Mesenchymal Stem Cells for the Treatment of Intestinal Ischemia-reperfusion Injury: a Protocol of Systematic Review and Meta-analysis of Animal Models

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Protocol

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Abstract

Introduction: Intestinal ischemia-reperfusion (I/R) injury is a common clinical event. Mesenchymal stem cells (MSCs) have been widely used to repair intestinal injury in animal models. However, the effects of MSCs on intestinal I/R injury therapy remain unclear. Thus, we will perform a systematic review and meta-analysis of controlled trials to evaluate the efficacy of MSCs in animal models of intestinal I/R injury.

Methods and analysis: We will search PubMed, Web of Science, Embase, Cochrane Library, Science Citation Index, China National Knowledge Information database, Wanfang Database, and the Chinese Scientific and Technological Journal Database in May 2021. We will include studies that evaluate the two different interventions for target MSCs to be maintained for the degree of histopathologic changes, mortality rate of rats, tumour necrosis factor α, and diamine oxidase. Two reviewers will independently screen titles and abstracts, perform a full article review, and extract study data. We will also use the SYRCLE tool to assess the risk of bias in the included studies. Furthermore, a random-effects meta-analysis will be conducted. Dichotomous and continuous outcomes will be analysed using risk ratios with 95% confidence intervals (CIs) and weighted mean difference with 95% CIs, respectively. For outcomes where different scales or different measurement methods have been used, the standardised mean difference will be applied. Subgroup and sensitivity analyses will be performed to explore the heterogeneity. Stata (version 12.0, Stata Corp, College Station, Texas, USA) will be used to analyse and pool the individual research results.

Ethics and dissemination: This systematic review and meta-analysis does not require an ethical approval because no human beings are involved. We aim to publish this systematic review in a peer-reviewed journal.

PROSPERO registration number: CRD42021231826

Strengths And Limitations Of This Study

- This systematic review will be the latest study to determine the efficacy of MSCs in animal models of intestinal I/R injury.
- This systematic review will be performed with rigorous study screening, data extraction, and risk of bias assessment.
- The expected major limitations of this review will be the clinical heterogeneity of the included trials and the diversity of the MSCs.
- The number of studies with eligible data for subgroup analyses and publication bias may be limited.

Introduction

Intestinal ischemia-reperfusion (I/R) injury is a common (1/1000 hospital admissions) and serious clinical event, which can be caused by different pathophysiological factors such as intestinal obstruction, volvulus, superior mesenteric artery embolism, haemorrhagic shock, severe trauma, and intestinal transplantation[1, 2]. The intestinal tissue is the largest reservoir of bacteria in the body. When ischemia occurs, the intestinal tissue is in a state of ischemia and hypoxia, and the energy metabolism and morphological structure of cells are seriously damaged; when the blood supply is restored, the intestinal bacteria shift, and the endotoxin carried by the bacteria enters the peripheral blood circulation, causing serious damage to the endothelial cells that could lead to acute inflammation and other reactions. In severe cases, it can cause inflammatory reactions in local and distant organs (such as the lungs [3] and liver [4]), promote the occurrence and development of multiple organ dysfunction syndrome, and lead to a variety of perioperative complications and high mortality[5, 6]. Due to delayed diagnosis and lack of efficient treatment, it is reported that the mortality of acute mesenteric ischemia patients is as high as 60–80%[7]. Another study found that intestinal I/R injury is becoming the biggest obstacle to improving the outcome of intestinal transplantation[8]. Studies on the mechanism of intestinal I/R injury have shown that its occurrence is mainly related to oxygen free radical injury[9], calcium overload[10], inflammatory cytokine release[11], and apoptosis[12]. Although the mechanism has been studied in-depth, treatments for intestinal I/R injury, including nitric oxide supplementation, antioxidants, anti-complement therapy, free-radical scavengers, anti-leukocyte therapy, glutamine supplementation, and glycine supplementation, are still inadequate[13].

Stem cell therapy has become a new strategy for the repair of various ischemia and reperfusion injury diseases[14]. As one of the most popular pluripotent stem cells, mesenchymal stem cells (MSCs) have been widely studied in the past decades[15]. MSCs are multipotent cells with low immunogenicity and immunoregulation[16–18], and can be easily isolated and expanded from the bone marrow and other tissues, including the placenta, amniotic fluid, umbilical cord tissues, adipose tissue, testis, or lungs[19, 20]. It has been reported that when tissue and organ damage occurs, MSCs can be transplanted into injured tissues to play a role in repair through differentiation and replacement of damaged cells[21, 22]. Furthermore, MSCs can also secrete many protective factors, such as the epithelial growth factor, vascular endothelial growth factor, transforming growth factors α and β, fibroblast growth factor, insulin-like growth factor type 1, to exert a protective effect through paracrine function[23, 24]. Several studies have confirmed that MSCs can repair the injury of many tissues and organs such as myocardial infarction[25], ischemic brain injury[26], spinal cord injury[27], and liver[28] and kidney [29] I/R injuries. Therefore, MSCs have the potential for application in a wide variety of degenerative disorders.

The first animal experiment to investigate MSCs for the treatment of intestinal I/R injury was conducted in 2009 and reported that the local administration of bone marrow-derived MSCs (BM-MSCs) can alleviate intestinal I/R injury in rats[12]. Subsequently, many studies on the effects of MSCs on animal models of intestinal I/R injury have been published. Shen et al. reported that BM-MSCs can reduce intestinal I/R injury in rats via a TNF-α-regulated mechanism[30]. Additionally, Jiang et al. found that BM-MSCs not only inhibit the release of proinflammatory cytokines and suppress the overexpression of proinflammatory genes, but also accelerate the expression of proliferative genes involved in intestinal

mucosal cellular regeneration[31]. MSCs can also protect against intestinal I/R injury by increasing the antioxidant capacity of small bowel tissues after the injury[32]. In addition, some studies found that the reduction of human bone MSCs can reduce the intestinal I/R injury mortality[33], and that human umbilical MSCs can provide an intestinal protective effect through nitric oxide dependent pathways[34]. Furthermore, studies have found that melatonin-supported adipose-derived MSCs[35], synergetic application of electroacupuncture and MSCs[36], HO-1-expressing BM-MSCs[37], IL-1β-activated adipose-derived MSCs [38], and IL-37 gene-modified MSCs also have a protective effect against intestinal I/R injury[39].

It has been confirmed that MSCs have therapeutic effects in animal models of intestinal I/R injury; however, the source of MSCs, administration dose, site of transplantation, and quality score in each study are very divergent that the overall therapeutic effect is difficult to evaluate, and there is no systematic review or meta-analysis on the effects of MSCs on therapy for intestinal I/R injury. To clarify the current situation and further studies on MSC therapy as a treatment for intestinal I/R injury, we will perform this systematic review and meta-analysis of all available experimental evidence to identify the efficacy of MSC-based therapies in animal models of intestinal I/R injury.

OBJECTIVE

The primary purpose of this systematic review is to examine the efficacy of MSCs in the treatment of intestinal I/R injury. Secondary specific aims are to determine the effects of different sources, administration doses, and administration sites of MSCs on intestinal I/R injury.

Methods And Analysis

This systematic review protocol was registered prospectively in the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42021231826). The protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement[40].

Eligibility criteria

Type of studies

We will only include studies on controlled trials in animals. Reviews, editorials, study protocols, clinical guidelines, commentaries, and letters will be excluded.

Type of participants

An established animal disease model of intestinal I/R injury will be included. There are no restrictions on specific modelling methods, species and origin, age, and sex of the animals. No patient involved in this study.

Type of interventions and comparators

The intervention group will use MSCs as a therapy for the treatment of intestinal I/R injury, without restricting the type of MSCs, dose of cells, and site of transplantation. For comparisons, the control group can be another intervention except for MSCs or placebo.

Types of outcome measures

Primary outcomes

1. Degree of histopathologic changes, which will be graded semi-quantitatively using the histologic injury scale previously described by Chiu et al[41].
2. Mortality rate of rats

Secondary outcomes

1. Inflammatory cytokine: tumour necrosis factor α (TNF-α)
2. Marker of intestinal permeability: diamine oxidase (DAO)

Patient and Public Involvement

No patient involved in this study.

Search methods for identification of studies

A literature search of PubMed, Web of Science, Embase, Cochrane Library, Science Citation Index, China National Knowledge Information database, Wanfang Database, and Chinese Scientific and Technological Journal Database will be conducted from the inception to May 2021. The identified studies will not be constrained by publication date, language, or publication status. Furthermore, the following search strategy will be applied: (Mesenchymal stem cells, Bone Marrow Stromal Cells, Mesenchymal Progenitor Cells, Mesenchymal Stromal Cells) AND (intestinal ischemia-reperfusion injury, intestinal IR injury, IIR injury).

Study selection

Two authors will independently screen the titles and abstracts of studies searched by Rayyan [42] and will download the full text of any potential studies for further screening. Any discrepancies will be resolved by discussion; if needed, a third reviewer will be consulted. Figure 1 shows the flow chart of the study selection procedure according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Data extraction and management

Two authors will independently extract the data of interest. They will also resolve any discrepancies by having a discussion; if needed, a third reviewer will be consulted. The form will aim to capture information on study characteristics, including study design, sample size, experimental methods, intervention types, control, outcomes, funding, and so on.

Assessment of the risk of bias in individual studies

Two authors will independently assess the risk of bias in each study using the SYRCLE tool[43]. This tool contains 10 entries related to selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. A “yes” judgement indicates a low risk of bias, a “no” judgement indicates a high risk of bias, and an “unclear” judgment means that insufficient details have been reported to properly assess the risk of bias. Any conflicts will be resolved by discussion; if needed, a third reviewer will be consulted.

Data synthesis

Stata (version 12.0, Stata Corp, College Station, Texas, USA) will be used to analyse and pool the individual research results. For dichotomous outcomes, we will calculate a pooled estimate of risk ratios with 95% confidence intervals (CIs) using a random-effects model. Continuous outcomes will be analysed using the weighted mean difference with 95% CIs. For outcomes where different scales or different measurement methods have been used, the standardised mean difference will be applied.

Assessment of heterogeneity

We will estimate the degree of heterogeneity among studies using the Cochrane Q statistic and the I^2 statistic. Heterogeneity will be considered as small when $I^2 < 50\%$ and substantial when $I^2 > 50\%$. Additionally, we will perform a sensitivity analysis by excluding studies with a high risk of bias and will plan subgroup analyses based on different types and sources of MSCs, administration dose, and methods of MSC administration if sufficient studies are available.

Publication bias

A funnel plot will be generated to examine the publication bias if more than 10 studies are included to assess this endpoint.

Ethics and dissemination

This review does not require ethical approval as a systematic review of published studies because there is no direct involvement of human participants. We will publish our findings in a peer-reviewed scientific journal. The dataset will be made available based on reasonable requests from the researchers.

Discussion

Being the first meta-analysis to identify the efficacy of MSC-based therapies in animal models of intestinal I/R injury is one of the strengths of this systematic review. In addition, we will also determine the effects of different sources, administration doses, and administration sites of MSCs on intestinal I/R injury. Moreover, conducting meta-analyses and systematic reviews of the evidence related to this clinical question may lead to further research in this field and could provide the latest evidence for the treatment of intestinal I/R injury.

We acknowledge the potential limitations of this study. First, we will include all types of MSCs. Although these inclusion criteria will contribute to increased pooled sample size, heterogeneity may be introduced. Nonetheless, we will conduct a subgroup analysis to evaluate the heterogeneity between different types of MSCs. Second, the strength of a systematic review and meta-analysis relies in part on the strength of available studies, and therefore may be limited due to the lack of randomised controlled trials in this area. Third, we also intend to perform subgroup analyses for the administration dose and site of MSCs. However, this may reduce the statistical power of data analysis.

Declarations

Authors' contributions

LYF, GL and ZGR devised the study. ZGR drafted the protocol, and all authors provided suggestions regarding manuscript revisions. The search strategy developed by ZGR will be performed by ZGR and LZZ, who will also independently screen the potential studies. ZGR, LZZ, LDS, ZZY, and SSH will independently extract data from the included studies, assess the risk of bias, and complete the data synthesis. ZGR and GL will arbitrate in cases of disagreement. All authors approved the publication of this protocol.

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Competing interest statement

No conflicts of interest to declare by any of the authors.

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Figures

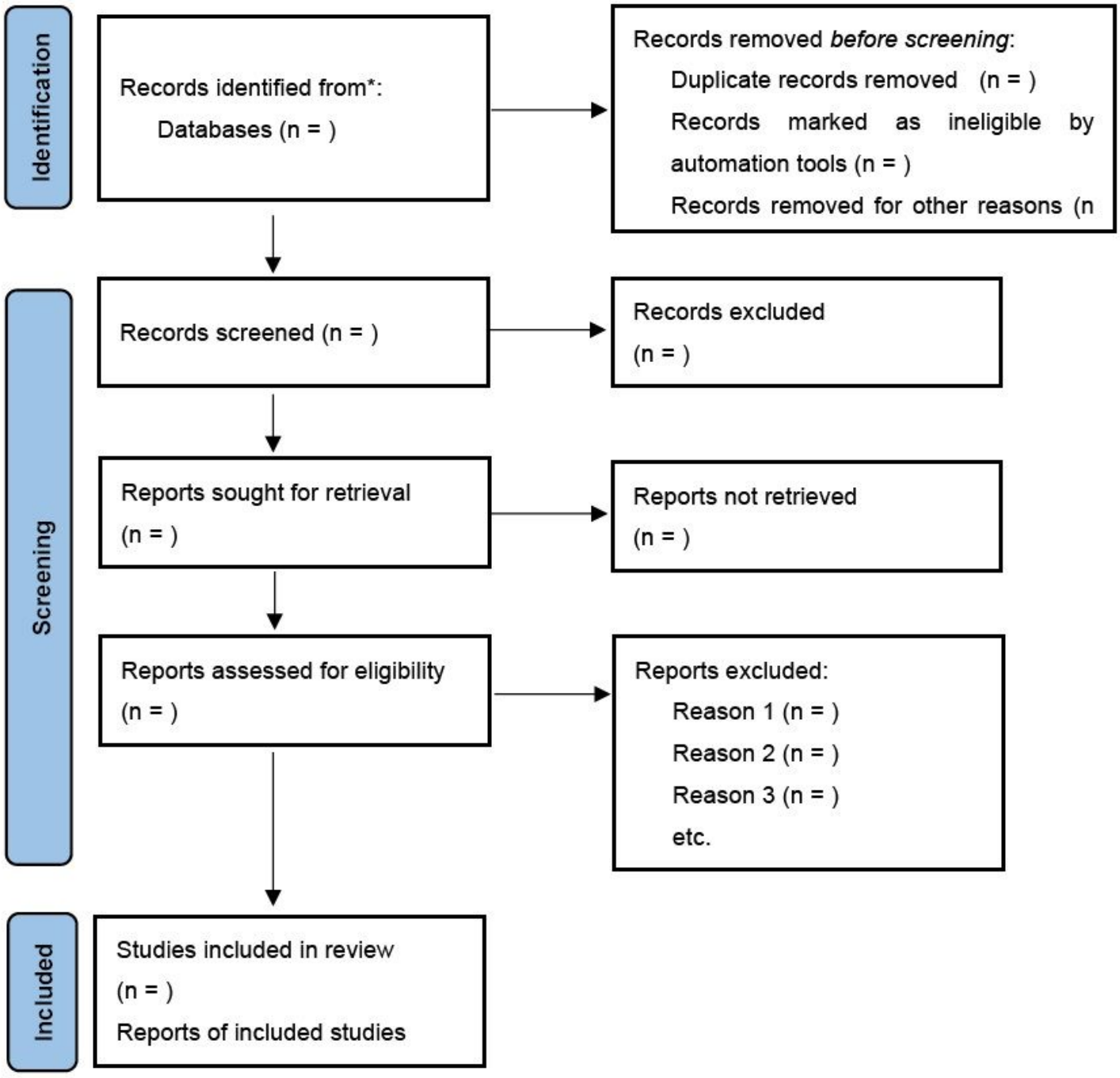

Figure 1

Flow chart of the study selection procedure. The flow chart of the study selection procedure is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.

Supplementary Files

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- PRISMAPchecklist.doc