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Review article

Optimisation of platelet concentrates therapy: Composition, localisation, and duration of action

Yuk-Lin Yung [a,b], Sai-Chuen Fu [a,b], Yau-Chuk Cheuk [a,b], Ling Qin [a,b], Michael Tim-Yun Ong [c], Kai-Ming Chan [a,b], Patrick Shu-Hang Yung [a,b,*]

[a] *Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region*
[b] *Lui Che Woo Institute of Innovative Medicine, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region*
[c] *Department of Orthopaedics and Traumatology, Alice Ho Miu Ling Nethersole Hospital, Hong Kong Special Administrative Region*

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Abstract

Platelet concentrates (PC) generally refers to a group of products that are prepared from autologous blood intended to enhance healing activities. PC therapy is now very popular in treating musculoskeletal injuries; however, inconsistent clinical results urge the need to understand the working mechanism of PC. It is generally believed that the platelet-derived bioactive factors are the active constituents, and their bioavailability in the vicinity of the lesion sites determines the treatment efficacies. Therefore, the composition, localisation, and duration of the action of PC would be key determinants. In this review, we discuss how different preparations and delivery methods of PC would affect the treatment outcomes with respect to clinical evidence about PC therapy for osteoarthritis, tendinopathies, rotator cuff tears, anterior cruciate ligament injuries, and bone fractures. This review can be used as a quick guide for the use of PC therapy and provide insights for the further optimisation of the therapy in the near future.

Keywords: composition; duration; localisation; platelet concentrates; platelet-rich plasma

Introduction

Platelet concentrates (PC) has currently attracted much attention in the field of regenerative medicine, with its high-safety profile, ease of preparation, and broad-application profile. The most common form of PC is platelet-rich plasma (PRP). In theory, the concept of PRP is to harness and concentrate the platelets, which have self-healing potential and are present in everyone's blood.

After wounding, platelet activation is regarded as the first line of events responding to injuries and initiating the healing responses, which involve release of sufficient bioactive factors that orchestrate various processes like angiogenesis and recruitment of healing cells to the lesion sites. PC therapy involves triggering the general natural healing process with a supplement of highly concentrated bioactive factors, regardless to the pathological processes or injury mechanisms. Thus, various forms of PC are used to boost up self-healing in a wide spectrum of musculoskeletal disorders or injuries, including osteoarthritis (OA), tendinopathies, rotator cuff tears, anterior cruciate ligament (ACL) injuries, and bone fractures. However, due to large variations in the preparation and administration methods, the clinical outcomes of PC therapies for musculoskeletal disorders or injuries are inconsistent.[1–5] Factors that may affect its treatment efficacies are as follows: (1) composition of PC; (2) localisation of PC to the region of interest; and (3) keeping PC *in situ* for sufficient duration to achieve the

* Corresponding author. Department of Orthopaedics and Traumatology, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, N.T., Hong Kong Special Administrative Region.
E-mail address: patrick@ort.cuhk.edu.hk (P.S.-H. Yung).

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therapeutic effect. In the following sections, we will explore how different preparations and delivery methods of PC would affect these factors and examine whether these factors have been addressed in the currently available best clinical evidences about the PC therapy for OA, tendinopathies, rotator cuff tears, ACL injuries, and bone fractures.

Previous reviews or systematic reviews about PRP or PC chiefly covered the biology of PRP, preparation of PRP, or effects of PRP on particular type of soft tissue injuries. This review combined an overview of PRP and a systematic review of its treatment effect on five major applications in order to evaluate the operational factors that may affect treatment effects. While previous reviews chiefly focused on the issues of composition and activation of PRP, this is the first review addressing the importance of localisation and duration of action of PRP.

Composition of PC

Forms of PC

Numerous preparations of PC were developed, but the terminology and classification have not been standardised yet. Three classification systems for PC were proposed including four families,[6] PAW,[7] and DEPA systems,[8] which are primarily based on composition (platelet, fibrin, activators, leukocytes, erythrocytes),[6,7] injecting dosage,[7] or preparation efficiency into account.[8] PAW and DEPA systems involve grading of PC according to the platelet count and preparation efficiency; however, there is still no clear indication of the platelet dose that offers the best treatment effect. Therefore, we prefer to follow the classification simply based on the presence of individual components suggested by the four-family system (Table 1). The most common form of PC is PRP: pure (P-PRP) and leucocyte PRP (L-PRP), which are prepared by centrifuging whole blood with anticoagulants and optionally supplementing with platelet activators (Ca2+ or thrombin) before use. These PRP preparations are liquid and therefore injectable; however, activation will lead to the formation of blood clot. Alternatively, PC could be prepared in solid form as platelet-rich fibrin (L-PRF, P-LRF) which are only useful for topical application[9] or surgical implantation.[10]

Preparation methods for PC

With the injectable nature and ease of preparation, PRP are most commonly used, and there are a number of commercially available PRP preparation devices (Table 2). Indeed, most commercially available devices are for PRP preparation, and fewer devices are available for PRF preparation. For PRP preparation, most of the devices involve the use of centrifugation to concentrate the platelets from blood with anticoagulants, and platelet activator is added before use. In some devices, special accessory to reduce the leucocyte counts is included. Most of the preparations use either closed or semi-closed systems. Compositional analyses of different PRP preparations revealed large variations in platelet and leucocyte counts. In order to determine the best kinds of preparations, further examination of the roles of individual components of PRP is necessary.

Commercial systems such as Cascade are commonly used for to generate P-PRF; while L-PRF is usually “homemade” by common centrifuge.[18] Many commercial systems such as Magellan, Gravitational Platelet Sequestration System[6] are developed to prepare PC as PRP. Their uses are more flexible since they can be applied by coating or immersion to the graft,[24] by spraying topically to the wound,[25] (e.g., with applicators CoAxial Spray Kit, Biomet Biologics), and most popularly by injection.

Constituents of PC

Platelet counts

The idea of using platelet supplementation to treat musculoskeletal injuries or disorder is primarily based on the ability of platelets to trigger healing response; however, the number of platelets required for efficacy remains unknown. A study of the concentration effect of platelet on ACL graft healing showed that the enhancement did not differ with 5-fold or 3-fold platelet concentration.[26] The inhibitory effect on proliferation of dog alveolar bone cells[27] and human oral fibroblasts and osteoblasts[28] was even observed with high dose of platelets. Moreover, the required number of platelets may vary according to the tissue types,[29] lesion size, and pathological conditions. Thus, it is difficult to define the quality standards for PRP simply based on platelet counts. As thrombocytopenia may not have direct impact on dermal healing[30] or tendon healing,[31] it is very likely that the absolute platelet count may not be the sole determinant for healing outcomes. It should also be noted that for PC to take a positive biological effect on different clinical conditions, the requirement for platelet conditions may be different. Other factors such as localisation and activation status should also be taken into considerations.

Leucocytes

As leucocytes express proinflammatory properties, their presence in PC is regarded as unfavourable, and it is speculated that L-PRP or L-PRF would have negative effects, especially for clinical conditions with chronic inflammation such as OA[32,33] and tendinopathies.[34] Moreover, L-PRP was found to be less effective than P-PRP in bone repair.[35] In contrast, the putative antibacterial function of leucocytes is regarded as favourable for wound healing[36]; however, it

Table 1
Composition of different platelet-rich products modified based on the four-family system.

Type of platelet concentrates	Contain leucocytes?	Need activation?	Status
Leucocyte platelet-rich plasma	Yes	Yes/No	Gel/liquid
Leucocyte platelet-rich fibrin	Yes	Yes	Solid
Pure platelet-rich plasma	No	Yes/No	Gel/liquid
Pure platelet-rich fibrin	No	Yes	Solid

Table 2
Common commercially available platelet concentrates systems.

PC class	System	Device name	Manufacturer	Reference
L-PRP	Closed	Haemonetics MCS+ 9000 cell separator: 995-E platelet apheresis set	Haemonetics Corp, Braintree, MA, USA	de Almeida et al., 2012[11]
		Magellan Autologous Platelet Separator System	Arteriocyte Medical Systems, Inc., Hopkinton, MA, USA	Castillo et al., 2011[12]
		MyCells	Kaylight Technologies Ltd, Holon, Israel	Kushida et al., 2014[13]
		RegenPRP	RegenLab, Le Mont-sur-Lausanne, Switzerland	Kaux et al., 2011[14]
	Semi-closed	Dr. Shin's System THROMBO KIT	GRAND AESPIO IMC., Seoul, Korea	Kushida et al., 2014[13]
		GenesisCS Component Concentrating System	Emcyte Corporation, Fort Myers, FL, USA	Kearney et al., 2013[15]
		GLO PRP	Glofinn Oy, Salo, Finland	Kushida et al., 2014[13]
		GPS III Platelet Concentrate System	Biomet Biologics, LLC, IN, USA	Castillo et al., 2011[12]
		KYOCERA Medical PRP Kit	KYOCERA Medical Corporation, Osaka, Japan	Kushida et al., 2014[13]
		Prosys PRS(PRP) Bio Kit	Prodizen Inc., Seoul, Korea	Oh et al., 2015[16]
		SmartPReP System	Harvest Technologies, Plymouth, MA, USA	Davenport et al., 2015[17]
	Open	JP200	BS Medical Co., Ltd., Tokyo, Japan	Kushida et al., 2014[13]
		Plateltex	PLATELTEX S.R.O., Praha, Czech Republic	Kaux et al., 2011[14]
L-PRF	Open	A-PRF	Process, Nice, France	Dohan et al., 2006[18]
		IntraSpin-L-PRF	Intra-Lock, Boca Raton, FL, USA	Dohan et al., 2009[19]
P-PRP	Closed	COBE spectra LRS Turbo (with a leukoreduction set)	Caridian BCT, Lakewood, CO, USA	Jo et al., 2015[20]
		Vivostat PRF	Vivostat A/S, AllerØd, Denmark	Antuña et al., 2013[21]
	Semi-closed	Arthrex ACP	Arthrex, Naples, FL, USA	Magalon et al., 2014[22]
		SELPHYL	Cascade Medical Enterprises, LLC, Wayne, NJ, USA	Kushida et al., 2014[13]
	Open	PRGF-Endoret	BTI Biotechnology Institute, Vitoria-Gasteiz, Spain	Sanchez et al., 2010[23]
P-PRF	Semi-closed	Cascade Autologous Platelet System	Musculoskeletal Transplant Foundation, NJ, USA	Castillo et al., 2011[12]

L-PRF = leucocyte platelet-rich fibrin; L-PRP = leucocyte platelet-rich plasma; PC = platelet concentrates; P-PRF = pure platelet-rich fibrin; P-PRP = Pure platelet-rich plasma.

depends whether bacterial infection is a primary concern to affect healing outcomes. The proinflammatory properties of leucocytes may override the potential benefits of its antibacterial functions.[32,37] Different leucocytes exhibit different roles. Lymphocytes and neutrophils are chiefly involved in adaptive and innate immune systems, respectively, whereas monocytes may take part in mediating healing responses. However, in most studies on PRP preparation involving leucocytes reduction, there are no further characterisations of different leucocytes.

Erythrocytes

Erythrocytes are removed in most preparation methods of PC; however, the extent of their removal is seldom reported. With respect to the observed treatment effects of autologous whole blood injection,[38] the presence of erythrocytes in PC may not hinder the treatment efficacies. Recently, the roles of heme in erythrocytes to trigger healing were discussed with respect to the heme-heme oxygenase system.[39] Nevertheless, during the injection or surgical implantation of PC, a certain degree of bleeding is unavoidable and the effect of erythrocyte contained in PRP may be negligible.

Platelet activation

It is believed that platelet-derived factors, such as transforming growth factor beta (TGF-β), platelet derived growth factor subunit B homodimer (PDGF-BB), and vascular endothelial growth factor (VEGF), are responsible for the beneficial effects of PRP to promote healing; thus, platelet lysate is used in some clinical trials.[40,41] These growth factors are normally stored in alpha granules of platelets and released upon platelet activation, which is a part of natural blood clotting pathway. During preparation of PRP, spontaneous blood clotting and consequently platelet activation are suppressed by the addition of anticoagulant, such as citrate (calcium chelator); thus, the addition of calcium later to PRP triggers platelet activation. Alternatively, thrombin is also used to catalyse fibrin formation, which leads to platelet activation. Some clinicians used nonactivated PRP, and they believed that collagen or thrombin naturally existed in the body can activate PRP in a slower manner.[42,43] The blood clot formation may also help to localise the growth factors to the target site. In essence, the functional form of PRP is a growth-factor-releasing platelet-fibrin clot. Current injection therapy with PRP thus requires post-injection clotting, while PRF can only be used for topical,[44] or intraoperative administration.[45–47] The platelet activation and clot formation should not be too rapid for PRP as it can hinder the injection process.

Fibrin clot

Fibrin clot is formed after platelet activation in PRP as loose meshwork and most of the growth factors are released within the 1st day of preparation.[48,49] In contrast, fibrin polymerised under centrifugation in PRF results in strong and dense fibrin architecture that entraps platelets and their growth factors for constant release over a longer period of time.[36,50] *In vitro* studies suggested that PRF was superior to PRP in

growth factor release[36] and stimulation of cellular activities related to healing responses.

In summary, the extent of platelet enrichment may not be the sole determinant of the therapeutic effects of PC. Leucocyte count and the integrity of the fibrin clot after platelet activation are also influential.

Localisation of PC

Apart from variations in composition, the localisation of PC to the lesion site is another major attribute to the treatment effects which may be overlooked previously. Depending on the intended applications, the success of localisation will be determined by the methods of delivery and the anatomy of the sites of delivery.

Methods of delivery

There are three major types of delivery of PC—injection, invasive implantation, and topical application. Topical application is efficient for localised delivery; however, it is only applicable for skin wound[9] and dental applications[51] but not for most musculoskeletal applications. Injection is minimally invasive for internal use and widely used in nonoperative treatments for musculoskeletal degenerative diseases. Only PC in liquid forms is applicable for injection. Accurate delivery can be achieved by real-time medical imaging, such as ultrasound-guided intratendinous injection of PRP for tendinopathies.[52] Injection during a surgical operation (rotator cuff repair, ACL reconstruction) is feasible, but its localisation is largely determined by the rate of fibrin clot formation. For intraoperative implantation, PC in solid form (PRF) is superior to liquid PRP in terms of localisation to the lesion sites,[10] whereas PRP can also be used by applying onto the grafts before implantation, such as tendon graft immersion in PRP in ACL reconstruction[24] and mixing PRP with bone graft in fracture repair.[2]

Sites of delivery

Although PC can be accurately localised to the lesion sites, spatial redistribution after application is difficult to control. This is dependent on the rate of fibrin clot formation after platelet activation as well as the availability of space to contain the volume of injected PC, which is in turn largely dependent on the anatomy of the lesion sites. For example, intra-articular injection for disorder enclosed in a confined compartment (e.g., joint capsule) allows better localisation.[53] This allows a more localised delivery of PRP to target tissues such as in OA and the midsubstance of the ACL graft. The injection volume of PRP should be optimised with the size of joints (hip, knee, wrist, finger).[54]

However, limited space to hold liquid in intratendinous injection may result in significant leakage, thereby limiting the injection volume.[55] Peppering technique is common to increase the injectant volume by repeating the injection at adjacent location, but this may induce some microinjuries to the tissue. Thus, the spatial availability of peritendinous tissues may also play a role in keeping the PRP in target site; for example, the infrapatellar fat pad underneath patellar tendon may prevent the PRP from leakage from the site injection, whereas there is very limited space in the vicinity of Achilles tendon and extensor carpi radialis brevis tendon (in tennis elbow). In case of ACL reconstruction, there is a challenge to localise PC at the small graft tunnel interface and different methods have been attempted.[1,56]

In summary, it is still difficult to localise PRP to the lesion sites by injection, and the local anatomy of the lesion sites will limit the injection volume and affect spatial redistribution after injection. It is preferable to achieve instant solidification (e.g., fibrin clot formation) after injection.

Duration of action of PC

After PC is delivered to the lesion sites, the temporal availability of platelet-derived factors will be the key factor to determine the treatment effects. The required duration of action for PC treatment may vary across different musculoskeletal lesions. For example, OA and tendinopathies represent chronic lesions, which are less likely to heal with a single and brief PC exposure. However, for traumatic injuries, PC promote healing safeguarded by surgical repair, thus it should fit into the normative recovery period of the surgical procedure. The retention of platelet/fibrin clot, the rate of release of platelet-derived factors, and the frequency of PRP applications will together define the duration of PRP action.

Retention of PC

For all forms of PC except platelet lysate, fibrin clot formation is resulted in the vicinity of lesion sites after application. Naturally, fibrin clot will be resorbed under the action of plasmin in around 5 days.[36] PRF forms more rigid fibrin clot under centrifugation than PRP, which may result in a longer retention of platelets to the lesion site.[36] In contrast, as PRP forms fibrin clot *in situ*, the rate of platelet activation and consequently fibrin clot formation will determine the initial retention of PC.

Rate of release of platelet content

The release of platelet content, including growth factors and small biomolecules, is triggered upon platelet activation from the platelet-fibrin clot. The alpha granules and dense granules from the platelets are secreted to the surrounding by exocytosis.[57] It has been shown that the dense fibrin matrix in PRF can serve as a growth factor reservoir by enmeshing them[36] and exhibit a slower release kinetics than PRP in which most of the platelet content is released rapidly within the 1st day of activation.[49] Moreover, types of platelet activators also affect the rate of release of platelet content. Calcium and thrombin can induce a dose-dependent release of growth factors (PDGF-BB, TGF-β, and VEGF) immediately[58,59]; however, collagen leads to a slower and more sustained release pattern.[60] In addition to release kinetics, rapid clearance[53] of

soluble bioactive factors in intra-articular space[61] may further reduce the bioavailability of platelet content.

Frequency of PRP application

Owing to the short retention of PC in the form of fibrin clot, repeated injections of PRP may be necessary to achieve the treatment effects. There are good clinical evidences showing that repeated injections of PRP can offer better clinical outcomes than single injection for patients with knee OA[62,63] and those with chronic patellar tendinopathy.[64] It suggests that a longer exposure to PRP may be necessary to treat these chronic conditions as functional improvement of the PRP-treated groups had a tendency to decrease over time.[63] However, the optimal frequency of PRP application for OA and tendinopathies may vary according to the disease conditions.

In summary, the brief retention of fibrin clot in the lesions site and the fast release of platelet content largely limit the bioavailability and treatment effects of PC. As repeated injections may cause extra microtrauma and irritation, a controlled delivery system for PRP may help to prolong the action of PRP with a single treatment.

Review of treatment effects of PC on musculoskeletal disorders

PC is a new treatment modality for various musculoskeletal injuries; however, a conclusive treatment effect is not yet reached. The inconsistent clinical outcomes were recorded in various systematic reviews,[1−3,5,38,56,65−71] which may be resulted from differences in composition, localisation, and duration of actions of PC according to different preparations and applications. In order to evaluate whether these factors affect treatment effects of PC, we collected Level I and II clinical studies with respect to the treatment efficacy of PC on five major musculoskeletal lesions including OA, tendinopathy, ACL rupture, rotator cuff tear, and bone fracture from published systematic reviews with some recent reports. Literature search was performed using the Google scholar database with the following keywords: “platelet” or “platelet concentrates” or “platelet rich plasma” or “PRP” and the various terms for clinical conditions “osteoarthritis” or “tendinopathy” or “tendinopathies” or “epicondylitis” or “tennis elbow” or “jumper's knee” or “rotator cuff” or “ACL” or “bone graft” or “bone fracture” up to April 2016. Only reports in English or Chinese were included. Information about treatment efficacy, leucocyte reduction, platelet activation, localised delivery of PC, as well as the use of repeated injection was extracted and tabulated in Table 3 for simpler interpretation. With respect to treatment efficacy, statistically significant positive or negative effect of PC in any of the measured outcomes was recorded as “positive” or “negative”, respectively, whereas “null” effect was recorded if there were no significant differences in all measured outcomes. Leucocyte reduction refers to the use of leucocyte reduction filter or single spin method[33] with clear indication to exclude buffy

Table 3
Efficacy of platelet concentrates on different musculoskeletal conditions with application conditions shown based on published controlled clinical studies with Level of evidence of I/ II.

Use (Number of studies)	Effectiveness		Application conditions				Major AE	Remarks for localisation
			Leucocyte reduction	Activation	Localisation	Repeated application		
Osteoarthritis (18)	+ve	16	5/16	10/16	16/16	15/16	0	PC is injected intra-articularly so they are confined in a small space to action.
	null	2	0/2	1/2	2/2	2/2	0	
	−ve	0	/	/	/	/	/	
Tendinopathies (23)	+ve	11	1/11	3/11	0/11	3/11	0	Intratendinous injection is not regarded as localisation
	null	11	2/11	1/11	0/11	3/11	0	
	−ve	1	0/1	0/1	0/1	0/1	0	
Rotator cuff tear (17)	+ve	7	3/7	7/7	6/7	0/7	0	Localization in rotator cuff tear refers to clot formation of PC in the tear site or tendon−bone interface
	null	9	8/9	6/9	2/9	1/9	1	
	−ve	1	1/1	1/1	1/1	0/1	0	
ACL surgery (9)	+ve	5	1/5	4/5	4/5	0/5	2	Localization in ACL reconstruction refers to clot formation of PC on the graft or in bone tunnel
	null	4	1/4	3/4	1/4	0/4	0	
	−ve	0	/	/	/	/	/	
Fracture/bone graft (3)	+ve	2	1/2	2/2	2/2	0/2	0	PC was mixed with the bone graft material to fill the fracture site.
	null	1	0/1	1/1	1/1	0/1	0	
	−ve	0	/	/	/	/	/	

Note:
Effectiveness: A report with statistically significant positive/negative result in any of the measured outcomes is regarded as positive/negative.
Leucocyte reduction: This refers to the use of leucocyte reduction filter or single spin indicating clear precaution to avoid buffy coat in preparation process.
Activation: This refers to the activation of platelet concentrates before application.
Localisation: This refers to the use of carrier, solid form of platelet concentrates or platelet concentrates applied in confined area in respect to the injured site. (Please refer to the individual remarks.)
Repeated application: This refers to any repeated application of platelet concentrates regardless of frequency.
Major adverse effect: This includes the report of any major complications in platelet concentrates group: allergy, infection. Minor side effect is not included: mild swelling, self-resolved pain, local heating.
ACL = anterior cruciate ligament; AE = adverse effects; PC = platelet concentrates.

coat in the preparation. Commercial products showing reduced level of leucocytes count in previous literatures were also included. Studies that involved the use of PRF or combine calcium and/or with PRP before application were regarded as PC with "Activation". Studies that involved the implantation of solid form of PC to the designated healing sites or injection into a confined compartment, such as intra-articular injection, were regarded as "localised" delivery, otherwise the treatments were described as "without localisation", such as peritendinous or intratendinous injection. Studies with repeated application of PC were regarded as treatments with longer duration of action as compared to single injection. Reports of major adverse effects are also included in Table 3.

OA

Out of 18 clinical studies,[62,72–88] 16 reported a positive effect of PC treatments for OA, and no major adverse effect was reported. Leucocyte reduction was not included in the reports of null effects, yet only one-third of reports with positive effects included leucocyte reduction. The benefits of leucocyte reduction on treatment efficacies for OA were still not confirmed. However, it was reported that leucocyte-reduced PC exhibited a better treatment effect for knee OA[6] and lower incident rate of minor adverse effects in the joint.[33] Although intra-articular injection was regarded as application with good retention to the lesion sites, application of PC to larger joints was less effective as null effect was reported for hip OA.[86] The majority of the positive reports included platelet activation and repeated injections. In fact, repeated injections of PC were found to be more effective than single injection.[62,76] With the carryover effects up to 12 months post injection,[66] it is likely that PC may also modify the disease process. Younger patients with OA showed a better positive response than older patients,[74] which may be related to reduced platelet count or slower healing process in the elderly; however, detailed records of platelet counts and treatment efficacies were not available.

Tendinopathies

For tendinopathies, the therapeutic effects of PC were inconsistent (11 +ve, 11 null, and 1 −ve effect) and varied among different anatomical sites. The beneficial effect of PC was more prominent in patellar tendinopathy (3 +ve),[89–91] but inconsistent in tennis elbow (7 +ve, 7 null)[42,43,92–103] and rotator cuff tendinopathy (1 +ve, 1 null, 1 −ve).[34,104,105] Achilles (2 null)[15,106] and hamstring (1 null)[17] tendinopathies was not responsive to PC treatment. PC was also less effective for noninsertional Achilles tendinopathy in aged patients.[107]

Leucocyte reduction and platelet activation were not commonly employed for PC treatment to tendinopathies. Although ultrasound-guided injection is generally included in PRP treatment for tendinopathy in order to localise PRP to the affected sites precisely, there are limited spaces to hold PRP in most tendinopathies,[55] except the infrapatellar space in case of patellar tendinopathy. It may help to explain the differences in treatment effects for tendinopathies in different anatomical sites. Repeated injection was found to be better than single injection for patellar tendinopathy in a Level II randomised prospective study,[64] but the use of repeated injection was also noticed in three reports of null effects. Whether the injected PC could stay at the lesion sites would be more deterministic. There was only one negative report, i.e., co-application of leucocyte-rich PC did not improve clinical outcomes and may have potential deleterious effects on healing tendons.[34]

Rotator cuff tear

Inconclusive clinical results on the efficacy of PC application on rotator cuff tear were found. Out of 17 reports, 7 showed positive effects,[20,108–113] 9 showed null effects,[21,45,46,105,114–118] and 1 showed negative effects.[47] However, it is remarkable that most of the positive reports (6/7) were with the localised application of PC to the tear site and all of them (7/7) were with platelet activation. Some of the surgeons applied liquid form of PC by injection on top of or into the rotator cuff tendon. PC may not be able to stay at the tear site and this reduced their potential beneficial effect. PC was localised to the tear site by suturing or clot formation, and its efficacy became more promising. A patient treated by suturing PRF side-to-side to close the tear showed improvement in the range of motion and pain relief[119] and decrease in the re-tear rates.[120] Some other studies demonstrated early healing compared with a control group and acceleration of the recovery process after rotator cuff repair.[108,121] In these studies, coat formation was checked after the intraoperative application of PC. Systematic reviews[4,122,123] did not distinguish clinical outcomes with different PC application methods. This may be the source of the discrepancy.

ACL surgery

Nine clinical studies were found with respect to application of PC in ACL reconstructive surgery, and the treatment effects were inconsistent (5 +ve, 4 null effects).[24,124–132] The use of leucocyte reduction and platelet activation did not differ between the reports of positive and null effects. However, most of the positive reports (4/5) involved procedures to ensure clot formation (activated platelet) on the graft, whereas only one out of the four null effect reports included clot formation step before graft fixation. It may suggest that the localisation of activated platelet on graft surface was essential to achieve positive treatment effects. Most reports agreed on the positive contribution of PC to graft maturation[1,56,71] but not to tunnel healing. This may be due to the smaller space of bone tunnel to accommodate the PC than that of the graft so that less platelet-derived factors can be available to tunnel healing. All included studies only applied PC intraoperatively, and there is no information about the effects of repeated application of PC.

Fracture/bone graft

Due to the small number of Level I and II clinical studies, the efficacy of PC on bone fracture healing was not conclusive. Two out of three studies[133–135] showed positive effect when PC was applied locally to the fracture site with the bone graft. One of the large-scale Level II studies ($n = 276$) compared the use of autograft and allograft with or without PC and found that surgery using allograft with PC showed similar result as surgery using autograft and significantly better result than that with allograft alone and lowered the infection rate for the use of allograft at 24- and 72-month evaluation.[133]

Summary and further optimisation of PC therapy

After the usage of PC for over 2 decades, there is still no standard for its applications. It is important to gather and analyse the past experiences to determine the optimal formulation of PC. Based on the results of literature review, it is likely that PC treatments were beneficial, but its efficacies are largely dependent on the ways of PC preparation and applications. The current evidence does not support leucocyte reduction as an essential step to secure treatment effects of PC, although it might be advisable to use PC with leucocyte reduction for OA. Similarly, platelet activation is not mandatory for treatment effects, but clot formation accompanied with platelet activation may help the localisation of platelets. In fact, whether the PC preparation could be localised to the lesion sites may be a deterministic factor. As a general observation, treatments with intraoperative delivery of solid form of PC (either PRF or PRP after activation) are more effective, and injections into anatomical sites with confined space (i.e., joint cavity) to retain PRP showed more consistent outcomes. Repeated application is preferable if it is feasible, which is attributed to the prolonged duration of action of PC; however, obvious disadvantages of injection are the pain caused and the potential infection risk, and therefore, the number of injection should be kept to a minimum.[53]

Several factors should also be considered in the future optimisation of PC therapy. First, the composition of PC such as the absolute platelet count and leucocyte count may need to be varied for different types of musculoskeletal disorders. Research can be focused on determining standard formulation for different diseases. Second, individual factors of the patients such as age,[2] sex,[5] exercise level,[67] and genotype[133] were shown to be related to the composition, and therefore, healing effect of the autologous PC should be taken into consideration. Finally, this review showed the importance of localisation and duration of action on the efficacy of PC therapy. Hence, a safe delivery system should be developed to localise and release the PC sustainably in the vicinity of the lesion sites, with considerations of the local anatomical features.

Conflicts of interest

All authors declare no conflicts of interest.

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