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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.

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-

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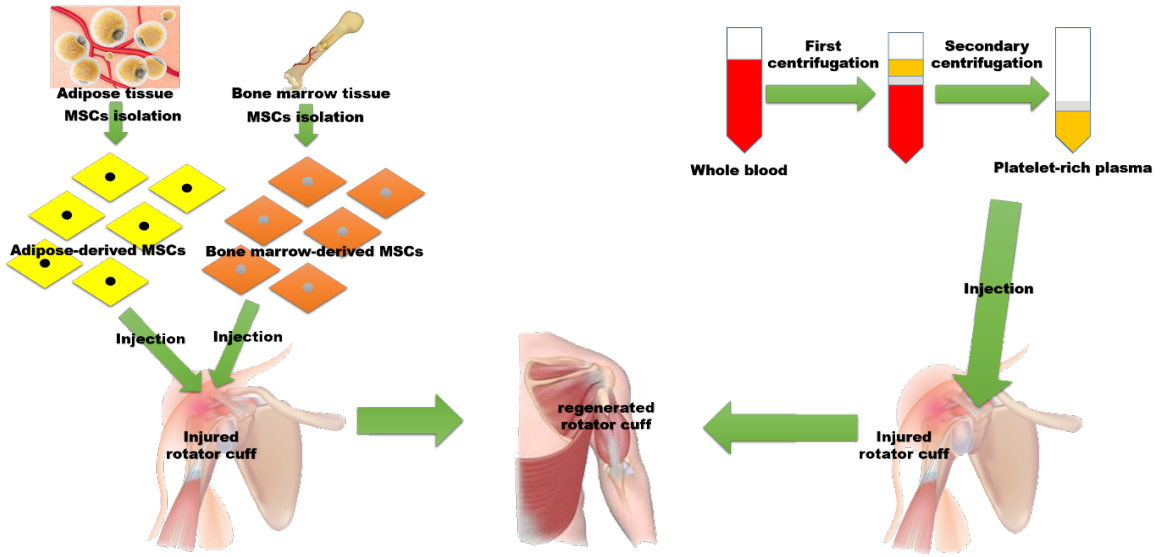

Figure 1. The importance of MSCs and PRP therapy for rotator cuff tears. The figure schematically demonstrates the ability of PRP and MSCs, especially AD- and BM-derived MSCs, in rotator cuff tear treatment.

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 single-row 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, 16, 25-33].

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

Table 1. Some clinical studies using PRP for the treatment of rotator cuff injury

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

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

Study	Volume of Whole Blood (mL)	Force (rpm) / Time(Min)				References
		First Centrifugation		Secondary Centrifugation		
Doaa H. Ibrahim et al	20	700–1500	15–20	2500–3500	10	[34]
Yasmin Khairy et al	nr	1000	10	3000	15	[15]
Serdar Kesikburun et al	54	3200	15	-	-	[28]
Ahmed Shams et al	10	3500	10	-	-	[23]
Andrew J. Carr et al	50	nr	nr	nr	nr	[35]
Roberto Castricini et al	9	1100	6	4500 relative centrifugal force [RCF]	5	[25]
Dong-wook Rha	25	1600×g	nr	2000×g	nr	[29]

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

Researchers	Clinical Trial Type	Number of Patients	Follow up (Months)	Outcome	Years/References
Brian J. Cole et al	åA Prospective Randomized Trial	62	24	There was improved tendon quality on post-operative MRI at 1-year	2019 [44]
Philippe Hernigou et al	A case-controlled study	45	24	There was a successful repair during an interval.	2014 [45]
Philippe Hernigou et al	Not reported	125	Not reported	There was no significant difference in the treatment of rotator cuff injury.	2015 [46]
Yong Sang Kim et al	A Clinical and Magnetic Resonance Imaging Study	182	28	There was significantly improve structural outcomes in terms of the retear rate. There were, however, no clinical differences in the 28-month period of follow-up.	2017 [43]
V. Havlas et al	A Preliminary study	10	6	using human cultured autologous MSCs in the treatment of rotator cuff tears is safe	2015 [47]
Sang Yoon Lee et al	A Pilot Study	12	12	Allo-ASC therapy was thus safe and effective in improving elbow pain, performance, and structural defects for 52 weeks.	2015 [48]

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].

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.

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Authors contribution's

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Conflict of interest

The authors have no conflicts of interest to declare.

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