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Biologics in shoulder and elbow pathology

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In recent years, orthobiologics have been of increasing clinical interest in the treatment of shoulder and elbow pathology. In some conditions, such as rotator cuff injury and lateral epicondylitis, there have been high-quality trials that support the use of platelet-rich plasma in reducing pain, restoring functionality, and improving clinical outcomes. However, as the numbers of both cellular-based biologics and the conditions being augmented by biologics continue to expand, there is a substantial need for high-quality investigations to support their routine use in most shoulder and elbow conditions. The purpose of this review is to summarize the current evidence of orthobiologics in the management of shoulder and elbow injury, as nonoperative treatment and as augments to operative treatment.

As defined by the American Academy of Orthopaedic Surgeons, orthobiologics are products made from substances found naturally in the body utilized to improve the healing of broken bones and injured muscles, tendons, and ligaments.[24] In recent years, the utility of biologics as adjuncts to both conservative and operative therapies for shoulder and elbow pathologies has been of increasing clinical interest. Owing to their convenience, safety in use, and their high concentrations of growth factors and mesenchymal stem cells (MSCs) thought to improve healing, biologics have been introduced in the treatment of many soft tissue and tendinous injuries despite a paucity of evidence as to their efficacy. The purpose of this review is to provide an overview of commonly utilized injectable orthobiologics and to summarize the available evidence on the use of orthobiologics for the management of shoulder and elbow injury.

Overview of biologic therapies used in the shoulder and elbow

Platelet-rich plasma

Platelet-rich plasma (PRP) is a promising biologic therapy used throughout orthopedics in the treatment of soft tissue and chondral injury. The promise of PRP is in its delivery of high concentrations of growth factors to injury sites, including platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, fibroblastic growth factor, insulin-like growth factor-I, and hepatocyte growth factor.[56] These factors are key mediators in injury repair, and the concentrated injections of these factors in PRP to a site of injury are thought to reduce inflammation and accelerate tendon and soft tissue healing. In addition, the ease of PRP acquisition and processing makes its use particularly appealing, allowing for both its isolated use in clinic and as an adjunct during surgery.

In any evaluation of PRP augmentation, it is important to note the significant heterogeneity in both the preparation of PRP and in the reporting of PRP characteristics in the published literature. Although several commercial devices produce PRP products, they differ significantly in preparation technique, which can result in significant variability in the concentration of platelets, growth factors, leukocytes, and cytokines being injected in the finished PRP product.[11] In addition, most studies inadequately analyze and report these characteristics, which when coupled with differing injection protocols and numbers of injections utilized limit the ability to effectively compare results between different investigations.

Cellular-based therapies

Cellular-based therapies are rapidly emerging in the management of soft tissue and chondral disease throughout orthopedics. In addition to possessing many of the same favorable concentrations of growth factors and cytokines found in PRP, cellular-based therapies also contain small concentrations of MSCs which harbor the potential to differentiate and improve healing in target tissues. Currently there are several sources of MSCs being utilized, including bone marrow, adipose tissue, synovial fluid, umbilical

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Figure 1 After extraction of bone marrow aspirate at the time of intervention, bone marrow aspirate concentrate (pictured) can be processed in minutes for injection to the site of injury.

cord blood, and placental tissue, but most available clinical evidence is centered on bone marrow aspirate concentrate (BMAC) and adipose-derived injections.[18] The MSCs derived from these therapies have been identified in vitro to differentiate into bone, cartilage, tendon, muscle, and adipose tissues, which has generated significant interest in their ability to improve healing in most tissue injuries.[47]

BMAC can be harvested at the time of surgery using a trocar to access the bone marrow of many different sites, including the iliac crest, humerus, femur, tibia, and calcaneus (Fig. 1).[12,15] It is commonly obtained at the iliac crest as this site has been identified to have the highest concentration of MSCs in processed BMAC preparations.[15] In operative management of shoulder and elbow pathology, it is also common to obtain BMAC from the proximal humerus due to the convenience in not requiring additional draping or preparation for BMAC extraction. Notably, the concentration of MSCs in BMAC is minimal, comprising only 0.001% to 0.01% of cells in the final preparation.[8] In addition, the harvesting of BMAC is more invasive and painful than that of PRP, potentially limiting the ability for it to be applied widely in a clinic setting.

Adipose-derived mesenchymal stem cells (ADSCs) are another attractive augmentation modality owing to their easy accessibility in peripheral adipose tissue with minimal donor site morbidity during lipoaspiration. In addition, adipose tissue contains much higher concentrations of stem cells than bone marrow (approximately one MSC per 100 cells in adipose compared with one in 100,000 in bone marrow).[53] Once aspirated, a number of different commercially available microfragmentation systems can be used to create an injectable product.

Biologic augmentation of shoulder injury

Rotator cuff tendon injury

Rotator cuff injuries are a common and increasingly prevalent pathology, resulting in over 4.5 million physician visits and 75,000 surgical repairs performed each year in the United States.[20,55] Despite high rates of patient satisfaction and functional outcome improvements, rotator cuff repairs, depending on tear size, have been identified as having on average a 26.6% rate of failure by two years after surgery.[41] As such, there has been significant interest in the role of orthobiologics to potentiate tendon healing and reduce risk of failure. Althpugh preclinical investigations of biologics in cuff injury are favorable yet scarce,[6] several high-level randomized controlled trials have examined biologic repair augmentation owing to reported benefits in tendon healing and strength using general tendon models.[4]

Operative management

Much of the published clinical studies of biologics in operative cuff repairs have examined differing PRP preparations injected at the time of arthroscopic repair. These findings have been analyzed in several meta-analyses which have displayed promising yet inconsistent results. An early systematic review on the effect of PRP injection at the time of arthroscopic RCR by Chahal et al reported on five investigations comprising 261 patients.[10] Using random effects modeling, they found no statistically significant difference in overall retear rates or Simple Shoulder Test, the American Shoulder and Elbow Surgeons Shoulder Score (ASES), UCLA, and Single Assessment Numeric Evaluation outcome measures between patients receiving PRP and those treated without PRP. These findings were similar to those of Zhao et al, who completed a meta-analysis of eight randomized controlled trials comprising 464 patients either receiving isolated arthroscopic RCR or a repair with concomitant PRP injection.[57] They too found no significant differences in retear rate or Constant and UCLA outcome assessments between either cohort.

Conversely, a more recent meta-analysis of 18 randomized controlled trials and 1147 patients was performed by Hurley et al.[27] In this report, those receiving PRP had significantly lower rates of incomplete tendon healing and had more favorable Constant and visual analog scale (VAS) outcomes at follow-up when compared to controls. Notably, they also analyzed the efficacy of platelet-rich fibrin, which showed no benefit in outcome or healing.

Published investigations of BMAC and ADSC augmentation at the time of arthroscopic repairs have also shown early promise. A 2014 study by Hernigou et al investigated 90 patients (45 matched pairs) receiving single-row RCR for tears less than three centimeters with and without BMAC augmentation.[25] When comparing MRI outcomes at six months after repair, all 45 patients with BMAC augmentation had evidence of healed repair in contrast to only 67% of those receiving no BMAC augmentation. Furthermore, at ten years after surgery, 87% of the BMAC cohort had intact repairs in contrast to only 44% of non-BMAC cohort. This promising investigation has been supported by the preliminary findings of Cole et al, who are currently performing a randomized trial of BMAC augmentation in arthroscopic RCR.[14] In their initial report, those receiving BMAC augmentation had significantly more favorable radiographic outcomes when assessed using Sugaya grading. However, there were no significant differences identified in any functional outcome assessment.

Recently Kim et al performed an investigation of ADSC augmentation of RCR.[33] In this matched cohort study, 35 patients received ADSCs loaded in fibrin glue at the time of cuff repair and were found to have a significantly lower retear rate on follow-up MRI than those without ADSC augmentation. However, clinical outcome assessments and postoperative range of motion evaluations were similar between the cohorts.

Nonoperative management

The role of PRP in the management of nonoperative rotator cuff tears and rotator cuff tendinopathy has also been clinically examined in recent years. Shams et al recently compared the efficacy of PRP injections compared with traditional corticosteroid injections in 40 patients with symptomatic partial rotator cuff tears.[51] In follow-up evaluations at 12 weeks after injection, those receiving PRP had significantly better Constant, ASES, and Simple Shoulder Test scores than those receiving corticosteroids, but at six months there was no significant difference in outcome. From these results, the authors concluded that PRP was a viable alternative therapy, particularly when considering the adverse effects of repeated steroid injections on cuff integrity.[45] Regarding tendinopathy, Rha et al examined the effect of PRP compared with dry needling in a randomized controlled trial of 39 patients with either tendinosis or a partial rotator cuff tear.[49] They identified sustained outcome improvement at six months after injection with no adverse effects. These results are in contrast to Kesikburun et al, who also completed a randomized controlled trial in 40 patients with a history of chronic rotator cuff tears.[30] At one year follow-up after injection, they found no significant difference in outcomes when compared with placebo.

Evidence for the nonoperative use of cellular therapies in rotator cuff injury is limited to a few small case series. Recently Jo et al investigated injections of varying concentrations of ADSCs in 20 patients with partial rotator cuff tears.[28] When compared with the baseline, mid- and high-dose ADSC injections were associated with an 80 percent improvement in the Shoulder Pain and Disability Index at six months after injection. In addition, postinjection arthroscopy identified that the volume of articular and bursal side defects decreased by 83% and 90% in the mid- and high-dose groups, respectively. Nonoperative BMAC-PRP augmentation of patients with partial tears was recently examined by Kim et al.[32] When compared with patients receiving only physical therapy, those receiving biologic injection were identified to have significantly lower VAS scores and significantly higher ASES scores at three months after injection. In a case series of 102 patients with either glenohumeral osteoarthritis and/or rotator cuff tears, Centeno et al examined nonoperative treatment with BMAC injection.[9] At final follow-up, there were significant improvements in DASH and Numeric Pain Scale Values along with an average subjective improvement of 48.8% reported by the cohort. These early studies support the use of cellular therapies in nonoperative management of rotator cuff pathology, but more adequately powered and well-designed prospective trials are needed to accurately examine their efficacy.

Biologic Augmentation of Other Shoulder Pathology

While much of the current literature regarding orthobiologics in shoulder injury is centered on the rotator cuff, other investigations are beginning to examine their use in other shoulder pathologies. In a randomized study of 195 patients with adhesive capsulitis, Kothari et al compared the efficacy of PRP injection, corticosteroid injection, and ultrasonic therapy.[34] At short-term follow-up 12 weeks after injection, those receiving a single injection of PRP had significant improvements in VAS, QuickDASH, and both active and passive range of motion compared with the other cohorts. These findings are supported in a case report by Aslani et al, who reported a greater than 70% functional improvement in a patient with chronic adhesive capsulitis after two PRP injections.[3] At this time further investigations regarding biologics for other common conditions, such as in the management of biceps tenosynovitis, have yet to be examined.

Biologic augmentation of elbow injury

Ulnar collateral ligament injury and reconstruction

The ulnar collateral ligament (UCL) provides stability at the medial elbow during valgus strain. Owing to the mechanics and repetitive nature of the throwing motion, overhead athletes, particularly baseball pitchers, are at increased risk of injury to the UCL. Although UCL injuries have been common among professional overhead athletes for some time, a trend toward early sport specialization has led to an increasing number of such injuries in youth athletes.[39] As such, safe and effective augmentations to standard treatment options are sought to improve healing and long-term function (Fig. 2).

A number of preclinical investigations have examined the use of orthobiologic agents in the treatment of ligamentous injuries, but none have been specific to the UCL. It is difficult to design laboratory-based studies that maintain fidelity to the unique biomechanical characteristics associated with UCL injuries in overhead athletes. However, nonbiomechanically accurate studies, similar to those carried out in animal models of other ligamentous injuries, would help to elucidate the underlying physiologic principles of orthobiologic UCL treatments.

Few published studies have examined the role of orthobiologic augmentation in the surgical management of UCL injuries. In 2015, Hoffman et al published a case report detailing a professional baseball pitcher with UCL instability who underwent UCL reconstruction with a biologic construct consisting of a dermal allograft, PRP, and MSC.[26] The authors reported that postoperative MRI at 17

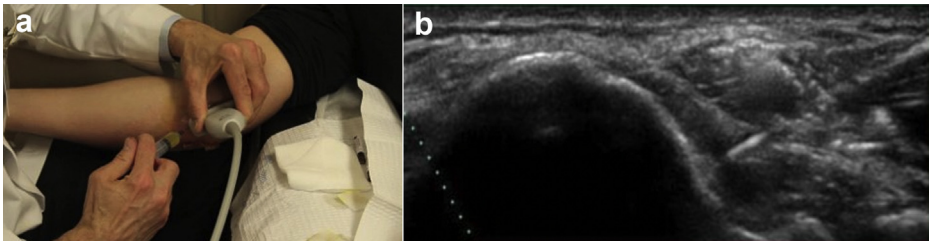

Figure 2 Platelet-rich plasma (PRP) injection for ulnar collateral ligament injury of the elbow. (**a**) After collection of a peripheral blood specimen and processing, PRP can be injected directly to the site of injury. (**b**) Using ultrasound guidance, PRP can be injected directly to the site of injury.

months demonstrated an intact dermal allograft with no retraction or deformity. They further commented that the pitcher was "doing very well" and throwing 86 miles per hour at 21 months post-operatively but did not state if he had returned to competition.

Dugas et al (2019) reported a case series of 128 overhead athletes, mostly at the high school and collegiate level, who underwent UCL repair with type-1 bovine collagen-dipped FiberTape (Arthrex) augmentation[19]. All study participants had MRI-confirmed partial or complete UCL tears. Study surgeons decided intraoperatively whether to complete the augmented repair procedure or a traditional reconstruction; only those receiving the augmented repair were included in analyses. Outcomes included Kerlan-Jobe Orthopaedic Clinic Shoulder and Elbow questionnaire scores at one and two years after procedure and time to return to play (RTP). Of those with full follow-up, 92% had a return to the same or higher level of competition at a mean time of 6.7 months (range not reported). Follow-up Kerlan-Jobe Orthopaedic Clinic Shoulder and Elbow questionnaire scores were significantly improved at two years compared with one year. No complications related to the collagen-dipped FiberTape were reported.

In the past decade, multiple clinical studies have also explored the use of orthobiologics in the nonoperative management of UCL injuries. Case reports and limited case series have anecdotally demonstrated positive outcomes following PRP injection.[22,40] In addition to this anecdotal evidence, a number of expanded clinical studies have reported on the topic.

Three such case series have been discussed at length in other review articles.[2,18,31,36] In short, Podesta et al found that among 34 athletes with symptomatic partial-thickness UCL tears, 88% treated with one PRP injection and a graded rehabilitation program returned to competition at an average time of 12 weeks. The study also reported significantly improved ultrasonographic medial joint space measurements and subjective questionnaire scores at follow-up.[48] In 2016, Dines et al reported similar outcomes in a cohort of 44 baseball players with MRI-confirmed UCL insufficiency treated with between one and three PRP injections in addition to standard conservative measures.[17] In this study, average time to return to competition was 12 weeks. They found that 73% of participants had an excellent or good outcome based on a modified Conway Scale vs. 27% with fair or poor outcomes. They hypothesized that initial tear characteristics accounted for some of the variation in outcomes as all 7 participants with distally based partial tears had poor outcomes. Finally, in 2017, Deal et al reported on a cohort of 25 high-school and collegiate throwing athletes with symptomatic grade 2 tears.[16] Each received two PRP injections and conservative measures. Within the study period, 22 (88%) of the athletes returned to competition at an average time of 12 weeks and 20 (80%) had full ligamentous reconstitution on follow-up MRI.

In 2019, two additional PRP-based studies were published. Kato et al examined the effects of PRP injections after both partial and full-thickness UCL tears in 30 baseball players.[29] Participants included amateur and professional-level players with MRI-confirmed UCL tears ranging in severity from grade 1 to grade 3. The intervention consisted of ultrasound-guided trephination and leukocyte-poor PRP injection followed by a graded rehabilitation protocol. Outcomes included RTP, VAS scores, DASH sports module scores, and ultrasonographic measurement of ulnohumeral joint space with valgus stress. Twenty-six participants returned to competition at an average time of just over 12 weeks (range, 10-18 weeks), whereas four had persistent symptoms requiring operative reconstruction. Of these four, three initially had grade 2 tears and one had a grade 3 tear. On follow-up at 6 months they found significant improvements in VAS scores, DASH scores, and joint space measurements.

In the only study published to-date that included a matched comparison group, Chauhan et al reported a retrospective cohort study of 544 Major League Baseball and Minor League Baseball players treated nonoperatively (with or without PRP injections) for UCL injuries between 2011 and 2015.[13] Data were abstracted from the Major League Baseball Health and Injury Tracking System. After retrospectively matching cases by age, position, throwing side, and league status (Major League Baseball or Minor League Baseball), they found players who received PRP experienced a significantly longer time to RTP. Average time to RTP in the PRP cohort was 25.4±14.1 vs. 20.1±13.6 weeks in the no-PRP cohort. A non-statistically significant increase in the rate of progression to operative UCL reconstruction was also seen in the PRP group (58%) vs. the no-PRP group (48%). The authors hypothesized that numerous factors which could not be controlled for given the nature of the Health and Injury Tracking System data such as heterogeneity in PRP preparations, injection protocols, time from injury to injections, and rehabilitation programs may have played a role in the overall negative findings of the study.

Although most studies have reported positive outcomes, the findings of Chauhan et al underscore the necessity of continued investigation into this evolving field. There is an important gap in the literature as no prospective randomized controlled trials have been carried out to date. If and when such studies occur, it will be important for investigators to rigorously control for factors such as tear pattern, location, and participants' level of competition.

Lateral and medial epicondylitis

Lateral epicondylitis, also known as tennis elbow, is a prevalent source of elbow pain and dysfunction, affecting 1%-3% of the population and often requiring conservative therapy.[35] The role of biologics in tennis elbow treatment has been extensively researched in several case series and meta-analyses.[1,7,21,38] In addition, several level I investigations have evaluated the efficacy of PRP in the treatment of lateral epicondylitis, which in general support its routine use. In 2010 Peerbooms et al conducted a randomized controlled trial on 100 patients randomized to receive either corticosteroid or PRP injection.[46] When comparing VAS and DASH outcome assessments in either group at one year after injection, the group receiving PRP had significantly better outcomes. Moreover, although the corticosteroid group had more favorable outcomes at short-term time points, they subsequently declined while the PRP group progressively improved at each assessment time point. This cohort was subsequently followed up at two years after injection by Gosens et al, who reported sustained outcome improvement in the PRP treated cohort.[23]

Similarly, in 2014 Mishra et al examined PRP treatment in a multicenter randomized controlled trial of 230 patients with chronic lateral epicondylitis.[43] Patients were evaluated at 12 and 24 weeks after injection and compared with active controls not receiving biologic therapy. At 12 weeks, there were no significant differences in outcome in either cohort, but at 24 weeks those who received leukocyte-rich PRP had significant decreases in VAS pain assessments when compared with controls. These studies, along with several other high-quality trials published in recent years,[42,44] provide some of the strongest evidence of the use of PRP in musculoskeletal pathology.

Investigations of cellular-based treatments of lateral epicondylitis are more limited than those of PRP augmentation, but in general also demonstrate favorable outcome improvement. In a case series of 30 patients with previously untreated lateral epicondylitis, Singh et al examined the efficacy of a single BMAC injection on functional outcomes.[52] Short-term evaluations up to 12

weeks after injection were performed using the Patient-rated Tennis Elbow Evaluation score. At both six and 12 weeks, mean outcome scores were significantly improved when compared with the baseline. The efficacy of ADSC injections in lateral epicondylitis was examined by Lee et al.[37] When considering VAS and modified Mayo clinic performance index for the elbow outcomes, patients had significant improvements in outcome by six weeks after injection that were sustained for the entire 52 week study period. In addition, ultrasound assessments of tendon healing were also performed and demonstrated a significant decrease in tendon defect size during the study period. While these early studies show safety and moderate efficacy of cellular-based biologic therapies, larger studies with a higher level of evidence are essential in determining clinical recommendations for their use.

In contrast to the robust literature on biologic augmentation of lateral epicondylitis, studies on the use of biologics in medial epicondylitis of the elbow are very limited. Recent investigations were performed by Varshney et al and Boden et al.[7,54] In both investigations, PRP treatment produced favorable outcomes, but both investigations included medial and lateral epicondylitis patient cohorts and did not stratify outcomes between the two conditions.

Distal biceps tendonitis

Limited investigations into the use of PRP for the treatment of distal biceps tendinopathy have been performed. In a small case series of six patients, Barker et al examined the efficacy of PRP injections via VAS and Mayo Elbow Performance outcome assessments.[5] At an average final follow-up of 16.3 months, all patients had complete resolution of their pain and had improvements in Mayo Elbow Performance scores (mean 68.3 preinjection with improvement to a mean score of 95 at final follow-up). In addition, all patients-reported subjective improvement after the injection and no complications were noted. Sanli et al also examined PRP injections in 20 patients with MRI-confirmed distal biceps tendonitis.[50] At a median follow-up of 47 months, all patients had significant improvements in pain and functional assessments and reported satisfaction with clinical and functional outcomes. These early studies support the promise of biologics in provided meaningful outcome improvement of distal biceps tendinopathy, but future studies are needed to confirm these preliminary results.

Conclusion

Biologic augmentation of muscular and tendinous injury has been of increasing clinical interest with the ambition of enhancing healing, reducing pain, and restoring functional outcomes. Despite widespread use and early promising results in a variety of soft tissue pathologies, there remains limited clinical evidence for the use of biologics, particularly cellular-based therapies, in most common injuries. Active and future prospective trials using standardized preparations of biologics are needed to allow for evidence-based recommendations of their use.

Conflicts of interest

Dr. Cole reports the following disclosures, none of which have any direct influence on the submitted work: other from Aesculap, other from NIH, other from Operative Techniques in Sports Medicine, personal fees from Ossio, personal fees and other from Regentis, other from Smith and Nephew, grants, personal fees and other from Arthrex Inc., other from Elsevier publishing, other from Bandgrip Inc., other from Acumed LLC, other from Encore Medical, LP, other from GE Healthcare, other from Merck Sharp & Dohme Corporation, other from SportsTek Medical, Inc., other from Vericel Corporation. All other authors have no disclosures to report.

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