ERECTILE DYSFUNCTION

Early Clinical Results of the Tolerability, Safety, and Efficacy of Autologous Platelet-Rich Plasma Administration in Erectile Dysfunction

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ABSTRACT

Introduction: Platelet-rich plasma (PRP) is useful in the treatment of different conditions and diseases as it contains concentrated levels of many growth factors.

Aim: The aim of this study was to investigate the effectiveness of autologous PRP application in the treatment of erectile dysfunction (ED) in patients with metabolic syndrome.

Methods: In this prospective study conducted in June 2019, 31 patients with ED were included. The International Index of Erectile Function—Erectile Function domain (IIEF-EF) questionnaires were used to evaluate erectile function (EF). After administering the intracavernous autologous PRP 3 times with an interval of 15 days, IIEF-EFs were evaluated 1, 3, and 6 months later.

Main Outcome Measure: IIEF in the 1st, 3rd, and 6th months and adverse events.

Results: While the mean IIEF-EF was 18 before the application, the mean IIEF-EF was 20 in the first, third, and sixth months after the procedure ($P < .001$). However, even though IIEF-EF values increased numerically, median value remained within the mild-moderate classification (scores between 17 and 21). Postprocedure sexual satisfaction scores were significantly higher than preprocedure values (8 vs 6, respectively; $P = .002$). In the first follow-up of a patient after the 3rd injection, a 4-mm diameter fibrotic plaque was observed on the ventral side in the middle of the penis shaft.

Conclusion: In conclusion, our findings suggest that larger studies as well as placebo-controlled studies are needed to add PRP to the treatment protocol in ED. **T Taş, Çakıroğlu, E Arda, et al. Early Clinical Results of the Tolerability, Safety, and Efficacy of Autologous Platelet-Rich Plasma Administration in Erectile Dysfunction. Sex Med 2021;9:100313.**

Key Words: Erectile Dysfunction; Metabolic Syndrome; Platelet-Rich Plasma; International Index of Erectile Function-Erectile Function Domain

INTRODUCTION

Erectile dysfunction (ED) is described as an inability to achieve or maintain a penile erection that is sufficient for sexual intercourse.[1] It is a common disease that may have a negative impact on male sexual health and quality of life.[2] It is estimated that the prevalence of ED in the general population varies between 30% and 65% in men between the ages of 40 and 80,[3] and by 2025, approximately 322 million men worldwide will be diagnosed with ED.[4] Previously, ED was seen as a completely psychogenic disease; however, current evidence suggests that ED pathogenesis is associated with a large number of factors. About 80% of patients have at least a partial organic etiology.[5] ED is associated with many comorbidities and risk factors such as diabetes mellitus (DM), obesity, age, alcohol, smoking, cardiovascular disease, depression, previous pelvic surgery and spinal cord injuries, and other psychological variables.[6–8]

Metabolic syndrome (MetS) is a metabolic disorder that includes at least three of hypertension, abdominal obesity,

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hyperglycemia, insulin resistance, and hypertriglyceridemia/hypercholesterolemia.[9] Obesity is an important risk factor for DM, hypertension, vascular disease, endothelial dysfunction, androgen deficiency, and MetS, all of which contribute to the pathophysiology of ED.[10] The epidemiological link between MetS and ED is well defined.[11] Men with severe ED with DM, advanced age, and/or hypertension often have less response to drugs and often require additional management strategies.[12]

Platelets have an important role in promoting wound healing and coagulation and include several growth factors responsible for regenerative functions (eg, fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor [VEGF]).[13] Therefore, owing to these growth factors, it has the potential to support the regenerative matrix and healing in damaged tissues.[14] Platelet-rich plasma (PRP) contains high concentrations of platelet growth factors derived from whole blood.[15,16] Over the past few years, the use of PRP as a therapeutic tool has led to significant progress in the field of regenerative medicine, especially dentistry, cosmetics and plastic surgery, wound healing and skin regeneration, orthopedics, and other fields.[17]

It has been reported that PRP has positive effects on ED in experimental studies.[18,19] However, there are no clinically adequate and satisfactory studies. Therefore, the aim of this study was to investigate the effectiveness of autologous PRP application for the treatment of ED in patients with MetS. We hypothesized that PRP injection into the penis would improve erection function.

MATERIALS AND METHODS

The institutional human study review committees of the Hisar Intercontinental Hospital Local Ethics Committee (approval number; 25.04.2019/09) approved this prospective study. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and written informed consent was obtained from all subjects. A total of 35 patients with ED associated with MetS aged between 42 and 70 years were included in the study. Assuming a change of 5 from the baseline IIEF-EF value, a superiority test for calculating an average sample size with a unilateral alpha level of 0.05 and a power level of 0.90 requires at least 16 sample sizes for evaluation at the 6th month.

For patients with MetS who had at least 1 of DM, impaired glucose tolerance, or insulin resistance, and at least 2 of hypertension (using systolic blood pressure >130, diastolic blood pressure >85 mmHg, or using antihypertensive), dyslipidemia (triglyceride level >150 mg/dl or HDL levels <40 mg/dl in male), or abdominal obesity (BMI> 30 kg/m^2 or waist circumference: men >94 cm) were included in the study. Patients with neurological deficits, who had previously received ED treatment (phosphodiesterase type-5 inhibitors, intracavernosal injections, etc.) and did not agree to participate in the study, were excluded. Sexual history was obtained using the International Index of Erectile Function (IIEF)[20,21] questionnaires. The severity of ED is often described as mild, mild-moderate, moderate, or severe in accordance with the six-item IIEF-Erectile Function (IIEF-EF) questionnaire, with a score of 0−10 indicating severe, 11−16 moderate, 17−21 mild−moderate, 22−25 mild, and 26-30 no ED.[22] IIEF-EF was evaluated before PRP injection, and 1, 3, and 6 months after PRP injection.

Preparation of PRP

To prepare PRP, blood from the patient was taken into a tube containing 1.5 ml anticoagulant citrate dextrose solution. The tubes were then centrifuged at 2,800 rpm for 8 minutes. The plasma layer separated from the red blood cells was taken and centrifuged again at 3,500 rpm for 10 minutes. In the laboratory environment, a solution containing 1,000−2,000 × 10^3/uL PRP was prepared. 3 cc PRP was injected into each corpora cavernosa with a 25 gauge needle (total amount = 3 * (1,000−2,000) *10^6). Topical anesthetic cream containing 25 mg lidocaine and 25 mg prilocaine (Eutectic Mixture of Local Anaesthetics (AstraZeneca UK)) was applied to the injection site. During intracavernosal injection, clamping (20 min) was performed with Stockmann penis clamp (Storz, Tuttlingen, Germany) to prevent escape of the PRP from the cavernosa without closing the dorsal artery and superficial/deep dorsal vein. Intracavernous autologous PRP was applied to the patients 3 times at an interval of 15 d. The injection sites vary by 1 cm in the mid-penile region. Owing to the limited number of studies on PRP and ED, there is no clear consensus. In this study, we used this dose and this time interval in line with similar studies with PRP.[23,24]

Statistical Analysis

The data were analyzed using IBM SPSS Statistics Standard Concurrent User V 25 (IBM Corp., Armonk, NY, USA) statistical package program. Descriptive statistics for categorical variables are given as number (n) and percentage (%). Summary statistics are given as mean ± standard deviation for normally distributed numerical variables and median, first and third quartile [M (Q1-Q3)] values for non-normally distributed numerical variables. The normal distribution of data for numerical variables was evaluated by Shapiro−Wilk normality test and Q-Q graphs. The values of the scale scores obtained before the procedure as well as those scores from the first, third, and sixth months after the procedure were evaluated by Friedman analysis. Bonferroni corrected multiple comparison test was used to determine the measurement time that was different in case of a significant difference in Friedman analysis. A $P < .05$ value was considered statistically significant.

RESULTS

The patients' demographic data are shown in Table 1. Four patients were excluded from the study because they were out of follow-up. The age distribution of 31 patients in the study was 54.41 ± 8.74 years. 26 of the patients (83.9%) were married,

Table 1. Patients' demographics

Variable	Value
Mean age	54.41 ± 8.74
Marital status, No (%)	
Single	1 (3.2)
Divorced	3 (9.7)
Widow	1 (3.2)
Married	26 (83.9)
Duration of ED, year	5.0 (3.0-8.0)
Mean BMI (kg/m^2)	30.82 ± 5.42
Hypertension, No (%)	16 (51.6)
Triglycerides (*mg/dL*), No (%)	
<150	15 (48.4)
≥150	16 (51.6)
HDL (*mg/dL*), No (%)	
<40	20 (64.5)
≥40	11 (35.5)
Dyslipidemia, No (%)	9 (29.0)
Mean fasting blood glucose	122 (109-148)
DM, No (%)	16 (51.6)
Impaired glucose tolerance, No (%)	11 (35.5)
Impaired glucose tolerance value ($n = 11$)	110.18 ± 3.71

and the BMI of the patients participating in the study was 30.82 ± 5.42. Hypertension was present in 16 patients (51.6%), dyslipidemia in 9 patients (29.0%), DM in 16 patients (51.6%), and impaired glucose tolerance in 11 patients (35.5%).

None of the patients experienced pain during the procedure, and slight subcutaneous bruising occurred after only 8 (8/93) applications at the injection site. In the first follow-up of a patient after the 3rd injection, a 4-mm diameter fibrotic plaque was observed on the ventral side in the middle of the penis shaft. This plaque was not noticed by the patient and did not cause pain, shortening of the penis, thinning, or curvature. No medical treatment was applied and no regression was observed in the plaque during follow-up. This patient had impaired glucose tolerance, hypertension, and abdominal obesity.

In total, 19 patients (61.29%) improved after 6 months. As seen in Table 2, the preprocedure IIEF-EF values of the patients were significantly lower than the first, third, and sixth months after the procedure ($P < .001$). There was no significant difference between the first, third, and sixth month IIEF-EF values after the procedure. After the procedure, the first, third, and sixth month orgasmic function values and preprocedure values were similar ($P = .112$). Postprocedure first, third, and sixth month sexual desire scores and pretreatment scores were similar ($P = .392$). Postprocedure sexual satisfaction scores were significantly higher than preprocedure values ($P = .002$). The overall satisfaction scores after the procedure were significantly lower than the preprocedure scores ($P < .001$).

DISCUSSION

ED is a pathology that causes a decrease in the quality of life in men as a result of not being able to achieve or maintain penile erection for successful sexual intercourse.[1] Indeed, ED affects ~35% of men over the age of 60 and ~50% of men over the age of 70.[25] Obesity, unhealthy diets, decreased physical activity, and smoking have been shown to contribute to ED.[26] In addition, DM, hypertension, cardiovascular disease, hyperlipidemia, MetS, hypogonadism, and psychiatric and psychological disorders are other contributing factors.[27] Decreased blood flow, arterial insufficiency or arterial stenosis resulting from vascular disease, and endothelial dysfunction leads to ED. Indeed, ED may be a symptom of an underlying vascular disorder. The probability of developing vasculogenic ED is increased 3.04 times in hypertension, 2.57 times in diabetes, and 1.83 times in dyslipidemia.[28,29] Prospective and cross-sectional studies revealed that obesity and MetS are associated with increased ED.[30]

Table 2. International Index of Erectile Function Erectile Function domain (IIEF-EF), sexual desire, orgasmic function, sexual satisfaction, and general satisfaction of patients

	Before procedure	First month	Third month	Sixth month		
	M	M	M	*M*		
Values	(Q_1–Q_3)	(Q_1–Q_3)	(Q_1–Q_3)	(Q_1–Q_3)	χ^2	*P*
IIEF-EF	18.00[a]	20.00[b]	20.00[b]	20.00[b]	**31.368**	**<.001**
	(8.25-22.75)	(9.00-23.00)	(9.00-23.00)	(9.00-23.00)		
Orgasmic function	7.00	7.00	7.00	7.00	6.000	.112
	(5.25-9.00)	(7.00-9.00)	(6.00-9.00)	(6.00-9.00)		
Sexual desire	9.00	9.00	9.00	9.00	3.000	.392
	(9.00-9.75)	(9.00-9.75)	(9.00-9.75)	(9.00-9.75)		
Sexual satisfaction	6.00[a]	8.00[b]	8.00[b]	8.00[b]	**15.000**	**.002**
	(6.00-10.00)	(6.00-12.00)	(6.00-12.00)	(6.00-12.00)		
General satisfaction	5.00[a]	4.00[b]	4.00[b]	4.00[b]	**20.351**	**<.001**
	(4.00-6.00)	(4.00-6.75)	(4.00-6.00)	(4.00-6.00)		

The superscripts *a* and *b* show differences between measurements. Measurement values are similar in months with the same letters.

Treatment management of ED is largely highly challenging and performed step by step because it does not have a specific and correctable etiology. Oral medications taken before sexual intercourse are the first treatment for ED resistant to lifestyle changes. Intracavernosal injections are an alternative to oral drugs in the treatment of ED. With this treatment, the drug is injected directly into the corpus cavernosa at the lateral base of the penis. The most commonly injected drug is prostaglandin E1, which stimulates cyclic adenosine monophosphate to induce smooth muscle relaxation and promote erections. In addition, intraurethral suppositories, vacuum-supported erectile devices, and penile prostheses are other treatment options.[27]

Regenerative treatments that aim not only to treat symptoms but also to restore the structure and function of the diseased erectile tissue are new treatment options for ED.[31] They allow long-term preservation of erectile function through a regenerative model that induces both nerve and muscle cell regeneration by regulating growth factors. The regenerative approaches currently being studied for ED treatment include PRP, amniotic fluid matrices, low-intensity extracorporeal shockwave therapy, and stem cell therapy.[31]

Platelet-based treatments are intensively studied in many areas of medicine. PRP is an autologous blood plasma that is rich in many factors and contains more than 4 times the platelet concentration of normal physiological serum.[32] PRP is known to contain active biological molecules such as VEGF, platelet-derived growth factor, epithelial growth factor (EGF), insulin-like growth factor, and fibroblast growth factor, and these growth molecules regulate cell regeneration.[24,33] Some of these growth factors have been shown to mediate the improvement of erectile function in both preclinical and clinical studies.[34] In animal studies in the cavernous nerve injury (CNI) model of ED, VEGF injection has been shown to recover erectile function more than placebo controls.[35] The endothelial nitric oxide synthase pathway mediates erectile function recovery caused by VEGF administration. This mechanism is the main component of the hypothesis that explains how these growth factors in PRP can improve erectile function.[36] 2 groups have published animal model studies on the effects of growth factors in PRP on improving erectile function in rats based on a CNI model. Wu et al[16,19] injected PRP into the corpora cavernosa in the CNI animal model. They observed a decrease in apoptotic markers, decreased fibrosis, and an improvement in erectile function in 4 weeks after a single injection. In another animal study, Ding et al[18] revealed that PRP administration resulted in significantly higher mean maximal intracavernosal pressure (ICP) and maximum ICP/MAP (mean arterial pressure) ratio. Histologically, they reported that the group receiving PRP had more myelinated axons and more nicotinamide adenine dinucleotide phosphate positive nerve fibers. The same group also showed that direct application of PRP to the suture area has higher ICP and more CN axons and promotes regeneration of CNs.[37] The limitation of these studies is that they involved a small number of experimental animals.

Wu et al optimized the PRP production technology in humans. They concluded that human PRP, prepared in accordance with advanced technology, contains a large number of growth factors and consequently promotes the recovery of erectile function.[16] Epifanova et al[33] reported that PRP application improved IIEF-5 in patients with ED. The authors concluded that PRP contains an amount of growth factors required for therapeutic effect, and the method is reliable due to the absence of adverse effects. In another study conducted by Matz et al,[38] they reported that the IIEF-5 score increased after PRP injection in patients with ED and Peyronie disease (PD). At the same time, 80% (4/5) of patients with PD who were followed up reported a subjective improvement in their degree of curvature initially. However, there were few patients in this study. In our study, we determined that the IIEF-EF values of patients with ED who received PRP increased significantly compared with before the application. Our results are compatible with previous studies. However, even though IIEF-EF values increased numerically, median value remained within the mild-moderate classification. Therefore, we can only mention that there is a numerical improvement in IIEF-EF values rather than a clinical improvement. In addition, postprocedure sexual satisfaction scores were significantly higher than preprocedure values. The reason for the increased sexual satisfaction values may be related to the increased frequency of sexual intercourse, as determined by the question "How many times have you attempted sexual intercourse in the last 4 weeks?". In the study, one patient developed a nonsymptomatic fibrotic plaque, whereas 8 patients had slight subcutaneous bruising after application. Fibrosis, a PD-like plaque and a penile curvature deformity are serious adverse reactions to intracavernous injection of vasoactive medication.[39–41] PD-like plaques may not present with clinical symptoms when they are small, as in our study. However, large plaques can cause penile curvature deformity and ED. Prior studies have not reported PD-like plaque formation as a result of PRP application. Culha et al stated that PRP can produce PD-like plaques in animal models.[42] Our study is the first study showing the formation of PD-like plaque after PRP application in humans. Even though the PD-like plaque formation is small, it leads to discussing the safety of PRP application.

PRP usage is not covered by state or private insurance. Therefore, patients who do not benefit from current standard medical treatments often accept the costs and uncertain risks of such treatments.[43] Using marketing channels to advertise PRP may be misleading as standard treatment of ED. Given the lack of supporting evidence regarding the effectiveness of PRP, the cost of treatment can be excessive. Therefore, the protocol and follow-up of these treatments should have certain standards at the level of evidence-based science.

The lack of a placebo group and the lack of dose and time adjustment are among the limitations of the study. The short

follow-up time of this study is another limitation. However, this study sheds light on future studies.

In conclusion, autologous PRP application provides short-term improvement in erectile function. Our findings suggest that larger studies as well as placebo-controlled studies are needed to add PRP to the treatment protocol in ED.

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STATEMENT OF AUTHORSHIP

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