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Mesenchymal and mononuclear stem cell therapy for acute ischemic stroke - A systematic review

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Abstract

Background: Studies have shown that stem cells have promising effect in ischemic stroke management. As an alternative therapy, the effectiveness and safety of mesenchymal (MSC) and mononuclear (MNC) stem cells in acute stroke are still unclear. This review evaluated the efficacy and safety of the use of MSC and MNC in acute ischemic stroke in terms of clinical and structural improvement. *Methods:* This is a systematic review which is conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. Our review focused on RCT, with acute ischemic stroke population using MSC or MNC, and evaluated the clinical and structural improvements, and safety outcome after administration of the stem-cells. *Results:* Eight studies were included, consisted of 155 patients in intervention and 408 in control group. In the MNC group, there was significant improvement of NIHSS within one month and achieved mRS ≤ 1 by six months. Slightly different from MNC, studies using MSC showed mRS improvement occurred after 3 months and NIHSS-motor improvement achieved after 2 years of infusion. One month after cell infusion, MRI showed structural improvement, with infarct expansion ratio of 0.9 ± 0.2 ($p < 0.05$). There was no differences in adverse events between intervention and control group in all studies.
Conclusions: This review show that MSC and MNC stem-cells are effective and safe to use as alternative treatment in acute ischemic stroke if other definitive measures could not be done or not available.

Keywords: Mesenchymal stem cell, mononuclear stem cell, acute ischemic stroke, systematic review

INTRODUCTION

Ischemic stroke is a prevalent disease with high burden globally. At 2019, data from 204 countries showed that prevalence of stroke is 101.47 million, with 76% being ischemic stroke. Stroke has become second-leading cause of death, and third-leading cause of death and disability combined.[1] Besides, intravascular thrombolytic infusion as definitive therapy for ischemic stroke often could not be administered because of its narrow windows period. Only 9.9% and 1.9% of patients were treated with intravenous thrombolytic or endovascular thrombectomy respectively, in many sites globally since 2008-2018.[2] Researchers have been trying to find alternative therapy to mitigate this limitation.

The early study in 2001 using stem-cells for ischemic stroke models showed significant improvement, thus making stem-cells as one of promising alternative in ischemic stroke management.[3] Later in 2005, a clinical study was done which showed that stem-cells appeared to be safe to use intravenously and gave rise to clinical improvement.[4] Stem cells inhibit neuronal apoptosis, protect mitochondrial function, and reduce microglial activation in acute phase of rat stroke models. Several studies have shown that stem cells reduced infarct size and resulted in functional recovery.[5]

Two types of stem cells which commonly used are mesenchymal (MSC) and mononuclear stem cells (MNC). MSCs can be obtained from bone marrow, abdominal fat, teeth, cord blood, and Wharton's jelly. MNC is also easy to harvest from the bone-marrow patients without resorting to ex-vivo expansion and could be used in acute time window.[6] During the acute stage, most preclinical studies have recommended that MSC

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transplantation be given within 48 hours. In animal studies, the optimal window for MSC infusion was between 3-30 days after the onset.[7] Meanwhile, MNC infusion is safe for acute ischemic stroke with onset of 24-72 hours.[8]

As an alternative therapy, the effectiveness and safety of MSC and MNC in acute stroke are still unclear. Several trials have been done clinically using mesenchymal or mononuclear stem cells in acute phase of stroke, though they used different doses, route of administrations and sources.[5,9] There has been systematic review and meta-analysis about stem cells in ischemic stroke published. However, they do not restrict the type of the cells to mesenchymal and mononuclear especially in acute phase of ischemic stroke. This review aims to evaluate efficacy and safety of stem cell and the use of MSC and MNC in acute ischemic stroke in terms of clinical and structural improvement.

METHODS

Study design and protocol

This study is a systematic review which is conducted based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline. Our review has been registered in PROSPERO (International Prospective Register of Systematic Reviews) by National Institute for Health Research (NIHR).

Inclusion and exclusion criteria

Our review focused on randomized clinical trial, with acute ischemic stroke population regardless of age, gender and region which has onset equal to or less than a month; using MSC or MNC, autologous or allogenic, irrespective of its route of administration (intraarterial, intravenous or intrathecal) as compared to standard or conventional acute ischemic stroke therapy.

Outcome

In this review, the treatment efficacy was assessed by improvement of National Institute of Health Stroke Scale (NIHSS), Barthel Index (BI), or modified Rankin Scale (mRS) and safety was assessed by adverse events observed after implantation of stem-cells. Structural improvement evaluation using neuroimaging such as Brain CT or MRI is preferred, but not obligatory. We excluded study with hemorrhagic stroke; observational or preclinical study.

Search strategy

Literature search was conducted on five databases (Cochrane, PubMed, Sciencedirect, EBSCOhost, and ProQuest) also on www.clinicaltrial.gov registry. We searched published studies up to January 2022. There was no language limitation. We only used electronical search and hand searching was not conducted. Articles were obtained using our institutional access. Keywords used in literature searching were: mesenchymal AND (stem cell therapy OR stem cell) AND acute AND ischemic AND stroke AND (clinical trial OR trial) NOT (hemorrhagic OR haemorrhagic).

Data extraction

Extraction was carried out following PRISMA 2020 guideline. We searched studies on databases and registry and screened based on our inclusion-exclusion criteria. There were two reviewers worked independently in all stages of searching and screening process. We extracted the following data in all of articles: author, design, year of publication, sample size, population, sample ages, route of administration, outcomes such as clinical improvement (NIHSS, Barthel Index, mRS) and structural improvement (neuroimaging such as Brain CT or MRI) categorized as primary outcomes, and side effects as secondary outcome. Study written in language other than English was translated using online translator.

Assessment of risk of bias

Risk of bias was assessed using Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) which included several domains: bias in randomization process, bias due to deviations from the intended intervention, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of reported result. All domains were analyzed and resulting in overall risk-of-bias judgment. Any missing or unclear data was confirmed by contacting the author. There were two reviewers involved and worked independently. Disagreement was solved with discussion involving a third reviewer.

Assessment of quality

In this review, we only included moderate and high quality studies. We used critical appraisal tool for randomized controlled trials by Centre for Evidence-Based Medicine (CEBM)-University of Oxford to assess the quality of studies. There were two reviewers involved independently in assessing the quality of studies.

RESULTS

Study selection

Literature search was conducted in five databases and one registry resulting in identification of 2,665 articles. There were 1,297 articles identified as duplicates, thus excluded from this review. Thirty-five articles were from EBSCOHost, 65 from SCOPUS, 1,194 from Springerlink, 49 from Pubmed, 23 from Cochrane Library, and two studies from clinicaltrials.gov. Title and abstract screening were done and yielded 12 studies. We applied the inclusion and exclusion criteria, resulting in 8 studies that were analyzed in this review. All studies were available in full-text by using our institutional access. (Figure 1)

Studies characteristics

Studies included were from different regions (USA, South America, Europe, and Asia), written in English and published in different years from 2011 until 2020. All studies were trials, but only three studies were RCT. Most studies included relatively small intervention groups (3-25 patients). In two studies using MSCs, a total of 19 cases were obtained from the intervention group and 15 in control group.[10,11] Meanwhile, in 6 studies with MNC, there were 136 patients in intervention group and 393 patients in control arms.[8,12-16] All patients were 40 to 78 years old. There were 2 studies that administered stem cells within 24-72 hours after onset, 1 study around 1 week of onset, and others varied between 10 days and around a month. Stem cells used in these studies were varied, almost all studies used autologous bone marrow stem cells, but only one used allogenic bone marrow stem cells and the other one used umbilical cord stem cells. Two studies used mesenchymal stem cells while others used mononuclear stem cells. Stem cells were administered either intra-arterially or intravenous with varied dose between studies. Baseline clinical scores varied among studies, from mild to severe disability. Five studies included patients who had been given thrombolytic therapy in intervention group. (Table 1, 2)

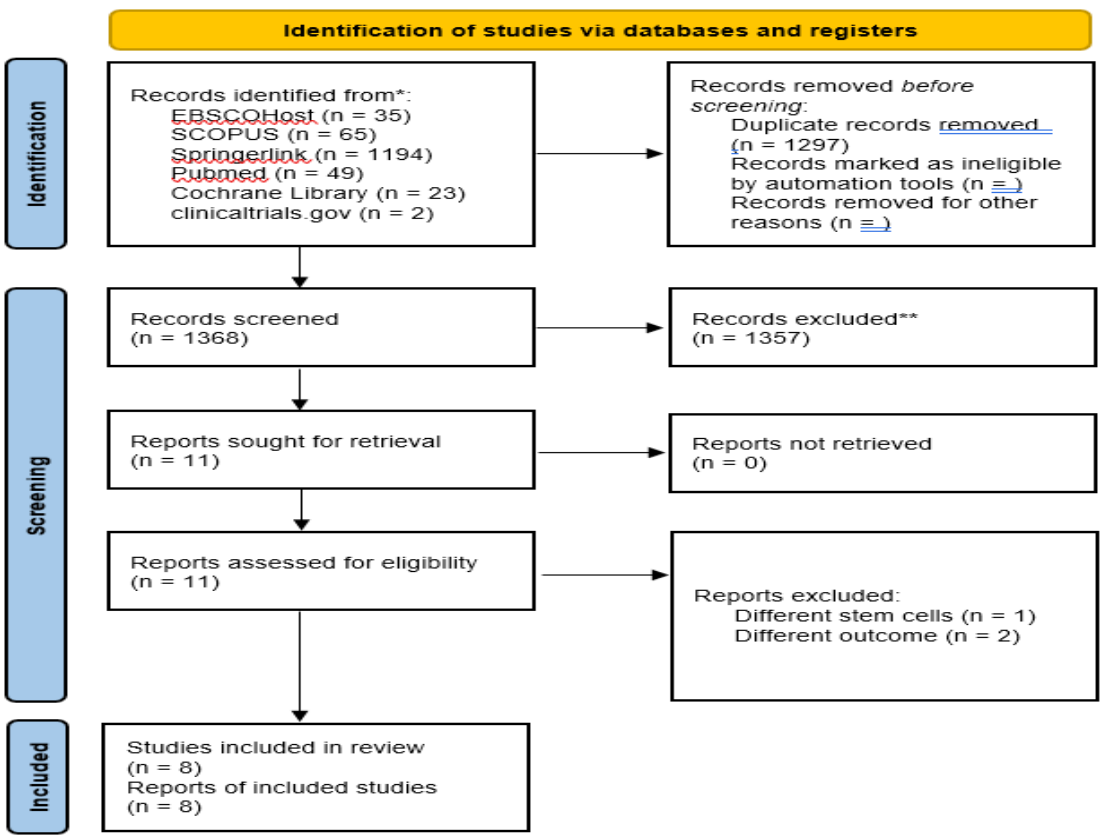

Figure 1. PRISMA flowchart in literature searching

Table 1: Characteristics of included studies (MSC)

Author, Years	Country	Study design	Sample size (age) (intervention: control)	Onset to cells administration	Stem cell's type	ROA	Cell dose	Baseline clinical score*	Other therapy*
Jiang, 2013[11]	China	Non-randomized, uncontrolled, trial	3 (40-57 yo)	11, 19, 22 days	UC-MSC	IA	$2x10^7$	mRS: 3-5	Aspirin, or aspirin and clopidogrel
Jaillard, 2020[10]	France	RCT	16 (mean 55, 46-58 yo) : 15 (mean 53, 45-63 yo)	Mean 32 (28-40) days	Autologous BM-MSC	IV	10 patients $1x10^8$; 10 patients $3x10^8$	NIHSS: mean 12 (11-16) mRS: mean 4 (3.5-4) BI: 47.5 (10-75)	Rehabilitation therapy, e.g. walk and hand therapy (100%); Thrombolysis (25%)

RCT: Randomized controlled trial; UC-MSC: Umbilical cord-mesenchymal stem cells; IA: Intraarterial; IV: Intravenous, ROA: Route of administration
*only in intervention group

There were different risks resulted after assessment in RCT and non-randomized studies. Overall analysis from RCT studies gave good results except one with high risk of bias because of randomization process (Prasad, *et al*).[10,12,14] Some baseline characteristics were not well balanced (mean infarct volume, previous transient ischemic attack, and number of patients which time from onset to randomization was in week 4)**.** These characteristics might affect the outcome, thus any differences between groups has to take these factors into consideration.[14] In non-randomized studies there were no study with low risk of bias in terms of overall risk. It happened because most studies had unclear or moderate risk in confounding and measurement of outcomes, with one having high risk in confounding domain**.**[8,11,13,15,16] Confounding domain became a problem because most studies had confounding factor that was not well-controlled, moreover one study did not mention whether they controlled the confounding factors.[8,11,13,16] Measurement of the outcomes became unclear risk because not all studies mention specifically whether the assessor did measurement blindly.[8,11,13,15,16] (Figure 2, 3)

Adverse events

There was no or insignificant differences of adverse events between intervention and control group during procedure or immediately after procedure in all studies.[8,10-16] Followed-up evaluation (1 week, 1 month, 3 months, 6 months) showed several adverse events but most of them were mild or asymptomatic.[10-13,16] Elevated hepatic transaminase and hematologic abnormality were seen within 5 days after procedure, but insignificant compared to control group.[14] Other study reported at 30 days, but it was only transient increment.[15] Severe adverse events happened but in few cases and mostly not study-related or inconclusive.[16] The reported severe adverse events were aspiration pneumonia, sepsis, and recurrent stroke (inconclusive, whether it was study related or not).[15,16] In two studies using BM-MNC intraarterially, MRI and Brain CT at followed-up evaluation showed no new ipsilateral infarct observed.[12,13] Few mortality events occurred and insignificant compared to control group. Deaths were attributed mostly to cardiac causes, not related to stem cells.[8,12-14,16] (Table 3)

Clinical improvement

Improvement was observed in intervention group. Study by Taguchi *et al*. reported significant

Table 2: Characteristics of included studies (MNC)

Author, Years	Country	Study design	Sample size (age) (intervention: control)	Onset to cells administration	Stem cell's type	ROA	Cell dose	Baseline clinical score*	Othertherapy*
Bhatia, 2018[12]	India	RCT	10 (57 ± 12.2 yo) : 10 (66 ± 7.4 yo)	Mean: 10 days	Autologous BM-MNC	IA	$5x10^8$	NIHSS: 10.6	Thrombolysis (10%)
Prasad, 2014[14]	India	RCT	59 (50.7 ± 11.6 yo) : 60 (52.5 ± 12.1 yo)	Median: 18.5 days	Autologous BM-MNC	IV	Mean $2.8x10^8$	NIHSS: 0-7 (3.3%), 8-14 (65%), 15-22 (31.7%)	Thrombolytic or mechanical thrombectomy were not given
Vahidy, 2019[16]	USA	Non-randomized, controlled, trial	25 (60.7 ± 13.3 yo) : 185 (63.7 ± 12.5 yo)	24-72 hours	Autologous BM-MNC	IV	Mean $9.1x10^6$ cells/kg	NIHSS: 11.9 ± 3.7 mRS: 0 (96%), 2 (4%)	Thrombolysis (64%)
Taguchi, 2015[15]	Japan	Non-randomized, controlled, trial	12 (67.4 ± 5.4 yo) : 59 (66.7 ± 9.0 yo)	10 days	Autologous BM-MNC	IV	6 patients 2.5 ± $0.5x10^8$; 6 patients 3.4 ± $1.3x10^8$	NIHSS: 16.6 ± 4.7	Thrombolysis (33.3%)
Freidrich, 2012[13]	Brazil	Non-randomized, single arm, trial	20 (mean 63, 30-78 yo)	6 ± 1.8 days	Autologous BM-MNC	IA	Mean $22x10^7$ ($5.1x10^7$-$60x10^7$)	NIHSS: mean 17 ± 5.6	Not mentioned
Savitz, 2011[8]	USA	Non-randomized, controlled trial	10 (55 ± 15 yo) : 79 (63 ± 12 yo)	24-72 hours	Autologous BM-MNC	IV	8 patients given $1x10^7$ cells/kg; 2 patients given $7x10^6$ cells/kg and $8.5x10^6$ cells/kg	Not mentioned in nominal scoring	Thrombolysis (100%)

RCT: Randomized controlled trial; BM-MNC: Bone marrow-mononuclear stem cells; IA: Intraarterial; IV: Intravenous, ROA: Route of administration
*only in intervention group

Risk of bias

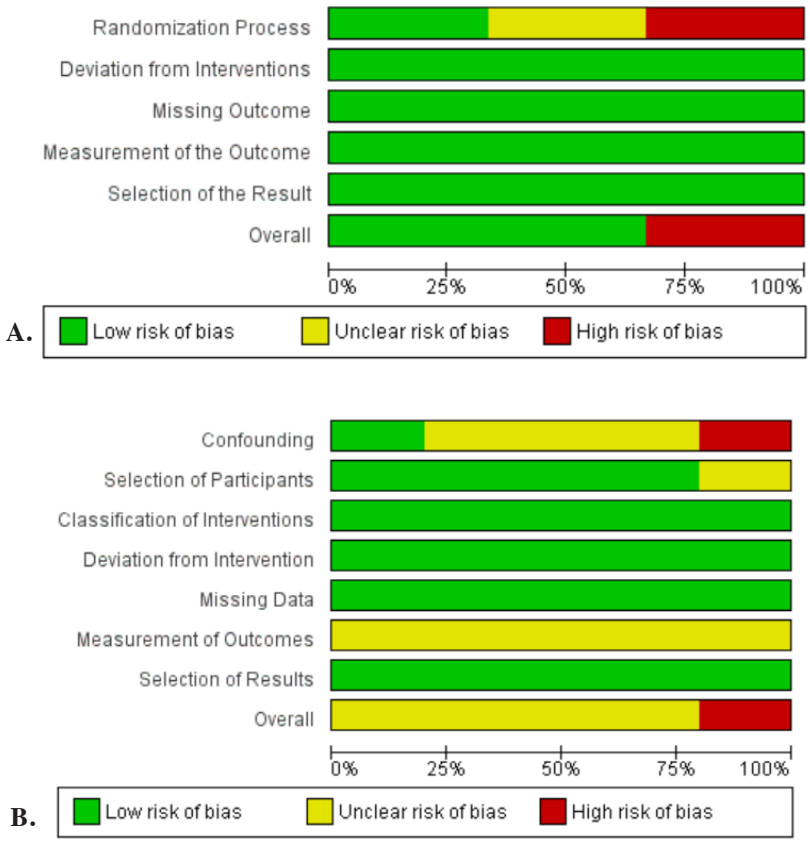

Figure 2. Risk of bias graph for A. RCT studies, and B. Non-randomized studies

Figure 3. Risk of bias summary for A. RCT studies, and B. Non-randomized studies

Table 3: Information of adverse events

Author, Years	Sample size (age) (intervention: control)	Stem cell's type	ROA	Cell Dose (Cells)	Adverse events
Jiang, 2013[11]	3 (40-57 yo)	UC-MSC	IA	$2x10^7$	No obvious adverse reactions
Bhatia, 2018[12]	10 (57 ± 12.2 yo) : 10 (66 ± 7.4 yo)	Autologous BM-MNC	IA	$5x10^8$	No obvious adverse reactions
Prasad, 2014[14]	59 (50.7 ± 11.6 yo) : 60 (52.5 ± 12.1 yo)	Autologous BM-MNC	IV	Mean $2.8x10^8$	No obvious adverse reactions
Vahidy, 2019[16]	25 (60.7 ± 13.3 yo) : 185 (63.7 ± 12.5 yo)	Autologous BM-MNC	IV	Mean $9.1x10^6$ cells/kg	Anemia (8), pain (1), vomiting (1), enzymes elevations (ALT 2, amylase 1, AST 4, lipase 1), hyperglycemia 1, haemorrhagic transformation 2, aspiration 1, hypotension 1
Jaillard, 2020[10]	16 (mean 55, 46-58 yo) : 15 (mean 53, 45-63 yo)	Autologous BM-MSC	IV	10 patients $1x10^8$; 10 patients $3x10^8$	No obvious adverse events
Taguchi, 2015[15]	12 (67.4 ± 5.4 yo) : 59 (66.7 ± 9.0 yo)	Autologous BM-MNC	IV	6 patients 2.5 ± $0.5x10^8$; 6 patients 3.4 ± $1.3x10^8$	Aspiration pneumonia and sepsis in 1 patient; Recurrent stroke (1)
Freidrich, 2012[13]	20 (mean 63, 30-78 yo)	Autologous BM-MNC	IA	Mean $22x10^7$ ($5.1x10^7$-$60x10^7$)	Pneumonia (3), UTI (2), and DVT (2)
Savitz, 2011[8]	10 (55 ± 15 yo) : 79 (63 ± 12 yo)	Autologous BM-MNC	IV	8 patients given $1x10^7$ cells/kg; 2 patients given $7x10^6$ cells/kg and $8.5x10^6$ cells/kg	Elevated transaminases enzymes (2 patients)

RCT: Randomized controlled trial; UC-MSC: Umbilical cord-mesenchymal stem cells; BM-MNC: Bone marrow-mononuclear stem cells; IA: Intraarterial; IV: Intravenous, ROA: Route of administration; UTI: Urinary tract Infection; DVT: Deep venous thrombosis; AST: aspartate aminotransferase; ALT: alanine aminotransferase

*only in intervention group

improvement in NIHSS at 1 month with mean NIHSS 11.6 ± 4.8 compared to baseline NIHSS 16.3 ± 3.3 in 11 patients. Non-significant improvement was also observed in mRS and BI, but none had mRS ≤ 2.[15] At 3 months after stem-cells infusion, 4/8 (50%) patients achieved mRS ≤ 1 with baseline NIHSS 8-14.[13] Meanwhile at 6 months, 8/10 (80%) patients achieved mRS ≤ 1 with baseline NIHSS 8-14.[12,13] Another study showed changes of mRS of at least 1 point at 6 months was observed in 9/9 (100%) patients, with 5/9 (55,5%) patients achieved mRS 0-2.[8] BI showed improvement in 6 months with 7/9 (77.7%) patients achieved BI ≥ 90 in the report by Savitz *et al*.; and also significant improvement in the report by Bhatia *et al*.[8,12] However, the improvement of mRS, BI, and NIHSS at 6 months was not significant compared to control group, and so did at one year followed-up.[12,14]

Significant improvements compared to control group were shown in some studies. Taguchi *et al*. showed that NIHSS at 7 days after onset

improved significantly.[15] Moreover, improvement at 3 months also observed in median mRS was shown by Vahidy *et al*, and better mRS in 9/10 (90%) stem-cells treated patients in Savitz *et al*.[8,16]

Studies using MSC gave different results. At 3 months, 2/3 of patients had improved mRS at 3 months (from 4-5 to 3), but no other improvement in 6 months.[11] Another study showed that at 6 months there were no significant differences among groups but at 2 years, significant differences were observed in motor-NIHSS (5.14 vs 2.53, control vs MSC group, $p = 0.03$), while NIHSS as global score, BI and mRS did not show differences as compared to control.[10]

Structural improvement

Only several studies evaluated improvement in structural changes, using varied radiology modality. Savitz *et al*, showed that improvement was observed at 1 month after cell infusion which evaluated using MRI, with IER (infarct expansion ratio) reached 0.9 ± 0.2 ($p < 0.05$).[8] Other studies had improvement at 3 and 6 months in terms of infarct size evaluated using MRI, but the results were not statistically significant.[14] At longer time-frame, functional-MRI was used for evaluation, and revealed significant improvements in MI-4a and MI-4p at 6 months ($p=0.04$ and $p=0.03$, respectively) and at 2 years ($p=0.031$ and $p=0.002$, respectively).[10] Significant improvement was also seen in terms of relative fractional anisotropy (using MRI-DTI (Diffusion Tensor Imaging) between ipsilesional and contralesional of rostral pons at 2 years compared to 1 month after infusion, but control group was not included in analysis.[16] A study using SPECT and PET-scan at 6 months followed up revealed that there was improvement in $CMRO_2$ at ipsilesional hemisphere compared to 1 month. But, they also revealed that $CMRO_2$ at contralesional also improved. Moreover, CBF improved in contralesional but none at ipsilesional hemisphere.[15]

DISCUSSION

The infusion of stem cells for acute ischemic stroke has been shown to enhance clinical and structural outcomes in this comprehensive study. The advantages of MNCs and MSCs were slightly different in this study. This could be due to differences in the contents, dosages, routes and timing of stem cell injection.

Onset to stem-cells infusion is one of the important factors in study outcome. An animal study demonstrated that injection of BM-MNC at 3 hours post-infarct gave barely detectable difference in infarct lesion and injection within 72 hours after ischemic onset was able to give significantly smaller infarct size compared to control group.[20] At longer time period, de Vasconcelos *et al*. showed that BM-MNC injection at 7 days post-infarct was still able to give significant results compared to control group, but 14 days post-infarct did not yield significant results.[21] Comparison between BM-MNC and BM-MSC were also evaluated and yielded significant results compared to control group, but insignificant when compared to one other, though BM-MNC gave better improvement.[21] Quite similar results were reported in our review. Stem-cells infused at 24-72 hours post-stroke gave significant results in terms of mRS, one study showed improvement structurally by 1 month and augmented over time.[8,16] Furthermore, infusion around 7 days post-stroke yielded different results among different studies, one study showed significant results of NIHSS in a week post-infusion compared to control, but others resulted in insignificant improvement of mRS or BI at longer time frame, or significant only compared to baseline.[10,12-16] Other studies infused at around 2-5 weeks gave insignificant results.[11,14] In Jaillard study, there was an improvement specifically for motor-NIHSS at 2 years, but not in earlier time-frame.[10] Structurally, improvement in early time-frame (6 months) was observed in the study evaluated using MRI.[10]

Route of administration was another consideration. In murine studies comparing intraarterial and intravenous human BM-MNC showed that intravenous stem-cells injected 48 hours after stroke resulting in significant improvement at 30 days structurally and behaviorally.[22] In contrast, intraarterial injection only showed significant behavior improvement (insignificant in structural evaluation) when injected with $1x10^4$ cells dose (but not in higher or lower dose).[22] It had been also been confirmed with murine stem-cells injected intraarterially, that gave insignificant results in all alternative doses.[22] Another murine study showed significant improvement in terms of sensorimotor function when BM-MNC was injected intraarterial and intravenously at 24 hours post-stroke evaluated within 7 days post-stroke.[23] Better improvement was seen in intravenous as compared to intraarterial route, but the difference was not significant.[23] Compared with 3 studies in our review which used BM-MNC and infused at around 1 week post-stroke, better results seemed to favor intravenous route rather than intraarterial route.[10,12-16] Significant improvement could be seen with infusion at earlier time-point as compared to

control.[15] However, there is not enough evidence to conclude intravenous route would result in better outcome.

Dosages might be another factor affecting the effectiveness of stem-cells. In these studies, different dosages were used regardless of stem-cells's type or its route. Nonetheless, dosage used in all studies were comparable with only slight differences observed, whether it was administered intraarterially or intravenously.

To date, there is no clinical study exclusively comparing the use of MSC and MNC in ischemic stroke. However, several studies have been done in rats or in different population, such as heart disease or another brain disease. Chung *et al*. showed that umbilical cord blood MNC gave significant axon survival rate observed in optic nerve crush-injury rat models, but not in chorionic plate-derived MSC.[17] Another study comparing BM-MNC and BM-MSC in chronic myocardial infarct rat models showed favorable results in BM-MSC, it gave significantly better improvement than BM-MNC.[18,19] None of these studies use ischemic stroke population. Moreover, only few studies of MSC were included in this review, therefore it is difficult to conclude whether one is better than the other. Future clinical study comparing the use of MSC and MNC is needed.

In measuring safety outcome of stem-cells therapy, all studies revealed no adverse events caused by stem-cells infusion, either immediately after infusion or during followed-up.[8,10-16] These findings was supported by other studies using similar stem-cells which yielded no significant adverse events observed as in clinical or preclinical study. Infusion of MSC either from umbilical cord, autologous or allogenic bone marrow, for acute myocardial infarction and ischemic heart failure did not show any significant adverse event in acute time frame (<24 hours).[24] However, significant neurological adverse events were reported in more than 24 hours after infusion, but there was no details given.[24] Recurrent stroke was reported in this review, but it was inconclusive whether it was caused by stem-cells infusion or due to other causes.[15,16] No significant adverse event was also reported in BM-MNC studies.[25] In clinical chronic stroke ischemic studies evaluated in meta-analysis, there was no significant mortality outcome compared to control group, using either BMMNC or MSC.[26] It is consistent with this review which showed that mortality occured, but probably not directly related to stem-cells injection.[8,12-14,16] These are consistent with structural evaluation using varied modalities which showed no new infarct or significant tumor growth.[12-14] Thus, administration of stem-cells either BMMNC or MSC in acute time-frame is relatively safe.

Several limitations appeared in this review. There were only a few studies of MSC in acute ischemic stroke, thus it was difficult to compare both type of stem-cells. The included studies had small sample sizes, ranging between 3 to 59 patients in intervention group. Second, large difference of ages were reported, between 30 and 79 years. Third, the onset of implantation has large variation from 24 hours to 40 days. The dose of stem cells used in each study is very different. Not all studies did radiologic evaluation and some of the studies which had imaging evaluation only reported adverse event, not improvement of stroke lesion. Different functional measurements were used (NIHSS, BI and mRS) with differing baseline severity.

In conclusion, mesenchymal and mononuclear stem-cells have been studied for years in animal and give favorable prospect for its use in the clinical settings of acute ischemic stroke. This review show that these stem-cells therapy are safe to use; thus widening the scope of stem-cell therapy to be an alternative treatment if other definitive measures could not be done or not available. However, the effectiveness of these stem-cell therapy may be different according to the onset of infusion time, with earlier administration giving better results. Future studies of MSC or MNC given in less than 1 week, comparing both types of stem-cells is needed.

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DISCLOSURE

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