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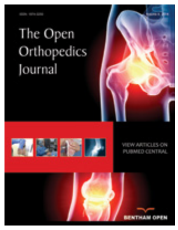

RESEARCH ARTICLE

The Role of Platelet Rich Plasma (PRP) and Other Biologics for Rotator Cuff Repair

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Abstract:

Background:

Surgical treatment of rotator cuff tears has consistently demonstrated good clinical and functional outcomes. However, in some cases, the rotator cuff fails to heal. While improvements in rotator cuff constructs and biomechanics have been made, the role of biologics to aid healing is currently being investigated.

Methods:

A selective literature search was performed and personal surgical experiences are reported.

Results:

Biologic augmentation of rotator cuff repairs can for example be performed wtableith platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs). Clinical results on PRP application have been controversial. Application of MSCs has shown promise in animal studies, but clinical data on its effectiveness is presently lacking. The role of Matrix Metalloproteinase (MMP) inhibitors is another interesting field for potential targeted drug therapy after rotator cuff repair.

Conclusions:

Large randomized clinical studies need to confirm the benefit of these approaches, in order to eventually lower retear rates and improve clinical outcomes after rotator cuff repair.

Keywords: Biologics, Platelet rich plasma, Regenerative medicine, Rotator cuff, Shoulder, Stem cells.

INTRODUCTION

The goal of rotator cuff repair is to restore function, improve pain, and to achieve healing of the involved tendons. Significant improvements in the biomechanics of rotator cuff repair constructs have been made over the past decade [1 - 3]. However, reported retear rates following rotator cuff repair have remained high [4 - 6]. Therefore attention has turned to ways in which the healing environment can be enhanced to promote healing of the rotator cuff tendons back to the bone. Specifically, biologically active materials have been designed to enhance the strength and quality of the repaired tissue at the tendon footprint. Many biologic factors contribute to the coordination and implementation of the healing response. In an attempt to augment healing after surgery, many investigators have studied how to enhance physiologic healing. These include addition of growth factors and cells to the repair site as well as the use of suture materials and different surgical repair techniques. The purpose of this paper is to highlight the role of platelet rich

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plasma (PRP) and other biologic agents used to enhance healing in rotator cuff repair.

OVERVIEW OF TENDON HEALING

When a tendon is injured, the body employs a complex healing response involving many signaling molecules. Generally, the healing process is thought to occur in three overlapping stages. The first stage (or "inflammatory phase") is an acute response lasting several days in which an inflammatory response results in infiltration of the wound site with red blood cells, leukocytes, and platelets [7]. The platelets contain important signaling molecules that coordinate the repair process. A fibrin clot is formed allowing for macrophages to remove necrotic waste [7]. Tenocytes are recruited and proliferate. The second stage (or "proliferative phase") begins approximately two days after injury [7]. Macrophages assume a reparative role and release growth factors as well as signaling molecules to recruit additional cells. Tenocytes start synthesizing a temporary matrix composed primarily of type III collagen [7]. The third or "remodeling" phase of healing begins 1-2 months after injury in which the type III collagen is replaced by biomechanically superior type I collagen.

PLATELET RICH PLASMA (PRP)

Platelet rich plasma (PRP) is a centrifuged blood product that contains a supraphysiologic amount of platelets. These platelets release biologic factors including basic fibroblast growth factor (FGF2), vascular endothelial growth factor (VEGF), and transforming growth factor β (TGF β) which have been shown to improve proliferation and collagen secretion of tenocytes *in vitro* [8 - 11]. In addition to promoting tendon cell growth, PRP has been shown to decrease oxidative stress that could lead to cell apoptosis [12].

Several studies have investigated the clinical results PRP has on rotator cuff healing [13 - 22]. Malavolta *et al.* recently published the results of their randomized controlled trial investigating the structural and functional outcomes of rotator cuff repairs with or without PRP at the time of surgery [17]. The two groups of 27 patients had complete full thickness tears of the supraspinatus and underwent single row repairs with or without the use of PRP. Both groups had significant improvement in functional scores at 2 years of follow-up as measured by the Constant and University of California at Los Angeles (UCLA) scores [17]. Overall, there were no differences in outcomes at 24 months between the two groups. In addition, the two groups had comparable retear rates as determined by magnetic resonance imaging (MRI) [17].

Wang *et al.* conducted a well-designed randomized controlled study investigating if PRP injections at 7 and 14 days postoperatively improved healing and early functional recoveries [20]. Sixty patients underwent arthroscopic double-row surgeries, half of which received postoperative PRP injections. Healing was assessed at 16 weeks postoperatively using MRI [20]. The authors concluded that PRP treatment did not improve early functional recovery, range of motion, strength, or pain levels. Furthermore, there was no statistically significant difference in structural integrity of the repair between the two groups [20]. However, there were 2 full thickness retears in the control group and 0 in the PRP group. This finding is consistent with previous reports, such as that of Castricini *et al.* who reported a higher rerupture rate in their control group of 10.5% *vs* 2.5% in the PRP group [14]. Their patient cohor consisted of 88 patients randomly assigned to two groups and completed a Constant score and had an MRI an average of 20 months postoperatively.

Charousset *et al.* conducted a case-control study with the intention of determining functional and structural differences between patients with double row rotator cuff repairs with or without PRP injections [23]. There were no differences in rotator cuff healing as assessed by MRI between the two groups. The retear rate was 35.5% for the PRP group and 40% for the control group [23]. However the size of the recurrent tears was smaller in the group of patients who received PRP [23]. Similar to the studies mentioned above, there were no functional differences between the two groups at a minimum of two years postoperatively.

A randomized controlled trial conducted by Jo *et al.* showed improvement in structural outcomes in patients who underwent arthroscopic rotator cuff repair of large to massive tears and received PRP [16]. There was a significantly lower retear rate in patients who received PRP (3.0%) compared to those who did not (20.0%) [16]. Patients who received PRP also had significantly larger cross sectional areas of the supraspinatus, leading the authors to conclude that PRP use increases the quality of the tendon healing postoperatively [16]. Importantly, PRP did not increase the speed of healing, and functional outcomes between the two groups were equivalent [16].

In a separate randomized contolled study, Randelli *et al.* found less postoperative pain and accelerated healing rates in patients with non- massive rotator cuff tears when PRP was used [18]. A total of 53 patients were included. The

UCLA, SST, Constant scores, and strength in external rotation were significantly higher in the PRP group at 3 months postoperatively, however, these differences were not evident at 6, 12, or 24 months postoperatively [18].

Given the conflicting results and varying protocols of the studies investigating PRP in the setting of rotator cuff repair, several authors have conducted meta-analyses of these studies in order to further assess the data [24, 25]. Warth *et al.* analyzed 11 level 1 or level 2 studies [25]. The results of the meta-analysis indicated that there were no global differences in clinical outcomes between patients who received PRP and those that did not [25]. Meta-regression did indicate that the overall gain in the Constant score was increased when PRP was placed at the tendon bone interface rather than over the surface of the repaired tendon [25]. Subgroup analysis revealed significantly lower retear rates with PRP application in patients who underwent double-row repairs for large (> 3 cm) rotator cuff tears [25]. This finding is of particular interest, as retear rates in large and massive rotator cuff tears are much higher than in smaller tears, making large and massive tears the main target for adjuncts to improve healing.

Vavken *et al.* conducted a meta-analysis and cost-effectiveness analysis on the use of PRP based on 13 published studies [24]. Different to the findings of Warth *et al*. the authors found PRP to be effective in reducing retear rates in the arthroscopic repair of small and medium sized rotator cuff tears, however there was no evidence that retear rates decreased for large and massive tears [24]. With the current cost of PRP, the cost-effectiveness analysis indicated that the use of PRP is currently not cost-effective [24]. The reductions in retear rates for small and medium sized rotator cuff tears is consistent with a trend noted in a systematic review by Chahal *et al.* [26]. While the impact of PRP injections on retear rates differed based on tear size in the two meta-analyses, overall the two reviews suggest PRP may play a role in the healing of rotator cuff repairs.

Given the inconsistent clinical results, the use of PRP to enhance healing of the rotator cuff following surgery remains an area of debate. Additional basic science research is needed to enhance our understanding of the tendon healing process and future randomized clinical studies with sufficient sample sizes are needed to determine the optimal timing, preparation, and concentration of PRP products to enhance physiologic healing.

MATRIX METALLOPROTEINASE (MMP) INHIBITORS

Matrix metalloproteinases (MMPs) are zinc-dependent proteases that maintain and model the extracellular matrix [27]. While numerous MMPs exist, generally their role in remodeling extracellular matrix inhibits tendon healing following rotator cuff repair. The tetracycline family of antibiotics has properties independent of their antimicrobial activity that allows them to inhibit MMPs and therefore reduce degradation and remodeling after rotator cuff repair [27]. Bedi and colleagues used a rat model to analyze the effects of oral doxycycline taken after rotator cuff repair [27]. They found that the perioperative use of doxycycline influences early healing after rotator cuff repair, resulting in greater amounts of fibrocartilage as well as improved collagen organization. When the repair was tested biomechanically, the group treated with doxycycline had a significantly greater load to failure at 2 weeks compared to controls [27].

In contrast, fluoroquinolone antibiotics have been argued to potentially favour tendinopathy and tendon ruptures. Accordingly, Fox *et al*. recently reported that fluoroquinolone treatment negatively influenced tendon healing in rats who underwent rotator cuff repair [28].

Of particular relevance in orthopaedic surgery, the use of the non-steroidal anti-inflammatory drug (NSAID) diclofenac was shown to significantly influence levels of MMP-2, MMP-3 and MMP-13 after rotator cuff repair in a rat model, eventually resulting in decreased biomechanical strength of the repair [29]. Cohen *et al.* demonstrated inferior healing and lower rotator cuff repair loads to failure in rats receiving celecoxib and indomethacin compared to contols [30]. In addition, the collagen was more organized in the control groups. This raises the question whether the use of NSAIDs after rotator cuff repair should be limited to avoid disturbance of the healing process.

Gotoh *et al.* found increased levels of MMP-3 and tissue inhibitor of MMP (TIMP)-1 in patients with rotator cuff tears who sustained re-tears after repair compared to those who did not [31]. These results suggest that up-regulation of TIMP-1 and MMP-3 is associated with postoperative tendon retear. This offers a potential research approach for targeted drug therapy after rotator cuff repair [31].

STEM CELL THERAPY

Mesenchymal stem cells (MSCs) derived from various origins have been investigated in animal studies to determine if their differentiation potential can be used to enhance healing of the rotator cuff tendon. Gulotta *et al.* investigated bone marrow derived MSCs in a rat model [32]. The investigators found evidence that the MSCs were present and metabolically active, however, the addition of MSCs to the healing rotator cuff insertion site did not improve the structure, composition, or strength of the healing tendon [32]. Using a rat model, Kida *et al.* simulated rotator cuff tears and repairs [33]. In one group, they drilled additional holes into the greater tuberosity to promote mesenchymal stem cell migration [20]. The authors found that the rats with the additional holes had more MSCs than the other group and there was also a higher ultimate force-to-failure of the repair [33]. Oh *et al.* used a rabbit model to investigate the effects of administration of adipose derived stem cells had on tendon healing and fatty infiltration [26]. They concluded that adipose derived stem cells may be able to improve muscle function, tendon healing, and decrease fatty infiltration after rotator cuff repair [34].

Clinical studies investigating MSCs are currently sparse. Beitzel *et al.* demonstrated that MSCs can be harvested in a reliable, consistent fashion from either the proximal humerus or distal femur [35]. Hernigou *et al*. collected bone marrow aspiration samples from the greater tuberosity in 125 patients with rotator cuff tears, and compared them to the samples of 75 patients with a healthy rotator cuff regarding the amount of MSCs [36]. Patients with rotator cuff tears showed a significant reduction in MSC content at the tendon-bone interface compared to the control group. Lower counts of MSCs were statistically correlated to patients age, delayed onset of symptoms and surgery, number of involved tendons, and fatty infiltration stage [36]. This study emphasizes the potential benfit of biologic augmentation in rotator cuff repair.

Ellera Gomes *et al.* published a study on 14 consecutive patients who underwent mini-open rotator cuff repair along with injection of autologous bone marrow mononuclear cells [37]. Magnetic resonance imaging analysis 12 months postoperatively demonstrated tendon integrity in all cases. Additional studies are needed to understand how to best utilize stem cells to promote tendon healing and quality.

CONCLUSION

Basic science studies investigating biologic factors to enhance healing of the rotator cuff show promise. However, clinical data is sparse, inconsistent and controversial. Further investigations are required to determine the best biological agents, uses, concentrations and routes of application. Presently we use PRP to augment healing in biologically challenged cases such as in revision repairs, inmiassive tears with poor quality tissue, and in biologically challenged hosts such as smokers and diabetics. We avoid the use of NSAIDS for 6 weeks post repair in all cases.

CONFLICT OF INTEREST

The authors report the following potential conflict of interest or source of funding: JAG, SJM, PJM, MP receive support from Steadman Philippon Research Institute. Corporate sponsorship for Steadman Philippon Research Institute is received from Ossur, Smith & Nephew Endoscopy, Siemens Medical Solutions, and Arthrex. P.J.M. also receives support from Arthrex, Myos, GameReady, and VuMedi.MP receieved support from Arthrex Inc.

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