INTRACAVERNOSAL INJECTION OF PLATELET-RICH PLASMA AS AN ALTERNATIVE TREATMENT OF ORGANIC ERECTILE DYSFUNCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

Objective: *To evaluate the effectiveness and safety of intracavernosal injections of platelet-rich plasma (PRP) as an alternative therapy for the treatment of erectile dysfunction.* ***Material &Methods:*** *We conducted a comprehensive literature search on Pubmed, Cochrane Library, ScienceDirect, Scopus, and Proquest databases for randomized controlled clinical trials (RCTs) until April 2023. The study protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42023424586).* ***Results****: Our results showed that PRP could improve MCID in IIEF-EF score (OR: 4.64; 95% CI: 2.20, 9.79; p < 0.0001; I2 = 77%) and PSV (MD: 9.63; 95% CI: 1.17, 18.09; p = 0.03; I2 = 73%). In addition, PRP administration was shown to be relatively safe, and there was no significant difference in post-injection VAS pain scores when compared to controls (MD: -0.09; 95% CI: -0.49, 0.31; p = 0.66; I2 = 84%).* ***Conclusion:*** *This systematic review and meta-analysis showed promising results regarding the effects of PRP administration on erectile dysfunction. However, due to the lack of quality and number of studies, these findings should be interpreted carefully, and further investigations are still needed.*

Keywords: *Platelet-Rich Plasma, Intracavernosal Injection, Erectile Dysfunction, IIEF-EF, Meta-Analysis.*

ABSTRAK

Tujuan:*Untuk mengevaluasi efektivitas dan keamanan injeksi intracavernosal platelet-rich plasma (PRP) sebagai terapi alternatif untuk pengobatan disfungsi ereksi.****Bahan & Cara:*** *Kami melakukan pencarian literaturs ecara komprehensif pada database Pubmed, Cochrane Library, Science Direct, Scopus, dan Proquest untuk uji klinis acak terkontrol hingga April 2023. Protokol dari penelitian ini telah terdaftar di International Prospective Register of Systematic Reviews (PROSPERO CRD42023424586).* ***Hasil:*** *Hasil analisis kami menunjukkan bahwa PRP dapat meningkatkan MCID pada skor IIEF-EF (OR: 4.64; 95% CI: 2.20, 9.79; p < 0.0001; I2=77%) dan PSV (MD: 9.63; 95% CI: 1.17, 18.09; p = 0.03; I2 = 73%). Selain itu, pemberian PRP juga terbukti relatif aman serta tidak didapatkan perbedaan yang signifikan dari skor nyeri VAS pasca injeksi dibandingkan kontrol (MD: -0.09; 95% CI: -0.49, 0.31; p = 0.66; I2 = 84%).* ***Simpulan:*** *Tinjauan sistematis dan meta-analisis ini menunjukkan hasil yang menjanjikan mengenai efek dari pemberian PRP untuk pengobatan disfungsi ereksi. Namun, karena kurangnya kualitas dan jumlah penelitian, temuan ini harus ditafsirkan dengan hati-hati, dan masih diperlukan penelitian lebih lanjut.*

Kata kunci: *Platelet-Rich Plasma, Injeksi Intracavernosal,Disfungsi Ereksi, IIEF-EF,Meta-Analisis.*

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INTRODUCTION

Erectile dysfunction (ED) is a pathological condition characterized by the inability of a man to obtain and maintain an erection that is rigid and firm enough for sexual intercourse.[1-2] This condition is often found in adult men, with prevalence reaching 50% in men aged 40-70 years.[3] By 2025, around 322 million men worldwide are estimated to have ED, doubling the global prevalence in 1995, with 155 million men diagnosed with ED.[4] Those who are afflicted with ED typically experience a lower health-related quality of life (HRQoL) compared to men without ED. Erectile dysfunction can increase

the risk of depression and anxiety, causing men to avoid sexual intercourse.[5] In addition, the partners of ED patients can also be significantly impacted as they experience decreased sexual satisfaction.[4,6]

Current evidence suggests that 80% of the primary pathology of ED is due to organic etiology, especially endothelial dysfunction in corpus cavernosa vasculature, which may reduce the release of nitric oxide and impair vasodilation.[7-8] The most commonly used treatment for ED is oral phosphodiesterase-5 inhibitors (PDE5i). However, this therapy cannot improve the pathological process of the penis. In advanced stages, many patients are unresponsive to these treatments, so they are often offered other treatments, such as intracavernosal injection of vasodilators, penile prosthesis implantation, external vacuum, and so forth. These treatment methods are used as second-line or even third-line options, but their long-term use is controversial and has been shown to cause various side effects.[6,9]

Recently, there has been increasing interest in regenerative therapies for ED that have the potential to correct the underlying pathology and restore spontaneous erectile ability.[10-11] Platelet-rich plasma (PRP) is an autologous blood product from part of the plasma fraction obtained through whole-blood centrifugation. This makes PRP have a platelet concentration above normal levels.[12] PRP is known to contain various growth factors that can play a role in regenerative functions, including stem cell mobilization, modulating inflammatory responses, and stimulating angiogenesis. These properties make PRP an attractive treatment in orthopaedics, surgery, dermatology, and even urology.[13-14]

However, the therapeutic use fulness of PRP has yet to be thoroughly investigated, making it critical to provide solid evidence for its use in treating ED.[13] As a result, we conducted a systematic review and meta-analysis to offer evidence-based information about the efficacy and safety of PRP injection as an alternative strategy for treating ED.

OBJECTIVE

This systematic review and meta-analysis aimed to evaluate the effectiveness and safety of intracavernosal injections of PRP as an alternative therapy for the treatment of ED.The study's findings are also intended to contribute to developing treatment recommendations and act as a foundation for future research.

MATERIAL & METHODS

We conducted a systematic review and meta-analysis using the procedure in the Cochrane Handbook for Systematic Reviews of Interventions and The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 for review reporting.[15-16] The protocol for this systematic review was filed with the International Prospective Register of Systematic Reviews (PROSPERO CRD42023424586).

The study search was performed comprehensively on five electronic databases, namely Pubmed, Cochrane Library, Science Direct, Scopus, and Proquest, until April 2023. The keywords used for the study search included: ("Platelet-Rich Plasma" OR "Platelet Rich Plasma" OR "PRP") AND ("Erectile Dysfunction" OR "Male Impotence" OR "Male Sexual Impotence" OR "Impotence") which were then modified using Boolean Operators on different databases to increase the sensitivity of searching (Table 1). We did not limit the publication time of the studies, but we did limit the studies to those conducted only in humans and reported in English.

The studies discovered from the electronic database were gathered in Mendeley Desktop and Rayyan.ai[17] to remove any duplicate entries. Two independent reviewers (MIRR and AFK) evaluated the remaining articles through reviewing their titles and abstracts. Any discrepancies that occur are rectified through discussion.

The inclusion criteria applied in this review were as follows: 1) a study with a randomized controlled trial (RCT) design published in a peer-reviewed journal; 2) with an adult male population diagnosed with organic ED; 3) receiving an intracavernosal injection of PRP; 4) with a placebo comparator; and 5) reporting at least one of the following outcomes: proportion of patients achieving Minimal Clinically Important Difference (MCID) based on International Index of Erectile Function-Erectile Function (IIEF-EF) domain, Sexual Encounter Profile Question-3 (SEP-3), Peak Systolic Velocity (PSV), End-Diastolic Velocity (EDV), Visual Analog Scale (VAS) pain score after injection, and all treatment-related adverse events. Studies that reported the use of additional interventions were also included if the drug was distributed equally across the groups. The exclusion criteria are: 1) data could not be extracted; 2) studies were conducted on non-humans; 3) articles were

inaccessible in full-text; and 4) studies without control groups, conference abstracts, case reports, case series, and reviews.

Two reviewers (MIRR and AFK) extracted the chosen studies independently using Google Sheets.The retrieved data included the author list and year of publication, study location, sample size, age, severity of ED, intervention dose, injection route, follow-up period, and presence of additional given interventions. The primary outcome we extracted was the proportion of patients who achieved MCID based on the IIEF-EF domain. Secondary outcomes included the proportion of patients who answered "Yes" to the SEP-3, mean PSV and EDV during the follow-up period, mean VAS pain score after injection, and any reported treatment-related adverse events.

The evaluation of bias was performed by two independent reviewers (MIRR and AFK) using the Cochrane risk-of-bias tool for randomized trials version 2 (RoB 2), which hasfive domains, including 1) randomization process; 2) deviation from the intended intervention; 3) missing outcome data; 4) outcome measurement; and 5) selection of reported outcomes. The assessment can be "Low", "High", or "Some concern" risk of bias.[18]

Data analysis was performed using Review Manager (RevMan) 5.4 with a 95% Confidence Interval (CI), and a statistically significant difference was indicated by a p-value <0.05. We collected dichotomous data in odds ratio (OR) and continuous data in mean difference (MD). The included studies were tested for heterogeneity, and the effect model was selected according to the test results. If $I^2 \leq 50\%$, heterogeneity was considered low, and a fixed effects model (FEM) was used. Conversely, heterogeneity was considered high if $I^2 > 50\%$, and a random effects model (REM) was used. Data reported as median and interquartile range or median and minimum to maximum range were converted to mean and standard deviation using the method proposed by Wan et al.[19] In addition, for analytical purposes, the 95% CI was also converted to standard deviation based on the method suggested by the Cochrane Handbook for Systematic Reviews of Interventions Chapter 6. In this study, we did not undertake analysis using change from baseline for continuous outcomes as this practice is not recommended by Cochrane.[16]

Table 1. Literature search strategy and keywords used.

Database	Keywords	Total
Cochrane Library	#1 Platelet-Rich Plasma OR Plasma, Platelet-Rich OR Platelet Rich Plasma #2 Erectile Dysfunction OR Dysfunction, Erectile OR Male Impotence OR Impotence, Male OR Male Sexual Impotence OR Impotence, Male Sexual OR Sexual Impotence, Male OR Impotence #1 AND #2	25
Proquest	(Platelet-Rich Plasma OR Plasma, Platelet -Rich OR Platelet Rich Plasma) AND (Erectile Dysfunction OR Dysfunction, Erectile OR Male Impotence OR Impotence, Male OR Male Sexual Impotence OR Impotence, Male Sexual OR Sexual Impotence, Male OR Impotence)	559
PubMed	#1 Platelet-Rich Plasma OR Plasma, Platelet-Rich OR Platelet Rich Plasma #2 Erectile Dysfunction OR Dysfunction, Erectile OR Male Impotence OR Impotence, Male OR Male Sexual Impotence OR Impotence, Male Sexual OR Sexual Impotence, Male OR Impotence #1 AND #2	63
Scopus	("Platelet-Rich Plasma" OR "Platelet Rich Plasma" OR "PRP") AND ("Erectile Dysfunction" OR "Male Impotence" OR "Male Sexual Impotence" OR"Impotence")	400
ScienceDirect	("Platelet-Rich Plasma" OR "Platelet Rich Plasma" OR "PRP") AND ("Erectile Dysfunction" OR "Male Impotence" OR "Male Sexual Impotence" OR "Impotence")	460

RESULTS

We identified a total of 1499 studies in the initial literature search. Following the first screening by title and abstract, 11 studies were considered for further examination by full-text screening. Subsequently, we excluded eight studies and retained three that qualified for our inclusion criteria for qualitative and quantitative synthesis. (Figure 1).[11,20,21]

The characteristics of the included studies are summarized in Table 2. This review had results from three RCTs conducted in Greece, Egypt, and the United States involving 230 participants. The mean age of the patients ranged from 48 to 58 years. In all studies, PRP was administered via intracavernosal injection, and only one study by Masterson et al.[11] reported the use of an additional PDE5i intervention. Overall, two studies were rated as "some concern" and one study was rated as "high" for risk of bias. A summary of the results of the risk of bias assessment using RoB 2 can be seen in Figure 2.

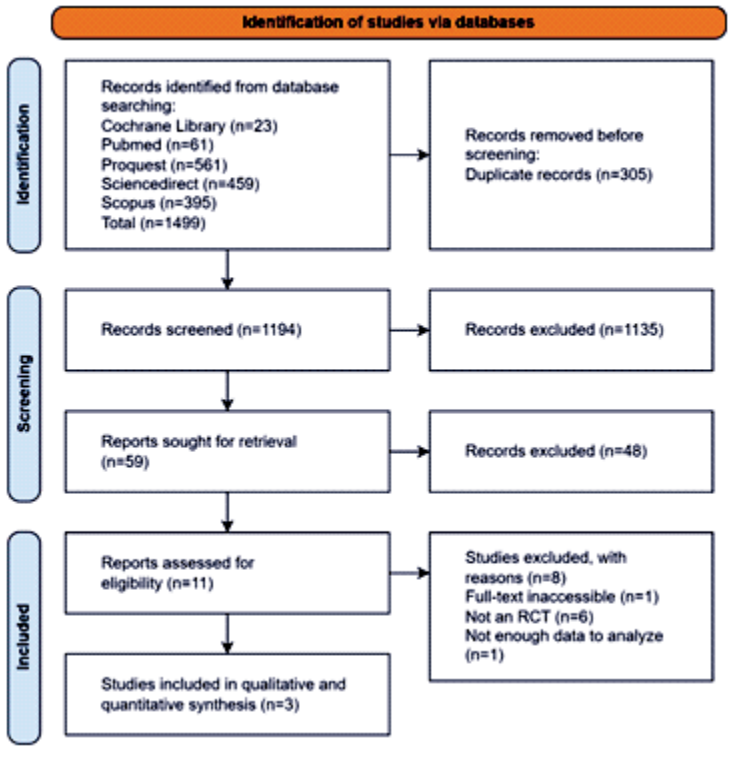

Figure 1. PRISMA Flow Diagram.

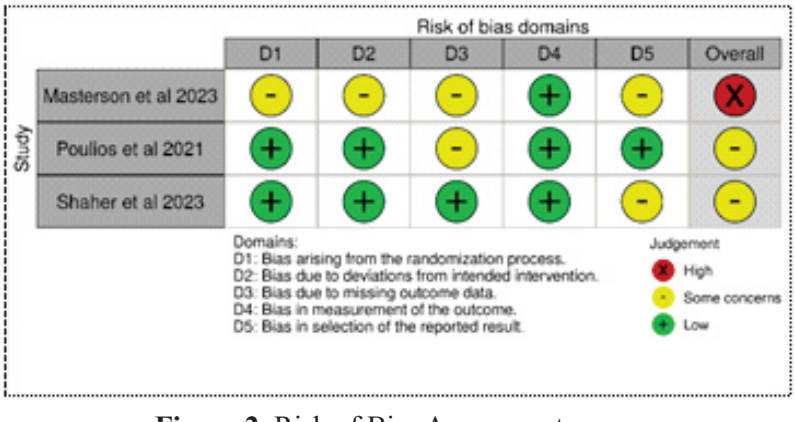

Figure 2. Risk of Bias Assessment

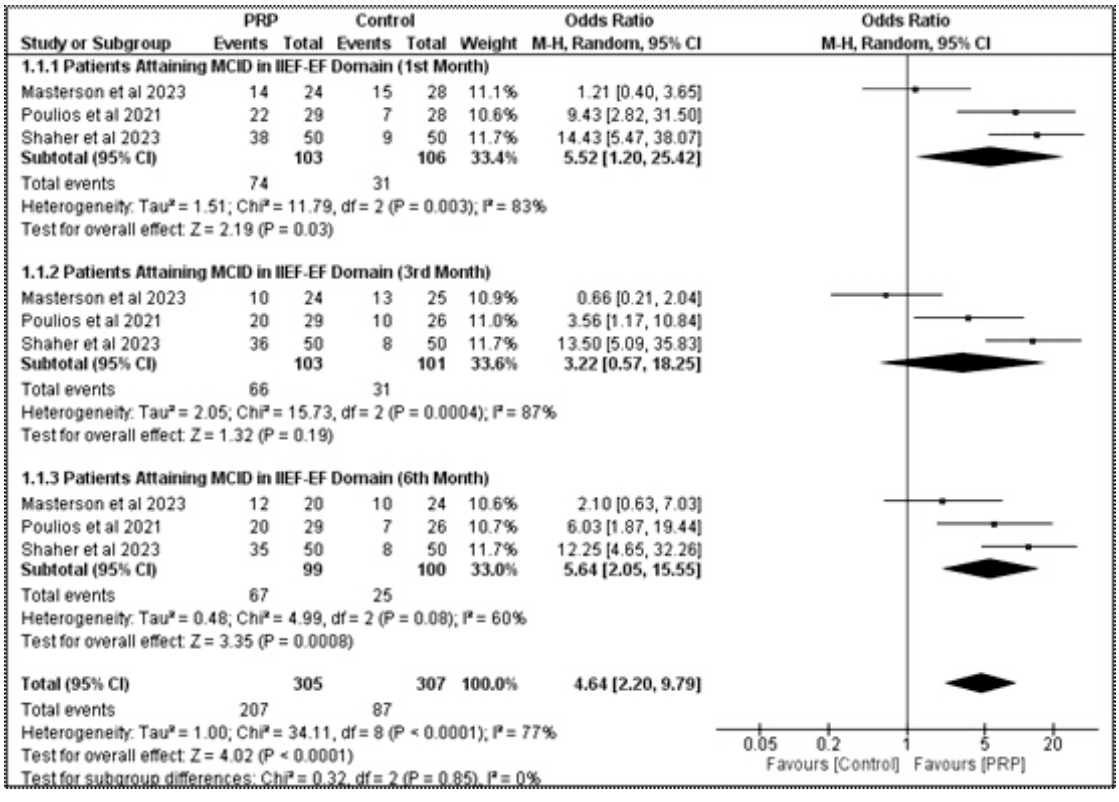

Figure 3. Forest Plot of the Meta-Analysis for the Effect of PRP on MCID in IIEF-EF Score.

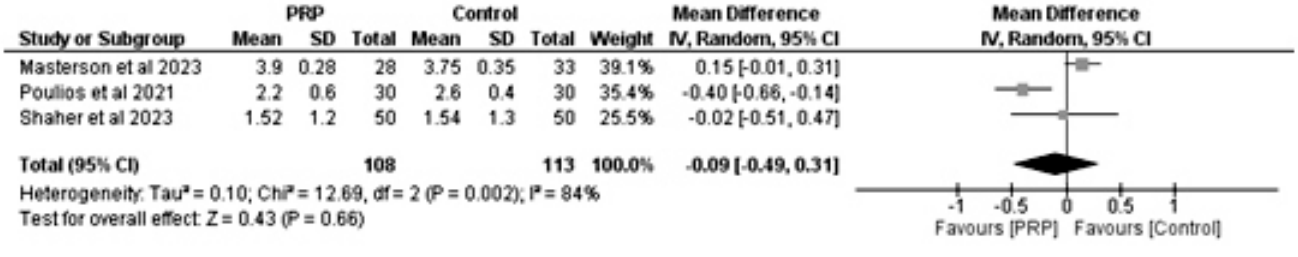

Figure 4. Forest Plot of the Meta-Analysis for the Effect of PRP on PSV.

Three studies reported the effect of PRP on the proportion of patients achieving MCID in the IIEF-EF. Analysis using a random effects model showed that patients who received PRP had a significantly higher likelihood of achieving MCID compared to controls, particularly at months 1 and 6 (OR: 4.64; 95% CI: 2.20, 9.79; $p < 0.0001$; I2 = 77%; Figure 3).[11,20,21]

Two studies reported the effect of PRP on SEP-3. The study by Poulios et al. demonstrated that PRP could significantly increase the proportion of positive answers of the SEP-3 at month 1 (15.5 ± 28.7 vs -3.6 ± 17.6, $p = 0.002$), month 3 (12.9 ± 28.3 vs -4.8 ± 33.9, $p = 0.028$), and month 6 (19.8 ± 28.6 vs -8.7 ± 29.1, $p < 0.001$) compared with controls.[21] These results are also aligned with a study by Shaher et al., which showed that the proportion of patients with positive answers was significantly higher in the PRP group compared to controls at months 1, 3, and 6 (78% vs. 0%, 70% vs. 0%, and 66% vs. 0%, respectively; $p < 0.001$).[20]

Two studies reported PSV (cm/sec) at month 6 after PRP administration. Analysis with a random effects model showed that patients who received PRP had significantly higher PSV compared to controls (MD: 9.63; 95% CI: 1.17, 18.09; $p = 0.03$; I2 = 73%; Figure 4).[11,20]

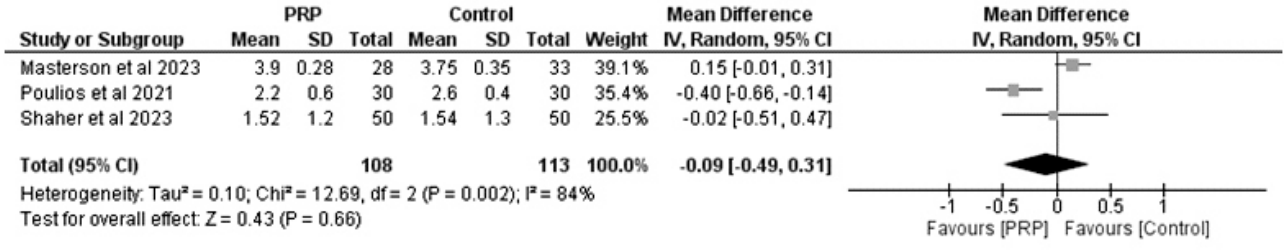

Figure 5. Forest Plot of Meta-Analysis for VAS Pain Score after Injection.

Table 2. Characteristics of the included studies

Author(s) (year)	Study Locations	Sample size		Age (Mean ± SD)		ED Severity		PRP Doses	Administration Route	Follow-up Period	Other Additional Interventions
		PRP	Control	PRP	Control						
Poulios et al. (2021)[21]	Greece	30	30	57.17 ± 8.17	57.83 ± 5.83	Mild Mild - moderate Moderate	20 32 8	10 ml (2 times with 1 month interval)	Intracavernosal injection (5 ml each on each side)	1, 3, and 6 months	None
Shaher et al. (2023)[20]	Egypt	55	54	55.67 ± 14.46	54.33 ± 14.47	Mild Mild - moderate Moderate	28 53 19	9 ml (2 times with 2 weeks interval)	Intracavernosal injection (proximal to the corona, distal to the root of the penis, and shaft of the penis, 3 ml each)	1, 3, and 6 months	None
Masterson et al. (2023)[11]	United States	28	33	47.5 + 12.89	48 ± 10.84	Mild Moderate	37 24	5 ml (2 times with 1 month interval)	Intracavernosal injection (2.5 ml each on each side)	1, 3, and 6 months	PDE5i (without dose modification)

ED: erectile dysfunction; **PDE5i:** phosphodiesterase-5 inhibitor; **PRP:** platelet-rich plasma; **SD:** standard deviation

Two studies reported the effect of PRP on EDV (cm/sec). The study by Shaher et al. showed that the PRP group had significantly lower EDV (median (IQR)) at months 1 (1 (0-2.25) vs 6 (5-6.25); $p < 0.001$) and months 6 (1 (1-3.0) vs 6 (5-7); $p < 0.001$) compared to controls [20]. Meanwhile, there was no significant difference in the proportion of patients who had EDV > 0 at month 6 between the PRP and control groups in the study by Masterson et al. (37.5% vs. 30.8%; $p = 0.616$).[11]

Three studies reported post-injection pain levels assessed by VAS scores. The analysis using a random effects model revealed that there was no significant difference in VAS scores between the PRP and placebo groups (MD: -0.09; 95% CI: -0.49, 0.31; $p = 0.66$; $I2 = 84\%$; Figure 5).[11,20,21]

Three studies reported adverse events, but only the study by Masterson et al.[11] reported quantitative data, so a meta-analysis was not conducted. The study by Masterson et al. showed only two minor adverse events, one in each study group, namely plaque formation in the PRP group and hematoma in the control group. No major adverse events (grade 3+) were reported in this study.[11] Meanwhile, other studies by Poulios et al. and Shaher et al. reported no adverse events during the follow-up period.[20,21]

DISCUSSION

PRP is an autologous blood-derived product containing a platelet concentration at least two to three times above average. PRP therapy has been used in various medical applications over the past decades, such as musculoskeletal disorders and alopecia, resulting in great interest in the potential of PRP in regenerative medicine.[22-23] In ED, the scientific foundation underlying the use of PRP is the high concentration of platelets and growth factors. PRP aims to restore the structure and function of erectile tissue as well as offers a cure for the underlying disease rather than treating symptoms.[24] PRP is known to contain many cytokines and growth factors, such as Vascular

Endothelial Growth Factor (VEGF), Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), Insulin-Like Growth Factor (IGF), and other biological mediators that play a role in angiogenesis, endothelial cell proliferation, stem cell migration, and tissue repair.[25-26] In an animal model with bilateral cavernous nerve injury, PRP was shown to have neuroprotective effects and can facilitate the recovery of erectile function through increased nitric oxide synthesis.[27] In another study, PRP was also shown to promote myelin regeneration and prevent corporal smooth muscle atrophy in streptozocin-induced diabetic rats.[28]

This meta-analysis included three RCTs that enrolled 230 participants with mild to moderate ED. Our findings proved that PRP administration could significantly improve the MCID in the IIEF-EF, SEP-3, and PSV compared to controls, even after six months of PDE5i discontinuation, particularly in the studies by Poulios et al.[21] and Shaher et al.[20] These findings are in alignment with a previous systematic review by Alkandari et al., which showed that the use of PRP is promising for the treatment of ED. However, it should be noted that the systematic review comprised two RCT studies derived from conference abstracts, four non-RCT studies, and five preclinical studies.[1] On the other way, this meta-analysis only included studies with RCT designs, thus making the findings more interesting.

Nevertheless, the limited number of studies and the heterogeneity of reported data prevent us from drawing definitive conclusions regarding EDV. In addition, the absence of significant differences in these outcomes may also be because most of the patients included in the study by Masterson et al.[11] had normal PSV and EDV at baseline. The dose of PRP used in that study was also relatively smaller compared to other studies, which administered 5 ml twice. In contrast to the other two studies that restricted patients from using the medication during the study, the patients in that study were also allowed to continue taking PDE5i. Regarding safety, there is limited data available, with Masterson et al. reporting one minor adverse event of plaque formation after PRP injection.[11] Meanwhile, two other studies reported no adverse events during the follow-up.[20-21] Similarly, there was no significant difference in the mean VAS pain score after injection, indicating that PRP is safe to use.[11,20,21]

While our findings provide evidence that PRP administration can significantly improve erectile function, it cannot be dismissed that using the IIEF assessment instrument is an entirely subjective indicator based on patient-reported outcomes. However, to date, there is no other validated and widely used instrument other than IIEF. Minimum clinically important difference (MCID) is considered an ideal and accurate method for evaluating the efficacy of clinical interventions and is therefore recommended for assessing ED treatment response. MCID in the IIEF-EF score is an improvement of 2 points or more in patients with mild or mild to moderate ED (IIEF-EF: 17-25) or 5 points or more in patients with moderate ED (IIEF-EF: 11-16) after treatment.[21,29] We also recommend utilizing more objective parameters, such as Doppler ultrasound, to assess the penile vascular state. In general, PSV higher than 35 cm/sec is considered normal, 25-35 cm/sec may indicate moderate arterial damage, and PSV lower than 25 cm/sec indicates severe arteriopathy. Meanwhile, EDV is the best indicator for venogenic impotence, and values over 3 cm/sec indicate venous dysfunction.[30]

This review has some limitations that need to be noted. Firstly, the lack of standardization of the dose and manufacturing method of PRP and the use of additional interventions may have contributed to the high heterogeneity of the studies. On the other hand, we were also unable to perform subgroup analysis due to difficulty accessing individual patient data. Secondly, there was a limited number of studies that qualified the inclusion criteria, with a relatively small sample size in each study. Thirdly, our results cannot be applied to patients with severe ED, as the studies we reviewed only included patients with mild to moderate ED. In addition, data limitations and differences in data reporting types meant that some results could not be analyzed. Based on these limitations, the findings from our review should be interpreted carefully. Further studies with larger sample sizes and focusing on advancing more comparable protocols, including methods of acquiring PRP, doses, and treatment schedules, are still needed.

CONCLUSION

This systematic review and meta-analysis yield positive results on the efficacy of PRP administration in treating ED as measured by the MCID in the IIEF-EF, SEP-3, and PSV. Moreover, the administration of PRP is anticipated to be safe

and well-tolerated compared to a placebo. Nevertheless, the data regarding the benefits of PRP in EDV remains a subject of controversy. To validate these findings, it is imperative to conduct multi-center clinical trials with larger sample sizes, considering the constraints of this review.

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