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ORIGINAL RESEARCH & REVIEWS

ERECTILE FUNCTION

Platelet-Rich Plasma (PRP) Improves Erectile Function: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial

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ABSTRACT

Background: Animal studies postulate that platelet-rich plasma (PRP) injections improve key elements of the pathophysiologic mechanisms leading to erectile dysfunction (ED).

Aim: To conduct the first double-blind, randomized, placebo-controlled trial assessing the efficacy and safety of PRP injections in patients with mild and moderate ED.

Methods: Sixty sexually active patients with mild and moderate ED were randomly assigned to two sessions, with a one-month difference, of 10 mL PRP (n = 30) or placebo (n = 30) intracavernosal injections. An FDA-approved separation system was used. Patients were evaluated at 1, 3 and 6 months after completion of the treatment protocol. A per-protocol analysis was applied. All participants withheld any ED treatment during the trial.

Outcomes: The achievement of minimal clinically important difference (MCID) in the International Index of Erectile Function − Erectile Domain (IIEF-EF) from baseline to 6 months after final treatment. Erectile function at all time points, as well as safety of PRP injections, were also evaluated.

Results: At 6 months, a MCID was achieved by 20/29 (69%) patients in the PRP group compared to 7/26 (27%) in the placebo group. The risk difference between the two groups was 42% (95%CI: 18−66), $P < 0.001$ and the baseline-adjusted mean between-group-difference in the IIEF-EF score was 3.9 points (95%CI: 1.8−5.9). Similarly, a statistically significant difference of both the number of participants attaining a MCID and the IIEF-EF score was also observed at the 1- and 3-month evaluation between the two groups. Accordingly, patients receiving PRP were more satisfied with the treatment. No adverse events were observed during the study period.

Clinical implications: Intracavernosal PRP injection therapy used as outlined in this trial appears to be a safe and effective short-term treatment for the management of mild to moderate ED.

Strengths & Limitations: We conducted the first clinical trial exploring the role of PRP in the management of ED. Conversely, our findings lack external validity due to single-center design. Furthermore, our results cannot be extrapolated to other PRP separation systems.

Conclusions: PRP intracavernosal injections may be a promising addition to the urologist's armamentarium for the management of ED. Still, further high-quality studies are warranted to corroborate our findings. **Evangelos P, Mykoniatis I, Pyrgidis N, et al. Platelet-Rich Plasma (PRP) Improves Erectile Function: A Double-Blind, Randomized, Placebo-Controlled Clinical Trial. J Sex Med 2021;XX:XXX-XXX.**

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Key Words: Platelet-rich plasma; PRP; Erectile function; Erectile dysfunction; Randomized controlled trial

INTRODUCTION

Vasculogenic erectile dysfunction (ED) is a complex, multidimensional disorder that predominantly manifests due to reduced penile blood flow, arterial insufficiency or stenosis, as well as endothelial dysfunction.[1] Most recommended treatments improve erectile function by enhancing penile hemodynamics without reversing the pathophysiologic mechanisms leading to ED.[2]

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Platelet-rich plasma (PRP) is an autologous plasma fraction produced from the centrifugation of whole blood that contains a 3- to 7-times higher mean platelet concentration compared to whole blood.[3] Due to the beneficial properties of growth factors contained in high concentrations in this fraction, numerous medical specialties have included PRP injections in the quiver of their offered treatment options.[4–9] Recently, PRP intracavernosal injections emerged as a promising, angiogenic, vasculogenic and regenerative treatment modality for ED.[10] Animal studies postulate that PRP injections may improve key elements of the pathophysiologic mechanisms leading to ED through anti-inflammatory, reparative, neuroprotective and neurotrophic effects.[11–14] Still, these mechanisms are yet neither adequately explored nor completely understood.

Despite the favorable outcomes of PRP and the exploding interest in regenerative medicine, limited data support its use as part of the established ED therapeutic algorithm.[15–17] Given the paucity of human clinical trials, there is currently an unmet need for high-quality studies exploring the use of PRP for the management of ED.[18] In this scope, we conducted the first double-blind, randomized, placebo-controlled clinical trial aiming to assess the efficacy and safety of PRP injections versus placebo in patients with non-severe ED.

METHODS

Study Design

This study was a prospective, double-blind, randomized, placebo-controlled clinical trial performed at the outpatient clinic of the First Department of Urology, Aristotle University of Thessaloniki, Greece. The study protocol was approved by our institutional review board (protocol number: 15538/8-10-18) and registered at ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT04050020). This study was performed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement and all participants provided written informed consent before enrollment.[19] The study was supported by a research grant from the European Society for Sexual Medicine (ESSM). Patients were recruited from October 2019 to April 2020 and the final results were obtained in October 2020.

Selection Criteria

The predefined inclusion criteria were: (i) Sexually active male patients 40−70 years old in a stable, heterosexual relationship for more than 3 months; (ii) Use of any phosphodiesterase type 5 inhibitor (PDE5i) intake during the month before screening; (iii) Presence of mild or moderate ED after washout from PDE5i or any other ED treatment, documented with a score of 11−25 in the International Index of Erectile Function-Erectile Function (IIEF-EF) domain; (iv) Agreement to suspend all ED treatments for the duration of the study and; (v) Agreement to attempt sexual intercourse at least four times every month for the duration of the study, without being under the influence of alcohol or recreational drugs, and document the outcome using the Sexual Encounter Profile (SEP) diaries.

The predefined exclusion criteria were: (i) Previous major pelvic surgery or trauma; (ii) Previous major penile surgery or radiation; (iii) History of priapism, penile fracture, Peyronie's disease, penile curvature or any other anatomical disorder affecting erectile function; (iv) Abnormal morning serum testosterone levels (lower than 300 ng/dL or greater than 1197 ng/dL); (v) Psychogenic ED; (vi) History of any severe medical and psychiatric condition impairing participation in the study and; (vii) Subjects having partners that reported during the study period sexual dysfunction or any other major medical condition limiting sexual activity as well as those who presented with age less than 18 years, breastfeeding or pregnancy.

Study Protocol

At initial screening, all eligible patients underwent detailed medical history by two experienced physicians, extensive physical examination and appropriate medical tests. Subsequently, a 1-month washout from PDE5i or any other ED treatment was applied while patients were asked to attempt sexual intercourse at least four times and record outcomes in the SEP diaries. After this 1-month period, the SEP dairies were evaluated, and all patients completed the IIEF-EF questionnaire.[20] If patients were still eligible, they signed a written informed consent and were randomized in a 1:1 ratio to two sessions, with a one-month interval, of 10 mL PRP or normal saline injections. Randomization was performed according to a computer-generated sequence developed by the study coordinating team. To ensure allocation concealment and minimize selection bias, assignment to groups was communicated by the coordinating center (DK and PK) via a web-based registration system to a member of the research team (AF). One research team member (FZ) was only responsible for blood sampling and preparation of the injections. To ensure the double-blind character of our study, all injections were concealed by tinfoil to make their content invisible to both the participants and the investigators. Subsequently, the prepared injections were delivered by two experienced urologists of our research team (EP or IM) who were responsible for the administration of treatment.

All included patients underwent the first session of PRP or placebo injections within the same visit. An additional administration was performed one month after the initial session. Accordingly, participants were assessed at 1, 3 and 6 months after completion of the treatment protocol. PDE5i intake or other ED treatments were prohibited throughout the whole duration of the study. Treatment-induced pain was evaluated after the end of each visit with a Visual Analogue Scale (VAS) ranging from 0 (no pain) to 10 (intolerable pain). To assess the effect of PRP on erectile function, participants returned, at each visit, the completed SEP diaries for the last month and filled out the IIEF-EF. The number of patients attaining minimal clinically important difference (MCID) was measured. MCID was considered as an improvement in the IIEF-EF of 2 or more points in patients

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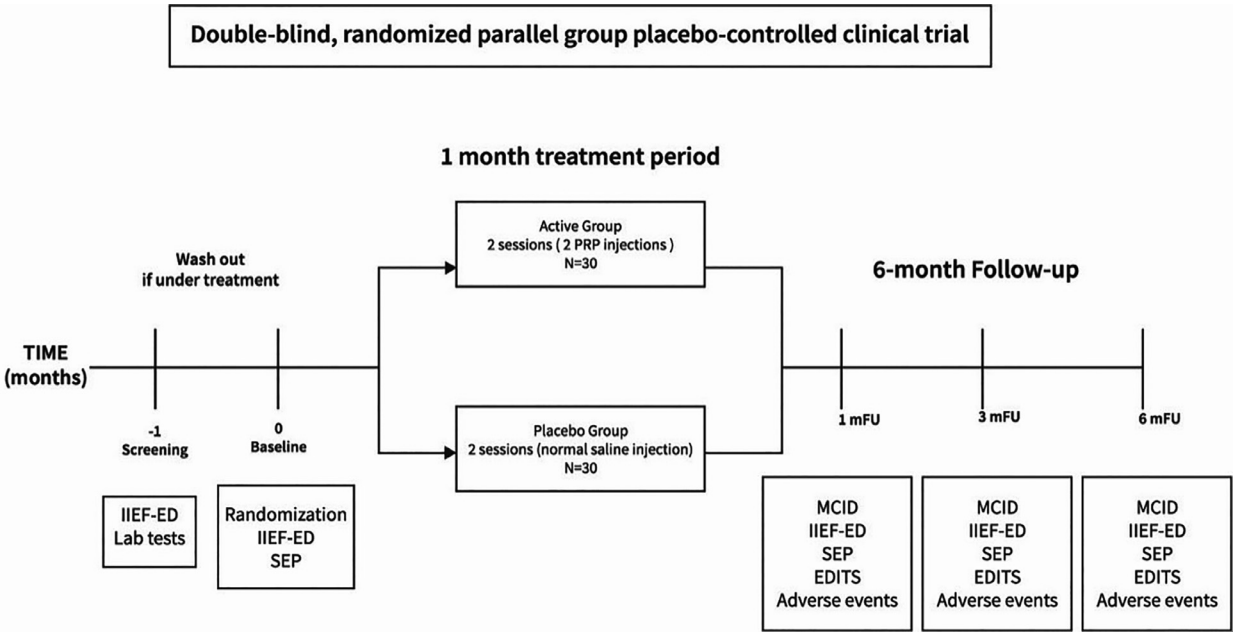

Figure 1. Study protocol.

EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; FU = Follow-up; IIEF-EF = International Index of Erectile Function-Erectile Domain; MCID = Minimal Clinically Important Difference; PRP = Platelet-Rich Plasma; SEP = Sexual Encounter Profile.

with mild or mild to moderate ED (IIEF-EF score: 17−25) or 5 or more points in patients with moderate ED (IIEF-EF score: 11−16) after treatment.[21] Additionally, to measure treatment satisfaction, all subjects completed the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) questionnaire.[22] At each follow-up visit, any adverse events were documented. The applied study protocol is depicted in Figure 1.

PRP Preparation and Administration

All patients underwent blood sampling in a 60 ml syringe containing 8 mL of anticoagulant. Preparation of PRP and placebo injections was performed in a separate room. Samples of patients randomized to placebo were dismissed and samples of patients randomized to PRP were processed by an FDA-approved autologous platelet separator (Magellan Autologous Platelet Separator; Arteriocyte Medical Systems, Hopkinton, MA) to yield approximately 10 mL of PRP. The Magellan Separator is a fully automated closed-loop processing system that requires limited intervention during processing. In particular, PRP is automatically separated from anticoagulated whole blood in approximately 15 minutes and dispensed into a separate sterile syringe. A comparative study among available commercial PRP separation systems has shown that the Magellan system offers high quality PRP.[23] One mL of PRP is used for a quality control analysis, while the remaining aliquot is ready for intracavernosal administration.

After preparation of the injection, patients were placed in a supine position and a penile tourniquet was clipped around the base of the penis. A total of 5 mL was infused in each corpus cavernosum − slowly retracting the needle for better distribution of PRP into the erectile tissue - over a 2-minute period to minimize platelet cell injury. The whole procedure was performed under sterile conditions without anesthesia. Following administration, additional compression of the penis was performed with a dressing placed around the penile shaft. The penile tourniquet was removed 20 minutes after the injections and patients were released. All patients were instructed to remove the compression bandage at home, 4 hours after the injection.

Outcomes

The primary outcome of our study was the proportion of patients in each group attaining MCID in the IIEF-EF domain from baseline to 6 months after the final treatment. Secondary outcomes included: (i) The proportion of patients in each group attaining MCID in the IIEF-EF domain from baseline to 1 and 3 months after final treatment; (ii) The mean change from baseline of the IIEF-EF between the two groups at 1, 3 and 6 months after final treatment; (iii) The mean change from baseline of positive responses to the question 3 of SEP between the two groups at 1, 3 and 6 months after final treatment; (iv) Treatment-induced pain and safety and possible side effects after PRP vs placebo injections.

Sample size calculation

Due to the lack of RCTs evaluating the role of PRP on ED, we, initially, performed a pilot study with 30 patients (15 in each group) to determine the appropriate sample size. This double-blind, placebo-controlled pilot study was conducted to compare the proportion of patients in each group attaining MCID in the IIEF-EF from

baseline to 6 months after the final treatment. In particular, at the 6-month evaluation, the proportion of subjects with MCID in the PRP group was 66.7% and in the placebo group 26.7%. Considering 80% statistical power and a 5% margin of error, we estimated a sample size of 23 participants per group. Assuming a 20% dropout rate, we recruited a total of 60 patients.

Statistical Analysis

We applied a per-protocol analysis. Categorical variables were estimated as frequencies with proportions, while continuous variables as mean ± standard deviation (SD) or median and interquartile range (IQR). We compared the categorical variables between the two treatment groups using the chi-squared (χ^2) and calculated their absolute risk difference with the 95% confidence intervals (CIs). Accordingly, we compared the continuous variables using the two-sample t-test or the Mann-Whitney test and estimated their mean differences with the corresponding CIs. Moreover, for continuous outcomes, the analysis of covariance (ANCOVA) was applied to assess the change from baseline between the two treatment groups, adjusting for the baseline value of each variable. Normality was evaluated both statistically with the Shapiro-Wilk test and visually with histograms, P-P and Q-Q plots. All statistical analyses were performed with the R statistical software (version 3.6.3) and two-sided *P*-values lower than 0.05 were considered statistically significant.

RESULTS

Patient Selection and Baseline Characteristics

We enrolled 60 patients that were allocated to either PRP (n = 30) or placebo (n = 30) injections and presented a median age of 58 (IQR: 51.5, 62) and 59 (IQR: 53.5, 61) years, respectively. The median ED duration was 78 (IQR: 48, 120) months in the PRP and 60 (IQR: 39, 117) months in the placebo arm. A total of 20 patients reported mild ED (PRP = 13, placebo = 7), 32 mild to moderate ED (PRP = 14, placebo = 18) and 8 moderate ED (PRP = 3, placebo = 5). No statistically significant differences were detected in the baseline characteristics between the two groups (Table 1). All participants underwent two sessions of PRP or placebo injections. Five participants, four in the placebo group and one in the PRP group, did not proceed for the follow-up evaluations due to the COVID-19 pandemic (dropouts not related to the study). The step-by-step study flow chart as well as the exact timepoint of each dropout are illustrated in Figure 2.

Minimal Clinically Important Difference in the IIEF-EF

Among participants presenting to the follow-up evaluations, 22/29 (76%) patients attained a MCID in the PRP group compared to 7/28 (25%) in the placebo group ($p < 0.001$) at 1 month. At this time point, 51% (95% CI: 29 to 73) more patients treated with PRP injections developed a MCID in the IIEF-EF scale compared to placebo. At 3 months, 20/29 (69%) patients achieved a MCID in the IIEF-EF scale after PRP injections versus 10/26 (39%) after placebo ($P = 0.018$). Therefore, 30 per 100 (95% CI: 5.3 to 56) additional subjects treated with PRP injections attained a MCID in the IIEF-EF scale compared to placebo. At 6 months, 20/29 (69%) patients reported a MCID in the IIEF-EF scale with PRP injections versus 7/26 (27%) with placebo ($P < 0.001$) and the risk difference between the two groups was 42% (95% CI: 18 to 66). All relevant statistical analyses are available in Table 2 and the raw data of all participants in Appendix 1.1.

Table 1. Baseline characteristics of the study participants

Baseline characteristics	Overall, n = 60	PRP, n = 30	Placebo, n = 30	*P-value*
Age (years)	58.5 (52.8, 62)	58 (51.5, 62)	59 (53.5, 61)	*0.92*
BMI (Kg/m^2)	28.6 (26.4, 31.6)	29.4 (26.6, 32.1)	28.5 (26, 30.4)	*0.26*
Smoking	35 (58%)	16 (53%)	19 (63%)	*0.60*
Hypertension	18 (30%)	10 (33%)	8 (27%)	*0.78*
Diabetes	15 (25%)	11 (37%)	4 (13%)	*0.074*
Hyperlipidemia	21 (35%)	12 (40%)	9 (30%)	*0.59*
CHD	7 (12%)	5 (17%)	2 (6.7%)	*0.42*
Testosterone (ng/dl)	507.5 (367.8, 581.8)	510.5 (428, 608.8)	448.5 (360.9, 563)	*0.21*
ED duration (months)	66 (48, 120)	78 (48, 120)	60 (39, 117)	*0.68*
ED severity				*0.25*
Mild	20 (33%)	13 (43%)	7 (23%)	
Mild to moderate	32 (54%)	14 (47%)	18 (60%)	
Moderate	8 (13%)	3 (10%)	5 (17%)	
IIEF-EF	19.9 ± 3.3	20.4 ± 2.9	19.4 ± 3.7	*0.28*
SEP Question 3 (Yes %)	46.7 ± 21.3	47.5 ± 20.1	45.8 ± 22.8	*0.77*

Statistics presented as mean ± SD or median (IQR).

BMI = Body Mass Index; CHD = Coronary Heart Disease; ED = Erectile Dysfunction; IIEF-EF = International Index of Erectile Function-Erectile Function; IQR = Interquartile Range; PRP = Platelet-Rich Plasma; SEP = Sexual Encounter Profile.

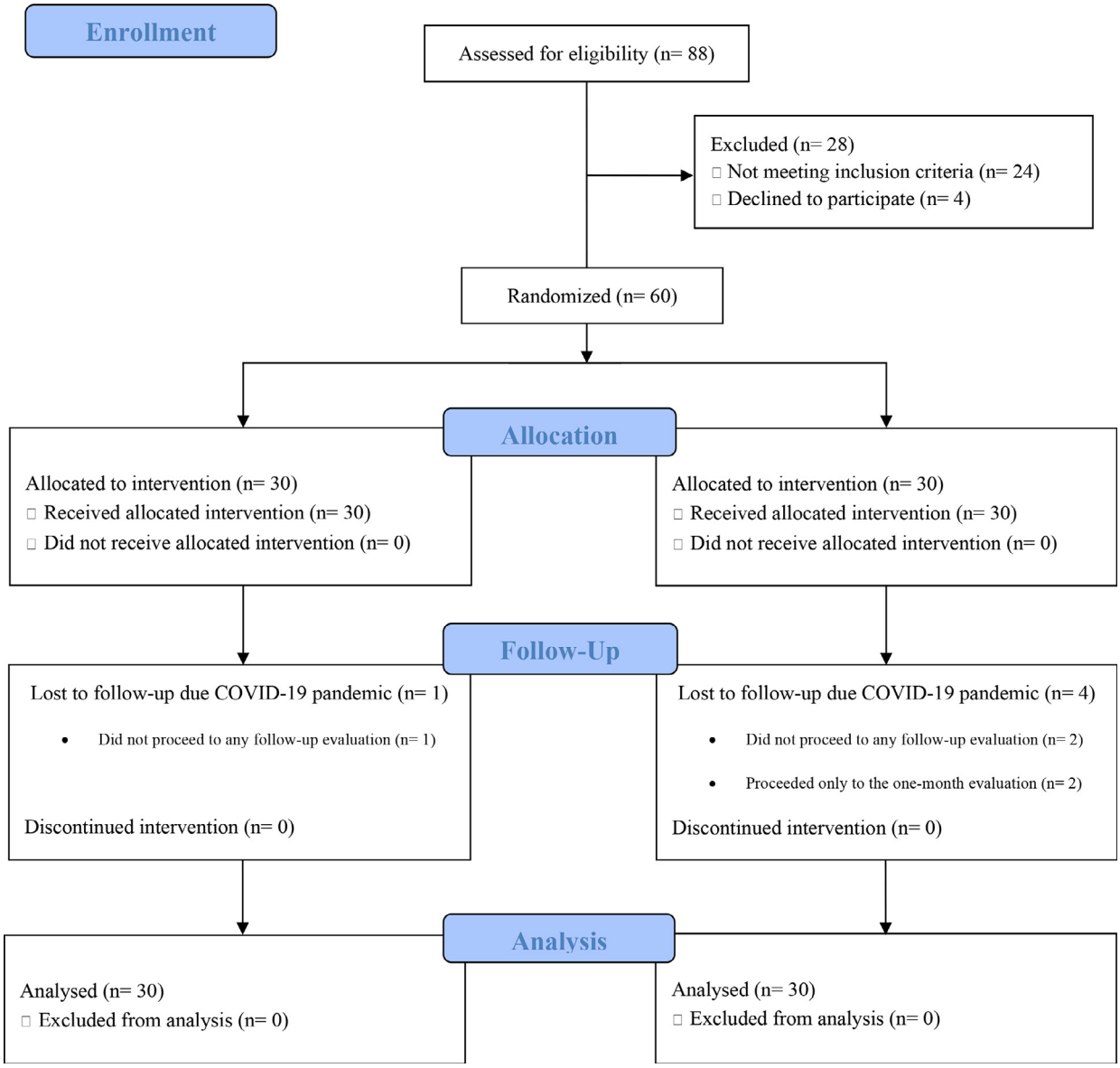

Figure 2. Study flow chart.

Erectile Function

At the baseline evaluation, the score of the IIEF-EF questionnaire and the proportion of "yes" responses to question 3 of SEP diaries did not differ between the two groups. PRP injections resulted in a statistically significant improvement of both the IIEF-EF and "yes" responses to SEP question 3 at all follow-up evaluations compared to placebo. The scores of the two questionnaires at all time points are presented in Figure 3a and 3b. In particular, adjusting for the baseline value, IIEF-EF domain score improved by 2.7 points (95% CI: 0.9 to 4.5, P = 0.004) at 1

Table 2. Comparative data of the two groups about patients attaining MCID in the IIEF-EF at the follow-up evaluations

Patients with MCID in the IIEF-EF	PRP	Placebo	RD (95% CI)	*Between-group p-value*
1month	22 / 29 (76%)	7 / 28 (25%)	51% (29, 73)	*<0.001*
3 months	20 / 29 (69%)	10 / 26 (39%)	30% (5.3, 56)	*0.018*
6 months	20 / 29 (69%)	7 / 26 (27%)	42% (18, 66)	*<0.001*

The bold cells indicate statistically significant p-values.
CI = Confidence Interval; ED = Erectile Dysfunction; IIEF-EF = International Index of Erectile Function - Erectile Function; MCID = Minimal Clinically Important Difference; PRP = Platelet-Rich Plasma; RD = Risk Difference.

month, 2.8 points (95% CI: 0.4 to 5.2, $P = 0.023$) at 3 months and 3.9 (95% CI: 1.8 to 5.9, $P = < 0.001$) at 6 months in patients treated with PRP compared to placebo. Similarly, the proportion of positive answers to question 3 of SEP improved by 19.4% (7.3 to 31.6, $P = 0.002$) at 1 month, 17.9% (2.1 to 33.6, $P = 0.028$) at 3 months and 28.6% (14.4 to 42.8, $P < 0.001$) at 6 months. All measures and comparisons can be seen in Table 3 and the corresponding raw data of all participants in Appendix 1.1 and 1.2.

Satisfaction and Safety

Patients receiving PRP injections were more satisfied with treatment and outcomes compared to placebo. In particular, the EDITS score after PRP compared to placebo was 62.7 ± 27.7 vs 34.5 ± 17, $P < 0.001$ at 1 month, 62.2 ± 27.4 vs 38.5 ± 24.3, $P < 0.001$ at 3 months and 63.2 ± 24.6 vs 32.8 ± 24, $P < 0.001$ at 6 months. Regarding treatment-induced pain, the mean VAS score of the two sessions was higher in patients undergoing placebo injections compared to PRP (2.6 ± 0.4 vs 2.2 ± 0.6, respectively, $P = 0.008$). No transient hemorrhagic adverse events (hematuria, local petechial bleeding or ecchymosis) or other side effects were reported during the injection and follow-up period in both groups. All relevant raw data are illustrated in Appendix 1.2.

DISCUSSION

Our findings demonstrate that intracavernosal injections with PRP are a safe and effective treatment modality for the management of non-severe ED. Based on our results, two sessions of PRP led to a statistically significant improvement of the erectile function compared to placebo and this effect was maintained for 6 months. More than two-thirds of participants in the active arm presented a MCID in the IIEF-EF scale at all follow-up evaluations, demonstrating that the improvement in erectile function may be clinically important. Furthermore, no major or minor adverse events occurred during the treatment and follow-up period. Of note, subjects receiving PRP displayed higher satisfaction rates compared to placebo, while subjects receiving placebo injections reported more pain during treatment.

To our knowledge, the present study is the first prospective, double-blind, randomized, placebo-controlled clinical trial evaluating the efficacy and safety of PRP intracavernosal treatment for ED. The beneficial effect of PRP injections on erectile function was demonstrated based on the measures of the three most established questionnaires in the literature: the IIEF-EF domain, the SEP diaries and the EDITS. Similarly, this beneficial effect remained significant compared to placebo or to baseline across multiple analyses at the short- and long-term evaluations. In terms of satisfaction assessed with the EDITS index score, the significant difference of PRP treatment versus placebo exceeded ten points, which is considered the benchmark for achieving a MCID.[24] Accordingly, the mean VAS pain score after each PRP session was relatively low indicating that PRP intracavernosal injections represent a patient-friendly ED treatment modality. Besides, the increased VAS score after normal saline injections versus PRP may rather be clinically irrelevant.

Still, the findings of the present study should be interpreted with caution in the context of some limitations. First of all, our results lack external validity as we performed a single-center clinical trial with strict eligibility criteria, relatively small number of participants and rather short follow-up. It should be stressed that the five dropouts, although not related to the study, might still have affected our findings. Since we could not handle missing data by applying the last-observation-carried-forward method due to the early time point of most dropouts or by performing a multiple imputation method due to the relatively small number of participants, we undertook a per-protocol analysis. Of interest, given that the sample size of our study was estimated based on the total number of participants with non-severe ED expected to attain a MCID in the IIEF-EF, our study was underpowered to perform any comparisons in patients with different degrees of ED (mild, mild to moderate, moderate). Moreover, it should be highlighted that the concentration of platelets and growth factors in a PRP fraction is predominantly based on the system used for its preparation.[23] Since we performed all PRP preparations with the Magellan Autologous Platelet Separator, our results cannot be extrapolated to other PRP separation systems. Accordingly, even though we performed a quality control analysis of all PRP samples, we did not evaluate the qualitative or quantitative composition of growth factors, cytokines or other molecules with regenerative properties. Therefore, the exact mechanism through which PRP improves erectile function remains unknown.

Indeed, to date, no consensus exists regarding the optimal platelet concentration in the PRP.[25] Some studies report that the therapeutic effect of PRP requires platelet concentrations greater than 200,000/ μL, while others greater than 1,000,000/ μL.[26] Based on the previous notion, PRP separation systems are divided into high- (platelet concentrations about 750,000/ μL) and low- (platelet concentrations about 500,000/ μL) yielding devices.[27] The Magellan Autologous Platelet Separator used in our trial is considered a high-yielding device and, therefore, produces higher concentrations of platelets and, in turn, molecules with regenerative properties.[23]

The beneficial effect of PRP in the regenerative and wound healing process is predominantly exerted through high concentrations of platelets and growth factors.[28,29] In particular, platelets contain multiple regenerative molecules such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF-1) and fibroblast growth factor (FGF), that improve angiogenesis stimulation, stem cell recruitment and inflammatory.[30] Regarding ED, in rat models with cavernosal nerve injury, PRP seems to improve erectile function by regenerating cavernosal nerves and by increasing nitric oxide synthesis, indicating that PRP may be effective for neurogenic ED.[11,12,31,32] Hence,

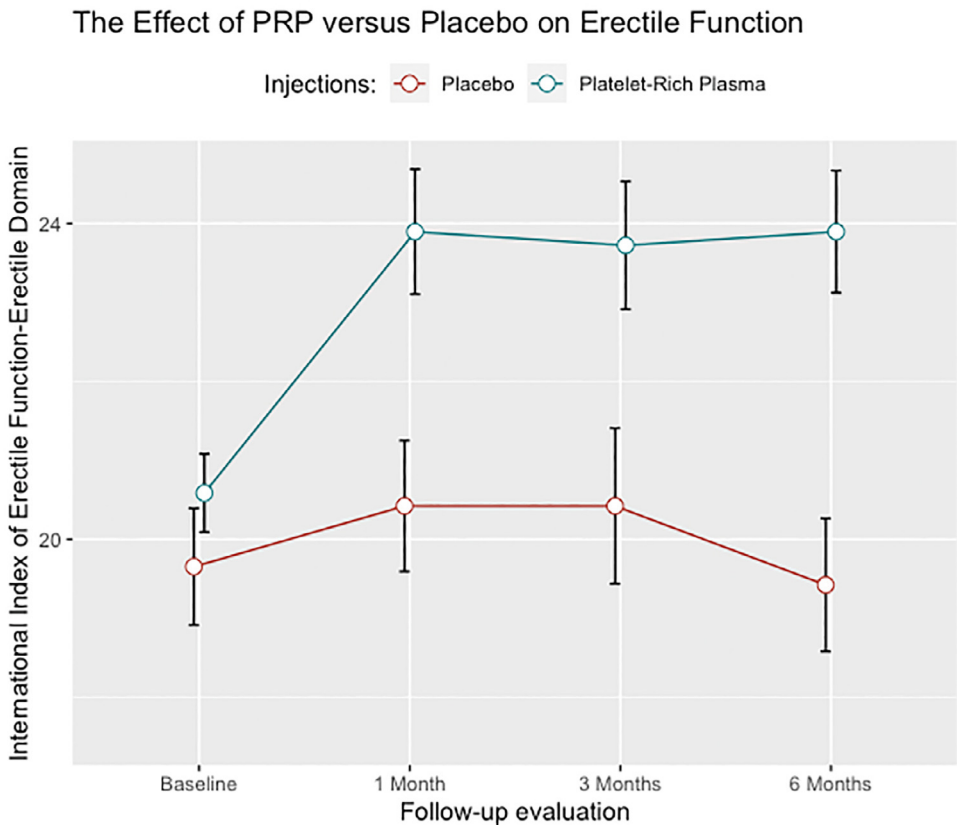

Figure 3a. The effect of PRP versus placebo on IIEF-EF. PRP = Platelet-Rich Plasma.; IIEF-EF = International Index of Erectile Function-Erectile Domain.

even though it is suggested that PRP might restore penile blood flow and regenerate smooth muscle cells, to date, no basic research study has evaluated the effect of PRP on vasculogenic ED.[15]

Despite the accumulating evidence from molecular and animal studies, limited data suggest the use of PRP in everyday clinical practice.[10] In two previous studies from a center in Russia, patients with ED were randomized to (i) three sessions of activated with 10% $CaCl_2$ intracavernosal PRP injections once weekly (Group 1, 30 patients); (ii) the same regime of PRP combined with PDE5i (Group 2, 30 patients) or; (iii) inactivated PRP once weekly for three weeks (Group 3, 15 patients). Across all groups and time points, a significant improvement in the erectile function compared to baseline was demonstrated and no adverse events were reported.[33] Moreover, the authors concluded that PRP contains the necessary concentration of growth factors for a therapeutic effect.[17] Nevertheless, in these studies, no placebo arm existed, and no long-term evaluations were performed.

Matz et al. examined retrospectively the safety and feasibility of the platelet-rich fibrin matrix (PRFM) in four patients with ED, eleven with Peyronie's disease and one with concomitant Peyronie's disease and ED. Among seven patients evaluated with the IIEF-5, the IIEF-5 increased by a mean of 4.14 points, while no major adverse events were reported in all patients.[16] Still, the absence of a comparator and the methodological concerns of the study limited the extrapolation of its findings.

Ruffo et al. assessed in two trials published as conference abstracts the effect of PRP combined with low-intensity shockwave therapy (LiST). In the first study, 100 patients received LiST twice weekly for 6 weeks alone (Group 1, 58 patients) or in combination with PRP injections once weekly for 6 weeks (Group 2, 55 patients).[34] In the other study, 112 patients received LiST once weekly for 6 weeks alone (Group 1, 53 patients) or in combination with PRP injections once every 2 weeks for 6 weeks (Group 2, 59 patients).[35] In both trials, at 12 and 24 weeks, combination treatment significantly improved erectile function compared to baseline or LiST monotherapy. Nevertheless, despite the fact that the mechanism of actions of shockwaves and PRP seem complimentary, well-designed placebo-control trials are needed to reach conclusions on such combination treatment.

In the post-PDE5i era, regenerative treatment modalities such as PRP, LiST as well as gene and cellular-based therapies have emerged as promising options for the management of ED.[36] Even though ten review articles stress the potential benefits of PRP on ED,[10,15,28,37–43] limited, human and translational

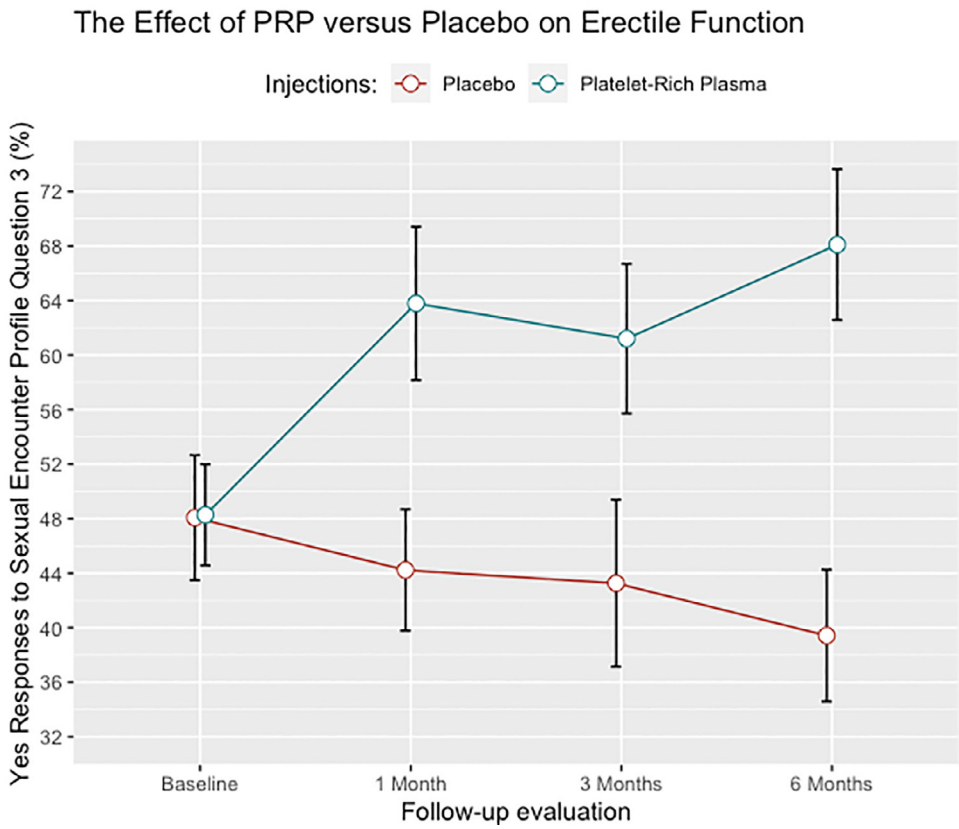

Figure 3b. The effect of PRP versus placebo on SEP Question 3 "Yes" response rate (%). PRP = Platelet-Rich Plasma.; SEP = Sexual Encounter Profile.

studies exist. However, there is an increasing number of relevant ongoing clinical trials and their outcomes are expected with great interest. The design of all registered clinical trials is summarized in Appendix 2. Nevertheless, future studies should produce evidence on PRP systems, preparation, composition, administration and frequency for the management of ED. Additionally, well-conducted molecular and animal studies may further elucidate the pathophysiological mechanisms of PRP leading to erectile function improvement in models with vasculogenic ED. Accordingly, trials assessing the efficacy of PRP as part of monotherapy or combination treatment for ED are deemed necessary. In particular, trials comparing PRP to PDE5i, LiST or other recommended ED treatments, as well as trials assessing the synergic effect of PRP with such recommended treatments are needed to determine the ideal therapeutic approach in patients with ED.

Table 3. Comparison of changes from baseline in the IIEF-EF and SEP Question 3 after PRP injections versus placebo unadjusted and adjusted for the baseline evaluation

Parameter		PRP Mean ± SD	Placebo Mean ± SD	Unadjusted mean difference (95% CI)	Adjusted mean difference (95% CI)	*Adjusted between-group p-value*
IIEF-EF	Baseline – 1 month	3.3 ± 3.8	0.8 ± 3	2.5 (0.7 to 4.3)	2.7 (0.9 – 4.5)	*0.004*
	Baseline – 3 months	3.1 ± 4.1	0.8 ± 5	2.4 (-0.1 to 4.9)	2.8 (0.4 – 5.2)	*0.023*
	Baseline – 6 months	3.3 ± 4	-0.2 ± 3.8	3.5 (1.4 to 5.7)	3.9 (1.8 – 5.9)	*<0.001*
SEP Question 3 (Yes %)	Baseline – 1 month	15.5 ± 28.7	-3.6 ± 17.6	19.1 (6.5 to 31.7)	19.4 (7.3 – 31.6)	*0.002*
	Baseline – 3 months	12.9 ± 28.3	-4.8 ± 33.9	17.7 (0.6 to 34.9)	17.9 (2.1 – 33.6)	*0.028*
	Baseline – 6 months	19.8 ± 28.6	-8.7 ± 29.1	28.5 (12.8 to 44.1)	28.6 (14.4 – 42.8)	*<0.001*

The bold cells indicate statistically significant p-values.
CI: Confidence Interval; IIEF-EF: International Index of Erectile Function - Erectile Function; SD: Standard deviation; SEP: Sexual Encounter Profile.

CONCLUSION

Our findings demonstrate that two PRP intracavernosal injections within a one-month interval were safe and effective for the improvement of erectile function in patients with mild and moderate ED. Overall, PRP intracavernosal injection treatment, as a new representative of the flourishing field of regenerative medicine, seems to be a promising addition to the urologist's armamentarium. Nevertheless, before it is accepted as part of the ED algorithm, further high-quality studies are warranted to corroborate our findings.

AUTHOR CONTRIBUTIONS

All authors participated in the drafting, writing, and editing of the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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STATEMENT OF AUTHORSHIP

Poulios Evangelos: Methodology, Investigation, Writing – Original Draft, Writing – Review & Editing; Ioannis Mykoniatis: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Funding Acquisition; Nikolaos Pyrgidis: Methodology, Writing – Review & Editing; Filimon Zilotis: Investigation, Data Curation; Paraskeui Kapoteli: Data Curation, Project Administration; Dimitrios Kotsiris: Investigation; Dimitrios Kalyvianakis: Investigation, Writing – Review & Editing; Dimitrios Hatzichristou: Conceptualization, Funding Acquisition, Supervision.

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SUPPLEMENTARY MATERIALS

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