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Review Article

Modifying Standard Dose of PRP for Long-term Clinical Outcome of MSK Pathologies

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Abstract

Currently, platelet-rich plasma (PRP) stands as a widely adopted treatment for musculoskeletal issues. Despite promising outcomes linked to PRP application in these conditions, crucial questions persist, such as definitive proof of its effectiveness in altering structures, establishing standard dosages, and devising optimal manual preparation methods to yield high-quality PRP. This review focuses on four key topics regarding the use of PRP in managing musculoskeletal ailments: (a) exploring PRP's composition and its significance, (b) assessing evidence supporting its effectiveness in treating injuries to tendons, joints, ligaments, and muscles, (c) comparing available PRP kits to gauge their cell count variations, and (d) emphasizing the importance of optimizing PRP dosage and its connection to both structural and physiological efficacy on an individual basis.

Keywords: Platelet-rich plasma, PRP, Musculoskeletal pathologies, Dose optimization

Introduction

Musculoskeletal (MSK) diseases stand as a leading cause of prolonged, intense pain and significant physical limitations, significantly impacting patients' quality of life [1-3]. This type of pain affects a vast number of individuals worldwide, nearly hundreds of millions [1,4]. Typical approaches to managing MSK pain involve traditional methods like "Rest, Ice, Compression, Elevation" therapy alongside physical therapy, corticosteroid injections, and specific rehabilitative exercises [1,5]. While these methods often aid in short-term pain relief and early functional recovery, they generally do not reverse the structural changes linked to degenerative conditions.

PRP (Platelets Rich Plasma) an orthobiological application has shown promising results in aiding the body to regenerate functional tissues for restoring degenerative or defective areas. Moreover, they offer therapeutic solutions for conditions where conventional therapies might not suffice [6-9]. However, relying on a standard "one-size-fits-all" approach for PRP preparation isn't ideal across

various MSK pathologies. This method tends to limit the immunomodulatory and angiogenetic responses crucial for tissue repair, ultimately leading to suboptimal patient care [6].

We argue for a shift away from this uniform PRP orthobiological preparation strategy toward more tailored and transformative approaches. These advancements involve adopting algorithms to determine cell dosing strategies and utilizing physiologically distinct PRP formulations specific to the varied pathologies under treatment [6]. This review delves into how adjusting the standard PRP dosage can significantly impact the long-term clinical outcomes of MSK pathologies. The focus here lies in addressing three primary challenging aspects related to using platelet concentrates for treating musculoskeletal conditions: (a) different procedures for preparing platelet concentrates, (b) the composition of these products primarily linked to the adopted methodological procedures, and (c) the clinical application in musculoskeletal conditions and the level of efficacy.

Importance of PRP and its Composition

Platelet-rich plasma (PRP) stands as the plasma faction within one's blood, holding a concentration of platelets above baseline following centrifugation. These platelets sized between 1 to 3 μm, manifest as irregularly shaped, non-nucleated cytoplasmic entities birthed from megakaryocyte precursor fragmentation within the red bone marrow [1]. Remarkably, within the platelet, coexist three distinct intra-platelet structures: α-granules, dense granules, and lysosomes [8,10]. Around the outer platelet cell membrane lies an array of glycoprotein receptors and adhesion molecules. In adult bodies, platelet concentrations average within the range of 150 to 350 × 106/μL in circulating blood [8]. Their significance extends across blood clot formation, thrombosis, hemostasis, immunity, inflammation, wound healing, haematological malignancies, and metabolic disorders [1].

Composition of Platelet-Rich Plasma

PRP, derived from autologous blood post-centrifugation, boasts rich platelet concentrations along with an array of growth factors, cytokines, chemokines, and proteins [1]. Table 1 encapsulates the pivotal growth factors integral to PRP's composition which play a pivotal role in tissue repair mechanisms.

Growth factor	Physiological action
Platelet-derived growth factors A and B	Mitogenic for mesenchymal cells and osteoblasts Regulates collagenase secretion and collagen synthesis Enhances macrophage and neutrophil chemotaxis, and mitogenesis in fibroblast, glial, or smooth muscle cells
Transforming growth factor-β	Promotes undifferentiated mesenchymal cell proliferation as well as endothelial chemotaxis and angiogenesis Regulates mitogenic effects of other growth factors including endothelial, fibroblastic, and osteoblastic mitogenesis Regulates collagenase secretion and collagen synthesis Inhibits lymphocyte and macrophage proliferation
Epidermal growth factor	Enhances endothelial chemotaxis or angiogenesis, as well as epithelial or mesenchymal mitogenesis Regulates collagenase secretion
Fibroblast growth factor	Promotes growth and differentiation of chondrocytes and osteoblasts Mitogenic for mesenchymal cells, chondrocytes, and osteoblasts
Connective tissue growth factor	Stimulates angiogenesis, platelet adhesion, and cartilage regeneration
Platelet factor 4	The fibroblast chemoattractant enhances the initial influx of neutrophils into wounds
Vascular endothelial growth factor	Stimulates angiogenesis, vessel permeability, and mitogenesis for endothelial cells

Insulin-like growth factors 1 and 2	Chemotactic for fibroblasts Stimulates protein synthesis and bone formation
Interleukin-8	The proinflammatory mediator helps in recruiting inflammatory cells
Keratinocyte growth factor	Stimulates endothelial cell growth, migration, adhesion, and survival Enhances angiogenesis

Table 1: PRP growth factors and their physiological actions [1,11].

The ongoing clinical trials reveal an exciting horizon: PRP potentially amplifies cartilage repair, alleviates arthritis symptoms, and uplifts joint function. Its multi-faceted role in anti-inflammatory ability and analgesic effects underscores its profound impact [1,11]. This is something we will investigate in the following section.

Evidence Regarding the use of PRP for MSK Pathologies

The wide application potential of PRP's mechanism is fascinating, hinting at its possible use across various ailments for boosting the body's healing. We will explore at these musculoskeletal ailments in detail and the type of PRP used (see Table 2).

Study	Design	Pathology	PRP Used (Commercial kit/manual preparation)	Control	N size	Outcomes	Follow-ups	Results
Lin, 2019 [24]	Randomized, dose-controlled, placebo-controlled, double-blind, triple-parallel	Knee osteoarthritis	RegenKit THT	1)Hyaluronic acid 2)Saline	53	WOMAC, IKDC score	1, 2, 6, and 12 months	Favoured PRP
de Vos 2011 [25]	RCT	Achilles tendinopathy	RecoverTM Kit, Biomet	Saline	27/27	VISA-A, Patient satisfaction, Return to Sports, Adherence to eccentric exercise, Ultrasound measures	6 wks; 3, 6 mos; 1	No difference
Creaney 2011 [26]	RCT	Elbow tendinopathy	Unspecified	Autologous blood	80/70	PRTEE	1, 3, 6 mos	Favour ed control
Thanasas 2011 [27]	RCT	Chronic Lateral Epicondylitis	Recover TM Kit, Biomet	Autologous blood	14/14	VAS pain, Liverpool elbow score	6 wks; 3, 6 mos	No difference
Rha 2013 [28]	RCT	Rotator cuff (tendinosis or partial tear)	Prosys PRP Kit	Dry needling	20/19	SPADI, ROM, Adverse effects, Ultrasound	3, 6 mos	Favoured PRP

Bubnov 2013 [29]	RCT	Muscle injury	Unspecified	Conservative therapy	15/15	VAS pain, Strength, ROM, Resistance assessment, Global function score	1, 7, 14, 21 days; 1 mos	No difference
Chew 2013 [30]	RCT	Plantar fasciitis	ACP® Double Syringe, Arthrex & Conservative	1) Extracorporeal shock wave therapy and Conservative; 2) Conservative alone	19/19/16	VAS pain, AOFAS ankle-hindfoot scale	1, 3, 6 mos	No difference
Kesikburun 2013 [31]	RCT	Chronic rotator cuff tendinopathy	Recover Kit, Biomet (GPS III System)	Saline	20/20	WORC, SPADI, VAS pain with Neer Impingement Sign, ROM	3, 6 wks; 3, 6 mos; 1 yr	No difference
Krogh 2013 [32]	RCT	Lateral Epicondylitis	Recover Kit, Biomet (GPS III System)	1) Saline;2) Glucocorticoid	20/20/20	PRTEE, ultrasound measures, pain score.adverse events	1, 3, 6 mos; 1 yr	No difference
Vetrano 2013 [33]	RCT	Jumper's knee	MyCells® Autologous Platelet Preparation System	Extracorporeal shock wave therapy	23/23	VISA-P, VAS pain, modified Blazina	2, 6, 12 mos	Favoured PRP
Dragoo 2014 [34]	RCT	Patellar tendinopathy	Recover Kit, Biomet (GPS III System)	Dry needling	10/13	VISA, Tegner, Lysholm, VAS pain, SF-12	3, 6 wks; 2, 3, 6 mos	No difference
Hamid 2014 [35]	RCT	Grade 2 Hamstring muscle pathologies	Recover Kit, Biomet (GPS III System) and Physiotherapy	Physiotherapy	14/14	Return to sport, BPI-SF pain scores	2.5 mos	Favoured PRP
Reurink 2014 [36]	RCT	Hamstring pathologies	ACP® Double Syringe, Arthrex	Saline	41/39	Return to sport, Rate of reinjury	2, 6 mos	No difference
Say 2014 [37]	Prospective comparative study	Plantar fasciitis	Not mentioned	Steroid	25/25	VAS, AFAS	6wks, 6 mos	Favoured PRP
Raeissadat 2014 [38]	RCT	Lateral Epicondylitis	Rooyagen Kit Leukocyteenriched PRP	Autologous Blood	23/22	VAS modified Mayo Clinic performance index for the elbow & PPT	4, 8 wks	Favoured PRP
Mishra 2006 [39]	Prospective comparative	Chronic elbow tendinosis	Recover Kit, Biomet (GPS III System)	Bupivacaine with epinephrine	15/5	VAS pain, Modified Mayo score	4wks; 2, 6 mos	Favoured PRP

Kaniki 2014 [40]	Retrospective comparative	Achilles tendon	ACP® Double Syringe, Arthrex, and Accelerated Rehabilitation	Accelerated Rehabilitation	72/73	Strength, ROM, Calf circumference, Leppilahti scale, AOFAS (PRP only)	6 wks; 3, 6, 12, 18, 24 mos	No difference
Gosens 2011 [41]	RCT	Tennis Elbow	Recover Kit, Biomet (GPS III System)	Steroids	51/49	VAS pain scale, DASH	1, 2, 3, 6, 12, 24 mos	Favoured PRP
Mishra 2013 [42]	RCT	Tennis Elbow	Recover Kit, Biomet (GPS III System)	Bupivacaine	112/1 13	Safety, VAS with resisted wrist extension, PRTEE, extended wrist exam, success rate	1, 2, 3, 6 mos	Favoured PRP
Wright Carpenter 2004 [43]	Retrospective comparative	Muscle pathologies (variety)	Orthokine®, Autologous Conditioned Serum	Actovegin/ Traumeel	18/11	Return to sport, MRI analysis	16 days	Favoured PRP

*Abbreviations: RCT = randomized controlled trial, PRTEE = patient-rated tennis elbow evaluation, VISA-A = Victorian institute of sport assessment scale Achilles, VAS = visual analogue scale, SF-12 = short form 12, SPADI = shoulder pain and disability index, ROM = range of motion, BPI-SF = brief pain inventory short form, DASH = disabilities of the arm, shoulder and hand, MRI = magnetic resonance imaging, EQ VAS = Euroqol visual analogue scale, FHSQ = foot health status questionnaire, PPT = pressure pain threshold, AOFAS AHS = American orthopaedic foot and ankle society ankle-hindfoot scale, AFAS = American foot and ankle score, WORC = Western Ontario rotator cuff index, wks = weeks, mos = months, yr = year.

Table 2: Comparing different dosages of PRP results in different MSK conditions.

Available PRP Commercial Kits

Several PRP commercial systems are available with a unique protocol for PRP preparation and administration. Table 3 shows a comparative study on PRP preparation aiming to analyse different common commercial separation systems, essentially evaluating final PRP products in terms of platelet concentrations. These PRP preparations involve two basic protocols (plasma-based and buffy-coat-based). Most of commercially available systems produce PRP by buffy-coat-based method where they yield higher concentrations of platelets compared to plasma-based systems [22].

Commercial PRP systems	Platelet concentration	PRP volume (ml)
PurePRP II (EmCyte, USA)	8x (1175*10^6/µL), 81% recovery rate	7/14ml
Genesis CS (EmCyte, USA)	6-10x	3-4/7ml
Arthrex Angel System (USA)	Up to 10x (856*10^6/µL)	2-20
Arthrex ACP Double Syringe USA	2-3x (500*10^3/µL)	4-6
RegenKit A (Switzerland)	1.6x (125*10^6/µL)	4-5
Biomet GPSIII (Zimmer, USA)	9.3x (273.6-1560*10^3/µL)	3/6ml
Magellan (USA)	3-7x (600-1500*10^3/µL)	3-10
Glo PRP (Finland)	4-9x	Adjustable
Ortho.pras (Spain)	2.2x	4-10
Prosys PRP Kit	5-7x	2

Y-PRP (Ycellbio, S Korea)	7-9x	1-2
Dr.PRP (SDD Medical Group, UK)	-	5
SW-PRP (S Korea)	-	2
Harvest Smart PReP (USA)	4.3-6.6x (800-2600*10^3/μL)	3/7/10ml
CPunT (Italy)	4-5x	10
MyCells (UK)/Tropocells (UK)/Cellenis PRP (Israel)	2-5x (800*10^3/μL)	2-3
PRF	(338*10^6/μL)	2
PRGF/Endoret (Spain)	2x	2
SmartPrep, Harvest Technologies	4-6x	3-4

Table 3: Comparing PRP cell count using commercial PRP kits that give higher cell count [6,22,23].

Importance of Correct Dosage in Healing

The quantitative measure of platelet concentration, singularly or in multiples exceeding the baseline, fails to precisely encapsulate the accurate count of functional platelets delivered to heal tissues. The calculation of platelet dose, or the total delivered platelets (TDP), necessitates multiplying the PRP volume administered in one treatment site by the known platelet count per volume (platelet concentration) [6]. In essence, this approach offers a more comprehensive view of how many platelets reach a designated treatment site, urging clinicians to embrace TDP as a superior parameter for PRP quality [12]. Giusti et al.'s findings underscore the requirement of delivering 1.5 × 106 platelets/μL to induce significant angiogenic responses, setting the threshold at 10.5 × 109 TDP for a 7 mL C-PRP treatment vial [12]. Yet, crucial gaps persist, necessitating investigations into optimal TDP dosing tailored for distinct tissue types (tendons, ligaments, cartilage), MSK pathologies (tendinopathy vs. tears), and the disorder's chronicity (acute vs. chronic) [6].

Bansal et al.'s experiment injecting PRP with 10 billion TDP in knee OA patients revealed sustained clinical effects in function, pain reduction, and inflammatory markers over 12 months [13]. This underscores the need to define C-PRP through absolute platelet concentrations for optimal dosing strategies [14,15]. A patient-centric treatment plan must dictate the prepared C-PRP volume, considering the required number of treatment sites and injection volumes per site to achieve the desired platelet dose, drawing from pre-procedure baseline whole blood platelet concentrations [6]. Multiple studies in the MSK domain showcase diverse outcomes post-PRP treatment, ranging from significant pain reduction to negligible effects [16,17]. The crux lies in platelet dosing and PRP bioformulations, pivotal in determining consistent pain relief [18].

In intradiscal PRP injections, the correlation between pain alleviation and PRP platelet concentrations emerges prominently [18], where higher counts (>1.0 × 106/μL) yield more promising results, aligning with Lutz et al.'s observations [19,6]. However, the quest for the optimal PRP platelet dose and bioformulation maximizing pain relief remains ongoing [18], with Yoshida et al.'s findings suggesting a threshold of at least 1.0 × 106/μL platelets in a 5mL plasma volume to trigger pain alleviation effects [20,6]. The variability in findings underscores the intricate relationship between platelet dosing, PRP bioformulations, and their tangible impact on pain relief, necessitating further nuanced investigations to establish concrete guidelines for optimal treatment.

Changing from one-size-fits-all to a Customized Cell Count of PRP for Better Results

The absence of definitive, universally accepted standards for formulating various orthobiological compounds remains an unfortunate reality [9]. Ditching the "one-size-fits-all" PRP approach across MSK pathologies is imperative. Failing to tailor ortho-biological PRP products specifically to tissues and individuals, considering platelet dose and personalized bioformulations, curtails patient care quality. This limitation stifles immunomodulatory and angiogenetic responses critical for tissue repair [6]. Our contention revolves around the urgent need to replace generalized PRP ortho-biological preparations with nuanced and transformative methodologies. These progressive strides involve employing algorithms to pinpoint cell dosing strategies tailored to pathoanatomic intricacies. Simultaneously, utilizing distinct PRP bioformulations geared for diverse tissues and pathologies within the same patient procedure is paramount. To navigate this, a deep understanding of the vast array of currently available ortho-biological products, spanning cell type, quality, quantity, and application volumes, becomes essential for achieving optimal dosing [6].

Consider PRP as a bespoke, autologous medication offering platelet dosing variability and diverse leukocyte constituents (lymphocytes, neutrophils, and monocytes). Each constituent serves as a potential driver for outcomes. Adjusting these PRP variables has the potential to amplify immunomodulatory activities, foster (neo)angiogenesis, and pave pathways for tissue repair and regeneration, ultimately culminating in tissue healing [6]. Adopting a strategy tailored to tissue type and pathology, PRP injectates were derived from whole blood units. The emphasis rested on platelet dosing and bioformulations, steering away from the notion of universal PRP preparations. For intra-articular knee joint and periarticular capsule injuries, the injection of neutrophil-poor (NP)-PRP yielded favourable clinical outcomes. Conversely, addressing intra-meniscal and ligament regions called for neutrophil-rich (NR)-PRP injections, following a double-spin preparation process utilizing 120 mL of whole blood [6]. Regarding dosing guidelines, Hutchinson and Rodeo's recommendation of a minimum of 1,000,000 platelets/μL was adhered to when treating isolated meniscus tears [21].

Discussion

PRP therapies exhibit promising outcomes by harnessing the body's inherent healing process to establish fresh functional tissues, replacing degenerative or defective ones. However, the literature presents a mosaic of studies showcasing inconsistent patient outcomes. The dimensions of this inconsistency are diverse: availability of numerous PRP devices with unverified efficacy in specific pathologies; absence of consensus regarding PRP quality standards; lack of validated PRP preparation guidelines; availability of multiple treatment sites; and the scarcity of certified regenerative orthopaedic educational programs.

To rectify this, we advocate a redesign of ortho-biological preparations and treatment approaches. Emphasizing high cell yield PRP optimization and deploying varied PRP formulations tailored to specific conditions is crucial.

Physicians must evade the "one size fits all" paradigm and intertwine bench research with clinical studies for enhanced efficacy and superior clinical outcomes. Future studies on platelet dosing effects and bioformulations should be performed across diverse pathological tissues, fortifying PRP ortho-biological strategies in musculoskeletal pathologies.

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