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Original Research Article

A Study of Platelet Rich Plasma Commonly Used in Neurosurgery Practice

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Abstract

AIM: No consensus is present regarding application modalities of platelet-rich plasma (PRP), commonly used in neurosurgery clinics. In this systematic review, the aim was to evaluate the potential role of PRP in neurosurgery practice after examining studies previously performed on this matter. In doing so, the preparation and activation of PRP, the appropriate dosage and concentrations used in the treatment were investigated.
MATERIALS and METHODS: A comprehensive and systematic literature search of numerous electronic databases was performed. Keywords used were related to PRP and neurological diagnosis. Studies that satisfied the inclusion criteria were retrieved, then the results were reported using the descriptive statistical methodology.
RESULTS: Ofthe 863 articles examined in detail, 27 were related to disc tissue pathologies, and four were related to complications occurred after spinal cord injury. After full-text review of these articles, nine were systematically evaluated.
CONCLUSION: It is important to prevent the preparation and application errors of PRP which is conventionally applied in clinics after being prepared using various kits and protocols. To achieve this aim, it is necessary to formulate clear protocols on how to prepare PRP for the treatment of which diseases, and which doses and durations should be used in the treatment. These protocols should take its place in the neurosurgical treatment guidelines. However, the differences that may be resulted in the application of different concentrations of PRP, which contains growth factors, should be evaluated promptly at the molecular level.

Keywords: Drug delivery systems, Spinal surgery, traditional injection, PRP with a relatively low concentration of very few leukocytes, PRP with high concentrations of leukocytes

INTRODUCTION

No satisfactory outcome has been achieved so farin the treatment of intervertebral disc degeneration and spinal cord injury, a serious medical condition, using current pharmacological agents or surgical modalities (Frobell et al., 2010; Lu et al., 2011; Yilmaz et al., 2013). Therefore, researchers have sought to repair damaged tissues using biological treatment modalities (Yasar Sirin et al., 2018; Yilmaz et al., 2016).

PRP is a biological product that has recently gained interest due to its effectiveness in the wound-healing process, hemostasis, and blood clotting (Frobell et al., 2010; Lu et al., 2011; Yasar Sirin et al., 2018; Yilmaz et

al., 2013; Yilmaz et al., 2016). Platelet (PLT), a component of PRP, contains a considerable number of cytokines and growth factors that play a significant role in the proliferation of degenerative cartilage tissue cells (Yasar Sirin et al., 2018), tissue healing and bone mineralization (Anitua et al., 2006). In addition, it includes many proteins and peptide structure involved in the synthesis of tissue matrix (Italiano et al., 2003; Nurden et al., 2008; Xie et al., 2014).

PRP has been reported to induce the release of bioactive proteins that affect macrophages, mesenchymal stem cells, osteoblasts, and/or annulus fibrosus cells (NPCs) / nucleus pulposus cells (NPCs), which accelerate the resorption of necrotic tissues and ensure the regeneration and healing of tissues (Charneux et al., 2017; Sampson et al., 2008; Wang et al., 2018). Thus, it can be used for the treatment of tissue damage through local injections in the field of neurosurgery (Bonilla et al., 2018; Charneux et al., 2017; Sampson et al., 2008; Wang et al., 2018).

Many studies have previously been performed on the effectiveness of PRP in the treatment of chronic degenerative intervertebral disc pathologies, lumbar facet joint syndrome, and spinal cord injury (Akeda et al., 2006; Chen et al., 2006; Comella et al., 2017; Hanci et al., 2015; Kim et al., 2014; Kubota et al., 2018; Levi et al., 2016; Mietsch et al., 2013; Mohammed et al., 2018; Pirvu et al., 2014; Sys et al., 2015; Tuakli-Wosornu et al., 2016). Some of these studies have suggested the usefulness of PRP in the treatment of mentioned disorders (Wu et al., 2016; Wu et al., 2017), however, some of them have contradicted this hypothesis (Yasar Sirin et al., 2018; Yilmaz et al., 2016). In some reports, PRP administered at different doses has been reported to be beneficial for the treatment (Yasar Sirin et al., 2018; Yilmaz et al., 2016).

However, no studies have separately investigated the effects of PLT and leukocyte (WBC) ratio in the PLT concentrations in the field of neurosurgery. In addition, it has not been elucidated to what extent WBC amount positively or negatively affects the outcome of the treatment.

In this systematic review, we aimed to evaluate the potential role of PRP in neurosurgery practice. In doing so, the preparation and activation of PRP, the appropriate dosage used in the treatment were investigated.

MATERIALS and METHODS

Search strategy

A comprehensive and systematic literature search of numerous electronic databases (17/04/1957-19/10/2018), including the Cochrane Library, Ovid, the National Library of Medicine at the National Institutes of Health was performed. Keywords used were as follow: “neurosurgery,” “disc,” “disc lesions,” “intradiscal,” “intervertebral disc degeneration,” “intradiscal disc degeneration,” “discogenic,” “lumbar disc herniation,” “chronic discogenic low back pain,”“ bone fusion in transforaminal lumbar interbody fusion,” “spinal fusion,” “lumbar facet joint syndrome,” “annulus fibrosus cell, ”“nucleus pulposus cell,” “epidural patch,” “spinal cord injury,” and “PRP/Platelet Rich Plasma”.

Protocols prepared by Karaarslan et al. (2018[a,b]) and Lijmer et al. (1999) were used to assess and analyse the quality of the selected studies. Letters to the editor, bibliographies, reviews, and meta-analyses were excluded from the study (Karaarslan et al., 2018[a]; Karaarslan et al., 2018[b]; Lijmer et al., 1999; Topuk et al., 2017; Yilmaz et al., 2016). The present study was conducted on the basis of the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Karaarslan et al., 2018[a]; Karaarslan et al., 2018[b]; Topuk et al., 2017; Yilmaz et al., 2016).

Eligibility criteria

Double-blind, placebo-controlled, randomized clinical trials or level-I searches were included in our study.

Statistical analysis

Microsoft Office Excel (2010) was used and the results were presented as the amount.

RESULTS

We retrieved 11,896 publications using the keyword “platelet-rich plasma”. However, 47 publications were retrieved using “platelet-rich plasma and/or neurosurgery”. Of 47 studies, five were reviews and no clinical studies were found.

The electronic database scan was carried out using the pre-determined keywords. Subsequently, clinical trials performed between September 1981 and 13 January 2017 was detected (Table 1).

In addition, five, one, one, one, one and four studies were retrieved using the keywords “PRP and/or disc (Comella et al., 2017; Hanci et al., 2015; Levi et al., 2016; Sys et al., 2011; Tuakli-Wosornu et al., 2016),” “PRP and/or disc lesions (Charneux et al., 2017),” “PRP and/or chronic discogenic low back pain (Hanci et al., 2015),” “PRP and/or bone fusion transforaminal lumbar interbody fusion(Kubota et al., 2018),” “PRP and/or annulus fibrosus cells(Pirvu et al., 2014),” and “PRP and/or nucleus pulposus cells (Akeda et al., 2006; Chen et al.,

Table 1. Types of articles and distribution by years

Keywords	Clinical Trials	Review	Total	Date Range
Platelet Rich Plasma	781	956	10.207	2018 Oct 17-1954 Apr 17
PRP	863	1521	14.882	2018 Oct 17- 1965 Dec
Platelet Rich Plasma /Disc	5	12	99	2017 Jan 13- 1986
Platelet Rich Plasma/ Disc Lesions	1	1	3	2018 Feb-2017 Dec
Platelet Rich Plasma/ Intradiscal	3	5	12	2017 Dec- 2016 Jan
Platelet Rich Plasma /Intervertebral Disc Diseases	1	3	14	2018 Jan- 2011 Jun 1
Platelet Rich Plasma /IDD*	1	3	5	2018 Jun 18- 2016 Dec
Platelet Rich Plasma /Discogenic	3	3	6	2018 Mar- 2016 Jun
Platelet Rich Plasma /CDLBP**	1	1	2	2018 Mar-2018 Jun
Platelet Rich Plasma /LDH***	1	1	2	2017 Dec-2016 Jan
Platelet Rich Plasma /BFTLIF[¥]	1	0	1	2018 Feb
Platelet Rich Plasma /Spinal Fusion	2	9	32	2017 Jun-2012 Sep
Platelet Rich Plasma /Lumbar Facet Joint Syndrome	2	0	2	2017 Sep- 2016 Nov
Platelet Rich Plasma / AFCs[+]	1	2	11	2018 Mar 1- 2017 Jan
Platelet Rich Plasma /NPCs[++]	4	2	17	2012 Aug
Platelet Rich Plasma /Edpidural Patch	1	0	1	2017 Dec
Platelet Rich Plasma /SCI[-]	4	4	18	2018 Apr 23- 1981 Sep

*IDD: Intradiscal Disc Degeneration; **CDLBP: Chronic Discogenic Low Back Pain; ***LDH: Lumbar Disc Herniation; [¥] BFTLIF: Bone Fusion Transforaminal Lumbar Interbody Fusion; [+]AFCs: Annulus fibrosus; [++]NPCs: Nucleus Pulposus; [-] SCI: Spinal Cord Injury

Table 2. Findings obtained from clinical trials of PRP applied in the field of neurosurgery

Author(s)	Specifying the concentrations of the blood components in the PRP content	Testing appropriate dosage and application duration to determine efficacy in treatment with a pilot study before application to the patient	Performing activation in preparation of PRP	Testing preclinically the PRP content at pharmacomolecular level	Demonstrating evidence about the therapeutical mechanism of PRP	Using a drug delivery system
Charneux et al., 2017	No	No	Yes	Yes	No	Yes, Gel form
Comella et al., 2017	No	No	No	Yes	No	No

Table 2. Continue

Levi et al., 2016	"WBC-rich" described," no concentration specified	No	No	No	No	No
Tuakli-Wosornu et al., 2016	No	No	No	No	No	No
Sys et al., 2011	No	No	No	No	No	No
Kubota et al., 2018	WBC: No PLT: Yes	No	Yes	No	No	Yes, Gel form
Singh et al., 2014	No	No	Yes	No	No	Yes, Gel form
Ibrahim et al., 2012	No	No	No	No	No	No
Rappl et al., 2011	No	No	No	No	No	No

2006; Kim et al., 2014; Mietsch et al., 2013)," respectively. Of these studies, the study related to a temporomandibular junction which was conducted Hanci et al. (2015) was excluded from the research. The study regarding the induction of proliferation and matrix structure of AFCs by PRP which was conducted by Pirvu et al. (2014) was excluded due to its *ex-vivo* design. The culture study of Kim and colleagues (Kim et al., 2014) evaluating the anti-inflammatory effect of PRP on NPCs and cell responses to TNF-α and IL-1 was also eliminated.

Furthermore, a study (Mohammed et al., 2018) shown as a clinical trial in the electronic database research was also excluded as it was observed that this was a review after full-text examination. Three studies (Akeda et al., 2006; Chen et al., 2006; Mietsch et al., 2013 performed on *in vitro* culture design were excluded from the research. Of the four clinical trials (Salarinia et al., 2017; Singh et al., 2014; Ibrahim et al., 2012; Rappl, 2011) of spinal cord injury, one study was excluded as it was observed that this was an *in vivo* research (Salarinia et al., 2017). Remaining nine studies (Charneux et al., 2017;Comella et al., 2017; Ibrahim et al., 2012; Kubota et al., 2018; Levi et al., 2016; Rappl, 2011; Singh et al., 2014; Sys et al., 2011; Tuakli-Wosornu et al., 2016) were systematically evaluated (Table 2).

There were no studies providing information about WBC/PLT values, and no studies clinically investigated the obtained PRP samples after testing them in a pre-clinical or clinical pilot trial. No studies also provided any data about dosage, application time, and the presence or absence of activation before the PRP administration. Although some studies satisfied the inclusion criteria, they were not Level of I studies.

DISCUSSION

A consensus has been reached on the fact that PRP obtained after centrifugation from autologous whole blood contains more platelets than normal blood (Yasar Sirin et al., 2018).While an initial spin separates the red blood cells and buffy coat/plasma layer, more PLT can be separated by means of systems using a second spin (Yasar Sirin et al., 2018; Yilmaz et al., 2016). PLT/WBC valuesin PRP content are known to be affected by the number, speed and time of centrifuge (Filardo et al., 2012; Yasar Sirin et al., 2018; Yilmaz et al., 2016).

Another important factor affecting the acquisition of PRP is reported to be the thickness of the needle used during blood collection from the donor. As the diameter of the needle of the syringe decreases, the release time of growth factors in PLT is affected and this may lead to premature activation of PLT. The appropriate needle gauge is reported to be 21-gauge (Andia et al., 2010; Lippi et al., 2006; Yasar Sirin et al., 2018; Yilmaz et al., 2016).

Some authors have suggested that PRP without WBC is more effective in treatment, even

if no scientific evidence has been revealed (Anitua, 1999; Dohan et al., 2009; Everts et al., 2008). However, some studies have reported that WBC in PRP content may play a significant role in the treatment due to its anti-infectious effects and its importance in immunoregulation (Anitua, 1999; Dohan et al., 2009; Everts et al., 2008; Yasar Sirin et al., 2018; Yilmaz et al., 2016). It is not clear whether monocytes, macrophages and mast cells should be present in the PRP content for the efficacy of the treatment (Dohan et al., 2009; McCarrel et al., 2012).

In addition, the presence or absence of WBC in PRP content, and the determination of appropriate concentration have led to controversy (Yasar Sirin et al., 2018; Yilmaz et al., 2016). Some studies have argued that WBC amount should be at lower (McCarrel et al., 2012; Mishra et al., 2012; Yasar Sirin et al., 2018) or higher (Moojen et al., 2008; Bryan et al., 2012) concentrations to minimize the catabolic effects and provide effective treatment.

Another important problem is that the half-life of growth factors in the PRP content is between 8 secs and 1.5 min after being taken out of the body. It should be noted that growth factors may lose their bio-efficacy if PRP is not absorbed into any drug delivery system as soon as it is obtained (Gokce et al., 2012; Yasar Sirin et al., 2018; Yilmaz et al., 2016).

Moreover, if no chemical or photo-activation procedures are performed after PRP has been obtained, platelets cannot be degraded, growth factors contained in the PRP content cannot be released into the environment, and the claimed improvement in the PRP-treated tissue would not stem from these growth factors (Gokce et al., 2012; Yasar Sirin et al., 2018; Yilmaz et al., 2016).

Levi D et al. (2016) investigated the effect of PRP, which is reported to be effective in various musculoskeletal disorders, in patients with discogenic lumbar pain. They treated patients with intradiscal PRP and evaluated the changes in function and pain. They used a commercial kit in the preparation of PRP and stated that the spin time was only 14 min (Levi et al., 2016). However, they did not provide any data about WBC/PLT concentrations in the obtained PRP content, they only defined eWBC as “WBC-rich”.

Furthermore, they did not provide clear information on the mechanism of action of PRP which contributed to the treatment at the pharmaco-molecular level (Levi et al., 2016). More importantly, it is observed that they injected intradiscal PRP obtained through a commercial kit without creating dose-response curves, even in the form of preclinical or clinical pilot trial, before starting the study (Levi et al., 2016).

In a study of Comella et al. (2017), 15 patients with degenerative disc disease underwent liposuction, then the stromal vascular fraction and PRP were obtained. The obtained samples were delivered into the disc nucleus of patients. The authors tested the samples containing PRP and stromal vascular fraction in terms of the presence of CD34. They also performed the differentiation assays for adipogenesis (fat), osteogenesis (Bone) and chondrogenesis (cartilage), and expressed that multi-potential mesenchymal stem cells were present in the samples (Comella et al., 2017).

Tuakli-Wosornu et al. (2016) used a commercial kit in patients who received intradiscal PRP. However, they did not provide any information about WBC/PLT values, and the obtained PRP samples were not clinically investigated after testing them in a pre-clinical or clinical pilot trial. They did not also provide any data about dosage, application time, and the presence or absence of activation before the PRP administration (Tuakli-Wosornu et al., 2016)

Kubota et al. (2018) examined the efficacy of PRP for bone fusion in transforaminal lumbar interbody fusion. They prepared PRP using 400 mL of peripheral venous blood samples taken during surgery. They also centrifuged the blood samples two times and provided data on the revolution per min value and duration of the centrifugation. More importantly, 22 mL of PRP was obtained, of which 2 mL was used to count the number of platelets, and then they added 0.5 mL of 1,000 U/mL liquid thrombin solution and 1 mL of 2% calcium chloride solution to the remaining 20 mL of PRP to activate the platelets during surgery. The authors did not evaluate the WBC content but presented PLT and PRP values for each case through tables (Kubota et al., 2018).

Singh et al. (2014) evaluated the efficacy of PRP in 25 spinal cord injury patients with pressure ulcers. They provided data on the amount of blood taken from patients, revolution per min value and duration of the centrifugation. Furthermore, they transformed PRP activated by calcium chloride in the gel formation, then applied it over the wound (Singh et al, 2014). However, they did not grant any data related to the WBC/PLT values, and the obtained PRP samples were not clinically investigated after testing them in a pre-clinical or clinical pilot trial. They did not also provide any clear information on the mechanism of action of PRP, which contributed to the treatment at the pharmaco-molecular level (Singh et al., 2014).

Ibrahim et al. (2012) evaluated the effectiveness of PRP in the management of bicipital tendinopathy amongst patients with spinal cord injury. In that study, they injected PRP into the participants’ biceps tendon. However, they did not give any precise information about the application dosage, time and the preparation of PRP (Ibrahim et al., 2012).

Rappl (2011) investigated the efficacy of PRP for the healing of wounds and pressure ulcers in 200 patients with spinal cord injury. However, they did not provide any clear information on the mechanism of action of PRP which directly ensured the healing. In addition, they did

not also give any precise data about the WBC/PLT values and the acquisition of PRP.

In conclusion, the aim was to determine the alpha significance value using the heterogeneity test (*Cochrane Q*) afterevaluating findings obtained from previously performed clinical trials (Karaarslan et al., 2018[a]; Karaarslan et al., 2018[b]; Lijmer et al., 1999; Topuk et al., 2016).

However, no level of I studies that satisfied all the research criteria was found. No clinical inferences could be made, and no clinical flow chart could be created since no common treatment protocols could be established for the aforementioned neurosurgical pathologies. The number of keywords used for scanning could be increased to eliminate this issue. However, this suggestion of researchers was rejected given that the scanning performed by the author in such a way would prevent making common binding inferences. Thus, only descriptive statistical results were presented. The limitation of this systematic review was the possibility that the authors could overlook the problems that might arise from source errors related to the selection, classification or collection of articles.

CONCLUSION

First of all, the most appropriate method that can be used for obtaining PRP should be determined. Subsequently, the concentrations of blood components such as PLT / WBC in PRP content and the application dosage of these contents for the treatment of the appropriate neurosurgical pathologies should be determined. PRP should preclinically be investigated with in *vitro* studies and *in vivo* studies using mammal subjects. In these studies, multi-center clinical settings involving volunteers (male/female and white/black) should be established with the guidance of neurosurgeons, pharmacologists, and toxicologists. Based on the results obtained from these clinical settings, the content, application dosage, application interval of PRP for the treatment of the suitable disorders should be determined.

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Competing interests

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