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Platelet Rich Plasma and Stem Cell Therapy: Setting Standards and Evidence



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Insights

In recent years, biologics have emerged as a growing area of innovation in orthopaedic surgery.
Recent epidemiological trends in patient populations as well as the rise in relevant clinical trials have contributed to the accelerated interest in biologics.

- While biologics may have the potential to treat many common orthopaedic injuries and conditions, there is limited evidence to support their use at this time.

- There are significant gaps in understanding of the "optimal" conditions under which different biologics work, coupled with methodological concerns in many existing studies.

- The decision to integrate biologics in clinical care should be done in accordance with the availability of appropriate evidence for the clinical problem of concern.

"Orthobiologics are substances derived from a patient's own tissues including bone marrow or blood that are filled with signalling molecules or cells that stimulate and enhance the repair of musculoskeletal injuries. Orthobiologics could help in delaying or avoiding more invasive treatments."



American Academy of
 Orthopaedic Surgeons (1)

"Despite considerable research effort, the majority of biological approaches have not yet achieved a sufficient evidence base to warrant widespread clinical application, and inappropriate use is a growing problem."

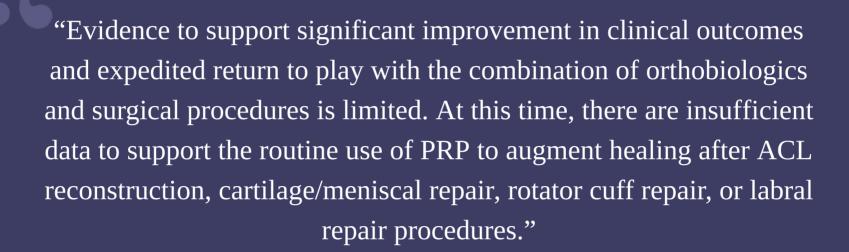
The field of orthopaedic surgery is continuously evolving with the introduction of many new innovations. Beyond advancements in robotics, which have traditionally dominated the innovation space in orthopaedics, there are now numerous novel technologies and approaches to care which have the potential to transform this field of surgery. These include augmented and virtual reality, 3D printing, emerging technologies for pain assessment, innovative monitoring solutions, activity trackers, and the use of big data to develop datadriven solutions in surgery (see our OE Insight "Innovations in Surgery: Redefining Tomorrow" for details). Among these innovations, perhaps the rise of biologics is undergoing a renaissance – with heightened focus on refining this therapeutic option and integrating it in clinical care. Biologics refer to active compounds that are obtained from living cells and can be produced by diverse biotechnology methods. While there is much interest in biologics, with recommendation for use for several injuries and orthopaedic conditions, there remains significant limitations and caveats in the body of evidence supporting their use. Understanding the "optimal" physical environment for biologics to work, as well as a critical analysis of the literature on their safety and effectiveness is not only necessary to set realistic expectations regarding the therapeutic capacity of biologics, but also identify key areas of research moving forward.

"It [PRP] was first thought to be beneficial in shoulder surgery to repair torn rotator cuff tendons. However, the results so far show little or no benefit when PRP is used in these types of surgical procedures. Recent research has been dedicated to the benefit of PRP in meniscus healing after meniscus repair; however, these studies are only in their infancy."

"Surgery to repair torn knee ligaments, especially the anterior cruciate ligament (ACL) is another area where PRP has been applied. At this time, there appears to be little or no benefit from using PRP in this instance."

"PRP has been used in a very limited way to speed the healing of broken bones. So far, it has shown no significant benefit."

Orthonaedic Surgeons (3)



et al. (2021) (4)

Categorizing Biologics

Throughout the last few decades, there has been a significant evolution of biologics used in orthopaedics. The first generation of biologics included hyaluronic acid, followed by platelet-rich-plasma (PRP) therapy, and stem cell therapy recently emerging as the third generation of biologics (5). With each passing year, new types of biologics are developed with applications to treat diverse musculoskeletal disorders (5). In this OE Insight, we will focus on PRP and stem cell therapies given their common use in clinical practice, with their characteristics outlined in Exhibit 1.

Exhibit 1: Characteristics of selected biologics (3) (6)

Biologics	Description
Platelet rich plasma therapy	 Blood consists of liquid (plasma) and solid components (red cells, white cells, and platelets) Platelets consist of proteins called growth factors that play an important role in healing injuries PRP is produced using a sample of patient's own blood Blood is taken from patient, platelets are separated from other blood cells and their concentration is increased through centrifugation, producing the PRP PRP is injected into the injured site; recently it has been used during specific types of surgeries to help tissues heal Promising results of PRP therapy are available for chronic tendon injuries and knee arthritis
Stem cell therapy	 Stem cells can differentiate to more than 200 different cell types in the body They can create new cells in existing healthy tissues and repair injured tissues Mesenchymal stem cells (MSC) are the most preferred form of therapy as they can differentiate to different tissues (e.g., muscles, bones, fat, cartilage) and obtained from different sources (e.g., bone marrow, adipose tissue, synovial tissue, peripheral blood) Promising results of stem cell therapy are available for bone-joint injuries and osteoarthritis-cartilage defects

"The high prevalence of painful and disabling orthopaedic conditions such as knee OA has also resulted in an exponential increase in the marketing of unproven biologics to relieve chronic pain."

> ——— Chu —— et al. (2019) (7)

"There are now over 400 complete or ongoing clinical trials evaluating the use of PRP and over 800 evaluating the use of MSCs in a range of clinical applications (see clinicaltrials.gov). Many of these trials have been designed and started with little knowledge of what preparations contain, and without comprehensive scientific understanding of the mechanisms by which it may produce benefit."
"We will only truly know if biological therapies can be of therapeutic benefit if the scientific/clinical community accepts that shortcuts cannot be taken, and adopts a responsible approach to the use of biological therapies including the generation of both an evidence base to support their use and an understanding of the principles of use."

Use of Platelet Rich Plasma and Stem Cell Therapy: Too Much Enthusiasm Too Fast?

Some key trends in orthopaedics that have influenced the rise in the use of biologics include (1):

- An aging, obese, and active population growth
- Changes in consumer priorities, including access, experience, and personalization
- Rise in the number of clinical trials

However, despite the elevated enthusiasm, it has been noted that the "race to the clinic has been at the expense of scientific understanding" (2). Significant methodological concerns have been identified in published studies of biologics, where methods are poorly reported and PRPs are inadequately described (8). There are clear dangers for patients when scientifically questionable biologic preparations are preferred at the expense of other potentially beneficial treatments (2).

"The effect of biological strategies relies on a complex interplay between the injury microenvironment and the biological preparations being delivered. Important injury factors contributing to variability include tissue type, and the mechanism and chronicity of injury. The therapeutic 'needs' of each injury will therefore be different."

> — **Murray** et al. (2018) (2)

"(Findings of a meta-analysis show) injection of LP-PRP (leukocyte-poor platelet-rich plasma) resulted in significantly better WOMAC scores than did injection of hyaluronic acid (mean difference, -21.14; 95% CI, -39.63 to -2.65) or placebo (mean difference, -17.84; 95% CI, -34.95 to -0.73) (in the treatment of knee osteoarthritis). No such difference was observed with LR-PRP (leukocyte-rich PRP) (mean difference, -14.28; 95% CI, -44.80 to 16.25)."

———— **Riboh** et al. (2015) (9)

Success: It Depends on Many Factors

The effectiveness of PRP therapy is dependent on several factors, including the body area being treated, overall health condition of the patient, acute or chronic nature of the injury, as well as the cellular makeup of the PRP itself (3). Indeed, not all PRP preparations are the same and there can be great variability in the number of leucocytes, red blood cells, growth factors, and cytokines depending on the method of preparation (2). It has been noted that the biologic preparation selection should be done in accordance with the pathology being treated, with growing evidence supporting the implementation of this approach (2). Age has been debated as an important factor influencing the availability, proliferative capacity, and differentiation potential of MSCs, however the evidence on this topic remains limited and conflicting thus far (10).

"Currently, there is a lack of consensus on the optimal preparation, source, delivery method, and dosing of biologic therapies in sports medicine applications, and this is exacerbated by a lack of sufficient experimental detail in most published studies. Ultimately, we need to identify the "biologic target" for different tissues and diverse pathologies. The ideal therapy depends on the goal of treatment."

Lamplot e (2019) (11) -----

"Many clinical trials have been initiated under the assumption that promising results obtained by preclinical studies would translate into a meaningful clinical effect in professional athletes. Although preliminary results of some studies have suggested that orthobiologics may play a role in the management of musculoskeletal injuries in athletes, allowing earlier return to play, decreased pain, and lower injury recurrence rate, other studies have not found similar results."
"Given the high variability in orthobiologics formulations, we urge team physicians to stay up-to-date with the most recent literature and orthobiologic preparation protocols for specific injuries. Meticulous and sterile preparation guidelines must be followed to optimize outcomes and minimize the risk for adverse events."

– Cole et 020) (4) –––––

Guidance: Setting a Common Standard

Notwithstanding the limited evidence supporting the use of biologics, there has been increasing efforts to provide guidance for clinicians to use biologics appropriately. There has been considerable progress in sports medicine where clinicians can turn to different guidance documents. For example, in "A Practical Guide for the Current Use of Biologic Therapies in Sports Medicine", Lamplot et al. (2019) summarize findings of Level 1 and Level 2 studies examining the safety and efficacy outcomes of using PRP and/or cell therapy for rotator cuff tears, tendinopathy, anterior cruciate ligament reconstruction, osteoarthritis, and chondral injury (11). Some of the common themes across the body of evidence they presented included the inconsistencies in the methodologies and findings across studies, as well as the need for more randomized controlled trials to examine the clinical utility of biologics for diverse injuries and conditions. There are also some targeted documents, including the "The 2020 NBA Orthobiologics Consensus Statement", where recommendations for the management of specific musculoskeletal injuries are presented, with indication that these recommendations may also be applicable to other recreational and professional athletes, as well as active individuals (4). Nonetheless, clinicians are

encouraged to remain abreast with the emerging knowledge given the rapidly changing research and regulatory landscape for

"In response to substantial patient demand for biologic treatment of orthopaedic conditions, the American Academy of Orthopaedic Surgeons convened a collaborative symposium and established a consensus framework for improving and accelerating the clinical evaluation, use, and optimization of biologic therapies for musculoskeletal diseases."

Chu et 019) (7)

Accountability

biologics in orthopaedics.

Given that biologics are here to stay, the orthopaedic surgery community has taken many initiatives to optimize future research in this area to facilitate the integration of biologics in routine clinical care. A recent consensus framework published by the American Academy of Orthopaedic Surgeons has several recommendations to improve the pathways to accountability for biologics, including developing detailed terminology to accurately classify biologics, standardizing reporting requirements, as well as establishing post-market monitoring and quality assessments of biologics (7). To accelerate the discovery, development, and delivery of biologics, the importance of developing trial frameworks for priority therapeutic areas is emphasized (7). As our knowledge base for biologics through our critical appraisal of the literature and situating emerging evidence in our current context of clinical care.

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