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Review

Efficacy and safety of platelet-rich plasma intracavernous injection for patients with erectile dysfunction: A systematic review, meta-analysis, and meta-regression

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Abstract *Objective:* Intracavernous injection might be offered to patients with erectile dysfunction (ED) who did not respond to the first-line oral treatment. Platelet-rich plasma (PRP) might offer improvement in erectile function since it contains numerous growth factors. This study aimed to evaluate the efficacy and safety of PRP intracavernous injection for patients with ED.

Methods: We conducted relevant literature searches on Cochrane Library, Medline, Scopus, and ClinicalTrials.gov databases using specific keywords. The results of continuous variables were pooled into the mean difference (MD) and dichotomous variables into the odds ratio along with 95% confidence interval (95% CI).

Results: A total of six studies were included. Our pooled analysis revealed that PRP intracavernous injection was associated with a significant increase in the erectile function domain of the International Index of Erectile Function at 1 month (MD 3.47 [95% CI 2.62–4.32], $p<0.00001$, $I^2=7\%$), 3 months (MD 3.19 [95% CI 2.25–4.12], $p<0.00001$, $I^2=0\%$), and 6 months (MD 3.21 [95% CI 2.30–4.13], $p<0.00001$, $I^2=0\%$) after the intervention when compared with baseline values. PRP was also superior to a placebo in terms of improvement in erectile function domain of the International Index of Erectile Function score at 1 month (MD 2.83, $p<0.00001$), 3 months (MD 2.87, $p<0.00001$), and 6 months (MD 3.20, $p<0.00001$) post-intervention. The adverse events from PRP injection were only mild without any serious adverse events.

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Conclusion: PRP intracavernous injection may offer benefits in improving erectile function in patients with ED with a relatively good safety profile.

1. Introduction

Erectile dysfunction (ED), also known as impotence, is the inability to achieve or maintain an erection that is sufficient for satisfactory sexual performance [1]. An erection occurs when blood flow to the penis increases due to the dilation of the penile blood vessels so that the penis can be filled with blood and enlarged [2]. This process is regulated by various factors, and interference with any of these factors can result in ED [2]. In general, patients with ED will experience one or more of the following signs: difficulty getting an erection, difficulty maintaining an erection, or decreased sexual desire [1]. The etiology of ED can be classified into psychological and organic (non-psychological) factors [1,3]. Psychological causes of ED include depression and anxiety, especially anxiety related to the inability to achieve an erection, while organic causes of ED are vascular disease, neurological disorders, hormonal disorders, anatomical disorders, and drugs [1,3].

Globally, the prevalence of ED varies from 13.1% to 71.2% [4]. A recent epidemiological study showed that approximately 25% of men aged 40—70 years have moderate ED and 10% of men have severe or complete ED [5]. The prevalence of ED increases with age where there is only about 22% combined moderate to severe ED at the age of 40 years but increases drastically to 49% at the age of 70 years [5]. This disorder certainly has an impact on the overall quality of life of an individual [4,5].

The management of ED is adjusted to its underlying cause [6—8]. Psychological counseling can offer some benefits in ED caused by stress, anxiety, depression, or relationship conditions [6—8]. In addition, lifestyle changes can also restore normal erectile function in the penis [6—8]. Lifestyle changes that can be made are quitting smoking, losing weight, exercising regularly, stopping using drugs or alcohol, and improving relationships with partners [6—8]. ED that does not improve with a conservative approach will usually require a therapeutic modality approach, such as treatment with drugs, treatment by injection into the penis (intracavernous), use of a vacuum device, low-intensity extracorporeal shock wave therapy, up to the installation of the prosthesis [6—8]. Drugs belonging to the phosphodiesterase type 5 inhibitor class, such as sildenafil, tadalafil, and vardenafil are often chosen as the first line of treatment for ED [6—8]. If the first-line therapy is not successful, then the second-line therapy such as intracavernous injections can be used [6—8].

One agent that recently has been widely studied to improve the ED of the penis is platelet-rich plasma (PRP) [9,10]. So far, platelets are known as blood components that have an important role in both wound healing and coagulation processes [9,10]. PRP itself has many platelet growth factors originating from whole blood such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), so that it may repair damaged penile tissue and restore erectile function [9,10]. Unfortunately, the evidence regarding the use of PRP in treating ED in humans is still unclear. This study aimed to analyze the efficacy and safety of PRP intracavernous injection for patients with ED.

2. Materials and methods

2.1. Eligibility criteria

This review was written following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement and Cochrane Handbook guidelines [11,12]. The protocol of this review has been registered in PROSPERO (CRD42023401208). In this review, we intended to conduct a two-step analysis: (1) assess the efficacy and safety of intracavernous injection of PRP for ED; (2) compare the effectiveness of intracavernous injection of PRP with a placebo as a treatment for ED. In order to reach our goals, we used the Population, Intervention, Comparison/Control, Outcome, Study design formula in compiling the inclusion criteria for this study:

1) Population: men aged ≥18 years old with a diagnosis of ED;
2) Intervention: receiving an intracavernous injection of PRP as the treatment modality for ED;
3) Control: may include no comparison group (single-arm) or use a placebo as control;
4) Outcome: having the data regarding the primary outcome (erectile function domain of the International Index of Erectile Function [IIEF-EF] with/without the secondary outcomes; the proportion of patients attaining minimal clinically important difference [MCID] in the IIEF-EF and the adverse events from PRP intracavernous injection);
5) Study design: an interventional prospective study (may be in the form of a randomized trial or non-randomized study).

Meanwhile, studies that met one or more of the following criteria were excluded from this review: (1) patients with ED caused by anatomical disorders, such as penile fracture, hypospadias, epispadias, Peyronie's disease, or penile curvature anomaly; (2) patients with a history of major penile surgery or radiation; (3) studies that combine PRP with other agents (*e.g.*, stem cells,

alprostadil, or papaverine) for intracavernous injection; (4) retrospective studies; (5) review articles; (6) studies that are not available in full-text form (abstract only).

2.2. Literature search and study selection

Two authors (Suharyani S and Leonardo M) independently used four databases (Scopus, Medline, Cochrane Library, and ClinicalTrials.gov) to search for relevant literature published in English up to February 11th, 2023. The following keywords were used to obtain relevant literature: "(platelet rich plasma OR PRP OR thrombocyte rich plasma OR P-shot) AND (erectile dysfunction OR ED OR erectile recovery OR sexual dysfunction)". Two independent authors (Suharyani S and Leonardo M) started the process of identifying eligible articles by eliminating duplicates and screening them based on their titles or abstracts. Articles that passed the initial screening were then assessed in the full-text format to test for their suitability with our eligibility criteria. All discrepancies were resolved through discussion with the third author (Hariyanto TI).

2.3. Data extraction

Two independent authors (Oentoeng HH and Lumban Tobing ERP) carried out the data extraction process into Microsoft Excel 2019 for tabulation. The following data were extracted: the authors' name, publication year, study design, sample size, dosage of PRP used for intracavernous injection, duration and severity of ED, baseline characteristics of participants (mean age, body mass index [BMI], hypertension, diabetes, and smokers prevalence), and outcomes of interest.

The outcomes of interest in this review were separated into primary and secondary outcomes. Only the primary outcome (IIEF-EF) was assessed in both sets of analysis. In the first set of analyses involving only single-arm intervention (without the comparison group), we compared IIEF-EF values at pre- (baseline) and post-PRP intracavernous injection at 1 month, 3 months, and 6 months. In the second set of analysis involving the comparison of PRP with a placebo, we observed changes in IIEF-EF scores from baseline to the follow-up period (at 1 month, 3 months, and 6 months) by deducting the values from the follow-up period with the baseline values (change = follow-up − baseline). The changes in these values in the two groups of intervention were then compared. The MCID in the IIEF-EF scores was defined as two or more points higher in the IIEF-EF scores of patients with mild or mild to moderate ED (IIEF-EF scores: 17–25) or five or more points higher in the IIEF-EF scores of patients with moderate ED (IIEF-EF scores: 11–16).

2.4. Risk of bias assessment

Two independent authors (Tansol C and Hariyanto TI) performed a risk of bias assessment of the included studies in this review using the appropriate tool. We used a tool from Cochrane Collaborations, namely Risk of Bias version 2 (RoB v2), which includes a methodological assessment of five domains: (a) randomization process; (b) deviations from intended interventions; (c) missing outcome data; (d) measurement of the outcome; and (e) selection of the reported results [13]. The authors' evaluations were categorized as "low risk", "high risk", or "some concerns" of bias [13].

Meanwhile, to assess the quality of non-randomized studies, we used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool from the Cochrane Collaborations [14]. ROBINS-I assessed the risk of bias in seven domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and selection of the reported results [14]. The results from the assessment using ROBINS-I will classify the study into "low risk", "moderate risk", or "serious risk" of bias [14].

2.5. Statistical analysis

We used mean difference (MD) along with 95% confidence interval (95% CI) for the analytical pooling outcomes of continuous variables by using the inverse-variance formula. For the outcomes of dichotomous variables, we used the Mantel–Haenszel formula to pool the results into the odds ratio (OR) along with 95% CI. At the start, the fixed-effect model was chosen as default in this review but if the heterogeneity was found to be significant (>50%), we would use the random-effect model instead. In this review, the *I*-squared (I^2) statistic was selected to assess the heterogeneity between studies with the following criteria: an I^2 value of ≤25% was considered as low heterogeneity; an I^2 value of 26%–50% was considered as moderate heterogeneity; and I^2 value of >50% was categorized as high or significant heterogeneity. The combined formula from Luo et al. [15] and Wan et al. [16] was used to change the data expressed in the form of the median and interquartile range (IQR) or data expressed as median, minimum, and maximum into means and standard deviations (SDs) for pooled analysis purposes. Meta-regression with a random-effects model was performed using a restricted-maximum likelihood for pre-specified variables including age, BMI, hypertension, diabetes, smokers, and duration of ED to see the interaction effect between PRP intracavernous injection and these variables in influencing the primary outcome (IIEF-EF) at pre- and post-intervention. A publication bias analysis was performed when there were more than 10 studies on each outcome of interest. All of these statistical analyses were carried out using an application from the Cochrane Collaboration of the United Kingdom, namely Review Manager 5.4 (Cochrane Informatics Technology Services).

3. Results

3.1. Study selection and characteristics

A literature search on four international databases yielded a total of 151 articles. After eliminating duplicates and

screening the articles based on their titles and abstracts, 136 articles were removed, leaving 15 articles. These 15 articles were assessed in a full-text form where nine articles did not meet our eligibility criteria (three articles were only reviews; three articles were only available in the abstract form; two articles were only protocol without any relevant data; and one article was not available in the English language), thus leaving six articles [17—22] for inclusion in the final analysis (Fig. 1). Two out of six studies have double-blind randomized clinical trial (RCT) designs, while the remaining four studies were prospective interventional studies. The number of samples varied from 15 to 100 people. Most of the included studies performed three sessions of 3 mL PRP intracavernous injection with 15 days intervals between injections. The mean duration of ED in the included studies ranged from 25.7 months to 78.7 months. A summary of the baseline characteristics and the details regarding PRP injection in the included studies can be found in Table 1 and Supplementary Table 1.

3.2. Quality of study assessment

Based on the assessment of the risk of bias by using RoB v2 from Cochrane Collaborations, it was found that all included RCTs [17,19] in this review had a "low risk" of bias in all five assessment domains (Fig. 2). On the other side, using the assessment from the ROBINS-I tool, all of the included non-randomized interventional studies were judged to have a "serious risk" of bias (Fig. 3). All of these non-randomized interventional studies did not have adequate blinding to the participants or outcome assessors so the results of outcome measurement may be influenced by their prior knowledge regarding the intervention received. Three out of four of these studies also did not acknowledge the presence of potential confounders and did not make any adjustments to the confounders in the analysis.

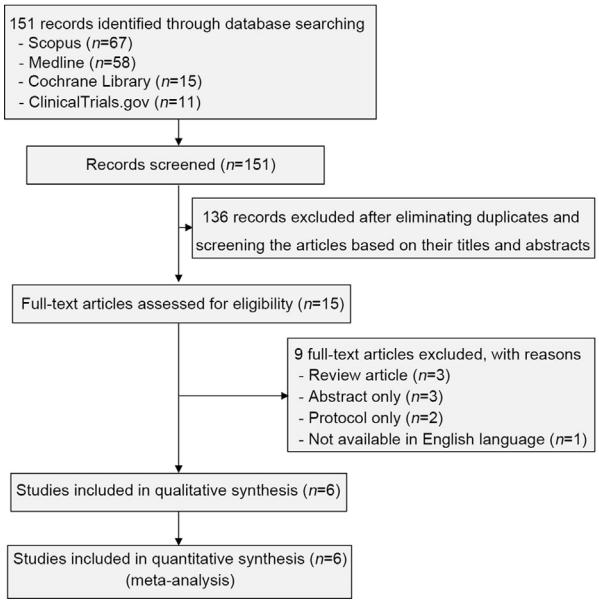

Figure 1 The Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

3.3. Efficacy of PRP intracavernous injection (pre- and post-intervention analysis)

3.3.1. IIEF-EF at baseline and 1 month after the intervention

Based on our pooled analysis of six studies ($n=377$), it has been demonstrated that intracavernous injection of PRP significantly increases the IIEF-EF score 1 month after the intervention when compared with baseline values in patients with ED (MD 3.47 [95% CI 2.62—4.32], $p<0.00001$, $I^2=7\%$, fixed-effect models) (Fig. 4A).

3.3.2. IIEF-EF at baseline and 3 months after the intervention

Based on our pooled analysis of five studies ($n=307$), it has been shown that intracavernous injection of PRP significantly increases the IIEF-EF score at 3 months after the intervention when compared with baseline value in patients with ED (MD 3.19 [95% CI 2.25—4.12], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 4B).

3.3.3. IIEF-EF at baseline and 6 months after the intervention

Based on our pooled analysis of five studies ($n=307$), it has been shown that intracavernous injection of PRP significantly increases the IIEF-EF score at 6 months after the intervention when compared with baseline value in patients with ED (MD 3.21 [95% CI 2.30—4.13], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 4C).

3.3.4. Adverse events

Four out of six included studies [17—20] reported the safety outcomes from PRP intracavernous injection. From these studies, two studies [17,20] reported no adverse events from PRP injection, such as pain, hematoma, or signs of infection. One study [19] reported only slight subcutaneous bruising which occurred in 8.6% of patients without any pain reported during the procedure.

A study by Poulios et al. [17] which compared PRP intracavernous injection with placebo injection showed that PRP offered less treatment-induced pain as evidenced by significantly less mean visual analog scale when compared with a placebo (mean±SD: 2.2±0.6 *vs.* 2.6±0.4, respectively, $p=0.008$). Meanwhile, a study by Shaher et al. [19] showed no statistically significant difference in the visual analog scale between PRP and a placebo (mean±SD: 1.52±1.2 *vs.* 1.54±1.3, respectively). Both studies [17,19] did not report other adverse events such as hematoma, bruises, ecchymosis, fibrous plaques, or penile deformities.

3.4. Efficacy of PRP versus a placebo (comparison analysis)

3.4.1. IIEF-EF at 1 month after the intervention

Our meta-analysis from the two RCTs ($n=157$) showed that PRP intracavernous injection was associated with a significantly higher increase in the IIEF-EF score from baseline to

Table 1 Characteristics of included studies.

Study	Design	Sample size, *n*	PRP injection dose	ED severity, %	ED duration, month[a]	Age, mean, year	BMI, mean, kg/m^2	HT, %	DM, %	Smoker, %
Poulios et al., 2021 [17]	Double-blind RCT	• 60 (intervention group: 30; control group: 30)	• Two sessions of PRP injection (1 month apart): a total of 5 mL PRP was infused in each corpus cavernosum over a 2 min period	- Mild: 33 - Mild to moderate: 54 - Moderate: 13	78.7±54.6	57.7	28.8	30	25	58
Schirmann et al., 2022 [18]	Prospective study	• 15	• Three sessions of PRP injection (15 days apart): 3 mL PRP was injected into each corpus cavernosum (total 6 mL) with additional of 6 mL injected subcutaneously	- Moderate: 60 - Severe: 40	NA	56.1	NA	46.7	66.7	93.3
Shaher et al., 2023 [19]	Double-blind RCT	• 100 (intervention group: 50; control group: 50)	• Two sessions of PRP injection (2 weeks apart): 3 mL PRP was injected into each corpus cavernosum at three different sites: 1 cm proximal to the corona, 1 cm distal to the root of penis, and at the mid-penile shaft	- Mild: 28 - Mild to moderate: 53 - Moderate: 19	43.5±14.1	54.9	25	32	32	55
Taş et al., 2021 [20]	Prospective study	• 31	• Three sessions of PRP injection (15 days apart): 3 mL PRP was injected into each corpus cavernosum with sites of injection varying by 1 cm in the mid-penile region	- NA	64.2±46.6	54.4	30.8	51.6	51.6	NA
Wong et al., 2021 [21]	Prospective study	• 30	• Three sessions of PRP injection (3 weeks apart): 1–2 mL PRP was injected into each corpus cavernosum	- NA	25.7	54.9	25.7	40	16.7	30
Zaghloul et al., 2021 [22]	Prospective study	• 34	• Eight sessions of PRP injection (1 week apart): 0.5 mL PRP was injected into each corpus cavernosum (total of 1 mL)	- NA	26.5±23.8	50.2	NA	5.9	38.2	35.3

BMI, body mass index; DM, diabetes mellitus; ED, erectile dysfunction; HT, hypertension; NA, not available; PRP, platelet-rich plasma; RCT, randomized clinical trial.

[a] Mean±standard deviation or mean.

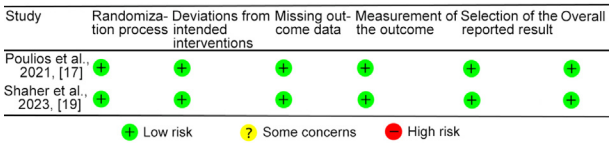

Figure 2 Risk of bias assessment of the included studies using the Risk of Bias version 2 tool.

Figure 3 Risk of bias assessment for non-randomized intervention study by using the Risk of Bias in Non-randomized Studies of Interventions tool. Notes: D1 represents the bias due to confounding; D2 represents the bias due to selection of participants; D3 represents the bias in classification of interventions; D4 represents the bias due to deviations from intended interventions; D5 represents the bias due to missing data; D6 represents the bias in measurement of outcomes; D7 represents the bias in selection of the reported result.

1 month after the intervention when compared with a placebo in patients with ED (MD 2.83 [95% CI 1.48–4.18], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 5A).

3.4.2. IIEF-EF at 3 months after the intervention

Our meta-analysis from the two RCTs ($n=155$) showed that PRP intracavernous injection was associated with a significantly higher increase in the IIEF-EF score from baseline to 3 months after the intervention when compared with placebo in patients with ED (MD 2.87 [95% CI 1.29–4.45], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 5B).

3.4.3. IIEF-EF at 6 months after the intervention

Our meta-analysis from the of two RCTs ($n=155$) showed that PRP intracavernous injection was associated with a significantly higher increase in the IIEF-EF score from baseline to 6 months after the intervention when compared with placebo in patients with ED (MD 3.20 [95% CI 1.75–4.64], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 5C).

3.4.4. MCID in the IIEF-EF at 1 month after intervention

Our meta-analysis from the two RCTs ($n=157$) showed that the number of patients who achieved MCID in the IIEF-EF at 1 month after the intervention was significantly higher in the PRP group than the placebo group (OR 12.21 [95% CI 5.74–25.97], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 5D).

3.4.5. MCID in the IIEF-EF at 3 months after the intervention

Our meta-analysis from the two RCTs ($n=155$) showed that the number of patients who achieved MCID in the IIEF-EF at 3 months after the intervention was significantly higher in the PRP group than the placebo group (OR 7.13 [95% CI 1.93–26.32], $p=0.003$, $I^2=68\%$, random-effect models) (Fig. 5E).

3.4.6. MCID in the IIEF-EF at 6 months after the intervention

Our meta-analysis from the two RCTs ($n=155$) showed that the number of patients who achieved MCID in the IIEF-EF at 6 months after the intervention was significantly higher in the PRP group than the placebo group (OR 9.21 [95% CI 4.39–19.34], $p<0.00001$, $I^2=0\%$, fixed-effect models) (Fig. 5F).

3.5. Meta-regression

Identification of risk factors that influence the relationship between PRP intracavernous injection and changes in the IIEF-EF at 1 month, 3 months, and 6 months post-intervention was done with meta-regression. Our meta-regression revealed that variability in those outcomes in ED patients receiving PRP treatment cannot be explained by known patient factors associated with predictors of treatment outcomes (Supplementary Table 2). From our meta-regression analysis, it was revealed that changes in IIEF-EF at 1 month post-intervention in ED patients were not significantly influenced by age ($p=0.2336$) (Supplementary Fig. 1A), BMI ($p=0.9550$) (Supplementary Fig. 1B), hypertension ($p=0.0975$) (Supplementary Fig. 1C), diabetes ($p=0.2239$) (Supplementary Fig. 1D), smokers ($p=0.7863$) (Supplementary Fig. 1E), or duration of ED ($p=0.6640$) (Supplementary Fig. 1F).

The association between PRP intracavernous injection with IIEF-EF at 3 months post-intervention was not significantly influenced by age ($p=0.9760$) (Supplementary Fig. 2A), BMI ($p=0.6656$) (Supplementary Fig. 2B), hypertension ($p=0.9184$) (Supplementary Fig. 2C), diabetes ($p=0.7694$) (Supplementary Fig. 2D), smokers ($p=0.6452$) (Supplementary Fig. 2E), or duration of ED ($p=0.8772$) (Supplementary Fig. 2F).

Our meta-regression analysis also revealed that the changes in IIEF-EF at 6 months post-intervention in patients with ED were not significantly influenced by age ($p=0.8299$) (Supplementary Fig. 3A), BMI ($p=0.8963$) (Supplementary Fig. 3B), hypertension ($p=0.9981$) (Supplementary Fig. 3C), diabetes ($p=0.4458$) (Supplementary Fig. 3D), smokers ($p=0.5264$) (Supplementary Fig. 3E), or duration of ED ($p=0.7673$) (Supplementary Fig. 3F).

3.6. Publication bias

The number of studies for each outcome of interest in this review is less than 10 studies where funnel plots and statistical tests to detect publication bias are less reliable [23,24], so publication bias analysis was not performed in this study.

4. Discussion

The results of our systematic review and meta-analysis showed that PRP intracavernous injection was associated with a significant increase in the IIEF-EF score during 1 month, 3 months, and 6 months after the intervention

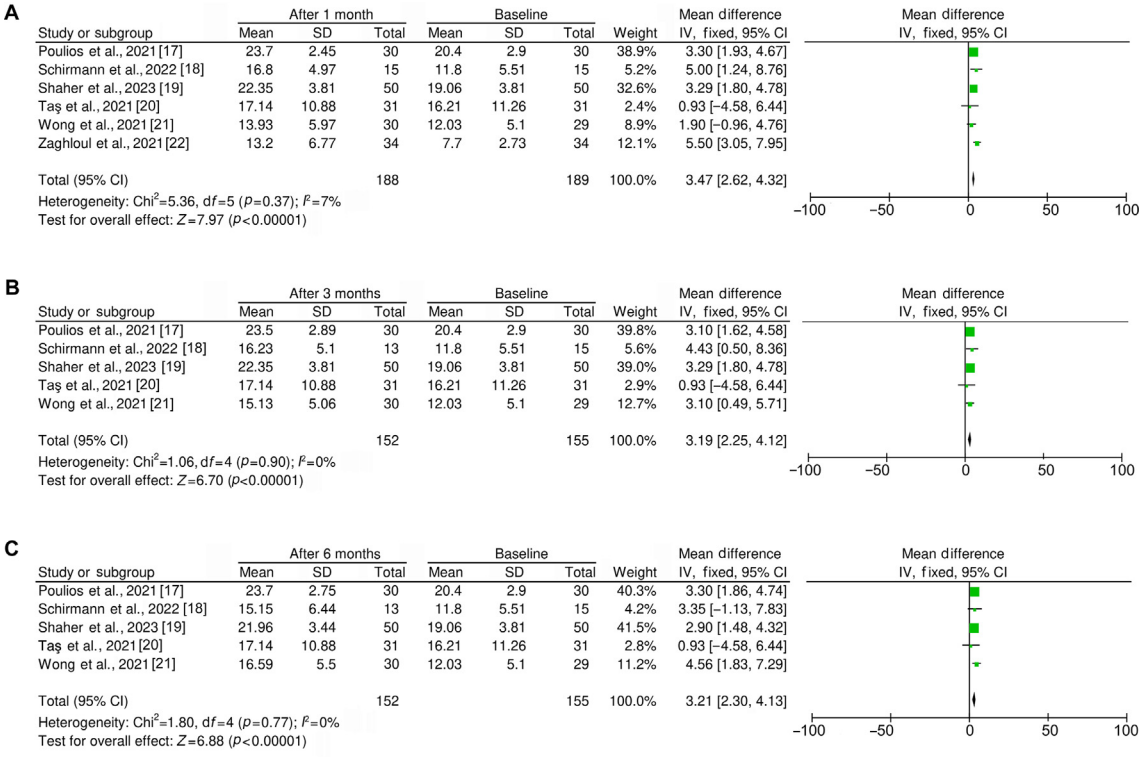

Figure 4 Forest plot that demonstrates the efficacy of post platelet-rich plasm intracavernous injection for patients with erectile dysfunction in terms of erectile function domain of International Index of Erectile Function outcomes at different time when compared with baseline values. (A) 1 month; (B) 3 months; (C) 6 months. CI, confidence interval; SD, standard deviation; IV, inverse-variance.

when compared with baseline values. Changes in the IIEF-EF scores at 1 month, 3 months, and 6 months post-intervention still showed significantly higher results when compared to the placebo. The results of our review also showed that PRP intracavernous injection was also relatively safe without any major or serious adverse events reported.

ED is the inability to achieve or maintain an erection sufficient for satisfactory sexual performance [25]. The condition can be caused by vascular, neurologic, psychological, and hormonal factors [25]. The risk factors for experiencing ED are quite diverse, ranging from diabetes mellitus, hypertension, obesity, age, dyslipidemia, alcohol, smoking, cardiovascular disease, medications, to psychological conditions [26]. ED therapy is still evolving, with current treatments including lifestyle modifications, oral therapy such as phosphodiesterase-5 inhibitors, vacuum erectile devices, and penile implant surgery [26]. PRP is still being developed in the field of regenerative medicine, and one of its benefits is in the treatment of ED [9,27]. PRP is plasma that comes from the whole blood fraction and has a high concentration (3–7 times higher than normal) [9,27]. PRP contains several growth factors such as FGF, PDGF, transforming growth factor-beta, VEGF, and insulin-like growth factor [9,27]. Each growth factor has its own role, with VEGF playing a role in the proliferation and differentiation of mesenchymal stem cells as well as angiogenesis [9,27]. The insulin-like growth factor plays a role in neurite outgrowth and restores smooth muscle integrity, while PDGF and transforming growth factor-beta play a role in angiogenesis and extracellular matrix and collagen synthesis [9,27]. FGF acts as neuroprotection, along with reducing fibrosis and increasing axonal myelination in the corpus cavernosum and nerve regeneration [9,27]. It is believed that all of these functions play a role in restoring erectile function.

As far as we know, this is the first systematic review and meta-analysis which comprehensively analyzes the efficacy and safety of PRP intracavernous injection for the treatment of ED. The previous study by Alkandari et al. [28] published in 2022 with an almost identical topic was only in the form of a systematic review without meta-analysis. However, there are some fundamental differences between the previous review by Alkandari et al. [28] and our current study.

First, the study by Alkandari et al. [28] was only in the form of a systematic review without meta-analysis. The weakness of systematic review studies that are not accompanied by meta-analysis is that if there are conflicting results within the included studies, then no solid conclusions can be drawn [29,30]. In addition, because it only presents a summary of the results of the included studies, the conclusions obtained from a systematic review are weaker than those accompanied by a meta-analysis [29,30]. The meta-analysis is able to present statistical data in the form of numbers accompanied by the corresponding 95% CIs and *p*-values obtained from the combined results of the included studies so that they are more useful

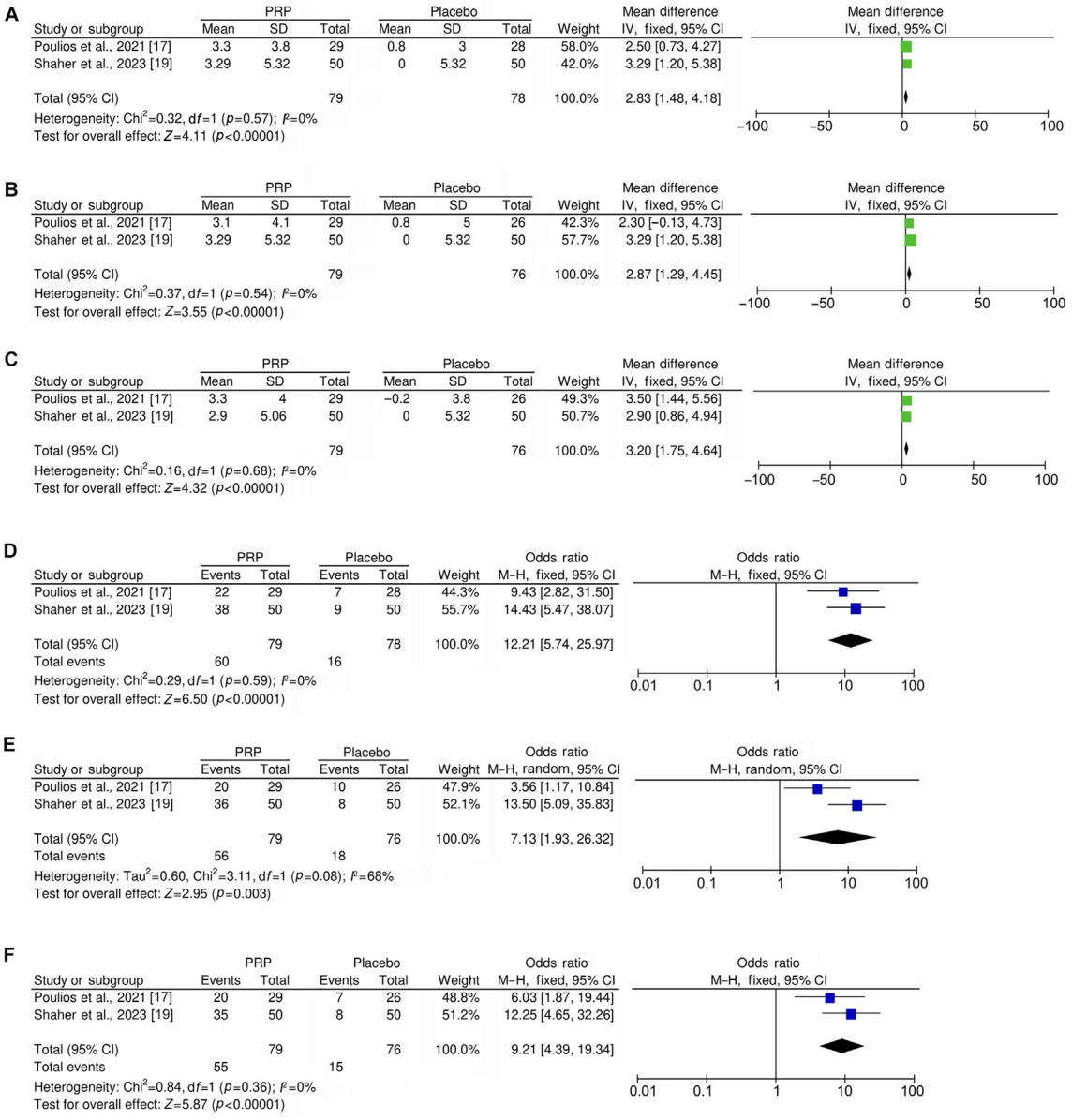

Figure 5 Forest plot that demonstrates the efficacy of post-PRP intracavernous injection for patients with erectile dysfunction in terms of changes in the IIEF-EF outcome at different time when compared with the placebo: (A) 1 month; (B) 3 months; (C) 6 months; and the post-PRP intracavernous injection and the number of patients with minimal clinically important difference in the IIEF-EF scores outcome at different time when compared with a placebo: (D) 1 month; (E) 3 months; (F) 6 months. CI, confidence interval; IIEF-EF, the erectile function domain of International Index of Erectile Function; PRP, platelet-rich plasma; SD, standard deviation; IV, inverse-variance; M—H, Mantel—Haenszel.

to guide clinical practice [29,30]. Our current study does not only carry out a systematic review but also presents the results of a meta-analysis so that stronger and more solid conclusions can be made.

Second, the previous review by Alkandari et al. [28] analyzed not only the use of PRP injection in ED but also Peyronie's disease. Out of a total of 18 articles included in their review, only 10 studies exclusively analyzed the benefits of PRP injection in ED [28]. Of these 10 studies, six were conducted on human populations, while the remaining four were animal studies [28]. If we examine these six in-human studies further, only two of them are full-text articles and the remaining four are only abstracts [28]. Abstracts are generally not recommended for inclusion in the meta-analysis unless the evidence is scarce and conflicting [31,32]. The reason is because that the data presented in the abstracts are very limited, both in the methods and results sections, so it will be difficult to assess the quality or risk of bias of the study [31,32]. Therefore, we have stated abstract-only articles as one of the exclusion criteria for this study. In addition, the two full-text articles included in the previous review by Alkandari et al. [28] also do not match our pre-defined eligibility criteria. Full-text articles by Chalyj et al. [33] was only available in Russian, so it cannot be included in our current study which requires full-text articles to be in

the English language. Another full-text article by Matz et al. [34] did not use PRP but platelet-rich fibrin matrix as an intervention. Platelet-rich fibrin matrix is essentially different from PRP due to the addition of calcium chloride solution in the PRP to convert fibrinogen into fibrin. Our current review requires that the intervention be given in the form of PRP injected into the intracavernous space. In addition, the study by Matz et al. [34] also did not have data regarding the primary outcome, namely the IIEF-EF, so it was not suitable for inclusion in our current review.

Third, the previous review by Alkandari et al. [28] did not fully comply with the PRISMA guidelines. The inclusion and exclusion criteria in their review were not very clear because they only consisted of two sentences without any clarity regarding the types of outcomes to be studied or the design of the studies to be included. Our current review used the Population, Intervention, Comparison/Control, Outcome, Study design format to formulate inclusion and exclusion criteria so that they are more replicable and easier for readers to understand. A previous review by Alkandari et al. [28] also did not clearly state the data extraction process or the risk of bias assessment in the methods section. In the results section, we cannot find the results of the risk of bias assessment from the included studies [28]. This makes the previous review by Alkandari et al. [28] be contrary to the PRISMA guidelines [11], which require a description of the data extraction process as well as the assessment of the risk of bias from included studies.

Finally, because it was only a systematic review, Alkandari et al. [28] was not able to minimize the presence of confounders which were very likely to affect the results of the research. Meanwhile, in our current review, we conducted a meta-regression analysis to see if there was an effect of several confounders such as age, BMI, hypertension, diabetes, smokers, and duration of ED on the results of the IIEF-EF scores. From the results of our regression analysis, it was found that these factors did not significantly influence the relationship between PRP intracavernous injection and the improvement of the IIEF-EF scores.

Our study has several limitations. First, the pooled analytical results of our study were only based on a small number of studies (six interventional studies) with a relatively small number of samples in each study (about 100) due to limited available evidence. Second, most of the included studies were only single-arm prospective interventional studies without any comparison group and only two studies (both are RCTs) included a placebo as the comparators; therefore, no solid evidence can be made regarding the superiority of PRP intracavernous injection when compared with a placebo. Third, information regarding the total cost of the procedure was lacking in the included trials, so it could not be analyzed further.

5. Conclusion

Our systematic review and meta-analysis suggests that PRP intracavernous injection may offer improvement in the erectile function of patients with ED, as evidenced by a significant increase in the IIEF-EF scores at 1 month, 3 months, and 6 months post-intervention. PRP intracavernous injection may also have superiority in the increment of IIEF-EF scores when compared with a placebo. Given the reported adverse events were only mild and self-limiting without any incident of serious adverse events, PRP intracavernous injection is relatively safe to be administered. Further RCTs with larger sample sizes and adequate controls are still needed to confirm the results of our study.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajur.2024.01.001.

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