The Role of Biologic Agents in the Non-operative Management of Elbow Ulnar Collateral Ligament Injuries

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Abstract

Purpose of Review Injuries to the elbow ulnar collateral ligament (UCL) are especially common in the overhead throwing athlete. Despite preventative measures, these injuries are occurring at increasing rates in athletes of all levels. UCL reconstruction techniques generally require a prolonged recovery period and introduce the potential for intraoperative complications prompting investigations into more conservative treatment measures based on specific patient and injury characteristics. The purpose of this review is to describe the current literature regarding the use of biologic augmentation in the management of UCL injuries. Specifically, this review will focus on the basic science background and clinical investigations pertaining to biologic augmentation utilizing platelet-rich plasma (PRP) and autologous stem cells.

Recent Findings Despite some evidence supporting the use of PRP therapy in patients with partial UCL tears, there is no current consensus regarding its true efficacy. Similarly, due to a lack of clinical investigations, no consensus exists regarding the utilization of autologous stem cell treatments in the management of UCL injuries.

Summary Management of UCL injuries ranges from non-operative treatment with focused physical therapy protocols to operative reconstruction. The use of biologic augmentation in these injuries continues to be investigated in the orthopedic community. Currently, no consensus exists regarding the efficacy of either PRP or autologous stem cells and further research is needed to further define the appropriate role of these treatments in the management of UCL injuries.

Keywords UCL · PRP · Autologous stem cells · Biologic augmentation

Introduction

Injuries to the elbow ulnar collateral ligament (UCL) have been well described within the orthopedic literature, especially in the setting of overhead throwing athletes. These injuries are often the result of repetitive valgus stress during the throwing motion and can lead to instability, pain, and loss of control/stamina [1•, 2, 3]. As the incidence of UCL injury has increased with improved diagnostic capabilities and earlier

participation in competitive overhead and contact sports, so too has our understanding of the anatomical and biomechanical components of the UCL and its function [2, 4, 5•].

Despite our improved understanding of the pathoanatomy and biomechanics of the UCL, injury rates continue to climb in overhead throwers of all ages and levels of competition [1•, 2–4, 5•, 6–8]. Management options include both non-operative and operative treatment options. Choosing between non-operative and operative management is influenced by many factors, including the location of the tear, degree of tear, and previous treatments attempted. As operative techniques have evolved, return to sport (RTS) rates have been reported between 80 and 94%; however, these procedures generally require at least 12 months of recovery and rehabilitation in addition to the risk of operative complications such as fracture, inadequate healing, nerve injury, and failure of fixation [1•, 2–4, 5•, 6–12, 13•].

While reconstruction remains the gold standard for complete UCL tears and other tears that have failed conservative management, it is important to understand that for select

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overhead athletes, non-operative treatment options have the potential for quicker return to sport without jeopardizing an acceptable outcome. This is especially true in patients with a low- to medium-grade (i.e., Grade I or II) proximal UCL tear who have not yet attempted conservative management¹⁵. Of recent interest is the addition of biologic agents to non-operative regimens for athletes with partial UCL tears. The most commonly available biologic injections include platelet-rich plasma (PRP), bone-marrow aspirate concentrate (BMAC), and mesenchymal stem cells (MSCs). This review will summarize the current understanding of biological treatment and augmentation strategies for management of elbow UCL injuries.

Diagnosis and Workup

Proper patient management relies on thorough history, physical examination, and radiographic assessment, with special attention to patient specific factors such as age, injury acuity, degree and location of tear, tissue quality, competition level, playing status, and time of season. Beyond patient-specific factors, when considering injury characteristics, several important distinctions must be made: the severity of the tear (complete or partial), the location of the tear (proximal, midsubstance, or distal), and the quality of the ligament tissue (typically attritional in repetitive-throwing athletes). With this in mind, the current gold standard for management of full thickness, attritional, midsubstance UCL tears in high-demand athletes, or elite throwers remains operative reconstruction [1, 13]. Conversely, first-line management in essentially all patients with incomplete UCL tears consists of non-operative management with early physical therapy with or without biologic augmentation. Similarly, conservative measures may also be considered in younger patients with full thickness tears in order to avoid operative intervention during years of skeletal immaturity and should also be considered in high school/college athletes who may plan to refrain from further competitive play in the future [1, 13].

On advanced imaging assessment, there are several important predictors of failure of non-operative management. A 2017 study performed by Frangiamore et al. [14] evaluated magnetic resonance imaging (MRI) findings of 32 professional pitchers at a mean age of 22.3 years who underwent an initial trial of non-operative management for UCL tears. They defined successful management as a return to the same level of play or higher at > 1 year while failure of management was defined as recurrent pain or weakness requiring surgical intervention after a minimum of 3 months rest when attempting a return to throwing program. In total, 11 (34%) pitchers required surgical intervention while 21 (66%) returned to the same level of play by 1 year. On evaluation of MRI findings, 9/11 (82%) of those who required surgical intervention suffered distal tears in the UCL while 17/21

(81%) of those who were successfully managed non-operatively had proximal tears. While adjusting for age, location, and evidence of chronic changes, they found that the likelihood of failing non-operative management was 12.4 times higher ($p = 0.02$) with a distal tear. Location of tear was the only statistically significant finding in the investigation, which highlights the importance of the anatomic location of these injuries when considering operative versus non-operative management. These findings may also be explained by the robust blood supply within the proximal UCL as compared to the relatively scarce blood supply to the distal UCL. A recent cadaveric study by Buckley et al. [15] investigated the macroscopic vascular anatomy of the elbow UCL and found a consistent, dense blood supply to the proximal UCL while also noting the distal UCL to be hypovascular. Additionally, the authors noted a possible osseous contribution of the proximal UCL from the medial epicondyle.

Hurwit et al. [16] conducted a survey of the American Shoulder and Elbow Surgeons (ASES) in 2017 to assess trends related to treatment of athletes presenting with UCL injury. The survey presented 7 distinct fictional clinical case scenarios of athletes with UCL injury with subsequent questions posed related to preferred treatment. The authors found that professional athletes and those with complete tears were indicated for operative management by consensus; however, no clear consensus was noted in patients with partial tears or nonprofessional athletes. Overall, 36.3% of respondents reported using PRP in their proposed treatment. Of those respondents using PRP for management of UCL injuries, 43.9% opted for leukocyte-poor (LP)-PRP, 16.6% for leukocyte-rich (LR)-PRP, and the remainder (39.4%) reported no preference. Additionally, 8% of respondents reported using stem cell injections with BMC being the most common form used (31.3%). This study reveals the lack of consensus among an experienced group of surgeons when treating partial tears or non-professional athletes. This further highlights the current controversial use of various biologics, such as PRP and BMC, in the setting of UCL injury.

Non-Operative Management with Biologic Agent Injection Therapy

Numerous non-operative treatments are used in the management of UCL injury. Although rest, bracing, physical therapy, and other modalities remain mainstays of non-operative management, the focus of this review is the use of biologic agents for augmentation of UCL healing. Due to poor intrinsic healing potential of tendons and ligaments, research into biological agents as standalone injections or used concurrently for augmentation of surgical repair has increased, with specific attention in the current literature on PRP and autologous stem cell formulations [1, 2–4, 5, 6–12, 13, 14, 15, 16, 17, 18, 19, 20–24]. In this review, we will focus on platelet-

rich plasma (PRP), bone marrow concentrate (BMAC), and mesenchymal stem cells (MSCs). These modalities can also be used as an augment to physical therapy.

PRP

PRP is the most commonly studied biologic agent in the setting of UCL injury. It is an autologous blood product of ultra-concentrated whole blood in a small volume of plasma with platelet concentrations higher than baseline [1•, 18, 19, 25, 26•, 27, 28•, 29]. The normal human platelet count ranges from 150 to 350,000/ μ l and some have defined PRP as a concentration exceeding 1,000,000/ μ l in 5 ml of plasma while others have suggested any plasma fraction that concentrates platelets greater than baseline to be considered PRP [26•, 27, 30, 31]. PRP contains over 300 distinct cytokines and growth factors/mediators including platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), transforming growth factor (TGF) beta-1, and basic fibroblast growth factor, which are known to recruit cells to stimulate angiogenesis and endothelial cell growth to increase blood flow. This is believed to ultimately create an environment for accelerated healing potential [1•, 2–4, 5•, 6–12, 13•, 14•, 15•, 16•, 17, 18•, 19•, 20–25, 26•, 27].

Furthering the complexity of PRP, bioavailability of growth factors can theoretically be altered with specific formulation changes, such as differential levels of leukocyte concentrations, namely leukocyte-rich (LR-PRP), or leukocyte-poor (LP-PRP), as well as methods of activation [26•, 27]. Current understanding is that LR preparations are associated with a pro-inflammatory state and thus potentially with elevated levels of catabolic cytokines [26•]. Further complicating the proper selection of the correct PRP formulation, as of 2019, there are over 16 commercially available PRP systems on the market, all with significant variation in their collection and preparation protocols with unknown implications on their clinical efficacy [26•]. Moreover, variability is even seen on an individual patient level, as platelet, cell, and growth factor levels have been shown to vary regardless of collection/formulation protocol [32]. Overall, variability both within individual patients as well as within PRP collection and formulation protocols makes it difficult to accurately assess specific biologic compositions of PRP and complicates accurate comparisons between studies [27].

While the overall orthopedic literature is heterogenous regarding PRP, there are reports of level I evidence recommending LR-PRP for lateral epicondylitis and LP-PRP for osteoarthritis of the knee [26•]. Further evidence also supports LR-PRP for patellar tendinopathy and PRP injections for plantar fasciitis [26•]. Efficacy of treatment with PRP for other musculoskeletal pathologies such as rotator cuff tendinopathy,

OA of the hip, donor site pain in ACL reconstruction, and high-ankle sprains remains unclear [26•].

The first investigation on the use of PRP in partial UCL tears was performed by Podesta et al. [33] in 2013. The authors prospectively reported 34 athletes with partial thickness UCL tears confirmed on MRI. All patients failed at least 2 months of conservative management and an attempt at return to play prior to a PRP injection. Each athlete underwent a single LR-PRP injection under ultra-sound guidance followed by a guided course of PT and were allowed to return to play based on clinical symptoms and physical examination. The investigators found that at a mean follow up of 70 weeks (range, 11–117 weeks), 30 (88%) of the athletes had returned to the same level of play at an average of 12 weeks (range, 10–15 weeks). They also found statistically significant improvements in Kerlan-Jobe Orthopedic Clinic Shoulder and Elbow (KJOC) score as well as the Disabilities of the Arm, Shoulder and Hand (DASH) score. Only 1 patient underwent subsequent operative intervention at 31 weeks post-injection due to persistent UCL insufficiency.

In 2016, Dines et al. [34] also reported on the effects of PRP injection on partial UCL tears in high-level throwing athletes. The retrospective review included 44 baseball players ranging from high school to professional athletes with an MRI confirmed partial UCL tear. All patients were treated with between 1 and 3 PRP injections with 15 (34%) patients reporting excellent outcomes, 17 (39%) with good outcomes, 2 (4.5%) with fair outcomes, and 10 (23%) with poor outcomes. Four (67%) of the 6 professional athletes returned to professional play. When looking at timing for return to play, they found the mean time from injection to return to throwing was 5 weeks and the mean time to return to competition was 12 weeks (range 5–24 weeks). They reported no complications and concluded that the use of PRP injections for partial UCL tears may be beneficial in young patients with acute damage to an isolated part of the UCL and in athletes unwilling/unable to proceed with surgical intervention and subsequent prolonged rehabilitation.

A 2017 study by Deal et al. [35•] presented a series of 25 athletes with MRI confirmed primary grade 2 UCL tears treated with a series of 2 LR-PRP injections separated by 2 weeks, bracing, PT, and a structured return-to-throwing protocol. Of these 25 patients, 23 were primary injuries while the remaining 2 were cases of reinjury after surgical intervention. Of the 23 primary injuries, 22 (96%) patients demonstrated stability of the UCL post-treatment and returned to play at the same level or higher level of competition. Repeat MRI demonstrated full ligament reconstitution in 20/22 (91%) patients who returned to sport with the remaining 2 (9%) MRIs displaying partial reconstitution. Patients were allowed to return to play at 6 weeks with a mean time to return to athletic competition of 82 days. These results ultimately led to the authors concluding that a 2-injection regimen of LR-PRP is a safe and effective

treatment in the management of primary partial tears of the UCL. One of the major limitations of the three aforementioned studies is the lack of a control group, large patient heterogeneity, and large variation in the non-operative protocol (e.g., number of injections, type of rehabilitation, and time to return to throwing).

Most recently, a 2019 study by Chauhan et al. [36•] performed a comparative study evaluating the outcomes of professional baseball players treated non-operatively with and without PRP injections for UCL injuries. The investigation utilized the Major League Baseball (MLB) Health and Injury Tracking System to identify 544 professional baseball players managed non-operatively for UCL injuries from 2011 to 2015. Of these athletes, 133 received treatment with PRP prior to initiating their non-operative treatment program while the remaining 411 did not receive PRP. In an attempt to reduce selection bias, a 1:1 matched comparison between groups was performed based on age, position, throwing side, and league status (major versus minor league). Overall, non-operative management resulted in a 54% return to play with those receiving PRP experiencing a significantly longer delay in return to throwing and return to play. The analysis also revealed that MLB and Minor League Baseball (MiLB) pitchers in the non-PRP group had a significantly faster return to throwing and MiLB pitchers experienced a statistically faster return to play. They found that PRP, MRI grade, and tear location were not significant predictors for return to play (RTP) or progression to eventual operative intervention. The overall findings of the study found that PRP did not improve RTP outcomes or ligament survivorship in players treated non-operatively for UCL tears. However, the authors noted that heterogeneity in PRP preparations, injection protocols, timing of injections, and rehabilitation protocols could not be accounted for.

In summary, at this point, there is currently no consensus on the true efficacy of PRP in the setting of UCL injury. While case series have shown good clinical and return to sport outcomes following PRP therapy in partial tears, it is possible that the patients who do well with PRP may also do well with traditional non-PRP conservative management. Larger randomized controlled studies are required to fully elucidate the true clinical effects of PRP. Additionally, the mechanism of PRP on a cellular and molecular level must be further characterized in order to identify key growth factors within PRP and clarify their roles in the UCL healing process. Furthermore, LR-PRP should improve tendon and ligament healing by stimulating an inflammatory cascade that can aid in tissue healing; the mechanistic differences between LR and LP-PRP are still unknown.

Autologous Stem Cells

While PRP utilizes hematologic factors to stimulate healing, another method of biologic augmentation is the direct

injection of cells that can differentiate into healthy tissue and secrete factors to produce a more favorable biological milieu for healing. Stem cells are progenitor cells with the ability to self-renew, display long-term viability, and differentiate into various tissue lineages [17, 37•]. Similar to PRP, treatment with mesenchymal stem cells remains an unclear and heterogeneous management option. Modalities of stem cell treatment include embryonic versus adult, pluripotent versus multipotent, de-differentiated versus pre-differentiated, harvest site (i.e., bone-marrow, adipose, vascular, muscular derived), pure stem cell versus bone marrow concentrate, connective tissue progenitors (CTPs) versus mesenchymal stem cells (MSCs), and gene-modified stem cells. Stem cells can be derived from both embryonic and adult sources; however due to ease of harvest as well as ethical considerations, stem cells typically used in orthopedic surgery are harvested from the bone marrow [38–40], adipose tissue [41, 42], peripheral blood [43], and even the subacromial bursa [17, 39]. To clarify, the term “stem cell therapy” is often misused and misinterpreted by both patients and providers. The definition of a mesenchymal stem cell is specific and requires fulfillment of both molecular and functional criteria [44•]. According to the criteria defined by the International Society for Cell Therapy (ISCT), these criteria include the ability of the cell to be plastic adherent when maintained at standard culture conditions, tri-lineage differentiation under standard in vitro differentiating conditions, and the presence of a specific cell surface marker profile [44, 45]. While stem cells can come from all lineages, mesenchymal stem cells have the ability to differentiate into osteocytes, tenocytes, chondrocytes, and adipocytes based on environmental stimuli [17, 39]. Furthermore, these definitions were noted for definition of mesenchymal “stromal” cells in cultured conditions and therefore the term “stem cell” should not even be used for minimally manipulated preparations in the USA [44, 45]. A critical distinction needs to be made between minimally manipulated cell preparations and laboratory cell populations that have undergone culture expansion and cell sorting [44•]. The current regulatory environment enforced by the Food and Drug Administration (FDA) does not allow for the manipulation of cells ex vivo and therefore most commercially available autologous preparations used within the USA contain versus few true stem cell by formal definition [44•]. Due to confusion regarding these definitions, there is some discussion about abandoning the term stem cells when using the minimally manipulated preparations and instead using the term connective tissue progenitor cell (CTPs) [44•]. CTPs do not possess the characteristics of self-renewal or the ability to reconstitute into all types of parenchymal cells of a specific tissue, but do have some limited capacity for tissue repair [44•].

The possible role of cell based therapy has been evaluated in a variety of orthopedic conditions, including rotator cuff repair [20, 29], ACL reconstruction [21], lateral epicondylitis

[22, 23], patellar tendinopathy [24, 46], and bone healing in the setting of fractures and nonunions [47]. However, while some of these investigations have reported favorable results, there remains no definitive evidence to support the use of stem cells in the management of any of these conditions at this time and further research is necessary.

Bone marrow aspirate concentrate (BMAC) is one of the most commonly used mesenchymal stem cell formulations. It is most commonly harvested from the iliac crest; however, other sources include the distal femur, proximal tibia, proximal humerus, or other long bones [47]. Once aspirated, the raw sample is typically mixed with an anticoagulant and centrifuged to isolate mononuclear cells. It is important to recognize that, just as with PRP, the lack of standardization among preparation protocols and proprietary systems results in significant variability in BMAC samples. Furthermore, there is data to suggest that aspiration at various locations using a small (10 mL) syringe maximizes progenitor cell concentrations [48]. However, the concentration of stem cells based on formal criteria in BMAC is relatively low with reports showing a 0.001 to 0.01% yield. Therefore, the efficacy of BMAC is likely due to additional components of the sample which may facilitate the healing process, including numerous growth factors such as PDGF, TGF- β , and BMP-2 and BMP-7 [47, 49].

The literature on stem cell therapy in the setting of UCL injuries is very limited. A 2015 case report from Hoffman et al. [50] reported on the use of dermal allograft with PRP and MSCs, similar to techniques reported in the rotator cuff literature [51, 52]. The report describes the treatment of a 25-year-old professional baseball pitcher diagnosed with UCL instability and ulnar neuritis. He was indicated for operative reconstruction with the above described technique in addition to ulnar nerve decompression. Post-operatively, the patient underwent occupational therapy for the hand/wrist and remained in a brace for 6 weeks with progression range of motion followed by the initiation of strengthening exercises after 6 weeks. At approximately 4 months post-operatively, he began a throwing program and at the time of publication (21 months post-op) reported no indication of ulnar neuropathy or instability with successful return to throwing.

While the literature on stem cell therapy in UCL injury is limited, there is a growing body of evidence for stem cell therapy in ligament healing in animal models. In an internal-control study in a partial ACL transection model in rats, Kanaya et al. [53] demonstrated intra-articular injection of BMC consistently led to higher load to failure than the contralateral side which underwent partial transection alone. Similarly, Oe et al. [54] demonstrated improved biomechanical and histologic outcomes when treating partial ACL transection in rats with BMC injection compared to saline control. Histologically, in rats and rabbits, it has been shown that partially transected ACLs treated with BMC heal with formation

of Sharpey-like fibers similar to the native bone-tendon interface, rather than typical fibrovascular scar formation, even following ligament reconstruction with soft tissue or bone-soft tissue grafts [55, 56].

Conclusion and Future Research Aims

The ongoing challenge in the management of ligamentous injuries, including the UCL, is partly related to the relatively avascular nature of the tissue resulting in a limited inherent healing potential [37, 57]. Although there is some data to support the use of PRP therapy in patients with partial tears, there remains no clear consensus on its true efficacy. Further research utilizing standardized techniques of PRP formulation, injection timing, number of injections, post-injection rehabilitation, and comparison with a control group is necessary. Similarly, the use of stem cell therapy in UCL injury is very primitive, which is consistent with the evolving nature of the field in general. While there have been promising preclinical results in animal models for improved healing with stem cell injections, the clinical benefits are yet to be elucidated. Additionally, investigations accounting for variability in radiologic degree of injury and location of tear are needed to further define the appropriate role of biologic augmentation in the management of UCL tears in overhead athletes.

Compliance with Ethical Standards

Conflict of Interest John M. Apostolakos, Kenneth M. Lin, James B. Carr II, and Christopher L. Camp have no conflicts of interest.

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