Safety and Efficacy of Bone Marrow Mesenchymal Stem Cells in the Treatment of Ischemic Stroke: A Meta-Analysis

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Abstract

Objective: We aimed to systematically evaluate the efficacy and safety of bone marrow mesenchymal stem cells (BMMSCs) in the treatment of ischemic stroke. **Methods:** Six Chinese and English databases were searched for related randomized controlled trials from the establishment of the databases to 28 February 2023. Two investigators performed screening and a comprehensive analysis and evaluated the quality of the studies. They extracted information from the included studies, and managed and analzsed the data using RevMan 5.4.1 software (The First College of Clinical Medical Science, China Three Gorges University). Finally, they performed meta and heterogeneity analyses and created a risk-of-bias map. **Results:** A total of 13 high-quality articles were included. The National Institute of Health Stroke Scale (NIHSS) scores of the experimental group differed significantly from those of the control group at 3 months (I^2 <50%, mean difference [MD] = −2.88, $P < 0.001$) after treatment. The Fugl–Meyer assessment (FMA) scores of the experimental group varied significantly from that of the control group at 1 month (I^2 >50%, MD = 15.94, $P < 0.001$), 3 months (I^2 >50%, MD = 12.71, $P < 0.001$), and 6 months (I^2 >50%, MD = 13.76, $P < 0.001$) after treatment, and the overall difference (I^2 >50%, MD = 14.38, $P \leq 0.001$) was significant. The functional independence measure (FIM) scores were significantly different from that of the control group at 1 month (I^2 >50%, MD = 20.04, $P = 0.02$), 3 months (I^2 >50%, MD = 15.51, $P < 0.001$), and 6 months (I^2 >50%, MD = 13.46, $P = 0.03$). There was no significant increase in adverse events compared with the traditional treatment regimen. **Conclusion:** To some extent, BMMSC transplantation can improve the neurological deficit, motor function, and daily living ability of patients with ischemic stroke.

Keywords: Bone marrow mesenchymal stem cells, efficacy, ischemic stroke, meta-analysis, safety

Introduction

Stroke is a brain injury caused by the sudden rupture of brain blood vessels or blood perfusion obstruction caused by vascular obstruction. With its high incidence, disability and recurrence rates, it is the world's second leading cause of death and the third major cause of disability, Ischemic stroke is the main type, accounting for 80%–85%.[1] After the occurrence of ischemic stroke, insufficient blood perfusion leads to cerebral edema, histiocyte hypoxia and necrosis and glutamate-induced excitotoxicity, which cause serious and irreversible damage to a patient's neurological function.[2] Traditional treatment regimens include thrombolytic therapy, percutaneous endovascular intervention therapy, rehabilitation therapy and antiplatelet therapy, but most patients have sequelae, such as disability. The repair effect of embryonic stem cells, neural stem cells, and mesenchymal stem cells (MSCs) has become a new direction for the treatment of stroke.

MSCs are a class of multi-directional differentiated stem cells with strong proliferative and regenerative capacities that can repair and maintain tissue lesions.[3,4] Since their discovery, their clinical value has been continuously explored, and current researches show that this method has good results in maintaining the hematopoietic microenvironment[5] and treating osteoarthritis,[6] polycystic ovary syndrome,[7] and other diseases. Furthermore, MSCs provide new ideas for the treatment of ischemic stroke. Animal experiments and clinical studies have found that MSCs specifically migrate into the damaged central nervous system, which can reduce mortality, promote both movement and sensation and is both safe and effective.

However, MSCs from different sources have different functions. Currently, only bone marrow MSCs (BMMSCs) have been shown to contain pluripotent stem cells in cloning transplantation. The mechanism of restoring damaged brain tissue may be the joint participation and mutual interaction of cell replacement, angiogenesis, and the secretion of neurotrophic factors in the repair of ischemic brain tissue.[8,9] There are many randomized controlled trials on BMMSCs for ischemic stroke, but differences in treatment duration and dosage can affect the results, so their efficacy and safety have

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not been clarified. Previous systematic reviews mainly focused on patient mortality and imaging information, so commonly used indicators were mortality or imaging outcomes. However, stroke patients often have limited daily functions and lower quality of life.

Therefore, the current study systematically evaluated the improvements in the quality of life of patients treated with BMMSCs after ischemic stroke for an extended period and assessed the overall efficacy and safety of the treatment to provide high-quality evidence for clinical practice.

Data and Methods

Databases

The First College of Clinical Medical Science, China Three Gorges University, Ethics Number 2023-086-01 on 2023/07/19. According to the PRISMA 2020 statement, researchers used computers to search randomized controlled trials and case-control studies on the use of MSCs in the treatment of ischemic stroke in six Chinese and English databases: China National Knowledge Infrastructure (CNKI), VIP, Wanfang, Embase, PubMed, and Cochrane Library. The Chinese search terms were 'mesenchymal stem cells', 'bone marrow mesenchymal stem cells', 'cerebral infarction', and 'stroke'. The English search terms were 'mesenchymal stem cells', 'bone marrow mesenchymal stem cells', 'cerebral infarction', and 'stroke'. The English search terms were 'mesenchymal stem cells' OR 'bone marrow mesenchymal stem cells' AND 'cerebral infarction' OR 'stroke.' The search time was from the databases' establishment to 28 February 2023. The retrieval strategy for the Pubmed database is as follows: (Mesenchymal Stem Cells [Mesh]) OR (((((Stem Cell, Mesenchymal [Title/Abstract]) OR (Mesenchymal Stem Cell [Title/Abstract])) OR (Stem Cells, Mesenchymal [Title/Abstract])) OR (Bone Marrow Mesenchymal Stem Cells [Title/Abstract])) OR (Bone Marrow Mesenchymal Stem Cell [Title/Abstract])) OR (Bone Marrow Stromal Cells [Title/Abstract])) AND (Stroke [Mesh] OR (((((((Strokes [Title/Abstract]) OR (Cerebrovascular Accident [Title/Abstract])) OR (CVA [Cerebrovascular Accident (Title/Abstract))) OR (Cerebrovascular Apoplexy [Title/Abstract])) OR (Vascular Accident, Brain [Title/Abstract])) OR (Brain Vascular Accidents [Title/Abstract])) OR (Vascular Accidents, Brain [Title/Abstract])) OR (Cerebrovascular Stroke [Title/Abstract])) OR (Strokes, Cerebrovascular [Title/Abstract])) OR (Apoplexy [Title/Abstract])). This system overview is not registered in any database.

Inclusion and exclusion criteria

According to the study objective, the inclusion criteria for this meta-analysis were as follows: (1) all patients with cerebral infarction who met the diagnostic criteria of the World Health Organization[10]; (2) interventions: patients in the trial group who were treated with BMMSCs or other treatments combined with BMMSCs, the control group, and patients undergoing other treatments; (3) randomized controlled studies; (4) a follow-up time of longer than 3 months, and according to the follow-up time, a subgroup analysis was performed; (5) the outcome indicators included more than two items; (6) complete raw data that could be directly or indirectly extracted for analysis; and (7) studies in Chinese and English. The exclusion criteria were as follows: (1) retrospective studies and cohort studies; (2) nonclinical studies and animal studies; (3) incomplete outcome indicators; (4) literature with a controversial design or high risk of bias; and (5) studies with an unreasonable experimental design.

Literature screening and data extraction

Two investigators independently screened the literature, extracted, and cross-checked the data. Any disagreement was resolved by discussion or determined by the third author. The extracted contents included the following: (1) the study author (s), publication year, and basic data of the patients; (2) intervention methods of the trial and control groups; (3) outcome indicators; (4) information about the risk assessment of bias; and (5) autologous MSC transplantation methods.

Literature quality evaluation

The risk of bias in the included studies was evaluated using the Cochrane risk-of-bias assessment tool. The evaluation included the following: (1) random sequence generation; (2) allocation concealment; (3) study and subject blinding; (4) outcome evaluation blinding; (5) incomplete outcome; (6) selective reporting; and (7) bias from other sources. A funnel diagram was used to analyze the publication bias of the included studies.

Outcome indicators

Dysfunction, as the most common sequela of patients with stroke, greatly affects the patients' quality of life, and the degree of dysfunction improvement is correlated with the recovery of brain injury. To evaluate the therapeutic effect objectively and effectively, this study chose to include several universal and mature evaluation scales as evaluation indicators. The main efficacy indicators were the National Institute of Health Stroke Scale (NIHSS), the Barthel Index (BI), the Fugl–Meyer Assessment (FMA), the FIM, and the modified Rankin Scale (mRS) scores. The lower the NIHSS and mRS scores and the higher the scores of the other indicators, the better recovery. The effect value of all indicators included in the meta-analysis was the mean difference (MD), and the analysis results were presented using a forest map.

Statistical methods

The data was managed and analyzed using RevMan 5.4.1 software. The MD and its 95% confidence interval were used as the effect size for continuous variables. If the measurement method or unit was inconsistent, the standardized MD was used as the effect size, while the odds ratio was used as the effect size for dichotomous variables. The heterogeneity of the included studies was analyzed using the I^2 test. When $I^2 = 0$, there was complete homogeneity among the studies. The included literatures were considered homogeneous when $I^2 \leq 50\%$ or $P > 0.1$, so a fixed-effects model was used.

When I^2 >50%, significant heterogeneity was indicated, and a random-effects model was used. Furthermore, α =0.05 was considered significant, except when otherwise noted.

Results

Literature screening results

A total of 3,004 Chinese and English articles were retrieved (CNKI: 1,056; VIP: 647; Wanfang: 788; Embase: 201; PubMed: 225; Cochrane Library: 87). Of those, 1,130 duplicate publications were eliminated, 345 articles were removed by initial screening, and 1,502 articles were removed after reading the abstract. Finally, 13 articles were included after reading the full text[11–23] [see Figure 1].

Basic characteristics of the included studies

All the included studies were randomized controlled trials and involved 692 study subjects, including 376 patients in trial groups and 336 patients in control groups. The outcome indicators included in the present study were NIHSS, BI, FMA, FIM, and mRS scores. The interventions in the trial and control groups are shown in Table 1. By observing the funnel chart, it was found that NIHSS, FMA, and FIM might have publication bias [Table 1].

Quality evaluation of the included studies

The results of the evaluation of study quality were as follows: none of the studies had a high risk of 'random sequence generation,' 15.4% of the studies reported 'allocation concealment,' 38.5% of the studies had a high risk of 'study and subject blinding,' 15.4% of the studies reported 'outcome evaluation blinding,' and 7.6% of the studies had a low risk of 'incomplete outcome.' No selective reporting or bias from other sources was found [see Figure 2 for details]. All articles were determined to be of high quality and met the inclusion conditions.

Meta-analysis results

Meta-analysis of the National Institute of Health Stroke Scale

A total of four articles reported NIHSS scores in patients with ischemic stroke before and after BMMSC treatment. The results showed that the NIHSS scores at 1, 6, and 12 months after BMMSC treatment were not significantly different from the scores of the control group, although the NIHSS scores at 3 months (I^2 <50%, MD = −2.88, P < 0.001) after treatment were significantly different from that of the control group, indicating that BMMSC treatment can reduce the NIHSS score [see Figure 3a for details]. The corresponding funnel diagram is shown in Figure 3b.

Meta-analysis of the Fugl–Meyer assessment

A total of three articles reported FMA scores in patients with ischemic stroke before and after treatment with BMMSCs. The FMA scores at 1 month (I^2 >50%, MD = 15.94, P < 0.001), 3 months (I^2 > 50%, MD = 12.71, P < 0.001), and 6 months (I^2 <50%, MD = 13.76, P < 0.001) after treatment were significantly different from those of the control group, suggesting that BMMSC treatment can improve the FMA score [see Figure 4a]. The corresponding funnel diagram is shown in Figure 4b.

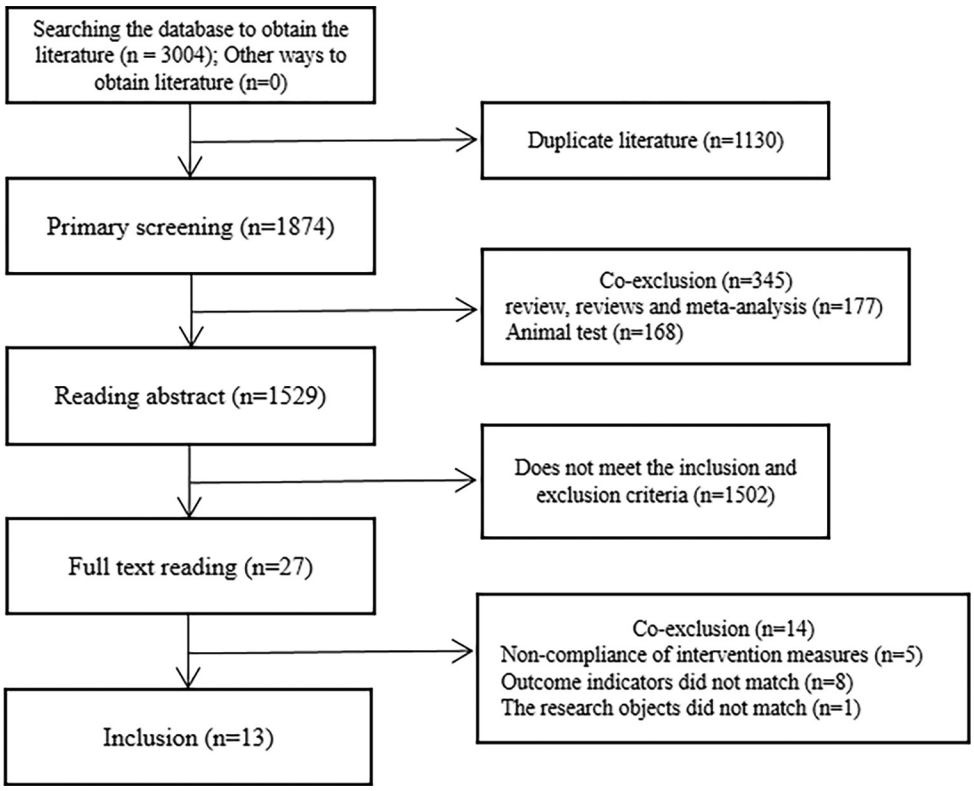

Figure 1: Literature screening process

Table 1: Basic features of the included studies

ID	Author/Year	Country	Study participants (n)		Gender (male) (n)		Age (year)	
			Experimental group	Control group	Experimental group	Control group	Experimental group	Control group
1	Xie XF *et al*. 2014[12]	China	30	30	19	18	51.4±7.2	53.7±6.1
2	Meng XG *et al*. 2009[16]	China	30	30	19	20	52.7±7.9	52.9±8.3
3	Wang X *et al*. 2014[15]	China	60	60	NA	NA	NA	NA
4	Zhao LX *et al*. 2013[14]	China	23	18	12	11	50.23±19.98	53.25±18.88
5	Chen WD *et al*. 2012[13]	China	43	43	NA	NA	NA	NA
6	He ZD *et al*. 2012[11]	China	20	18	12	11	56.4±7.9	54.3±8.7
7	Liu DH *et al*. 2014[17]	China	29	29	18	20	55.34±3.63	56.87±4.49
8	Jaillard *et al*. 2020[21]	France	16	15	11	11	53 (45-63)	55 (46-58)
9	LEE *et al*. 2010[20]	Korea	16	36	8	26	64.0±11.6	64.9±14.5
10	Chung *et al*. 2021[19]	Korea	39	15	17	10	63.03±14.36	64.27±13.25
11	Savitz *et al*. 2019[18]	USA	29	19	20	15	62.9±10.81	59.3±10.03
12	LEE *et al*. 2021[22]	Korea	31	13	15	9	63.4±14.0	61.5±13.0
13	Jin *et al*. 2017[23]	China	10	10	9	6	50.8±17.43	53.1±13.07

ID	Intervention measure		Outcome index	MSC treatment mode
	Experimental group	Control group		
1	Control group measures + BMSC	Aspirin, fluvastatin sodium and other drugs treatment + rehabilitation training	NIHSS, Bl	Subarachnoid injection; Once a week, 2 times in total.
2	Control group measures + BMSC	Aspirin, simvastatin sodium and other drugs + rehabilitation training	FIM, FMA	Static note; 1 time
3	Control group measures + BMSC	Biaspirin + Atorvastatin + Probucol Tablets	FIM	Intravenous injection; 1 time
4	Control group measures + BMSC	Nutritional nerve drugs + rehabilitation training, etc	NIHSS	Subarachnoid injection; 1 time
5	Control group measures + BMSC	Statins and antiplatelet drugs + rehabilitation training	FIM, FMA	Subarachnoid injection + intravenous drip; 1 time
6	Control group measures + BMSC	Neuroprotective drugs, aspirin, simvastatin sodium and other drugs + rehabilitation training	NIHSS, Bl	Static drop; 1 time
7	Control group measures + BMSC	Brain protectant, improving blood circulation, statins and antiplatelet drugs + rehabilitation training	NIHSS, FMA	Intrathecal injection/intravenous injection; Once/5-10 days, 4 times in a row.
8	Control group measures + BMSC	Rehabilitation training	BI, NIHSS, mRS	Intravenous injection; 1 time
9	BMSC	N/A	mRS	Intravenous injection; 2 times, 2 weeks apart.
10	Control group measures + BMSC	Angioplasty/stenting, thrombolytic therapy, etc	mRS	Intravenous injection; 1 time
11	Conventional therapy + BMSC	Conventional treatment + placebo	NIHSS, BI, mRS	ICA injection; 1 time
12	Control group measures + BMSC	Rehabilitation	FAM	/
13	Control group measures + BMSC	Routine medical treatment	BI, NIHSS, mRS, FAM, FIM	Subarachnoid injection

BMSC: Bone marrow mesenchymal stem cells, MSC: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: Modified Rankin Scale, ICA: Internal Carotid Artery

Meta-analysis of the Barthel Index

A total of four articles reported BI scores in patients with ischemic stroke before and after treatment with BMMSCs. There were no significant differences in BI scores between the two groups at 3 months (I^2 >50%, MD = 8.56, P = 0.10) and at 6 months (I^2 >50%, MD = 11.11, P = 0.08); however, the scores at 12 months or more (I^2 >50%, MD = 7.33, P = 0.53) were significantly different after treatment [see Figure 5a]. The corresponding funnel diagram is shown in Figure 5b.

Meta-analysis of the modified Rankin Scale score

A total of four articles reported mRS scores in patients with ischemic stroke before and after treatment with BMMSCs. There were no significant differences in mRS scores between the two groups at 3 months (I^2 <50%, MD = 0.11, P = 0.21) and at 6 months (I^2 >50%, MD = 0.01, P = 0.97), However, at 12 months or more (I^2 >50%, MD = −0.37, P = 0.16), the scores were significantly different after treatment [see Figure 6a]. The corresponding funnel diagram is shown in Figure 6b.

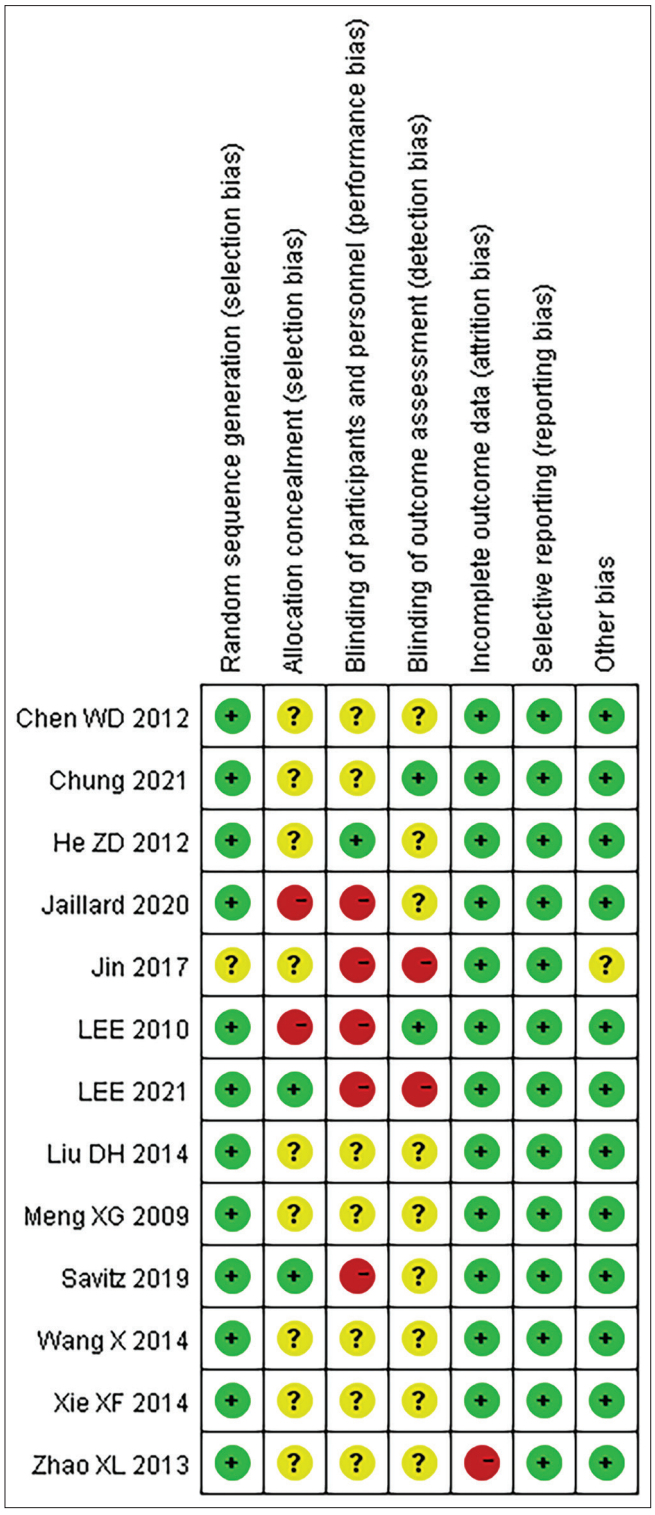

Figure 2: Assessment of risk of bias

Meta-analysis of the functional independence measure

A total of three articles reported FIM scores in patients with ischemic stroke before and after treatment with BMMSCs. The FIM scores at 1 month (I^2 >50%, MD = 20.04, P = 0.02), 3 months (I^2 >50%, MD = 15.51, P < 0.001), and 6 months (I^2 >50%, MD = 13.46, P = 0.03) after treatment varied significantly from those of the control group [see Figure 7a]. The corresponding funnel diagram is shown in Figure 7b.

Adverse events of the treatment

Only a small number of studies reported minimal adverse events, with no significant increase compared with the control group. They could not be combined for the systematic analysis, and most adverse events were well-tolerated fever and mild headache, which could be relieved spontaneously and be safer.

Publication bias

A publication bias test was performed by plotting the funnel chart of each outcome index. The results showed that the research points of the NIHSS, FMA, BI, and mRS scores were symmetrically distributed, although there might have been publication bias due to the asymmetry of the FIM distribution.

Discussion

In addition to causing ischemic necrosis of local brain tissue, ischemic stroke also leads to nonspecific inflammation of local tissue, which aggravates brain tissue necrosis at the ischemic site. Currently, thrombolysis and endovascular procedures are commonly used in clinical practice, but an ideal treatment for neurological impairment is lacking. Some studies have shown that BMMSCs can promote the recovery of neural function and reduce the volume of cerebral infarction, and BMMSC transplantation is safe and effective in the repair and reconstruction of brain tissue.[24,25] This meta-analysis showed that BMMSCs promoted the recovery of nerve injury, motor capacity, and activity function in patients with ischemic stroke compared with traditional treatment methods. This finding is similar to the results of another systematic review of an animal model and the lesion site of ischemic stroke treated with BMMSCs.[26] The clinical results of the model of improved cerebral ischemia and spinal cord injury after transplantation showed that fewer apoptotic cells were detected with IV BMMSC transplantation, which means BMMSCs may have an inhibitory apoptosis effect.[27]

Angiogenesis is positively correlated with the survival and recovery of patients with stroke.[28] Bone marrow MSCs can secrete vascular endothelial and placental growth factors to promote angiogenesis in the cerebral ischemic area, form a microenvironment supporting neurogenesis, and participate in the remodeling of the injured region.[27] After co-cultivating BMMSCs with cortical neurons under a simulated anoxic condition, BMMSCs can secrete various neurotrophic factors, which can synergistically promote neurogenesis in the stroke injury area and maintain activity in the brain's white matter.[29]

In addition to the above mechanisms of action, BMMSCs also treat ischemic stroke by promoting the transformation of neural lineage cells, inducing neural cell formation and regulating cerebral blood flow, blood–brain barrier permeability, and the endogenous repair process.[30] Through these mechanisms, BMMSCs repair nerve cells, regulate vascular ecology, and

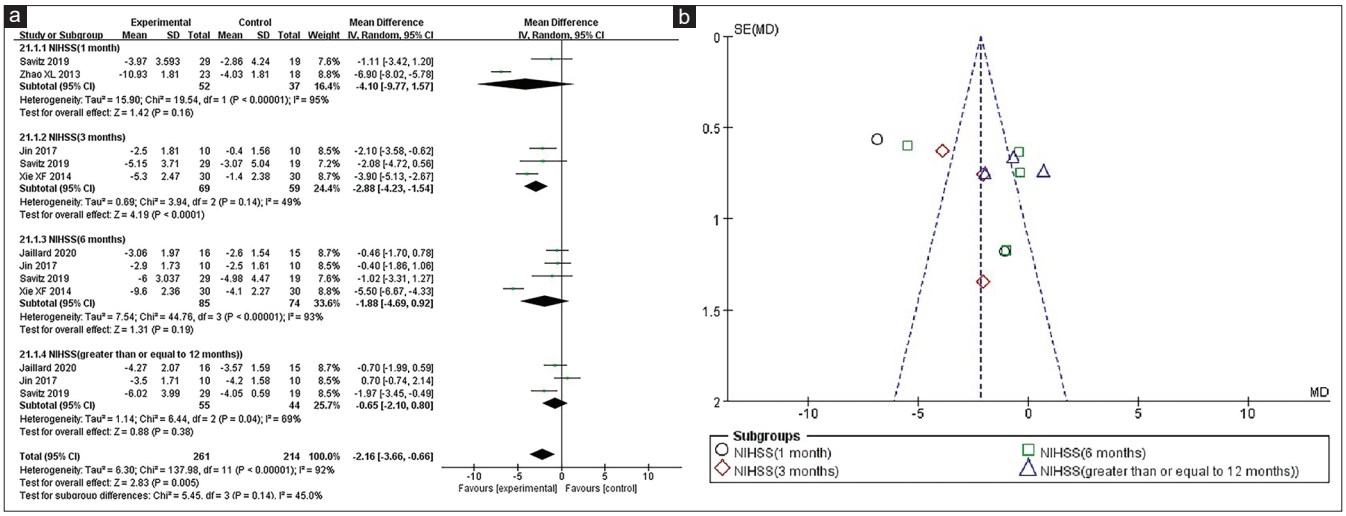

Figure 3: NIHSS scores at 1, 3, 6 and 12 months after treatment (a: Forest plot; b: Funnel plot). BMSC: Bone marrow mesenchymal stem cells, MSCs: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: modified Rankin Scale

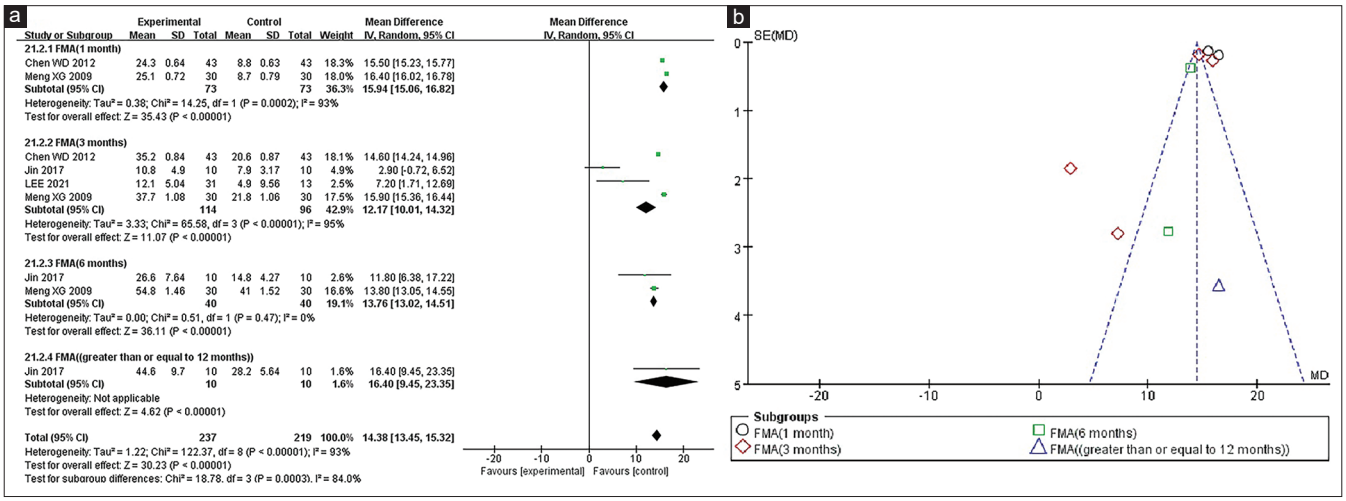

Figure 4: Scores of FMA 1 and 3 months after treatment (a: Forest plot; b: Funnel plot). BMSC: Bone marrow mesenchymal stem cells, MSCs: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: modified Rankin Scale

help to improve the exercise and living abilities of patients with ischemic stroke.

Compared with other MSCs, BMMSCs have the advantages of powerful homing to damaged tissue, low immunogenicity, and strong paracrine functions.[31] Combined with its pluripotent stem cell function, transplantation is more likely to be promoted on a large scale in clinical practice, although the timing of transplantation, its route, combined treatment measures, and different species as sources of BMMSCs will affect its clinical application effect. Furthermore, BMMSCs treatment has a longer time window than thrombolysis.[32] In Zhang *et al*.'s study, optical imaging and immunohistochemistry revealed better implantation of BMMSCs in infarcted border zones when high doses of BMMSCs were transplanted 1 or 4 weeks after ischemia.[33] This indicates that the neuroprotective effect of transplanted BMMSCs in the hyperacute phase is not obvious, and it may take time before the body produces higher concentrations of chemokines, thus promoting the homing of BMMSCs to the injured tissues. Moreover, the functional recovery of patients after high-dose BMMSC transplantation at 4 weeks was better than that of patients with low-dose BMMSCs transplantation.

It is not appropriate to transplant BMMSCs in the hyperacute period of ischemic stroke, while the transplantation in the recovery period may require an increase in the number of transplanted cells to be effective. At present, the most common implantation methods are IV injection, carotid artery injection, and intrathecal injection. Direct injection into the brain can cause intracranial infection, local reactions and other adverse effects, with limited clinical application. By comparing the arterial, venous, and intracerebral routes for BMMSCs transplantation, the results showed that patients who underwent intra-arterial

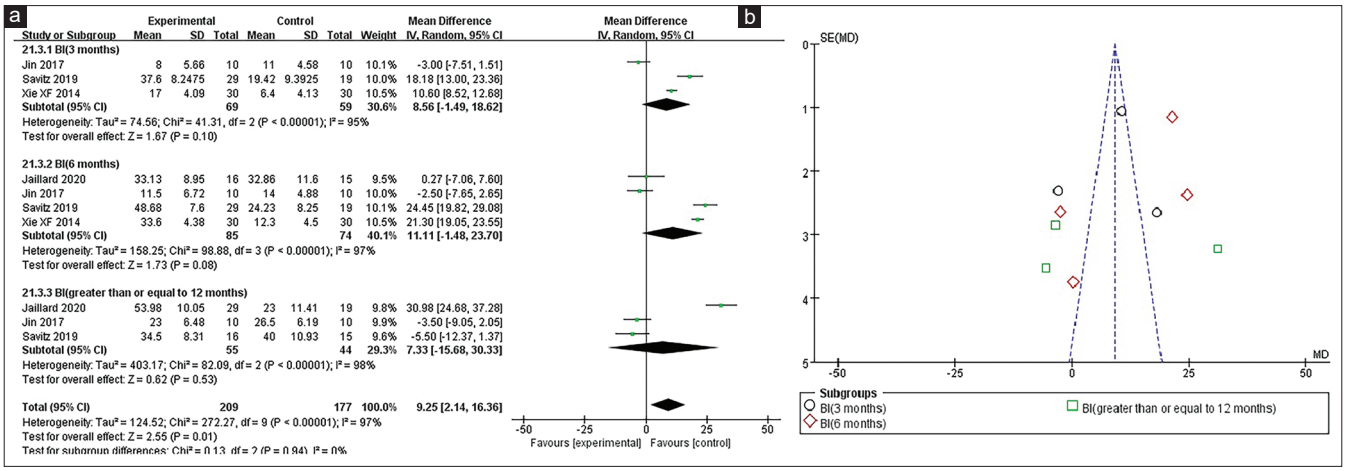

Figure 5: BI scores at 3, 6 and 12 months after treatment (a: Forest plot; b: Funnel plot). BMSC: Bone marrow mesenchymal stem cells, MSCs: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: modified Rankin Scale

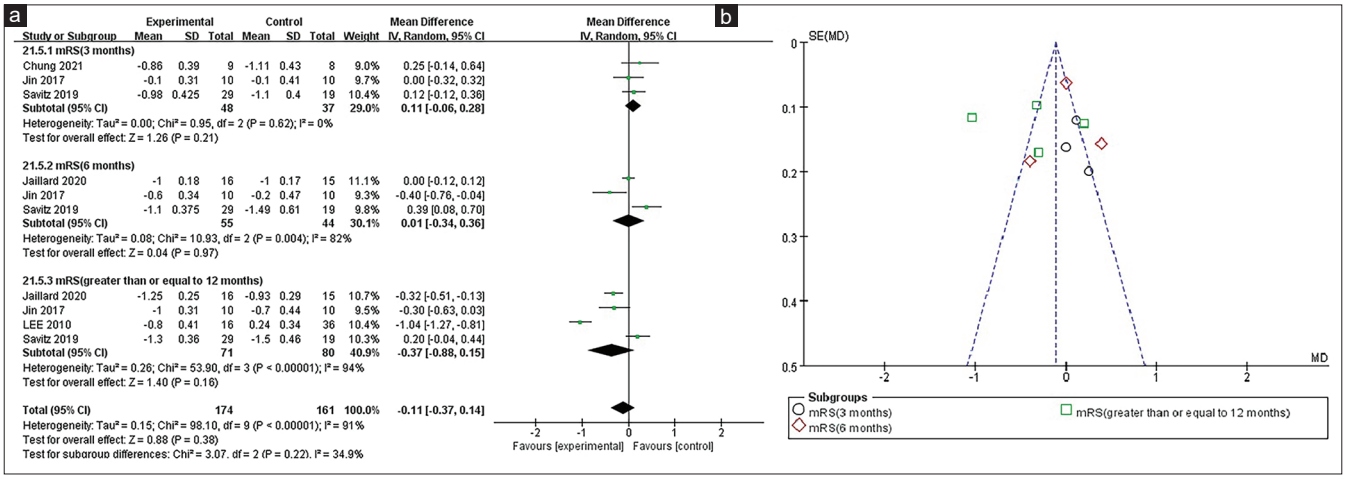

Figure 6: mRS Scores at 3, 6 and 12 months after treatment (a: Forest plot; b: Funnel plot). BMSC: Bone marrow mesenchymal stem cells, MSCs: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: modified Rankin Scale

transplantation had the best and fastest neurological recovery. However, the final choice of transplantation route should be determined according to the actual situation.

The results of many indicators in this article revealed heterogeneity among the studies. This might be because the severity of a subject's first stroke may be inconsistent due to variations in the levels of the hospitals in the study, and those with higher severity may be transferred to higher-level hospitals. There are also differences in the ability of different hospitals to treat ischemic stroke, and patients with better economic conditions will choose hospitals at higher levels. The degree of change of the final outcome indicators is heterogeneous. It is expected that following an increase in related research, the research results at different hospital levels will be analyzed in sections.

This article analyzed the efficacy and safety of BMMSCs in the treatment of ischemic stroke through comprehensive searches, improved the levels of evidence, and fully demonstrated the treatment of nerve, movement, and independent function at different time points by time grouping.

However, this study has several limitations. Due to the small sample size and limited reports of some studies, the data could not be further grouped according to different transplantation methods and transplantation time. Similarly, the mortality rate cannot be calculated together. Most studies did not have a placebo and were not blinded, and some indicators were heterogeneous. Furthermore, given the publication bias of the FIM, in the future, researchers should expand the search terms and include additional databases. Some indicators may have publication bias. Because of the small number of studies, publication bias cannot be further reduced except for subgroup analysis.

Conclusion

In summary, BMMSCs transplantation can improve the neurological deficit, motor function, and daily living ability

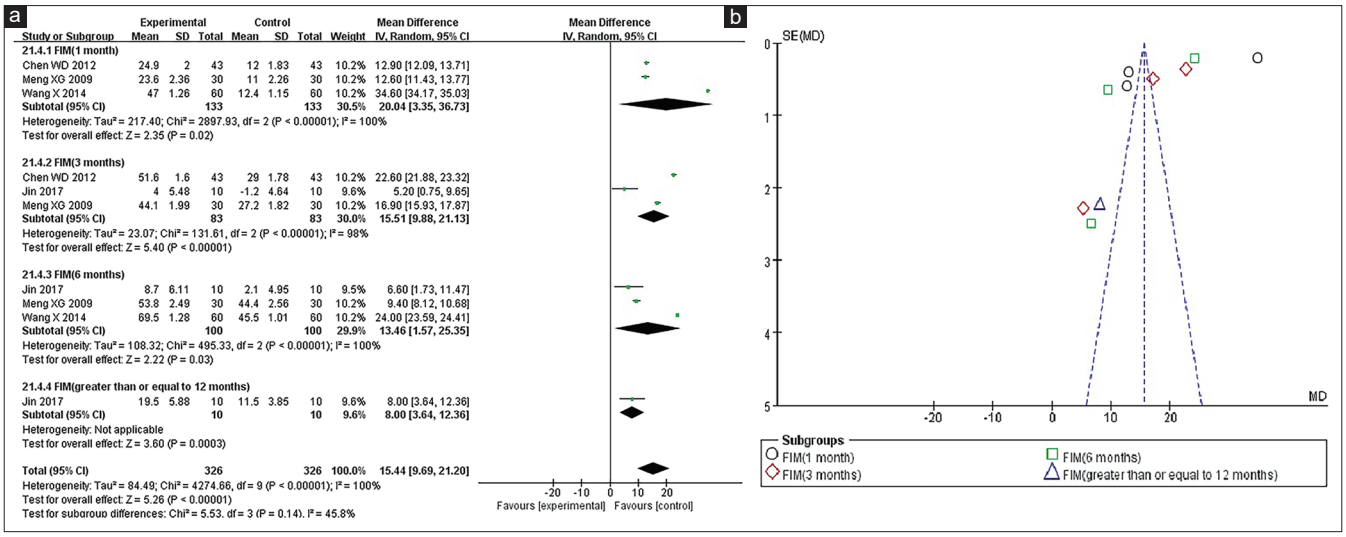

Figure 7: FIM scores at 1, 3, and 6 months after treatment (a: Forest plot; b: Funnel plot). BMSC: Bone marrow mesenchymal stem cells, MSCs: Mesenchymal Stem Cells, CNKI: China National Knowledge Infrastructure, NIHSS: National Institutes of Health Stroke Scale, BI: Barthel Index, FMA: Fugl–Meyer Assessment, FIM: Function Independent Measure, mRS: modified Rankin Scale

of patients with ischemic stroke. There was no significant difference in adverse events compared with conventional treatment, and BMMSCs transplantation showed good efficacy and safety.

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Conflicts of interest

There are no conflicts of interest.

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