International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

The Role of Mesenchymal Stem Cell-Derived Exosomes in Treating Myocardial Ischemia/ Reperfusion Injury: A Systematic Review Protocol

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ADMINISTRATIVE INFORMATION

Support - Supergenics Therapeutic Sdn Bhd.

Review Stage at time of this submission - Data extraction.

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 6 November 2024 and was last updated on 6 November 2024.

INTRODUCTION

Review question / Objective How do mesenchymal stem cell (MSC)-derived exosomes mitigate myocardial ischemia/ reperfusion (I/R) injury, and what are the underlying mechanisms of their action?

Condition being studied Myocardial I/R injury is a significant complication arising from reperfusion therapy in ischemic heart disease (IHD), often resulting in heart failure, arrhythmia, and adverse cardiac remodeling. Due to their paracrine effects, MSC-derived exosomes have gained attention as promising therapeutic agents for myocardial I/R injury. They deliver bioactive molecules, such as microRNAs (miRNAs), that modulate key cellular pathways related to survival, inflammation, oxidative stress, and angiogenesis.

METHODS

Search strategy This systematic review will follow the Preferred Reporting Items for Systematic Review and Meta-analysis of Protocol (PRISMA-P) guidelines and the Population, Intervention, Comparison, Outcome, and Study framework. A comprehensive search will be conducted using three main databases; Ovid MEDLINE, Scopus, and Web of Science, employing the following keywords: (Exosome AND (mesenchymal stem cells OR mesenchymal stromal cells) AND (myocardial ischemia OR myocardial infarction OR cardiac infarction OR myocardial ischemia*reperfusion* OR ischemia*reperfusion* OR ischemic heart disease OR hypoxia*reoxygenation* OR myocardium OR cardiomyocyte OR hypoxia OR reperfusion OR reoxygenation). The titles and abstracts of eligible studies will be screened based on relevance to MSC-derived exosomes and their effects on myocardial I/R injury. There will be no geographical

or publication date restrictions, but only studies published in English will be included. Additional studies will be identified by manually screening the references of included articles.

Participant or population 1. Adult human patients: This includes adults of any age or gender who have had myocardial infarction (MI) or myocardial I/R injury, regardless of the MI cause.
Exclusion: Other IHD and pregnant participants.

2. Animal studies: Includes preclinical models of myocardial I/R injury in animal models, regardless of age, weight, or species.
Exclusion: Other IHD models.

3. In vitro studies: Includes cardiomyocyte cell lines from any source, whether primary or commercially purchased.
Exclusion: Other cell lines.

Intervention Studies using MSC-derived exosomes as an intervention in the experimental group will be included, regardless of the exosome source, isolation method, route of administration, dose, or duration of intervention applied to the heart.
Exclusion: Studies using modified exosomes (e.g., combined with other drugs or compounds, conjugated, etc.) or administering exosomes to a different organ part.

Comparator The comparator groups received either no intervention, standard therapy, or a placebo, with conventional reperfusion treatment included as background therapy.
Exclusion: Studies using modified exosomes (e.g., combined with other drugs or compounds, conjugated, etc.) or administering exosomes to a different organ part.

Study designs to be included Clinical studies (randomized or non-randomized controlled trial parallel), and preclinical studies (in vivo, in vitro, ex vivo) will be included. Quasi-experimental studies (single arm/non-controlled study), observational studies, editorials, reviews, and abstract/ conference proceedings will be excluded.

Eligibility criteria Any clinical or preclinical studies reporting the effect of MSC-derived exosomes on myocardial I/R injury.

Information sources The primary databases searched will be Ovid MEDLINE, Scopus, and Web of Science, using the specified set of keywords: Exosome AND (mesenchymal stem cells OR mesenchymal stromal cells) AND (myocardial ischemia OR myocardial infarction OR cardiac infarction OR myocardial ischemia*reperfusion* OR ischemia*reperfusion* OR ischemic heart disease OR hypoxia*reoxygenation* OR myocardium OR cardiomyocyte OR hypoxia OR reperfusion OR reoxygenation).

Main outcome(s)
• Infarct size: changes in infarct size, reported as the mean percentage of the infarct area, along with the standard deviation (SD), or simply noted as present or absent in reduced infarct size.
• Cardiac function: changes in left ventricular ejection fraction, fractional shortening, and end-systolic volume, reported as mean values with accompanying SD.
• Cardiomyocyte viability: changes in cardiomyocyte viability, reported as the mean value with SD.
• Cardiac injury markers: changes in the levels of lactate dehydrogenase or creatine kinase-MB, reported as the mean value with SD.

Additional outcome(s) Changes in apoptosis, oxidative stress, inflammation, and angiogenesis markers, signaling pathways, and specific miRNAs involved.

Data management Two reviewers (N.A.O.B. and A.U.) will independently extract data from the included studies using a predefined, standardized data collection form. Any disagreements will be resolved through discussion with a third reviewer (A.A.H.). A data spreadsheet will be created with Microsoft Excel to compile relevant information. The following data will be extracted:
• Study characteristics: First author's name, publication year, article title, country of study, and study design.
• Intervention details: study population, models, source of exosomes, particle size, purification method, route and timing of administration, treatment duration, and dosage.
• Comparators: groups receiving no treatment, standard therapy, or placebo.
• Outcomes of interest as described in the PICOS framework.

Quality assessment / Risk of bias analysis The risk of bias (RoB) will be analyzed independently by two reviewers (N.A.O.B. and A.U.). Any disagreement will be resolved through discussion with a third reviewer (A.A.H.).
For randomized clinical trials, the Cochrane RoB 2.0 tool. will be used. Animal studies will be assessed using the Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) RoB tool.

• The main components of the SYRCLE RoB tool are as follows:
• Selection bias: random sequence generation, baseline characteristics, allocation concealment.
• Detection bias: random housing, blinding, random outcome assessment.
• Attrition bias: incomplete outcome data.
• Reporting bias: selective reporting.
• Other bias.
For in vitro studies, a customized RoB tool based on the Joanna Briggs Institute (JBI) checklist for non-randomized experimental studies (2020) will be used. The customized RoB tool includes the following domains:
• Reporting quality: source of exosomes, purification method, delivery routes, dosage.
• Performance bias: reliable tools or reagents used to measure outcome.
• Detection bias: use of appropriate controls and multiple outcome measurements.
Each domain will be evaluated to determine whether the RoB is high, moderate, low, or unclear. However, the RoB score will not be used as an eligibility criterion for study inclusion.

Strategy of data synthesis Study characteristics and outcome data will be tabulated and described narratively. A meta-analysis will be conducted if the data allows. The RoB will be summarized and reported narratively.

Subgroup analysis Subgroup analyses will explore how various factors influence the therapeutic effects of MSC-derived exosomes in myocardial I/R injury. These subgroups will consider the source of MSCs, exosome purification methods, delivery routes, exosome dosage, timing of administration, and the presence of specific miRNAs within the exosomes. By analyzing these subgroups, the review aims to uncover whether these factors contribute to variations in exosome therapy effectiveness, providing insights for optimizing treatment protocols for myocardial I/R injury.

Sensitivity analysis A sensitivity analysis will only be conducted if a meta-analysis is performed.

Language restriction English.

Country(ies) involved Malaysia.

Keywords Mesenchymal stem cells; exosomes; myocardial ischemia/reperfusion injury; hypoxia/reoxygenation.

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