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Use of Platelet Rich Plasma in Urological Conditions

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1. ABSTRACT

Introduction: Platelet-rich plasma (PRP) has become an increasingly popular therapeutic tool across various medical specialties since its introduction in 1958. Defined as a concentrated solution of platelets and growth factors derived from autologous blood, PRP supports tissue repair and regeneration processes. PRP's composition includes high concentrations of platelets and growth factors that facilitate angiogenesis, connective tissue remodeling, and cellular repair, making PRP a promising treatment option for complex urological conditions and beyond.

Purpose of the study: This review aims to summarize the applications and efficacy of PRP in treating specific urological conditions such as erectile dysfunction, Peyronie's disease, urethral stricture, hypospadias, interstitial cystitis and urinary incontinence.

Materials and Methods: To provide a comprehensive summary of current knowledge on this topic, a literature review of English-language articles, with an emphasis on recent publications, was conducted. The review utilized the PubMed database and included 51 studies accessed prior to October 2024.

Conclusions: PRP therapy appears to be a promising, safe, and minimally invasive treatment option for several urological conditions. Studies suggest that PRP may benefit erectile function, reduce symptoms in Peyronie's disease, and improve outcomes in conditions related to the urethra and bladder, with minimal reported adverse effects.

However, the lack of standardized PRP preparation protocols and large placebo-controlled trials poses a challenge to fully establishing its efficacy. Further research is necessary to confirm PRP's effectiveness, optimize preparation and administration methods, and develop guidelines for its clinical application in urology.

KEYWORDS: platelet rich plasma, erectile dysfunction, Peyronie's disease, urethral stricture, hypospadias, interstitial cystitis, urinary incontinence.

2. INTRODUCTION

PRP is a relatively new method used in medicine. The first references in the literature appeared around 1958, but the largest surge in new publications can be observed from 2012 onwards, with a growing number of scientific papers each year containing the search term "platelet-rich plasma.".

PRP is a biological product defined as a fraction of autologous blood plasma with a platelet concentration above the baseline value (prior to centrifugation) [1]. PRP is an autologous blood-derived product containing a rich concentration not only of platelets but also various growth factors, cytokines, chemokines, and proteins [2]. This unique and potent composition of growth factors not only promotes repair, regeneration, and alteration of angiogenesis but also plays a key role in connective tissue remodeling and cell cycle regulation [3]. Due to the lack of a standardized method for the preparation and application of PRP, there is a wide variety of preparation techniques. However, the main principle is the preparation of concentrated platelets from the patient's own blood. All PRP preparation protocols follow a generic method, starting with the collection of approximately 10 to 60 ml of venous blood from the patient and placing it in tubes containing an anticoagulant, either citrate dextrose or sodium citrate solution, to prevent clotting and premature release of alpha granules. The whole blood is then centrifuged and separated into three layers based on specific gravity: the lower layer contains red blood cells (RBCs) with leukocytes, the middle layer is PRP, and the upper layer is platelet-poor plasma (PPP) [4]. In addition to the higher concentration of platelets, other parameters such as the presence or absence of leukocytes and activation must be considered in PRP. This determines the type of PRP used in various pathologies [1].

Both the device used for platelet separation and the subsequent application of the PRP product are regulated by the U.S. Food and Drug Administration (FDA). Any use of PRP beyond blood transfusion is considered "off-label use," which is not prohibited by FDA regulations as long as it is performed by a physician with the intent to practice medicine [5].

PRP has found applications in many fields of medicine, including plastic surgery, pediatric surgery, cardiac surgery, gynecology, orthopedics, ophthalmology, urology, dentistry, dermatology, and sports medicine [3,6]. This review aims to summarize the application of PRP in urological conditions.

3. HISTORY OF PRP

Platelets in blood were discovered in 1881 by Italian pathologist Giulio Bizzozero, who identified these cells in peripheral blood and named them. He then described the role of

platelets in the hemostatic process and highlighted the vascular wall's role in inhibiting platelet adhesion[7].

The term "platelet rich plasma" was first introduced in 1954 by Kingsley et al. to describe plasma with a platelet count higher than that of peripheral blood [8]. It was first used as a blood transfusion product in the 1970s for a young man with thrombocytopenia [9]. Although the operation was successful, it was not until 1969 that suitable methods for storing platelets were developed. Around this time scientists discovered that platelets are the source of fibroblast growth-promoting activity and many other growth factors. The most important include: platelet derived growth factor (PDGF), transforming growth factor b1 (TGF-b1), transforming growth factor b2 (TGFb2), insulin-like growth factor (IGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and hepatocyte growth factor [10]. These factors are responsible for enhancing cell repair and proliferation by e.g. reducing inflammation or stimulating angiogenesis.

Over the years, PRP has begun to be used widely in other areas of medicine. Clinical application of PRP was described in 1975 by Oon and Hobbs [11]. In the 1980s PRP was discovered in oral and maxillofacial surgery. In 1987 it was used in open heart surgery performed by Ferrari et al. to avoid excessive blood transfusion [12]. Later it was applied in the musculoskeletal recovery caused by injuries, including arthritis, tendonitis, ligament injuries, and muscle strains [13]. In 1999 PRP was introduced in another field of medicine - dentistry. PRP was effectively used following dental implant surgery to promote faster bone regeneration and healing time. Later PRP has become an important tool used in dermatology, especially in tissue reproduction, wound-healing, skin regeneration, and hair loss [9]. Now PRP is a part of the treatment of various dermatological conditions such as alopecia, ulcers, skin rejuvenation, acne, hypertrophic scars, hyperpigmentation, and hypopigmentation [14]. Recently, PRP has emerged as a promising treatment for common urologic conditions including Peyronie's disease and erectile dysfunction [15]. With a history spanning 70 years, the role of PRP in medicine continues to evolve and is still being explored.

4. STATE OF KNOWLEDGE

4.1. ERECTILE DYSFUNCTION

Erectile Dysfunction (ED) is a widespread male sexual dysfunction that is multidimensional and can be caused by a change in any of the components of the erectile response: organic, relational, and psychological [16]. It can be caused by many different factors: vascular, neurological, psychological, and hormonal. Diseases that coexist with ED are diabetes, hypertension, hyperlipidemia, obesity, testosterone deficiency, and prostate cancer treatment. In addition, we can also mention psychological states such as relationship problems or fear of these disorders and drugs and substances that can cause or exacerbate ED. Consequently, the initial treatment approach predominantly emphasizes lifestyle modifications to address the underlying causes effectively [17]. Traditional ED therapies have included PDE-5 inhibitors, ICIs, and surgical implantation of prostheses. As a result of interest in regenerative therapies, PRP has emerged as a potential treatment option. PRP has been demonstrated to be safe for various human applications [18].

Matz et al. were the first to publish a study in 2018 on the use of PRP in the treatment of ED, which found that none of the 17 patients studied reported adverse events or worsening of ED [19]. After this study, only two more were published in 2021. One of them included 31 patients who had ED associated with metabolic syndrome.
During 6 months of follow-up, 19 (61%) had improved International Index of Erectile Function questionnaire IIEF-EF scores, suggesting potential efficacy [20]. Another study involved 60 men with mild to moderate ED randomly assigned to receive two intravenous injections of 10 ml of PRP or 10 ml of saline 1 month apart. In the placebo group, 76% achieved IIEF MCID in the PRP group at 6 months, compared with only 25% in the placebo group [21]. Thomas A Masterson et al. conducted a prospective, randomized, double-blind, placebo-controlled clinical trial and determined that PRP was safe, although they found no difference in efficacy between PRP and placebo [19].

PRP, through its vasculogenic, neuroprotective, neurotrophic, repairing, and anti-inflammatory effects, may affect key elements of the pathophysiological pathways leading to ED. Based on the available research, these mechanisms have not yet been thoroughly investigated, analyzed, and understood. The results of the available human studies demonstrate efficacy and safety, but they are conducted on small numbers of people, and most do not include a placebo [20].

Fromanco et al. conducted a prospective, randomized cohort study to assess the response to PDE5-Is before and after PRP injection in a cohort of 150 patients with vascular ED. Eighty percent of patients resumed sexual activity at the 1-month follow-up, and improved IIEF-5 scores were observed after PDE5-Is. Increased intracavernous blood flow was also noted after pharmacological stimulation. In addition, mean platelet volume (MPV) has been proposed as a predictive biomarker of treatment outcome, with lower MPV values being associated with a greater likelihood of treatment response [23].

The literature on Platelet-Rich Plasma (PRP) is limited, but existing studies consistently demonstrate that the treatment is safe, with no reports of serious side effects. Although only a few studies have been identified, they all indicate that patients did not experience any significant adverse effects after receiving injections. Additionally, placebo treatments have also shown a measurable impact on patients with erectile dysfunction (ED). Multiple credible biological explanations have been suggested for this, including alterations in arousal and the activation of central dopaminergic pathways [21].

4.2. PEYRONIE'S DISEASE

Peyronie's disease (PD) is an acquired connective tissue disorder of the tunica albuginea of the corpora cavernosa, characterized by fibrotic patches and plaque formation. These plaques can hinder the uniform expansion of the cylindrical tunica albuginea during penile erection, leading to curvature and deformity of the penis. The exact cause is unknown, but the dominant theory suggests repeated microtrauma to the tunica during sexual intercourse, followed by abnormal wound healing in predisposed individuals [24].

The treatment of Peyronie's disease in its stable phase distinguishes between pharmacological and surgical approaches, depending on the severity of penile deformity and associated symptoms. Surgical treatment is reserved for patients with severe penile curvature

that makes sexual intercourse difficult. Surgery remains a fast and reliable treatment option. However, less invasive, controversial “regenerative” treatment methods are emerging, such as low-intensity extracorporeal shockwave therapy (Li-ESWT), intracavernous stem cell therapy (SCT), and platelet-rich plasma (PRP) injections [25].

In a prospective study published in 2022 by Achraf et al., 65 patients with Peyronie's disease were included to examine the effects of PRP on curvature, pain relief, and erection improvement after the final PRP session (each patient had an average of 6.1 injections). PRP administration showed significant improvement in PD regression, assessed by measuring penile curvature, the Visual Analog Scale (VAS) for pain, and the International Index of Erectile Function (IIEF-5) questionnaire. Both groups showed improvement in the curvature angle and a reduction in average penile curvature compared to baseline, with the first group improving by −16.88° (SD = 3.35) and the second group by −17.27° [25].

In 2023, Zugail et al. published a prospective, non-randomized cohort study where 54 patients received 5–6 mL of PRP injected into the plaque after creating multiple channels along the entire longitudinal axis of the plaque. Additionally, penile vacuum therapy was applied starting on day 14 after each session for 30 minutes daily. Despite promising results, showing an improvement in penile curvature from 53.98 ± 23.19° at baseline to 30.09 ± 20.61° post-treatment ($p = 0.001$), it is impossible to determine whether the benefits were due to PRP injections or the vacuum therapy [26].

In 2023, Alshuaibi et al. also used a combined treatment approach involving percutaneous needle tunneling followed by penile modeling and PRP injections. However, unlike the aforementioned protocols, patients received treatment after artificially induced erections and under general anesthesia. Results from the cohort of 36 patients suggest a statistically significant improvement in penile curvature, with an average improvement difference of 16.85 ± 14.81 (mean curvature before treatment 57.5 ± 20.61° vs. 40.86 ± 25.13° post-treatment; $p = 0.0001$). Unfortunately, these promising results are limited by the assessment of penile curvature improvement based on patient-taken photographs and the absence of validated questionnaires to assess erectile dysfunction and PD [27].

At present, there are not many studies demonstrating the efficacy of PRP in Peyronie's disease. Repeated PRP injections into Peyronie's plaque appear to be partially effective, but large, placebo-controlled, multicenter trials are required to confirm or refute the efficacy of PRP.

4.3. URETHRAL STRICTURE

Urethral stricture is a narrowing of the urethra due to scar tissue, which leads to obstructive voiding dysfunction with potentially serious consequences for the entire urinary tract. Its prevalence among men in industrial countries is estimated at 0.9%. It produces obstructive and irritative urinary symptoms and can ultimately impair renal function. Urethral strictures can be caused by diagnostic or therapeutic urological procedures. These procedures are being performed ever more commonly, because the population is aging; thus, urethral strictures will probably become more common as well [28].

Direct vision internal urethrotomy (DVIU) is the first-line treatment for US in men; however, stricture recurrence is still a problem, with a stricture-free rate of around 20% in

long-term follow-up [29].

In 2019 Rezaei et al. compared two groups of patients with bulbar US who underwent urethrotomy and submucosal local injection of PRP or saline solution in the control group at the same time. The follow-up time was 3 months.

After 12 months of follow-up, the rates of recurrence and stricture length in case of recurrence were significantly lower in the PRP group [30,31].

4.4. HYPOSPADIAS

Hypospadias is one of the most common congenital anomalies in men. The condition is typically characterized by proximal displacement of the urethral opening, penile curvature, and a ventrally deficient hooded foreskin [32].

There is unanimous agreement amongst hypospadias surgeons to use an intermediate layer to cover the neourethra. Dartos fascia and tunica vaginalis (TV) flaps are the most preferred tissues to be used. Tissue glue, sealants and biomaterials are also useful where there is a paucity of local tissue to cover the neourethra. But these blood-derived products have associated infectious and allergic risks [33].

In 2018 Mahmoud et al. carried out a clinical trial about distal or mid-penile hypospadias repair. They compared two groups: for group 1 they used a PRP sheet cover age for urethroplasty and for group 2, a preputial dartros flap. The authors observed a significant difference between both groups in rate of global complications and superficial wound infection (more frequent in group 2), so they concluded that PRP might be considered as an alternative coverage layer for hypospadias repair [34,35].

4.5. INTERSTITIAL CYSTITIS

The tight connections between urothelial cells and the regenerative capacity of these cells enable the urinary bladder epithelium to function as a barrier. This barrier protects against the penetration of pathogens, toxic substances, and urea nitrogen from the urinary bladder into the bloodstream [36]. Interstitial cystitis is a chronic inflammatory disease of unknown pathophysiology, occurring with dysfunction of the urinary bladder epithelium, which disrupts its barrier function. Barrier dysfunction is caused by increased permeability of damaged mature apical cells, decreased proliferation, and increased apoptosis of urothelial cells. Excessive activation of mast cells, neural hyperactivity, and neurogenic inflammation also play a role [37,38]. This mechanism may be responsible for triggering symptoms in patients with interstitial cystitis [39].

Patients suffering from interstitial cystitis complain of pain, urinary frequency, nocturia, and urgency [40]. These symptoms without other pathologic findings allow the diagnosis of interstitial cystitis [41]. In treating interstitial cystitis, it is imperative to restore the protective barrier function of the transitional epithelium. Current conventional methods of treatment include cystoscopic hydrodistention, intravesical botulinum toxin A or hyaluronic acid injection, administration of pentosan polysulfate, chondroitin sulfate, a non-steroid anti-inflammatory drug, sacral neuromodulation, and psychotherapy. Unfortunately, none of these therapies provide lasting treatment effects [42]. Platelet-rich plasma (PRP) is rich in growth factors that promote cell proliferation. Platelets are anucleate cells involved in wound healing.

They secrete proinflammatory and anti-inflammatory cytokines, which can help reduce neuropathic pain by triggering new inflammation promoting the resolution of persistent, unresolved inflammation [43,44].

Clinical studies examining the effect of PRP on interstitial cystitis are promising. In 2018 Jhang et al. published a study in which forty patients with interstitial cystitis were given four intravesical injections of PRP. As a result, the Global Response Assessment (GRA) improved after the first injection. Repeated intravesical injections of PRP have been proven to reduce pain and frequency of urination. In addition, the study showed that PRP therapy had good effects also in patients with interstitial cystitis who did not respond to conventional therapy [39]. In other studies, in 2022, Jhang et al. showed that PRP therapy reduces urinary tract infection episodes and positively affects urothelial regeneration. In the studies, twenty-nine patients were enrolled [45]. To observe the elimination of inflammation and regeneration of bladder epithelial cells, a study was conducted using Western blotting and transmission electron microscopy (EM). These studies showed significant improvement associated with tight junction defects of urothelial cells. This is important because it is the tight junction defects that cause the loss of barrier integrity and leakage of urine into the suburothelial layer, which activates sensory receptors, resulting in symptoms of bladder irritation [46]. Studies using EM had their limitations: there was no placebo control group, and the number of samples was small, which increased the margin of error. Intravesical injections could also cause damage to the bladder, which could affect the study results.

Currently, there are no standards for the preparation of PRP for intramural injections into the bladder. Animal studies have shown that adding physiological saline to the platelet pellet instead of plasma has better healing and angiogenesis effects. In addition, it has been shown that better therapeutic effects are achieved with a PRP pre-incubation at 4 °C, and cryoprecipitate supplementation improve the angiogenic and regenerative properties of PRP [47]. The studies conducted show that intravesical PRP injections are effective in interstitial cystitis, however, further randomized studies are necessary.

4.6. URINARY INCONTINENCE

Platelet-rich plasma (PRP) therapy has emerged as a novel approach for addressing urinary incontinence, particularly stress urinary incontinence (SUI), through its regenerative potential in urological tissues. PRP is derived from the patient's own blood and contains a high concentration of platelets, which release growth factors essential for tissue healing and regeneration. Key growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and vascular endothelial growth factor (VEGF), are known to promote cellular proliferation, collagen synthesis, and increased vascularization, all of which may counteract the tissue weaknesses contributing to urinary incontinence [48].

Recent research on PRP's effects in urinary incontinence has focused on its potential to enhance the urethral sphincter's functionality and reinforce periurethral musculature, often compromised in cases of SUI. Studies involving periurethral PRP injections suggest that PRP may stimulate muscle regeneration and elasticity, thereby enhancing urethral support and reducing incontinence episodes [49]. In 2021 Yuang-Hong Jiang, Ping-Jui Lee, and Hann-

Chorng Kuo conducted a prospective study involving 35 patients with stress urinary incontinence (SUI) caused by intrinsic sphincter deficiency (ISD). Each patient received four monthly injections of 5 mL platelet-rich plasma (PRP), containing 2.5–5 times the platelet concentration of peripheral blood, administered at five sites around the external sphincter.
The main outcome was improvement in SUI severity measured by a visual analogue scale (VAS), with secondary outcomes including the Global Response Assessment score and urodynamic parameter changes. Complete dryness was achieved in 20% of patients, moderate improvement in 40% [49].

While small-scale trials show encouraging results, outcomes can vary depending on factors such as PRP preparation methods, injection protocols, and patient characteristics. A randomized controlled trial compared PRP injections to traditional treatments for SUI, finding significant improvements in continence with PRP, indicating that it may serve as an effective alternative or adjunct to surgical interventions [50].

Safety is a critical consideration; as PRP is derived from the patient's own blood, it is generally well-tolerated with minimal adverse reactions, primarily limited to temporary discomfort at the injection site. However, the long-term safety of repeat PRP treatments, which may be necessary to sustain therapeutic benefits, remains under investigation [50].

In conclusion, PRP therapy holds potential as a minimally invasive option for managing urinary incontinence, especially for those seeking alternatives to surgery. Further high-quality clinical research is essential to establish standardized application protocols, determine the best-suited patient populations, and confirm the effectiveness and longevity of PRP as a treatment option [51].

5. CONCLUSIONS

Platelet-rich plasma (PRP) is an autologous blood plasma rich with growth factors and platelets that can produce pro- and anti-inflammatory cytokines, chemokines and other proteins. It is useful for tissue regeneration and promoting angiogenesis, making it a promising therapy option that can be used in various specialties, including urology.

PRP can serve as a primary treatment and supportive therapy tool. It may impact various factors, often targeting pathways that lead to diseases, with erectile dysfunction among them. It has also proven valuable in conditions associated with excessive tissue formation, such as Peyronie’s disease and urethral stricture, leading to regression and reduced recurrence rates. Its impact on muscle regeneration and elasticity is beneficial for treating urinary incontinence, resulting in improved urethral support and fewer incontinence episodes. PRPs direct anti-inflammatory effect can be used for treating interstitial cystitis, as it reduces both pain and urinary frequency. Furthermore, it shows promise as a treatment option for patients who do not respond to conventional therapy. In cases of hypospadias, the use of PRP as an addition to urethroplasty has shown to reduce complications and superficial wound infections.

Although PRP seems to be a promising tool, the literature about its usage in urology is still limited. Performed studies have limitations, such as not standardized PRP preparation methods and injection protocols. To confirm the effectiveness of PRP in urology, further research and standardized protocols are needed.

6. DISCLOSURE

Conceptualization: AM, JS, AH, KJ, OS, JW, DD, DR, Software: AM, JS, AH, KJ, OS, JW, DD, DR, Check: AM, JS, AH, KJ, OS, JW, DD, DR, Formal analysis: AM, JS, AH, KJ, OS, JW, DD, DR, Investigation: AM, JS, AH, KJ, OS, JW, DD, DR, Resources: AM, JS, AH, KJ, OS, JW, DD, DR, Data curation: AM, JS, AH, KJ, OS, JW, DD, DR, Writing rough preparation: AM, JS, AH, KJ, OS, JW, DD, DR, Writing review and editing: AM, JS, AH, KJ, OS, JW, DD, DR, Visualization: AM, JS, AH, KJ, OS, JW, DD, DR, Supervision: AM, JS, AH, KJ, OS, JW, DD, DR, Project administration: AM, JS, AH, KJ, OS, JW, DD, DR

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