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META-ANALYSIS

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Effectiveness and Safety of Autologous Bone Marrow Stromal Cells Transplantation After Ischemic Stroke: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1 Wenying Cao
ABCDEF 2 Pan Li

1 Department of Neurology, The Ninth People's Hospital of Chongqing, Chongqing, P.R. China
2 Department of Radiation Oncology, The Ninth People's Hospital of Chongqing, Chongqing, P.R. China

Corresponding Author: Pan Li, e-mail: lipan_1983@126.com
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Background: Autologous bone marrow stromal cells (BM-SCs) transplantation might be a potential therapy for stroke. Although a series of clinical trials were performed to assess the effectiveness and safety of BM-SCs transplantation after ischemic stroke, the results are still conflicting. This study aimed to pool previous controlled trials to assess the effectiveness of BM-SCs-based cell therapy after ischemic stroke.

Material/Methods: Relevant studies were searched among online databases. Barthel index (BI) or modified Barthel index (mBI), National Institutes of Health Stroke Scale (NIHSS), and Rankin Score (mRS) were used to assess therapeutic effects. The frequencies of adverse events were extracted for assessing safety of stem cell therapy. Data analysis was performed by using Review Manager 5.3.

Results: Patients who received cell therapy had significantly lower NIHSS score (–1.85) than the controls. In addition, there might be some benefits in daily activity measured by mBI, but this meta-analysis failed to demonstrate significant benefits of BM-SCs-based cell therapy in increasing the proportion of mRS ≤2 patients. We did not find any severe adverse events associated with BM-SCs-based cell therapy.

Conclusions: Although BM-MNCs/MSCs transplantation might generate some benefits in lowering the grade of impairment caused by ischemic stroke, large RCTs are required to further confirm the effectiveness of BM-MSCs/MNCs-based cell therapy and to optimize the conditions require for best therapeutic effects.

MeSH Keywords: Mesenchymal Stromal Cells • Meta-Analysis • Stroke

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Background

Stroke accounts for approximately 11% of all deaths worldwide and is the most common cause of adult-acquired disability [1,2]. Among all stroke cases, ischemic stroke and intracerebral hemorrhage (ICH) account for about 80-85% and 15–20%, respectively. Intravenous thrombolysis by using tissue plasminogen activator (tPA) is the only approved treatment for acute ischemic stroke. However, tPA has very narrow time window (within 4.5 h after onset) of application. Therefore, only a minority of patients (2% to 4%) can receive timely therapy [3]. It is necessary to develop more effective therapeutic practices.

Cell therapy might be a promising strategy for stroke. Bone marrow-derived mononuclear cells (BM-MNCs) and mesenchymal stem cells (BM-MSCs) both are bone marrow stromal cells (BM-SCs) and are most frequently used in preclinical and clinical neurorestorative studies in stroke. BM-MNCs/MSCs have self-renewal capacity and pluripotency to differentiate into several mesenchymal cellular lineages, including osteoblasts, chondroblasts, adipocytes, myocytes, and fibroblasts [4,5]. They can also differentiate into non-mesenchymal lineages, including neurons and glial cells [6]. Preclinical studies observed that BM-MNCs/MSCs transplanted either intracranially or intravascularly could migrate to damaged brain tissue and exert a neuroprotection effect by inhibiting apoptosis, decreasing perinfarct inflammation, and promoting angiogenesis [7–9]. This mechanism makes BM-MNCs/MSCs therapy a potential therapy for stroke. Therefore, during the past decade, a series of clinical trials was performed to assess the effectiveness and safety of BM-SCs transplantation after stroke. However, the results are still conflicting. Due to the small number of patients recruited in individual trials, the statistical power of the conclusions is weak. One recent single-arm meta-analysis showed this cell therapy could effectively improve National Institutes of Health Stroke Scale (NIHSS) scores, modified Barthel index (mBI) score and modified Rankin score (mRS) [10]. However, without comparison with a control group, there might have observational bias. Therefore, this study aimed to pool previous controlled trials to assess the effectiveness of BM-SCs-based cell therapy after ischemic stroke.

Material and Methods

Study search and selection

This study generally followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Study selection and data extraction were performed by 2 authors independently. Relevant studies published from 1 Jan 2000 to 1 Sept 2014 were searched among PubMed, Medline, Embase, and the Cochrane database. We only included randomized or non-randomized controlled trials that assessed effectiveness of BM-MNCs/MSCs-based cell therapy in either ischemic stroke patients. Studies with unclear or without extractable data were excluded.

Data extraction

The basic data extracted from original studies included: family name of the first author, year of publication, type of stoke, study design, number of patients, mean age, type of cell used, route of cell delivery, number of cells injected, time interval from stroke to therapy, follow-up, baseline NIHSS score, and outcome indicator measured. To assess the effectiveness of cell therapy, the outcome indicators used to assess therapeutic effectiveness include modified Rankin Score (mRS), Barthel index (BI) or modified Barthel index (mBI), and National Institutes of Health Stroke Scale (NIHSS). The frequencies of adverse events were extracted for assessing safety of stem cell therapy.

Statistical analysis

Original data were pooled and analyzed by using Review Manager 5.3 (the Cochrane Collaboration). The risk ratio (RR) and corresponding 95% confidence intervals (CI) of mRS ≤2 (cell therapy *vs.* control) were estimated. For the discontinuous data, including BI or mBI and NIHSS score, weighted mean difference (WMD) and corresponding 95% (CI) was estimated. The chi-square based Q test and I^2 value were used to assess between-study heterogeneity, which also determines the methods used for making estimation. The random-effects model (DerSimonian and Laird method) was used when $p < 0.1$ in Q test or $I^2 > 50\%$, which indicates significant heterogeneity. Otherwise, the fixed-effects model based on Mantel-Haenszel method was applied. If unacceptable high heterogeneity was observed, the sources of heterogeneity were further explored. If significant clinical heterogeneity existed, subgroup analysis was performed. $p<0.5$ in Z test was considered statistically significant in the pooled results.

Results

Based on searching and screening with the preset criteria, 5 trials [11–15] were finally included in this meta-analysis. The general searching and screening process is summarized in Figure 1. The basic features of the 5 trials are given in Table 1. The 5 trials involved a total of 228 patients, among which 104 were in the cell therapy group and 124 were in the control group. Two studies used BM-MSCs [11,12] and 3 studies used BM-MNCs [13–15]. Four studies transplanted cells through IV injection [11–13,15] and 1 used IA injection [14]. The number of cells injected ranged from 5×10^7 to 2.6×10^8. The time interval from stroke to cell therapy varied from several days

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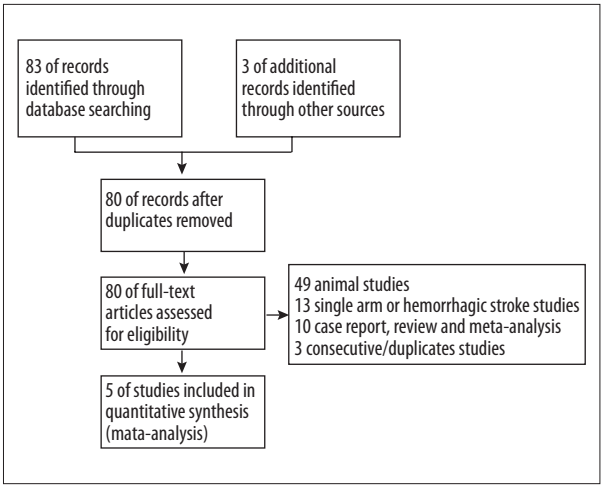

Figure 1. The searching and screening process.

to several months after stroke. Four trials reported outcome with 6-month follow-up, while 1 study reported 5-year outcome. Generally, modified Rankin score (mRS), Barthel index (BI), modified BI (mBI), and National Institutes of Health Stroke Scale (NIHSS) scores are the 3 indicators most used to assess clinical outcomes of cell therapy.

The effect of BM-MSCs on BI or mBI score

Two studies reported BI and 2 studies reported mBI at the end of follow-up. Generally, although the cell therapy group had slightly higher BI or mBI score, the mean difference was not significant between cell therapy and control group (WMD: 2.50, 95%CI: –4.69 to 9.68, p=0.50, I^2=46%) (Figure 2). Subgroup analysis was performed by stratifying BI and mBI. Subgroup using mBI as the indicator of daily activities of living reported significantly higher mBI score in the cell therapy group than in the controls (WMD: 7.44, 95%CI: 1.82 to 13.06, P=0.009, I^2=0%) (Figure 2), but no significant difference was observed in the BI subgroup (WMD: –3.24, 95%CI: –12.14 to 5.65, P=0.47, I^2=0%) (Figure 2).

The effect of BM-MSCs on NIHSS score

Two studies reported NIHSS at the end of follow-up. Generally, the mean difference of NIHSS score was significant lower in the cell therapy group than in the control group (WMD: –1.85, 95%CI: –2.77 to –0.93, P<0.0001, I^2=24%) (Figure 3).

Table 1. The key characteristics of trials included.

Study	Type of stroke	Baseline NIHSS score	Study design	No patients		Mean age (yrs)		Type of cells	Route of Delivery	No. cells injected	Time interval from stroke to therapy	Follow-up	Outcome measured
				E	C	E	C						
Lee 2010	MCA ischemic stroke	≥7	RCT	16	36	64	64.9	Autologous BM-MSCs	IV	5×10^7 (2 times with 2 weeks interval)	19 to 37 days	5 years	mRS
Bhasin 2012	chronic ischemic stroke	4–15	NRCT	12	12	46.5	47.08	Autologous BM-MNCs	IV	5.5×10^7	Mean 9.3 months	6 months	mBI
Moniche 2012	MCA ischemic stroke	≥8	NRCT	10	10	66.9	67.4	Autologous BM-MNCs	IA	Mean 1.6×10^8	5 to 9 days	6 months	mRS, BI, NIHSS
Prasad 2014	subacute ischemic stroke	Median 12	RCT	60	60	50.7	52.5	Autologous BM-MNCs	IV	Mean 2.6×10^8	Median of 18.5 days	6 months	mRS, BI, NIHSS
Bhasin 2011	MCA ischemic or hemorrhagic stroke	4–15	NRCT	6	6	42	46.5	Autologous BM-MSCs	IV	$5–6\times10^7$	Mean 9.3 months	6 months	mBI

RCT – randomized controlled trial; NRCT – non-randomized controlled trial; BM-MNCs – bone marrow mononuclear cells; N.A. – not available; MCA – middle cerebral artery; IC – intracerebral; IA – intra-arterial; IV – intravenous; mRS – modified Rankin Score; BI – Barthel index; mBI – modified BI; NIHSS – National Institutes of Health Stroke Scale.

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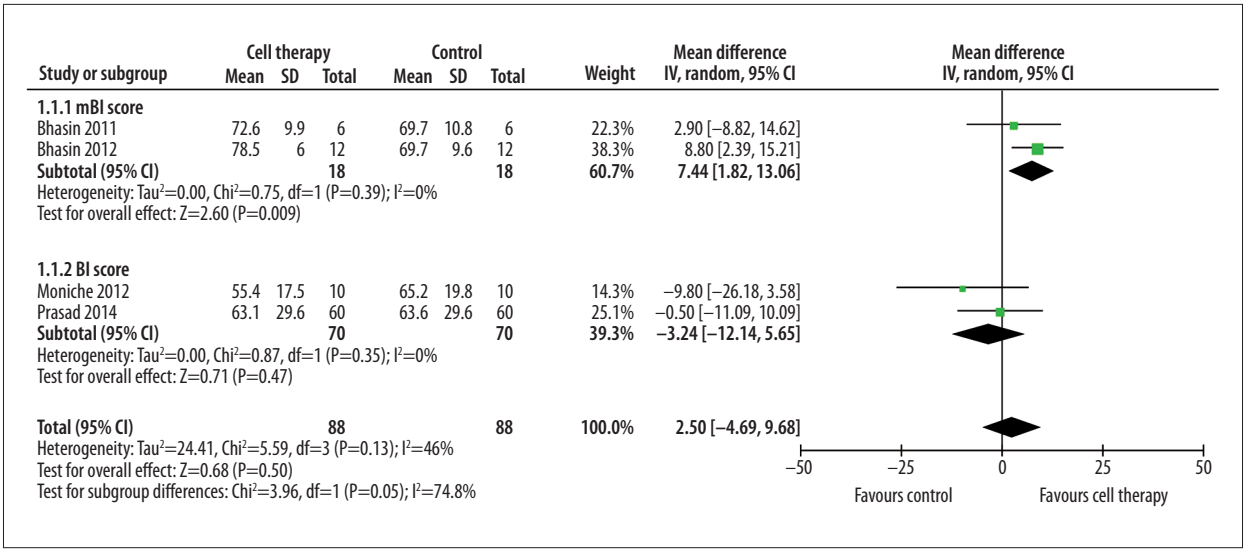

Figure 2. Meta-analysis of BI or mBI score after BM-MNCs/MSCs transplantation.

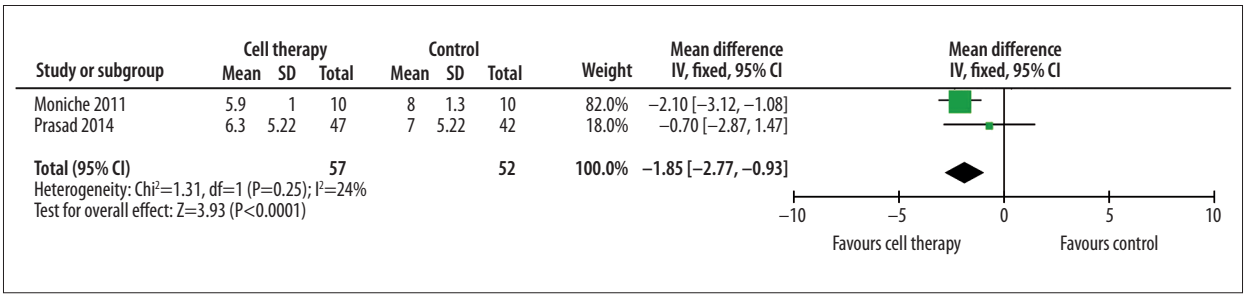

Figure 3. Meta-analysis of NIHSS score after BM-MNCs/MSCs transplantation.

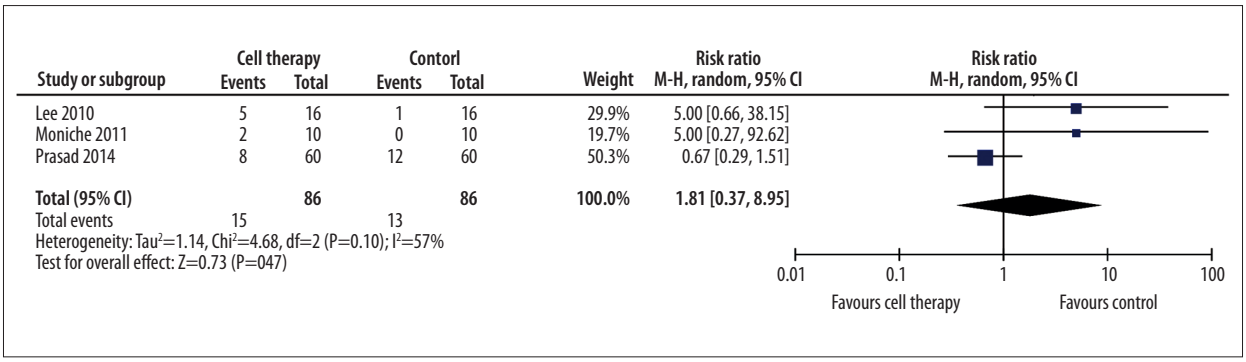

Figure 4. Meta-analysis of mRS distribution after BM-MNCs/MSCs transplantation.

The effect of BM-MSCs on mRS

Three studies reported the change in mRS at the end of follow-up. Due to the non-randomized design of some studies, we only compared the proportion of patients with mRS ≤2 before and after cell therapy in the experimental arm. The meta-analysis did not find significant change in the proportion of patient in the mRS ≤2 group before and after cell therapy (13/86 *vs.* 15/86) (RR: 1.81, 95%CI: 0.37 to 8.95, p=0.47) (Figure 4).

Safety assessment of BM-MSCs transplantation

Infection, recurrence of stroke, and death were used to assess the safety of BM-MSCs transplantation. Our meta-analysis did not find any difference in these 3 indicators between the cell therapy and control group (Figure 5).

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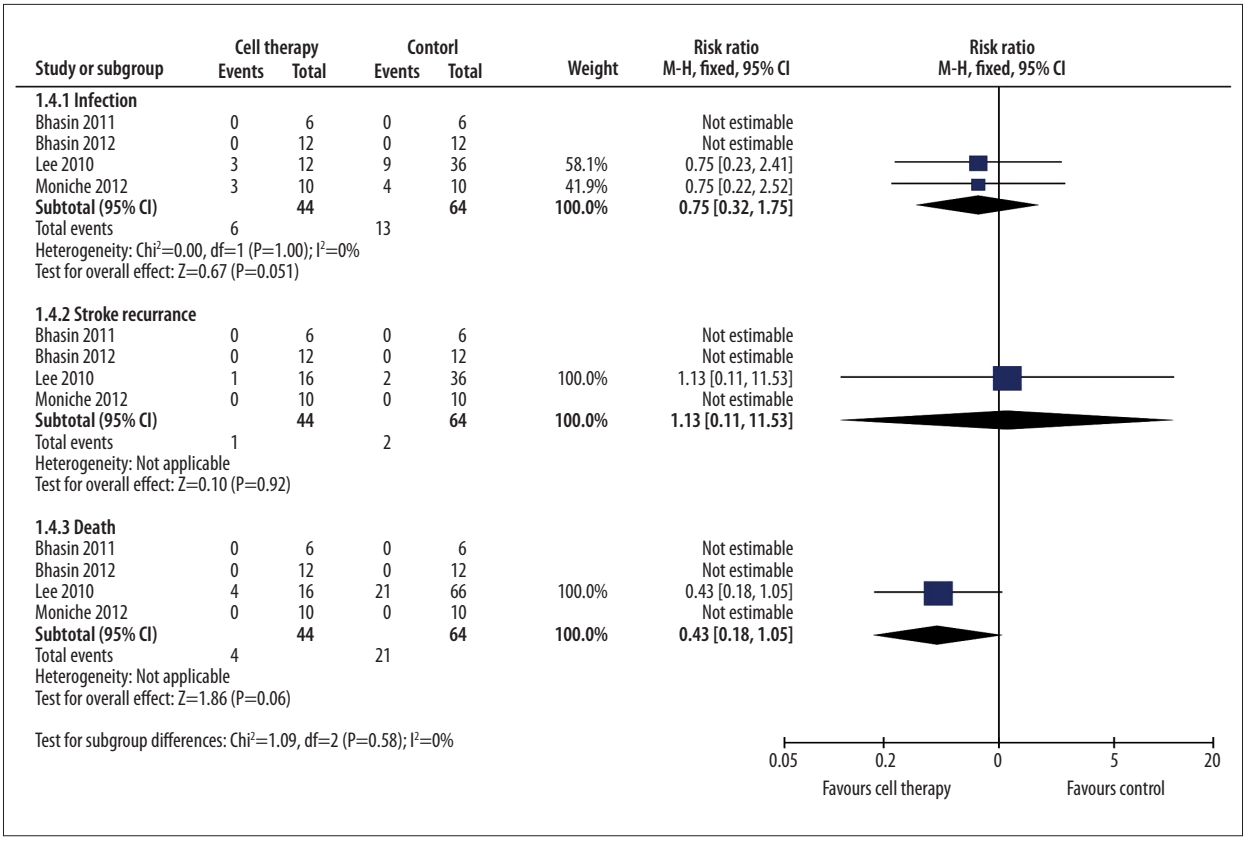

Figure 5. Meta-analysis of severe adverse effects of BM-MNCs/MSCs transplantation.

Discussion

In animal models, transplantation of BM-MNCs or MSCs could reduce inflammation, decrease the infarct size in the brain, and improve neurological function in several models of stroke through multiple mechanisms [16–18]. A recent meta-analysis based on 46 preclinical animal studies also confirmed these effects [19]. Previous preclinical studies observed that although BM-MSCs and BM-MNCs could transdifferentiate into neuronal-like *in vitro*, they did not have basic neuronal functional properties [20,21]; this transdifferentiation seldom happens *in vivo* [16]. In fact, a study based on animal models showed that only a very small proportion (about 0.02%) of the intravenously delivered BM-MNCs migrate to the ischemic area of the brain, while most of the transplanted cells develop a macrophage/microglial phenotype [22]. Therefore, transdifferentiation is not the key mechanism mediating the possible therapeutic effects. Generally, the transplanted cells have a stimulating effect on release of cytokines and neurotrophic factors, including brain-derived neurotrophic factor (BDNF), basic fibroblast growth factor (bFGF), nerve growth factor, vascular endothelial growth factor (VEGF), insulin-like growth factor-1, hepatocyte growth factor (HGF), and stem cell factor [9,22]. These factors can induce angiogenesis, reduce neuronal apoptosis, enhance axonal regeneration, rebuild synapses and dendrites, and promote differentiation of endogenous neural stem and progenitor cells [9,22]. These effects do not necessarily require the presence of transplanted cells at the injury site in the brain. Therefore, the paracrine effects of transplanted cells might be fundamental to positive clinical outcomes. However, in clinical trials, data on the exact effects of BM-MNCs/MSCs-based cell therapy after stroke are still conflicting.

This study, based on 5 double-arms trials, demonstrated that BM-derived stromal cells might have some benefits in lowering the grade of impairment caused by ischemic stroke. Patients who received cell therapy had significantly lower NIHSS score controls. The lowered NIHSS score was a powerful indicator of excellent outcome after stroke. In fact, a 1-point increase of NIHSS score decreases the likelihood of an excellent outcome by 17% [23]. In addition, there might be some benefits in activities of daily living as measured by mBI. However, the studies involved a limited number of patients and were conducted by a same research team, so the statistical power of the finding might be weak. Clinical trials usually define favorable outcome of stroke as mRS grade ≤2 [24]. However, this meta-analysis failed to demonstrate significant benefits of BM-MSCs/MNCs-based cell therapy in increasing the proportion of mRS ≤2 patients. Due to the small number of trials and patients included, this finding is also inconclusive. This study did

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not find any severe adverse events associated with cell therapy, suggesting it is a relatively safe intervention.

This study also has several limitations. Firstly, the number of trials and the number of patients recruited in each trial were small. In addition, different trials reported different clinical outcomes, which makes it hard to use the same scale to summarize the results. These limitations significantly weaken the statistical power of the findings. Secondly, to develop an effective cell therapy strategy, several factors, including eligibility criteria of the patients, timing, and route and dose of cell transplantation, should be considered in clinical practice. However, based on the available evidence, these factors still need to be optimized. These factors also might have contributed to the heterogeneity of this study. Patients with moderate, but not mild or severe, stroke might be more suitable for cell therapy, since patients with mild strokes generally have uniformly good outcome and patients with severe stroke are less likely to respond to the intervention and thus are unlikely have good outcome. The 5 trials recruited patients with basic NIHSS scores ranging from 4 to 20, which means minor, moderate, and moderate-to-severe patients were all recruited. Therefore, their different responses to cell therapy might generate observational bias.

Conclusions

Although BM-MNCs/MSCs transplantation might generate some benefits in lowering the grade of impairment caused by ischemic stroke, large RCTs are required to further confirm the effectiveness of BM-MSCs/MNCs-based cell therapy and to optimize the conditions required for best therapeutic effects.

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