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Extracellular Vesicles Secreted by Bone Marrow Stem Cells Mediate Angiogenesis for the Treatment of Diabetic Ulcers: A Systematic Review and Meta-Analysis of Preclinical Studies

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 August 2023 and was last updated on 20 August 2023.

INTRODUCTION

Review question / Objective We conducted this meta-analysis to evaluate the therapeutic efficacy of BMSCs-EV in treating DU and to expedite the clinical translation of BMSCs-EV therapy for DU.

Rationale Diabetic ulcers (DU) typically occur in patients with vascular diseases and diabetes. Extracellular vesicles secreted by bone marrow-derived stem cells (BMSCs-EV) represent a cell-free therapy that has emerged as a promising alternative for treating DU, especially due to significant advancements in the understanding of their role in promoting angiogenesis. However, their application in DU treatment remains in the preclinical stage, and their effectiveness is still uncertain.

Condition being studied In recent years, stem cell therapy has emerged as one of the most promising approaches to accelerate the healing of chronic lower limb ulcers .Recent studies have indicated that extracellular vesicles derived from BMSCs can accelerate the healing of various chronic wounds, such as chronic lower limb ulcers, diabetic wounds, and burns. However, the evidence for using BMSC-EVs in the treatment of chronic lower limb ulcers remains in the preclinical stage and is uncertain.

METHODS

Participant or population This includes any in vivo animal model of diabetic ulcers.

Intervention This includes studies that investigate the use of extracellular vesicles (EVs) derived from bone marrow mesenchymal stem cells (BMSCs) for the treatment of diabetic ulcers. The administration of BMSC-EVs can be done through heterologous, allogeneic, or autologous approaches, including application via hydrogel for MSC-EVs.

Comparator This includes any type of comparator.

Study designs to be included Randomized controlled trials.

Eligibility criteria When studies met the following criteria, they were included in this meta-analysis: (1) The study provided a detailed procedure for establishing diabetic ulcer animal models, including diabetic ulcers, diabetic foot, or diabetic wounds; (2) Stem cells were derived from human or animal bone marrow; (3) The article described the detailed procedures for identifying and extracting extracellular vesicles; (4) The treatment group used only extracellular vesicles or combined extracellular vesicles with other materials, while the control group received PBS or other dressings or remained untreatedExclusion Criteria (1) Articles not published in English. (2) Studies providing repetitive or redundant data. (3) Studies classified as letters, case reports, reviews, etc. (4) Data not provided or inaccessible for extraction.

Information sources The databases are limited to Pubmed, Cochrane Library, MEDLINE, and EMBASE. Two researchers will independently search the specified databases. The following subject terms and free terms will be used for the search, including "extracellular vesicles," "vesicles," "microparticles," "nanovesicles," "diabetic wounds," "diabetic foot," "wound infection," "lacerations," "lower limb chronic wounds," "lower limb," "diabetic foot," and "diabetic ulcers." Additionally, the researchers will track the references of the retrieved literature and manually search mainstream search engines such as Baidu, Google, and others to identify unpublished grey literature.The databases are limited to Pubmed, Cochrane Library, MEDLINE, and EMBASE.

Main outcome(s) The primary outcome measures include wound closure rate and vascular density in the animal models.

Additional outcome(s) The secondary outcome measures include a-SMA and CD31 levels.

Quality assessment / Risk of bias analysis SYRCLE's risk of bias tool for animal studies, which was developed by the Systematic Review Centre for Laboratory Animal Experimentation and based on the Cochrane Collaboration risk of bias tool, was used to conduct the quality assessment. The SYRCLE tool covers selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. Each term was divided into three grades: a judgment of "Yes" implies low risk, a judgment of "No" implies high risk, and an unclear risk implies insufficient details to assess the risk of bias . Two reviewers independently assessed the risk of bias. In cases of disagreement, a third reviewer joined the discussion to reach consensus.
The risk of bias of the preclinical studies was assessed using the SYRCLE risk of bias tool, and two study mentioned generating sequences by weight, which indicated a high risk of bias, while the other randomly assessed the outcome. Two studies randomly grouped and housed the mice; in another two studies, the outcomes were assessed by independent observers blinded to the intervention . Attrition and other biases were low risks for the nine studies because they reported the outcome indicators in detail. However, it is difficult to evaluate baseline characteristics because none of the studies provided baseline data. None of the studies described allocation concealment or blinding methods for performance or detection bias.

Strategy of data synthesis Data analysis was performed using RevMan 5.4.1. For dichotomous variables, the odds ratio (OR) or relative risk (RR) was used, and for continuous variables, the mean difference (MD) or standardized mean difference (SMD) was used. The combined effect size was tested using a 95% confidence interval (CI).

Subgroup analysis Subgroup analyses stratified by Wound Healing Rate and Angiogenesis.

Sensitivity analysis The results of meta analysis are recombined and analyzed by changing the statistical model, changing the amount of effect, removing individual studies, cutting and complement methods to evaluate whether the research results are stable or not.

Country(ies) involved China.

Keywords Extracellular vesicles secreted; bone marrow stem cells; mediate angiogenesis; diabetic ulcers; meta-analysis; preclinical studies.

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