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Leonard B. Goldstein *

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Short Communication

The Effects of Platelet Rich Plasma as a Treatment Modality For the "Unhappy Triad" – A Multisystemic Review

Raheel Ramzan, James Keane, Leonard B. Goldstein *

Serves as A.T. Still University's assistant vice President for clinical education development.

***Corresponding Author:** Leonard B. Goldstein, serves as A.T. Still University's assistant vice President for clinical education development.

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Abstract

The "Unhappy Triad" traditionally identifies an injury that affects the anterior cruciate ligament (ACL), the medial collateral ligament (MCL), and the medial meniscus (MM). It occurs in an estimated twenty-five percent (25%) of acute knee injuries [1]. Due to a recent increased prevalence of lateral meniscus (LM) tears the "Unhappy Triad" may be more accurately described as an injury that consists of tears of the ACL, MCL, and the LM [2,3]. Acute simultaneous rupture in the "unhappy triad" of the knee is a rare but severe injury.

Key words: medial meniscus; fibrochondrocyte; kartogenin

Introduction

The "Unhappy Triad" traditionally identifies an injury that affects the anterior cruciate ligament (ACL), the medial collateral ligament (MCL), and the medial meniscus (MM). It occurs in an estimated twenty-five percent (25%) of acute knee injuries [1]. Due to a recent increased prevalence of lateral meniscus (LM) tears the "Unhappy Triad" may be more accurately described as an injury that consists of tears of the ACL, MCL, and the LM [2,3]. Acute simultaneous rupture in the "unhappy triad" of the knee is a rare but severe injury. Platelet rich plasma (PRP), is a natural concentrate of autologous growth factors from the blood, and is considered to stimulate cell proliferation. PRP can drive therapeutic cells toward chondrogenesis in the damaged site, and can induce autocrine growth factors for cartilaginous healing. Current evidence for PRP treatment for articular cartilage lesions primarily involves animal studies and lack consistent results, therefore requiring more investigation. With further studies, we would be able to move into human trials and extrapolate data on whether or not PRP is a useful tool in healing cartilaginous injuries.

Discussion:

PRP consists of autologous concentrates, meaning PRP is a preparation derived from whole blood [21], and these concentrates are released during platelet activation, i.e. during times of injury. The platelets secrete growth factors, such as transforming growth factor-beta (TGF-β), insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF) which can stimulate localized tissue regeneration [9]. Secreted growth factors have also been shown to stimulate meniscal cell migration [14], stimulate fibrochondrocyte migration [14], allow for cell chemotaxis, proliferation and differentiation, removal of tissue debris, angiogenesis and laying down extracellular matrix [13].

10-25% of the periphery of the menisci are supplied by a peri-meniscal capillary plexus and the meniscal stroma does not receive any vessels. The posterolateral meniscus also does not receive peripheral vessels; however, the anterior and posterior horns of the menisci have sufficient blood supply. The overall inadequate blood supply can complicate treatment via PRP The lack of blood flow limits the impact that PRP has on the cartilaginous structures because less circulating platelets reach the damaged sites, thus leading to minimal growth factor release.

The qualities of PRP shown by various studies depict the potential that PRP has for healing menisci injuries, however, there have been discrepancies in the literature when experimentation was performed. One study explored in vitro and in vivo animal trials and found that PRP treatment caused upregulation of meniscal cell viability and synthesis of sulphated glycosaminoglycans compared to control groups [15]. Another study used mesenchymal stem cells to engineer meniscal tissues which were combined with a composite loaded with leukocyte-rich PRP and implanted into the avascular zone of the menisci of rabbits; this study showed no improvement compared to controls [16]. A further study investigated patients undergoing arthroscopic meniscal repairs presenting with knee pain and explored the impact of PRP on knee pain and function; it was found that there was a statistically significant improvement in pain, knee function and cartilage thickness between treatment and control groups [17].

The lack of consistency between studies demonstrates the need for further investigation of PRP as a treatment modality for meniscal injuries.

ACL injury intervention with PRP provides conflicting data as well [9] however, there are revolutionary models of healing that are being used to explore the tissue regeneration of torn ACLs. For example, Zhang et. al

discussed that kartogenin (KGN) promotes the differentiation of mesenchymal stem cells into chondrocytes and this can lead to the repair of destroyed cartilage [10]. KGN requires an effective carrier, and the authors of the study focused on PRP. They found that the KGN-PRP treatment promoted cartilage formation in rabbits and slowed down inflammation which promoted recovery after ACL reconstruction [10]. Although this study was an animal model, it showed positive outcomes linked with PRP as a treatment modality along with other effective compounds. PRP is thought to strengthen primary ACL repairs because it offers structural support for a clot, which is normally not formed at the ACL tear site, and is a source of growth factors [14]. Another study incorporated the use of a water-soluble polysaccharide, SOWPa, from the roots of *Sanguisorba officinalis* for the healing of the ACL post-ACL reconstruction surgery in a rabbit model; this investigation found that the addition of this polysaccharide assisted PRP in decreasing apoptosis and increasing cell viability, migration and differentiation of ACL fibroblasts, which are pivotal for the integrity and homeostasis of the ACL, via blocking the TLR-4/NF- κB pathway, typically involved in inflammatory processes[18]. The use of PRP was also examined as a utility for reducing femoral and tibial tunnel enlargements in patients undergoing ACL reconstructions, however, this study concluded that the use of PRP is not effective in preventing tunnel enlargement [19]. Similar to menisci treatments, ACL treatments lack consistency with research and many studies are shaped with animal models which are difficult to translate to the human population. However, there is potential for transition from current research to human trials with the use of external compounds supplementing PRP to further expand our knowledge of this treatment option.

MCL injuries occur frequently in contact sports, however, they are more likely to heal at a faster rate than the ACL because of their vascularity [11]. Research has been done using animal models, similar to the ACL studies, to explore MCL tissue regeneration using PRP. One study specifically used platelets with a high quantity of growth factors called PRGF-Endoret. It was found that the administration of this mixture accelerated tissue healing post-injury. It was also found that at 6 weeks, collagen fibers became more aligned and cell shape became narrower which indicates that the PRGF-Endoret was targeting inflammatory processes, which thus led to improved healing [12]. On the other hand, a study was conducted that looked into the dosing of PRP to accelerate MCL healing postoperatively in a rabbit model; it was found that low dosages of PRP at the time of injury does not improve ligament healing, and doubling this dosage would negatively affect ligament strength and histologic characteristics 6 weeks post-injury [20] This indicates that further investigation must be done to determine correct dosing and timing of PRP administration post-injury for the most optimal resolution of injury. MCL studies show parallels to the other ligament studies in that many utilize PRP on animal models and depict a range of data to be analyzed.

This shows that we must continue to investigate PRP further and perhaps combine it with other compounds prior to injection to determine if significant histological alignment occurs.

Conclusion:

In summary, PRP has undergone a gauntlet of animal studies and throughout these investigations discussed herein, there have been minimal reports of negative outcomes related to safety. We understand that PRP has optimal efficacy when injected in areas with adequate blood supply, and therefore locations with limited blood supply, such as the menisci, can lead to less effective PRP treatment [8]. However, multiple studies have proven to show contradicting data and thus more investigation in this area is required. Such research is being conducted utilizing novel substrates that are combined with PRP to promote healing, such as Karotegnin [10] and SOWPa [18]. During the injection process, it was found that specific dosing of PRP could modulate healing of ligaments where low dosages do not improve healing and doubling the dosage negatively impacts ligament strength and histology [20].The dosing studies demonstrate that not only should we continue to examine how PRP impacts our ligaments, but we should also examine the quantity of PRP that impacts our ligaments and what is the limit of platelet injection that our ligaments can take before reaching their tipping point. The majority of the studies collected herein discussed animal trials which can serve as a framework for this research, however, if more knowledge is desired then this data must be replicated in human trials to determine if consistency can be achieved.

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