



Biological Implications of Platelet-Rich Plasma Injection for The Treatment of Knee Osteoarthritis: A Review

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ABSTRACT

Osteoarthritis (OA) is a chronic musculoskeletal condition that commonly affects the knee and other joints. The disability associated with OA results in a considerable economic burden particularly joint replacement surgery and job-related loss of productivity. Until now, most cures research has focused on treatments to reduce pain and prevent functional decline. Analgesics and anti-inflammatory have short-term clinical benefits with some effect sizes which are generally small to moderate. Intra-articular therapies for OA (such as Hyaluronic Acid and corticosteroids) are also proposed but their benefits are limited to a few weeks. Platelet-rich plasma (PRP) injection into the affected joint is receiving increasing interest such as biologic therapy for OA. Current variability in the numerous PRP preparation and injection protocol in addition to considerable heterogeneity between studies make it difficult to establish recommendations regarding which type of PRP to use and for which indications. This manuscript will advance a systematic review of biological effect of PRP as a treatment for knee OA.

Keywords: Platelet-Rich Plasma – Biological implications – Injection Protocol - knee osteoarthritis

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Received 02 March 2019, Accepted 07 April 2019

Please cite this article as: Lachkar A *et al.*, Biological Implications Of Platelet-Rich Plasma Injection For The Treatment Of Knee Osteoarthritis: A Review. American Journal of Pharmacy & Health Research 2019.

INTRODUCTION

Osteoarthritis (OA) is a chronic musculoskeletal condition that commonly affects the knee and other joints. It is a major public health worldwide problem. The disability associated with OA results in a considerable economic burden particularly joint replacement surgery and job-related loss of productivity. Until now, most cures' research has focused on treatments to reduce pain and prevent functional decline. Analgesics and anti-inflammatory have short-term clinical benefits with some effect sizes which are generally small to moderate¹. Intra-articular therapies for OA (such as Hyaluronic Acid and corticosteroids) are also proposed but their benefits are limited to a few weeks². Platelet-rich plasma (PRP) injection into the affected joint is receiving increasing interest such as biologic therapy for OA. This article will advance a systematic review of biological effect of PRP as a treatment for knee OA.

Biological Mechanisms Of PRP In The Context Of OA:

Recent progress in molecular biology has supplied new understandings regarding OA pathophysiology in which growth factors, inflammatory mediators, chondrocyte apoptosis and imbalance between catabolic and anabolic mechanisms plays an important role. Several cytokines such as transforming growth factor β , interleukin-1 β , nitric oxide synthetase and proteases all appear to be required for cartilage destruction in the pathogenesis of OA³. PRP is an autologous blood product that contains an elevated concentration of platelets above that of whole blood; it may be beneficial in OA by interfering with inflammatory and catabolic events. Activation of PRP releases a sustained release of biologically active growth factors, platelet-derived growth factor, transforming growth factor- β , type I insulin-like growth factor and vascular endothelial growth factor⁴. These proteins are responsible for chondrocyte apoptosis inhibition, bone and vessel remodeling, inflammatory modulation and collagen synthesis^{4,5}. Pre-clinical literature supports the use of PRP injections to regenerate damaged joint tissue in OA. In vitro studies show a direct effect of PRP on cartilage with increases in chondrocyte proliferation and enhanced production of proteoglycans and type II collagen⁶⁻⁸; it also provides positive effects on meniscal cells⁹ and synoviocytes¹⁰. Research suggests also a direct analgesic effect via augmentation of cannabinoid receptors¹¹.

Methods of Preparation of Prp and Injection Protocol:

There is a wide variation in the reported protocols for standardization and preparation of PRP (table 1); this reflects the lack of evidence supporting one particular protocol over another. Most studies in knee OA have administered PRP injections weekly. One to four PRP injections have

been used with the most common being three injections; injection volumes have ranged from 3 to 8mL. Different activating agents have been described; most studies have used calcium to activate platelets although some authors do not activate platelets prior to injection. One of the most variable aspects of the PRP preparation technique is the centrifugation protocol. Studies used single or double-spin technique with inconsistent spin speed and times. The studies that have used a single-spin technique with spin speeds around 1500rpm and spin times around 8min report a leukocyte-poor PRP (LP-PRP) by excluding leukocytes and neutrophils in particular; those ones that have used a double-spinning approach with spin speeds and times of up to 3400rpm and 15min for the second spin report a leukocyte-rich PRP (LR-PRP) product¹²⁻²⁷. While some believe that superior outcomes are obtained with LP-PRP because of deleterious effects of proteases and reactive oxygen species released from white cells, others think that leukocytes are an important origin of enzymes and cytokines which may be important for infections^{28, 29}. However, more adverse events were described by patients who received the LR-PRP product³⁰. Recently, a classification system of PRP protocol was proposed by DeLong *et al.*³¹; it is based on three components: (1) the absolute number of platelets, (2) the manner in which platelet activation occurs, and (3) the presence or absence of white cells.

Table 1: PRP preparation and injection protocols

Author	Centrifugation Protocol	Leukocyte Rich/poor	Injection Frequency	Injection Approach	Injection Count	Volume Injected(ml)
Filardo et al. [12]	C1: 1480 rpm for 6 min C2: 3400 rpm for 15 min	Rich	Weekly	Not reported	3	5
Vaquerizo et al. [13]	C1 : 580 g for 8 min	Poor	Fortnightly	External Suprapatellar	3	8
Raeissadat et al. [14]	C1: 1600 rpm for 15 min C2: 2800 rpm for 7 min	Rich	Four weekly	Lateral midpatellar in extended knee Position or anteromedial In flexed knee position	2	4 a 6
Angoorani et al. [15]	C1 (women):1600 rpm for 6 min C1 (men) 1800 rpm for 6 min C2: 2000 rpm for 5 min	Not reported	Four weekly	Not reported	2	5
Smith [16]	C1 : 1500 rpm for 5 min	Poor	Weekly	Lateral Parapatellar	3	3 a 8
Simental-Mendia et al. [17]	C1: 1800 rpm for 10 min C2: 3400 rpm for 12 min	Poor	Fortnightly	Inferolateral	3	3
Duymus et al. [18]	C1 : 3700 rpm for 7 min	Not reported	1 Month	Suprapatellar	5	2
Battaglia et al. [19]	C1: 1800 rpm for 15 min C2: 3500 rpm for 10 min	Not reported	Fortnightly	Lateromedial and caudocranial	5	3
Di Sante et al. [20]	C1: 3100 rpm for 9 min C2: 3100 rpm for 9 min	Not reported	Weekly	Not reported	3	3
Cerza et al. [21]	Single	Poor	Weekly	Superolateral	4	5,5
Sanchez et al. [22]	C1: 580 g for 8 min	Poor	Weekly	Not reported	3	8
Patel et al. [23]	C1: 1500 rpm for 15 min	Poor	3 weekly	Supralateral	1 vs 2prp	8
Gormelli et al. [24]	C1: 1500 rpm for 6 min C2: 3500 rpm for 12 min	Not reported	Weekly	Superolateral	3 vs 1	5
Lana et al. [25]	C1: 300 g for 5 min C2: 700 g for 17 min	Not reported	Fortnightly	Lateral Midpatellar	3	5
Paterson et al. [26]	C1: 2000 rpm for 5 min C2: 3000 rpm for 3 min	Not reported	Weekly	Anteromedial	3	5
Dallari et al. [27]	C1: 1400 rpm for 6 min C2: 3400 rpm for 15 min	Not reported	Weekly	Lateromedial and caudocranial	3	5

Outcomes and Clinical Implications:

At 6 months following three PRP injections Sampson et al.³² reported that 50% of their patients with knee OA showed greater cartilage volume at the intercondylar notch and femoral condyles using ultrasonography to quantify knee cartilage. In his uncontrolled study involving 15 patients with no or early knee OA and received a single PRP injection, Halpern³³ found there are no significant structural changes at 12-month follow-up assessed using magnetic resonance imaging. However, given the lack of high-quality studies, no clinical guidelines can be made at this time to recommend for or against the use of PRP for the management of knee OA³⁴⁻³⁶.

CONCLUSION:

The safety and simplicity of PRP injection appears to be an effective solution for symptomatic OA knees; it can also be an interesting and promising option for both clinicians and patients with significant reduction in pain and improvement in knee function after treatment. Current variability in the numerous PRP preparation and injection protocol in addition to considerable heterogeneity between studies make it difficult to establish recommendations regarding which type of PRP to use and for which indications.

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