SEXUAL MEDICINE REVIEWS ORIGINAL RESEARCH

Platelet-Rich Plasma Therapy for Male Sexual Dysfunction: Myth or Reality?

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ABSTRACT

Introduction: Platelet-rich plasma (PRP) found its use in treating different conditions and diseases, because concentrated plasma PRP consists of many growth factors. Their interaction with surrounding cells, intracellular matrix, and mediators at the site of injection leads to tissue regeneration. Angiogenic, vasculogenic, and regenerative effects of PRP may be used for erectile dysfunction (ED) and Peyronie's disease (PD) treatment.

Aim: To present a current data review of preclinical and clinical trials on PRP use for treating ED and PD.

Methods: Up-to-date literature on PRP use for ED and PD treatment was analyzed. The search was based on Pubmed, Cochrane Library, clinicaltrials.gov databases, with the following key words: "platelet-rich plasma" and/or "erectile dysfunction" and/or "Peyronie's disease" and/or "sexual dysfunction."

Main Outcome Measures: The main outcome measures for preclinical trials on ED were erectile function, assessed with intracavernous pressure, and pathologic analysis of penile tissue. The main outcome measures for clinical trials on ED included penile duplex Doppler ultrasound scanning and validated questionnaires. The main outcome measures on PD were pathologic analysis of penile tissue for preclinical trials, as well as penile duplex Doppler ultrasound scanning, penile curvature angle measuring, and validated questionnaires for clinical trials.

Results: 4 preclinical and 6 clinical trials were described and analyzed in this article. Limitations for both preclinical and clinical trials included small groups, short follow-up periods, a lack of control groups or groups with placebo, and the lack of quality and quantity analysis of PRP.

Conclusion: Available data show the lack of adverse reactions with PRP treatment. The studies that we found were limited by small groups. This is why the data on safety and effectiveness should be taken carefully. However, it is important to mention that PRP therapy has the potential for treating male sexual dysfunction and may be useful in andrology. **Epifanova MV, Gvasalia BR, Durashov MA, et al. Platelet-Rich Plasma Therapy for Male Sexual Dysfunction: Myth or Reality? Sex Med Rev 2019;XX:XXX–XXX.**

Key Words: Platelet-Rich Plasma; Erectile Dysfunction; Peyronie's Disease; Sexual Dysfunction; Regenerative Medicine; Growth Factors; Cell Therapy

INTRODUCTION

Platelet-rich plasma (PRP) is autologous blood plasma that contains platelet concentrations that exceed physiological standards by 3–7-fold. When the platelet count in the final cell product is >1,000,000 U/μL,[1] PRP shows its therapeutic effect.[2]

PRP has been used in many branches of medicine for several decades. A number of studies demonstrated absence or a minimum of adverse effects, as well as effectiveness of PRP therapy in cosmetology,[3] ophthalmology,[4–6] sports medicine,[7] cardiology,[8] trauma surgery,[9] plastic surgery,[10] tissue engineering,[11] restoration of nerves and nerve trunks,[12,13] and treatment of type 2 diabetes mellitus[14] and its complications.[15]

Due to the widespread use of PRP in various branches of medicine and the absence of a standardized protocol for production of the cell product, each specialist needs to adapt and optimize this protocol.[16] Future adoption of a common standard will probably eliminate the variability of effectiveness of PRP.[16–18] Use of the unified protocol may also resolve the

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current problem of group representation in studies conducted, which, in turn, will allow for meta-analysis.

CLASSIFICATION OF PRP

Currently, there is no unified classification for PRP. The adoption of a unified international classification is an important issue.[17] The most popular is the classification of Dohan Ehrenfest et al,[19] accepted in 2009 and based on presence or absence of blood cells and fibrin: pure platelet-rich plasma, leukocyte- and platelet-rich plasma, pure platelet-rich fibrin, and leukocyte- and platelet-rich fibrin.

QUALITATIVE COMPOSITION OF PRP

PRP contains a lot of growth factors. Vascular endothelial growth factor,[20] platelet-derived growth factor (PDGF),[21] fibroblast growth factors,[22] epidermal growth factor,[23] and insulin-like growth factor−1[24] are the most studied and significant for regenerative processes (Table 1).

Thus, the regenerative potential of PRP is aimed at restoring blood flow, stabilizing the composition of the extracellular matrix and smooth muscle cells, and it may be applied in the treatment of certain urologic conditions. Up-to-date preclinical and clinical studies on PRP use in the treatment of erectile dysfunction (ED) and Peyronie's disease (PD) cited in international databases, such as PubMed, Cochrane Library and ClinicalTrial, will be discussed below.

ED AND PD

ED is a pathologic condition when a man cannot get or keep an erection firm enough to have sexual intercourse (WHO). Scientists at Boston University School of Medicine revealed a relationship between men's age and the presence of ED: ED prevalence was 22% in men <40 years old and 49% in men <70 years old.[25] According to the Global Online Sexuality Survey, there is a tendency toward increased prevalence of ED, although the patients with ED are getting younger.[26,27]

ED pathogenesis is complex. Moreland[28] showed an association between ED and the loss of corporal smooth muscle mass in relation to the total area of penile tissue, as well as a positive correlation with disease severity. Oxidative stress also shifts the ratio of

Table 1. Platelet growth factors and their specific functions for tissue restoration[4]

Growth factor	Receptors	Function
VEGF	VEGFR-1	Vascular development activation before the primitive vessels formation Cell migration (mononuclear and polynuclear phagocytes) Negatively modulate pathological vascularization, opposite of VEGFR-2
	VEGFR-2 The most important receptors of VEGFR-family	Stimulates mitogenesis Trigger for endothelial cell mitosis and differentiation Activated during angiogenesis it launches the platelet-activating factor production by endothelial cells, promotes their mitosis and migration and increases vascular permeability
	VEGFR-3	Lymphatic endothelial cells proliferation, migration, differentiation and life cycle
	Neuroprolin-1 Neuroprolin-2	Enhance VEGFR-2 signaling
	Heparan Sulphate Proteoglycan	VEGF reservoir Promotes binding of VEGF-receptor
PDGF	PDGFRα PDGFRβ	Angiogenesis stimulation via VEGF production Increase of perivascular cell proliferation and migration
FGF	FGF-receptors	VEGF system regulation Recruitment, proliferation and differentiation of vascular smooth muscle cells and pericytes → vessel maturation Activation of endothelial cells proliferation Collateral vessel formation by monocyte/macrophage recruitment (monocyte chemoattractant protein-1) Myogenesis
EGF	EGF-receptors	Recruitment, proliferation and differentiation of vascular smooth muscle cells and pericytes → vessel maturation Migration of endothelial cell progenitors VEGF system enhancement
IGF	IGF-receptors	Migration and proliferation of endothelial cell progenitors Inducing VEGF expression Decrease apoptosis

EGF = epidermal growth factor; FGF = fibroblast growth factor; IGF = insulin-like growth factor; PDGF = platelet-derived growth factor; VEGF = vascular endothelial growth factor.

collagen types I, IV, and III toward the latter.[29] Castela et al[30] demonstrated an age-dependent increase in expression of p42/44 mitogen-activated protein kinases, with messenger transforming growth factor−beta (TGF-β1) contributing to collagen deposition and penile fibrosis.

ED treatment is necessary for not only mental, but also somatic, health of men of any age. According to the meta-analysis performed by Guo et al,[31] men with ED have a higher risk ($P < .001$) of coronary events than those without ED. Based on the data of the Prostate Cancer Prevention Trial, the number of cardiovascular events per man with ED (including death from myocardial infarction) is twice as high as compared with men without ED.[32,33]

However, most often, patients are not informed about such potential risks and, due to their cultural, social, and psychological features or habits, they do not pay proper attention to this condition, despite the desire to have a satisfying and regular sex life.[34−36] Today, there is an opportunity to offer patients PRP therapy as a non-surgical treatment option, in addition to the 3 existing lines of therapy.[37,38]

Another condition that might be treated with PRP is PD. According to the American Urological Association, PD is an acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, penile deformity,[39] ED (in 40−60%),[40−42] or distress.[39] According to the systematic review by Nehra et al,[43] which includes publications from 1965−2015, PD prevalence rates vary from 0.5−20.3 % within certain population groups. The exact pathogenesis of PD is still unclear. PD is considered a multifactorial disease characterized by both a genetic predisposition and a traumatic event with inflammation of the penile tissue.[44,45] The association between PD and Dupuytren's contracture was discovered because of the expression of identical genes involved in the myofibroblast differentiation with further plaque formation.[46] Recently, special attention has been paid to TGF-β1 as a cytokine that affects the modification of the extracellular matrix and induces fibrosis in the tunica albuginea of the penis.[47−52]

According to the American Urological Association's guidelines, PD conservative treatment comprises verapamil or interferon α-2b injection therapy, with a great number of adverse events. Extracorporeal shock wave therapy is used for pain management. Injection therapy with collagenase clostridium histolyticum (CCH) is actively studied and used simultaneously.[39] However, CCH is effective only for plaque destruction by fermentation and does not affect the inflammatory process and regeneration of damaged penile tissue.[53,54]

PDGF, vascular endothelial growth factor, fibroblast growth factors, epidermal growth factor, insulin-like growth factor−1, and other growth factors, including TGF-β1 and mediators, affect vasculogenesis and angiogenesis, which are crucial for tissue regeneration in ED and PD. Therefore, PRP is hypothesized to produce its therapeutic effects on sexual dysfunction at the site of administration.[55] Contact of platelets with exposed endothelium in wounds or damaged tissues leads to the release of growth factors from α-granules. Growth factors start working in synergy with tissue repair mechanisms, such as chemotaxis, cell proliferation, angiogenesis, and extracellular matrix remodeling.[56] Given this, an increase in the platelet concentration in the damaged tissue was hypothesized to result in the release of a greater number of biologically active factors and, consequently, an improvement of the healing process.[57] In addition to the above processes, mRNA transcription is stimulated in the cell, activating new cascade pathways that promote angiogenesis, endothelization, and collagen formation, which result in tissue regeneration.[58]

METHODS

This review was produced using PubMed, Cochrane Library, clinicaltrials.gov databases, and Internet search. The search was divided into 2 stages. The first stage included a search with the following keywords: "platelet-rich plasma" and/or "PRP" and "erectile dysfunction" and/or "ED" and/or "sexual dysfunction." 10 publications were found: 2 were excluded because they did not pertain to andrology, and, for another 4 publications, the full text in English was not provided. Thus, 4 articles were selected for consideration: 3 preclinical studies[59−61] and 1 human study.[62] We also have the data of the study in Russian.[63,64] The following abstracts were found in the Internet with the same keywords: 1 preclinical study[65] and 3 clinical studies.[66−68]

The second stage included a search with following keywords: "platelet-rich plasma" and/or "PRP" and "Peyronie's disease" and/or "PD." 2 articles were found: 1 preclinical study[52] and 1 clinical study.[62] 2 clinical studies,[55,69] 1 case report,[70] and 3 abstracts[66,71,72] were found on the Internet with the same keywords (Table 2).

MAIN OUTCOME MEASURES

For preclinical studies on ED, the main outcome measure was erectile function (EF) evaluated using electrical stimulation studies, such as intracavernous pressure (ICP), and pathologic analysis of penile tissue. For clinical studies on ED, the main

Table 2. Summary of preclinical and clinical studies

	ED	PD
Preclinical study	Ding et al[59] Wu et al[60] Wu et al[61]	Culha et al[52]
Clinical study	Matz et al[62] Epifanova et al[64]	Matz et al[62] Virag et al[69] Virag et al[55] Marcovici et al[70]
Abstract	Liao et al[65] Kumar[66] Banno et al[67] Alkhayal[68]	Kumar[66] Virag et al[71] Virag et al[72]

ED = erectile dysfunction; PD = Peyronie's disease.

outcome measures were penile duplex Doppler ultrasound scanning and results of the International Index of Erectile Function (IIEF-5). In a preclinical study on PD, pathologic analysis of penile tissue was used as the main outcome measure. In clinical studies, penile duplex Doppler ultrasound scanning and, if a plaque was present, its size, and angle of the penile curvature were used, as well as validated questionnaires: Peyronie's disease questionnaire (PDQ) and IIEF-5.

ED

Ding et al[59] studied a PRP effect on regeneration and restoration of the cavernous nerve function after its damage. PRP effect was studied 3 months later. ICP was measured to evaluate erectile function. EF in the PRP group was improved; the ICP was significantly higher than that in the non-treated group, but lower than that in the placebo group ($P < .05$). The myelination of cavernous nerve axons in the group treated with the cell product was significantly higher than that in the non-treated group, but also lower than that in the placebo group ($P < .05$).[59] The study limitations included small sample of animals and PRP administration to the site of cavernous nerve injury. In addition, the scientists used a non-standard method of electrical field stimulation, and non-quantitative nerve regeneration estimation was performed.[59]

Preclinical studies were also conducted in Taiwan by C Wu et al in 2012[60] and Y Wu et al in 2013.[61] In the study from 2012,[60] rats in the experimental group received intralesional PRP therapy immediately after the cavernous nerve damage. 4 weeks later, ICP was 1/3 higher in rats treated with the cell product compared with animals that did not receive PRP therapy ($P < .05$). After treatment, the number of myelinated axons of the cavernous and dorsal nerves in animals was significantly higher than in the non-treated group ($P < .05$), according to pathologic analysis. PRP administration significantly reduced the level of apoptotic markers (TGF-β1, TUNEL, PI) and, consequently, apoptotic cells, including the marker of the cavernous body fibrosis, TGF-β1 ($P < .05$). A decrease in fibrosis was also confirmed by histologic study of penile tissue. Absence of the type III collagen and prevalence of the type I collagen was observed in the specimens from the treated group. The authors believe that the growth factors of platelet α granules acted as accelerators of nerve repair processes due to their neuroregenerative and neuroprotective effects, and also inhibited the process of fibrosis in the cavernous bodies.[60] This study is limited to the small sample of rats, which does not allow us to consider the use of PRP therapy as an effective or safe method of treatment, despite the positive results obtained.

In the study by Y Wu et al,[61] PRP production technology in humans was optimized. The study revealed the most effective activators (chitosan, serotonin) and incubation temperature, contributing to the release of a larger number of PDGF. ICP and nitric oxide synthase-synthase levels in the animal group treated with optimized PRP were the closest to the control group. The authors concluded that human PRP, prepared according to the developed technology, contains a large number of growth factors and, consequently, promotes the recovery of erectile function.[61] This study is limited to a small sample of rats and the use of a non-conventional electrical field stimulation method to evaluate ICP. Besides PDGF, other growth factors and the platelet count should have been evaluated, because the platelet count was directly correlated with the number of growth factors.

In 2013–2015, in Moscow, Epifanova et al[64] conducted a clinical study to assess the safety and effectiveness of PRP in ED treatment. The protocol was developed, and the technology of PRP production was optimized. The quantitative and qualitative composition of growth factors in non-activated PRP before and after freezing was evaluated (Table 3). The patients were randomly divided into 3 groups: 30 patients who received intralesional therapies with PRP activated by 10% $CaCl_2$ solution; 30 patients who received intralesional therapies with PRP, activated with 10% $CaCl_2$ solution, combined with phosphodiestrerase type 5 (PDE-5) inhibitors; and 15 patients who received inactivated PRP. PRP was injected 3 times at weekly intervals. EF improvement was registered from day 28 and persisted throughout the entire follow-up period. In group 1, a statistically significant increase in peak systolic velocity (PSV) ($P = .005$) and resistance index (RI) ($P = .001$), as well as in IIEF-5 ($P = .046$) and the sexual encounter profile (SEP) ($P = .001$) scores, was observed. In group 2, PSV ($P = .028$) and RI ($P = .129$) values, as well as IIEF-5 ($P = .046$) and SEP ($P < .05$) scores improved. In group 3, a statistically significant difference was found in IIEF-5 and SEP ($P < .05$) scores, as well as in PSV and RI ($P > .05$) values. According to measurement via the EndoPAT device (Itamar Medical, Caesarea, Isreal), endothelial function significantly improved in all groups at 6 months compared with baseline ($P = .018$).[63] The authors conclude that PRP contains the amount of growth factors necessary for therapeutic effect. The absence of adverse effects indicates safety of the method.[63,64] Although the results show improvements in EF at the end of the study, the limitations include the absence of a group with placebo or other treatment methods, as well as long-term results.

Matz et al[62] evaluated safety and feasibility of the platelet-rich fibrin matrix (PRFM) for the treatment of frequent urologic conditions, such as ED, PE, and female urinary incontinence. Patients received 1–8 injections of 4–9 mL of PRFM. The mean value was 2.1 intralesional injections with PRP per man. Adverse effects or worsening of the disease were not observed in patients during the 15 months of the study. The IIEF-5 score for men increased on average by 4.14 points.[62] The authors rightly emphasize that confirmation of their conclusions regarding safety of PRFM would require a study with a larger sample of subjects, and assessment of efficacy would require usage of objective study methods rather than questionnaires only.

PD

Regarding PD, the first clinical studies "PRP for PD" with confirmed safety are from 2014.[55,62,69] However, the first

Table 3. Growth factors concentration in not activated PRP before and after cryopreservation (μg/mL)[64]

Growth factors	Before freezing	A 2-week interval of freezing	A 2-month interval of freezing
FGF-acid	1.85 (0.14–5)	0.14 (0.14–5)	2.3 (0.68–9.7)
FGF-basic	0.14 (0.14–37)	23.8 (0.28–70)	56 (11–120)
PDGF-AA	1,133 (51–1,500)	1,145 (900–1,400)	1,016 (423–1,500)
PDGF-BB	2,102 (1,350–2,500)	4,757 (3,097–6,000)	3,194 (3,078–7,000)
VEGF	14.9 (7.1–30)	29 (1.1–100)	29 (19–50)
VEGF-D	20.1 (15.4–30)	35 (4.7–70)	29.4 (4.7–60)

FGF = fibroblast growth factor; PDGF = platelet-derived growth factor; PRP = platelet-rich plasma; VEGF = vascular endothelial growth factor.

preclinical study by Culha et al[52] was published in 2018. PD modeling was performed by injection of 0.1 mL TGF-β1.[52] And PD treatment was performed by injection of 0.1 mL PRP in tunica albuginea. The authors conclude that PRP therapy is not effective for PD and can even be used to model PD as not being inferior to TGF-β1. PRP injection results in fibrosis ($P < .0001$), increase in type III/type I collagen ratio, and collagen/smooth muscle ratio ($P = .001$). In this study, the authors did not determine the qualitative and quantitative composition of growth factors and platelets in PRP prepared. A single injection is not sufficient for therapeutic effect, because the PRP therapy is considered to be a course therapy. Also, the authors reasonably noted that they used a relatively subjective scoring system for fibrosis score instead of a quantitative evaluation.[52]

In 2014, in 2 months, Virag et al[69] conducted 4 sessions of PRP therapy with hyaluronic acid (HA) in 13 patients with PD, whose average age was 57.5 years. PRP therapy with HA was performed with local anesthesia in the affected part of the tunica albuginea. On average, for 9 months' follow-up, 10 (77 %) of 13 patients showed a 30% decrease in curvature, and the density and size of plaques decreased in 7 cases (53 %). IIEF-5 scores were improved in all patients. The authors did not analyze the PRP composition. Although the author states that HA stabilizes and prolongs the effects of PRP,[69] additional groups should be created to receive PRP and HA monotherapy. There were also no placebo groups or groups with another current and commonly used treatment method, such as CCH injection.

Virag[55] continued his research and published the results of the study of 90 patients as early as 2017. The course of treatment consisted of 4 injections every 15 days; in addition, before the injection, fibrous or calcified plaques were punctured with a 22G or 18G needle. According to the results of the study, it was possible to reduce the angle of penile curvature to 6.54−10.51°, and the thickness of the tunica albuginea to 1.11−0.52 mm. Calcifications persisted; however, their density decreased in 6 patients. Statistically significant improvement was registered according to the PDQ and IIEF-5 questionnaires. Regarding adverse effects, patients reported only hematoma (10%) and ecchymosis (6.7%). The authors also did not analyze the PRP composition.[55] There were no placebo control groups or groups with another existing and common treatment method, such as CCH injection.

Marcovici[70] described a clinical case of PD treatment with PRP. 2 PRP injections were performed at the point of maximum penile curvature, and daily use of a penile pump was prescribed. 2 months later, the angle of penile curvature was significantly reduced.[70] To describe the effect better, Marcovici[70] should have performed penile ultrasound scanning, recorded the presence/absence of calcifications, and used PDQ and IIEF-5.

As stated above, Matz et al[62] evaluated the effect of PRFM injections in PD treatment. IIEF-5 score increased by 4.14 from baseline, and 80% of patients reported a decrease of penile curvature angle. No serious adverse effects were reported.[62] In this study, the number of injections for different patients within the same disease was different. The authors themselves do not deny the role of placebo in the treatment of sexual dysfunction and emphasize the need to add a placebo group to subsequent studies. The limitation of this study is also a small sample of patients.

LITERATURE SYNOPSIS

To summarize, the limitations of the available data on the use of PRP in the treatment of sexual dysfunction should be noted. Despite studies conducted, more quality animal studies are required for better understanding of the mechanism of PRP action before PRP therapy will be approved for clinical trials and clinical practice by regulatory authorities. The urgency of new pathogenically based treatment research is due to the different efficacy of the 3 lines of therapy that are recommended by international guidelines and limited by patient's objective contraindications.[37,38]

The authors of this literature review noted the following general limitations in the design of the reviewed studies. The first is the absence of control groups, placebo groups, and comparison groups with PDE-5 inhibitors for ED studies and verapamil/CCH groups for PD studies. The absence of a common protocol on the duration of treatment can also be referred to general limitations. It is believed that therapy with PRP is a course treatment. Due to the fact that many effects are realized by the paracrine and autocrine mechanisms, time is required for the cumulative effect to manifest.

In addition, the ED degree and penile curvature degree that can be safely and effectively adjusted with PRP should be

determined. What are the relative and absolute contraindications to PRP therapy? Does age influence outcomes of patients with ED or PD?

A new limitation follows from above. It is necessary to resolve the current question about the volume and frequency of injections. A single injection is not likely to be enough to maintain the necessary concentration of growth factors at the site of injection and maintain cascades of reparative reactions. PRP realizes its therapeutic potential and affects the key elements of ED and PD pathogenesis through proinflammatory,[73] regenerative, reparative, anti-inflammatory,[74] neuroprotective and neurotrophic[60,73] effects of growth factors of which it consists. A possible positive relationship between a number of growth factors released from α-granules and the platelet concentration in the final cell product should be taken into account.[57,63,64]

CONCLUSION

PRP is a safe and pathogenically based treatment method but still experimental for ED and PD. Although the exact mechanisms of PRP action have not yet been elucidated, it is believed that PRP realizes its therapeutic potential through the regeneration of the endothelium, smooth muscle cells, and connective tissue. The authors analyzed the preclinical and clinical studies cited in international databases. However, the available data are currently insufficient to make a systematic review and meta-analysis. In this regard, it is necessary to conduct large, placebo-controlled, multicenter studies that can confirm or deny the effectiveness of PRP.

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