Efficacy and safety of mesenchymal stem cells for cerebral infarction: A meta-analysis

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Abstract. Cerebral infarction is one of the leading causes of death in adults, impairing patients' quality of life and imposing a heavy burden on families. With current therapeutic approaches, functional recovery after cerebral infarction remains suboptimal. Mesenchymal stem cells (MSCs), due to their broad availability, low immunogenicity, and multipotent differentiation potential, have promise in the treatment of ischemic cerebral infarction. The present study aimed to evaluate the efficacy and safety of mesenchymal stem cells in the treatment of cerebral infarction. VIP Information, China National Knowledge Infrastructure, Wanfang Data, PubMed, Cochrane Library and Web of Science were systematically searched up to October 2024 using the search terms 'mesenchymal stem cells', 'cerebral infarction', and 'randomized controlled trials', which yielded 19 randomized controlled trials for meta-analysis. The efficacy of mesenchymal stem cells in the treatment of cerebral infarction was better than that of conventional treatment, and mesenchymal stem cell therapy decreased the neurological deficit score (National Institutes of Health Stroke Scale) and improved the motor function score (Fugl-Meyer Assessment) and functional independence score (Functional Independence Measure, FIM). Mesenchymal stem cells have a high safety profile in the treatment of patients with cerebral infarction. Most of the adverse effects reported were fever and headache, which resolved spontaneously or following treatment. Umbilical cord mesenchymal stem cells were more effective than bone marrow mesenchymal stem cells. There was no significant difference between transplantation methods. This may be due to the small number of included studies.

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Key words: mesenchymal stem cell, cerebral infarction, randomized controlled trial, systematic review, meta-analysis

Introduction

Cerebral infarction is one of the main causes of death among adults in China. Between 2004 and 2005, the crude mortality rate of cardiovascular and cerebrovascular diseases was 136.6/100,000 people, and the standardized mortality rate was 120.1/100,000 people. Among these, intracerebral hemorrhage accounted for 50.4% of the deaths from cardiovascular and cerebrovascular disease, followed by cerebral infarction, which accounted for 24.8% (1). Cerebral infarction not only reduces quality of life but also imposes a heavy economic burden on the patient and their family (2). The current treatment methods for cerebral infarction primarily include interventional therapy, surgery and drug treatment. A survey of 408 elderly patients with hemiplegia due to acute ischemic stroke revealed that their standardized scores on the Stroke-Specific Quality of Life Scale 1 month after discharge were (56.30±5.21)%, only reaching a moderate level; the actual scores were even lower at (136.35±5.38), indicating suboptimal functional recovery following cerebral infarction injury (2).

Mesenchymal stem cells (MSCs) are adult SCs with self-renewal and multi-directional differentiation potential, and come from a range of sources, including bone marrow, fat, umbilical cord and other tissue. MSCs exhibit low immunogenicity and easy *in vitro* culture expansion, and have demonstrated potential therapeutic value in the treatment of various diseases including cerebral infarction, Parkinson's disease, arthritis, spinal cord and sciatic nerve injury (3). SC therapy plays multiple roles in ischemic cerebral infarction, including neuroprotection through reducing apoptosis and inflammation, promoting angiogenesis and endogenous neurogenesis, modulating immune responses, and potentially differentiating into neural cells to replace damaged tissue. Clinical studies on mesenchymal SC (MSC) transplantation for ischemic cerebral infarction have been conducted, confirming its safety and feasibility in both the acute and chronic phases; preliminary evidence indicates that motor function recovery can be improved through various administration routes, such

as intravenous, intra-arterial, and intracerebral methods (4,5). MSC therapy may be an effective method to improve the prognosis of patients with cerebral infarction. It is helpful for clinicians to understand the effectiveness and safety of MSCs in the treatment of cerebral infarction to provide a basis for the feasibility of future clinical application. The present study focused on the efficacy and safety of MSCs in the treatment of cerebral infarction, aiming to provide a novel approach for the treatment of cerebral infarction in addition to traditional thrombolysis, drug and rehabilitation treatment. The present study also aimed to provide a reference for exploring optimized therapeutic protocols of MSCs for cerebral infarction.

Materials and methods

Search strategy. VIP Information (qikan.cqvip.com), China National Knowledge Infrastructure (cnki.net), Wanfang Data (wanfangdata.com.cn/index.html), PubMed (pubmed.ncbi.nlm.nih.gov), Cochrane Library (cochranelibrary.com) and Web of Science (https://webofscience.clarivate.cn/) were searched from the establishment of the database to October 2024 for studies on the treatment of cerebral infarction with MSCs. The Chinese literature search terms were as follows: 'Mesenchymal stem cells', 'stem cells', 'mesenchymal cells', 'cerebral infarction', 'ischemic stroke', 'stroke', 'stroke', 'randomized controlled trial', 'RCT', 'randomized'. English literature search terms included 'mesenchymal stem cell', 'stem cell', 'cerebral infarction', 'stroke' and 'randomized controlled trial'.

Inclusion criteria. Inclusion criteria were as follows: i) Randomized controlled trials, with or without blinding; ii) patients meeting the diagnostic criteria for cerebral infarction; iii) use of MSC treatment, or MSCs combined with other treatments (such as drug or rehabilitation therapy); iv) use of other treatment as a control group (such as conventional drug therapy, rehabilitation, placebo); v) studies reporting National Institutes of Health Stroke Scale score (NIHSS) (6), Fugl-Meyer Assessment (FMA) (7), Functional Independence Measure (FIM) (8), Barthel Index(BI) (9), modified Rankin scale score (mRS) (10), adverse events or adverse reactions following treatment (such as infection, immune response, tumor formation); vi) studies with complete original data that can be directly or indirectly extracted for analysis (mean, standard deviation, sample size) and vii) studies written in Chinese and English. There were no restrictions on age, sex or ethnicity of patients.

Exclusion criteria. Exclusion criteria were as follows: i) Retrospective studies, case reports, reviews, meta-analyses, conference abstracts and other non-randomized controlled trials; ii) animal studies, *in vitro* experiments or non-clinical studies; iii) lack of control group or non-randomized grouping; iv) high risk of bias (unclear randomization methods, inadequate allocation concealment); v) incomplete data regarding outcome indicators and inability to extract data for primary or secondary outcomes and vi) unavailable full text.

Literature screening. Studies were checked for plagiarism, then the titles and abstracts of the literature were read for preliminary screening according to the aforementioned criteria. Duplicate articles were removed. For articles with duplicate data, the study containing the most complete data was retained.

Data extraction. Excel (Version 12.1.0.24034, wps.cn) was used to extract data as follows: Cell type, transplantation method, intervention, sample size, age, sex, follow-up time, outcome indicators and adverse reactions. For missing data, it was attempted to contact the authors of the original study for complete information. Studies for which missing data could not be obtained were excluded.

Quality assessment. The risk assessment was performed using the bias assessment tools recommended by the Cochrane Collaboration (11). The assessment contents included randomization methods, allocation concealment, blinding, blinded assessment of study outcomes, integrity of outcome data, selective reporting of study results and other sources. Risk of bias was reported as high, low or unclear.

Statistical analysis. Meta-analysis was performed using RevMan 5.4.1 (https://www.cochrane.org) and Stata16.0 (https://www.stata.com) software. Among the continuous variables, the mean difference (MD) was used as the effect size for those with the same measurement method and unit, and the odds ratio (OR) was used as the effect size for dichotomous variables, both of which were expressed as 95%CI. Heterogeneity was analysed using the Pearson χ^2 and I^2 tests, with $P>0.1$ indicating no heterogeneity and $P<0.1$ indicating heterogeneity. $I^2=0$ means studies are completely homogeneous, and $I^2>50\%$ means that there is significant heterogeneity; If there was no significant heterogeneity between studies, a fixed-effect model was used for analysis, and a random-effects model was used after excluding significant sources of heterogeneity. $P\leq0.05$ was considered to indicate a statistically significant difference. Sources of heterogeneity were investigated using sensitivity and subgroup analyses. Subgroup analyses were performed for cell type, transplantation method and length of follow-up for the primary outcome measures.

Publication bias analysis. RevMan 5.4.1 software was used to draw the funnel plot and assess the presence of publication bias by observing the symmetry of the funnel plot. If the funnel plot presents a symmetrical inverted funnel shape, it suggests a low risk of publication bias; if the funnel plot shows an obvious asymmetry, it indicates the existence of potential publication bias. Stata 16.0 software was used to conduct Egger's test. $P<0.05$ was considered to indicate statistically significant publication bias.

Results

Included studies. A total of 5,374 articles were retrieved initially. After duplicate checking, 3,493 articles were included. After reading the titles and abstracts of the articles, 66 articles were included for full-text assessment. A total of 18 articles that did not meet the requirements were excluded, and 48 articles were included for full-text reading. After excluding 29 articles during full-text reading, 19 articles (12-30) were included (Fig. 1). Of these, 13 were in Chinese (14,15,19-21,23-30) and

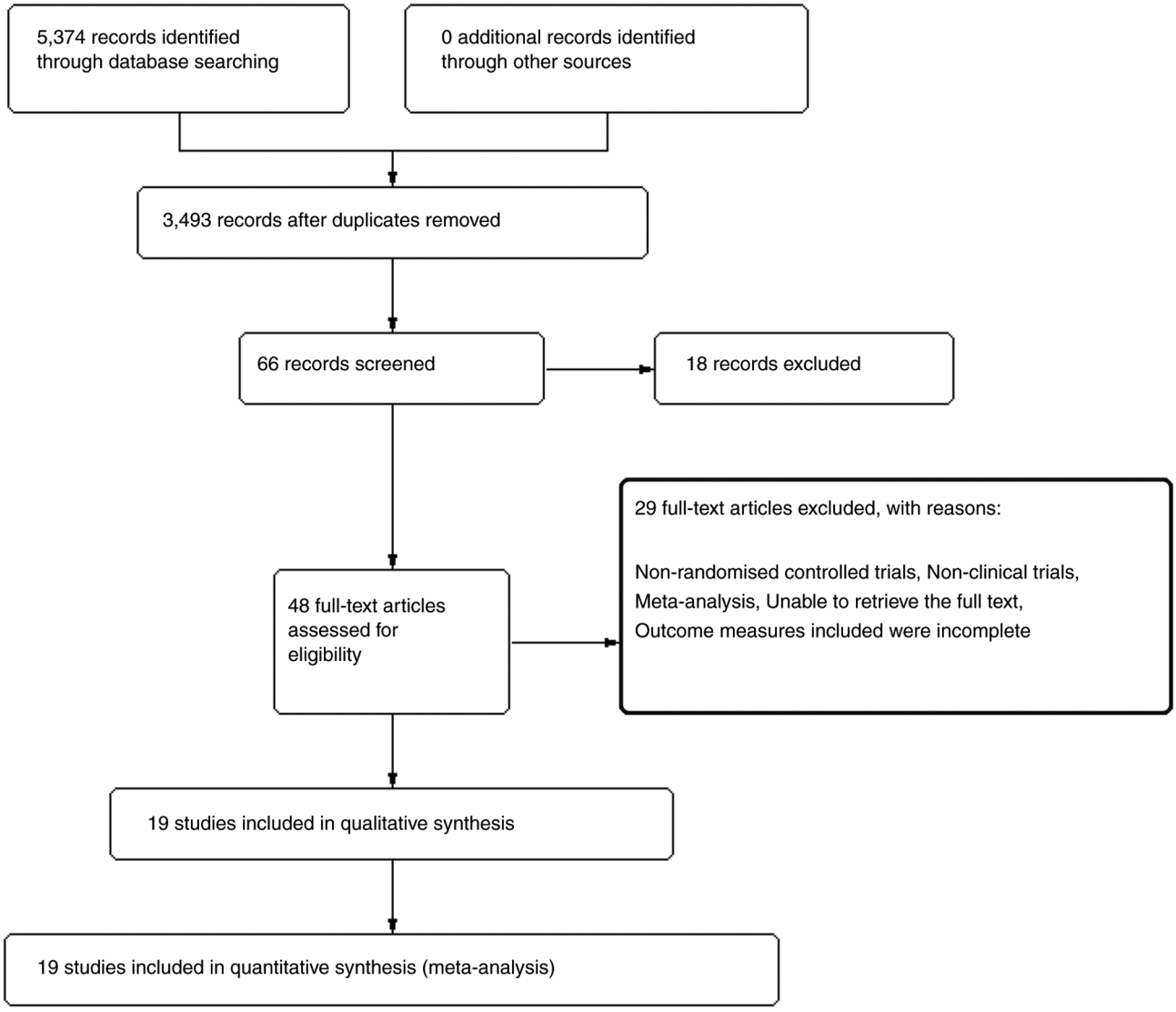

Figure 1. Literature screening process.

six were in English (12,13,16-18,22). All studies described the baseline comparability between the experimental group and the control group. The intervention measures were primarily MSCs + conventional treatment vs. conventional treatment. The total sample size was 1,366 cases, with 697 cases in the experimental group and 669 cases in the control group (Table I).

Outcome measures of the included studies. Among outcome indicators, the data successfully extracted for the BI (18) and mRS (13) indicators were insufficient, each corresponding to only one study, therefore these were not analyzed. The outcome indicators included in the analysis of this study are NIHSS, FMA, and FIM. All included studies used NIHSS to assess the degree of neurological deficit. The NIHSS score ranges from 0 to 42, with higher scores indicating more severe neurological deficit. All included studies used FMA to assess motor function recovery. The total FMA score ranges from 0 to 100, with higher scores indicating better motor function. FIM was used in all studies to assess functional independence. The FIM score ranges from 18 to 126 points, with higher scores indicating better functional independence. Assessment time points include baseline and post-treatment. NIHSS, FMA and FIM score data were extracted by two independent investigators.

Risk of bias of included studies. The included studies were randomized controlled trials, and the risk of bias of the included studies was primarily due to blinding after randomization (Fig. 2).

Meta-analysis of NIHSS score. A total of 11 articles (13,14,16-18,20,22,24,27,28) reported the NIHSS scores of neurological deficit in patients before and after treatment. The qualitative test (I^2=91%, P<00001) showed heterogeneity, so a random effects model was used for meta-analysis. The combined effect size [Weighted Mean Difference WMD=-1.42 (95%CI: -2.83 to -0.01, Z=1.98, P=0.05)] demonstrated the NIHSS score of the MSC treatment group was significantly lower than that of the control group, indicating that MSC therapy decreased the degree of neurological deficit of patients and had a positive effect on improving the neurological function of patients (Fig. 3).

Table I. Study characteristics.

First author, year	Cell type	Transplantation method	Interval	Tx time, days	Intervention		Age, years		Follow-up time, months	Outcome measures	Adverse effects	(Refs.)
					E	C	E	C				
Wang *et al*, 2014	BMSC	Not reported	30-60 days	Not reported	BMSC + con	Con	56.3	56.3 (median)	1 and 6	FIM	No adverse effects	(21)
Tian *et al*, 2018	UBMSC	22 LP; 23 IV	14-30 days	30	UBMSC + con	Con	62.2± 2.1	60.6±1.7 (mean)	1, 2 and 3	NIHSS; FMA	Not reported	(14)
Zhou *et al*, 2018	UBMSC	LP	1 year	21	UBMSC + con	Con	56.3± 5.3 (mean)	56.3±5.2 (mean)	12	BI; FIM	Fever, rash	(15)
Xiao *et al*, 2015	UBMSC	LP	1-13 years	Not reported	UBMSC + con	Con	51.9± 5.2 (mean)	52.3±5.0 (mean)	6	FIM	Not reported	(19)
Xie *et al*, 2014	BMSC	LP	7 days	14	BMSC + con	Con	51.4±7.2 (mean)	53.7±6.1 (mean)	3 and 6	NIHSS; BI	Fever; headache	(20)
Hu *et al*, 2013	UCMSC	LP + IV	1-72 months	NA	UBMSC + con	Con	60.8±15.2 (mean)	59.2±13.8 (mean)	0.25, 1, 3	FMA; FIM	Fever; dizziness and headache; backache	(26)
Liu *et al*, 2014	BMSC	LP	1-21 days	20~40	BMSC + con	Con	55.3±3.6 (mean)	56.8±4.3 (mean)	1 and 3 FMA	NIHSS;	No adverse effects	(23)
Feng *et al*, 2014	UBMSC	20 LP; 30 IV	14-30 days	30	UBMSC + con	Con	61.4±11.3 (mean)	60.2±11.8 (mean)	1, 2, 3 s	NIHSS; FMA	Fever	(24)
Wang *et al*, 2013	UBMSC	IV	Not reported	7~10	UBMSC + con	Con	62.6±7.1 (mean)	62.2±6.3 (mean)	0.5	FMA	No adverse effects	(25)
Chen *et al*, 2012	BMSC	LP	1-12 months	14	BMSC + con	Con	49.3±20.8 (mean)	57.3±9.5 (mean)	6	NIHSS	Fever; headache	(28)
Chen WD *et al*, 2012	BMSC	LP + IV	Not reported	Not reported	BMSC + con	Con	45.9±10.9 (mean)	45.9±10.9 (mean)	1, 3, 5	FMA; FIM	No adverse effects	(29)
Meng *et al*, 2009	BMSC	IV	42 days	Not reported	BMSC + con	Con	52.7±7.9 (mean)	52.9±8.3 (mean)	1 month, 3 and 6	FMA; FIM	Fever; headache	(30)

Table I. Continued.

First author, year	Cell type	Transplantation method	Interval	Tx time, days	Intervention		Age, years		Follow-up time, months	Outcome measures	Adverse effects	(Refs.)
					E	C	E	C				
He *et al*, 2012	BMSC	IV	Not reported	Not reported	BMSC + con	Con	56.4±7.9	54.3±8.7 (mean)	3	NIHSS; BI	Not reported	(27)
Fang *et al*, 2019	BMSC	IV	7 days	Not reported	BMSC	Pbo	49.4±10.8 (mean)	52.8±14.9 (mean)	3, 6, 12 48	NIHSS; BI; mRS	No adverse effects	(13)
Chung *et al*, 2021	BMSC	IV	5-89 days	NA	BMSC + con	Con	63.0±14.3 (mean)	64.2±13.2	3 months	mRS	No adverse effects	(12)
Hess *et al*, 2017	BMSC	IV	1-2 days	1h	BMSC	Pbo	61.8 (median)	62.6 (medin)	12	NIHSS; BI; mRS	Halitosis; fever, and nausea vomiting	(18)
Prasad *et al*, 2014	BMSC	IV	7-30 days	NA	BMSC + con	Con	50.7±11.6 (mean)	52.5±12.1 (mean)	12	NIHSS; BI; mRS	Epilepsy	(22)
Jin *et al*, 2017	BMSC	LP	Not reported	NA	BMSC + con	Con	50.8±17.4 (mean)	53.1±13.0 (mean)	84	NIHSS; BI; FMA; FIM; mRS	Fever	(17)
Bhatla *et al*, 2018	BMSC	IA	0-14 days	10 min	BMSC + con	Con	57.0±12.2 (mean)	66.0±7.3 (mean)	6	NIHSS; mRS	No adverse effects	(16)

BMSC, bone marrow mesenchymal stem cell; UBMSC, umbilical cord blood mesenchymal stem cell; UCMSC, umbilical cord mesenchymal stem cell; AMSC, adipose mesenchymal stem cell; con, conventional treatment; LP, lumbar puncture; IV, intravenous injection; IA, arterial injection; Interval, Interval between the onset of cerebral infarction and participant enrollment; plb, placebo; NIHSS, National Institutes of Health Stroke Scale; BI, Barthel Index; FMA, Fugl-Meyer Assessment; FIM, Functional Independence Measure; mRS, modified Rankin scale.

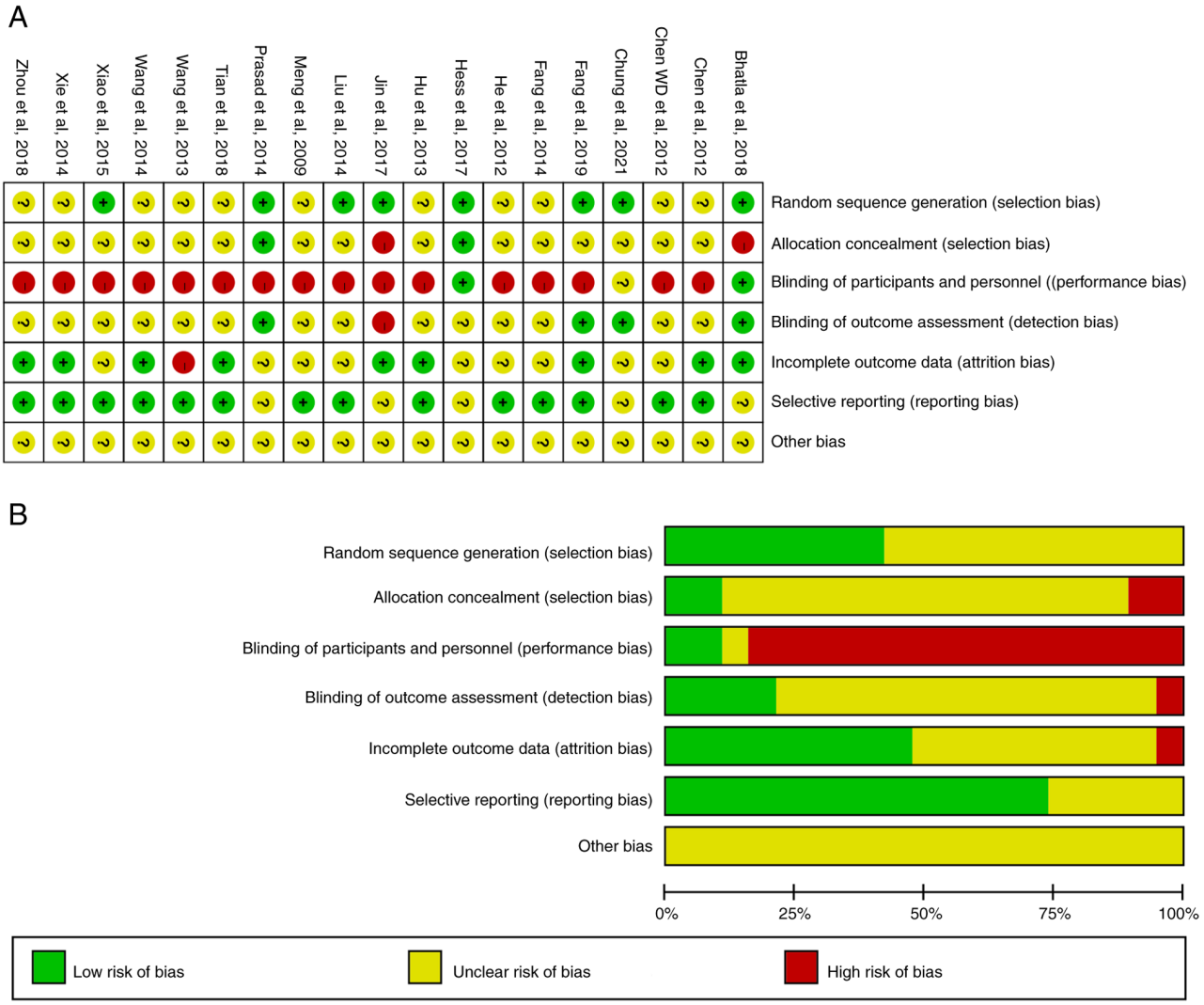

Figure 2. Bias risk diagram of 19 randomized controlled trials. (A) Risk of bias graph and (B) Risk of bias summary.

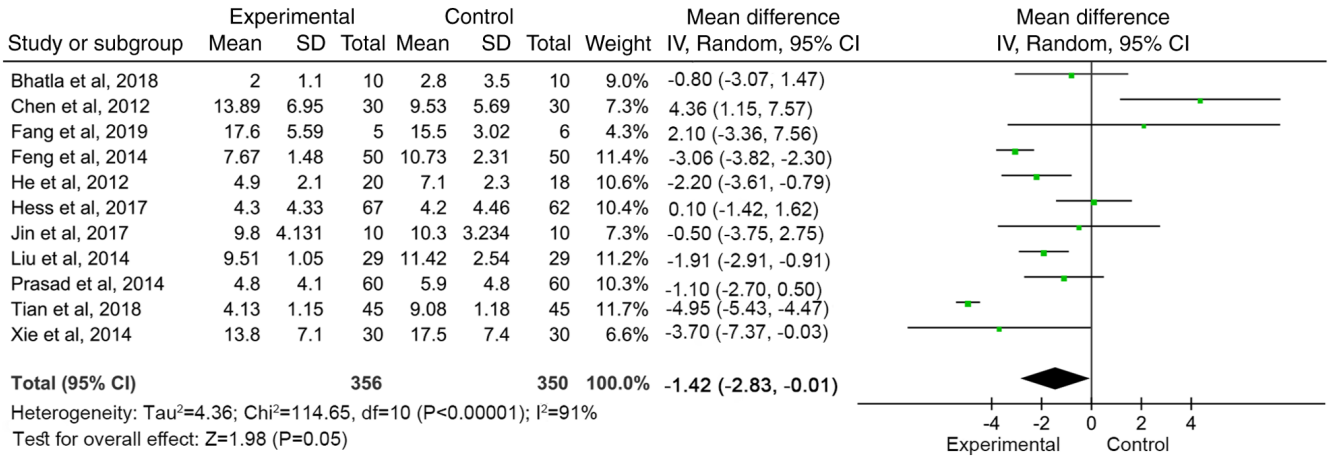

Figure 3. Forest plot of National Institutes of Health Stroke Scale score. df, degrees of freedom.

Meta-analysis of motor function score (FMA). A total of seven articles (12,14,24,26,29,30) reported the motor function scores before and after treatment. The results were heterogeneous (I^2=77%, P=0.0002), so a random effects model was used for meta-analysis. The combined effect size [WMD=11.14 (95%CI: 7.73-14.55, Z=6.40; P<0.00001)] indicated that compared with conventional treatment, MSC treatment significantly improved motor function scores (Fig. 4).

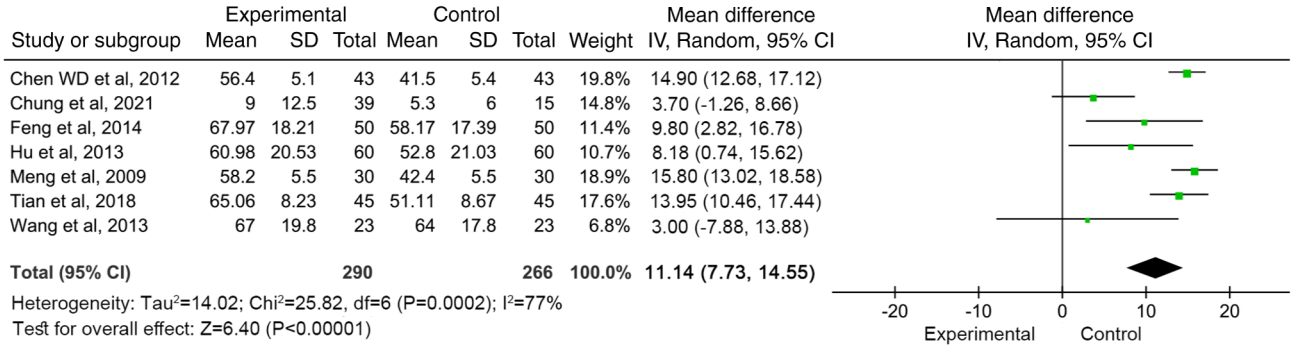

Figure 4. Forest plot of Fugl-Meyer Assessment score. df, degrees of freedom.

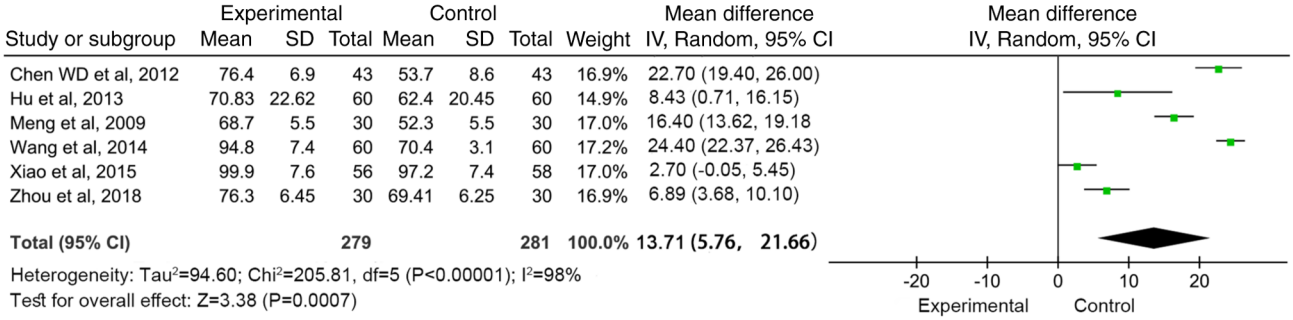

Figure 5. Forest plot of Functional Independence Measure score. df, degrees of freedom.

Meta-analysis of functional independence score (FIM). A total of six articles (15,19,21,26,29,30) reported the functional independence score before and after treatment. The results were heterogeneous (I^2=98%, P<0.00001), so a random effects model was used for meta-analysis. The combined effect size [WMD=13.71 (95%CI: 5.76-21.66, Z=3.38; P=0.0007)] indicated that compared with conventional treatment, MSC treatment significantly improved the functional independence score (Fig. 5).

Subgroup analysis. For the primary outcome, NIHSS, subgroup analyses were performed based on cell type, transplantation modality and follow-up time. In addition, among the 11 studies (13,14,16-18,20,22,24,27,28) with outcomes including NIHSS, bone marrow MSCs were all autologous [Hess *et al* (18) did not mention the source]. The number of cells was 3.0-5.0x10^6/kg (28), 5x10^6/kg (Fang *et al*, 2019) (13), 1x10^7/kg (Liu *et al*) (23), and not mentioned in the remaining studies. In research on umbilical cord MSCs, one study indicated that the source of the cells was Shenzhen Baker Biotechnology Co., Ltd., with a cell count of 3x10^7/kg (24), while another study (14) did not mention the source or quantity of the cells.

The improvement in NIHSS was more significant in the UBMSC group (WMD=-4.03, 95% CI: -5.88 to -2.18, P<0.0001), while the effect was weaker in the BMSC group (WMD=-0.79, 95% CI: -1.92 to 0.34, P=0.17; Fig. 6). There was a significant difference between the groups (P=0.05).

There was no significant difference in NIHSS between the groups based on transplantation method (total effect size P=0.17; Fig. 7). Follow-up period was divided as follows: Short-term, <3 months; medium-term, 3-6 months and long-term, >6 months. The MSC group showed the most significant improvement in NIHSS scores at 3-6 months follow-up (WMD=-2.40, 95% CI: -3.90 to -0.90, P=0.002). There was no significant difference between the treatment and control groups during short- and long-term follow-up (Fig. 8).

Safety analysis. A total of nine studies (15,17,18,20,22,24,26, 28,30) reported adverse effects such as low-grade fever, dizziness, headache, backache, depression, urinary and respiratory tract infection and rash; seven studies (12,13,16,21,23,25,29) reported no adverse reactions, and three studies (14,19,27) did not mention adverse reactions.

Sensitivity analysis. To assess the impact of studies at high risk of bias on the results of meta-analysis, sensitivity analyses were performed and excluded the only study with a high risk of bias (Tian *et al*) (14). Heterogeneity was significantly reduced after exclusion of the aforementioned study (I^2, 91 vs. 75%), and the overall effect size changed from -1.42 (95% CI: -2.83 to -0.01, Z=1.98, P=0.05) to -1.11 (95%CI: -2.22 to 0.01, Z=1.94, P=0.05). Although there was a slight change in the effect size, there was no notable change in its direction and significance, indicating that the results of the meta-analysis were robust.

Publication bias analysis. Funnel plots were used to test the publication bias of the primary outcome, NIHSS (Fig. 9). Funnel plots showed notable asymmetry, suggesting some publication bias. For more robust analysis of publication bias, Egger's test was performed for NIHSS, which showed no significant publication bias (P=0.461).

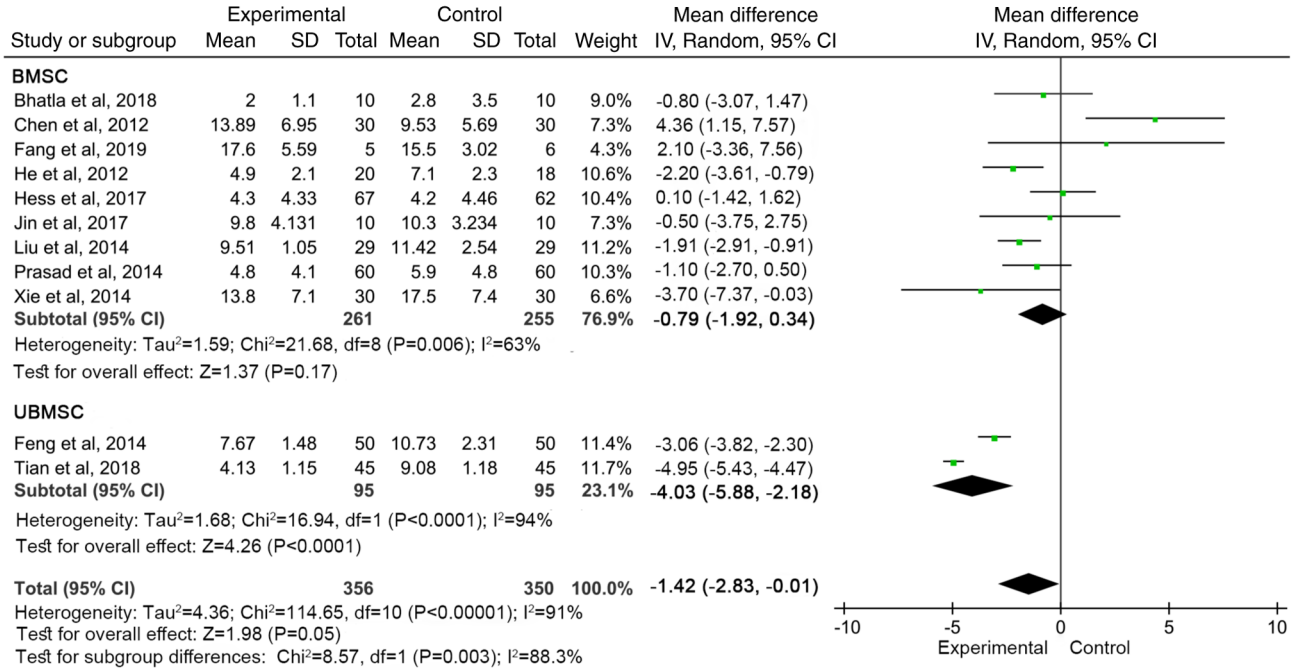

Figure 6. Subgroup analysis by National Institutes of Health Stroke Scale score. df, degrees of freedom. BMSC, bone marrow mesenchymal stem cell; UBMSC, umbilical cord blood mesenchymal stem cell.

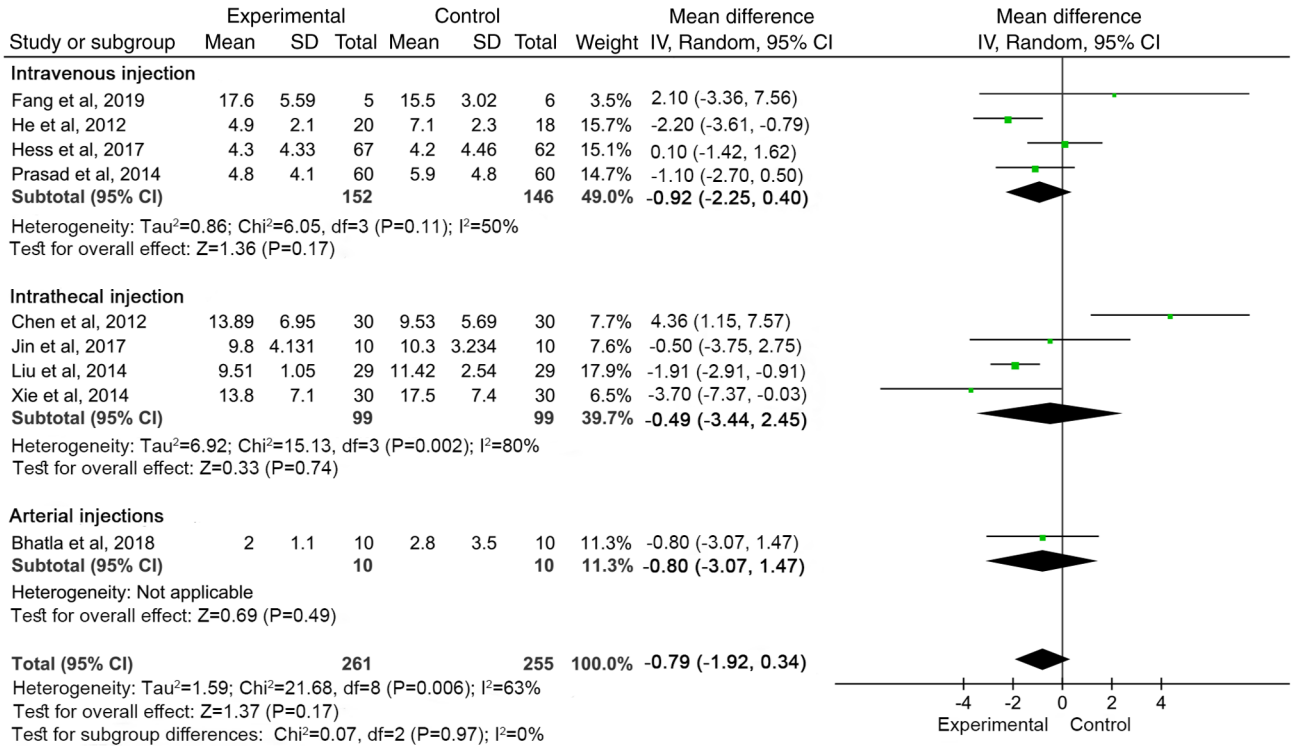

Figure 7. National Institutes of Health Stroke Scale) score subgroup analysis by transplantation modality. df, degrees of freedom.

Discussion

MSCs originate from tissue such as bone marrow, adipose tissue and umbilical cord. Bone marrow MSCs have relative ease of procurement. Nevertheless, as the donor age advances, the proliferative, self-renewal and differentiation capabilities of bone marrow MSCs decrease, thereby giving rise to disparities in the efficacy of SC treatment (31,32). By contrast, adipose and umbilical cord MSCs are not subject to such constraints. Umbilical cord MSCs exhibit the advantages of rapid proliferation and high differentiation potential (33,34). Cortical MSCs are derived from cortical bone. They have a stronger ability to differentiate into osteoblasts. They are mainly used in bone regeneration and orthopedics. Compared with bone

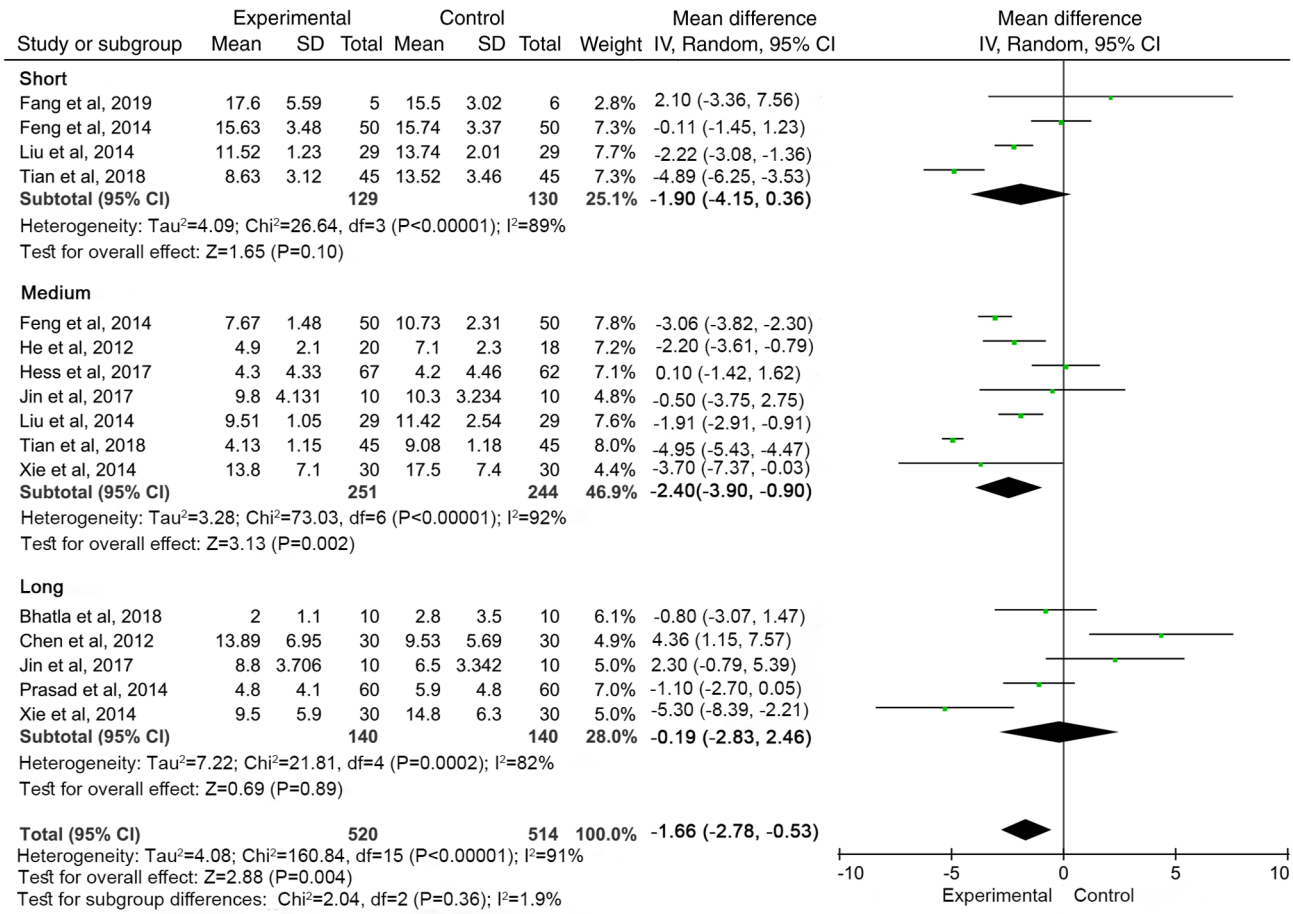

Figure 8. National Institutes of Health Stroke Scale) score subgroup analysis by follow-up time. df, degrees of freedom.

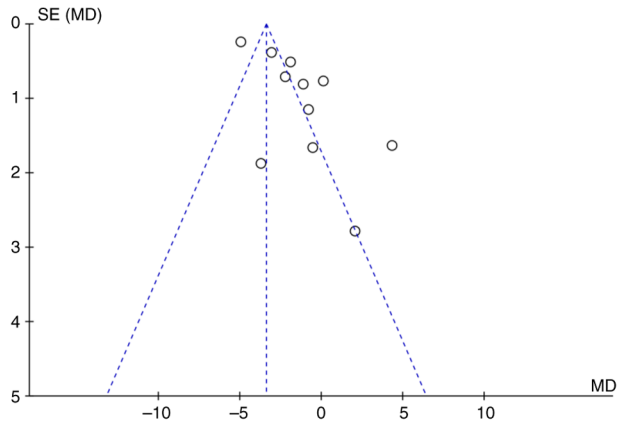

Figure 9. Funnel plot of National Institutes of Health Stroke Scale score.

marrow mesenchymal stem cells, research on cortical MSCs is relatively limited (35,36). MSCs have demonstrated potential in the treatment of a number of diseases, including ischemic cerebral infarction, myocardial ischemia, multiple sclerosis, idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, osteoarthritis, acute kidney injury and inflammatory bowel disease (37). SC therapy serves multiple roles in ischemic cerebral infarction, such as neural repair, vascular regeneration, anti-inflammatory and anti-apoptotic effects. MSCs traverse the blood-brain barrier to reach the ischemic regions of the brain (38). They serve a number of functions such as mitigating inflammatory responses, substituting for nerve cells that have undergone ischemic apoptosis, secreting neurotrophic factors, facilitating the repair of blood vessels within the brain and diminishing cell apoptosis (28-32,39-43). Compared with traditional treatment, MSCs improve the symptoms of neurological deficit and ability to perform daily living activities. The present study have shown that patients treated with MSCs have better recovery of limb motor and language function than those treated with conventional treatment. However, its effectiveness is affected by a variety of factors, such as the source of the cell, the mode of administration and the timing of treatment.

Although one study demonstrated high risk of bias (14), sensitivity analyses suggested a limited effect on the overall results. Future studies should focus on the implementation of randomization procedures, allocation concealment and blinding to improve the quality of studies.

In clinical trials, NIHSS, FMA, and FIM are commonly used to assess cerebral infarction (6-8). The present study showed that MSC therapy could improve FMA score and FIM score. The NIHSS score results show that the effect sizes of Chen *et al* (28) and Fang *et al*'s study (13) are both located to the right of the null line in the forest plot, which has a certain impact on the combined effect results. For Chen *et al*'s study (28), the abnormal effect size may be due

to differences in the NIHSS scoring method and the culture conditions of mesenchymal stem cells; for Fang *et al*'s study (13), it is considered to be caused by the small sample size. After excluding the study with the greatest impact on the results (Chen *et al*) (28), the pooled effect size WMD=-1.91 (95%CI: -3.25 to -0.57, Z=2.79, P=0.005). This meant that the MSC treatment group demonstrated lower NIHSS score than the control group, indicating that MSC therapy can reduce the degree of neurological deficit and have a positive effect on improving the neurological function of patients. Sensitivity analysis suggested that the Tian *et al* (14) may be one of the main sources of heterogeneity. Heterogeneity was significantly decreased after the study was excluded, but the overall effect size remained significant, supporting the positive effect of MSC treatment in patients with cerebral infarction. However, the presence of high heterogeneity suggests that future studies should focus on standardised patient selection, intervention and follow-up time to reduce heterogeneity and improve the reliability of results. In conclusion, MSC transplantation can improve neurological and motor function in patients with ischemic cerebral infarction. This heterogeneity may be due to differences in patient characteristics, SC source and treatments, details of interventions, and length of follow-up between studies.

Among the studies included, nine reported adverse reactions (15,17,18,20,22,24,26,28,30). The adverse reactions included low-grade fever, dizziness, headache, back pain, depression, urinary and respiratory tract infections, and rash, all of which resolved spontaneously or after treatment. The most common adverse reactions were fever and headache, and there were no serious adverse reactions such as to tumorigenicity or toxicity. MSCs have a high safety profile in the treatment of cerebral infarction. However, in the future, it is necessary to continue to pay attention to the potential risks, such as abnormal cell proliferation and immune-related problems. Safety of MSCs from different sources, preparation processes and administration methods may vary, which needs to monitored and evaluated in clinical applications.

Among the 11 studies included that involved NIHSS scores (13,14,16-18,20,22,24,27,28), six fell outside the 95% confidence interval of the funnel plot (14,16,22-24, 29), which may be attributed to heterogeneity among the studies and differences in sample sizes. Small-sample studies are prone to large sampling errors, leading to significant fluctuations in effect size estimates, exacerbating differences between results from small- and large-sample studies and increasing overall heterogeneity, thereby causing funnel plot asymmetry. Additionally, small-sample studies are more likely to yield negative results, while journals tend to publish positive findings, which further contributes to publication bias. and MSCs from bone marrow are the most widely used. Lumbar puncture, the method of obtaining cells, is an invasive operation, which not only causes pain and infection risk to patients, but also raises the threshold for clinical development. MSCs derived from the umbilical cord are easy to obtain and have high proliferative and differentiation capabilities. Unlike bone marrow-derived MSCs, those from the umbilical cord do not require a bone marrow puncture, avoiding invasive procedures. Due to the lack of clinical studies using umbilical cord MSCs, more research is needed in the future to determine the optimal source of MSCs. Due to the complexity and heterogeneity of the studies, it was not possible to draw definitive conclusions. Due to limited data and different transplantation routes, it was difficult for each subgroup sample to fully represent the overall characteristics, which may interfere with the effect estimation and weaken the reliability of the results.

MSCs are transplanted in a variety of ways, including stereotactic implantation or craniotomy for direct injection into the brain parenchyma, intravenous infusion and arterial and transarachnoid injection (4,5,40,43). The most common method of transplantation is intravenous infusion. Compared with intracerebral injection, intravenous infusion is simpler to perform, carries lower risk, involves less invasiveness and avoids damage to normal brain tissue caused by direct injection. However, some studies have shown that intravenous administration can reduce efficacy to some extent (5). Cells need to pass through the systemic circulation and blood-brain barrier to reach the brain. Directed transplantation in the brain is most effective, but normal brain tissue may be damaged during implantation (4). Craniotomy is generally not accepted by patients. Intrathecal injection has been used to inject stem cell suspension into the subarachnoid space through lumbar puncture, so SCs can circulate with cerebrospinal fluid to the surface of the brain. This method has the advantage of being minimally invasive and can partially overcome the physiological limitations of the blood-brain barrier, allowing the cells to be closer to central nervous system targets; lumbar puncture has a low probability of infection and the risk of cerebrospinal fluid leakage; therefore, clinical use needs to balance the benefits and safety (44). The present study found no significant differences between intravenous infusion, arterial injection and intrathecal injection. In clinical studies, the design of transplantation modalities is highly heterogeneous, such as the number of cells transplanted and whether cerebrospinal fluid is replaced by intrathecal injection, and the number of included studies is small, which may affect the results. More research is needed in the future to compare the efficacy of transplantation methods. This may be due to the small number of included studies and the inconsistency in the design of transplantation modalities. More research is needed to determine the optimal transplantation modality.

The efficacy of MSCs varies depending on the length of follow-up. MSCs may exert neuroprotective effects in the early stages because of their ability to combat toxic and inflammatory responses. The present study demonstrated MSC therapy improved NIHSS score more than conventional therapy during the medium-term follow-up period, and there was no significant difference between the treatment and control groups during the short- and long-term follow-up. However, the high degree of heterogeneity between studies limits the generalizability of the results. However, the high degree of heterogeneity between studies limits the generalizability of the results. Future studies should standardize MSC treatment regimens, patient selection criteria and outcome measures to decrease heterogeneity and provide more reliable evidence. Due to incomplete data, subgroup analyses were not performed for age, cerebral infarction severity and duration of cell transplantation.

The present study did not conduct subgroup analysis by age because most of the patients were aged 50-60 years. It was

not possible to assess the severity of cerebral infarction due to incomplete data. It was difficult to analyze the differences in treatment outcomes between different transplantation times, as only two studies (16,18) accurately recorded the timing of cell transplantation. The time of cerebral infarction onset in patients ranged from 1-2 days to 1-12 months. Patients with cerebral infarction onset of 1-12 months include those with onset of 1-2 days. However, we cannot obtain more detailed timing data from each study, so we are unable to perform subgroup analysis based on the duration since cerebral infarction onset. Due to the scarcity of data, the present study did not further analyze the source of cells and the number of cells transplanted.

The present study had limitations. Only six databases were searched, and the included articles were in Chinese and English, which presents risk of bias. Second, most studies did not have placebo-controlled trials, did not blind participants and treatment regimens and did not report allocation concealment. Although studies were consistent in terms of participants, intervention and outcome measures, providing a relatively homogeneous basis for subsequent meta-analysis, there may still be differences in terms of patient characteristics, SC-related treatments, SC transplant dose and follow-up time, resulting in heterogeneity in subsequent analyses. Additionally, the literature search for this study has certain limitations. Some of the included studies, particularly those published in Chinese, are not indexed in common international databases but can be accessed through specialized Chinese academic databases. This may affect the accessibility of this portion of the evidence for non-Chinese researchers, however these studies are available upon request. To assess the efficacy and safety of MSCs in the treatment of cerebral infarction, more high-quality studies are needed, including large-sample, multicenter randomized controlled trials that follow scientific norms to minimize the impact of publication bias.

In conclusion, MSC transplantation can improve the neurological function and motor function of patients with ischemic cerebral infarction and the safety is high. Due to the small sample size of the included studies, the quality of the articles was not high and there was a risk of bias. Therefore, in the future, large-sample, multi-center and rigorously designed clinical trials are needed to validate the present data.

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Availability of data and materials

The data generated in the present study, and studies cited which are published in Chinese may be requested from the corresponding author.

Authors' contributions

YJ, QC, YY, YX, XH and YL wrote the manuscript. YJ, QC and YY performed the literature review. YL and XH collected the data. YJ and YL confirm the authenticity of all the raw data, YJ, YX and XH analyzed the data. YL and QC designed the study and reviewed the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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