Clinical Neurology and Neurosurgery 146 (2016) 1–11

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Effect of stem cell-based therapy for ischemic stroke treatment: A meta-analysis

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ARTICLE INFO

Article history:
Received 12 January 2016
Received in revised form 8 April 2016
Accepted 10 April 2016
Available online 21 April 2016

Keywords:
Ischemic stroke
Cell transplantation
Clinical trial
Meta-analysis

ABSTRACT

Stroke is a major cause of death and long-term disability worldwide. Cell-based therapies improve neural functional recovery in pre-clinical studies, but clinical results require evaluation. We aimed to assess the effects of mesenchymal stem cells on ischemic stroke treatment.

We searched the PubMed, Embase and Cochrane databases until July 2015 and selected the controlled trials using mesenchymal stem cells for ischemic stroke treatment compared with cell-free treatment. We assessed the results by meta-analysis using the error matrix approach, and we assessed the association of mesenchymal stem cell counts with treatment effect by dose-response meta-analysis.

Seven trials were included. Manhattan plots revealed no obvious advantage of the application of stem cells to treat ischemic stroke. For the comprehensive evaluation index, stem cell treatment did not significantly reduce the mortality of ischemic stroke patients (relative risk (RR) 0.59, 95% confidence interval (CI) 0.29–1.19; ln(RR) 0.54, 95% CI −0.18 to 1.25, p = 0.141). The National Institutes of Health Stroke Scale was also not significantly improved by stem cell treatment (standardized mean difference (SMD) 0.94, 95% CI −0.13 to 2.01, p = 0.072). The European Stroke Scale was significantly improved using the stem cell treatment (SMD 1.15, 95% CI 0.37–1.92). The dose-response meta-analysis did not reveal a significant linear regression relationship between the number of stem cells and therapeutic effect, except regarding the National Institutes of Health Stroke Scale index.

In conclusion, our assessments indicated no significant difference between stem cell and cell-free treatments. Further research is needed to discover more effective stem cell-based therapies for ischemic stroke treatment.

Contents

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http://dx.doi.org/10.1016/j.clineuro.2016.04.011
0303-8467/

1. Introduction

Stroke is an important cause of death and disability in adults. Globally, 250–400 of every 100,000 people die from stroke every year [1,2]. Additionally, stroke is the third most common cause of death in the United States. More than 750,000 new and recurrent strokes occur each year, and 160,000 people die annually from stroke [3].

Despite the high prevalence of stroke, there remain limited options for therapy, especially in restoring lost neurological function. Currently, the major method to treat ischemic stroke involves the use of recombinant tissue plasminogen activator, but the time window limits this approach [4]. Rehabilitation could facilitate functional recovery in stroke patients. However, its effects remain not optimal [5]. Therefore, researchers are seeking new methods to treat ischemic stroke to reduce mortality and restore neurological function. Vascular interventional radiology is one of the emerging fields for possibly improving the clinical outcomes of ischemic stroke patients [6,7]. In recent years, adult stem cells have been a focal point in the treatment of ischemic stroke in preclinical and clinical research. Cell-based therapies reduce infarct size and improve neural functional recovery in pre-clinical studies [8–10].

Mesenchymal stem cells (MSCs) are a type of adult non-hematopoietic pluripotent cells in the human body. MSCs have several advantages in clinical applications, such as easy collection, lack of ethical issues, pluripotency, the secretion of trophic factors and safety [11]. Furthermore, MSCs have demonstrated beneficial, therapeutic effects in various diseases, such as acute graft-versus-host disease [12,13], Crohn's disease [14], systemic lupus erythematous [15], myocardial infraction [16], and arthritis [17]. In 2007, members of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA) generated consensus-based guidelines on cell therapies for stroke, entitled "Stem cells as an Emerging Paradigm in Stroke" (STEPS) [18]. In 2011, the third meeting of STEPS convened to discuss the action of cell therapy and clinical trials design [19]. Despite stem cells having received a large amount of attention for stroke treatment, the number of controlled clinical trials remains limited. Therefore, the guidelines are formulated based on preclinical research and observational studies.

A previous study conducted a systematic review of cell therapies for stroke, but the evidence was based on a single-arm analysis [20]. In this study, we collected controlled clinical trials of ischemic stroke treatment with MSCs and conducted an updated systematic review to assess the treatment effects of MSCs for ischemic stroke.

2. Methods

2.1. Data sources and searches

We searched PubMed, Embase and the Cochrane Central Register of Controlled Trials with the keywords "cerebral arterial thrombosis"; "ischemic stroke"; "cerebral infraction"; "stem cell"; "cell transplantation"; "mesenchymal"; "stromal"; and "clinical". We did not apply any language restrictions; and we collected all relevant articles through July 2015. We also searched the reference lists of the identified trials.

2.2. Data selection

QW and FD identified eligible reports, and discrepancies were resolved through discussion. The eligibility criteria included the following requirements: (1) controlled clinical trial; and (2) use two comparison groups, in which one group received MSC therapy or other types of stem cells except for hematopoietic stem cell (HSCs) or colony-stimulating factor (CSF) treatment, and the other group received treatment without cells.

2.3. Data analysis

We assessed the results of our meta-analysis using the error matrix approach. The error matrix approach has been validated in systematic reviews of cholecystectomy and inguinal hernia [21,22]. We assessed all of the trials for the risk of bias (by the level of evidence) and the risk of random error and design error. Data are presented in a three-dimensional Manhattan plot [23].

We measured the risk of bias with the Cochrane Collaboration's instrument for bias risk assessment [24]. The risk of bias graph was provided. The following components were used to assess bias: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective reporting; and other bias. Trials with low risk for all components were defined as having an overall low risk of bias. However, masking the surgeon to the allocation is difficult; the trials were deemed to have a low risk of bias if the patients and the assessors were both masked. Overall, the risk of bias was defined as follows: 1a for a meta-analysis of low-bias risk randomized controlled trials and/or level 1 of evidence; 1b for low-bias risk randomized controlled trials and/or level 1 of evidence; 1c for a meta-analysis of all randomized controlled trials and/or level 1–2 of evidence; 1d for high-bias risk randomized controlled trials and/or level 2 of evidence; 2a for cohort studies with concurrent controls without randomization; 2b for cohort studies with controls in the past without randomization; 3a for case control studies; 3b for retrospective studies; 4 for before-after studies (without control groups); and 5 for case reports and case series.

The risk of random error was evaluated by the standard error (SE) as the algorithm suggested by the Cochrane Collaboration [24]. A standard error less than 0.20 represented a low risk for random error, 0.20–1.00 represented a moderate risk, and greater than 1.00 represented a high risk. Studies with a high risk of random error were excluded and considered irrelevant for decision making.

We predefined the risk of design error by classifying the clinically relevant outcomes according to the Grading of Recommendations Assessment, Development and Evaluation approach [25]. The results that are the most important for clinical decision making are represented by the highest bars in the upper-left portion of a Manhattan plot. Publication bias was assessed by funnel plots. We used simple and elementary inequalities and approximations to estimate the median and quartile to the mean and the variance for such trials, as previously described [26]. A dose-response meta-analysis was conducted to assess the association of MSC counts with treatment effects [27].

2.4. Statistical analysis

We used the inverse variance method to pool continuous data, and the results are presented as the standardized mean differences with 95% confidence intervals (CIs). We used the Mantel-Haenszel method for dichotomous data, and the results are presented as the relative risks with 95% CIs. We assessed the statistical heterogeneity with I^2. In the absence of statistical heterogeneity (<50%), we used a fixed-effects model; otherwise, we used a random-effects model. All of the tests were two tailed, and a p-value less than 0.05 was deemed statistically significant. We analyzed the data using Review Manager (version 5.3, The Cochrane Library, London, United Kingdom) and STATA (version 12.0, StataCorp LP, TX, USA) software.