Effect of Platelet-Rich Plasma and Mesenchymal Stem Cells as Two Biological Alternatives in Rotator Cuff Injury Treatment: A Mini-Review

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ABSTRACT

The rotator cuff injury introduces as significant damage of trauma and others factors, and currently recognized as a prevalent orthopedic problem. Thus, many clinical procedures have been demonstrated to reduce the complication of rotator cuff injury with varying degrees of success. Platelet-Rich Plasma (PRP) is being enchantingly agreed as one of the most effectiveness strategies for the symptomatic treatment of rotator cuff injury. Many confusing parameters can influence the result of PRP including size of rotator cuff injury, patient age, PRP producing strategy, and number and timing of PRP injections. However, there is some evidences which support beneficial effect PRP in term relieving pain and restoring function, along with minimal adverse effect, in compared with corticosteroids, and other nonsurgical methods. Besides platelet-rich plasma, Mesenchymal Stem Cells (MSCs) are another biological alternative that can be used to treat rotator cuff injuries. Due to lack of large clinical trials applicability, these biological cells have challenges fairly similar to PRP. In conclusion, there is a need for further research to understand the potential application of both of these alternatives as a safe and effective therapeutic option for rotator cuff injuries.

Article Type:
Review Paper

Keywords:
Platelet-rich plasma, Mesenchymal stem cells, Rotator cuff injury

Introduction

The rotator cuff consists of four muscles in addition to tendons that serve to fix the ball of the shoulder within the joint [1, 2]. They also help to rotate the arms and assist in lifting [1, 2]. Any damage to these muscles or tendons causes irreparable injury to the shoulder, which results in pain and inflammation [1, 2].

Rotator cuff problems, including rotator cuff tears, are one of the most prevalent orthopedic conditions (the occurrence probability is approximately 7% to 34%), and that have increase its outbreak annually and the risk of sustaining such an injury rises with age [1-3].

While the common therapeutic modalities for rotator cuff tears include both surgical and nonsurgical management (e.g. exercise and rehabilitation), these methods are inefficient to treat this disease and can lead to unin-
tended consequences [4, 5]. Furthermore, these methods do not have the ability to reverse the loss of structure and mobility in the shoulder [6]. Because of the challenges associated with conventional therapies, efforts to find more efficient and safe treatments for rotator cuff tears continue [7]. Among these new treatments, biological methods, including Platelet-Rich Plasma (PRP) and Mesenchymal Stem Cells (MSCs), are considered both efficient and safe (Figure 1) [8].

**Use of platelet-rich plasma in rotator cuff injury treatment**

The results of numerous studies have shown that various growth factors and cytokines, including basic Fibroblast Growth Factor (bFGF), Vascular Endothelial Growth Factor (VEGF), Insulin-like Growth Factor 1 (IGF-1), Bone Morphogenetic Proteins (BMP), and Transforming Growth Factor-β3 (TGF-β3) may have a favorable effect on tear healing [9, 10].

PRP, a biological concentrate that contains a large amount of a number of growth factors, such as Transforming Growth Factor-β1 (TGF-β1), angiopoietin-1 (Ang-1), and Angiopoietin-2 (Ang-2), can be considered a therapeutic factor for the improvement of rotator cuff tear healing [9, 11-13].

Data obtained from in vivo studies appear to indicate that the application of PRP may have a therapeutic effect on rotator cuff tears [14]. Furthermore, some clinical trial studies also reported positive outcome of therapeutic usage of PRP in patients with rotator cuff tears in short-term [15-18]. So that, re-tear rate, pain, and shoulder function in patient were among the symptoms that were improved by using PRP in patients with rotator cuff tears [19]. Thus, PRP therapy is suggested as an auxiliary therapy in arthroscopic rotator cuff repair for ameliorated short period of time outcomes [19]. However, several clinical studies have reported contradictory findings in terms of the appropriateness of PRP for rotator cuff tears [20].

Several confounding factors could have led to these contradictions, including patient age, number and timing PRP injection, the different protocols and materials used in Randomized Clinical Trials (RCTs) to produce and processing the PRP, along with the various commercial methods that are available for this procedure, as well as a lack of homogeneity in studies and differences in the sizes of rotator cuff tears and the methods used for this damaged tissue repair [3].

For example, some studies have shown that PRP can play a role in reducing vascularity and cellularity and improving apoptosis in rotator cuff tears [21]. In addition, previous studies have demonstrated that PRP can considerably reduce re-tear rates in rotator cuff tears larger than 3cm in anterior-posterior length by combination with a double-row technique [22].

One research study demonstrated that PRP was most successful at relieving pain and restoring function in symptomatic partial rotator cuff tears in comparison with other...
treatments, including corticosteroids [23]. However, most level I and II clinical studies have reported that platelet-rich plasma was not efficacious in terms of treating patients with rotator cuff tendinopathy compared to controls [3].

Thus, high-quality evidence and data associated with the therapeutic use of PRP for rotator cuff tear treatment is insufficient and remains limited, and small clinical trial just also demonstrates hopeful result of PRP use in rotator cuff tendinopathy cure; however, more clinical trials are needed to increase the number of findings and improve understanding of the function of PRP for the treatment of rotator cuff injury [24].

Some clinical studies using PRP for the treatment of rotator cuff injury are listed in Table 1 [15, 23, 25-33].

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Clinical Trial Type</th>
<th>Number of Patients</th>
<th>Follow Up (Months)</th>
<th>Outcome</th>
<th>Years/ References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberto Castricini et al</td>
<td>A Randomized Controlled Trial</td>
<td>48</td>
<td>16</td>
<td>There was no significant difference in the treatment of rotator cuff injury</td>
<td>2011 [25]</td>
</tr>
<tr>
<td>Pietro Randelli et al</td>
<td>A prospective Randomized Controlled Trial study</td>
<td>53</td>
<td>24</td>
<td>There was no significant difference in the treatment of rotator cuff injury</td>
<td>2011 [26]</td>
</tr>
<tr>
<td>Pietro S. Randelli et al</td>
<td>A pilot study</td>
<td>14</td>
<td>24</td>
<td>There was a significant decrease in VAS scores and significant increases in the UCLA.</td>
<td>2008 [27]</td>
</tr>
<tr>
<td>Serdar Kesikburun et al</td>
<td>A Randomized Controlled Trial</td>
<td>40</td>
<td>12</td>
<td>There was no significant difference in the treatment of rotator cuff injury</td>
<td>2013 [28]</td>
</tr>
<tr>
<td>Dong-wook Rha et al</td>
<td>A Randomized Controlled Trial</td>
<td>39</td>
<td>6</td>
<td>There was no significant difference in the treatment of rotator cuff injury. No severe adverse effects were observed in either group.</td>
<td>2012 [29]</td>
</tr>
<tr>
<td>Chris Hyunchul Jo et al</td>
<td>A Prospective Cohort Study</td>
<td>42</td>
<td>16</td>
<td>There was no significant difference in the treatment of rotator cuff injury</td>
<td>2011 [30]</td>
</tr>
<tr>
<td>Chris Hyunchul Jo et al</td>
<td>A Randomized, Single-Blind, Parallel-Group Trial</td>
<td>48</td>
<td>12</td>
<td>There was a significantly improved structural outcomes, as evidenced by a decreased retear rate and increased CSA of the supraspinatus.</td>
<td>2013 [31]</td>
</tr>
<tr>
<td>Chris Hyunchul Jo et al</td>
<td>A Randomized Controlled Trial</td>
<td>74</td>
<td>12</td>
<td>There was a significant improved the quality, as evidenced by a decreased retear rate and increased CSA of the supraspinatus.</td>
<td>2015 [32]</td>
</tr>
<tr>
<td>Ho-Won Lee et al</td>
<td>Prospective Clinical Research</td>
<td>60</td>
<td>6</td>
<td>PRP injection was more effective than exercise therapy for the first 3 months.</td>
<td>2019 [33]</td>
</tr>
<tr>
<td>Yasmin Khairy et al</td>
<td>A Randomized Controlled Trial</td>
<td>60</td>
<td>3</td>
<td>There was improves patients’ quality of life clinically, functionally and structurally.</td>
<td>2019 [15]</td>
</tr>
<tr>
<td>Ruben Du-kan et al</td>
<td>A prospective study</td>
<td>69</td>
<td>24</td>
<td>There was significant difference in the clinical and radiological results treatment of rotator cuff injury at 3 months</td>
<td>2019 [16]</td>
</tr>
<tr>
<td>Doaa H. Ibrahim et al</td>
<td>A Randomized Controlled Trial</td>
<td>30</td>
<td>Approximately 2</td>
<td>There was a significant improvement in the tear and effusion</td>
<td>2019 [34]</td>
</tr>
</tbody>
</table>

In addition, some protocols and materials used in PRP preparation for the treatment of rotator cuff injury are listed in Table 2 [15, 23, 25, 28, 34, 35].

**Use of mesenchymal stem cells in rotator cuff injury treatment**

Apart from PRP, Mesenchymal Stem Cells (MSCs) are another biological alternative that can be used to treat rotator cuff injuries too [36]. MSCs are one type of adult stem cells that are among the most widely used for discovering efficient approaches to cell therapies [37]. Currently, a growing body of evidence recommends that MSCs play a crucial role in comforting tissue regeneration by improving cell proliferation, differentiation, and growth processes, as well as inhibiting inflammation and...
secreting a wide range of growth factors and cytokines associated with repair [37]. Furthermore, due to their immunomodulatory, immunogenicity, and fairly easy separation, MSCs are considered a therapeutic alternative for musculoskeletal conditions, such as rotator cuff injuries [38, 39].

As biological agents, bone marrow- and adipose-derived MSCs are two of the most important sources of MSCs for treating various conditions, including rotator cuff injuries [38]. These particular stem cells offer the benefit of a paracrine mechanism in addition to proliferation, differentiation, and anti-apoptotic activity [38-40].

Table 2. Some protocols and materials used in PRP preparation for the treatment of rotator cuff injury

<table>
<thead>
<tr>
<th>Study</th>
<th>Volume of Whole Blood (mL)</th>
<th>Force (rpm) / Time(Min)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doaa H. Ibrahim et al</td>
<td>20</td>
<td>700–1500 15–20</td>
<td>2500–3500 10</td>
</tr>
<tr>
<td>Yasmin Khairy et al</td>
<td>nr</td>
<td>1000 10 3000</td>
<td>15</td>
</tr>
<tr>
<td>Serdar Kesikburun et al</td>
<td>54</td>
<td>3200 15</td>
<td>-</td>
</tr>
<tr>
<td>Ahmed Shams et al</td>
<td>10</td>
<td>3500 10</td>
<td>-</td>
</tr>
<tr>
<td>Andrew J. Carr et al</td>
<td>50</td>
<td>nr nr</td>
<td>nr</td>
</tr>
<tr>
<td>Roberto Castricini et al</td>
<td>9</td>
<td>1100 6 4500 relative centrifugal force [RCF]</td>
<td>5</td>
</tr>
<tr>
<td>Dong-wook Rha</td>
<td>25</td>
<td>1600×g nr</td>
<td>2000×g nr</td>
</tr>
</tbody>
</table>

Table 3. Some clinical studies using MSCs for the treatment of rotator cuff injury

<table>
<thead>
<tr>
<th>Researchers</th>
<th>Clinical Trial Type</th>
<th>Number of Patients</th>
<th>Follow up (Months)</th>
<th>Outcome</th>
<th>Years/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brian J. Cole et al</td>
<td>A Prospective Randomized Trial</td>
<td>62</td>
<td>24</td>
<td>There was improved tendon quality on post-operative MRI at 1-year</td>
<td>2019 [44]</td>
</tr>
<tr>
<td>Philippe Hernigou et al</td>
<td>A case-controlled study</td>
<td>45</td>
<td>24</td>
<td>There was a successful repair during an interval.</td>
<td>2014 [45]</td>
</tr>
<tr>
<td>Philippe Hernigou et al</td>
<td>Not reported</td>
<td>125</td>
<td>Not reported</td>
<td>There was no significant difference in the treatment of rotator cuff injury</td>
<td>2015 [46]</td>
</tr>
<tr>
<td>Yong Sang Kim et al</td>
<td>A Clinical and Magnetic Resonance Imaging Study</td>
<td>182</td>
<td>28</td>
<td>There was significantly improve structural outcomes in terms of the retear rate</td>
<td>2017 [43]</td>
</tr>
<tr>
<td>V. Havlas et al</td>
<td>A Preliminary study</td>
<td>10</td>
<td>6</td>
<td>There were, however, no clinical differences in the 28-month period of follow-up.</td>
<td>2015 [47]</td>
</tr>
<tr>
<td>Sang Yoon Lee et al</td>
<td>A Pilot Study</td>
<td>12</td>
<td>12</td>
<td>Allo-ASC therapy was thus safe and effective in improving elbow pain, performance, and structural defects for 52 weeks.</td>
<td>2015 [48]</td>
</tr>
</tbody>
</table>
Numerous preclinical studies and one clinical study have confirmed the positive effects of bone marrow- and adipose-derived MSCs on animal models and patients with rotator cuff injuries, respectively [38, 41].

Similar to PRP, however, bone marrow- and adipose-derived MSCs are limited in terms of their use in a clinical setting [3, 42]. Therefore, there is a need for further research to understand the potential application of MSCs as a safe and effective therapeutic option for rotator cuff injuries. Although, an unpublished clinical trial performed on 18 patients with rotator cuff injuries reported that use of adipose-derived MSCs can contribute to the repair of partially torn rotator cuffs [43]. Furthermore, the adipose-derived MSCs treatment used in this study received safety approval from the Food and Drug Administration (FDA) for its use in rotator cuff injuries [43].

Recently, according to the results of a prospective randomized trial, the ability to use bone marrow-derived MSCs to improve patients undergoing arthroscopic rotator cuff repair has been confirmed [44]. In this study, it was demonstrated that injection of bone marrow-derived MSCs could supply a treatment strategy for 34 patients with a full-thickness supraspinatus tear or partial thickness converted to full thickness tear after one year’s follow-up [44]. Some clinical studies using MSCs for the treatment of rotator cuff injury are listed in Table 3 [44-48].

In addition to mesenchymal stem cells, their exosomes can also be used as adjuncts to aid in shoulder regeneration because of their paracrine mechanism and regeneration ability [49]. For instance, Wang et al. (2019) reports that adipose-derived MSCs-Exosomes can significantly reduce degeneration and atrophy and ameliorate muscle repair and biomechanical characters in torn rotator cuff muscles [50]. Furthermore, Shi et al. (2019) demonstrate that the local injection of bone marrow-derived MSCs-Exosomes stimulate tendon regeneration by inhibiting apoptosis and inflammation mechanism and improving the proportion of tendon-resident stem/progenitor cells [51]. These results supply a basis for the potential clinical administration of exosomes derived MSCs in tendon healing.

**Conclusion and Future Perspective**

PRP may be accounted as a hoping option for the treatment of rotator cuff injury, and preclinical and clinical evidence to date have demonstrate that PRP is safe. However, verified results of its efficiency has been combined and highly variable depending on the specific parameters, such as patient age, number and timing PRP injection, the different protocols and materials used in Randomized Clinical Trials (RCTs) to produce and processing the PRP. More high-quality huge clinical trials will be necessary in providing our understanding of this treatment strategy in near future.

Due to repairing ability of MSCs, especially AD-MSCs and BM-MSCs, in musculoskeletal regenerative medicine, they could be used as one of most important cell source for disease treatment. MSC-Based therapy could help propel progress to a rotator cuff injury, especially now that great progress is being made in isolating and differentiating adipose-derived and bone marrow-derived mesenchymal stem cells. Although pre-clinical and clinical studies have provided promising results for the use of these cells in the disease treatment, however, larger and higher-quality studies are needed to gain a more accurate understanding of the therapeutic mechanism and efficacy of this strategy in future.

Taken together, the preclinical studies’ results strongly suggested that PRP and MSCs may play a curative role in rotator cuff injuries, however, further clinical studies are needed to reach greater potential for therapeutic application.

**Ethical Considerations**

**Compliance with ethical guidelines**

All ethical principles were considered in this article.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Authors contribution's**

Review, draft-writing: Mohsen Sheykhasan; Review & editing: Hamed Manoochehri, Pouria Samadi, Reza Fotouhi-Ardakani; Supervision: Naser Kalhor.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**Acknowledgements**

We express my deepest gratitude to Mrs. Farzaneh Chitsaz for her help in figure preparation.
References


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