META-ANALYSIS

Meta-Analysis of Platelet-Rich Plasma in the Treatment of Lower Extremity Venous Ulcer

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ABSTRACT

Objectives • The therapeutic effect of platelet-rich plasma on lower extremity venous ulcers was systematically analyzed.

Methods • A computerized system search was conducted to screen literature that met the inclusion criteria using the method of "subject words + free words." Keywords included "platelet-rich plasma," "lower extremity venous disease," "lower extremity chronic venous insufficiency," "venous ulcer," and "lower extremity venous ulcer." Literature that met the inclusion criteria was searched in four commonly used Chinese databases (HowNet, Chinese biomedical literature, Wanfang, and VIP) and three commonly used foreign databases (Embase, PubMed, and Cochrane Library). The search period extended from the establishment of the databases to December 2021. After extracting the relevant data, a meta-analysis was performed using RevMan 5.3 software to compare the overall effective rate and adverse effects of platelet-rich plasma in the treatment of lower extremity venous ulcers.

Results • The meta-analysis of the overall efficacy rate in the four selected papers showed no heterogeneity among the studies ($P = .35 > 0.1$, $I^2 = 0\% < 50\%$); therefore, a fixed-effect model was used to combine the statistical data. The software analysis results indicated a significant difference in the overall efficacy rate between the experimental group and the control group (OR = 2.09, 95% CI = 1.23-3.34, $P = .002$), with the experimental group showing better results than the control group. The analysis of the four selected papers also suggested potential differences in adverse reactions between the two groups after treatment, but the comparison of safety differences was not significant (OR = 2.13, 95% CI = 0.45-6.79, $P = .17$).

Conclusion • Platelet-rich plasma is effective in the treatment of lower extremity venous ulcers; however, there is no clear safety advantage. This finding needs to be confirmed by large-scale, multi-center research. (*Altern Ther Health Med.* [E-pub ahead of print.])

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BACKGROUND

Lower extremity venous ulcer is an ulcer caused by increased venous pressure due to obstructed venous blood flow, with or without the presence of varicose veins. These ulcers account for 45.00% to 90.00% of all leg ulcers, with an incidence rate of approximately 1.50%. Lower extremity venous ulcers are characterized by prolonged symptoms and signs indicating abnormal form and function of the venous system. They are primarily classified into two types: venous obstruction and venous valve reflux. The venous obstruction type is typically caused by venous thrombosis, external pressure on the vein, or venous tumors that lead to venous blockage. In the venous valve reflux type, the venous valves fail to close completely, resulting in partial venous blood reflux. The incidence of lower extremity venous ulcers is rising rapidly due to the gradual aging of the global population.[1] The cost of treating venous ulcers in the lower extremities is higher than in other countries. Additionally, the social and economic burden of these ulcers is increasing due to factors such as the aging population, the global spread of smoking, and the rising prevalence of type 2 diabetes. Platelet-rich concentrate (PRC) has emerged as a significant trend in fibrin sealant technology in recent years. In particular, platelet-rich fibrin (PRF) has gradually been applied to the treatment of chronic wounds, achieving promising healing outcomes. Currently, PRF is widely used in stomatology, wound repair, bone regenerative medicine, and other fields, with numerous reports highlighting its positive effects on chronic wound healing. Platelet-rich plasma, a concentrated component of platelets obtained from whole blood after centrifugation, is a practical method for preventing or treating the onset or recurrence of lower

extremity venous ulcer disease. When platelet receptors are activated, various growth factors are released, containing a significant amount of fibrin, which is beneficial for promoting the wound repair process in tissues or cells at the site of the ulcer.[2] Today, platelet-rich plasma has demonstrated therapeutic effects in several fields, including burn plastic surgery and orthopedics, and has been shown to be relatively effective.[3]. However, large-sample, randomized controlled evidence supporting the use of platelet-rich plasma for the treatment of lower extremity venous ulcers remains limited. The objective of this research is to systematically analyze the results of randomized controlled trials on the use of platelet-rich plasma for lower extremity venous ulcers in current clinical practice, applying statistical principles to evaluate its clinical efficacy. This analysis aims to provide an evidence-based foundation for its clinical application, and to comprehensively assess the clinical efficacy and safety of platelet-rich plasma in the intervention of lower extremity venous ulcers. The findings are presented as follows.

DATA AND METHODS

Literature search

A computer system was used to search four commonly used Chinese databases (HowNet, Chinese biomedical literature, Wanfang, and VIP) and three commonly used foreign databases (EMBASE, PubMed, and Cochrane Library). The corresponding English keywords included "platelet-rich plasma," "venous disease of lower limbs," "synchronous venous insufficiency of lower limbs," "venous ulcer," and "venous ulcer of lower limbs." The search utilized a combination of "subject terms + free words" to expand the scope, and references were screened to identify all literature that met the selected criteria. The specific search period extended from the establishment of the databases to the end of December 2021.

Document access standards

Inclusion criteria: (1) Published literature in Chinese and English, (2) The study design was a randomized controlled trial, (3) The investigation's observation outcomes included relevant indexes for both the test group (TG) and the control group (CG), such as the overall effective rate and adverse reactions.

Exclusion criteria: (1) Studies that solely reported the clinical effect of platelet-rich plasma on lower extremity venous ulcers. (2) Literature with incomplete or unreported information on relevant indicators and data. (3) Studies not focused on venous ulcers of the lower limbs. (4) Repeated papers, reviews, or conference publications involving the same research population. (5) Studies with an obviously insufficient sample size, specifically those with fewer than 50 cases.

Literature screening and data extraction

Two to three team members will independently evaluate the selected documents, conduct their own screenings, and be responsible for extracting relevant data. Cross-checking will be performed to ensure accuracy, and any discrepancies will be resolved by a third team member. If any information in the literature is found to be inaccurate, the core author of the paper will be contacted as necessary, and the research team will work to refine the data details. Initially, the titles and abstracts of the literature will be reviewed for preliminary screening to remove inconsistent studies. The full content of the remaining literature will then be read for a more thorough screening process. A self-designed data extraction form will be used to effectively capture the information from the included studies, covering: (1) basic information of the article, such as title, core author, and publication date; (2) case grouping, where the subjects in the research literature are randomly divided into two groups: the platelet-rich plasma group and the routine group; (3) quality-related factors, such as whether the study is randomized and whether there is dropout or loss to follow-up among the research subjects; and (4) relevant data indicators, including treatment effect and adverse reactions. The evaluation criteria for treatment effects will follow the guidelines specified in the literature.

Quality evaluation of selected studies

The quality of the research will be assessed using the risk of bias assessment tool provided by Cochrane and the modified Jadad evaluation scale. The Cochrane tool evaluates seven key items, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential sources of bias. Each item in the article will be evaluated for bias risk as "low," "unclear," or "high." The modified Jadad scale assesses the quality of the studies based on four criteria: the method of random sequence generation, allocation concealment, the blinding process, and the handling of follow-up losses. Based on the comprehensive evaluation score, the included studies will be categorized as high quality (scoring between 4-7 points) or low quality (scoring between 1-3 points).

Statistical methods

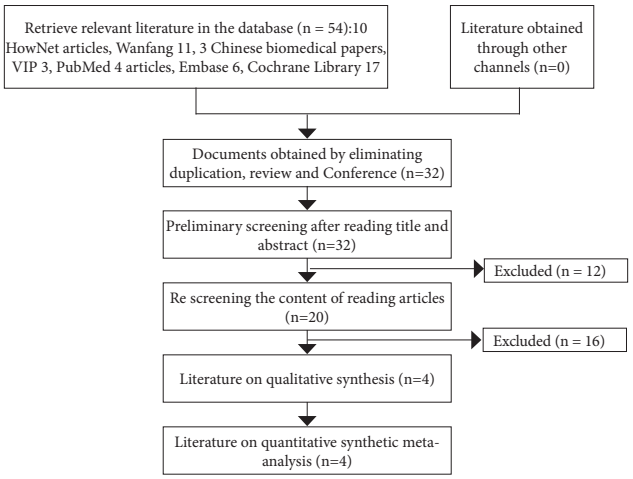
The selected research data were systematically analyzed using RevMan 5.3 software. The odds ratio (OR) was used to represent categorical data, while continuous data were expressed as mean difference (MD), both with a 95% confidence interval (CI) and a significance level of $\alpha = 0.05$, with $P < .05$ indicating a statistically significant difference. The heterogeneity among the studies was assessed using the I^2 statistic. If I^2 is less than 50%, it indicates low heterogeneity. When I^2 exceeds 50%, significant heterogeneity is considered to exist among the studies, prompting the use of a random effects model to explore potential causes and conduct subgroup analyses. If I^2 is below 50%, heterogeneity is deemed low, and if I^2 equals 0, the studies are considered homogeneous, in which case a fixed effects model is applied. When heterogeneity is minimal or absent and $P \leq .05$, the study is regarded as statistically significant, indicating a meaningful difference between the two treatment methods. Conversely, if these criteria are not met, the study does not show significant statistical differences. Additionally, the degree of publication bias in the selected literature was analyzed.

RESULTS

Search results

A total of 54 relevant papers were initially identified, including 10 from China HowNet, 11 from the Wanfang database, 3 from the China Biomedical Literature database, 3 from the VIP database, 4 from PubMed, 6 from EMBASE, and 17 from the Cochrane Library. Using Note Express software, 22 papers were excluded due to being reviews, duplicates, or conference papers. After reviewing the titles and abstracts, 12 papers that did not meet the inclusion criteria were further excluded. The remaining 20 papers underwent full-text review, resulting in 4 papers (2 in Chinese and 2 in English) being selected for the final meta-analysis. The literature screening process is illustrated in Figure 1.

Figure 1. Flowchart of the article being filtered



Overall effective rate

For the overall effective rate, the meta-analysis of the four selected papers indicated no heterogeneity among the studies ($P = .35 > 0.1$, $I^2 = 0\% < 50\%$); therefore, a fixed effects model was used to combine the statistical data. The software analysis revealed a significant difference in the overall effective rate between the experimental group (EG) and the control group (CG) (OR = 2.09, 95% CI = 1.23-3.34, $P = .002$). See Table 1.

Table 1. Comparison of the overall effective rate of the two groups

Investigation or Subgroup	EG		CG		Odds Ratio	
	The number of events	total number	The number of events	total number	Weight	M-H, Fixed, 95%*CI*
Xu qiang 2014	29	30	26	30	5.0%	4.46[0.47,42.51]
Ren junwen 2017	27	32	21	32	18.9%	2.83[0.85,9.40]
Stacey 2000	31	42	31	44	45.6%	1.18[0.46,3.04]
Manuel 2016	31	31	30	30		Not estimable
Total (95%*CI*)		250		247	100.0%	2.09[1.23,3.34]
overall events	227		201			

Note: Nonuniformity: χ^2=3.53, df = 4 ($P = .35$); $I^2 = 0\%$. The test of overall effect: Z=2.97 ($P = .002$)

Safety

The software analysis of the four selected papers suggested potential differences in adverse reactions between the two groups following treatment, but these differences were not statistically significant (OR = 2.13, 95% CI = 0.45-6.79, $P = .17$). This indicates that the safety comparison between the two groups was not significant. See Table 2.

Table 2. Safety comparison

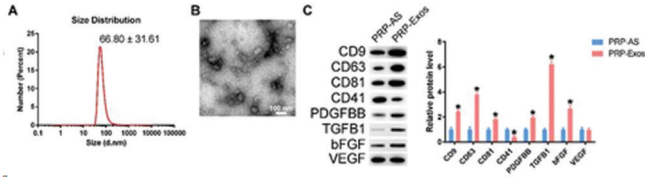
Investigation or Subgroup	EG		CG		CG	
	The number of events	The number of events	The number of events	Total	Weight	M-H, Fixed, 95%*CI*
Xu qiang 2014	0	30	0	30		Not estimable
Ren junwen 2017	0	32	0	32		Not estimable
Stacey 2000	2	42	0	44	14.1%	5.49[0.26,117.88]
Manuel 2016	0	31	0	30		Not estimable
Total (95%*CI*)		250		247	100.0%	2.13[0.45,6.79]
overall events	7		3			

Note: Nonuniformity: χ^2=0.46, df = 1 ($P = .50$); $I^2 = 0\%$. The test of overall effect: $Z = 1.23$ ($P = .17$).

Literature publication bias

RevMan 5.3 software was used to analyze the data from the 4 selected papers and assess the degree of publication bias in the results. The final analysis showed that the funnel plot of the overall effective rate for the experimental and control groups did not display a completely symmetrical distribution, indicating a certain degree of bias in the study results.

Figure 2. Characterization of different PRP-Exos: (A) Particle size distribution measured by DLS. (B) Morphological observation using transmission electron microscopy. (C) Western blotting and quantitative analysis of exosome surface markers and cargo. The scale is 100 nm. $P < .05$ compared with PRP-AS.

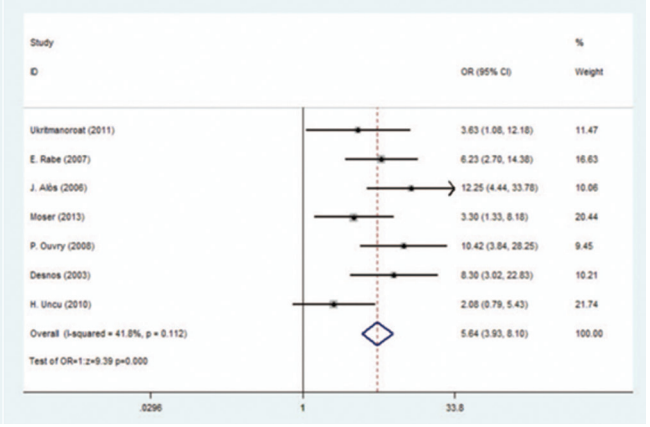


DISCUSSION

Traditional treatment methods for lower extremity venous ulcers often require extended intervention periods. Surgical options, such as skin grafting, can be associated with significant trauma, low survival rates, and high recurrence rates. Moreover, some patients are unable to tolerate surgery, as shown in Figure 2.[4-5] Currently, there are no highly effective treatments available for lower extremity venous ulcers, and different therapeutic approaches can significantly impact patients' quality of life.

Several studies have demonstrated that platelet-rich plasma (PRP) contains various effective growth factors, including vascular endothelial growth factor and epidermal growth factor (see Figure 3).[6-8] These growth factors work synergistically to accelerate tissue and blood vessel formation and stimulate nerve repair, thereby improving the therapeutic effect. Additionally, other research has shown that PRP has antibacterial properties against *Staphylococcus aureus*, playing a crucial role in combating infection, maintaining wound integrity, and promoting healing.[9] In recent years,

Figure 3. Forest plots evaluating the effectiveness of foam sclerotherapy versus liquid sclerotherapy.



with rapid advancements in science and technology, PRP has been increasingly applied to the treatment of lower extremity venous ulcers, achieving relatively favorable clinical outcomes. Studies have confirmed that PRP-targeted intervention in granulation tissue associated with refractory venous ulcers of the lower limbs results in the detection of multiple growth factors.[10] Furthermore, PRP is rich in fibrin, which provides a biological scaffold for chemotactic cells and growth factors, accelerating wound contraction and healing.[11-13] In addition to its platelet-rich components, PRP contains growth factors that stimulate tissue regeneration.

In this study, four randomized controlled trials were included, involving 167 subjects in the EG and 165 subjects in the CG, with a total sample size of 332 cases. One article was rated as quality grade A, and three were rated as quality grade B, indicating that the selected articles were of high quality. As the studies were conducted in hospital or community settings, patient turnover was low. The evaluation criteria for lower extremity venous ulcers used in this study strictly adhered to internationally accepted clinical standards, ensuring that the outcome indicators are highly reliable.

This meta-analysis systematically reviewed four prospective, randomized controlled trials, involving 332 patients with lower extremity venous ulcers. By summarizing and analyzing efficacy indicators such as overall efficacy rate and adverse effects, the study concluded that the overall efficacy rate of patients with lower extremity venous ulcers significantly improved with the intervention of platelet-rich plasma. Since the 1990s, there have been reports on the application of platelet-rich plasma therapy, particularly in the treatment of chronic wounds.[14] There are various methods for obtaining platelet-rich plasma, but no standardized approach exists. The most common method involves extracting the patient's own blood, separating it by centrifugation, and removing certain blood components, including white blood cells and red blood cells.[15] The concentrated platelet-rich plasma obtained through this process contains a high concentration of growth factors, with a platelet concentration of 1×10^9/ml, which is considered the ideal concentration for effective intervention.

The concentration of platelet growth factors in the study group was significantly lower than that reported in the CG in a study published in 2000. It is hypothesized that the platelet growth factor concentration in this study group is considerably lower than that in the 2000 CG study. The other three research papers are more recent and closer in time to the current study. The overall treatment effect shows that outcomes in the EG are significantly better than those in the CG. However, due to the limited sample size, a comprehensive analysis involving large samples and randomized, double-blind clinical trials is still necessary to objectively evaluate the safety and feasibility of using platelet-rich plasma for treating lower extremity venous ulcers.

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AUTHORS' CONTRIBUTIONS
All authors have read and agreed to the published version of the manuscript.

FUNDING
Not applicable.

AVAILABILITY OF DATA AND MATERIALS
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE
The study was approved by the hospital's ethics committee.

CONSENT FOR PUBLICATION
The patients have given their consent for publication. Written informed consent was obtained from the patients for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

COMPETING INTERESTS
The authors declare that they have no competing interests.

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