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Current Concept Review

Platelet-rich plasma and other injectables in the young athlete

Akbar N. Syed, MD, Kevin Landrum, BS, Theodore J. Ganley, MD*

Division of Orthopaedics, Children's Hospital of Philadelphia, Philadelphia, PA, USA

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ABSTRACT

Pediatric sports participation and subsequent injuries have increased in parallel. Additionally, pediatric athletes and families are highly invested in rapid return to pre-injury status and the ability to sustain high impact loads and tension. Recently, an increase and diversification of biologically derived substances, known as orthobiologics, have been used to accelerate tissue healing. While commonly used in adults, the indications are ambiguous, and evidence for effectiveness is conflicting. Despite this, an interest in pediatric indications for orthobiologics has increased as both a standalone intervention and as a supplement to current treatment. There is a dearth of literature pertaining to the pediatric population, which warrants a review of what research has been performed. The purpose of this review was to critically examine the indications and results of orthobiologics in immature athletes. Much of the existing literature is composed of case studies or studies performed with relatively small sample sizes. As such, we believe more research is needed in almost every context for absolute guidelines and recommendations to be established. While orthobiologics have been purported to provide a significant healing benefit to augment the treatment of sports injuries, we find no additional benefit compared to standard treatment.

Key Concepts:

1) While orthobiologics have been used in small sample sizes to provide additional healing for pediatric patients being treated for sports-related injuries, there is little research in large cohorts of pediatric athletes.
2) Adding to the ambiguity, the literature that does exist presents conflicting findings regarding benefits of orthobiologics.
3) Orthobiologics have the potential to provide significant advanced healing benefits, however significantly more research of larger cohort size, higher evidence level, and a pediatric-only population is necessary for absolute guidelines and recommendations to be made.

Introduction

The injured athlete is highly motivated for a rapid return to the pre-injury status, which has led to the increased and widespread use of biologically derived substances purported to accelerate musculoskeletal tissue healing. Platelet-rich plasma (PRP) and mesenchymal stem cells (MSC) are the most commonly used orthobiologics [1,2]. A conceptual role in healing is depicted in Fig. 1. Supra-physiological concentrations of orthobiologics may create an environment for enhanced cellular regeneration, which may accelerate healing and return to function [2]. The use of PRP for musculoskeletal pathologies in adults is extensive and diverse; however, the indications for treatment evidence are ambiguous, and the results can be conflicting. Despite the extensive usage of PRP, there is a paucity of literature among the pediatric population, with most research being case studies or performed with small sample sizes [3]. The purpose of this article is to provide a comprehensive review of the potential application of PRP and other therapeutic injectables in adolescents and young athletes (< 25 years).

Common injectables and rationale for use

PRP has been shown to have both osteogenic and osteoinductive properties, as well as the potential for enhancing stem cell recruitment, angiogenesis, and extracellular matrix production [4]. At a cellular level, it modulates inflammation and immune responses by providing an abundance of key growth factors, producing a synergistic effect that is dependent on dosage, cell concentration type, and host/injury factors [5]. The combination of these factors makes PRP a viable option to accelerate healing. The 2 predominant PRP formulations are pure platelet-rich plasma, also called leukocyte-poor platelet-rich plasma, and

* Corresponding author: Division of Orthopaedics, The Children's Hospital of Philadelphia, The Hub for Clinical Collaboration, 3500 Civic Centre Boulevard, 4th Floor, Philadelphia, PA 19104, USA.
E-mail address: ganley@chop.edu (T.J. Ganley).

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Figure 1. The healing triad. The interaction of various "signals," "scaffold," and "cell" plays a role in healing, and each of these steps can be amplified or augmented. Signals can be amplified by using healing factors like platelet-rich plasma (PRP), while cells and scaffolds can be augmented by using mesenchymal stem cells (MSC)/bone marrow concentrate (BMC) and bone graft/minced cartilage, respectively.

leukocyte-rich platelet-rich plasma; however, a detailed description of each of these is beyond the scope of this review [2]. The preparation of PRP is shown in Fig. 2.

MSC are obtained from 2 common sites: bone marrow (bone marrow mesenchymal stem cells [BM-MSC]) or adipose tissue (adipose-derived mesenchymal stem cells [Ad-MSC]). Adipose tissue is considered superior in terms of accessibility, quantity that can be collected, ease of isolation, low patient morbidity, low risk of rejection, and high proliferative rate [6]. Highly concentrated BM-MSC is known as bone marrow aspirate concentrate. MSCs function by increased cell differentiation into the target cell and by secreting various cytokines and growth factors that lead to vascularization and cellular proliferation. Additionally, they also exert immunomodulatory effects reducing inflammation [6].

Orthobiologic utilization in the young and immature athlete

In sports medicine, orthobiologics have been used in the young athlete for musculoskeletal injuries involving the ligaments, cartilage, muscles, tendons, and, in some cases, fractures. However, most of the evidence-based literature is restricted to adults.

Ligament injuries

Anterior cruciate ligament (ACL) injuries in young athletes have been increasing at a dramatic rate, and treatment is evolving to reduce complication rates [7]. The use of orthobiologics has been reported in conservative and operatively treated patients. Herdea et al. [8] reported an improved response following PRP injection during nonoperative management of 17 adolescent athletes (11-17 years old) with grade 2 ACL injury. Patient pain perception and Lysholm score improved following PRP injection with a return-to-sport rate of 83.3% 1 month following injection [8]. Berdis et al. [9] evaluated outcomes of 143 patients (151 knees) with a mean of 16 years (range, 8-21 years) undergoing ACL reconstruction coupled with biologic augmentation of PRP and a porous collagen carrier. The study reported a higher return to pre-injury level with a faster recovery rate and a lower rate of ipsilateral ACL revision surgery at the end of 24 months when compared to existing literature on ACL reconstruction without biologics [9]. However, another study, while not exclusive to the "young athlete" with a mean age of 24.7 years, studied the effects of Ad-MSC in ACL reconstruction and found no significant difference in outcomes (pain scores, knee function, activity level, and MRI-based graft maturation) at 12 months after surgery when compared to the control group [10]. Due to the conflicting data from the limited studies available, no absolute guidelines can be interpreted concerning the role of orthobiologics in ACL injuries in the growing athlete. Additionally, no study has examined the use of orthobiologics in other knee ligament injuries such as medial patellofemoral ligament (MPFL) and Medial Collateral Ligament (MCL) injuries among adolescents or young athletes.

Among over-head throwing athletes, *ulnar collateral ligament (UCL) injuries* are particularly common. Nonoperative management is commonly employed in partial tears while surgical reconstruction is performed for complete tears. The role of orthobiologics in nonoperative management of UCL injuries has been studied in a mix-cohort of young athletes (12-33 years) with MRI-confirmed partial thickness UCL tears with an average follow-up of 70 weeks. The study reported that the athletes, who had failed 2 months of nonoperative treatment, experienced a statistically significant improvement in several clinical outcomes and had a satisfactory return-to-play rate with an average return to play of 12 weeks [11]. In a study among young throwing athletes (16-28 years) with a mean age of 17.3 years, the use of PRP in the treatment of UCL insufficiency produced outcomes much better than conservative treatment; however, a separate study among professional baseball players with a mean age of 23.6 years showed no difference in treatment with PRP [12,13]. Operative management of UCL injuries is challenging due to an extended rehabilitation program and raises the potential for orthobiologics to enhance recovery. These available studies on the use of orthobiologics in UCL injuries are promising but small and, similar to other injuries, warrant further investigation.

Meniscal injuries

Isolated meniscal injuries can be initially managed conservatively; however, operative management is indicated in cases of failed conservative management or severe tears (grade 3) [14]. Healing following a meniscal repair is unpredictable due to the nature of blood supply in meniscal tissue, and in these cases, biological adjuvant may enhance the healing response, as shown by a recent study conducted in a mixed cohort of patients (13-40 years) undergoing meniscal repair, which found slightly improved clinical outcomes for patients who had PRP injected at the lesion site at the conclusion of the procedure [15]. In a recent study, 55 conservatively managed adolescent athletes with grade 2 meniscal injuries were augmented with PRP and showed greater pain relief, better clinical outcomes, and a satisfactory return to sports at the end of 1 month [8]. Another study with a 3-month follow-up evaluated the role of PRP in adolescent patients < 17 years with grade 2 meniscal injuries and reported similar outcomes [14]. Biological augmentation in meniscal injuries needs to be studied in larger cohorts to ascertain an improvement in the natural history of nonoperatively treated meniscal injuries and to similarly develop recommendations for the role of orthobiologics in operatively treated meniscal injuries.

Cartilage and bone injuries

Articular cartilage lesions in the adolescent knee are concerning for the development of premature osteoarthritis with the major causes being an osteochondral fracture and osteochondritis dissecans (OCD) [3]. The effects of PRP injections into the knee after fixation of OCD lesions were studied by Sharma et al. [16] who found PRP injection into the knees of 6 patients (mean age 21.1 years) after fixation of a grade 3 OCD lesion resulted in good functional outcomes and a 100% union rate of the chondral fragment. In a case report of a 14-year-old male athlete, bilateral unstable trochlear OCD elbow lesions were managed surgically (debridement, loose body removal, microfracture, and osteochondral allograft) and augmented with a solution of PRP, BioCartilage (Arthrex), and native minced cartilage with fibrin glue [17]. The patient had appropriate postoperative progress, and at the end of the 2-

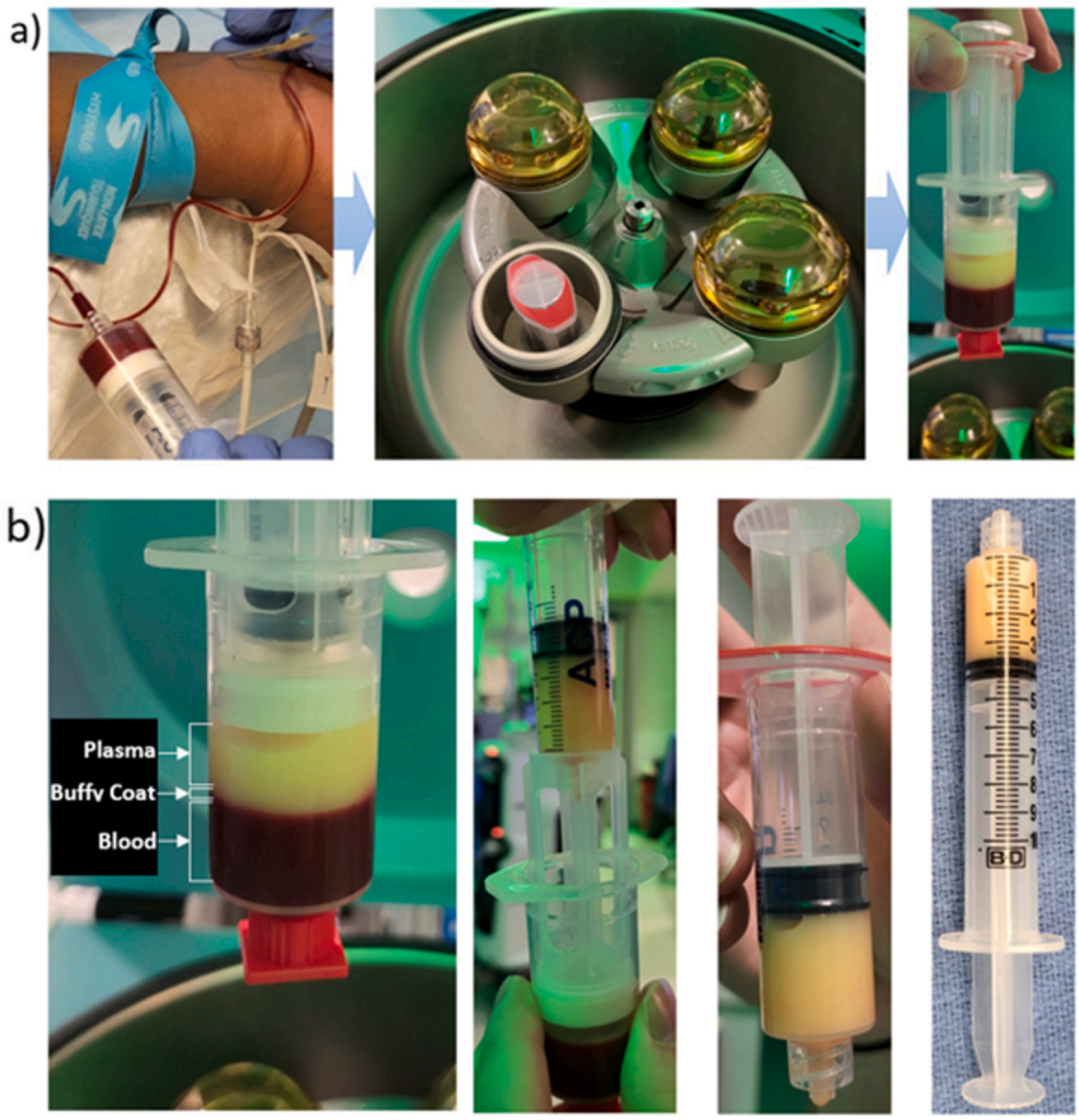

Figure 2. Preparation of platelet-rich plasma (PRP). (a) Blood is drawn in a syringe → Loaded in the centrifuge → Separation into layers. (b) PRP extracted for centrifuged syringe and ready for use.

year follow-up, he had excellent results with no limitations on sports participation [17]. Sánchez et al. [18] used PRP-augmented operative management in a 12-year-old soccer player with a large, nontraumatic avulsion of knee articular cartilage. The patient returned to play at 18 weeks and returned to competition without any recurrent symptoms at 38 weeks [18]. Freitag et al. [19] reported excellent results following treatment of a post-traumatic chondral defect in the knee in 26-year-old karate athlete with Ad-MSC 12 months after surgical intervention that failed to alleviate symptoms. Following Ad-MSC injection, the patient had good functional outcomes with complete filling of the chondral defect involving the medial facet of the patella at 12 months [19]. More investigation is warranted to determine the indications and therapeutic value of orthobiologics in cartilage lesions of different sizes and various locations. While the above cases are anecdotal testimonials to the potential for orthobiologics for articular injuries, studies of larger sample size are needed to establish generalizability and external validity of the benefits provided by these agents.

Orthobiologics have been used to treat bone-related pathologies. In a case series involving 7 adolescent patients, the use of PRP in forearm post-traumatic nonunion in young patients treated with intramedullary nailing showed complete recovery with 100% union rates [20]. Another case series described 3 adolescent patients with sesamoid injuries who were treated with PRP and were able to return to activities pain-free [21].

Muscle and tendon injuries

In athletes, *overuse injuries* such as hamstrings injuries are common among athletes and orthobiologics are being explored as treatment options to shorten recovery periods. In a small case-control study conducted on athletes (mean case age of 23, mean control age of 26), no significant difference in return to sport time was found between a group who underwent routine rehabilitation and another that received PRP injections along with routine rehabilitation [22]. However, in 2 subsequent studies with lower limb muscle injuries in younger athletes with a mean age of 22 years and a median age of 21 years, the use of PRP significantly shortened the return to play [23,24].

Tendon injuries and the use of orthobiologics in their treatment are currently understudied in the young athlete population. Two studies reported promising short-term outcomes with the use of PRP in patients, mean ages 25.5 and 26.9 years, with Jumper's knee [25,26]. One case report details a 17-year-old basketball player with insertional

patellar tendinosis following fixation of partial patellar tendon avulsion who was treated with PRP, bone marrow aspirate, and autologous fat graft from Ad-MSC and showed excellent functional outcome and a full return to sports at 6 months [26]. In another case study, an 18-year-old lacrosse player with a full-thickness patellar tendon tear was treated with PRP alone. At 2 months, I was able to return to full activity without pain or limitation [27]. Similar to the use of these agents in articular injuries, the use of orthobiologics in the young adult athletes reported above cannot be considered evidence to promote use in pediatric or adolescent athletes until further data is reported.

Summary

With a dramatic increase in competitive sports among young athletes, orthobiologics have been considered a potential tool to treat sports injuries. With the paucity and conflict in the literature concerning orthobiologic use, the judgment of pediatric sports medicine physicians plays an important role in providing an appropriate course of action for incorporating orthobiologics into treatment plans. Evidence-based medicine is essential to optimize a patient's recovery, and further investigation is needed to determine if biological substances hold the potential for an accelerated recovery pathway in athletes.

Additional links

- American Academy of Orthopaedic Surgeons OrthoInfo: Orthobiologics (Regenerative Medicine) FAQ.
- Journal of the AAOS: Orthobiologics: Current Status in 2023 and Future Outlook.
- Orthobiologics: Common Treatment Options.

Author contributions

Landrum Kevin: Data curation, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Ganley Theodore:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Syed Akbar N:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Theodore Ganley reports a relationship with Arthrex that includes: travel reimbursement. Theodore Ganley has received research support from Allosource and Vericel. He has also received education payments from Paladin Technology Solutions and hospitality and education payments from Arthrex. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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