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Review Article

Mesenchymal Stem Cell Therapy to Reduce the Neurological Deficit of Chronic Ischemic Stroke Patients: A Systematic Review

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Abstract

Current ischemic and hemorrhagic stroke treatments are limited by a narrow golden period and lack of regenerative benefits, so stem cell therapy emerges as an ideal candidate for functional recovery in stroke patients. Stem cell therapy, still being studied, is expected to repair ischemic areas damaged by stroke to restore their physiological functions and reduce neurological deficits in chronic stroke patients. This study aimed to determine the therapeutic efficacy of MSCs in reducing neurological deficits in chronic ischemic stroke patients. We conducted a systematic review. We searched PubMed, Cochrane Library, Science Direct, and Springer Link from inception until December 2022 for cohort studies dealing with mesenchymal stem cell therapy for patients with ischemic stroke. The citation-searching method in this study collected 1,038 articles using the advanced searching method and 8 articles using the citation-searching method, bringing the total number of articles to 1,046. Determination of synonyms using MeSH to facilitate the making of keywords. All articles found are then included on the Rayyan QCRI website, which can assist reviewers in selecting journals. The number of articles used in this study were 2 English-language research articles discussing the potential of MSCs therapy to improve nerve function in chronic ischemic stroke patients with NIHSS scores in the last 10 years (2012-2022) with a cohort study design and had passed the ROBINS-I quality and risk of bias assessment with a low risk of bias. The exclusion criteria used were articles with systematic reviews and meta-analyses and articles that were not accessible in full text. Based on the results of a systematic review study conducted, the conclusion that can be drawn is that MSCs therapy has proven effective in reducing neurological deficits in chronic ischemic stroke patients in terms of the decreased NIHSS score.

Keywords : mesenchymal stem cell, chronic ischemic stroke, neurological deficit, NIHSS
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INTRODUCTION

Stroke is a global problem that is being faced by the world. The latest 2019 Global Burden of Disease (GBD) shows that stroke remains the second leading cause of death and the third leading cause of death and disability worldwide (Feigin et al., 2022). The blockage of blood vessels characterises neurological disorders in stroke and is the leading cause of acquired physical disability in adults (Kuriakose and Xiao, 2020; Murphy and Werring, 2020). The World Health Organization (WHO) shows that 7.9% of deaths in Indonesia are caused by stroke (Mutiarasari et al., 2019).

Neurological deficits in stroke patients are characterized by disabilities, that as paralysis, sensory disorders, language disorders, problems in thinking and memory, and emotional disturbances that can be suffered for a lifetime. One of the assessment tools for the neurological deficit in stroke is the National Institutes of Health Stroke Scale (NIHSS), the golden standard for defining stroke severity. The interpretation of the NIHSS is a score of >25 very severe, 14-25 severe, 5-14 moderate, and <5 mild. The American Heart Association report that almost 75% of stroke patient suffer from dysfunction and disability for a lifetime (Go et al., 2014; Yang et al., 2016).

Currently, effective treatments for stroke are intravenous tissue plasminogen activator (tPA; alteplase) and endovascular thrombectomy. This therapy, given within 4.5 hours, is first-line treatment but only about one-third of patients with acute ischemic stroke experience functional improvement. Current ischemic and haemorrhagic stroke treatments are limited by a narrow golden period and lack of regenerative benefits, so stem cell therapy emerges as an ideal candidate for functional recovery in stroke patients (Hess et al., 2017; Permana et al., 2022). Current stroke therapy does not benefit chronic stroke patients significantly (Chiu et al., 2022). Stem cell therapy, still being studied, is expected to repair ischemic areas damaged by stroke to restore their physiological functions and reduce neurological deficits in chronic stroke patients. This research is expected to improve functional recovery in stroke patients so that they can replace the current stroke therapy (Manley and Steinberg, 2012). This study aimed to determine the therapeutic efficacy of mesenchymal stem cells (MSCs) in reducing neurological deficits in chronic ischemic stroke patients.

METHODS

The research used was a systematic review. The literature used is reviewed with the principles of the PICOS framework Participants: chronic ischemic stroke patient, Interventions: administration of mesenchymal stem cells therapy, Comparisons: different doses of mesenchymal stem cells, Outcomes: improvement in neurological function as measured by the difference in changes in the NIHSS score, and Study Design: cohort studies, which provides data explicitly and makes it easier for researchers to find journals relevant to the topics discussed by researchers. We followed the preferred reporting items for systematic review (PRISMA) statement for conducting a systematic review.

Search Strategy

We searched PubMed, Cochrane Library, Science Direct, and Springer Link from inception until December 2022 for cohort studies dealing with mesenchymal stem cells therapy for patients with ischemic stroke. The following search terms were used: “stroke” OR “ischemic stroke” OR “cerebrovascular attack" AND “mesenchymal stem cell” OR “stem cell” OR “mesenchymal cell” OR “stroma cell” OR "MSC" OR "MSCs"

Apart from the strategy mentioned above, another manual search was done to identify any further published studies via screening the reference lists of relevant papers and reviews.

Selection Criteria

Inclusion Criteria

Each population must meet inclusion criteria that can be taken as a sample.

1. A study that addresses the therapeutic potential of MSCs to improve neurological function in chronic ischemic stroke patients who have experienced stroke symptoms for more than one month.
2. The study design that can be used is a cohort study
3. Research articles published within the last 10 years (2012-2022).
4. English research articles.
5. Research articles that passed the ROBINS-I quality and risk of bias assessment with a low risk of bias.
6. Articles include outcomes assessed from the NIHSS score.

Exclusion Criteria

Exclusion criteria are population criteria that cannot be sampled.

1. Article with systematic review and meta-analysis.
2. Articles that cannot be accessed in full text.

Data Extraction

Data were extracted based on inclusion and exclusion criteria. Relevant data for this study included the author's name, year of publication, study design, type of stroke, sample size, average age, route of stem cell therapy, type of stem cell, and stem cell dose. Risk assessment can be done using the Risk Of Bias In Non-Randomized Studies-of Interventions (ROBINS I). All data collected is then stored on the Rayyan QCRI web.

Data Analysis

Data analysis in this systematic review used descriptive analysis with a quantitative approach. This method coherently describes the research results and the relationships between the variables studied by collecting, processing, analysing, and interpreting data in narrative form. Data analysis was performed from studies that met the inclusion and risk of bias criteria. The data analysed included author, year, country, study design, study sample, type and dose of MSCs, injection method, research findings, statistical tests, research results, and research conclusions.

RESULTS

Study Selection

The study selection process was carried out using advanced searching and citation searching. The advanced searching method uses Boolean operators in several international and national journal databases. These databases are PubMed, Science Direct, Springer, and the Cochrane Library. The number of articles obtained with the Boolean operator was 1,038 from 69 PubMed, 2 from Springer Link, 25 from Cochrane, and 942 from Science Direct. The citation-searching method in this study collected eight articles and added 1,038 articles using the advanced searching method, bringing the total number of articles to 1,046. Determination of synonyms using MeSH to facilitate the making of keywords. All articles found are then included on the Rayyan QCRI website, which can assist reviewers in selecting journals. All selection stages are summarized in the PRISMA flowchart in Figure 1.

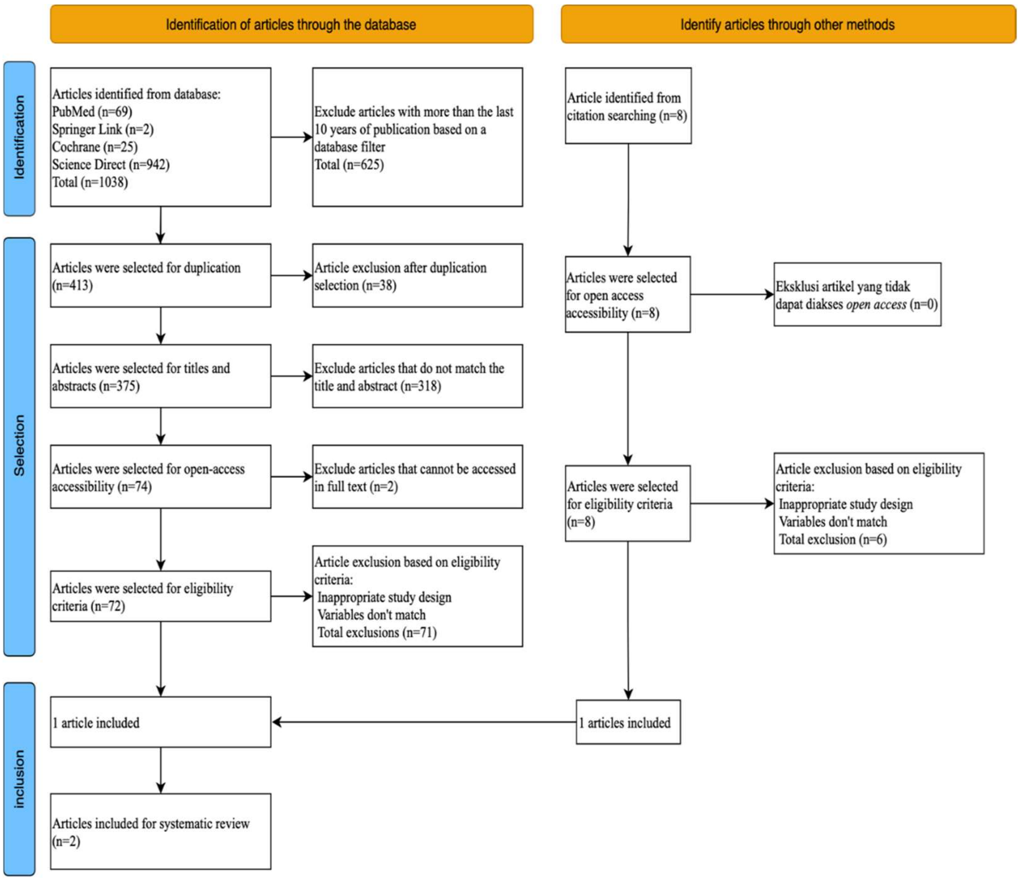

Figure 1. PRISMA flowchart of article selection

Study Quality and Risk of Bias

Articles collected through a screening process based on the PRISMA flowchart resulted in two articles. Articles that pass the journal quality selection are then subjected to a risk of bias assessment using ROBINS-I. Two articles that have undergone critical appraisal show a low risk of bias and can be included to proceed to the next stage, namely, conducting an article review.

Characteristics of Study and Research Sample

A total of two articles with cohort studies research design were eligible for use in this systematic review. The included research articles are in English and come from California. Subjects in the literature used in this study were chronic ischemic stroke patients. The study used as a source of systematic review has research subjects aged 18-75 years. The number of subjects included in the reviewed literature was 33 people. More complete characteristic data and research samples are listed in Table 1 and Table 2.

Table 1. Characteristics of article research

Writer	*Year*	*Languange*	*Location*
Levy et al.,	*2019*	*English*	*California*
Steinberg et al.,	*2019*	*English*	*California*

Data Extraction Results

Two articles have been obtained then extraction was performed in tabular form by grouping based on the research sample, type and dosage of MSCs, injection method, research findings, and statistical tests. Details of data extraction can be seen in Table

Table 2. Data extraction

Writer, Year	*Negara*	*(n) Sampel*	*Intervention and Therapeutic Dose*	*Study Design*	*Outcome*
Levy et al., 2019	*United States*	*15*	*Mesenchymal stem cells (MSC) by intravenous injection, dosed:* *Cohort 1 = 0.5 x* 10^6 *cells/kg BW;* *Cohort 2 = 1 x* 10^6 *cells/kg BW;* *Cohort 3 = 1.5 x* 10^6 *cells/kg BW.*	*Cohort studies*	*NIHSS score decrease by 1-2*
Steinberg et al., 2019	*United States*	*18*	*Mesenchymal stem cells (MSCs) by stereotactic injection, dosed* *Cohort 1 = 2.5 x* 10^6 *cells;* *Cohort 2 = 5 x* 10^6 *cells;* *Cohort 3 = 10 x* 10^6 *cells.*	*Cohort studies*	*NIHSS score decreased by 1.9-2.1*

Levy et al.'s research (2019) used allogeneic BMSCs. This study used 36 patients with a diagnosis of chronic ischemic stroke and had an NIHSS score of 6-20. There were 13 subjects enrolled at the University of California, San Diego, 19 at Arizona, and 4 at the University of California, Irvine. The dose given to the subjects was that five subjects received 0.5×106 cells/kg in section 1/Cohort 1, five subjects received 1.0×106 cells/kg in section 1/Cohort 2, five subjects received 1.5× 106 cells/kg in section 1/Cohort 3, and 21 subjects in section 2 received 1.5 × 106 cells/kg. However, in our systematic review study, only 15 subjects were included in section 1. Bonemarrow-derived mesenchymal stem cells are administered to patients via intravenous injection. After being given stem cells, observations were made on the patient's NIHSS score and there was a significant decrease in the NIHSS score, namely decreasing to 1 in the 6^{th} month and a decrease of 2 in the 12^{th} month (Levy et al., 2019).

The study of Steinberg et al. (2019) used SB623, a cell product containing allogeneic modifications of BMSCs. Bonemarrow-derived mesenchymal stem cells. This study used 18 patients diagnosed with chronic ischemic stroke with an average NIHSS score of 9.3 with a moderate NIHSS interpretation. Patients were divided into three cohorts, six patients each; three cohorts received a single dose of 2.5 × 106, 5.0 × 106, or 10 × 106 SB623 cells transplanted using the stereotactic MRI technique. The stereotactic injection was performed into three subcortical peri-infarct areas. Injections were made at three points in space 5-6 mm from the target. After being given stem cells, observations were made on the patient's NIHSS score, and the NIHSS score decreased significantly, namely decreasing to 1.9 at 12 months and 2.1 at 24 months (Steinberg et al., 2019).

DISCUSSION

All phases of life contain a special population of cells called stem cells, which have the capacity to self-renew and specialise into several cell lineages. Mesenchymal stem cells (MSCs) are a type of mesodermal stem cell that has the capacity to renew itself and also shows multilineage differentiation. The benefits of MSCs in stroke treatment can be through six mechanisms, namely weakening inflammation through immunomodulation, releasing trophic factors to enhance therapeutic effects, inducing angiogenesis, triggering neurogenesis, reducing infarct volume, replacing damaged cells.

Based on the results of the review of the article studies, the results were the same regarding an increase in neurological function as indicated by a decrease in the patient's NIHSS score. It relates to the mesenchymal stem cell mechanism that can treat stroke through six mechanisms: attenuating inflammation through immunomodulation, releasing trophic factors to enhance therapeutic effects, inducing angiogenesis, triggering neurogenesis, and reducing infarct volume, replacing damaged cells.

Based on the two selected articles, it is stated that there was a decrease in the NIHSS score. It indicates that mesenchymal stem cells therapy improves the patient's neurological function. However, one article used stereotactic injection from the two articles, while one used intravenous injection. Although both show results that improve neurological function in patients, both injections have their drawbacks. Intravenous injection is considered less invasive when compared to stereotactic injection. However, the intravenous injection can make the injected stem cells distribute to other organs that are not intended so that they can cause oedema in the target organ. The stereotactic injection is considered more appropriate for chronic stroke types because it can be precisely injected into the infarct area even though the technique is more invasive (Kawabori et al., 2020)

One of the mechanisms of MSCs in treating stroke is reducing inflammation through immunomodulation (Wang et al., 2018). Even though the stroke has long since passed, the immune response can remain active for a long time. This is because antigens are released from dead brain cells, which continue to trigger the immune system to respond. In chronic strokes, the body's immune system may not be able to distinguish between healthy and damaged brain tissue, and may attack healthy tissue (Chamorro et al., 2012). MSCs can reduce inflammation through immunomodulation by increasing the secretion of anti-inflammatory cytokines and reducing the expression of proinflammatory cytokines (Zhang et al., 2021). Huang et al.'s study (2014) proved that the role of IL-6 as an anti-inflammatory cytokine is mediated through its inhibitory effect on TNFa and IL-1 proinflammatory cytokines (Huang and Zhang, 2019). Another critical role of mesenchymal stem cells in treating stroke is that they can replace damaged cells. Research by Fu et al. (2019) shows that MSCs will enhance the wound-healing process in damaged tissue after mobilization and migration to injured tissue (Fu et al., 2019). Research by Zhang et al. (2022) states that MSC transplantation can replace damaged cells through its potential to differentiate into neurons and glial cells under appropriate conditions (Zhang et al., 2022). If proinflammatory cytokines are inhibited, this can reduce inflammation in the ischemic area and improve neurological function in ischemic stroke patients. Some of these mechanisms are one of the reasons mesenchymal stem cells can reduce neurological deficits, ultimately improving neurological function in stroke patients.

Based on the systematic review results, both journals used mesenchymal stem cells derived from bone marrow. Both use allogeneic mesenchymal stem cells. The thing that needs to be observed from allogeneic stem cell administration is the body's immune reaction because stem cells do not originate from the body itself. Based on the results of the two journals, there was no immune reaction from the samples using allogeneic stem cells. Some side effects of giving stem cells are headaches, nausea, vomiting, and fatigue. However, it was stated in the article by Steinberg et al. (2019) that these side effects were not caused by stem cell administration but were the result of the surgical process when stem cell injections were performed (Steinberg et al., 2019).

Therapy regarding mesenchymal stem cells also needs further research regarding the dose, type of stem cell, time, and the correct route for administering stem cells. Some of the drawbacks of this therapy are the risk of causing tumorigenesis, even though MSCs are included in the low category. The risks associated with tumorigenesis after stem cell transplantation are widely discussed in the literature. Stem cells can be compared to tumour cells because of their ability to proliferate for a long time, high viability, and resistance to apoptosis (Musiał-Wysocka et al., 2019). So that at this time, there is still a need for research to develop therapy from stem cells so that it can be a treatment for chronic ischemic stroke. Stem cell treatment for stroke patients holds significant promise, but it also faces several challenges in the future. Some of the main challenges include selecting the right type of stem cell, safety risks such as tumor formation and immune rejection, and difficulties in ensuring that stem cells can survive and integrate with damaged brain tissue. In addition, a deeper understanding of the mechanism of action, cost issues, and regulatory and ethical constraints are also obstacles to the development of this therapy. However, research is continuing to overcome these obstacles and advance this therapy as an effective solution for stroke patients.

CONCLUSION

The conclusion that can be drawn is that MSCs therapy has proven effective in reducing neurological deficits in chronic ischemic stroke patients in terms of the decreased NIHSS score. In addition, injecting stereotactic stem cells in chronic ischemic stroke may be more appropriate than intravenous injection.

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