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Corresponding author:
Yuanxia Zou

zouyxped@swmu.edu.cn

Author Affiliation:
The Affiliated Traditional Chinese Medicine Hospital, Southwest Medical University.

Mesenchymal Stem Cells-Derived Extracellular Vesicles/Exosome for Acute Kidney Injury in Preclinical Rodent Models: a systematic review and meta-analysis

Zou, YX; Kantapan, J; Dai, J; Mazhar, M; Li, JC; Su, HW; Dechsupa, N; Wang, L.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 August 2024 and was last updated on 23 August 2024.

INTRODUCTION

Review question / Objective The efficacy of MSC-EVs/exo vs control group on preclinical animal models.

Rationale In recent years, an increasing number of studies19, 22-26 have been conducted to assess the effectiveness of MSC-EVs/exo on AKI models. However, the specific influencing factors are still unclear due to the great difference in treatment effect. Therefore, we conducted an updated meta-analysis focusing on the efficacy of MSC-EVs/exo vs control group in preclinical rodent models to provide the latest evidence for human clinical trials.

Condition being studied I: randomized controlled animal experiments on the application of MSC-EVs/exo for the treatment of AKI were conducted from the establishment of the database until Jan.2024. II: the intervention group—various MSC-EVs/exo (MSC means different types of stem cells). III: the control group—AKI model or placebo (blank or saline or phosphate-buffered saline). IV: outcome measure—the primary outcome was the level of Scr. The secondary outcomes were levels of BUN, the renal injury score, the proinflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, the anti-inflammatory factor IL-10, percentage of apoptotic cells detected by TUNEL, and proliferating cell nuclear antigen (PCNA, a marker to detect proliferation of renal tubular epithelial cells). V: the included study contained at least the primary outcome measures. VI: the original data of the included study were complete.

METHODS

Search strategy We searched the databases including Web of Science, PubMed, Embase from database inception to February 29, 2024, and other search engines (google, geenmedical). The search terms were as follows: ("EVs" or "extracellular vesicles" or "exosome") and ("AKI" or "acute kidney injury" or "IRI" or "ischemia-reperfusion injury" or "renal ischemia-reperfusion" or "acute renal failure"). The search was limited to rodent models and published in English.

Participant or population Animals.

Intervention various MSC-EVs/exo (MSC means different types of stem cells).

Comparator Negative control group (AKI animal model, PBS treatment group, saline treatment group etc).

Study designs to be included I: randomized controlled animal experiments on the application of MSC-EVs/exo for the treatment of AKI were conducted from the establishment of the database until Jan.2024. II: the intervention group—various MSC-EVs/exo (MSC means different types of stem cells). III: the control group—AKI model or placebo (blank or saline or phosphate-buffered saline). IV: outcome measure—the primary outcome was the level of Scr. The secondary outcomes were levels of BUN, the renal injury score, the proinflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, the anti-inflammatory factor.

Eligibility criteria I: duplicate publications. II: the experiments were not performed on rodent models. III: incomplete data information. IV: commentary, review, letter, case report, conference abstract and so on; V: the articles with unavailable full texts.

Information sources N/A.

Main outcome(s) SCr.

Additional outcome(s) The secondary outcomes were levels of BUN, the renal injury score, the proinflammatory factors such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, the anti-inflammatory factor IL-10, percentage of apoptotic cells detected by TUNEL, and proliferating cell nuclear antigen (PCNA, a marker to detect proliferation of renal tubular epithelial cells).

Data management We reviewed the titles and abstracts of all articles and excluded articles that were not relevant to the topic and those that did not meet the eligibility criteria. The remaining articles were assessed by full-text reading. Studies that met the inclusion criteria were imported into the electronic literature management program Endnote20. Two independent researchers (ZYX and DJ) performed the study selection and data extraction independently and in a double-blind manner. Cross-checking was performed, and any disagreements were submitted to a third investigator (LJC) for discussion and resolution.

Quality assessment / Risk of bias analysis The SYRCLE tool for assessing risk of bias in animal studies was used for bias risk assessment. Publication bias was assessed using a funnel plot. When publication bias was indicated, the number of missing studies was further evaluated using the Trim-fill method, and the pooled risk estimation was recalculated with the addition of these missing studies.

Strategy of data synthesis We reviewed the titles and abstracts of all articles and excluded articles that were not relevant to the topic and those that did not meet the eligibility criteria. The remaining articles were assessed by full-text reading. Studies that met the inclusion criteria were imported into the electronic literature management program Endnote20.The extracted data from the included studies primarily include the following information: first author's name, publication year, country, method of model induction, sample sizes in the two groups, MSC-EVs/exo's cell origins, diameter, dose, injection methods, therapy time, and measurement time. In studies where corresponding results were not presented, data was extracted from graphs using Engauge Digitizer version 4.1 software. The meta-analysis of the literature was conducted using RevMan 5.3 (https://www.cochrane.org/) and StataMP 17 (https://www.stata.com) software. Given that the outcome indicators were continuous variables, the standard mean difference (SMD) was utilized as the sample statistic to analyze the effect of the study, and a 95% confidence interval (CI) was provided. Heterogeneity of the results was evaluated using a combination of the Q-test and I^2 statistics. A P-value of ≥ 0.1 and $I^2 < 50\%$ were considered indicative of low heterogeneity30, in which case a fixed-effects model was employed for the meta-analysis. Conversely, if the P-value was 50%, significant heterogeneity among the study results was assumed. In instances of significant heterogeneity, meta-regression was conducted to explore its sources, followed by subgroup analysis. If the source of heterogeneity could not be identified, a random-effects model

was applied. Sensitivity analyses were conducted to explore the stability of the results. Publication bias was assessed using a funnel plot. When publication bias was indicated, the number of missing studies was further evaluated using the Trim-fill method, and the pooled risk estimation was recalculated with the addition of these missing studies.

Subgroup analysis MSC cell source, cell diameter, cell injection method.

Sensitivity analysis The sensitivity analysis revealed that none of the individual studies had a significant impact on the outcome of Scr.

Country(ies) involved China, Thailand.

Keywords Mesenchymal stem cells; Extracelluar vesicles; Exosome; Acute kidney injury; Meta-analysis.

Contributions of each author

Author 1 - Yuanxia Zou.
Email: zouyxped@swmu.edu.cn
Author 2 - Jiraporn Kantapan.
Email: jiraporn.kan@cmu.ac.th
Author 3 - Jian Dai.
Email: daijian940902@163.com
Author 4 - Maryam Mazhar.
Email: maryam@swmu.edu.cn
Author 5 - Jianchun Li.
Email: lijianchunchina@swmu.edu.cn
Author 6 - Hongwei Su.
Email: ximi47325@163.com
Author 7 - Nathupakorn Dechsupa.
Email: nathupakorn.d@cmu.ac.th
Author 8 - Li Wang.
Email: wangli120@swmu.edu.cn