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Current State for Clinical Use of Stem Cells and Platelet-Rich Plasma ☆

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In the management of common orthopaedic pathology involving tendons, ligaments, bone, and articular cartilage, the application of small molecules and biologic compounds has expanded greatly in the past decade. In particular, the use of platelet-rich plasma (PRP) and stem cells has gained significant attention for potential therapeutic augmentation of healing, modulation of inflammatory cascades, and pain modulation. Despite the increase in clinical application and interest, there has been a paucity of high level of evidence studies supporting the use of these biologic agents. This article examines the current state for the clinical use of stem cells and PRP, with review of the most recent clinical studies involving the treatment of tendon, ligament, bone, and cartilage injury. Current evidence regarding safety profile, therapeutic effect, and validated outcome scores are reported. Though plagued by inconsistency in experimental testing and low numbers of large, multicenter randomized controlled trials, the use of stem cells and PRP appears to have a positive clinical effect with minimal systemic side effects or complications. Further study is needed to elucidate the specific therapeutic indications, dosing regimen, and efficacy of treatment in short and long follow-ups is needed to document the role and effectiveness of these treatments in clinical practice.
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Introduction

The use of small molecules and biologically active compounds for the nonoperative and operative treatment of common orthopaedic pathology has risen significantly in the past decade. Platelet-rich plasma (PRP) and stem cells, specifically, have emerged as innovative therapies aimed at augmenting repair processes in structures with low healing potential (ie, cartilage and tendon/ligament complexes) while also stimulating new healing in chronic pathologies (ie, osteonecrosis). The ability of these compounds to serve as a biologic scaffold for cell development at injury sites, while also modulating inflammation and providing nociceptive effects, has made them a candidate for widespread use in orthopaedic medicine.[1] Despite significant clinical and research interest in these therapies, there is limited high-level clinical evidence to guide their usage. Furthermore, it is difficult to discern consensus recommendations for indications for therapy, preparation techniques, and dosing protocols across the numerous lower level evidence reports. This article compiles the most recent clinical evidence to support the use of PRP and stem cell therapies in the treatment of common tendon and ligament pathology, focal cartilage defects and global joint osteoarthritis (OA), and the stimulation of bone healing and new bone growth. Specific focus was directed to the highest level studies, the overall efficacy of treatments via validated outcomes scores and the presence of serious clinical side effects (if any) that have been documented in their clinical use.

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Treatment of Tendon and Ligament Pathology With PRP and Stem Cells

PRP and stem cell therapies have emerged as an innovative option in the surgical and nonsurgical management of tendons and ligaments. Among the most prevalent

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areas include the rotator cuff, extensor tendons of the forearm, patellar tendon, Achilles tendon, and anterior cruciate ligament (ACL), whereas less frequent uses include treatment for partial ulnar collateral ligament (UCL) elbow tears and hamstring injuries.

Rotator Cuff Healing With PRP and Stem Cells

Rotator cuff healing has been a major source of research involving both PRP and stem cells. There have been several Level I, randomized controlled trials (RCTs) examining the effects of PRP on rotator cuff healing.[2-6] Research has shown the results after PRP application for large to massive tears at 1 year and found a significantly lower re-tear rate (20% vs 55.6%), an increased cross-sectional area for the PRP group as well as improved overall shoulder function.[2] Review of the literature for subacromial PRP injection vs placebo for treatment of chronic rotator cuff tendinopathy or tears at 1 year and found PRP to have equivalent results to placebo in terms of quality of life, pain, disability, and shoulder range of motion.[3] In terms of surgical intervention, the use of platelet-rich fibrin matrix during arthroscopic rotator cuff repair has not significantly improved perioperative morbidity, clinical outcomes, or structural integrity compared to placebo.[4] Furthermore, for PRP usage in single-row rotator cuff repairs, no improvement in clinical outcomes over controls was observed.[5] The use of plasma rich in growth factors has been studied as an augment to arthroscopic rotator cuff repairs, but a significant difference in rotator cuff healing or clinical function at 1 year follow-up was not found.[6] Warth et al recently performed a meta-analysis and meta-regression of randomized trials evaluating platelet-rich product usage during arthroscopic repair of full-thickness rotator cuff tears. The authors concluded that there was no statistically significant difference in outcomes scores or re-tear rates vs placebo, and that PRP application at the tendon-bone interface led to improved Constant scores vs application over the superior aspect of the tendon. In addition, re-tear rates were significantly decreased when PRP was used to augment double-row repairs of tears that were greater than 3 cm in length from anterior posterior.[7]

Biologic augmentation of rotator cuff repairs has also been studied. The effects of bone marrow-derived mesenchymal stem cells on rotator cuff healing was recently evaluated in 45 patients using postoperative magnetic resonance imaging (MRIs), and at 10-year follow-up, 87% of the patients in the stem cell group had intact rotator cuffs vs only 44% in the control group.[8] Furthermore, the effects of bone marrow mononuclear cells on augmentation of rotator cuff repair has been studied, and results show that at minimum 1-year follow-up there were an increase in University of California, Los Angeles scores and MRI confirmed tendon integrity in 100% of the repairs.[9]

Forearm Extensor Tendon

PRP use for treatment of lateral epicondylitis, or tennis elbow, has been subject to some of the highest level studies in the literature. In a Level I study, Thanasas et al[10] compared PRP with autologous whole blood for treatment of tennis elbow, and found PRP to have greater short-term pain relief but equivalent outcomes at 6 months. An additional Level I study comparing PRP to corticosteroid injections found that PRP was associated with a greater success in terms of reduction of 25% on visual analog scale (VAS) pain scores and improvement in disabilities of the arm, shoulder, and hand (DASH) outcome scores. Furthermore, the DASH scores of the corticosteroid group returned to baseline, whereas those in the PRP group significantly improved.[11] Krogh et al[12] also conducted a randomized, double-blind trial comparing PRP to corticosteroid and saline injections. The authors examined 18 patients and found no difference in pain reduction at 3 months between the 3 methods, with glucocorticoid having improved pain reduction at 1-month post-injection. However, this study was limited by its follow-up, as only 27% of patients who were assigned at the initiation of the trial completed the 1-month follow-up. In the largest study completed as of now, Mishra et al compared PRP to an active control group in a double blind, prospective, randomized, and multicenter trial, with study groups of 56 patients who received needling with PRP injection and 63 who received needling without. At 6-month follow-up, the patients who received PRP had greater improvement in pain scores, lower rates of significant elbow tenderness, and higher overall success rates without significant complications.[13] These studies suggest that corticosteroid injections may have greater initial pain relief, but PRP injections are more efficacious in the long term.

Patellar Tendon

Numerous injection treatments have been used to treat patellar tendinopathy, including both PRP and tissue-engineered injections. Clarke et al examined the effect of tenocyte-like cells derived from skin biopsy for treatment of refractory patellar tendinopathy. The cell group had a significantly higher mean Victorian institute of sport assessment (VISA) score, a significantly faster improvement and a highly significant effect of treatment compared to injection with autologous plasma alone. Both groups had decreased hypoechogenicity and tear size on ultrasound, with the cell group having decreased thickness as well.[14] Of note, a patient in the cell-injection group sustained a traumatic patellar tendon rupture while playing football. An intraoperative biopsy was obtained, showing normal appearing tendon cells, supporting the authors' hypothesis that the injected cells produce collagen and recreate the tendon. PRP injection has also been evaluated in comparison to dry needling alone in a randomized, Level I study in which significantly improved VISA scores at 12 weeks were observed in the PRP group, but the difference was not significant at >26 weeks.[15] The dry needling group had significantly improved Lysholm scores at >26 weeks compared to PRP injection. The authors concluded that PRP can accelerate the healing process in the short term, but the effects fade over time.

Achilles Tendon

Achilles tendinopathy and tears are other areas of interest involving treatment with PRP. A Level I comparative study examining the effects of PRP vs saline for Achilles tendinopathy, in addition to eccentric therapy, showed no difference