Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2023 Mar 19; 11(F):163-170.
https://doi.org/10.3889/oamjms.2023.11516
eISSN: 1857-9655
Category: *F - Review Articles*
Section: *Systematic Review Article*

Stem Cell Versus Platelet-rich Plasma for Knee Osteoarthritis: A Systematic Review

I Wayan Suryanto Dusak[1], Agus Eka Wiradiputra[2], I Gusti Ngurah Paramartha Wijaya Putra[2], I Gde Made Satya Wangsa[3]*

[1]Department of Orthopedics and Traumatology, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia; [2]Department of Orthopedics and Traumatology, Bhayangkara Hospital, Denpasar, Bali, Indonesia; [3]Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia

Edited by: Eli Djulejic
Citation: Dusak IWS, Wiradiputra AE, Putra IGNPW, Wangsa IGMS. Stem Cell Versus Platelet-rich Plasma for Knee Osteoarthritis: A Systematic Review. Open Access Maced J Med Sci. 2023 Mar 19; 11(F):163-170. https://doi.org/10.3889/oamjms.2023.11516
Keywords: Knee osteoarthritis; Mesenchymal stem cells; Outcome; Platelet-rich plasma
***Correspondence:** I Gde Made Satya Wangsa, Faculty of Medicine, Udayana University, Denpasar, Bali, Indonesia. Email: satyawangsa@rocketmail.com
Received: 30-Jan-2023
Revised: 18-Feb-2023
Accepted: 9-Mar-2023

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

AIM: The objective is to compare the outcomes of intra-articular injection of mesenchymal stem cells (MSCs) to platelet-rich plasma (PRP) as a treatment modality for knee osteoarthritis (OA).

METHODS: Systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses and PICO criteria for the past 10 years of publications. Keywords used to search with Boolean operator: "knee OA" AND "MSCs" AND"PRP" AND "outcome." All selected articles were assessed for their quality based on strengthening the Reporting of Observational Studies in Epidemiology checklist.

RESULTS: We selected five articles of prospective cohort studies, which involved 54 patients whom received combination therapies of MSCs+PRP, 206 patients received MSCs only treatment and 86 patients received PRP only treatment. It was shown that MSCs had superior outcomes compared to PRP treatment in terms of VAS and KOOS, where combinations of MSCs and PRP treatment had no significant difference compared to the MSCs treatment alone. Nonetheless, each treatment showed a significant improvement of KOOS, VAS, WOMAC, IKDC, knee, and function knee scores from their baselines.

CONCLUSION: Intra-articular injections are effective and safe for the management of knee OA. MSCs treatment has superior effect on the treatment outcomes compared to PRP treatment. Combination of both treatments is comparable to MSCs treatment alone.

Introduction

Osteoarthritis (OA) is the most common form of joint disorder, which could get progressively worse over time. The main symptoms in OA patients are pain, stiffness, and swelling [1]. OA is often found in the hands, hips, and knees and has affected 302 million people around the world [2]. The number of people affected by OA with symptoms is increasing due to the increasing number of elderly people and the incidence of obesity. Symptomatic knee OA also affects the elderly population (60 years and over) with a percentage of 13% women and 10% men [3].

The main goal of various current OA treatments is to relieve symptoms and improve patient functionality. However, there are some disadvantages and limitations to the use of these therapies [4]. Oral analgesics and anti-inflammatory drugs (NSAIDS) may be known to be helpful for the short-term management of knee OA but less effective when used for a longer period. In addition, a long-term use significantly increases the risk of serious side effects [5]. Some of the most common side effects of irrational use of NSAIDS include dyspepsia to gastric ulcers. Meanwhile, studies on biomechanical interventions (knee braces, knee sleeves, foot orthoses, and lateral wedge insoles) often yield mixed and contradictory conclusions. In addition, the benefits offered are generally short-term [4], [5]. To date, total knee arthroplasty coupled with non-operative therapy is the definitive treatment for severe OA. However, this modality is considered quite expensive and is associated with various adverse effects [4], [6].

Orthobiologic-based treatment applied to joints affected by OA, including the knee joint, has promising potential to treat this disease because it is not only less invasive but also cheaper than operative therapy. Some examples of this type of therapy are mesenchymal stem cells (MSC) [4], [5], [7], [8] and platelet-rich plasma (PRP).

Based on the research, MSC as multipotent cells that can be isolated from human tissues plays an important role in the degenerative process. It is known that the older and the more severe the degree of OA a person is, the number of MSCs in the subchondral bone marrow will decrease [6], [9], [10], [11], [12]. Other studies suggest that the regeneration process by MSCs requires

the direct transfer of these cells to the site of injury [13], [14]. Although it is associated with some undesirable side effects; such as fever, constipation and fatigue, the benefits provided by MSC are reported to be greater, based on an investigation of some recent literature [4].

On the other hand, PRP has a higher platelet concentration than baseline because it is obtained by centrifugation of whole blood. Nowadays, the use of PRP has developed so that it is not only used in the treatment of tendon and ligament injuries but has also been used in the treatment of cartilage injuries including knee OA [5], [15]. Unfortunately, the difficulty of standardization in PRP production causes controversy in the interpretation of research results and the use of this modality [5], [15]. Although the regenerative approach of these modalities for the management of knee OA looks promising, before this therapy can be recommended for clinical use globally, it is necessary to carry out further research with higher quality and level of evidence to identify the effectiveness, safety, and ingredients as well as the most optimal method in its application. Comparison between modalities is also important. Therefore, this systematic review aims to compare the outcomes of intra-articular injection of MSCs to PRP as a treatment modality for knee OA.

Methods

Literature search and selection

- The literature search was conducted based on *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* in Figure 1 to achieve transparency. The PICO criteria were applied to address the research question and inclusion criteria:
- Population (P): patients with knee OA,
- Intervention (I): who received MSCs treatment,
- Comparison (C): compared to PRP treatment or a combination of both treatments,
- Outcome (O): are there significant differences in terms of the therapy outcomes such as The Knee Injury and Osteoarthritis Outcome Score (KOOS), Visual Analog Scale (VAS), The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index, and International Knee Documentation Committee (IKDC) scores?

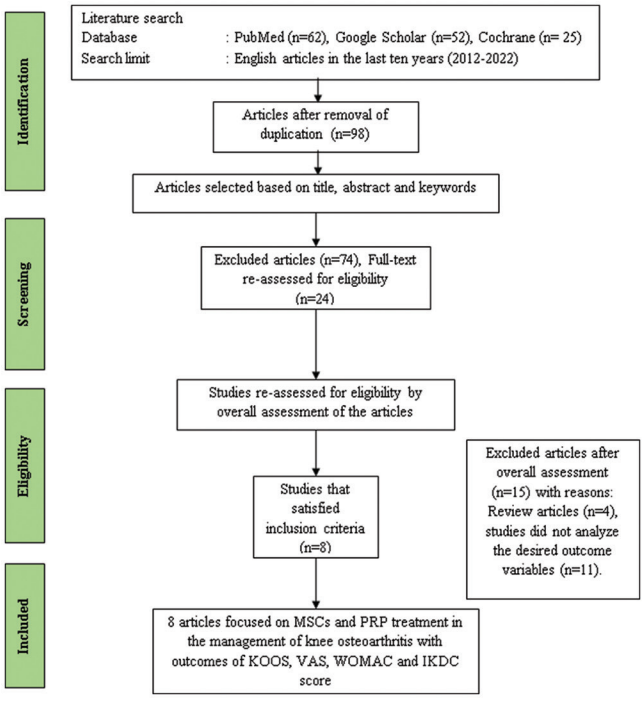

Figure 1: Selection flow chart based on PRISMA

Targeted articles were within 10 years of publication and were extracted based on the: Countries in which the study took place, and methods (study design, settings, sample size, and period of study, participants' demographics). Inclusion criteria for the articles were: (1) articles must be in English and full version, (2) comparison studies between MSC with PRP or MSC with MSC+PRP, (3) intervention must be specific on knee OA, and (4) study design must be cohort studies with randomized or non-randomized controlled trial design. Studies with no full article and unclear study design and method of intervention were excluded. Each article was then assessed for quality based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist in Table 2.

PubMed, Google Scholar, and Cochrane were used as databases. We identified keywords relevant to the topic using the Boolean operator to be specific on the topics. Keywords used: "knee OA" AND "MSCs" AND"PRP" AND "outcome." We then proceeded with the initial selection process of assessing the title and abstract. After that, we selected articles based on PICO to match with inclusion criteria. The overall assessment of articles by scanning through methods, results, discussion, and other essential components of the article. Finally, careful review of all sections was done to complete the systematic review procedure.

Data collection

We extracted some key points from the selected articles manually. The collected data needed for this systematic review were the name of the main author, country of origin, year of publication, study design, the total number of participants involved in the study, mean age of the involved patients with treatment, types of treatment, and outcome variables of each study. Quantitative data of each outcome variables were shown to showcase the results of knee arthritis management.

Table 1: Characteristics of studies included in this systematic review

First author (publication year)	Country	Study design	Sample size (N)	Disease grade	Mean or median age (years)	Identified outcome	Results summary	Excluding systemic disease and other form of arthritis	Excluding samples with history of other treatments
Koh *et al.* [16] (2014)	Korea	Prospective cohort	MSCs + PRP: 21 PRP: 23	ICRS Cartilage Injury Evaluation Package - Grade I: 0 - Grade II: 1 (PRP = 1; MSCs+PRP = 0) - Grade III: 20 (PRP = 11; MSCs+PRP = 9) - Grade IV: 23 (PRP = 11; MSCs+PRP = 12)	PRP: 52.3 MSCs+PRP: 54.2	The Knee Injury and Osteoarthritis Outcome Score (KOOS)	1. Patients in the MSCs+PRP group showed better improvements in the KOOS subscales for pain compared to PRP only group (81.2 ± 6.9 vs. 74.0 ± 5.7; P < 0.001). 2. The MSCs+PRP group had significantly better improvement in the VAS compared to PRP only group (10.2 ± 5.7 vs. 16.2 ± 4.6; P < 0.001).	No, only other form of arthritis was excluded	Not specific, including samples with failure of conservative treatment but excluding intra articular interventions within 3 months
Bastos *et al.* [17] (2018)	Brazil	Prospective cohort	MSCs: 9 MSCs + PRP: 9	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 0 - Grade II: 5 (MSCs = 4; MSCs+PRP = 1) - Grade III: 8 (MSCs = 3; MSCs+PRP = 5) - Grade IV: 3 (MSCs = 2; MSCs+PRP = 1)	MSCs: 54.7 MSCs+PRP: 60.4	KOOS	1. There was significant improvement of KOOS throughout the 12 months for both groups of MSCs and MSCs+PRP treatment (MSCs: baseline 25.5 SD 8.0 vs. 12 months MSCs 50.3 SD 26.6; P = 0.025, MSCs+PRP: baseline 38.1 SD 20.4 vs. 12 months 68.2 SD 24.7; P = 0.012) 2. No difference between groups for the KOOS subscales and global score improvements at 12-month end-point (p>0.05) 3. MSCs showed significant improvement in the subscales of pain (p = 0.035), function, daily living activities (p = 0.035) and sports/ recreational activities (p = 0.027) 4. MSCs+PRP showed significant improvement in the subscales of pain (p = 0.012), function and daily living activites (p = 0.017) as well as quality of life (p = 0.027).	Yes	Yes
Espinosa *et al.* [6] (2020)	Spanyol	Prospective cohort	MSCs: 26 MSCs + PRP: 24	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 0 - Grade II: 13 (MSCs = 8; MSCs+PRP = 5) - Grade III: 7 (MSCs = 5; MSCs+PRP = 2) - Grade IV: 25 (MSCs = 13; MSCs+PRP = 12)	MSCs+PRP: 56 PRP: 54.6	- VAS - The Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index	1. The decrease of mean value of VAS for bone marrow mesenchymal stromal cells (BM-MSCs) with PRP intervention was found significant at 12 months (from 5.3 SD 1.9 to 3.5 SD 2.5; P = 0.01) compared to PRP treatment alone (5 SD 1.8–4.5 SD 2.2; P = 0.389) 2. PRP treatment alone showed significant improvement of WOMAC score from baseline to 12 months, (31.9 SD 16.2 to 22.3 SD 15.8; P = 0.002) compared to combination of BM-MSCs with PRP (33.4 SD 18.7–23.0 SD 16.6; P = 0.053).	No, only other form of arthritis was excluded	Not specific, including samples with previous failed treatment with hyaluronic acid but excluding NSAID therapy
Estrada *et al.* [4] (2020)	Argentina	Prospective cohort	MSCs: Bone marrow (27), adipose - derived (33) PRP: 29	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 29(PRP: 29; MSCs: 0) - Grade II: 27(PRP: 0; MSCs Bone Marrow: 27) - Grade III: 33(PRP: 0; MSCs Adipose-derived: 33) - Grade IV: 0	Median age of total group: 61	- International Knee Documentation Committee (IKDC) score - Knee score - Function knee score	1. There were three types of treatment: Bone Marrow Aspirate Concentrate (BMAC), adipose-derived mesenchymal stem cell (ATDSC) and PRP. All the three treatment groups showed significant improvement at 90 days and improvement was maintained during follow-up (p < 0.05). 2. All the three treatment groups showed comparable improvement in IKDC, knee and function knee score from baseline to 360 days postoperative (p>0.05).	Yes	Yes

(Contd...)

Table 1: ***(Continued)***

First author (publication year)	Country	Study design	Sample size (N)	Disease Grade	Mean or median age (years)	Identified outcome	Results summary	Excluding systemic disease and other form of arthritis	Excluding samples with history of Other Treatments
Dulic *et al.* [18] (2021)	Serbia	Prospective cohort	MSCs: 111 PRP: 34	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 0 - Grade II: 91(MSCs: 49; PRP: 12) - Grade III: 58(MSCs: 46; PRP: 12) - Grade IV: 26 (MSCs: 16; PRP: 10)	MSCs: 56.9 PRP: 58.8	-KOOS -VAS -WOMAC -IKDC	1. Participants in BMAC group showed higher KOOS score after 3 months of treatment compared to PRP groups (mean difference (MD) = 9.087; P = 0.035). There was significant mean difference in pre-intervention values of each BMAC and PRP treatment comparing at 12 months (BMAC = -25.345; P < 0.001; PRP = −15.586; P = 0.010). 2. BMAC group showed better VAS than PRP group after 3 days and 7 days of treatment (3 days mean difference (MD) = −2.523, P < 0.001 and 7 days MD = −3.010, P < 0.001). There was also significant decrease of VAS during follow up (3, 7, 14 and 21 days after treatment) compared to baseline (p < 0.001). 3. WOMAC score showed significant at 12 months of treatment compared to baseline for each treatment group: BMAC and PRP (BMAC MD = 20.007, P < 0.001; PRP MD = 17.064, P = 001). However, there was no significant difference of WOMAC score between the two treatment groups until 12 months (p>0.05). 4. Regarding IKDC score, BMAC showed better score than PRP at 1 month after treatment (MD = 12.354; P = 0.002), at 6 months (MD = 9.728; P = 0.033). Eventhough there was no consistent significant difference between the BMAC and PRP groups at all measures (3, 9 and 12 months after treatment), the BMAC group showed better results.	Yes	Not explained
Bastos *et al.* [19] (2019)	Brazil	Prospective cohort (RCT)	MSCs: 16 MSCs + PRP: 14	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 2 (MSCs = 1; MSCs+PRP = 1) - Grade II: 10 (MSCs = 7; MSCs+PRP = 3) - Grade III: 11 (MSCs = 5; MSCs+PRP = 6) - Grade IV: 7 (MSCs = 3; MSCs+PRP = 4)	MSCs: 55.7 MSCs+PRP: 60.8	- KOOS - Knee ROM (hyperextension, flexion, and total flexion)	1. Both groups showed significant improvement in almost all KOOS domains (symptoms, pain, function daily living, sports/recreation, and global score). Only the quality of life was not significantly different in the MSCs+PRP group, while the group that received MSCs alone experienced a significant increase (Mean difference (95% CI) = 23.5 (9.4–37.6); P = 0.009) 2. After 12 months of follow-up, the mean percentage improvement in the pain domain (KOOS) was found to be higher in the group that received MSCs+PRP, while the mean percentage increase in the quality of life domain (KOOS) was found to be better in the group that only received MSCs. 3. Regarding to Knee ROM which consists of flexion, total flexion and hyperextension, the two study groups did not show significant differences (after 12 months of follow-up).	Yes	Yes

(Contd...)

Table 1: ***(Continued)***

First author (publication year)	Country	Study design	Sample size (N)	Disease Grade	Mean or median age (years)	Identified outcome	Results summary	Excluding systemic disease and other form of arthritis	Excluding samples with history of Other Treatments
Baria *et al.* [21] (2022)	USA	Prospective cohort (RCT)	PRP: 30 MSCs: 28	Kellgren-Lawrance Osteoarthritis Grade: - Grade I: 8(PRP = 6; MSCs = 2) - Grade II: 13(PRP = 8; MSCs = 5) - Grade III: 23(PRP = 12; MSCs = 11) - Grade IV: 14 (PRP = 4; MSCs = 10)	MSCs: 51.9 MSCs: 56.1	- KOOS - VAS	1. Results from primary outcome calculation and analysis in the pain domain (KOOS) showed no difference in the two study groups (PRP 80.38 ± 16.07 vs. MSCs 81.61 ± 16.37; P value = 0.67) at 6 months post injection. 2. It was found that there were significant improvements both clinically and statistically from all KOOS and VAS domains in each study group, without significant differences when the two groups were compared to each other. The only significant difference was found at1 month post-injection data observation in the symptoms domain (KOOS) with mean PRP 72.24 ± 17.85 vs. MSCs 63.10 ± 13.01; P = 0.03)	Yes	Yes, 6 weeks prior
Venosa *et al.* [20] (2022)	Italy	Prospective cohort (RCT)	PRP: 19 MSCs + PRP: 19	Joint Cartilage Breakdown Outerbridge Classification: - Grade I: 0 - Grade II: 0 - Grade III: 0 - Grade IV: 38(PRP: 19; MSCs+PRP: 19)	PRP: 56.4 MSCs+PRP: 55.8	- IKDC - KOOS -VAS	1. In both study groups (PRP and PRP+MSCs) the mean IKDC values were not significantly different (PRP 76.9 ± 2.8 vs. PRP+MSCs 78.2 ± 2.2; P value>0.05). However, both study groups showed an increase in IKDC scores after 12 months of follow-up compared to baseline. 2. Analysis of the KOOS score data did not show any significant differences in all domains when comparing the two study groups.However, the baseline KOOS score in patients receiving PRP alone (62 ± 10) was slightly higher than the group with PRP+MSCs (53 ± 20) 3. Improvements were also found in the baseline VAS score, where the VAS score of the group with PRP fell from an average of 6.09 ± 2.33 (before treatment) to 3.42 ± 2.55 (after 12 months follow-up) and the group with PRP+MSCs decreased from 6.19 ± 1.97 (before treatment) to 3.32 ± 2.43 (after 12 months follow-up)	Yes	Yes

Results

Literature selection

All selected articles were published in the past 10 years. We selected eight articles of prospective cohort studies which all came from different countries across Asia, Europe, and America continents listed in Table 1. The eight studies included 87 patients whom received combination therapies of MSCs+PRP, 250 patients received MSCs only treatment and 149 patients received PRP only treatment.

It was shown that MSCs had superior outcomes compared to PRP treatment in terms of VAS and KOOS [6], [16], [17], [18], [19], where combinations of MSCs and PRP treatment had no significant difference compared to the MSCs treatment alone. However, the distinction could be found when the combination of the two compared to PRP treatment alone. Nonetheless, each treatment showed significant improvement in KOOS, VAS, and WOMAC from their baselines.

Interestingly, there were several findings regarding WOMAC score comparison between the two groups. One study found no difference in WOMAC score between the two groups [18], with improvements from baseline did happen regardless. On the other, one study found PRP group to have better WOMAC scores than MSCs with PRP treatment group [6]. Both studies were conducted longitudinally in the same period of follow-up until 12 months after treatment.

Table 2: Articles assessment with STROBE checklist

Author	STROBE Checklist										
	Title and abstract	Background	Objectives	Study design	Setting	Participants (Methods)	Variables	Data sources/ measurement	Bias	Study size	Quantitative variables
Koh *et al.*	●	●	●	●	●	●	●	●	●	●	●
Bastos *et al.*	●	●	●	●	●	●	●	●	●	●	●
Espinosa *et al.*	●	●	●	●	●	●	●	●	●	●	●
Estrada *et al.*	●	●	●	●	●	●	●	●	●	●	●
Dulic *et al.*	●	●	●	●	●	●	●	●	●	●	●
Bastos *et al.*	●	●	●	●	●	●	●	●	●	●	●
Baria *et al.*	●	●	●	●	●	●	●	●	●	●	●
Venosa *et al.*	●	●	●	●	●	●	●	●	●	●	●

Author	STROBE Checklist										
	Statistical methods	Participants (result)	Descriptive data	Outcome data	Main results	Other analyses	Key results	Limitations	Interpretation	Generalisability	Funding
Koh *et al.*	●	●	●	●	●	●	●	●	●	●	●
Bastos *et al.*	●	●	●	●	●	●	●	●	●	●	●
Espinosa *et al.*	●	●	●	●	●	●	●	●	●	●	●
Estrada *et al.*	●	●	●	●	●	●	●	●	●	●	●
Dulic *et al.*	●	●	●	●	●	●	●	●	●	●	●
Bastos *et al.*	●	●	●	●	●	●	●	●	●	●	●
Baria *et al.*	●	●	●	●	●	●	●	●	●	●	●
Venosa *et al.*	●	●	●	●	●	●	●	●	●	●	●

● : Fulfilled criteria
● : Half-met criteria
● : Unfulfilled criteria

Both treatments also showed improvement from baseline for IKDC, knee ROM, knee, and function knee scores. IKDC however, was also found different in three studies, where two study found no difference between the two treatment groups [4], [20]. However, another one showed MSCs had better IKDC score compared to PRP group at 1 month after treatment [18]. Differences of results interpretation might be related to methodological aspects of the studies.

Risk of bias

Based on the STROBE checklist in Table 2, all the five articles had the most of fulfilled criteria, thus well written.

Discussion

MSCs are multipotent cells that have been used in various types of regenerative therapy because they can differentiate into osteocytes and chondrocytes. The use of MSCs utilizes the modulation of immune responses and inflammatory mechanisms underlying OA disease. These cells can be isolated from human tissues such as adipose tissue or bone marrow. The important role of MSCs in the regeneration process is to recruit other cells so that the healing process of tissue damage occurs faster [4], [5]. On the other hand, PRP is known to have the ability to reduce inflammatory stress and promote anabolism through regulation of the joint environment [22].

Several research have proven the clinical effects of MSC and PRP. MSC therapy is known to be a more effective modality for pain relief compared to PRP. Cao *et al.* in an article that comprehensively compared hyaluronic acid (HA), corticosteroids (GCs), PRP, and MSCs, demonstrated that MSC was most effective in relieving pain, stiffness, and improving dysfunction compared to the other three modalities in the article. In addition, from a safety perspective, both MSC and PRP are reported to be well tolerated by OA patients who use them for a long period [23]. Similar results were also shown by the studies of Lamo-Espinosa *et al*. [6] and Dulic *et al*. [18].

However, this result is different from the study conducted by Estrada *et al*., where neither MSC nor PRP showed any difference in functional scores in knee OA patients, although both were statistically significant in increasing these scores when compared to baseline. This conclusion may be influenced by differences in study methods, where the study of Estrada *et al*. did not randomize the treatment group but chose the type of treatment based on the severity of the patient's symptoms [4].

Several studies have also identified the combination of the two modalities discussed in this article. The results of Bastos *et al*.'s study regarding the combination of MSC and PRP as a treatment for knee OA stated that MSC with or without combination with PRP had thehighest percentage improvement in KOOS when compared to GCs [21]. It was also confirmed that there is no additional benefit was found by adding PRP to the use of MSC [17].

This review provides a reliable current comparison of the outcomes in intra-articular injection of MSCs to PRP as a treatment modality for knee OA. However, the number of studies is limited because several studies did not analyze the desired outcome variables but each studies that were presented came from different countries that may given various demographic background. Two studies also did not specifically exclude history of systemic illness in the samples. Systemic illness such as obesity, bone factors, nutrients, and genetic may become risk factor that interfere the outcomes [23]. These also explained the challenge of studies in OA because a lot of cases were associated with other systemic disease. Although, the bias had been minimalized using several assessments. It could not be denied that several details in the procedure might interfere the outcomes such as lack of quality control of the cells. Two studies did not use PRP or MCP as the first line treatment. These two studies included patients with history of HA and NSAID treatment. Although, these studies mentioned that the samples had been declared failed in the first therapy we still can presumed that this therapy may interfere the outcome and disease grade before the therapy. Those studies also did not mention for how long the samples got the therapy. A long period of HA and NSAID might have effects on the samples [23]. Additional variable such as Kellgren-Lawrance OA Grade post follow up can be added in the future studies as an objective outcome that can be measured by blinded authors.

Conclusion

Intra-articular injections are effective and safe for the management of knee OA. MSCs treatment has superior effect on the treatment outcomescompared to PRP treatment. Combination of both treatments is comparable to MSCs treatment alone. This systematic review could be used as reference for the establishment of standard of care for patients with knee OA.

Author Contribution

All authors contributed to conceptualizing, data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

References

1. CDC. Osteoarthritis. CDC; 2022. Available from: https://www.cdc.gov/arthritis/types/osteoarthritis.htm [Last accessed on 2022 Jun 14].
2. Kolasinski SL, Neogi MC, Hochberg MC, Oatis C, Guyatt G, Block J, *et al*. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Rhematol. 2020;72(2):220-33.
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. Clin Geriatr Med. 2010;26(3):355-69. https://doi.org/10.1016/j.cger.2010.03.001. Erratum in: Clin Geriatr Med. 2013;29(2):ix. PMid:20699159
4. Estrada E, Décima J, Rodríguez M, Di Tomaso M, Roberti J. Patient-reported outcomes after platelet-rich plasma, bone marrow aspirate, and adipose-derived mesenchymal stem cell injections for symptomatic knee osteoarthritis. Clin Med Insights Arthritis Musculoskelet Disord. 2020;13:117954412093108. https://doi.org/10.1177/1179544120931086 PMid:32669883
5. Fibel KH, Hillstrom HJ, Halpern BC. State-of-the-art management of knee osteoarthritis. World J Clin Cases. 2015;3(2):89-101. https://doi.org/10.12998/wjcc.v3.i2.89 PMid:25685755
6. Lamo-Espinosa J, Blanco J, Sánchez M, Moreno V, Granero-Moltó F, Sánchez-Guijo F, *et al*. Phase II multicenter randomized controlled clinical trial on the efficacy of intra-articular injection of autologous bone marrow mesenchymal stem cells with platelet rich plasma for the treatment of knee osteoarthritis. J Transl Med. 2020;18(1):356. https://doi.org/10.1186/s12967-020-02530-6 PMid:32948200
7. Bennell KL, Hunter DJ, Paterson KL. Platelet-rich plasma for the management of hip and knee osteoarthritis. Curr Rheumatol Rep. 2017;19(5):24. https://doi.org/10.1007/s11926-017-0652-x PMid:28386761
8. Andia I, Maffulli N. New biotechnologies for musculoskeletal injuries. Surgeon. 2019;17(4):244-255. https://doi.org/10.1016/j.surge.2018.08.004 PMid:30170915
9. Murphy JM, Fink DJ, Hunziker EB, Barry FP. Stem cell therapy in a caprine model of osteoarthritis. Arthritis Rheum. 2003;48(12):3464-74. https://doi. org/10.1002/art.11365 PMid:14673997
10. Haynesworth SE, Baber MA, Caplan AI. Cytokine expression by human marrow-derived mesenchymal progenitor cells *in vitro*: Efects of dexa-methasone and IL-1 alpha. J Cell Physiol. 1996;166(3):585-92. https://doi.org/10.1002/(SICI)1097-4652(199603)166:33.0.CO;2-6 PMid:8600162
11. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects

in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331(14):889-95. https://doi.org/10.1056/NEJM199410063311401

PMid:8078550

12. Knutsen G, Drogset JO, Engebretsen L, Grøntvedt T, Isaksen V, Ludvigsen TC, *et al*. A randomized trial comparing autologous chondrocyte implantation with microfracture. Findings at five years. J Bone Joint Surg Am. 2007;89(10):2105-12. https://doi.org/10.2106/JBJS.G.00003

PMid:17908884

13. Grassel S, Ahmed N. Influence of cellular microenvironment and paracrine signals on chondrogenic differentiation. Front Biosci. 2007;12:4946-56. https://doi.org/10.2741/2440

PMid:17569622

14. Sekiya I, Larson BL, Vuoristo JT, Reger RL, Prockop DJ. Comparison of effect of BMP-2,-4, and-6 on *in vitro* cartilage formation of human adult stem cells from bone marrow stroma. Cell Tissue Res. 2005;320(2):269-76. https://doi.org/10.1007/s00441-004-1075-3

PMid:15778851

15. Paoloni J, De Vos RJ, Hamilton B, Murrell GA, Orchard J. Platelet-rich plasma treatment for ligament and tendon injuries. Clin J Sport Med. 2011;21(1):37-45. https://doi.org/10.1097/JSM.0b013e31820758c7

PMid:2120016

16. Koh YG, Kwon OR, Kim YS, Choi YJ. Comparative outcomes of open-wedge high tibial osteotomy with platelet-rich plasma alone or in combination with mesenchymal stem cell treatment: A prospective study. Arthroscopy. 2014;30(11):1453-60. https://doi.org/10.1016/j.arthro.2014.05.036

PMid:25108907

17. Bastos R, Mathias M, Andrade R, Bastos R, Balduino A, Schott V, *et al*. Intra-articular injections of expanded mesenchymal stem cells with and without addition of platelet-rich plasma are safe and effective for knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2018;26(11):3342-50. https://doi.org/10.1007/s00167-018-4883-9

PMid:29511819

18. Dulic O, Rasovic P, Lalic I, Kecojevic V, Gavrilovic G, Abazovic D, *et al*. Bone marrow aspirate concentrate versus platelet rich plasma or hyaluronic acid for the treatment of knee osteoarthritis. Medicina (Kaunas). 2021;57(11):1193. https://doi.org/10.3390/medicina57111193

PMid: 34833411

19. Bastos R, Mathias M, Andrade R, Amaral R, Schott V, Balduino A, *et al*. Intra-articular injection of culture-expanded mesenchymal stem cells with or without addition of platelet-rich plasma is effective in decreasing pain and symptoms in knee osteoarthritis: A controlled, double-blind clinical trial. Knee Surg Sports Traumatol Arthrosc. 2019;28(6):1989-99. https://doi.org/10.1007/s00167-019-05732-8

PMid:31587091

20. Venosa M, Calafiore F, Mazzoleni M, Romanini E, Cerciello S, Calvisi V. Platelet-rich plasma and adipose-derived mesenchymal stem cells in association with arthroscopic microfracture of knee articular cartilage defects: A pilot randomized controlled trial. Adv Orthop. 2022;2022:6048477. https://doi.org/10.1155/2022/6048477

PMid:35529427

21. Baria M, Pedroza A, Kaeding C, Durgam S, Duerr R, Flanigan D, *et al*. Platelet-rich plasma versus microfragmented adipose tissue for knee osteoarthritis: A randomized controlled trial. Orthopaedic J Sports Med. 2022;10(9):23259671221120678. https://doi.org/10.1177/23259671221120678

PMid:36147791

22. Kon E, Di Matteo B, Delgado D, Cole BJ, Dorotei A, Dragoo JL, *et al*. Platelet-rich plasma for the treatment of knee osteoarthritis: An expert opinion and proposal for a novel classification and coding system. Expert Opin Biol Ther. 2020;20(12):1447-60. https://doi.org/10.1080/14712598.2020.1798925

PMid:32692595

23. Cao Z, Li Y, Gao F, Wu R, Dou P, Wang W, *et al*. Mesenchymal stem cells: A new choice for nonsurgical treatment of OA? Results from a Bayesian network meta-analysis. Biomed Res Int. 2021;2021:6663003. https://doi.org/10.1155/2021/6663003

PMid:33614784