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ORIGINAL ARTICLE

Regenerative treatment with platelet-rich plasma in patients with refractory erectile dysfunction: short-term outcomes and predictive value of mean platelet volume

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ABSTRACT

BACKGROUND: The vast majority of erectile dysfunction (ED) treatments are currently symptomatic and do not influence disease progression. Regenerative medicine may potentially reverse or stop the progression of complicated ED by restoring erectile capacity. We aimed to evaluate potential safety and effectiveness and the clinical correlates of platelet function before platelet-rich plasma (PRP) injection in men with vascular ED unresponsive to phosphodiesterase-5 inhibitors (PDE-5is).

METHODS: A number of 150 patients with vascular ED were enrolled in an open-label, single arm, multicenter, prospective, interventional, non-randomized study. After 1-month pharmacological washout from PDE-5is, the 5-item International Index of Erectile Function (IIEF-5) questionnaire was administered and dynamic penile duplex ultrasound (d-PDU) was performed. Patients then underwent intracavernous PRP injection. One month after treatment, IIEF-5 and d-PDU were evaluated. Primary aim of the study was to assess efficacy and safety of PRP treatment by evaluating the proportion of patients achieving minimal clinically important differences (MCID) in the IIEF-5 questionnaire. Secondary endpoint was to determine whether MPV could correlate with improvement in d-PDU parameters.

RESULTS: Most patients (80%) had a significant improvement in ED symptoms (IIEF-5 Score: 12±2.6 *vs.* 19±3.0; P<0.0001) and in PSV (32±3.5 cm/s *vs.* 42±7.6 cm/s; P<0.0001) after d-PDU evaluation. The ROC curve analysis showed a significant accuracy (72.1%, CI: 64.0-80.2, P≤0.0001) for MPV in identifying men clinically responding to PRP with favorable MCID≥5 at 1 month follow-up. The MPV<8.95 fL was identified as the best predictor of success rate with a sensitivity of 90% and a specificity of 54.1%.

CONCLUSIONS: This study provides the first evidence that PRP could represent an effective and safe option for patients poorly responding to PDE-5is. MPV higher than 8.95 fL may identify patients with poor response to treatment that might benefit of successive re-challenge with PRP.

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KEY WORDS: Platelet-rich plasma; Mean platelet volume; Erectile dysfunction.

Erectile dysfunction (ED) is a highly complex and multifactorial disorder that begins with endothelial dysfunction (EDfs), which is caused by reduced penile blood flow, arterial insufficiency or stenosis.[1]

The vast majority of modern and recommended treatments can enhance erectile function by increasing blood flow without any influence on the underlying disease or on the pathophysiologic mechanisms leading to ED.[2, 3] ED is a prevalent sexual disorder among adult males and it has been traditionally associated with lower testosterone levels reported in elder males.[4] However, recent epidemiological studies suggest an increasing incidence of ED in men younger than 40 years.[5] Due to the complexity of erection, there are many potential mechanisms that can be involved; therefore, it is crucial to identify the specific causes of ED.[6] Advances in diagnostic and treatment modalities offer opportunities to identify and manage young men with ED.[5]

Furthermore, a growing number of patient suffering from vascular ED are becoming non responder to the common treatment such as phosphodiesterase-5 inhibitors (PDE-5is).[7] Recently, alternative therapeutic strategies have been explored to treat non-responsive patients with vasculogenic ED.[3]

Platelet-rich plasma (PRP) is an autologous plasma fraction produced from the centrifugation of whole sample of blood that contains an average of 3- to 7-times higher mean platelet concentration compared to whole blood.[8]

PRP injections became a treatment option in various medical fields, especially in orthopedics', because of the high concentration of growth factors they contain,[9] such as, vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF).[10] Several studies have demonstrated the potential of these growth factors in improving erectile function in both preclinical and clinical studies.[11] Recently, there is a growing number of scientific studies supporting the use of intracavernousal PRP injections as a promising, angiogenic and regenerative treatment modality for ED.[10]

Multiple studies in animal models postulate that PRP injections have the potential to improve the pathophysiologic mechanisms leading to ED through several mechanisms: anti-inflammatory, reparative, neuroprotective and neurotrophic effects. PRP seems able to promote the healing of soft and hard tissue accelerating the repair of aged and damaged tissue.[12, 13] However, the complete mechanisms of action and their long-term effects are not completely understood. Despite all the favorable outcomes of PRP in regenerative medicine, limited data supports its use for the treatment of ED. Further clinical studies involving larger samples are required to better define effectiveness and safety of PRP injections.[14]

For this purpose, we conducted a study involving a large sample of subjects affected by vascular ED who did not respond to the conventional ED treatments with PDE-5is. The primary objective of this study was to assess the efficacy and safety of a single injection of PRP in regenerating compromised penile cavernous arteries in patients suffering ED of any severity. Secondary endpoint was to understand any potential correlates between platelet morphology, specifically MPV, at baseline and the clinical outcomes of PRP treatment.

Materials and methods

Study protocol

We conducted an open-label, single arm, multicenter, prospective, interventional, non-randomized study. The data utilized in the present study were collected as "secondary outcome" from an ongoing perspective protocol, approved from local ethical committee. All centers adhered to a standardized protocol, according with manufacturer instructions, to make results comparable. Data were collected in a shared database. The study was conducted between February 2022 and February 2023 in accordance with the Declaration of Helsinki and was approved by the Internal review Board (protocol number 313/2020). Patients were treated in accordance with local blood and transfusion centers that accepted the production and use of autologous PRP for non-transfusional purpose due to the lack of treatment for non-responder ED at the common treatments

like PDE-5 inhibitors. Written informed consent was obtained from all subjects. All patients provided consent to share their anonymized information for the current study as well as future research purposes.

All eligible patients underwent a comprehensive assessment including a detailed medical history, physical examination and appropriate blood cell count. Following a 1-month washout period from PDE-5is, or any other ED treatment, IIEF-5 questionnaire was administrated, and d-PDU was performed. Only patients with diagnosed vascular ED entered the study and underwent the PRP intracavernous injection within two-week timeframe. After one-month post treatment period, the IIEF-5 questionnaire was administered again and a new vascular study with d-PDU was performed.

The primary outcome of the study was to determine the improvement in the IIEF-5 questionnaire score defined by a minimal clinically important difference (MCID)≥5[15] and to determine the eventual improvements observed in d-PDU parameters.

Study population

Out of 450 patients screened only 150 were eligible for the study (Table I).

Inclusion criteria for entering the study were:

• sexually active male patients older than 18ys-old, defined by self-reported sexual activity;

• only non-responder patients to the use of phosphodiesterase type 5 inhibitor (PDE-5i) intake during the three months before screening. Patients were classified as non-responders to PDE-5is if they had properly taken at least two different medications at the maximum dose for a minimum of 4 times;

• normal blood platelet number defined by a range of 150-400 x10^3/mcl;

• normal hormonal serum profile (total testosterone, prolactin, thyroid function tests). The following ranges were used as normal references for the analyses: 8.35-28.67 nmol/L (testosterone), 2.1-17.7 ng/mL (prolactin), 0.55-4.78 μIU/mL (thyroid stimulating hormone [TSH]) and 0.70-1.76 ng/dL (free thyroxine [fT4]);

• presence of ED documented both with a score of 5-item International Index of Erectile Function (IIEF-5) between 6 and 21 (normal value >22) and vascular PSV<35 cm/s (normal value >35 cm/s) in at least one cavernous artery at penile Doppler ultrasound (PDU);

• agreement to suspend all ED treatments for the duration of the study;

• agreement to attempt sexual intercourse at least four times a month for the duration of the study, without being under the influence of alcohol or recreational drugs.

Exclusion criteria were:

• previously non-nerve-sparing prostatectomy;

• not controlled metabolic disease (diabetes with glycated hemoglobin >7% (normal value <7%), hypertensions with systolic blood pressure >140 mm/Hg (normal value <140 mmHg) and/or diastolic blood pressure >90 mm/hg (normal value <90 mmHg);

• previous history of priapism or severe penile deviation (>45°);

• low serum testosterone levels (lower than 320 ng/dL);

• high prostate specific antigen (PSA) values (Total PSA >4 ng/mL);

• psychogenic ED (assessed with PDU normal velocities values);

TABLE I.—*Characteristics of the sample at baseline and after the treatment.*

	BMI (kg/m^2)	Age (years)	IIEF-5 pre-treatment	IIEF-5 post-treatment	MPV (fL)	PSV pre-treatment (cm/s)	PSV post-treatment (cm/s)
Minimum	18	18	6	11	7.00	19.00	26.00
25° perc.	20	30	10	16	8.30	27.45	37.75
Median	25	51	12	19	9.30	32.20	42.10
75° perc.	30	61	14	21	10.13	36.30	45.20
Maximum	37	73	16	24	11.90	45.00	65.00

IIEF-5: 5-Item International Index Of Erectile Function; MPV: mean platelet volume; PSV: peak systolic velocity.

• any history of psychiatric condition impairing participation in the study;
• any history of pelvic surgery or radiotherapic treatment;
• any history of hematological diseases;
• ESWT therapy in the previous year;
• age less than 18 years old.

Penile blood flow studies

In all patients, the d-PDU parameters were evaluated after a pharmacological stimulation test with 10 mcg prostaglandin-1 (PGE-1) and subsequent audiovisual sexual stimulation, as previously described.[16] Flow parameters included peak systolic velocity (PSVs), end diastolic velocities (EDVs) and Resistance Index (RI). The ultrasound evaluation of the cavernous arteries was conducted with a dedicated ultrasound for vascular studies using broadband linear array transducer and power-Doppler software.[17] Vascular ED was determined by the presence of an impaired blood inflow in at least one of cavernous arteries (PSV≤35 cm/s) after 20 min of maximal pharmacological stimulation.[18]

PRP preparation and administration

Before the PRP injection, the patients were prepared by disinfection of the injection site using alcohol-based solutions. PRP was prepared under the supervision of the last author (A.A.). A small volume of autologous venous blood was obtained by venipuncture (20 mL). A complete blood cell count and cell volume (MPV) was obtained separately from a 3ml vial performed by standard automated hematology analyzer. Tubes contained an anticoagulant (usually acid citrate dextrose or sodium citrate solution). PRP was obtained through a process of centrifugation 6 vials of entire blood at 1500 rpm for fifteen minutes according to the manufacturer indication (regenLAB®, En Budron b2, 1052 Le Mont-sur-Lausanne, Swiss)[19] which separates the whole blood into its different components depending on their different density gradients – red bloods cells, leucocytes, and platelet. After the centrifugation the upper-most PRP layer was removed. The specific layer, containing the highest concentration of platelets, was then extracted and injected into the corpora cavernosa (mean volume 8.1±1.8 mL PRP)[20] as soon as it was prepared. A topical anesthetic cream containing 25 mg lidocaine and 25 mg prilocaine, was the applied to the site of injection. Finally, a rubber band was applied around the penile root which was removed 20 minutes after the injection. Using a 10 mL syringe (25Ga needle), 5 mL of PRP was injected into each corpora cavernosa at two different lateral sites, 1 cm distal to mid-penile shaft (Figure 1).

Statistical analysis

Normally distributed data are expressed as means±standard deviation (SD) while non-parametric data are expressed as median. Kolmogorov-Smirnov Test has been used to assess the parameter distribution while paired *t*-test and Wilcoxon Test were employed to evaluate normally distributer and non-parametric data, re-

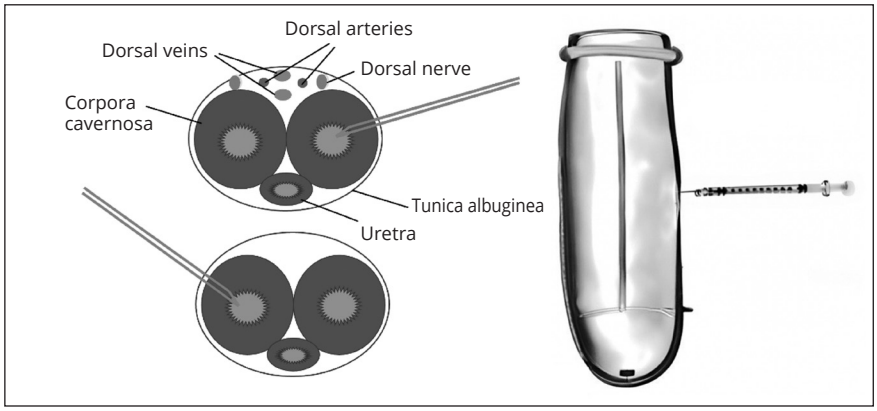

Figure 1.—A) Schematic figure of injection site; B) intracavernous injections (injections need to be bilateral) latero lateral view.

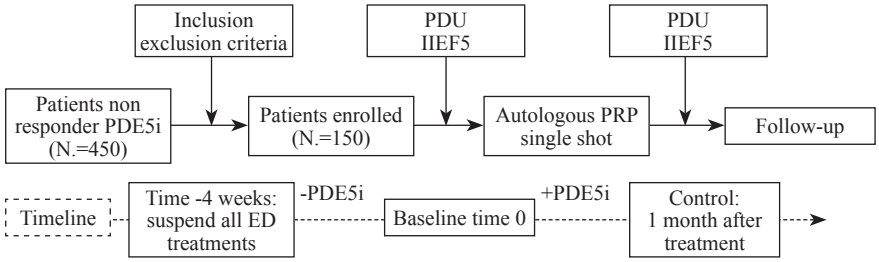

Figure 2.—Study flow-chart.
PDE-5is: phosphodiesterase type 5 inhibitors; ED: erectile dysfunction; PDU: penile dynamic ultrasound; IIEF-5: 5-Item International Index of Erectile Function.

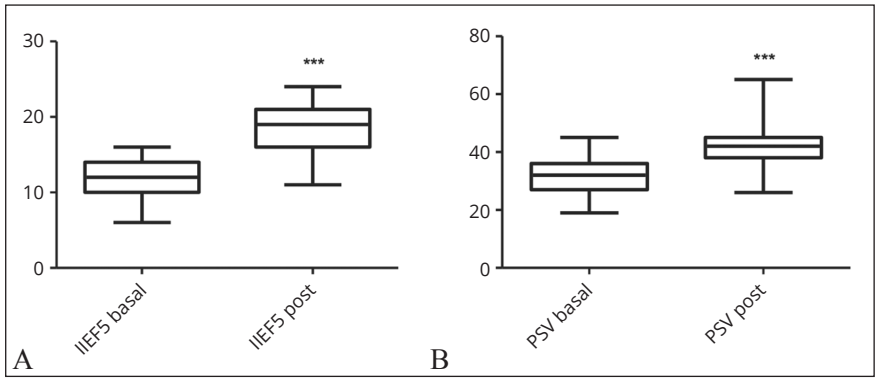

Figure 3.—Variation of A) 5-item international index of erectile function (IIEF-5) Score (P<0.0001); and B) PSV (peak systolic velocity - cm/second, P<0.0001) before and after the treatment.

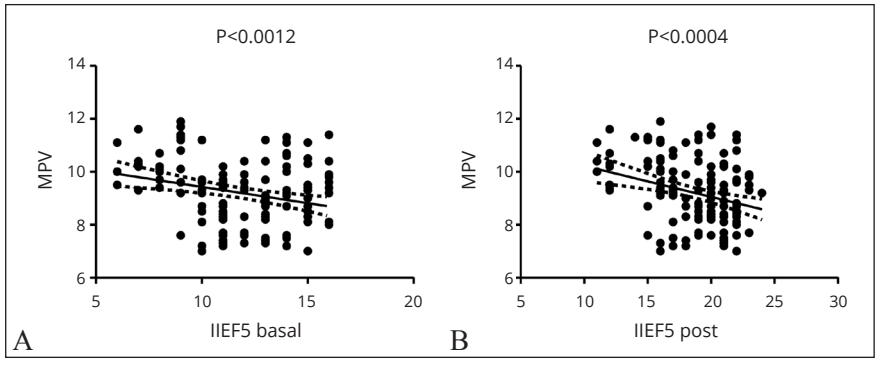

Figure 4.—Correlation between 5-item International Index of Erectile Function (IIEF-5) Score and mean platelet volume (MPV – fl). A, B) Pre- and post-treatment (respectively =P<0.0012 and P<0.0004).

spectively. Clinical and biochemical data were compared before and after treatment. Statistical analysis was performed using software SPSS 21.0 (SPSS Inc., Chicago, IL, USA). A P value <0.05 was taken as statistically significant.

Results

A total of 150 subjects (age: 51±16.7), who met the study's inclusion and exclusion criteria were enrolled. All patient completed the scheduled evaluations and concluded the study, with a follow-up period of one month as showed in the flow-chart (Figure 2).

No serious adverse events were recorded during all the study, however 16 subjects experienced dull pain during injections and 2 patients reported a slight subcutaneous hematoma at the injection site the day after the procedure. In both cases it completely disappeared after 3 days. Characteristics of the sample, before and after treatment, are summarized in Table I.

After one month following a single shot of PRP 80% of patients returned back to sexual activity by using PDE-5is and achieved an improvement in IIEF-5 questionnaire (12±2.6 pre-treatment *vs.* 19±3.0 post-treatment; P<0.0001, Figure 3A) as scored by MCID. Moreover, a sig-

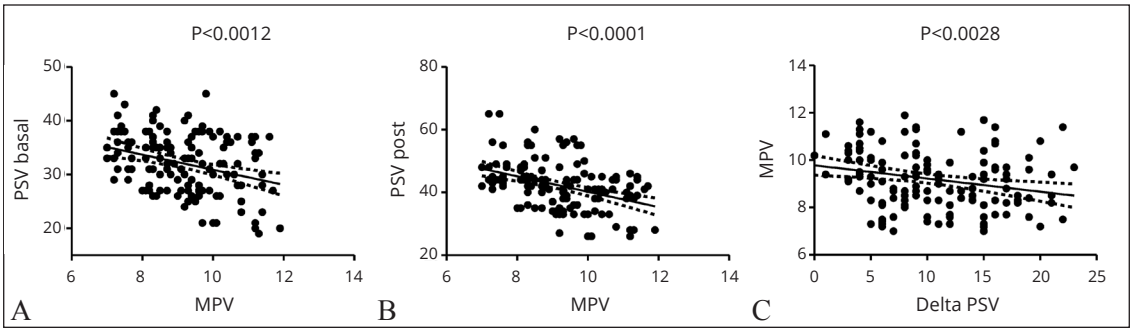

Figure 5.—Correlation between mean platelet volume (MPV – fl) and (A) basal PSV (peak systolic velocity cm/second) (P<0.0001); B) post-treatment PSV (P<0.0001); and C) delta variation between basal and post treatment PSV (P<0.0028).

TABLE II.—*Linear regression shows that PRP treatment on vascular erectile dysfunction (ED) is a dependent variable correlated to mean platelet volume (MPV – fL), delta PSV (ΔPSV) variation between pre- and post-treatment show a strong significancy (P<0.008).*

Model	Coefficient *				
	Non-standard model		Standard coefficient		
	B	Se	Beta	T	Sign.
(Constant)	14.137	0.819		17.267	0.000
IIEF-5 pre	-0.091	0.042	-0.194	-2.182	0.031
IIEF-5 post	-0.054	0.045	-0.132	-1.204	0.231
PSV pre	-0.616	0.219	-2.709	-2.821	0.005
PSV	0.540	0.216	3.320	2.494	0.014
ΔPSV	-0.581	0.216	-2.541	-2.685	0.008

IIEF-5: 5-Item International Index of Erectile Function; PSV: peak systolic velocity.
*Dependent variable: MPV.

nificant improvement of vascular blood flow of cavernous arteries was indicated by a significant increase of peak systolic velocity (PSV: 32±5.5 cm/s pre-treatment *vs.* 42±7.6 cm/s post-treatment; P<0.0001) evaluated by d-PDU after pharmacological stimulation (Figure 3B).

A correlation analysis between IIEF-5 score and MPV revealed a in inverse relationship, both pre- and post- treatment (respectively= P<0.0012; r: -0.456 and P<0.0004; r: -0.523. Figure 4) and same inverse correlation between PSV and MPV at baseline (P<0.0001; r: -0.683) and post-treatment (P<0.0001; r: -0.647, Figure 5A, B). The inverse correlations persisted when examining the delta variations of PSV before and after treatment (P<0.0028; r: -0.587, Figure 5C).

Among the parameters examined, linear regression analysis showed that PRP treatment was effective on vascular ED and this effect was strictly related to the MPV at baseline, as reported in Table II. The results of linear regression analysis revealed a strong significance between

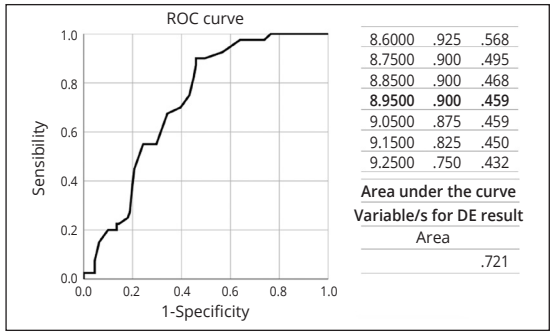

Figure 6.—ROC curve shows that the treatment efficacy depends on mean platelet volume (MPV) and that the best response is for MPV values below 8.95 fl. (curve coordinate: 0 non responder, 1 responder).

the improvement in vascular function expressed in Delta PSV variation (P<0.008) and the MPV values (Table II).

The ROC analysis demonstrated that MPV had a significant accuracy (72.1%, CI: 64.0-80.2, P≤0.0001) in identifying men clinically responding to PRP with favorable outcomes (MCID in

IIEF-5 Score). An MPV<8.95 fL was determined as the optimal threshold with a sensitivity of 90% and specificity of 54.1% (Figure 6).

Discussion

Only few studies have been published regarding the use of intracavernous PRP injections as a treatment for ED and the exact mechanism of action is under investigation yet. As far as we are aware, only two randomized placebo-controlled studies have investigated the efficacy and safety of this treatment but no study has been carried out by using Duplex Ultrasound blood flow parameters.

Poulios *et al.* found that 69% of patients with mild to moderate ED achieved MCID compared with 27% in the placebo group.[21] Accordingly, patients with mild to moderate ED at baseline were investigated by Shaher *et al.* who reported 76% improvement in MCID *vs*. 16% placebo.[22] The first study had a short follow-up at three months, while the latter had last observation carried forward at 6 months, both concluded regarding the necessity to further investigate on the optimal platelet concentration in the PRP. Based on the previous experience, our PRP separation systems allows to produce a five-fold increase in platelet concentration over whole blood.[19]

PRP is an autologous product rich in platelets that contains high concentrations of growth factors and active protein. These components are supposed to stimulate tissue restoration and healing when applied to the targeted area. Furthermore, recent evidences suggest that PRP may have a neuroprotective function and could promote nerve regeneration and help metabolism.[23-25] In addition, PRP has the great advantages to be easy to prepare, having a high biosafety and no side effects have been reported. Although there is a growing enthusiasm surrounding the use of PRP for ED, conclusive data supporting its effectiveness are still lacking.[26]

Based on our results, this is the first report on a one-shot injection of PRP on clinical outcomes in large series of male subjects suffering for vascular ED unresponsive to PDE-5 inhibitors. Our findings confirmed that intracavernous injections with PRP are a safe and effective treatment in vascular ED management. The advantage of our technique is represented by one-shot injection of hyper-concentrated PRP obtained from our prepared kit. We demonstrated that a single session of PRP led to a statistically significant improvement of the erectile function, as evidenced by improvements in both IIEF-5 questionnaire scores and PSV at the d-PDU after one month compared to baseline. However, it is important to note that not all patients reported comparable improvements. As far as we know, no study had ever proposed any biomarker to predict success rates of PRP in patients treated nor the number of injections to be programmed. In order to better define why some patients had a stronger response and why the regenerative mechanism differed between the subjects of our cohort we compared the efficacy of the treatment with the baseline MPV. Interestingly, we firstly found that a smaller volume was associated with a higher response. This finding suggest that the mean platelet volume may be useful as a predictive factor for treatment outcomes in PRP therapy for vascular ED. This is the first time in literature that it is reported the possible cause of the efficacy of PRP in ED. The innovation of the present study compared to all the previous propose that the outcome of the treatment is related to MPV values. Further researches are necessary to better define the underlying mechanism and to develop targeted treatment approaches based on patients' characteristics, including MPV. Previous clinical studies have demonstrated that the size of the platelets could be considered as an indicator of platelet function and can indicate their regenerative activity.[27]

As a matter of fact, larger platelets have shown higher activity in orthopedic regenerative application use whereas the activity of profibrotic factors, *i.e.*, PDGF and TGF, may be required for its action.[28] On the contrary, larger platelets may not be useful for endothelial regenerative purposes, due to the fact that also patients at increased cardiovascular risk exhibit higher MPV and this correlates with the occurrence of major cardiovascular events. Indeed, platelets with higher MPVs were detected in patients with vasculogenic ED thus representing a useful tool in monitoring disease progression.[29] Moreover,

several studies reported an association between ED and CVD. The link between these conditions might reside in the interaction between androgens, chronic inflammation,[30] and cardiovascular risk factors that determines endothelial dysfunction and atherosclerosis, resulting in disorders of penile and coronary circulation.[31]

Even if the use of stem cell therapy is not universally recognized in guidelines,[32] we believe that MPV may have an important role in vascular ED patients.[33] To this purpose, we demonstrated that MPV is an important predictor of platelet function with regard to the potential use of PRP as regenerative treatment in vasculogenic ED.

Our data confirm, for the first time, that lower MPV is correlated to a better response to one-shot PRP treatment. We postulate that small platelets leads to a lower risk of micro-clotting and a production of a lower pro-inflammatory cytokines pattern such as IL-1, IL-6, and TNF alpha, thus, they initiate fibrosis and inflammatory processes. In fact we found an inverse correlation between both IIEF-5 Score and PSV *vs*. MPV before and after the treatment. Also, we studied the delta variations of PSV before and after treatment and the inverse correlations was maintained. Performing a ROC curve analysis, we found that the optimal MPV cut-off for the best clinical response is 8.95 fL. It is noteworthy that even patients with a higher MPV value showed some degree of response and no one patients reported a lack of efficacy. In accordance with these findings, we suggest to evaluate patients' MPV prior to PRP injection; lower MPV values are expected to have a higher success rate with a single dose treatment, whereas patients having MPV higher than 8.95 fL are expected to have limited improvement and could benefit from a repeated PRP injections.

Limitations of the study

We acknowledge some limitations of this study. First of all, it is a non-randomized trial, which implies cautious interpretation of the results. Indeed, we conducted this open-label study keeping in mind previous favorable results obtained from other authors in RCTs.[21, 22] Furthermore, it is important to underline that our study had a relatively short follow-up period which might have limited the possibility to assess long-term outcomes and potential adverse events. As a matter of fact, after one-month evaluation, the patient's response to PDE-5is improved significantly by using ED treatments with same molecule and same dosages reported before the application of PRP. Additional research with long-term follow-up and comprehensive safety assessment is warranted to better understand treatment's effectiveness and safety profile.

Conclusions

This is the first study on vascular correlates after intracavernous PRP treatment for ED in a large outpatient population. Our findings suggest that PRP treatment can improve penile erection in 80% of patients as well as penile blood flow in men poorly responding to PDE-5is therapies. We propose for the first time that a baseline MPV below 8.95 fL may be a cost-effective biomarker for PRP success rates after one-shot treatment; thus, we can identify in advance patients with a higher likelihood of treatment response with a good sensibility (90%) but lower specificity (54%).

However, to further validate the data acquired, results from randomized placebo-controlled studies are necessary to better understand whether MPV correlates with PRP efficacy and the impact of single *vs*. repeated PRP injections on erectile function in male ED. Moreover, long-term efficacy and safety of PRP should be better assessed.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Davide Francomano and Gabriele Antonini contributed equally. All authors read and approved the final version of the manuscript.

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