



Review Article

Clinical outcome and safety of stem cell therapy for ischemic stroke: A systematic review and meta-analysis

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ABSTRACT

Background: Several reports on stem cell administration have emerged proving it to be an ideal therapeutic approach for improving neurological functions in ischemic stroke patients. However, some studies also show disappointing results, with some reporting no statistically significant improvements among several different parameters. Several challenges also arise relating to safety and nonscientific aspects, such as ethics.

Methods: We performed a systematic review and meta-analysis to evaluate the effect of stem cell therapy on the clinical outcomes of ischemic stroke patients. A systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. A thorough literature search was conducted on PubMed, Scopus, and Cochrane databases. Articles were selected systematically based on the PRISMA protocol and reviewed completely. A total of 19 publications pertaining to stem cell therapy on the ischemic route were included and reviewed. Efficacy outcomes were measured with the National Institutes of Health Stroke Scale, modified Rankin Scale, or Barthel Index.

Results: The results of the meta-analysis indicate that the efficacy outcomes suggest favorable results after stem cell therapy, although not all study results are statistically significant. Stem cell therapy in stroke cases showed a better outcome than standard conservative therapy alone, although our analysis shows that many factors can influence this outcome, and significant effects can only be seen after several months.

Conclusion: The results of this study show promising and satisfying efficacy and a relatively low rate of serious adverse events.

Keywords: Clinical outcome, Ischemic stroke, Safety, Stem cell therapy

INTRODUCTION

Ischemic stroke is the main subtype of stroke and occurs in about 70% of all stroke cases (85–87% in the United States),^[5] with the remainder being caused by intracerebral or subarachnoid hemorrhage. Ischemic stroke occurs when a sudden loss of blood flow due to thrombosis or embolism occludes cerebral vessels resulting in loss of neurological function.^[28] Apart from its debilitating effect on individuals, stroke also poses a major financial burden worldwide on health resources.^[7] Even though a majority of stroke patients survive the initial year after the incident, more than 10% experience long-term disabilities.^[34]

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Due to these disabilities, standard interventions (including intravenous thrombolysis and mechanical endovascular clot retrieval) have been shown to improve outcomes, including survival, and residual disability.^[1,27,38] The effect is time-dependent, however, and warrants immediate management of ischemic stroke patients to prevent a worse outcome.^[1,27] Only about 10% of patients with stroke can receive immediate treatment for stroke revascularization therapy, even in dedicated stroke centers.^[26]

Intravenous recombinant tissue plasminogen activator, currently the only approved substance for ischemic stroke intervention, has a narrow efficacy time window of only 4.5 h, and reportedly only up to 5% of patients are able to receive this therapy.^[29] In light of these challenges, further studies, the development of new therapeutic methods with a broader and less strict time window, and less invasive methods are essential for improving the outcomes of ischemic stroke patients.

Recently, reports of stem cell administration have emerged, suggesting that it is an ideal therapeutic approach for improving neurological functions in ischemic stroke patients.^[8] Stem cell therapy has been shown to promote endogenous neuroprotective and brain repair processes, including immunomodulation, neuronal, vascular, and glial remodeling.^[11]

Animal studies have proven that various types of stem cells are able to improve neurological functions that occur after cerebral stroke.^[21] Moreover, various clinical trials have also shown promising results, suggesting that stem cell therapy is feasible, safe, and can promote recovery in patients with ischemic stroke.^[4] However, some studies also show varying results, with some reporting no statistically significant improvements in several different parameters.^[13,17,31] Moreover, several challenges arise in the process of realizing stem cell therapy, namely, safety as well as other nonscientific challenges including the need for complex regulatory approval, high production costs, preservation, and transfer of cells.^[17,21,33,37,39]

We performed a systematic review and meta-analysis to evaluate clinical outcomes of ischemic stroke patients after stem cell therapy. To explore any future hypotheses, it was important to undertake this systematic review to obtain basic information and data on the efficacy of stem cell therapy for ischemic stroke cases. It is also necessary to help clinicians and stakeholders in the decision-making process to determine whether stem cell therapy for ischemic stroke patients needs to be promoted, and to determine its benefits and associated challenges.

MATERIALS AND METHODS

Eligibility criteria

There was a full-text cohort study including clinical trials on adult patients (>18-years-old) with ischemic stroke, in

any phase of the disease (acute, subacute, or chronic), who received stem cell therapy with intracerebral, intraventricular, subarachnoid, intra-arterial, intravenous, intraperitoneal, or intranasal administration. Reviews, unpublished articles, letters to the editor, abstracts, and studies not written in English were excluded from the study.

Type of outcome measures

Clinical outcome measured with:

- Modified Rankin Scale (mRS)
- National Institute of Health Stroke Scale (NIHSS)
- Barthel Index (BI)

We also assessed that the safety of stem cell therapy outlined in these studies by determining the number and severity of any adverse events.

Information sources

This systematic review was conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines as shown in [Figure 1].^[25] Studies were obtained by searching PubMed, Cochrane, and Scopus electronic databases during March 2021. We applied language restriction to our search, only studies published between 2010 and 2021, and articles in English were included in the study.

Search protocol

The study question was formed using the patient/population, intervention, comparison, and outcomes model. The authors used the following search keywords to search all trials registers and databases: stem cells therapy AND (ischemic stroke OR ischemic brain) AND (mRS OR NIHSS OR BI).

Data collection and analysis

We screened all records by the title and abstract as our search strategy. Three authors (ATP, PL, and AAF) independently assessed the inclusion of all potential studies. The search results were first excluded based on the relevancy of the titles and then on the relevancy of the abstracts. Non English publications were automatically excluded from the study. Full-text articles were then assessed by all authors for potentially eligible randomized and controlled trials (RCTs) and cohort studies. The reasons for exclusion of studies were noted and reported. Included studies are shown in [Table 1].

Data extraction and management

For eligible studies, three review authors (HF, MAF, and NSS) independently extracted data using the data extraction form on characteristics of patients and interventions, study quality, and outcomes of interventions.^[14] For measured outcomes

Table 1: Summary of the literatures included in the study.

| Author | Study Design | Patients | Age | Sample Size | Type of Graft | Number of Transplanted Cells | Route of Administration | Functional Outcome | | |
|--|--------------------|----------|--|--|---|--|-------------------------|---|--|--|
| | | | | | | | | NIHSS | mRS | BI |
| Jaillard et al., 2020 ^[17] | RCT | 31 | 53 | 15 controls 16 treatments | Autologous bone marrow-derived MSC | 100 and 300×10 ⁶ | Intravenous | 12.75±1.507 13.5±2.466 | 4±0 3.875±0.16 | 42.5±14.51 45±18.82 |
| Chen et al., 2014 ^[9] | RCT | 30 | 52.8±9.0 50.1±7.7 | 15 controls 15 treatments | PBSC | 3–8×10 ⁶ | Intra-cerebral | 9.6±1.3 9.3±0.5 | 2.8±0.4 2.9±0.3 | n/a n/a |
| Hess et al., 2017 ^[13] | RCT | 134 | 18–33 | 63 controls 71 treatments | Multipotent Adult Progenitor Cells | 400–1,200×10 ⁶ | Intravenous | 13.4±3.7 13.3±3.5 | n/a n/a | n/a n/a |
| Prasad et al., 2014 ^[31] | RCT | 120 | 18–75 | 60 controls 60 treatments | Autologous bone marrow mononuclear stem cells | 280.75×10 ⁶ | Intravenous | 11±4.44 13±4.44 | n/a n/a | n/a n/a |
| Lee et al., 2010 ^[23] | RCT | 52 | 64.6±13.6 | 36 controls 16 treatments | Autologous bone marrow MSC | 5×10 ⁷ | Intravenous | 10.63±3.0 10.17±3.6 | 4.8±0.5 4.4±0.9 | n/a n/a |
| Savitz et al., 2019 ^[33] | RCT | 48 | 60.7±10.4 | 19 controls 20 treatments | Autologous Bone Marrow Derived ALD-401 | 3.8×10 ⁶ | Intra-arterial | n/a | n/a | n/a |
| Zhang et al., 2019 ^[39] | Prospective cohort | 9 | 42 (30–49) 43 (41–45) 48 (37–54) | 3 (12 m) 3 (24 m) 3 (72 m) | Neural Stem Cells (NSI-566) | 12×10 ⁶ 24×10 ⁶ 72×10 ⁶ | Intra-cerebral | 5.33±3.51 7.67±2.08 6±1 | n/a n/a n/a | n/a n/a n/a |
| Banerjee et al., 2014 ^[2] | Non-RCT | 5 | 57 (45–75) | 5 treatments | CD34± stem cell | 2.42 (1.2–2.79)×10 ⁶ | Intra-arterial | 5.128±10.4 | 3.8±0.837 | n/a |
| Honmou et al., 2011 ^[16] | Non-RCT | 12 | 60.5 (41–73) | 12 treatments | Autologous bone marrow-derived MSC | 1.2 (0.6–1.6)×10 ⁸ | Intravenous | 8.25±5.545 | n/a | n/a |
| Jiang et al., 2013 ^[18] | Prospective cohort | 4 | 48.5 (40–59) | 4 treatments | Umbilical cord-derived MSC | 2×10 ⁷ | Intra-arterial | n/a | 4±0.816 | n/a |
| Bhasin et al., 2012 ^[6] | Non-RCT | 24 | 46.58±10.99 47.08±9.90 | 12 controls 12 treatments | Autologous bone marrow-derived MSC | 55 (50–58)×10 ⁶ | Intravenous | n/a n/a | n/a n/a | 49.92±10.03 48.75±10.57 |
| Kalladka et al., 2016 ^[20] | Non-RCT | 11 | 78 (68–82) 69 (61–75) 64 (60–68) 66 (61–71) | 3 (2 m) 3 (5 m) 3 (10 m) 2 (20 m) | Human neural stem cell (CTX0E03) | 2×10 ⁶ 5×10 ⁶ 10×10 ⁶ 20×10 ⁶ | Intra-cerebral | 7.67±1.53 8±2 7.33±0.577 6.5±0.707 | 4±0 3.67±0.577 2.67±0.577 3±0 | 11±1 11.67±2.517 14.33±1.53 13.5±2.12 |
| Steinberg et al., 2019 ^[34] | Non-RCT | 18 | 64 (33–75) | 6 (2.5 m) 6 (5 m) 6 (10 m) | Modified bone marrow MSC (SB623) | 2.5×10 ⁶ 5×10 ⁶ 10×10 ⁶ | Intra-cerebral | 9.3±1.7 | 3.22±0.43 | n/a |

(Contd...)

Table 1: (Continued).

| Author | Study Design | Patients | Age | Sample Size | Type of Graft | Number of Transplanted Cells | Route of Administration | Functional Outcome | | |
|--|---------------------|--------------------|------------------------------|-------------------------------|------------------------------------|----------------------------------|-------------------------|----------------------------|--------------------------|--|
| | | | | | | | | NIHSS | mRS | BI |
| Laskowitz et al., 2018 ^[21] | Non-RCT | 10 | 65.5 (45-79) | 10 treatments | Umbilical cord blood stem cell | 1.68 (0.84-2.92)×10 ⁹ | Intravenous | 11.2±1.62 | 4.4±0.52 | 18.8±12.26 |
| Qiao et al., 2014 ^[32] | Prospective cohort | 6 | 61.5 (3-85) | 6 treatments | MSC | 0.5×10 ⁶ /kgBW | Intravenous | 8.167±5.84 | 4±1.095 | 40.83±33.38 |
| Vahidy et al., 2019 ^[37] | Non-RCT | 210 | 63.7±12.5 60.7±13.3 | 185 controls 25 treatments | Autologous bone marrow-derived MSC | 10×10 ⁶ /kgBW | Intravenous | n/a n/a | 0.395±0.854 0.08±0.4 | n/a n/a |
| Chung et al., 2021 ^[10] | RCT | 54 | 64.27±13.25 63.03±14.36 | 15 controls 39 treatments | Autologous bone marrow-derived MSC | 1×10 ⁶ /kgBW | Intravenous | 14.47±5.32 11.36±5.20 | 4.47±0.83 4.26±0.75 | 19.8±25.5 28.28±26.63 |
| Prasad et al., 2012 ^[30] | Non-RCT | 11 | 54 (38-70) | 11 treatments | Autologous bone marrow-derived MSC | 40×10 ⁶ | Intravenous | 12.27±5.16 | 3.45±1.04 | 34.09±22.23 |
| Jin et al., 2017 ^[19] | RCT | 20 | 53.10±13.068 50.80±17.428 | 10 controls 10 treatments | Autologous bone marrow-derived MSC | 1×10 ⁷ | Intra-cerebral | 10.70±3.713 12.30±3.945 | 4.10±0.994 4.60±0.699 | 15.00±8.498 14.50±13.006 |
| Author | 6 months | | | 12 months | | | 24 months | | | Notes |
| | NIHSS | mRS | BI | NIHSS | mRS | BI | NIHSS | mRS | BI | |
| Jaillard et al., 2020 ^[17] | 9.4±4.7 8.94±5.2 | 3±0.66 3±0.63 | 77.86±25.40 80.63±30.87 | n/a n/a | n/a n/a | n/a n/a | 8.43±4.96 7.73±5.78 | 3.07±1.1 2.75±0.93 | 85±20.48 82±27.83 | Insignificant clinical outcome, except for motoric score |
| Chen et al., 2014 ^[9] | 9.4±1.2 6.7±1.7 | 2.7±0.5 2.5±0.5 | n/a n/a | 8.7±1.9 5.5±1.8 | 2.7±0.5 2.1±0.3 | n/a n/a | n/a n/a | n/a n/a | n/a n/a | Significant clinical outcome improvement |
| Hess et al., 2017 ^[13] | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | Insignificant results |
| Prasad et al., 2014 ^[31] | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | n/a n/a | Insignificant results |

(Contd...)

Table 1: (Continued).

| Author | Study Design | Patients | Age | Sample Size | Type of Graft | Number of Transplanted Cells | Route of Administration | Functional Outcome | | |
|--|--------------|----------|-------------|--------------|---------------|------------------------------|-------------------------|--------------------|------------|---|
| | | | | | | | | NIHSS | mRS | BI |
| Lee et al., 2010 ^[2,3] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Improvement on early post-treatment phase, no improvement later on |
| | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | |
| Savitz et al., 2019 ^[33] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | |
| Zhang et al., 2019 ^[39] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement. |
| | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | imaging revealed new neural tissue formation |
| | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement |
| Banerjee et al., 2014 ^[2] | 2.2±1.92 | 1.6±1.14 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement |
| Honnou et al., 2011 ^[16] | n/a | n/a | n/a | 1.583±2.0207 | n/a | n/a | n/a | n/a | n/a | Significant improvement |
| Jiang et al., 2013 ^[18] | n/a | 3.25±0.5 | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Small size of samples, significant improvement |
| Bhasin et al., 2012 ^[6] | n/a | n/a | 78.67±11.35 | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement on modified BI only |
| | n/a | n/a | 69.75±9.90 | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement |
| Kalladka et al., 2016 ^[50] | 5.67±2.08 | n/a | n/a | 4.33 ±2.08 | n/a | 12.67±1.15 | 5.67±1.15 | n/a | 12±1.73 | Improved neurological function, no controls |
| | 6.33±3.055 | n/a | n/a | 6.33±2.89 | n/a | 14.67±2.08 | 5.67±4.04 | n/a | 14.33±3.51 | |
| | 4.33±0.577 | n/a | n/a | 4.67±1.154 | n/a | 14.67 ±3.21 | 4±1.73 | n/a | 13.33±1.53 | |
| | 3.5±2.12 | n/a | n/a | 3.5±3.53 | n/a | 16±2.83 | 4±0 | n/a | 17.5±3.53 | |
| Steinberg et al., 2019 ^[34] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement of NIHSS score. Insignificant result of mRS |

(Contd...)

Table 1: (Continued).

| Author | Study Design | Patients | Age | Sample Size | Type of Graft | Number of Trans-planted Cells | Route of Administration | Functional Outcome | | |
|--|--------------|------------|-------------|-------------|---------------|-------------------------------|-------------------------|--------------------|-------------|--|
| | | | | | | | | NIHSS | mRS | BI |
| Laskowitz et al., 2018 ^[22] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Significant improvement |
| Qiao et al., 2014 ^[32] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Improved neurological function |
| Vahidy et al., 2019 ^[37] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Favorable safety |
| Chung et al., 2021 ^[10] | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | n/a | Insignificant overall results. Significant improvement of lower extremity motor function |
| Prasad et al., 2012 ^[30] | 4.8±5.473 | 2.09±1.3 | 79.09±20.23 | n/a | n/a | n/a | n/a | n/a | n/a | n/a |
| Jin et al., 2017 ^[19] | 8.20±3.490 | 3.90±1.101 | 29±12.867 | 6.50±3.342 | 3.40±0.966 | 41.5±17.646 | 5.70±3.199 | 3.10±1.101 | 47±24.060 | Lumbar subarachnoid injection. significant neurological improvement |
| | 9.40±3.806 | 4.00±0.816 | 26±16.799 | 8.80±3.706 | 3.60±0.699 | 37.5±15.855 | 8.60±3.688 | 3.00±1.333 | 51.5±26.146 | |

RCT: Randomized and controlled trial, MSC: Mesenchymal stem cells, PBSC: Peripheral blood stem cells, NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Scale, BI: Barthel index

(NIHSS, mRS, and BI), we extracted or reanalyzed the mean difference between the experimental and control group (with its 95% confidence interval [CI] as reported by the study authors. We extracted the mean difference of outcome in each arm for continuous outcomes (mean difference of NIHSS, mRS, and BI after 6 months, 12 months, and 24 months). Two review authors (AM, IHK, and NS) entered all data into Review Manager (RevMan) software, version 5.4.^[36]

Assessment of study quality and risk of bias in included studies

The review authors independently assessed risk of bias for each included study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions for nonrandomized studies: Risk of Bias in Nonrandomized Studies of Interventions* (ROBINS-I) for nonrandomized studies and *Risk of Bias 2* (RoB 2) for randomized studies.^[14] Any disagreement was resolved by discussion or by involving a third assessor. We summarized judgments in the “risk of bias” tables along with the characteristics of the included studies and interpreted the results of meta-analyses in light of the overall “risk of bias” assessment.^[24,35]

Measures of treatment effect

We presented the results of the continuous data as mean difference with 95% CI to combine trials that measured the same outcome and same comparison. A meta-analysis was planned if the data were appropriate for pooling. Summary of estimates was presented as mean difference for the outcomes. Consequently, both fixed-effects and random-effects meta-analyses were used, although the latter was prespecified in the protocol. If pooling was inappropriate, a narrative synthesis was implemented. The definitions of CI, heterogeneity, and P-value were conventional (CI 95%; I² <40%: unimportant; 30–60%: moderate; 50–90%: substantial, 75–100%: considerable; P < 0.05: significant; and P value for interaction < 0.1: significant).^[15] Review Manager (version 5.4) software was used for the meta-analysis.^[36]

RESULTS

A total of 173 studies were identified and screened. Of these, 31 studies were assessed for eligibility, 19 studies were included in the qualitative review,^[2,6,9,10,13,16–20,22,23,30–34,37,39] and four studies were included in the meta-analysis.^[6,9,19,31] [Table 1] shows a summary of the included studies.

Demographic results

The 19 studies in the review included 800 patients with a median age of 60.5 years (range 30–85 years). Male participants dominated in the study, comprising 236 (62.26%) of the participants versus 143 (37.73%) females.

The patients were then divided into two groups: an experimental/therapy group (379 patients) and a control group who did not receive stem cell therapy administration (421 patients). Adverse events were reported 467 times in 19 different studies. Of those 467 documented adverse events, 103 (27.18%) were serious. A summary of the results is shown in [Table 2].

Risk of bias analysis

The risk of bias risk assessment of the studies involved was measured by ROBINS-I for nonrandomized studies and the RoB 2 tool. The result is shown in [Figures 2 and 3].

Stem cell versus control group outcome comparison

Out of all the 19 studies included in this review, 4 (21.05%) studies were able to be included in the quantitative analysis for the 6-, 12-, and 24-months posttherapy neurological outcomes measured in NIHSS, mRS, and BI, respectively. The comparison was undertaken between those who received and those who did not receive stem cell therapy at the time when the baseline neurological functions were measured.

6-month outcome

6-month NIHSS

Out of the four studies included in the meta-analysis, three were eligible to be included in the analysis for the improvement in the NIHSS score by calculating the mean difference between the baseline and 6-month posttherapy scores. The assessment was carried out to assess the difference in mean NIHSS scores in the stem cell therapy and control groups after 6 months. The results showed a favorable trend in the stem cell therapy group and these results were statistically significant (MD = 1.48; 95% CI –2.68–0.28; P = 0.02; and I² = 83%). The results of the complete analysis, including a diagram, are shown in [Figure 4].^[9,17,19]

6-month mRS

In the analysis of improvement in mRS scores, three out of four studies included in the meta-analysis provided the necessary

Table 2: Demographic results.

| Description | Number n (%) |
|---------------------------------------|---------------------------|
| Total patients, n | 800 participants |
| Patients with stem cell therapy, n | 379 participants (47.4%) |
| Patients without stem cell therapy, n | 421 participants (52.6%) |
| Median Age | 60.5 years (30–85) |
| Median (min–max) | |
| Gender | |
| Male, n | 236 participants (62.26%) |
| Female, n | 143 participants (37.73%) |
| Adverse events, n | 467 events |
| Serious adverse events, n | 103 events (27.18%) |

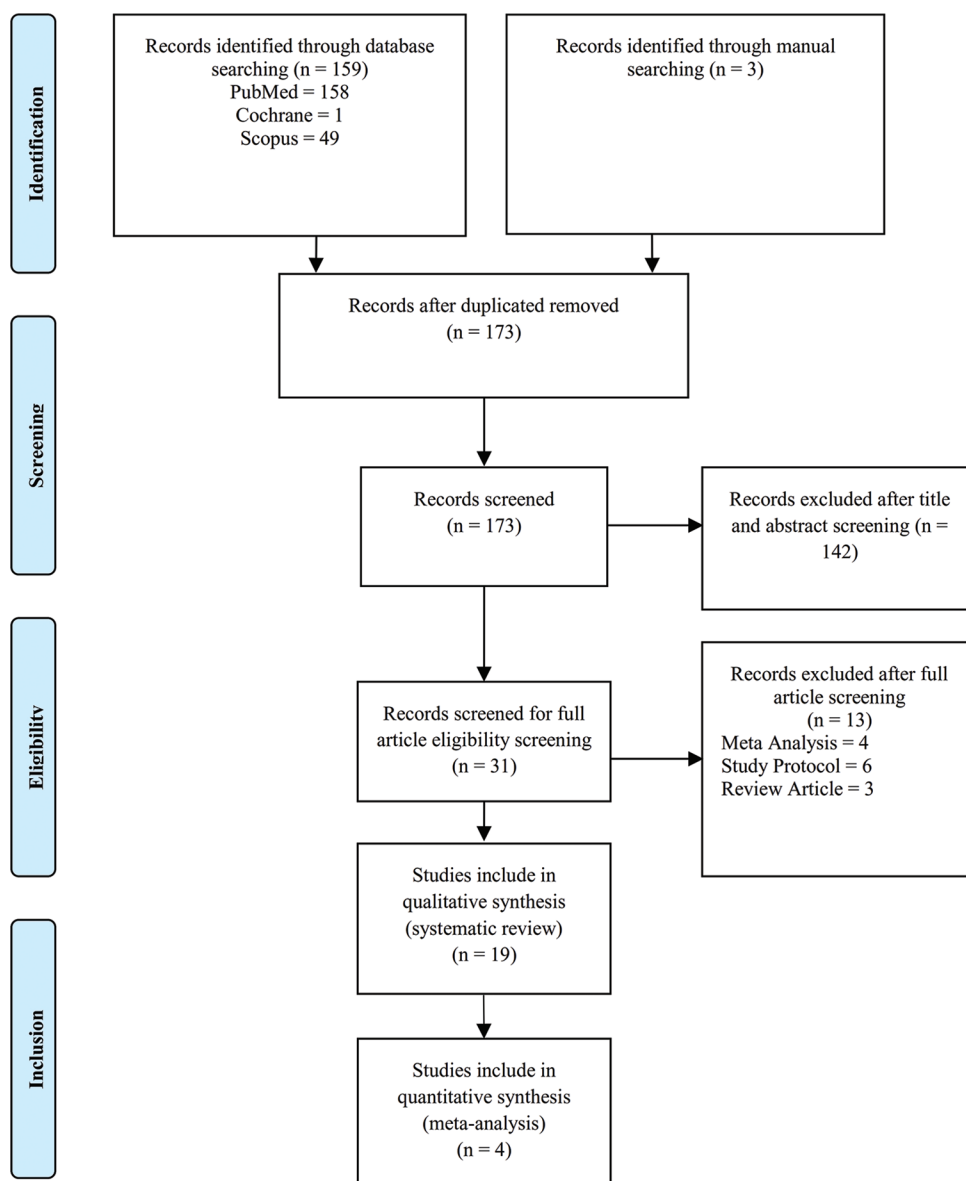


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines flowchart.

data so that the mean difference between baseline and 6-month posttherapy scores could be calculated. The assessment evaluated the mean difference in mRS scores in the stem cell therapy and control groups after 6 months of observation. Despite not being statistically significant, the difference between two groups indicated a more favorable result in patients who received stem cell therapy (MD = -0.27 ; 95% CI -0.52 – 0.17 ; $P = 0.33$; and $I^2 = 93\%$), as shown in [Figure 5].^[9,17,19]

6-month BI

In terms of improvement of BI scores at 6-month posttherapy, three studies yielded extractable data for calculation out of the four studies included in the meta-analysis. The difference in mean BI scores in the stem cell

therapy and control groups after 6 months was assessed for this analysis. The analysis indicated a more favorable outcome in those who received stem cell therapy, although these numbers were not statistically significant (MD = 2.09 ; 95% CI -4.70 – 8.88 ; $P = 0.55$; and $I^2 = 84\%$). [Figure 6] shows the quantitative analysis of the difference in BI after 6 months of observation.^[9,17,19]

12-month outcome

12-month NIHSS

From four studies included in the meta-analysis, two studies were able to be analyzed for the analysis of improvement in the NIHSS score by calculating the mean difference between

baseline and posttherapy for 12 months. The analysis of these two studies indicated a more favorable outcome (as indicated by the NIHSS scores at the 12th month) in the stem cell therapy compared to the control group (MD = -1.17; 95% CI -4.69–2.36; *P* = 0.52; and *I*² = 96%). However, these differences were not statistically significant, as shown in [Figure 7].^[9,19]

12-month mRS

Two out of the four studies included in the meta-analysis were able to be analyzed to determine mRS score improvement by calculating the mean difference between the baseline and 12-month posttherapy mRS scores. From those two studies, a meta-analysis of the mean difference of mRS scores in the 12th month between the stem cell therapy and control groups indicated a statistically more favorable trend toward the group receiving stem cell administration (MD = -0.53; 95% CI -0.92--0.15; *P* = 0.007; and *I*² = 80%). This result is shown in [Figure 8].^[9,19]



Figure 2: Result of ROBINS-I assessment. (a), Risk assessment of bias using ROBINS-I for nonrandomized studies in each study. (b), the proportion of bias risk assessment results using ROBINS-I for the nonrandomized study.

24-month outcome

24-month NIHSS

Assessment regarding the improvement of NIHSS score was analyzed from two out of the four studies included in the meta-analysis through the calculation of the mean difference between baseline and 24-month posttherapy scores. Each study yielded different conclusions and the pooled analysis indicated statistically insignificant results, with the result slightly in favor of the stem therapy in comparison with the control group (MD = -0.12; 95% CI -2.81–2.58; *P* = 0.93; and *I*² = 90%). The forest-plot of the analysis is shown in [Figure 9].^[17,19]

24-month mRS: The mean difference between the baseline and 24-month posttherapy mRS scores was able to be analyzed in two out of the four studies included in the meta-analysis. The obtained result of the analysis indicated a more favorable outcome in patients who received stem cell therapy group compared to those who did not

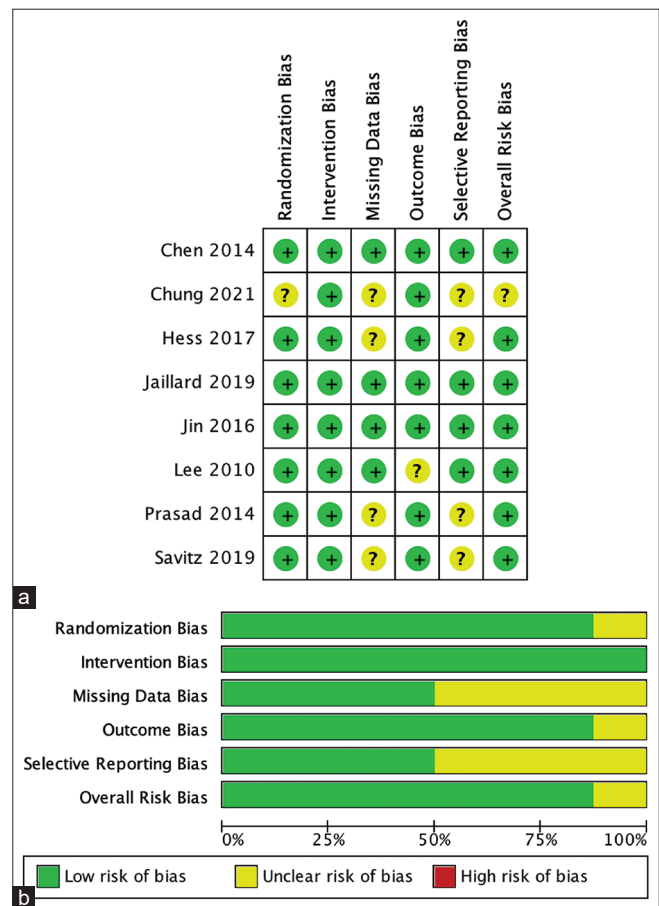


Figure 3: Result of RoB 2 assessment. (a) Risk assessment of bias using RoB 2 for randomized studies in each study. (b) The proportion of bias risk assessment results using RoB 2 for the randomized study.

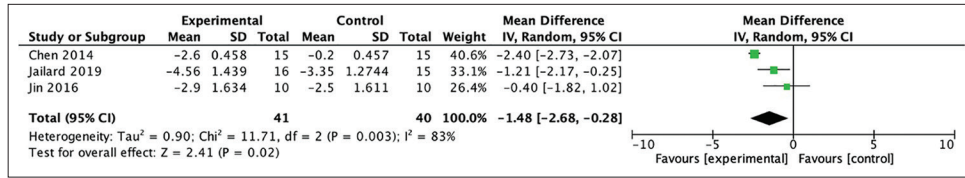


Figure 4: Calculation of the mean difference in NIHSS scores after 6 months between stem cell therapy and control groups in three studies. The mean difference was statistically greater in the stem cell therapy group and this result was statistically significant (MD = -1.48; 95% CI -2.68–-0.28; P = 0.02; and I² = 83%).

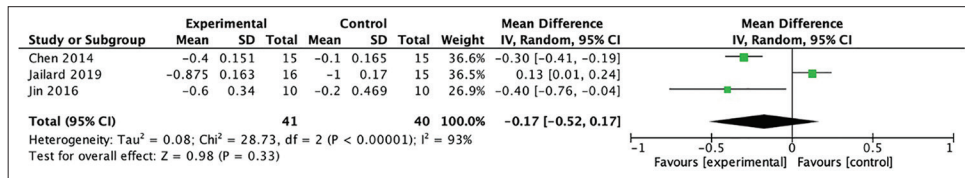


Figure 5: Calculation of the mean difference in mRS scores after 6 months between the stem cell therapy and control groups in three studies. The mean difference was statistically greater in the stem cell therapy group, although this result was not statistically significant (MD = -0.27; 95% CI -0.52–0.17; P = 0.33; and I² = 93%).

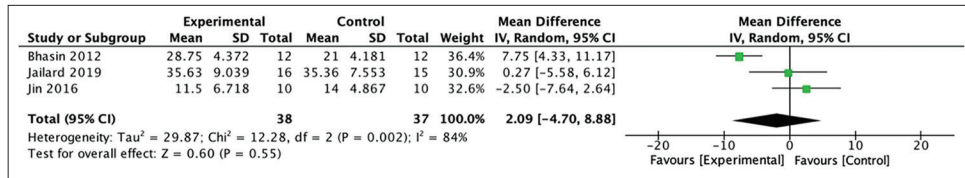


Figure 6: Calculation of mean difference in BI scores after 6 months between stem cell therapy and control groups in three studies. The mean difference was statistically greater in the stem cell therapy group, although this result was not statistically significant (MD = -0.27; 95% CI -0.52–0.17; P = 0.33; and I² = 93%).

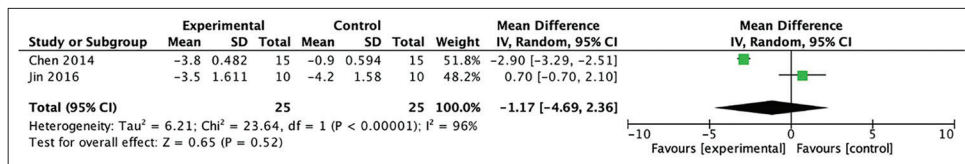


Figure 7: Calculation of the mean difference in NIHSS scores after 12 months between the stem cell therapy and control groups in two studies. The mean difference was statistically greater in the stem cell therapy group, although this result was not statistically significant (MD = -1.17; 95% CI -4.69–2.36; P = 0.52; and I² = 96%).

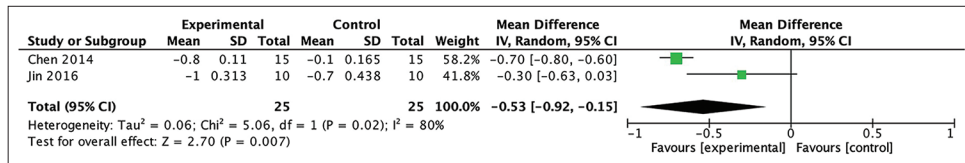


Figure 8: Calculation of the mean difference in mRS scores after 12 months between the stem cell therapy and control groups in two studies. The mean difference was statistically greater in the stem cell therapy group, and this result was statistically significant (MD = -0.53; 95% CI -0.92– -0.15; P = 0.007; and I² = 80%).

(MD = -0.35; 95% CI -0.74–0.03; P = 0.07; and I² = 67%). However, statistical analysis proved that this result had no statistical significance. The diagram of the analysis is shown in [Figure 10].^[17,19]

24-month BI

In all four studies included in the meta-analysis, two were able to be included in the meta-analysis for the improvement in BI scores by calculating the mean difference between baseline

and 24-month posttherapy scores. The pooled analysis of those two studies yielded a statistically insignificant difference in outcomes after 24 months of observation between those groups. The result showed a slightly more favorable outcome for those who received stem cell therapy compared to the control, although it did not reach significance (MD = -0.62; 95% CI -10.89-9.64; $P = 0.93$; and $I^2 = 80\%$). The forest-plot of this analysis is shown in [Figure 11].^[17,19]

DISCUSSION

Outcome improvement after administration of stem cell therapy

6-month outcome

Improvements in outcome were measured 6-, 12-, and 24-month posttherapy, by comparing the stem cell group to the control group. Analysis of the 6-month improvement of the NIHSS suggested favorable results for the stem cell group. The three studies included in the meta-analysis also showed favorable results for the stem cell group. Hence, stem cell therapy can show a significant improvement in neurological deficits after 6 months compared to control groups thus indicating that significant neural tissue repair occurs in the brain, which is the main target of stem cell therapy.^[9,17,19]

In regard to the improvement of mRS analysis after 6 months, the trend also showed a favorable outcome toward the stem cell group, but this result was not statistically significant. A forest-plot analysis showed that the study by Jaillard *et al.* (2020) was the only study out of three studies that suggested more favorable results for the control group.^[17] This is in line with the results of the previous RCTs, which also applied mesenchymal stem cell (MSC) therapy by the intravenous route.^[3,13] However, the delay before MSC administration may be relevant since the BI score at 1 year was improved in the treated group, which had cell therapy administered 36 h after stroke onset in another study.^[13,17]

Analysis of the improvement in BI score after 6 months showed more favorable results in the stem cell group, although this number was also not statistically significant. The study by Jin *et al.* (2017) showed favorable results for the control group, in contrast to the two other studies showing favorable results for the stem cell group.^[9,17,19] In the study by Jin *et al.*, improvement of functional neurological outcome was seen after 24 months. Transplanted mononuclear cells used in the study improved prognosis a couple of years later. The specific mechanism of this delayed efficacy is unknown; however, it is supposed that after the bone marrow-derived mononuclear cells (BM-MNCs) have produced new neurons and glial cells, they require time to connect with other

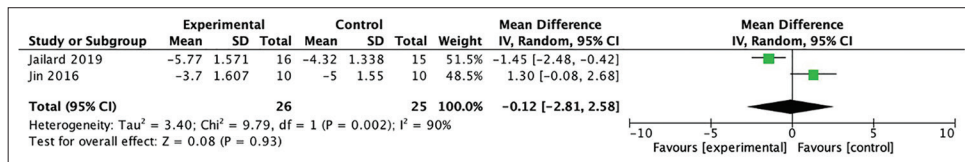


Figure 9: Calculation of the mean difference in NIHSS scores after 24 months between the stem cell therapy and control groups in two studies. The mean difference was statistically greater in the stem cell therapy group, although this result was not statistically significant (MD = -0.12; 95% CI -2.81-2.58; $P = 0.93$; and $I^2 = 90\%$).

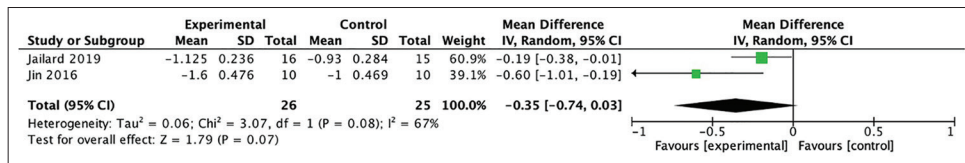


Figure 10: Calculation of the mean difference in mRS scores after 24 months between the stem cell therapy and control groups in two studies. The mean difference was statistically greater in the stem cell therapy group, although this result was not statistically significant (MD = -0.35; 95% CI -0.74-0.03; $P = 0.07$; and $I^2 = 67\%$).

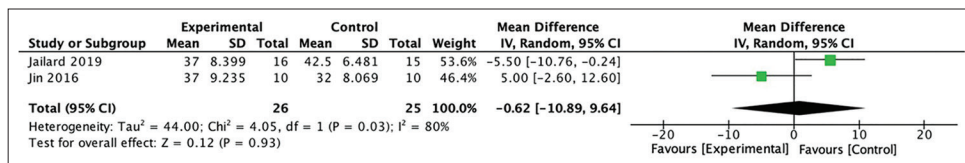


Figure 11: Calculation of the mean difference in BI scores after 24 months between the stem cell therapy and control groups in two studies. The mean difference was statistically greater in the control group, although this result was not statistically significant (MD = -0.62; 95% CI -10.89-9.64; $P = 0.93$; and $I^2 = 80\%$).

neurons, but these hypotheses need verification with further *in vitro* tests.^[19]

12-month outcome

The 12-month NIHSS outcome analysis showed favorable results for the stem cell group although these were not statistically significant. The results of this analysis need to be interpreted with caution; however, since only two studies conducted a meta-analysis for this 12-month NIHSS analysis.^[9,19] Jin *et al.* (2017) showed favorable results for the control group. The explanation for the delayed efficacy in the use of BM-MNC cells in this study was hypothesized to be that it took longer to contact (and have a therapeutic effect on) damaged neuron cells, as mentioned earlier.^[19]

Similarly, analysis of the 12-month mRS scores showed a more statistically significant favorable outcome in the stem cell group compared to the control group. Both included studies showed these results.^[9,19] The results of the study by Chen *et al.* (2014) showed that there is a significant improvement in mRS from baseline to 6 months, including up to 12 months. This supports the conclusion of this study, when taken together with NIHSS and other neurological improvement tests results, as this study provides the first clear evidence showing that intracerebral implantation of autologous stem cells could provide significant continuous improvement to the motor function of hemiplegic limbs in stroke patients.^[9]

24-month outcome

The outcome analysis of 24-month NIHSS scores showed more favorable results in the stem cell group, but it was not statistically significant. The results of this analysis also need to be interpreted with caution since only two studies conducted a meta-analysis on this 24-month NIHSS analysis.^[17,19] In the 24-month analysis, the study by Jin *et al.* still showed no improvement in NIHSS score, but significant improvement in the stem cell group occurred after 36 months, thereby supporting the hypotheses of delayed stem cell neuronal contact that the researchers previously mentioned.^[19]

A quantitative analysis of the improvement in mRS scores after 24 months revealed better results from the stem cell group compared to the control group, although this was not statistically significant. Both studies show a trend toward the stem cell group, but Jaillard *et al.* (2019) showed insignificant results. More disappointing results were found in the 24-month BI analysis, which showed a favorable trend toward the control group, although this was not statistically significant.^[17,19] The study by Jaillard *et al.* (2019) showed favorable results for the control group.

The results of these two analyses support the findings from the study by Jaillard *et al.* described previously in which

delayed MSC administration may affect the outcome. Despite this study showing evidence of the hypotheses of delayed continuous improvement in outcome of stem cell therapy, as we can see in mRS that favors stem cell group after 24 months, although it is still insignificant.^[17]

Adverse events

Among the studies chosen for this review, a total of 467 adverse events were reported; 27.18% or 103 of these adverse events were serious. These statistics should be interpreted with caution; however, since not all studies reported adverse events as part of their research.^[20,23] Despite this limitation, most studies reported that stem cell therapy was safe when administered as therapy for cases of stroke. Moreover, several reported adverse events were procedure-related, and not due to the stem cells administration itself. This observation is in accordance to the results of the majority of the previous studies, in which most stem cell therapy trials were reported to be safe, aside from their effect on improved functional outcome.^[12] Safety itself is dependent on multiple factors, including the host and the stem cells themselves. Indeed, type, source, dose, route of delivery, and time from onset of stroke to stem cell administration all contribute to the safety and outcome of stem cell therapy in stroke patients.^[40]

CONCLUSION

According to our review, stem cell therapy for stroke cases showed a better outcome than standard conservative therapy alone, although our analysis shows that many factors can influence the outcome, and significant effects can only be seen after several months. The results of this study suggest that stem cell therapy has promising efficacy and is associated with a relatively low rate of serious adverse events. However, a larger and more targeted study comparing outcomes between stem cells therapy and conventional therapy is needed to strengthen our conclusions. Such a study needs to compare routes of stem cell administration, types of stem cell, timing from the onset of stroke to intervention, and stem cell dosage, as no studies have previously compared these factors directly.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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