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

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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?

Targeted articles were within 10 years of publication and were extracted based on: 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.
1. There was significant improvement 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).
3. The decrease of mean value of VAS for bone marrow mesenchymal stem 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)
4. 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 = 0.003).

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 activities (p = 0.017) as well as quality of life (p = 0.027).

Table 1: Characteristics of studies included in this systematic review

<table>
<thead>
<tr>
<th>First author and year</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size (N)</th>
<th>Disease grade</th>
<th>Mean or median age (years)</th>
<th>Identified outcome</th>
<th>Results summary</th>
<th>Excluding systemic disease and other form of arthritis</th>
<th>Excluding samples with history of other treatments</th>
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</thead>
<tbody>
<tr>
<td>Koh et al [16] (2014)</td>
<td>Korea</td>
<td>Prospective cohort</td>
<td>MSCs: 21 + PRP: 23</td>
<td>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)</td>
<td>PRP: 52.3 MSCs+PRP: 54.2</td>
<td>The Knee Injury and Osteoarthritis Outcome Score (KOOS)</td>
<td>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 &lt; 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 &lt; 0.001). No, only other form of arthritis was excluded</td>
<td>Not specific, including samples with failure of conservative treatment but excluding intra articular interventions within 3 months</td>
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<tr>
<td>Bastos et al [17] (2018)</td>
<td>Brazil</td>
<td>Prospective cohort</td>
<td>MSCs: 9 + MSCs: 9</td>
<td>18-year cohort</td>
<td></td>
<td></td>
<td>1. There was significant improvement of KOOS subscales 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) No difference between groups for the KOOS subscales and global score improvements at 12-month end-point (p=0.05)</td>
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<tr>
<td>Espinosa et al [8] (2020)</td>
<td>Argentina</td>
<td>Prospective cohort</td>
<td>MSCs: 26 + PRP: 24</td>
<td>Kellogg-Lawrence 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)</td>
<td>MSCs: 54.7 MSCs+PRP: 60.4</td>
<td>KOOS</td>
<td>1. The decrease of mean value of VAS for bone marrow mesenchymal stem 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 = 0.003) No, only other form of arthritis was excluded</td>
<td>Not specific, including samples with previous failed treatment with hyaluronic acid but excluding NSAID therapy</td>
<td></td>
</tr>
<tr>
<td>Estrada et al [4] (2020)</td>
<td>Argentina</td>
<td>Prospective cohort</td>
<td>MSCs: Bone marrow derived: (33) + PRP: 29</td>
<td>Kellogg-Lawrence Osteoarthritis Grade: - Grade I: 29(PRP: 29; MSCs: 0) - Grade II: 27(PRP: 0; MSCs Bone Marrow: 27) - Grade III: 33(PRPR: 0; MSCs Adipose-derived: 33) - Grade IV: 0</td>
<td>Median age of total group: 61</td>
<td>International Knee Documentation Committee (IKDC) score - Knee score - Functional knee score</td>
<td>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 &lt; 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&lt;0.05). Yes</td>
<td>Yes</td>
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### Table 1: (Continued)

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size (N)</th>
<th>Disease Grade</th>
<th>Mean or median age (years)</th>
<th>Identified outcome</th>
<th>Results summary</th>
<th>Excluding systemic disease and other form of arthritis</th>
<th>Excluding samples with history of Other Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulic et al. [18] (2021)</td>
<td>Serbia</td>
<td>Prospective cohort</td>
<td>MSCs: 111 PRP: 34</td>
<td>Kellgren-Lawrence Osteoarthritis Grade: - Grade I: 0</td>
<td>MSCs: 56.9 PRP: 58.8</td>
<td>KOOS</td>
<td>VAS</td>
<td>WOMAC</td>
<td>IKDC</td>
</tr>
<tr>
<td>Bastos et al. [19] (2019)</td>
<td>Brazil</td>
<td>Prospective cohort (RCT)</td>
<td>MSCs: 16 MSCs + PRP: 14</td>
<td>Kellgren-Lawrence Osteoarthritis Grade: - Grade I: 2 (MSCs = 1; MSCs+PRP = 1)</td>
<td>MSCs: 55.7 MSCs+PRP: 60.8</td>
<td>KOOS</td>
<td>Knee ROM (hyperextension, flexion, and total flexion)</td>
<td>Yes</td>
<td>Yes</td>
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<td></td>
<td></td>
<td>- Grade II: 10 (MSCs = 7; MSCs+PRP = 13).&lt;br&gt;- Grade III: 11 (MSCs = 5; MSCs+PRP = 6).&lt;br&gt;- Grade IV: 7 (MSCs = 3; MSCs+PRP = 4)</td>
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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 1: (Continued)

<table>
<thead>
<tr>
<th>First author (publication year)</th>
<th>Country</th>
<th>Study design</th>
<th>Sample size (N)</th>
<th>Disease Grade</th>
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<th>Excluding samples with history of Other Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baria et al. [21] (2022)</td>
<td>USA</td>
<td>Prospective cohort (RCT)</td>
<td>PRP: 30</td>
<td>MSCs: 28</td>
<td>Kellgren-Lawrence Osteoarthritis Grade: - Grade I: (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)</td>
<td>MSCs: 51.9 - KOOS: 56.1</td>
<td>- KOOS - VAS</td>
<td>Yes</td>
</tr>
<tr>
<td>Venosa et al. [20] (2022)</td>
<td>Italy</td>
<td>Prospective cohort (RCT)</td>
<td>PRP: 19</td>
<td>PRP+MSCs: PRP: 19</td>
<td>Joint Cartilage Breakdown Outerbridge Classification: - Grade I: 0 - Grade II: 0 - Grade III: 0 - Grade IV: 38 (PRP: 19; MSCs+PRP: 19)</td>
<td>PRP: 56.4 - MScs+PRP: 55.8</td>
<td>- IKDC - KOOS - VAS</td>
<td>Yes</td>
</tr>
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</table>

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.
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 the highest 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 give 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-Lawrence 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 outcomes compared 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

PMid:20699159
PMid:3269883
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