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Effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds: A meta-analysis

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Abstract

We performed a meta-analysis to evaluate the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds. A systematic literature search up to March 2022 was performed and 1435 subjects with diabetic foot ulcer wounds at the baseline of the studies; 723 of them were treated with platelet-rich plasma, and 712 used control. Odds ratio (OR) with 95% confidence intervals (CIs) was calculated to assess the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds using the dichotomous method with a random or fixed-effect model. The use of autologous platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control (OR, 1.95; 95% CI, 1.49-2.56, $P < 0.001$). The use of allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control (OR, 6.19; 95% CI, 2.32-16.56, $P < 0.001$). The use of autologous and allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. Though, the analysis of outcomes should be with caution because of the low number of studies in certain comparisons, for example, allogeneic platelet-rich plasma compared with control.

KEYWORDS

allogeneic, autologous, complete-healed, control, diabetic foot ulcer wounds, platelet-rich plasma

Key Messages

- We performed a meta-analysis to evaluate the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds.

Fan Gong and Yun Zhang contributed equally to this article and should be considered co-authors.

- The use of autologous and allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control.
- Though, the analysis of outcomes should be with caution because of the low number of studies in certain comparisons, for example, allogeneic platelet-rich plasma compared with control.

1 | INTRODUCTION

Diabetic foot ulcer wounds are the leading cause of leg amputations in the world. Neuropathy, peripheral arterial disease, foot deformities, and undetected minor trauma are accountable for the progress of foot ulcer wounds. Once the foot ulcer wound appears, healing must be completed very fast since the ulcer is a portal to infection resulting in leg amputation in numerous subjects. Apart from repeat trauma in the insensitive foot with or without ischemia, changes in wound healing biology must also be considered. Subjects with diabetes have decreased wound healing, resulting in foot ulcer wounds turning chronic.[1] Chronic foot ulcer wounds are frequently delayed in the inflammatory phase with decreased granulation tissue formation.[2] Wound healing is a complex procedure involving multiple cell populations, extracellular matrix, and soluble mediators, for example, growth factors and cytokines.[3] Several irregularities in diabetes that can change wound healing biology have been reported. The interplay between the accumulation of advanced glycation end-products and inflammation can result in diabetic foot ulcer wounds.[4] The harmful influence of hyperglycemia on neutrophil function is an additional factor that can influence the wound healing cascade. Enzymes released by neutrophils comprising elastases and metalloproteinases can produce degradation of the extracellular matrix and peptide growth factors involved in healing.[5] Also, abnormal expression of growth factors has been observed in diabetic foot ulcer wounds.[6] Given these pathologic irregularities seen in diabetes, specific synthetic growth factors topically used to manage diabetic foot ulcer wounds have been suggested; these comprise recombinant human platelet-derived growth factor, recombinant human basic fibroblastic growth factor, or recombinant human vascular endothelial growth factor.[7] For example, the platelet-derived growth factor is released upon platelet degranulation and plays a role in all phases of wound healing. Also, platelet-derived growth factor stimulates mitogenicity and chemotaxis of neutrophils, fibroblasts, macrophages, and smooth muscle cells to the wound place.[8] Growth factor levels are reduced in chronic ulcers and the effectiveness of recombinant human platelet-derived growth factor, and recombinant human vascular endothelial growth factor has been reported in diabetic foot ulcer wound treatment. Even though the fact that the food and drug Administration approved topical usage of recombinant human platelet-derived growth factors (Becaplermin, Regranex®), additional well-designed trials are needed to define the role of recombinant human platelet-derived growth factors in managing diabetic foot ulcer wounds.[9] Though, single growth factors can be inadequate to encounter the biological complexities of diabetic foot ulcer wounds. An additional method recommended for managing diabetic foot ulcer wounds is using platelet-rich plasma depending on the richness and complex secretion of these cells that comprise more than 300 proteins.[10] Also to coagulation and related proteins, platelet-rich plasma comprises proteases and protease inhibitors, antimicrobial proteins, cytokines, and growth factors among others.[11] Using platelet-rich plasma to manage diabetic foot ulcer wounds might be a useful method depending on the pathophysiology of wound healing in diabetes; though, a good indication concerning such a method is missing.[12] It has been recommended that platelet-rich plasma must be used on diabetic foot ulcer wounds which continue unhealed after standard management.[13] Though, the costs related to managing diabetic foot ulcer wounds with platelet-rich plasma are higher than using standard treatment.[14] For that reason, the application of this therapeutic method in health care systems can be hard and must be depending on its cost-effectiveness. This meta-analysis aims to evaluate the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds. Platelet-rich plasma is commonly prepared as autologous platelet-rich plasma and allogeneic platelet-rich plasma. In the fields of veterinary medicine and human medicine, autologous platelet-rich plasma could be considered an effective adjunctive therapy in promoting the healing of skin wounds in animals. Similarly, autologous platelet-rich plasma has been verified as a feasibility and safety treatment for venous leg ulcers. So this meta-analysis was done using the autologous platelet-rich plasma and allogeneic platelet-rich plasma.

2 | METHOD

2.1 | Study design

The current meta-analysis of included research studies regarding the epidemiology statement,[15] with a pre-established study protocol. Numerous search engines including, OVID, Embase, PubMed, and Google Scholar databases were used to collect and analyse data.

2.2 | Data pooling

Data was collected from randomised controlled trials, observational studies, and retrospective studies investigating the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds and studying the influence of different outcomes. Only human studies in any language were considered. Inclusion was not limited by study size. Publications excluded were review articles and commentary and studies that did not deliver a measure of an association. Figure 1 shows the whole study process. The articles were integrated into the meta-analysis when the following inclusion criteria were met:

1. The study was a prospective study, observation study, randomised controlled trial, or retrospective study.
2. The target population was subjects with diabetic foot ulcer wounds.
3. The intervention program was based on platelet-rich plasma and control.
4. The study included platelet-rich plasma compared with control.

The exclusion criteria were:

1. Studies that did not determine the influences of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds.
2. Studies with subjects treated with medication other than platelet-rich plasma and control.
3. Studies did not focus on the effect of comparative results.

2.3 | Identification

A protocol of search strategies was prepared according to the PICOS principle,[16] and we defined it as follows: P (population): subjects with diabetic foot ulcer wounds; I (intervention/exposure): platelet-rich plasma; C (comparison): platelet-rich plasma compared with control; O (outcome): complete-healed diabetic foot ulcer wounds; and S (study design): no restriction.[17]

First, we conducted a systematic search of OVID, Embase, Cochrane Library, PubMed, Google Scholar databases till March 2022, using a blend of keywords and similar words for diabetic foot ulcer wounds, platelet-rich plasma, control, autologous, allogeneic and complete-healed diabetic foot ulcer wounds as shown in Table 1. All the recruited studies were compiled into an EndNote file, duplicates were removed, and the title and abstracts were checked and revised to exclude studies that have not reported an association between platelet-rich plasma and control of diabetic foot ulcer wounds.

2.4 | Screening

Data were abridged on the following bases; study-related and subject-related characteristics in a standardised form; last name of the primary author, period of study, year of publication, country, region of the studies, and study design; population type, the total number of subjects, demographic data, clinical and treatment characteristics, categories, qualitative and quantitative method of evaluation, information source, outcome evaluation, and statistical analysis.[18] When there were different data from one study based on the assessment of the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds, we extracted them independently. The risk of bias in these studies; individual studies were evaluated using the two authors independently assessed the methodological quality of the selected studies. The "risk of bias tool" from the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 was used to assess methodological quality.[19] In terms of the assessment criteria, each study was rated and assigned to one of the following three risks of bias: low: if all quality criteria were met, the study was considered to have a low risk of bias; unclear: if one or more of the quality criteria were partially met or unclear, the study was considered to have a moderate risk of bias; or high: if one or more of the criteria were not met, or not included, the study was considered to have a high risk of bias. Any inconsistencies were addressed by a reevaluation of the original article.

2.5 | Eligibility

The main outcome focused on the assessment of the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds and an analysis of the platelet-rich plasma compared with control was extracted to form a summary.

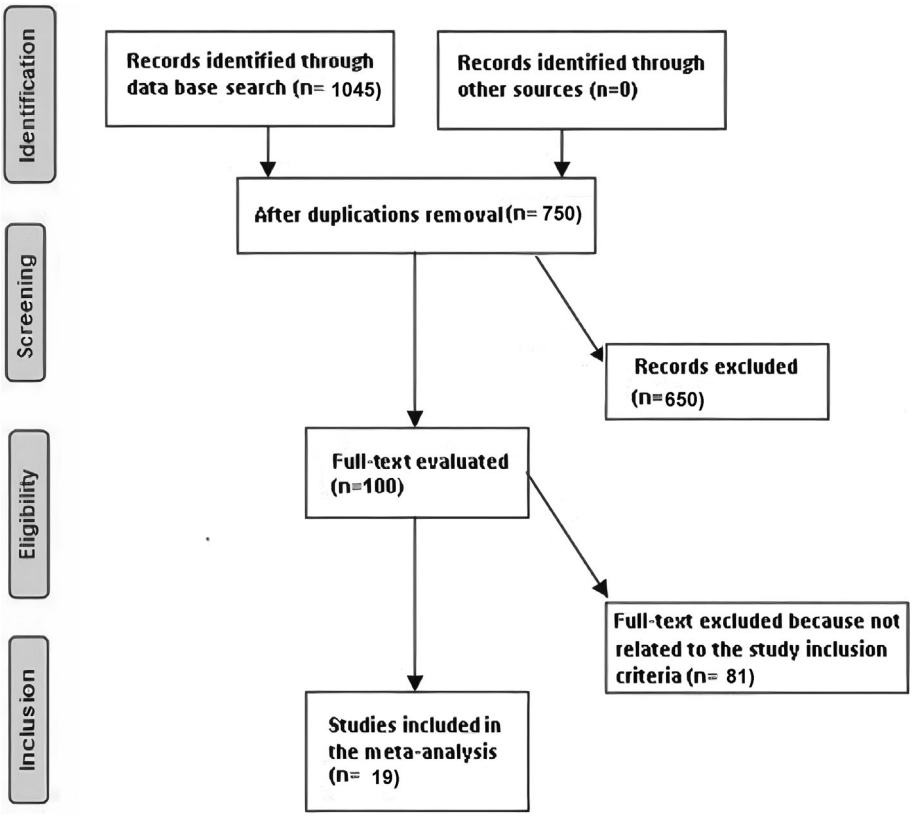

FIGURE 1 Schematic diagram of the study procedure

TABLE 1 Search strategy for each database

Database	Search strategy
Pubmed	#1 "diabetic foot ulcer wounds"[MeSH Terms] OR "platelet-rich plasma"[All Fields] OR "autologous"[All Fields] #2 "allogeneic"[MeSH Terms] OR "diabetic foot ulcer wounds"[All Fields] #3 #1 AND #2
Embase	'diabetic foot ulcer wounds'/exp OR 'platelet-rich plasma'/exp OR 'autologous'/exp OR "serological conversion" #2 'allogeneic'/exp OR 'diabetic foot ulcer wounds' #3 #1 AND #2
Cochrane library	(diabetic foot ulcer wounds):ti,ab,kw (platelet-rich plasma):ti,ab,kw OR (autologous): ti,ab,kw (Word variations have been searched) #2 (serological conversion):ti,ab,kw OR (allogeneic):ti,ab,kw OR (diabetic foot ulcer wounds) #3 #1 AND #2

2.6 | Inclusion

Sensitivity analyses were limited only to studies reporting and analysing the influence of the platelet-rich plasma compared with control. Comparisons between platelet-rich plasma and controls were performed for subcategory and sensitivity analyses.

2.7 | Statistical analysis

The present meta-analysis was based on the dichotomous method with a random- or fixed-effect model to calculate the odds ratio (OR) and 95% confidence interval (CI). The I^2 index was calculated which was between 0 and 100 (%). Values of about 0%, 25%, 50%, and 75% indicated no, low, moderate, and high heterogeneity, respectively.[20] When I^2 was more than 50%, the random effect model was selected; while it was less than 50%, the fixed-effect model we used. A subcategory analysis was completed by stratifying the original evaluation per outcome categories as described before. A P-value <0.05 was considered statistically significant for differences between subcategories of the current analysis. Publication bias was evaluated quantitatively using the Egger regression test (publication bias considered present if $P \geq 0.05$), and qualitatively, by visual examination of funnel plots of the logarithm of ORs vs their standard errors (SE).[16] All P-values were determined using 2 tailed test. The statistical analyses and graphs were presented using Reviewer Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

TABLE 2 Characteristics of the selected studies for the meta-analysis

Study	Country	Total	Platelet-rich plasma	Control
Steed, 1992[21]	USA	13	7	6
Steed, 1996[22]	USA	36	18	18
Driver, 2006[23]	USA	72	40	32
Kakagia, 2007[24]	Greece	32	16	16
Jeong, 2010[25]	Korea	100	52	48
Saad Setta, 2011[26]	Egypt	24	12	12
Li, 2012[27]	China	117	59	58
Karimi, 2016[28]	Iran	50	25	25
Ahmed, 2017[29]	Egypt	56	28	28
Rainys, 2019[30]	Lithuania	69	35	34
Elsaid, 2020[31]	Egypt	24	12	12
Liao, 2020[32]	China	200	100	100
Habeeb, 2020[33]	Egypt	44	22	22
Hossam, 2021[34]	Egypt	160	80	80
Alamdari, 2021[35]	Iran	90	43	47
Hossam, 2021[34]	Iran	90	43	47
Helmy, 2021[36]	Egypt	80	40	40
Meamar, 2021[37]	Iran	17	10	7
Tofigh, 2022[37]	Iran	161	81	80
Total		*1435*	*723*	*712*

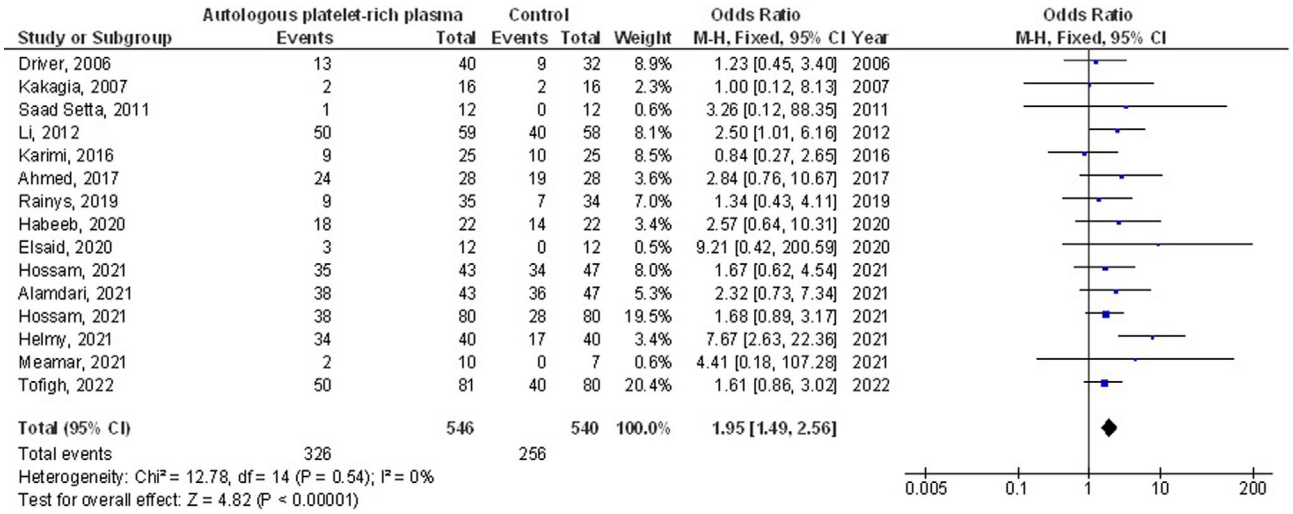

FIGURE 2 Forest plot of the effect of autologous platelet-rich plasma compared with control on complete-healed diabetic foot ulcer wounds outcomes

3 | RESULTS

A total of 1045 relevant studies were screened, of which 19 studies between 1992 and 2022, met the inclusion criteria and were involved in the meta-analysis.[21–37] Data obtained from these studies were shown in Table 2.

The selected studies included 1435 subjects with diabetic foot ulcer wounds at the baseline of the studies; 723 of them were treated with platelet-rich plasma, and 712 used control.

The study's size ranged from 13 to 200 subjects at the start of the study. 15 studies reported data stratified to the autologous platelet-rich plasma compared to control,

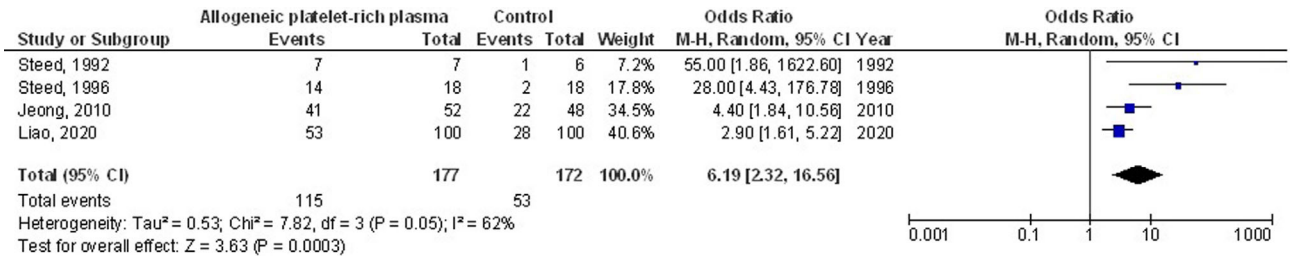

FIGURE 3 Forest plot of the effect of allogeneic platelet-rich plasma compared with control on complete-healed diabetic foot ulcer wounds outcomes

and 4 studies reported data stratified to the allogeneic platelet-rich plasma compared to control.

The use of autologous platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control (OR, 1.95; 95% CI, 1.49-2.56, $P < 0.001$) with no heterogeneity ($I^2 = 0\%$) as shown in Figure 2. The use of allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control (OR, 6.19; 95% CI, 2.32-16.56, $P < 0.001$) with moderate heterogeneity ($I^2 = 62\%$) as shown in Figure 3.

It was not applicable to set adjustments of individual factors such as age, ethnicity, and gender into stratified models to study their effect on the comparison results because there have been no reported data regarding these variables. Moreover, there was no evidence of publication bias ($P = 0.88$), according to the visual inspection of the funnel plot and quantitative measurements using the Egger regression test. However, most of the included randomised controlled trials were shown to have low methodological quality, no selective reporting bias, as well as relatively incomplete outcome data and selective reporting.

4 | DISCUSSION

The current meta-analysis involved 19 studies recruiting 1435 subjects with diabetic foot ulcer wounds at the baseline of the studies; 723 of them were treated with platelet-rich plasma, and 712 used control.[21–38] The use of autologous platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. The use of allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. Yet, the analysis of results must be done with attention due to the low sample size of some of the selected studies found for the meta-analysis, 14 out of 19 studies with less than 100 subjects as sample size; recommending the necessity for additional studies to confirm these findings or perhaps to significantly impact confidence in the effect assessment Though, the analysis of outcomes should be with caution because of the low number of studies in certain comparison, for example, allogeneic platelet-rich plasma compared with control.

The platelet-rich plasma's safety profile does not vary from standard management in terms of the possibility of incidence of wound problems or reappearances; though, platelet-rich plasma might reduce the risk of adverse events. The biological hypothesis underlying platelet-rich plasma use is depending on the lack of growth factors in chronic wounds.[10] Platelet-rich plasma purposes to correct biological features related to reduced healing by providing a physiologic pool of cytokines with healing activity. Though single recombinant growth factors (ie, recombinant human platelet-derived growth factor, recombinant human vascular endothelial growth factor, recombinant human basic fibroblastic growth factor) have revealed some advantages,[9] the interaction of multiple growth factors and cytokines is needed to encounter the requirements of chronic ulcer wounds. Though, the outcomes of this study must be understood with carefulness since there were no statistical differences in the epithelialized area. Furthermore, there is no accessible indication of whether this management progresses the level of pain or health-associated quality of life at the end of the intervention. The low number of controlled studies with a low number of subjects and alterations in methodology can bias the variables, the number of complete healed wounds is the most related and it was used in all studies. Additional result variables, for example, decrease of the ulcer wound area[28,39] or volume[21,28] based on the quality of the measuring tool. In general, diabetic foot ulcer wounds are of variable depth, limiting the rationality of the isolated area measurements. Furthermore, the depth of some diabetic foot ulcer wounds is not evident as eyesight and unexpected tunnelling might produce result values. Relapses or additional amputations vary among studies but their incidence form part of a more inclusive method, which comprises not only glycemic control but also proper definitive divesting after healing

and management in a multidisciplinary setting.[21] In a retrospective controlled study, comprising 50 diabetic foot ulcer wounds related to peripheral vascular disease in each group (platelet-rich plasma and control), platelet-rich plasma dressing significantly reduced the healing time after restoring blood circulation utilising percutaneous transluminal angioplasty.[40] Platelet-rich plasma might be specified as local management establishing part of an interdisciplinary inclusive program vital for the healing of diabetic foot ulcer wounds. Though, peripheral neuropathy, foot deformity, and augmented plantar stress will continue after biological healing, causing reappearances. The findings of this study showed that though platelet-rich plasma influences positively ulcer wound healing, the management treatment requires some standardisation to generate robust data to progress evidence-based guidelines. Clinical studies were critically analysed with a focus on the variability of platelet-rich plasma technologies, which cover two characteristics: first, platelet-rich plasma arrangement, and second, the usage process. To recognise the present level of showing and the difference in platelet-rich plasma protocols, we reviewed relevant data in the articles comprised for meta-analysis. Showing these two main features of the intervention is needed to allow reproducibility and comparison between studies. Other formulations without fibrinogen, referred to as platelet-rich plasma lysates or releases were used in the earliest studies.[21] Whether fibrinogen donates to wound healing is indistinct since positive outcomes have been found with both formulations. Allogeneic platelets activated with thrombin but without plasma, fibrinogen was effective in some protocols[21]; though, thrombin-activated platelet-rich plasma (allogeneic platelets and plasma) was also effective.[40] Sometimes, the terms platelet gel and platelet release are interchanged, which confuses.[41]

This meta-analysis showed the influence of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds.[42–49] However, further studies are still needed to illustrate these potential relationships as well as to compare the effect of platelet-rich plasma compared with control on the outcomes studied. These studies must comprise larger more homogeneous samples. This was suggested also in a previous similar meta-analyses study which showed similar promising outcomes of platelet-rich plasma in improving the hepatocellular carcinoma and reducing the complete-healed diabetic foot ulcer wounds.[50–52] Well-conducted randomised controlled trials are needed to assess these factors and the combination of different ages, ethnicity, and other variants of subjects; since our meta-analysis study could not answer whether different ages, ethnicity, and gender are associated with the results.

In summary, the data suggest that the use of autologous platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. The use of allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control.

4.1 | Limitations

There may be selection bias in this study since so many of the studies found were excluded from the meta-analysis. However, the studies excluded did not satisfy the inclusion criteria of our meta-analysis. Also, we could not answer whether the results are associated with age, ethnicity, and gender or not. The study designed to assess the effect of platelet-rich plasma vs standard management for the treatment of diabetic foot ulcer wounds was based on data from previous studies, which might cause bias induced by incomplete details. The meta-analysis consisted of 19 studies; 14 of them were small, ≤100. Possible bias-inducing factors were the variables including age, sex, and the nutritional status of subjects. Unfortunately, there might be some unpublished articles and missing data which might lead to bias in the studied effect.

5 | CONCLUSIONS

The use of autologous platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. The use of allogeneic platelet-rich plasma resulted in significantly higher complete-healed diabetic foot ulcer wounds compared with control. Yet, the analysis of results must be done with attention due to the low sample size of some of the selected studies found for the meta-analysis, recommending the necessity for additional studies to confirm these findings or perhaps to significantly impact confidence in the effect assessment. Though, the analysis of outcomes should be with caution because of the low number of studies in certain comparisons, for example, allogeneic platelet-rich plasma compared with control.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current meta-analysis are available from the corresponding author via reasonable request.

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REFERENCES

1. Blakytny R, Jude EB. Altered molecular mechanisms of diabetic foot ulcers. *Int J Low Extrem Wounds*. 2009;8(2):95-104.
2. Gary Sibbald R, Woo KY. The biology of chronic foot ulcers in persons with diabetes. *Diabetes Metab Res Rev*. 2008;24(S1): S25-S30.
3. Velnar T, Bailey T, Smrkolj V. The wound healing process: an overview of the cellular and molecular mechanisms. *J Int Med Res*. 2009;37(5):1528-1542.
4. Hennessey PJ, Ford EG, Black CT, Andrassy RJ. Wound collagenase activity correlates directly with collagen glycosylation in diabetic rats. *J Pediatr Surg*. 1990;25(1):75-78.
5. Menke NB, Ward KR, Witten TM, Bonchev DG, Diegelmann RF. Impaired wound healing. *Clin Dermatol*. 2007;25(1):19-25.
6. Jude E, Blakytny R, Bulmer J, Boulton AJM, Ferguson MWJ. Transforming growth factor-beta 1, 2, 3 and receptor type I and II in diabetic foot ulcers. *Diabet Med*. 2002;19(6):440-447.
7. Barrientos S, Brem H, Stojadinovic O, Tomic-Canic M. Clinical application of growth factors and cytokines in wound healing. *Wound Repair Regen*. 2014;22(5):569-578.
8. Heldin C-H, Westermark B. Mechanism of action and in vivo role of platelet-derived growth factor. *Physiol Rev*. 1999;79: 1283-1316.
9. Martí-Carvajal AJ, Gluud C, Nicola S, et al. Growth factors for treating diabetic foot ulcers. *Cochrane Database Syst Rev*. 2015; 10:CD008548.
10. Andia I, Abate M. Platelet-rich plasma: underlying biology and clinical correlates. *Regen Med*. 2013;8(5):645-658.
11. Anitua E, Andia I, Ardanza B, Nurden P, Nurden A. Autologous platelets as a source of proteins for healing and tissue regeneration. *Thromb Haemost*. 2004;91(1):4-15.
12. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, et al. Autologous platelet-rich plasma for treating chronic wounds. *Cochrane Database Syst Rev*. 2016;5:1-58.
13. Picard F, Hersant B, Bosc R, Meningaud JP. The growing evidence for the use of platelet-rich plasma on diabetic chronic wounds: a review and a proposal for a new standard care. *Wound Repair Regen*. 2015;23(5):638-643.
14. Lo Roura MJ, Verdú Soriano J. Conferencia nacional de consenso sobre las úlceras de la extremidad inferior (CONUEI). *Documento de Consenso*. 2018;1:1-146.
15. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA*. 2000;283(15):2008-2012.
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34.
18. Gupta A, Das A, Majumder K, et al. Obesity is independently associated with increased risk of hepatocellular cancer–related mortality. *Am J Clin Oncol*. 2018;41(9):874-881.
19. Higgins JPT, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
20. Sheikhbahaei S, Trahan TJ, Xiao J, et al. FDG-PET/CT and MRI for evaluation of pathologic response to neoadjuvant chemotherapy in patients with breast cancer: a meta-analysis of diagnostic accuracy studies. *Oncologist*. 2016;21(8):931-939.
21. Steed DL, Goslen JB, Holloway GA, Malone JM, Bunt TJ, Webster MW. Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical vs placebo. *Diabetes Care*. 1992;15(11): 1598-1604.
22. Steed DL, Edington HD, Webster MW. Recurrence rate of diabetic neurotrophic foot ulcers healed using topical application of growth factors released from platelets. *Wound Repair Regen*. 1996;4(2):230-233.
23. Driver VR, Hanft J, Fylling CP, Beriou JM, Autologel Diabetic Foot Ulcer Study Group. A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. *Ostomy Wound Manage*. 2006;52(6):68.
24. Kakagia DD, Kazakos KJ, Xarchas KC, et al. Synergistic action of protease-modulating matrix and autologous growth factors in healing of diabetic foot ulcers. A prospective randomized trial. *J Diabetes Complicat*. 2007;21(6):387-391.
25. Jeong S-H, Han S-K, Kim W-K. Treatment of diabetic foot ulcers using a blood bank platelet concentrate. *Plast Reconstr Surg*. 2010;125(3):944-952.
26. Saad Setta H, Elshahat A, Elsherbiny K, Massoud K, Safe I. Platelet-rich plasma vs platelet-poor plasma in the management of chronic diabetic foot ulcers: a comparative study. *Int Wound J*. 2011;8(3):307-312.
27. Li L, Wang C, Wang Y, et al. Impact of topical application of autologous platelet-rich gel on medical expenditure and length of stay in hospitals in diabetic patients with refractory cutaneous ulcers. Sichuan da Xue Xue Bao. Yi Xue Ban. *J Sichuan Univ Med Sci Ed*. 2012;43(5):762-765.
28. Karimi R, Afshar M, Salimian M, Sharif A, Hidariyan M. The effect of platelet rich plasma dressing on healing diabetic foot ulcers. *Nurs Midwifery Stud*. 2016;5(3):e30314.
29. Ahmed M, Reffat SA, Hassan A, Eskander F. Platelet-rich plasma for the treatment of clean diabetic foot ulcers. *Ann Vasc Surg*. 2017;38:206-211.
30. Rainys D, Cepas A, Dambrauskaite K, Nedzelskiene I, Rimdeika R. Effectiveness of autologous platelet-rich plasma gel in the treatment of hard-to-heal leg ulcers: a randomised control trial. *J Wound Care*. 2019;28(10):658-667.
31. Elsaid A, el-Said M, Emile S, Youssef M, Khafagy W, Elshobaky A. Randomized controlled trial on autologous platelet-rich plasma vs saline dressing in treatment of non-healing diabetic foot ulcers. *World J Surg*. 2020;44(4):1294-1301.
32. Liao X, Liang JX, Li SH, et al. Allogeneic platelet-rich plasma therapy as an effective and safe adjuvant method for chronic wounds. *J Surg Res*. 2020;246:284-291.
33. Habeeb TA, Elsayed AA, Mohamed H, et al., Platelet-Rich Plasma (PRP) Bio-Stimulant Gel Dressing in Treating Chronic

Non-Healing Leg and Foot Ulcers; Cost and Effectiveness. Randomized Controlled Clinical Trial. 2020.
34. Hossam EM, Alserr AHK, Antonopoulos CN, Zaki A, Eldaly W. Autologous platelet rich plasma promotes the healing of non-ischemic diabetic foot ulcers. A randomized controlled trial. *Ann Vasc Surg*. 2021;82:165-171.
35. Alamdari NM, Shafiee A, Mirmohseni A, Besharat S. Evaluation of the efficacy of platelet-rich plasma on healing of clean diabetic foot ulcers: a randomized clinical trial in Tehran. *Iran Diabetes Metab Syndr Clin Res Rev*. 2021;15(2):621-626.
36. Helmy Y, Farouk N, Ali Dahy A, et al. Objective assessment of platelet-rich plasma (PRP) potentiality in the treatment of chronic leg ulcer: RCT on 80 patients with venous ulcer. *J Cosmet Dermatol*. 2021;20(10):3257-3263.
37. Meamar R, Ghasemi-Mobarakeh L, Norouzi MR, Siavash M, Hamblin MR, Fesharaki M. Improved wound healing of diabetic foot ulcers using human placenta-derived mesenchymal stem cells in gelatin electrospun nanofibrous scaffolds plus a platelet-rich plasma gel: a randomized clinical trial. *Int Immunopharmacol*. 2021;101:108282.
38. Tofigh AM, Tajik M. Comparing the standard surgical dressing with dehydrated amnion and platelet-derived growth factor dressings in the healing rate of diabetic foot ulcer: a randomized clinical trial. *Diabetes Res Clin Pract*. 2022;185:109775.
39. Saldalamacchia G, Lapice E, Cuomo V, et al. A controlled study of the use of autologous platelet gel for the treatment of diabetic foot ulcers. *Nutr Metab Cardiovasc Dis*. 2004;14(6):395-396.
40. Miłek T, Baranowski K, Zydlewski P, Ciostek P, Mlosek K, Olszewski W. Role of plasma growth factor in the healing of chronic ulcers of the lower legs and foot due to ischaemia in diabetic patients. *Adv Dermatol Allergol/Post py Dermatologii i Alergologii*. 2017;34(6):601-606.
41. Saldalamacchia G, Lapice E, Cuomo V, et al. Uso del gel dipiastrine autologo per la cura delle ulcere del piede diabetico. *Giornale Italiano di Diabetologia e Metabolismo*. 2004;24(10):3-5.
42. Harb HS, Elberry AA, Rabea H, Fathy M, Abdelrahim MEA. Performance of large spacer vs nebulizer T-piece in single-limb noninvasive ventilation. *Respir Care*. 2018;63(11):1360-1369.
43. Harb HS, Laz NI, Rabea H, Abdelrahim MEA. Prevalence and predictors of suboptimal peak inspiratory flow rate in COPD patients. *Eur J Pharm Sci*. 2020;147:105298.
44. Nicola M, Elberry A, Sayed O, Hussein R, Saeed H, Abdelrahim M. The impact of adding a training device to familiar counselling on inhalation technique and pulmonary function of asthmatics. *Adv Ther*. 2018;35(7):1049-1058.
45. Osama El-Gendy A, Saeed H, Ali AMA, et al. Bacillus Calmette–Guérin vaccine, antimalarial, age and gender relation to COVID-19 spread and mortality. *Vaccine*. 2020;38(35):5564-5568.
46. Saeed H, Ali AMA, Elberry AA, Eldin AS, Rabea H, Abdelrahim MEA. Modeling and optimization of nebulizers' performance in non-invasive ventilation using different fill volumes: comparative study between vibrating mesh and jet nebulizers. *Pulm Pharmacol Ther*. 2018;50:62-71.
47. Saeed H, Mohsen M, Salah Eldin A, et al. Effects of fill volume and humidification on aerosol delivery during single-limb noninvasive ventilation. *Respir Care*. 2018;63(11):1370-1378.
48. Saeed H, Mohsen M, Fink JB, et al. Fill volume, humidification and heat effects on aerosol delivery and fugitive emissions during noninvasive ventilation. *J Drug Delivery Sci Technol*. 2017;39:372-378.
49. Saeed H, Salem HF, Rabea H, Abdelrahim MEA. Effect of human error, inhalation flow, and inhalation volume on dose delivery from Ellipta® dry-powder inhaler. *J Pharm Innov*. 2019;14(3):239-244.
50. del Pino-Sedeño T, Trujillo-Martín MM, Andia I, et al. Platelet-rich plasma for the treatment of diabetic foot ulcers: a meta-analysis. *Wound Repair Regen*. 2019;27(2):170-182.
51. Qu S, Hu Z, Zhang Y, et al. Clinical studies on platelet-rich plasma therapy for chronic cutaneous ulcers: a systematic review and meta-analysis of randomized controlled trials. *Adv Wound Care*. 2022;11(2):56-69.
52. Dai J, Jiang C, Sun Y, Chen H. Autologous platelet-rich plasma treatment for patients with diabetic foot ulcers: a meta-analysis of randomized studies. *J Diabetes Complicat*. 2020;34(8):107611.

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