic acid (HA) and platelet-rich plasma (PRP).

Objective

Prior studies have found that both HA and PRP had a therapeutic effect on KOA. This study aims to perform a systematic review regarding whether PRP is superior to HA for KOA.

Method

We conducted a comprehensive literature search using Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines for prospective randomized control trials (pRCTs) in three international databases PubMed, Google Scholar, and ScienceDirect from 2019-2022. Two researchers independently searched the reviews, extracted, and cross-checked the data. The disparity when choosing the literature was resolved by discussion. The modified Jadad was scale used to assess the quality of the included studies. Cochrane risk of bias 2 tool (RoB-2) was used for determininzg risk of bias.

Results

Twenty three studies were eligible for inclusion. Four pRCT with the highest Jadad score were selected as best evidence. Risk of bias assesment concluded two studies having a low risk of bias, one is high risk of bias, and the other possesses some concerns.. Three studies found no difference in patient-reported outcomes between PRP and HA group and one study concluded that PRP is more effective than HA in treating KOA.

Conclusion

Intra-articular injections of PRP and HA are effective interventions for KOA. However, there is not enough evidence of PRP superiority over HA.

INTRODUCTION

The American College of Rheumatology defines osteoarthritis (OA) as a heterogeneous group of disorders that cause joint symptoms and indicators linked to defect articular cartilage integrity and ultimately result in "joint failure[1,2] It was considered a degenerative joint disease resulting from wear and tear. Nowadays, it's the complex combination of biomechanical and mechanical insults that exceeds the joint's ability to repair itself.[1] OA affects about 3.3 to 3.6% of the population globally. It causes moderate to severe disability in 43 million people, making it the 11th most debilitating disease worldwide.[3,4] In 2016, the enormous disease burden caused by OA led to the Osteoarthritis Research Society International (OARSI) submission of a White Paper, describing OA as a Serious Disease.[5,6] There are many predilection sites for OA, such as knee, hip, hand, etc, but the most common one is the knee and hip respectively.

Knee osteoarthritis (KOA) as one type of arthritis, that especially occurs in the elderly, yet the incidence shows an increasing trend at an alarming rate. It has become a great burden of disability, pain, and socioeconomic cost worldwide.[7] After the age of 60, women (13%) are more likely than males (10%) to develop symptomatic KOA.[7] Pain, one

of distinct features of KOA, is the most common symptom for a patient who decides to visit health care and is prior to disability.[8] First-line pharmacological therapy to treat OA is a Non-steroidal anti-inflammatory drug (NSAID); chronic use of NSAID leads to many systemic side effects such as gastrointestinal bleeding, hepatotoxic, and other.[9]

One of other treatment modalities for KOA is intra-articular injection. This method is preferred since it has less or almost none systemic effects. One of the most popular solutions nowadays is Hyaluronic Acid (HA) and Platelet Rich Plasma (PRP). Hyaluronic acid is identical to a substance that synoviocytes produce. Hence , it works like a lubricant and shock absorber in the joints.[10] Platelet-rich plasma (PRP) is a portion of whole blood acquired by centrifugation of autologous blood to separate and extract the plasma and portion of the blood, resulting in high concentrations of platelets.[11] Thus, PRP contains a higher concentration of platelet-derived growth factors (PDGFs) than autologous platelets.[12] Platelets facilitate tissue repair through degranulation from alpha granules, which involves the release of PDGF, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), basic fibroblastic growth factor (bFGF), and transforming growth factor-β1 (TGF-β1).[13]

The purpose of this study was to compare the outcomes between intra-articular injection of hyaluronic acid and Platelet-rich plasma in knee osteoarthritis by using several indicators such as EuroQOL-visual analog scale (EQ-VAS), visual analog score (VAS), Western Ontario Mcmaster Osteoarthritis Index score (WOMAC score), International Knee Documentation Committee (IKDC) score, and Tegner score

METHOD

The present study was performed in accordance with the guideline by Cochrane Collaboration Research of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist to improve transparency.[14,15] We chose the modified Jadad scale to ensure the quality of the literature we picked.[16] The writer also used Assessment risk of bias using the Cochrane Risk of Bias 2 (RoB2) Tool.[17,18]

SEARCH STRATEGY

This study conducted a thorough search of published literature to find a complete, peer-reviewed paper on evaluating intra-articular injection of HA versus PRP for KOA by two independent reviewers (G.I and Y.A). In case of disparity, two reviewers solved it through a discussion. The literature was searched through PubMed, Science Direct, and Google Scholar using Boolean operators with the following keywords: “Knee Osteoarthritis” or “Knee OA” and “Hyaluronic Acid” or “HA” and “Platelet-rich Plasma” or “PRP” and “Randomized Controlled Trial”.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria for this study are: (1) Study Design: included pRCTs of KOA treated with intra-articular HA and PRP. (2) Study Participants: Individuals diagnosed with KOA, either clinically or radiographically, regardless of their gender, age, or race. (3) Study Intervention: group intervention included intra-articular HA or PRP. (4) Study Outcome Measures: At least one of the predetermined outcomes that were reported: WOMAC, EQ-VAS, VAS, IKDC, Tegner score, and other indicators.

The exclusion Criteria for this study including: (1) Non-RCT literature. (2) Duplicate published literature. (3) Studies on which the data could not be extracted.

QUALITY OF LITERATURE

A modified Jadad scale was used to assess the quality of the literature. Several criteria include randomization, blinding, withdrawals, dropouts, inclusion/ exclusion criteria, adverse effects, and statistical analysis.[16] The sum for every literature score from 0 to 8. The score 0 to 3 indicated low-quality studies, whereas scores 4 to 8 indicated high-quality studies.[9] The consensus was achieved by a process of deliberation and agreement over the selection of literature that may offer the most robust evidence, given the available facts at the time

ASSESSMENT RISK OF BIAS

The Cochrane Risk of Bias 2 (RoB2) Tool which consists of five domains which about randomization process, Deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Then, the sum of five domains then labelled into low-risk, some concern, and high-risk bias.[17,18]

RESULT

LITERATURE SEARCH AND SELECTION

We screened to report relevant results based on inclusion and exclusion criteria which were downloaded full articles that met the criteria and underwent data extraction. As seen on Figure 1, among 1064 studies found using our search strategy, 187 were excluded based on duplication. Additional 683 studies were excluded based on title screening, and further 123 studies were excluded after reading the abstract. The remaining 23 studies were reviewed, and the final article included in this review was 4 studies.

CHARACTERISTIC OF LITERATURE

The characteristics of the 4 literature can be found in Table 1. Total number of patients included in this study is 447, 198 were treated with PRP, and 194 received HA. All literature was published between 2018 and 2022, among these four studies, all are pRCTs.

QUALITY

Upon assessing the literature through a modified Jadad scale, one of the studies by Tavassoli et al. achieved the

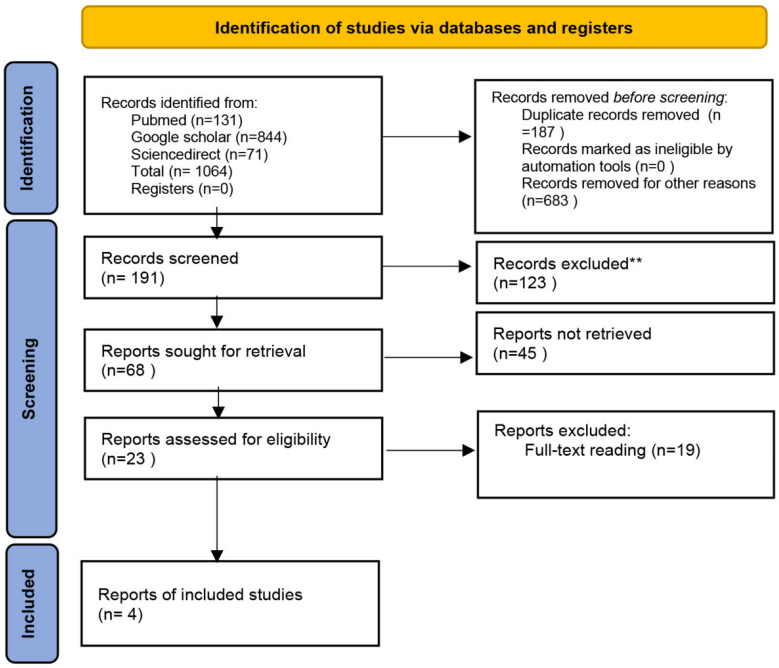

Figure 1. The diagram flow of PRISMA

highest score, mentioning both inclusion and exclusion criteria.

All studies have the similarity of lacking an approach to assess adverse effect criteria. Nevertheless overall, all studies were recorded to have scored above 4, interpreted as high-quality studies as seen on Table 2.

RISK OF BIAS

RoB-2 tools were used to assess the risk of bias in included literature. Domain one assessed concerns regarding randomization, and four studies (100%) were rated as low risk of bias. All studies (100%) were rated as low risk of bias in domain 2, which is regarding deviation from intended intervention, and also rated as low risk of bias in domain 3, which is regarding missing outcome data.

All studies in domain 4 about measurement of the outcome rated as low risk. One study in domain 5 assessed the selection of the reported result was regarded high risk of bias, the rest is either low risk (50%) or some concerns (25%). Overall, two studies are regarded as having a low risk of bias, one is high risk of bias,and the other possesses some concerns as seen on Figure 2 and Figure 3.

OUTCOME

The available research have consistently demonstrated that both PRP and HA treatments result in substantial improvements for KOA as evaluated using several indicators including WOMAC, EQ-VAS, IKDC, VAS, and Tegner scores. Three studies using WOMAC score as an indicator for functional improvement. Two of them reported significant decrease in WOMAC score in PRP group compared to HA group, and one study by Wang et al. reported no significant differences in WOMAC score between PRP and HA. Two studies by Martino et al. and Lin et al. observed PRP group showed significant reduction in IKDC Score compared to HA group

Overall, among the four trials that were examined, the findings from three prospective studies by Wang et al., Martino et al., and Lin et al. indicated that there was no difference in patient reported outcome observed between the groups receiving PRP and HA. In contrast, the study conducted by Tavassoli et al. reached the conclusion that PRP demonstrates a considerably superior efficacy compared to HA in the treatment of KOA, with a statistically significant difference.

DISCUSSION

Osteoarthritis, the most common form of chronic progressive arthritis, especially in the knee, accounted for immense pain, disability, and economic burden. The etiology and pathogenesis are multi-factorial, its thought as a resultof biomechanic and or mechanical process that exceeds cartilage's capabilities to regenerate itself.[1] First-line treatment of mild-moderate KOA (Kellgren-Lawrence ⩽3 or Ahlback ⩽3) includes lifestyle modification and NSAID to relieve pain.[19]

Chronic usage of NSAIDs led to many adverse systemic side effects such as gastrointestinal problems, etc. Hence current alternative trend is to administer intra-articular solutions such as HA and PRP to provide relief.[20-23]

Since the application of intra-articular injection of HA and PRP has soared in the last decade, it is crucial to understand the mechanism and efficacy of both. For this study, we use only high-quality randomized controlled trials, which we assess using modified Jadad score. We also assess

Table 1. Characteristics of included studies

Author and year	Study	Ethical approval	Sample size				Gender (M/F)				Age (years±SD)				OA classification	Clinical outcome	Follow up
			PRP	HA	PRP-2	NS	PRP	HA	PRP-2	NS	PRP	HA	PRP-2	NS			
Wanget al. (2022)	pRCT	Yes	54	56	-	-	12/42	16/40	-	-	61.87±5.46	63.00±5.33	-	-	KL 1-2	WOMAC	1,3,6 mo
Martino et al. (2019)	pRCT	Yes	85	82	-	-	53/32	47/35	-	-	52.7±13.2	57.5±11.7	-	-	KL 1-3	IKDC, EQ-VAS,Tegner score	2,6,12,24 mo
Lin. et al, (2018)	pRCT	Yes	31	29	-	27	9/22	10/19	-	10/17	61.17±13.08	62.53±9.9	-	62.23±11.71	Ahlback OA stage 1-3	WOMAC, IKDC	1,2,6,12 mo
Tavassoli et al. (2019)	pRCT	yes	28	27	28	-	5/23	8/19	6/22	-	63.23±8.03	63.30±8.87	66.04±7.58	-	Ahlback OA stage 1-2	WOMAC, VAS	1,2,3 mo

Abbreviation:
P: Prospective; RCT: Randomized control trial; PRP : Platelet Rich Plasma; PRP-2: Double dose of PRP; HA: Hyaluronic acid; NS: Normal Saline; KL: Kellgren-Lawrence; WOMAC: Western Ontario and McMaster Universities Arthritis Index scores; IKDC: International Knee Documentation Committee; EQ-VAS: EuroQOL-visual analog scale; VAS: Visual analog Score

Table 2. Modified Jadad scale of included studies

Author	Was the research described as randomized?	Was the approach of randomization appropriate?	Was the research described as blinding?	Was the approach of blinding appropriate?	Was there a presentation of withdrawals and dropouts?	Was there a presentation of the inclusion /exclusion criteria?	Was the approach used to assess the adverse effects described	Was the approach of statistical analysis described	Total
Wang et al. (2022)	1	1	1	1	0	0	0	1	5
Martino et al. (2019)	1	1	1	1	1	0	0	1	6
Lin et al. (2018)	1	1	1	1	0	0	0	1	5
Tavassoli et al. (2019)	1	1	1	1	1	1	0	1	7

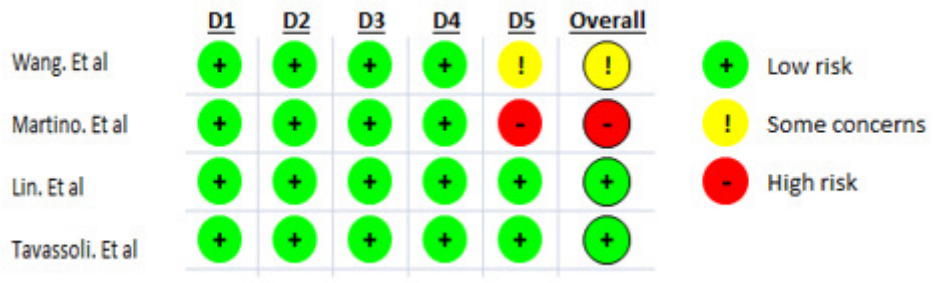

Figure 2. Risk of bias assessment using ROB2 tools

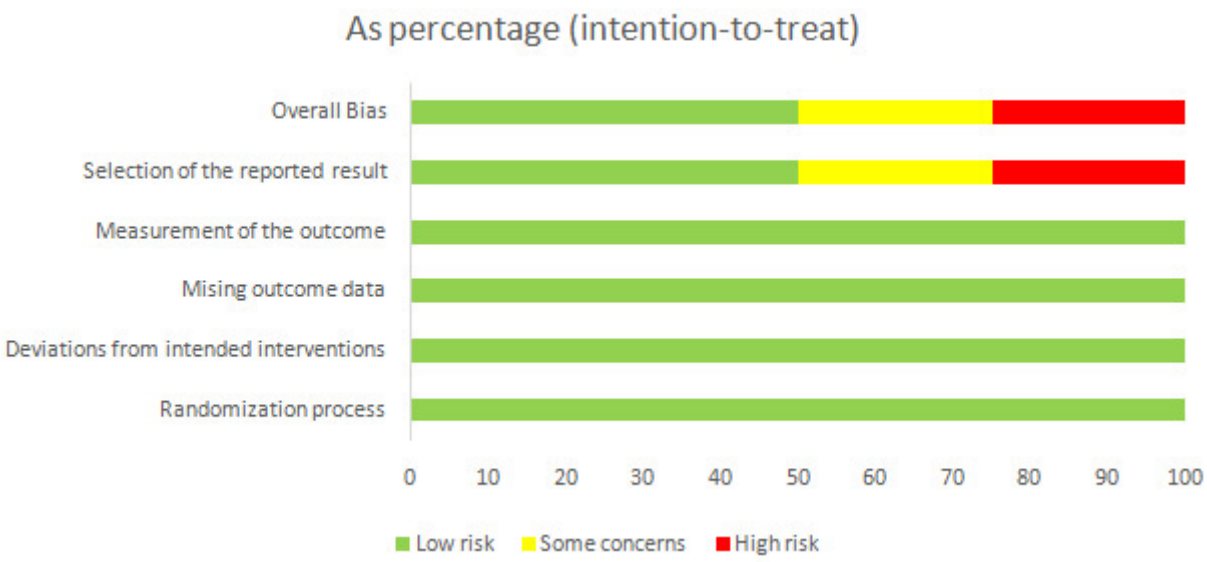

Figure 3. Graphical presentation of risk of bias

the risk of bias from the aforementioned studies using the ROB2 tool.

All the studies showed that both PRP and HA yield significant improvement for KOA assessed by several indicators such as WOMAC, EQ-VAS, IKDC, VAS, and Tegner scores. On the other hand, out of four studies we reviewed, the data based on three prospective studies showed no significant comparison between PRP and HA groups.[20-23] In contrast, Tavassoli. Et al. concluded that PRP is significantly better than HA (P<.001) for treating KOA. His study also stated that the highest efficacy of PRP was observed in both groups at week four, with about 50% decrease in the symptoms compared with about 25% decrease for HA, and stated that PRP efficacy increases after multiple injections.[23] This correlates with studies from Lin et al. that showed PRP clinically significant functional improvement for at least 1 year of therapy.[22] Martino et al.also revealed that the re-intervention rate at 24 months was significantly lower in the PRP group (22.6% vs 37.1%, P=.036).[21] We observed that duration of therapy seems to play role in PRP usage. For long-term usage, PRP seems to be superior to HA. However there is insufficient data for objective outcome improvement for PRP uses in KOA.

Several differences were observed from all studies that may interfere with the outcome. First, the preparation of PRP and HA. PRP which is acquired from the centrifugation of autologous blood to separate the plasma and blood components, acts as a vector for many growth factors.[24] Other literature stated that growth factor contained in PRP promotes tissue repair, which is more aligned with OA pathogenesis.[25] Numerous methods can be used to prepare a PRP solution, yet there needs to be more standardization on how to prepare it. Many ways can be used to achieve a higher concentration of average platelet, as higher platelet concentration is associated with a higher concentration of growth factor.[24,26] All studies we reviewed aimed for leucocyte-poor PRP with different methods.[20-23] The double-spin method is recommended to prepare PRP to achieve higher concentration of average platelet compared to the single-spin method.[24] Two studies (Tavasolli and Martino et al.) used the double-spin method. However, there is a slight difference in rpm and minutes. Meanwhile, two other studies (Wang and Lin et al.) used single-spin method. Platelet activator using 10% calcium chloride was also used in one of the studies by Martino et al.. Activation of PRP is not required when injected into soft tissue as the natural

collagen type I acts as a natural activator.[24] The science behind the ideal preparation of PRP is still in research. We only found two of our studies that stated their PRP checked for quality tests.

On the other hand, HA, one of the most essential components of synovial fluid, plays a role in lubricating the joints.[25] Several clinical studies demonstrated that HA has the effect of relieving joint pain, thus reducing disability. The latest guidelines for KOA did not recommend HA as a primary therapy, which possesses no impact on cartilage regeneration.[27] Other than that, HA is regarded as symptomatic therapy unrelated to the underlying pathogenesis of KOA, and studies from stated that the effectiveness of HA decreases after multiple applications.[25,28] HA is provided by several manufacturers which vary in molecular weight. Based on the data from four studies defined the use of high molecular weight HA (HMWHA) for the treatment of OA. HWHA defined as a molecular weight above 1.000kDa.[25] HMWHA is preferred to low mollecular weight HA (LMWHA) because, the latter has an ability to act as a pro-inflammatory up-regulation, promoting the activation and maturation of dendritic cells, releasing pro-inflammatory cytokines such as interleukin1 beta (IL-1β), tumor necrosis factor α (TNF-α), IL-6, and IL-12. Besides that, it also increased the expression of chemokines and promoting cell proliferation.[29,30]

The number of injections also varied among these studies, including single injection, and multiple injections which were repeated at different times. One study by Tavasolli et al. also compared single injection vs double injection of PRP, resulting in double injection being better than single injection or HA treatment (WOMAC total score 61.57±11.29 vs 63.71±9.87).

Beyond those differences in this study, the mechanism of PRP and HA in the change of KOA was an essential factor that may influence the outcome. The therapeutical effects of HA may be attributed to improved lubrication. Growth factors in PRP are fundamental to stimulate the proliferation and differentiation of chondrocytes, regulate collagenase, and thus regenerate the cartilage.[31] The combination of HA and PRP may be more beneficial than alone. Another study concluded that the combination of HA and PRP resulted in better outcomes than HA alone for up to one year and PRP alone for up to three months.[32]

Nevertheless, few limitations were inexorable. First, the follow-up time was relatively short, and PRP and HA's long-term efficacy and safety could not be evaluated. Second, only one study used NS as a placebo hence we cannot determine whether the PRP and HA given had a placebo effect. Third, the amount of PRP (mL) differs in each study ranging from 4 mL to 5 mL. Lastly, in terms of grading the OA, some studies use KL grading, and the rest use Ahlback grading, which may affect the credibility of effectiveness.

CONCLUSION

We concluded that intra-articular injection of HA or PRP could improve the total WOMAC, IKDC, VAS, and Tegner score however, there is uncertainty regarding whether the PRP is superior to HA since there was no standardized procedure for preparing PRP solution, which can affect the results. Other than that, there is no consensus regarding the dosage of PRP injected. Also, all the indicators used were very subjective. Hence we can not conclude that PRP affected cartilage repair. In the future, some objective indicators including MRI to assess cartilage or pathological studies will be essential to be included in the outcome assessment.

Submitted: June 21, 2023 EST, Accepted: February 04, 2024 EST

REFERENCES

1. Koster J, Warwick D. *Apley's Concise System of Orthopaedics and Fractures Third Edition*. Taylor & Francis; 2005.

2. Sarzi-Puttini P, Cimmino MA, Scarpa R, et al. Osteoarthritis: An overview of the disease and its treatment strategies. *Semin Arthritis Rheum*. 2005;35(1):1-10. doi:10.1016/j.semarthrit.2005.01.013

3. Bortoluzzi A, Furini F, Scirè CA. Osteoarthritis and its management - Epidemiology, nutritional aspects and environmental factors. *Autoimmun Rev*. 2018;17(11):1097-1104. doi:10.1016/j.autrev.2018.06.002

4. Watkins-Castillo S, Andersson G. *United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS)*.; 2014. http://www.boneandjointburden.org

5. Hawker GA. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*. 2019;37(5).

6. Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. *Osteoarthr Cartil*. 2020;28(3):242-248. doi:10.1016/j.joca.2020.01.002

7. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. *Osteoarthr Cartil*. 2022;30(2):184-195. doi:10.1016/j.joca.2021.04.020

8. Glyn-Jones S, Palmer AJR, Agricola R, et al. Osteoarthritis. *Lancet*. 2015;386(9991):376-387. doi:10.1016/s0140-6736(14)60802-3

9. Zhang Y, Zhou L, Liu X, et al. The effectiveness of the problem-based learning teaching model for use in introductory Chinese undergraduate medical courses: A systematic review and meta-analysis. *PLoS One*. 2015;10(3):e0120884. doi:10.1371/journal.pone.0120884

10. Chen LH, Xue JF, Zheng ZY, Shuhaidi M, Thu HE, Hussain Z. Hyaluronic acid, an efficient biomacromolecule for treatment of inflammatory skin and joint diseases: A review of recent developments and critical appraisal of preclinical and clinical investigations. *Int J Biol Macromol*. 2018;116:572-584. doi:10.1016/j.ijbiomac.2018.05.068

11. Cole BJ, Seroyer ST, Filardo G, Bajaj S, Fortier LA. Platelet-rich plasma: Where are we now and where are we going? *Sports Health*. 2010;2(3):203-210. doi:10.1177/1941738110366385

12. Andia I, Sánchez M, Maffulli N. Joint pathology and platelet-rich plasma therapies. *Expert Opin Biol Ther*. 2011;12(1):7-22. doi:10.1517/14712598.2012.632765

13. Eppley BL, Woodell JE, Higgins J. Platelet quantification and growth factor analysis from platelet-rich plasma: Implications for wound healing. *Plast Reconstr Surg*. 2004;114(6):1502-1508. doi:10.1097/01.prs.0000138251.07040.51

14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;62(10):1006-1012. doi:10.1016/j.jclinepi.2009.06.005

15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71

16. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. doi:10.1016/0197-2456(95)00134-4

17. Sterne JAC, Savović J, Page MJ, et al. RoB 2: A revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:1-8. doi:10.1136/bmj.l4898

18. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial | Cochrane Training. Published online 2021.

19. Ringdahl E, Pandit S. Treatment of knee osteoarthritis. *Am Fam Physician*. 2011;83(11):1287-1292.

20. Wang YC, Lee CL, Chen YJ, et al. Comparing the Efficacy of Intra-Articular Single Platelet-Rich Plasma(PRP) versus Novel Crosslinked Hyaluronic Acid for Early-Stage Knee Osteoarthritis: A Prospective, Double-Blind, Randomized Controlled Trial. *Med*. 2022;58(8):1028. doi:10.3390/medicina58081028

21. Di Martino A, Di Matteo B, Papio T, et al. Platelet-Rich Plasma Versus Hyaluronic Acid Injections for the Treatment of Knee Osteoarthritis: Results at 5 Years of a Double-Blind, Randomized Controlled Trial. *Am J Sports Med*. 2019;47(2):347-354. doi:10.1177/0363546518814532

22. Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH. Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. *Arthroscopy*. 2019;35(1):106-117. doi:10.1016/j.arthro.2018.06.035

23. Tavassoli M, Janmohammadi N, Hosseini A, Khafri S, Esmaeilnejad-Ganji SM. Single- and double-dose of platelet-rich plasma*versus*hyaluronic acid for treatment of knee osteoarthritis: A randomized controlled trial. *World J Orthop*. 2019;10(9):310-326. doi:10.5312/wjo.v10.i9.310

24. Dashore S, Chouhan K, Nanda S, Sharma A. Preparation of Platelet-Rich Plasma: National IADVL PRP Taskforce Recommendations. *Indian Dermatol Online J*. 2021;12(7):12. doi:10.4103/idoj.idoj_269_21

25. Zhang HF, Wang CG, Li H, Huang YT, Li ZJ. Intra-articular platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: A meta-analysis. *Drug Des Devel Ther*. 2018;12:445-453. doi:10.2147/dddt.s156724

26. Kikuchi N, Yoshioka T, Taniguchi Y, et al. Optimization of leukocyte-poor platelet-rich plasma preparation: a validation study of leukocyte-poor platelet-rich plasma obtained using different preparer, storage, and activation methods. *J Exp Orthop*. 2019;6(1). doi:10.1186/s40634-019-0190-8

27. Chen P, Huang L, Ma Y, et al. Intra-articular platelet-rich plasma injection for knee osteoarthritis: a summary of meta-analyses. *J Orthop Surg Res*. 2019;14(1):1-11. doi:10.1186/s13018-019-1363-y

28. Marinho A, Nunes C, Reis S. Hyaluronic acid: A key ingredient in the therapy of inflammation. *Biomolecules*. 2021;11(10):1518. doi:10.3390/biom11101518

29. Murakami T, Otsuki S, Okamoto Y, et al. Hyaluronic acid promotes proliferation and migration of human meniscus cells via a CD44-dependent mechanism. *Connect Tissue Res*. 2018;60(2):117-127. doi:10.1080/03008207.2018.1465053

30. Kavasi RM, Berdiaki A, Spyridaki I, et al. HA metabolism in skin homeostasis and inflammatory disease. *Food Chem Toxicol*. 2017;101:128-138. doi:10.1016/j.fct.2017.01.012

31. Leitner GC, Gruber R, Neumüller J, et al. Platelet content and growth factor release in platelet-rich plasma: A comparison of four different systems. *Vox Sang*. 2006;91(2):135-139. doi:10.1111/j.1423-0410.2006.00815.x

32. Lana JFSD, Weglein A, Sampson SE, et al. Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee. *J Stem Cells Regen Med*. 2016;12(2):69-78. doi:10.46582/jsrm.1202011