# Platelet-Rich Plasma Injections for Erectile Dysfunction and Peyronie's Disease: A Systematic Review of Evidence



Mohammad H. Alkandari, MD,[1] Nawar Touma,[2] and Serge Carrier, MD[1]


## ABSTRACT

**Introduction:** Erectile Dysfunction (ED) and Peyronie's Disease (PD) are debilitating medical conditions affecting patients' quality of life (QoL). Platelet-rich plasma (PRP) injections are one of the various emerging approaches proposed to treat these medical conditions.

**Aim:** To describe the evidence of the potential role of PRP injections in ED and PD.

**Methods:** The authors conducted a systematic review according to the PRISMA statement using the following databases in November 2019: The National Library of Medicine (PubMed), Ovid Medline, Cochrane, Scopus, Embase, and Embase classic. The search was performed using keywords drawn from studies on the use of PRP in ED and PD in clinical and preclinical studies.

**Results:** Eighteen articles met the inclusion criteria for review, including 12 studies on the use of PRP in humans and 6 on the use of PRP in rats. Ten studies reported on the efficacy of PRP in ED exclusively, 7 in PD exclusively and one in both conditions. In humans, 6 and 3 studies showed promising results in PD and ED, respectively. No major complications were noted. Unwanted minor side effects were noted by studies reporting on PD, including mild penile bruising, ecchymosis, hematomas as well as transient hypotension noted in 2 out of 90 patients.

**Conclusion:** PRP injections for the treatment of ED may be promising, but no recommendation can be made because of scarce evidence. Safety and effectiveness of this therapy in the treatment of ED and PD require further preclinical and clinical studies with standardized protocols to gain an adequate insight into its potential implications. Patients should be offered to be part of such trials to better understand PRP potential. **Alkandari MH, Touma N, Carrier S, Platelet-Rich Plasma Injections for Erectile Dysfunction and Peyronie's Disease: A Systematic Review of Evidence. Sex Med Rev 2022;10:341–352.**




**Key Words:** Peyronie; Erectile Dysfunctions; Platelet-Rich Plasma

## INTRODUCTION

Erectile dysfunction (ED) and Peyronie's disease (PD) are pervasive male sexual conditions. ED is the inability to attain and maintain a firm penile erection sufficient for sexual intercourse. In the United States alone, it has been estimated that ED affects as many as 30 million men. In a study conducted by Goldstein et al., it appears that ED prevalence ranges from 37.2% in Brazil to 48.6% in Italy [1], meanwhile the prevalence is correlated to the age of the population [2]. Similarly, PD is a debilitating disease caused by collagen depositions and fibroelastic proliferation altering the penile connective tissue framework. It may cause progressive penile curvature and pain or even erectile dysfunction in around 20% of patients [3]. Affected sexual relationships have an impact on the quality of life (QoL) of men and women. When discussing a debilitating problem like ED or PD and their management, the patient and his partner should be included in the discussion [4]. As it profoundly affects the QoL of patients, an ED-specific QoL questionnaire may be used to assess the psychosocial effects [5].

Various approaches have been used to treat ED, ranging from less invasive behavioral approaches or pharmacotherapy, to more invasive modalities, such as intracavernosal injections (ICI) and penile implants. Recently, there are emerging treatments with controversial use referred to as "regenerating", such as low intensity extracorporeal shock wave therapy (Li-ESWT), intracavernous stem cell therapy (SCT) and platelet-rich plasma (PRP) injections. Trademarked as Priapus Shot, the latter has been marketed as a regenerative medicine [6].

Although the use of PRP in urology is still in its infancy, its debut in other fields of medicine, such as orthopedics and

Received April 25, 2020. Accepted December 3, 2020.

[1]McGill University Health Center, Department of Surgery, Division of Urology, Montreal, Quebec, Canada;

[2]McGill University, Montreal, Quebec, Canada



https://doi.org/10.1016/j.sxmr.2020.12.004

plastics, was in 1987. There have been studies conducted in these fields discussing its safety and efficacy, but despite more than 30 years of use, its physiological properties and effects remain poorly understood and controversial in the context of autologous injections. As per AUA and SMSNA recommendations, PRP has a promising potential that is yet to be proven. A better understanding of this emerging controversial modality is essential in guiding physicians dealing with patients suffering from ED or PD. In this article, we describe the evidence around the effectiveness and safety profile of autologous PRP injections in men with the aforementioned diagnoses.

## METHODOLOGY

A systematic search of the National Library of Medicine (PubMed), Ovid Medline, Cochrane, Scopus, Embase and Embase classic databases was performed according to the PRISMA statement in November 2019. This was done using the following combinations of keywords: ("Penile Induration" AND "Platelet-Rich Plasma") OR ("Erectile Dysfunction" AND "Platelet-Rich Plasma"). A subsequent search in relevant articles bibliographies and reviews was conducted to identify pertinent publications. Non duplicate titles were screened. Full text articles and abstracts were included in the current review. The inclusion criterion was the use of PRP in male patients (humans and experimental animals) suffering of ED and/or PD. All PRP preparations and injections methods were considered. Studies in languages other than English or French were excluded.

## RESULTS AND DISCUSSION

A flowchart of the literature search is presented in Figure 1. The electronic search described above returned 222 articles. Six additional articles were found following a search in relevant articles bibliographies. After duplications were removed, 204 articles were screened by titles and abstracts. Further, 164 articles were excluded because they did not pertain to PRP in the context of ED or PD. Among the remaining 40 articles that underwent full-manuscript assessment (see Annex 1) 22 studies were excluded: one included only a female population, 8 were reviews, 2 were descriptive studies, 9 did not relate to the use of PRP in ED or PD, one study was only available in Russian and finally one article's abstract did not contain results and its manuscript was unavailable. As a result, 18 articles were kept for the purpose of the current review: 6 prospective cohort studies, 3 prospective comparative trials, 1 case report, 2 retrospective studies and 6 randomized-controlled trials (RCTs). Between them, twelve articles reported on the efficacy of PRP in humans (Table 1) and 6 studied the effect of PRP in rats (Table 2).

Among the 12 human-based studies, 5 reported on PRP efficacy in ED, 6 in PD and 1 in both. The number of patients ranged from 9 to 100, except in 1 case-report reporting on a single patient. The protocols varied across studies with mean follow-up periods stretching from 4 weeks to 1 year. Half of the studies (6) detailed their PRP preparation protocol, but none reported on the classification system used to characterize their final product. One abstract reported on a study still in progress in 2019 [7]. Four studied PRP efficacy in conjunction with another modality, such as Li-ESWT, phosphodiesterase type 5 inhibitors and vacuum therapy [7−10]. Three protocols included fracturing plaques by needling prior to injections [11−13] and 1 study reported using a different type of PRP solution, a platelet-rich fibrin matrix [14]. In humans, 6 studies showed favorable outcomes toward the use of PRP in PD [11−13,15−17] and 3 others showed favorable results toward its use in ED [9,10,18].

With respect to the 6 rat-based studies, 5 preclinical studies reported on the efficacy of PRP in ED and one in PD. They included between 23 and 30 Sprague-Dawley rats aged between 6 and 44 weeks and weighing between 250 and 600 grams. All preclinical protocols included a control or a sham group. In ED, 2 studied the effects of PRP injections in diabetic rats and 3 in those with cavernous nerves (CNs) injury. Four of them elaborated on their PRP preparation protocol without characterizing their products through a classification system. All preclinical studies on ED showed favorable outcomes, unlike the one on PD.

As for complications reported in humans, 4 studies reported no complications [7−9,18]. Among the studies reporting any kind of side effects, none had reported major events, such as serious infections, like HIV. All minor complications were noted in PD studies [11−15]. One study showed that 4 patients (25%) had mild pain and 1 (6.3%) had bruising after platelet-rich fibrin matrix injections for PD [14]. Similarly, Marcovici et al. noted mild penile bruising at injection site [15]. A third study registered ecchymosis in 15 patients (16.7%), marked hematomas in 9 patients (10%) and a transient hypotension after anesthetic agent injection in 2 patients (2.2%) [12]. An article recruited for this review documented superficial hematomas in 10% of injection sites among a 50-patient sample size [11]. Lastly, one noted multiple self-resolving ecchymosis and one marked hematoma (7.7%), possibly due to an iatrogenic venous puncture [13].

### Background of Platelet-Rich Plasma

Autologous blood is drawn and centrifuged to obtain a platelet-rich plasma fluid with a concentration reaching up to 7 times physiological levels. In order to maximize its therapeutic effect, the product is injected when its concentration is more than 1,000,000 U/mL [19]. Tissue restitution occurs through paracrine and autocrine effects of various secreted products. In fact, platelets secrete various chemokines and cytokines mediating inflammation and various growth factors (GFs) stimulating an immune response and promoting wound healing. For instance, PF-4, one of the secreted GFs, attracts neutrophils and eosinophils, PDGF and TGF-b stimulate collagen synthesis, and IGF-1 promotes growth [20]. VEGF and EGF are other GFs present in PRP promoting blood vessels formation as described in Figure 2 [21]. PRP is thus believed to provide rejuvenation of tissues by stimulating the restoration of blood flow (ie,

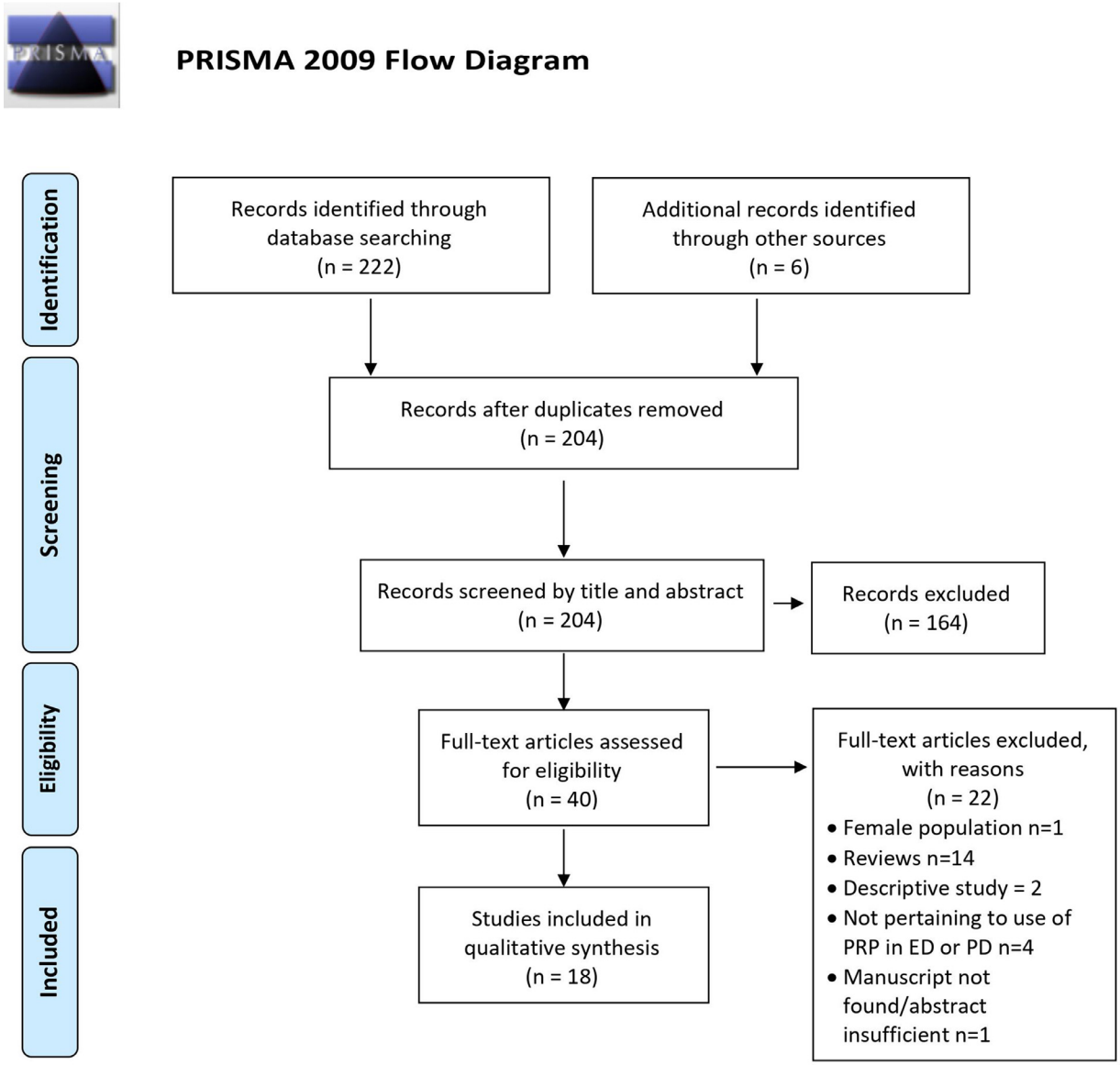


**Figure 1.** Systematic search strategy conducted in adherence to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines.

vasculogenesis and angiogenesis), stabilization of the extracellular matrix through downstream collagenase secretion and collagen synthesis, and tissue regeneration (ie, epithelial cells mitogenesis). To maximize GFs release, some have studied the impact of various activating agents like calcium chloride ($CaCl_2$) or thrombin on platelets. The rationale is that platelets' activation produces a conformational change resulting in a cascade of degranulation and aggregation, thus maximizing GFs release [22].

## Classification Systems of Platelet-Rich Plasma

Currently, there are 3 PRP classification systems. In 2009, Ehrenfest et al. proposed to classify PRP in 4 main groups based on 3 parameters: the technical characteristics (ie, preparation kits and centrifugation), the content (ie, platelets and leucocytes) and the fibrin architecture supporting the cellular content [23]. In 2012, Mishra et al. proposed a classification system based on the content of white blood cells, PRP activation status and platelet concentration in the solution. In 2016, Magalon et al. proposed the DEPA classification system (Dose, Efficiency, Purity, and Activation). The latter is a complete classification system based on quantifying each of the 4 components. However, a subsequent review by Alves et al. highlighted the need to register the quantification methodology in the CE medical device preparing the PRP solution as it cannot be determined by the user. Therefore, the DEPA system might be complicated to use in certain settings. Overall, because of its simplicity, the classification proposed in 2009 by Ehrenfest is mostly accepted and used [19], but it lacks the characterization

**Table 1.** Summary of all human-based studies evaluating PRP effect in ED and/or PD

| Study | Disease; N (age)* | Protocol | PRP preparation protocol description | Mean follow-up (range)† | IIEF5 score (range) | | *P*-value | Other outcome(s) | Complications | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before | After | | | | |
| Chalyj et al. [1]; prospective randomized-controlled trial¶ | ED; 75 (n/a) | 3 injections at weekly interval in all Grps<br>Grp1: activated PRP (10% $CaCl_2$); n = 30 | No | 24 | n/a | n/a | $P < .05$ | SEP: n/a | None | Significant increase in PSV, IIEF-5 and SEP scores in all Grps.<br>Significant increase in RI in Grp 1 and Grp 3.<br>Endothelial function significantly improved in all Grps after 6 months compared to baseline ($P = .018$). |
| | | Grp2: activated PRP + PDE5-I; n = 30 | | | n/a | n/a | | SPV: n/a | | |
| | | Grp3: inactivated PRP; n = 15 | | | n/a | n/a | | RI: n/a | | |
| Ruffo et al. [2]; prospective randomized-controlled trial¶ | ED; 100 (n/a) | PRP (obtained from EDTA centrifuged blood)<br>Grp 1: Li-ESWT (twice/wk.) + PRP (once/wk.); n = 55 | Yes | 24 | n/a | n/a | At 12 wk.: $P < .03$<br>At 24 wk.: $P < .001$ | PSV | n/a | After 12 wks.: IIEF5 and PSV scores significantly improved for both procedures.<br>After 24 wks.: significantly higher IIEF and PSV scores in Grp 1, while stable in Grp 2. |
| | | Grp 2: Li-ESWT twice/wk. for 6 wks.; n = 58 | | | n/a | n/a | n/a | | | |
| Alkhayal et al. [3]; prospective cohort trial | ED; 61 (43) | PRP injections (Magellan TruPRP) according to American cellular medicine association protocol. | No | 11 (4–59) | 12.5 (5–20) | 17 (5–24) | $P < .001$ | GAQ: 88.5% | None | Results seem to appear about 3–4 wks. after treatment initiation. |
| | | | | | | | | SEP3: 78% | | |
| Epifanova et al. [4]; prospective cohort trial | ED; 10 (44.25) | Six rounds of activated PRP (10% $CaCl_2$) and 12 LI-ESWT procedures (4000 waves/penis) for 6 wks. Injections at middle and distal CC B/L. | No | 8.5 | 12.4 (9–18) | 18.6 (15–23) | n/a | GAQ: 100% | None | All patients noted positive treatment effect. |
| | | | | | | | | SEP3: 100% | | Mean SEP score improved from 1.6 (1–2) to 3.7 (3–5).<br>Mean PSV score improved from 29.87 cm/s (14.10–48.60) to 39.69 (24.00–59.20).<br>Mean RI score improved from 0.86 (0.69–1.00) to 0.91 (0.78–1.00).<br>Trial is still in progress in 2019. |
| | | | | | | | | PSV: 38.9% | | |
| | | | | | | | | RI: 5.5% | | |
| Virag et al. [5], 2017; prospective cohort trial | PD; 90** (n/a) | 8 mL (6 PRP + 2 HA) (Regen Lab SA, Switzerland) obtained via autologous blood was injected 4 times every 15 days. Mechanical action with 18G/22G needles (BD MicrolanceTM 3). All | Yes | 12 wks. after 1st session, then 2 additional sessions monthly and every 12 wks, if necessary. (total: ≥12 wks.) | 13.82 +/- 3.7 | 17.91 ± 3.2 | $P = .008$ | Penile curvature and thickness. Self-administered 5-item questionnaire and PDQ. | Ecchymosis in 16.7% and marked hematoma in 10%. Transient hypotension after local anaesthesia in 2 patients (2.2%). | Significant improvement of PD.<br>Angle reduction was 39.65%§ (from 44.1° to 26.02°).<br>Younger patients achieved better results.<br>73.3% of the patients were classified as having satisfactory results.<br>67.8% felt an improvement,<br>62.2% had decrease in deformation, |

(continued)

**Table 1.** Continued

| Study | Disease; N (age)* | Protocol | PRP preparation protocol description | Mean follow-up (range)† | IIEF5 score (range) | | *P*-value | Other outcome(s) | Complications | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before | After | | | | |
| | | patients had at least 5 sessions. | | | | | | | | 46.7% had easier intercourses<br>43.3% had improved erections.<br>70% judged the treatment as positive.<br>Based on angulation, thickness and self-administered questionnaire: 73% were satisfied, 12.2% belonged to unsatisfied Grp and 14.4% belonged to the Grp with bad results. |
| Virag et al. [6]; prospective cohort trial | PD; 13 (57.5) | 8 mL (6 PRP + 2 HA) of PRP obtained via autologous blood was injected every 2 wks for 2 months. Plaques were fractured with an 18G needle before injections. | Yes | 4 wks. after last injection, then at 12, 24 wks. and annually | n/a | n/a | n/a | Deformation evolution by photo/ ultrasound, short version IIEF5 and global satisfaction | One hematoma possible due to an iatrogenic venous puncture with no subsequent consequences. Multiple self-resolving ecchymosis. | Possible sexual penetrations in 7 patients.<br>77 % patients had gained 30° after 9.3 months.<br>Decrease of density and surface of plaques on Ultrasound in 53 %.<br>One case witnessed worsening of curvature between the 2nd and 3rd session.<br>IIEF-5 score was either unchanged or better in all cases. |
| Virag et al. [7]; prospective cohort trial | PD; 50 (56.3) | 8 mL (PRP + HA) of PRP obtained via autologous blood was injected every 15 days x 4 sessions, then monthly (4–8 session in total). Plaques were fractured with an 25G needle before injections. | Yes | 24 | 17.7 | 21.1 | n/a | PDQ questionnaire, angulation and thickness evolution, auto-evaluation in 5 items quoted from 5 to 25. | Superficial hematoma (10% of injection sites) | 38% had ED.<br>Average duration of PD was 21 months (5–120).<br>10% had calcified plaques.<br>38% improvement in curvature angle (47° ± 37 average initial angulation).<br>Average maximum thickness decreased from 4.4 to 3.3 mm.<br>Average PDQ score improved by 52% (10.5 to 5)<br>Average IIEF-5 score increased by 19% (17.7–21.1).<br>Results showed 26% good, 58% partial and 16% negative.‡‡<br>Authors noted PRP+HA to be efficient in 84% of patients. |
| PD; 75 (54) | 6 sessions of PRP + HA (Regen Lab SA, Switzerland) injections under U/S. | No | 12 and 24 | n/a | n/a | n/a | PDQ 1 & 3 | questionnaires, deformation and thickness evolution, sexual activity and ED. | n/a | 36.9% decrease of angulation ($P < .05$).<br>26.7 % decrease of thickness ($P < .05$).<br>37% patients with ED reported improved functions (IIEF-5).<br>60% had easier sexual intercourses.<br>79 % noted deformation improvements.<br>Overall, 82.7% considered that they improved.<br>Patients with angulation > 60 degrees and calcified plaques had lesser good results (45.4% vs 78%). |

(continued)

**Table 1.** Continued

| Study | Disease; N (age)* | Protocol | PRP preparation protocol description | Mean follow-up (range)† | IIEF5 score (range) | | *P*-value | Other outcome(s) | Complications | Comments |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Before | After | | | | |
| | | | | | | | | | | Authors claimed study design to be case-control, but no control Grp was found. |
| Notsek et al. [9], 2019; Prospective comparative trial†† | PD; 59 (n/a) | Grp1: intralesional PRP injection; n = 32 | No | 24 | n/a | n/a | $P < .05$ | Angulation, pain, plaque size and softness | n/a | All domains improved in both, Grps and were statistically significant. Comparing Grp 1 to Grp 2:<br>• curvature angulation decreased in 50% vs 22.2%<br>• plaque decreased in size in 50% vs 14.8%<br>• plaque softness improved in 59.4% vs 29.6%<br>• IIEF-5 score improved in 56.3% vs 3.7 %<br>• pain reduction in 84% vs 29.6% of patients |
| | | Grp2: NaCl 0.9%; n = 27 | | | n/a | n/a | | | | |
| Matz et al. [10]; Retrospective | ED and PD; 17 (46) | Average of 2.1 (1-8) injections of 4-9 mL of PRFM (PRP + 10% $CaCl_2$) received. | Yes | 62 | n/a | n/a | n/a | Clinical information, survey data and safety related questions | 4 mild pain. 1 bruising. All in PD cases. | No decrease in any score. IIEF-5 score improved by 4.14 points (9.1%) in patients receiving PRFM therapy for ED and PD.<br>No decrease in IIEF-5 was noted in any patient.‡<br>Authors believe that a significant placebo effect exists in research involving male sexual health. |
| Banno et al. [11]; Retrospective | ED; 9 (56) | PRP in conjunction to already established pharmaco- and vacuum therapies. | No | ≥4 | 15.6 (12–20) | 19.9 (11–27) | $P = .157$ | n/a | None | PRP may be a safe and effective supplemental therapy for penile rehabilitation. |
| Marcovici et al. [12]; Case report | PD; 1 (54) | 1 mL autologous PRP at first visit. A penile pump used for 10 min BID for 6 wks. 2nd injection at 4 wks. | Yes | 8 | n/a | n/a | n/a | Patient satisfaction | Mild penile bruising at injection site | Patient was pleased with the result. |

*In years;
†In wks.;
‡None had a decrease in any domain, possible placebo effect as per authors; Grp = group; n/a: data not available;
§reduction seen after one month and an average of 3–5 additional sessions
¶did not mention whether randomization was blinded or not
**aged 25–77 years, median 56 years.
††did not mention whether randomization occurred
‡‡Authors stratified results in 3 categories (good, partial and negative response). Good if PPC > 30% for ≥2 items and/or final angulation < 25° and a PN > 16; negative if PPC < 10 and PN < 11; and partially improved if in between.

**Table 2.** Summary of all pre-clinical studies evaluating PRP effect in ED or PD

| Study | Disease; N (age)* | Animal (weight) | Protocol | PRP preparation protocol description | Outcome measure(s) | *P*-value | Comments |
|---|---|---|---|---|---|---|---|
| Culha et al. [13]; prospective randomized-controlled trial† | PD; 20 (36-44) | Male Sprague-Dawley rats (300-350 g) | Four Grps (n = 5):<br>1. Sham: 0.1 mL NaCl 0.9% (day 1)<br>2. PD: 0.1mL TGF-b (day 1) (R&D Systems)<br>3. PD + PRP: 0.1 mL TGF-b (day 1) + 0.1mL PRP (day 15)<br>4. PRP: 0.1 mL PRP (day 1)<br>PRP was obtained via autologous blood.<br>Preparation: Centrifugation in PRP kit (GLO-PRP kit, Finland).<br>Midpenile tissue for analysis was excised in all rats after being sacrificed by 45 days. | Yes | Fibrosis | Grps 2, 3 and 4 vs Grp 1: $P < .0001$<br>Grp 2 vs Grp 3 vs Grp 4: $P = .122$ | More intense fibrosis in all Grps compared to sham Grp. |
| | | | | | Collagen/smooth muscle ratio | $P = .001$ (between all Grps) | Ratios:<br>Grp 1 ($1.14 \pm 0.13$) < Grp 3 ($2.5 \pm 0.5$) < Grp 4 ($3.4 \pm 0.5$) < Grp 2 ($3.8 \pm 0.45$).<br>No significant difference was found when sham Grp was excluded. |
| | | | | | Type III/I collagen ratio | $P = .003$ (between all Grps) | Ratios:<br>Grp 1 ($1.2 \pm 0.45$) < Grp 2 (3) < Grp 4 ($3.1 \pm 0.5$) < Grp 3 ($3.6 \pm 0.5$).<br>No significant difference was found when sham Grp was excluded.<br>PRP Grp showed PD-like effects in rats, statistically not significant ($P = .221$). |
| Ding et al.[14]; prospective randomized-controlled trial† | ED; 24 (12) | Male Sprague-Dawley rats (250-300 g) | Three Grps (n = 8):<br>1. sham surgery Grp¶<br>2. CN dissection + a 2-min crushing injury with hemostatic clamp and no further intervention<br>3. CN dissection + a 2-min crushing injury with hemostatic + PRP gel immediate application at site of injury.<br>PRP was obtained from 6 aged-matched rats.<br>Preparation: centrifugation + $CaCl_2$ + bovine thrombin to form gel. EF and nerve regeneration assessment at 3 months. | Yes | CN electrostimulation (erectile response) | Increase in ICP:<br>• Grp 3 vs Grp 2: $P < .05$<br>Increase in ICP/MAP‖:<br>• Grp 1 vs Grp 2: $P < .05$<br>• Grp 3 vs Grp 2: $P < .05$<br>• Grp 1 vs Grp 3: $P < .05$ | PRP treated Grp had higher maximal ICP and ICP/MAP ratio than injured control Grp, but lower ICP/MAP ratio than sham Grp. |
| | | | | | Toluidine blue staining of myelinated axons | Increase in myelinated axons:<br>• Grp 1 vs Grp 2: $P < .05$<br>• Grp 3 vs Grp 2: $P < .05$<br>• Grp 1 vs Grp 3: $P < .05$ | PRP treated Grp had significantly more myelinated axons than injured control Grp, but less than sham Grp. |

(continued)

**Table 2.** Continued

| Study | Disease; N (age)* | Animal (weight) | Protocol | PRP preparation protocol description | Outcome measure(s) | *P*-value | Comments |
|---|---|---|---|---|---|---|---|
| | | | | | NADPH-diaphorase staining of penile nerve fibers | Increase in NADPH-diaphorase +ve fibers:<br>• Grp 1 vs Grp 2: $P < .05$<br>• Grp 3 vs Grp 2: $P < .05$<br>• Grp 1 vs Grp 3: $P < .05$ | PRP treated Grp had significantly more NADPH-diaphorase-positive nerve fibres in the dorsal nerves than injured control Grp, but less than sham Grp. |
| Wu et al. [15]; prospective randomized-controlled trial† | ED; 24 (12) | Sprague-Dawley rats (450-600 g.) | Three Grps (n = 8):<br>1. Sham surgery Grp¶<br>2. Vehicle-only Grp (normal saline injection)<br>3. PRP Grp<br>All Grps but sham had bilateral CNs crush injury using a hemostat clamp for 2 min.<br>Pre-treated PRP derived from 6 rats' blood was applied at time of injury. EF assessment and penile tissue collection done at 1 month. | Yes | ICP | Increase in Grp 3 vs Grp 2: $P < .05$<br>Decrease in Grp 2 vs Grp 1: $P < .05$ | PRP resulted in significant recovery of EF, as compared with normal saline Grp ($P < .05$).<br>Grp 3 lacks remodeling and inflammation (successful nerve regeneration) and had a significant preservation of CNs myelinated axons and a lower apoptotic index compared to Grp 2. |
| | | | | | Number of myelinated axons in: | Cavernous nerve | Increase in Grp 3 vs Grp 2: $P < .05$<br>Decrease in Grp 3 vs Grp 1: $P < .05$ |
| | | | | | | Dorsal penile nerve | Increase in Grp 3 vs Grp 2: $P < .05$ |
| | | | | | Collagen type change | Decrease in Grp 3 vs Grp 2: $P < .05$ | |
| | | | | | Number of apoptotic cells | Decrease in Grp 3 vs Grp 2: $P < .05$ | |
| | | | | | Caspase-3 and TGF-b1‡ | Decrease in Grp 3 vs Grp 2: $P < 0.05$ (TGF-b1) | |
| Wu et al. [16]; prospective randomized-controlled trial† | ED; 24 (12) | Sprague-Dawley rats (450–600 g.) | Four Grps (n = 6):<br>1. Sham surgery Grp¶<br>2. Vehicle-only Grp (normal saline injection)<br>3. General PRP Grp<br>4. Optimized PRP Grp<br>All Grps but sham had bilateral CNs crush injury using a haemostat clamp for 2 min. Pre-treated PRP obtained via 6 aged-matched rats was applied at the time of injury.<br>EF assessment and penile tissue collection done at 1 month. | Yes | CN electrostimulation (erectile response) | Increase in ICP:<br>• Grps 3 and 4 vs Grp 2: $P < .05$<br>• Grp 4 vs Grp 3: $P < .05$<br>Decrease in ICP:MAP ratio§<br>• Grps 2 and 3 vs Grp 1: $P < .05$ | Optimized PRP had the largest amount of PDGF-AB and showed a synergistic effect on release of growth factors ($P < .05$).<br>Functional improvement after bilateral CN injury when given the optimized PRP ($P < .05$).<br>Optimized PRP was more stable, and its injection in CC facilitated recovery of EF. |
| | | | | | Histology of penile tissue (nNOS +ve fibres) | Increase in Grps 3 and 4 vs Grp 2: $P < .05$<br><br>Decrease in Grps 2 and 3 vs Grp 1: $P < .05$ | |
| Gur et al. [17]; prospective comparative trial | ED; 30 (n/a) | Male Sprague-Dawley rats (n/a) | Two Grps (n = 15):<br>1. Control<br>2. STZ-induced diabetic (45mg/kg, 8 wks.). | No | EF | n/a | EF and ICP partially restored after injecting PRP or Clopidogrel.<br>EF completely improved after combination of PRP and |

(continued)

**Table 2.** Continued

| Study | Disease; N (age)* | Animal (weight) | Protocol | PRP preparation protocol description | Outcome measure(s) | *P*-value | Comments |
|---|---|---|---|---|---|---|---|
| | | | In vivo erectile responses measured after PRP or clopidogrel injection and their combination in anesthetized rats.<br>eNOS, nNOS, HIF-1α and VEGF expression determined in penile tissue by Western blot. | | | | Clopidogrel.<br>Clopidogrel caused marked relaxation (from a parallel in vitro study) in CC of diabetic and control rats. |
| | | | | | ICP | | |
| Liao et al. [18]; prospective comparative trial | ED; 23 (6) | Male Sprague-Dawley rats (n/a) | Three Grps:<br>1. Control Grp (no STZ injection or diabetic rat with no ED); n = 8<br>2. Normal saline IC injection in diabetic rats with ED; n = 7<br>3. PRP IC injection in diabetic rats with ED; n = 8<br>EF assessed at 1 month. | No | ICP<br>undisclosed EF parameters | n/a | Increase in all erectile function parameters at 28 day post PRP treatment.<br>PRP showed tissue-protective effects of corpus cavernosum. |

*In weeks; n/a: data not available; Grp = group
†Did not mention whether randomization was blinded or not.
‡mRNA expression of caspase-3 and TGF-b1 in corpus cavernosum.
§ICP:MAP ratio is an indicator of erectile response. The higher, the better response recorded.
¶surgery with no further manipulation (ie, injury or injection)

of the total volume, the presence of red blood cells and the concentration of platelets [21].

## Preclinical Evidence of PRP in ED

The aim of this review is to shed light on the current PRP use-related evidence in ED and PD. In this regard, some scientists studied lab animals with ED secondary to injured cavernous nerves (CNs). PRP-injected rats showed statistically significant improvements in intracavernous pressure (ICP), an indicator of resolving erectile function (EF) [22]. Liao et al. postulated that PRP- treated diabetic rats with ED had improved EF through tissue preservation of the corpus cavernosum [24]. Supporting that claim, Ding et al. showed that PRP potentiates regeneration and recovery of EF in rats after bilateral CNs injury [25]. Similarly, Cho et al. highlighted its regenerative benefits post facial nerve axotomy [26]. GFs like IGF-1, VEGF and brain derived neurotrophic factor with the presence of neurotrophins improve EF after CNs injury by enhancing axonal regenerations [27–29]. Neurotrophins present in PRP in addition to its biomaterial including fibrin, fibronectin and vitronectin could be responsible for the observed benefits [30–32]. Interestingly, Wu et al. discovered optimal conditions for obtaining higher concentrations of PDGF-beta in PRP solution; this newly formed solution would maximize nerve regenerative capacities and functional outcomes [22]. Again, this is supporting the idea that PRP biomaterial is critical for its regenerative potential, antiapoptotic, and antifibrotic effects.

## Clinical Evidence of PRP in ED and PD

In humans, on the one hand, PRP demonstrated promising results on microscopic and macroscopic levels in studies reporting on ED. In fact, PRP injections significantly improved EF based on intracavernosal peak systolic velocity (PSV), IIEF-5, and sexual encounter profile (SEP) scores independently of whether PRP was activated by calcium or used in conjunction to another treatment [7,9,19]. Other modalities like Li-ESWT have been discussed as other innovative options. It appears that the concurrent use of PRP could prolong Li-ESWT notable improvements for up to 24 weeks [10]. It is noteworthy that previous studies were only available as abstracts. Although no available full manuscript was available for the latter study, authors properly defined the significance of results. Conversely, a study by Chalyj et al. was available in an incomplete abstract [9]; its main results were reported in a review conducted by one of the co-authors [19]. They reported improvements of IIEF-5 scores without indicating a baseline reference thus making comparison harder to make. Also, Epifanova et al. indicated that their trial was still in progress so no definitive conclusion can be taken away at this time [7].

On the other hand, this unique therapeutic approach showed conflicting results for the treatment of PD. Marcovici et al. displayed pre- and post-treatment photos of a single patient

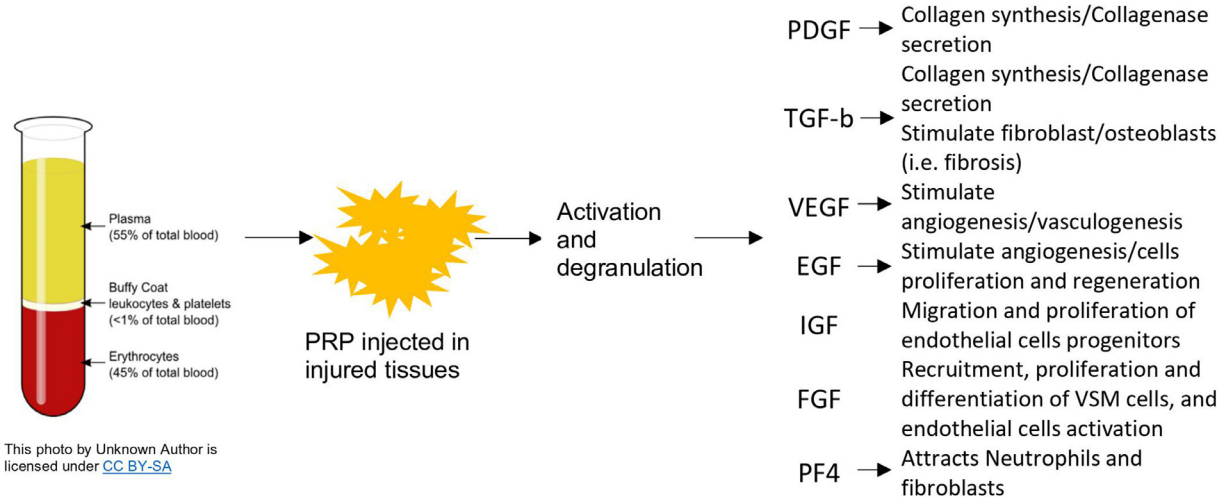




**Figure 2.** Overview of platelet-rich plasma mechanism of action. Abbreviations: PRP, platelet-rich plasma; PDGF, platelet-derived growth factor; TGF-b, transforming growth factor beta; VEGF, vascular endothelial growth factor; EGF, epidermal growth factor; IGF, insulin-like growth factor; FGF, fibroblast growth factor; PF-4, platelet-factor 4; VSM, vascular smooth muscle.

showing PRP benefits in PD after 8 weeks of treatment [15]. An improvement was clearly noted and the patient was satisfied. However, this result cannot be extrapolated, given it was only noted in one case. On the contrary, data by Notsek and Boiko [16] shows that the group receiving normal saline 0.9% instead of PRP had still noted plaque softening and a decrease in both size and angle of curvature as well as improvements of pain sensation and IIEF-5 score. Although these improvements were all statistically inferior to those experienced by the PRP-treated group, a question should be raised: is there a placebo effect in PD treatment by needling alone? This question needs to be addressed with high-powered RCTs.

Animal models help to better understand treatment mechanisms. Culha et al. concluded that PRP has PD-like effects in rats, though not statistically significant, as PRP-treated group had similar histologic characteristics seen in the diseased group [33]. Conversely, this finding conflicts with the previously mentioned human-based case-report that demonstrated satisfactory results after 8 weeks of treatment [15].

PRP has not been established to be efficient in improving penile deformation for easier sexual intercourse in humans despite some studies reporting it [11–13,15,17]. It has however shown some promising results in reducing pain in PD [16].

Despite its current use in humans, there is no solid scientific evidence that PRP might be effective in the treatment of ED and PD. Optimal data on its safety and efficacy are still lacking.

## PRP Injections Adverse Effects

In the plastic surgery and dermatology literature, no serious adverse effects secondary to PRP injections were noted when used for the treatment of various conditions such as periorbital hyperpigmentation or wound care in diabetic patients [34]. Minor complications like infection at the site of injection could be avoided with proper precautions and preparation [35]. Although none of the studies showed serious or major complications afflicted to patients, nonscientific media including BBC, Forbes, and CTV news reported in May 2019 about 2 patients infected with HIV while undergoing a vampire facial treatment with PRP in a New Mexico beauty salon. The New Mexico Regulation and Licensing Department's deputy director of boards and commissions, Kathy Ortiz, said that the site did not have a practice license and was thus closed [36].

## PRP Injections Associated Financial Burden

Studies did not include the cost of PRP injections. Associated costs are usually not covered to diseased men desperately seeking an improvement in these conditions. These costs can be substantial, ranging from $1,500 to $3,000 per injection as per the providers listed under the Priapus shot trademark registered with the U.S. Patent and Trademark office. To compare, Li-ESWT would cost between $2,000 and $5,000, whereas intracavernosal stem cell (ISC) injections may range from $6,000 to $10,000 per injection in centers around the world based on an internet search conducted in 2015 by Jenkins et al [37].

## General Limitations

The authors of this systematic review noted a number of limitations to the current studies. Firstly, nearly half of the human-based studies with ED had only been written as abstracts and lacked important details that could only be found in the manuscripts [7–11,16–18]. For example, Chalyj et al. concluded in their abstract that activated PRP led to significant increase in IIEF-5 score, but did not indicate a baseline reference [9]. In addition, all studies, but Matz et al. did not comment on the number of injections or on their concentration. Furthermore,

protocols lacked homogeneity; some had shorter follow-up periods than others, ranging from 4 weeks only to annual follow-ups. It is important to provide longer follow-up periods to allow therapeutic effects to manifest as PRP injections consist of a course treatment [19]. Moreover, PRP preparations varied considerably. While, some studies reported an addition of hyaluronic acids (HA) to the preparation [11–13,17], one reported on the efficacy of Li-ESWT combined with $CaCl_2$-activated PRP. It is reported that HA stabilizes the solution [13] and that $CaCl_2$ promotes clots formation for a longer and controlled release of GFs from the clot for a maximal effect [22,30,38]. Another limitation of one particular study was that patients selection included only those with moderate baseline IIEF-5 scores, thus excluding those who might have more or less notable responses [8]. More importantly, not all of the studies included a control or a placebo/sham group, and only 6 were randomized (35%). For instance, Virag et al. did not include a control group as they used PRP with HA on patients with PD, but rather compared their results with Berookhim's trial [39] which studied the natural course of PD in the absence of any intervention [12]. This comparison highlighted a favorable outcome of PRP in PD, but no solid conclusion can be drawn as there was no control arm.

Preclinical studies used different strategies to measure their outcomes and had different PRP preparation protocols as well, making them difficult to compare. Moreover, these preclinical studies used a low number of testing animals. For example, all but Gur et al. had fewer than ten subjects in their experimental or control groups.

## CONCLUSION

PRP injection appears to be more of a promising innovative treatment modality for ED than for PD, although it might be useful for pain relief. Safety and effectiveness of this therapy in the treatment of ED and PD demand further preclinical and clinical studies with standardized protocols to gain an adequate insight into its potential implications. The magnitude of the benefits and long-term safety in humans remains yet to be determined. Patients should be offered to be part of well-constructed studies in order to better understand its potential use in Urology. In line with the recent AUA and SMSNA recommendations, the authors recommend the aforementioned and hope that this review constitutes a basis for the development of further RCTs in humans to provide an evidence-based risk-benefit assessment.

## SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.sxmr.2020.12.004.

**Corresponding Author:** Serge Carrier, MD, FRCS(C), Department of Surgery, Division of Urology, McGill University Health Center Montreal, MUHC GLEN- Royal Victoria Hospital Site, 1001 Decarie Boulevard, Room D05.5726, Montreal, Quebec H4A 3J1, Canada. Tel: 514-934-1934 ext.: 35486/34808; Fax: 514-843-1552; E-mail: serge.carrier@mcgill.ca

*Conflict of Interest:* No conflict of interest for this paper.

*Funding:* This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## REFERENCES

1. Goldstein I, Goren A, Li VW, et al. Epidemiology update of erectile dysfunction in eight countries with high burden. ***Sex Med Rev*** 2019.
2. Moreira Jr ED, Abdo CHN, Torres EB, et al. Prevalence and correlates of erectile dysfunction: Results of the Brazilian study of sexual behavior. ***Urology*** 2001;58(4):583–588.
3. Hellstrom W, Bivalacqua TJ. Peyronie's disease: Etiology, medical, and surgical therapy. ***J Androl*** 2000;21(3):347–354.
4. Wagner G, Fugl-Meyer K, Fugl-Meyer A. Impact of erectile dysfunction on quality of life: Patient and partner perspectives. ***Int J Impot Res*** 2000;12(S4):S144.
5. Meyer JP, Gillatt D, Lockyer R, et al. The effect of erectile dysfunction on the quality of life of men after radical prostatectomy. ***BJU Int*** 2003;92(9):929–931.
6. Scott S, Roberts M, Chung E. Platelet-rich plasma and treatment of erectile dysfunction: Critical review of literature and global trends in platelet-rich plasma clinics. ***Sex Med Rev*** 2019.
7. Epifanova M, Gvasalia B, Chaliy M, et al. Combined therapy for treating erectile dysfunction: First results on the use of low-intensity extracorporeal shock wave therapy and platelet-rich plasma. ***BJU Int*** 2019;123(Suppl. 3):25.
8. Banno JJ, Kinnick TR, Roy L, et al. The efficacy of platelet-rich plasma (PRP) as a supplemental therapy for the treatment of erectile dysfunction (ED): Initial outcomes. ***J Sex Med*** 2017;14 (2 Suppl. 1):e59–e60.
9. Chalyj ME, Grigorjan VA, Epifanova MV, et al. The effectiveness of intracavernous autologous platelet-rich plasma in the treatment of erectile dysfunction. [Russian]. **Urologiia (Moscow, Russia: 1999)** 2015(4):76–79.
10. Ruffo A, Franco M, Illiano E, et al. Effectiveness and safety of platelet rich plasma (PrP) cavernosal injections plus external shock wave treatment for penile erectile dysfunction: First results from a prospective, randomized, controlled, interventional study. ***Eur Urol Suppl*** 2019;18(1):e1622–e1623.
11. Virag R, Sussman H. 011 ultrasound guided treatment of Peyronie's disease with plasma rich platelets (PRP) and hyaluronic acid (HA). ***J Sex Med*** 2016;13(5):S5–S6.
12. Virag R, Sussman H, Lambion S, et al. Evaluation of the benefit of using a combination of autologous platelet rich-plasma and hyaluronic acid for the treatment of Peyronie's disease. **Sex Health Issues** 2017;1:1–8.

13. Virag R, Sussman H, Lobel B. Nouveau traitement de la maladie de Lapeyronie par injection de plasma autologue enrichi en plaquettes (PRP) et acide hyaluronique. Résultats préliminaires. **e-mémoires de l'Académie Nationale de Chirurgie 2014;13(3):96–100.**
14. Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. **Investig Clin Urol 2018;59(1):61–65.**
15. Marcovici I. PRP and correction of penile curvature (Peyronie's disease). ***Am J Cosmetic Surg* 2019;36(3):117–120.**
16. Notsek M, Boiko M. PO-01-083 platelet-rich plasma therapy of Peyronie's disease. ***J Sex Med* 2019;16(5 Suppl. 2):S70.**
17. Virag R, Sussman H. PS-05-007 plasma rich platelets and hyaluronic acid improves Peyronie's disease: A case control study of 75 cases. ***J Sex Med* 2017;14(4):e121.**
18. Alkhayal S, Lourdes M. PO-01-091 platelet rich plasma penile rejuvenation as a treatment for erectile dysfunction: An update. ***J Sex Med* 2019;16(5 Suppl. 2):S71.**
19. Epifanova MV, Gvasalia BR, Durashov MA, et al. Platelet-rich plasma therapy for male sexual dysfunction: Myth or reality? **Sex Med Rev 2020;8(1):106–113.**
20. Nagar P, Viswanath D. Platelet rich plasma/platelet rich fibrin-uses in pediatric dentistry: A review. **J Dent Oral Biosci 2012;3:44–46.**
21. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. ***Skin Appendage Disord* 2018;4(1):18–24.**
22. Wu YN, Wu CC, Sheu MT, et al. Optimization of platelet-rich plasma and its effects on the recovery of erectile function after bilateral cavernous nerve injury in a rat model. **J Tissue Eng Regen Med 2013;10(10):E294–E304.**
23. Ehrenfest DMD, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte-and platelet-rich fibrin (L-PRF). ***Trends Biotechnol* 2009;27(3):158–167.**
24. Liao CH, Wu YN, Chiang HS. Effects of platelet rich plasma on improving erectile dysfunction in streptozotocin-induced diabetic rats. ***J Urol* 2018;199(4 Suppl. 1):e582–e583.**
25. Ding XG, Li SW, Zheng XM, et al. The effect of platelet-rich plasma on cavernous nerve regeneration in a rat model. **Asian J Androl 2009;11(2):215–221.**
26. Cho HH, Jang S, Lee SC, et al. Effect of neural-induced mesenchymal stem cells and platelet-rich plasma on facial nerve regeneration in an acute nerve injury model. ***Laryngoscope* 2010;120(5):907–913.**
27. Chen KC, Minor TX, Rahman NU, et al. The additive erectile recovery effect of brain-derived neurotrophic factor combined with vascular endothelial growth factor in a rat model of neurogenic impotence. ***BJU Int* 2005;95(7):1077–1080.**
28. Jung G, Kwak J, Yoon S, et al. IGF-I and TGF-$\beta$ 2 have a key role on regeneration of nitric oxide synthase (NOS)-containing nerves after cavernous neurotomy in rats. ***Int J Impot Res* 1999;11(5):247.**
29. Hu W, Hu L, Li S, et al. Reconstruction of erectile reflex circuit by autologous vein graft combined with use of insulin-like growth factor. ***Zhonghua Yi Xue Za Zhi* 2004;84(15):1280–1282.**
30. Wu CC, Wu YN, Ho HO, et al., et al. The neuroprotective effect of platelet-rich plasma on erectile function in bilateral cavernous nerve injury rat model. **J Sex Med 2012;9(11):2838–2848.**
31. Lee HW, Reddy MS, Geurs N, et al. Efficacy of platelet-rich plasma on wound healing in rabbits. ***J Periodontol* 2008;79(4):691–696.**
32. Marx RE. Platelet-rich plasma: Evidence to support its use. ***J Oral Maxillofac Surg* 2004;62(4):489–496.**
33. Culha MG, Erkan E, Cay T, et al. The effect of platelet-rich plasma on Peyronie's disease in rat model. **Urol Int 2018;102(2):218–223.**
34. Hu Z, Qu S, Zhang J, et al. Efficacy and safety of platelet-rich plasma for patients with diabetic ulcers: A systematic review and meta-analysis. **Adv Wound Care (New Rochelle) 2019;8(7):298–308.**
35. Ellabban NF, Eyada M, Nada H, et al. Efficacy and tolerability of using platelet-rich plasma versus chemical peeling in periorbital hyperpigmentation. **J Cosmet Dermatol. 2019;18(6):1680–1685.**
36. Dunham J. Clients of spa that offered vampire facials infected with HIV. CTV News. April 30, 2019, 2019.
37. Jenkins LC, Mulhall JP. The new business of ED therapy. **J Sex Med 2015;12(12):2223–2225.**
38. Toyoda T, Isobe K, Tsujino T, et al. Direct activation of platelets by addition of CaCl 2 leads coagulation of platelet-rich plasma. ***Int J Implant Dent* 2018;4(1):23.**
39. Berookhim BM, Choi J, Alex B, et al. Deformity stabilization and improvement in men with untreated Peyronie's disease. **BJU Int 2014;113(1):133–136.**