Stem Cell Therapy in Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Amit Kumar, Dimple Rawat, Kameshwar Prasad

Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Abstract

Background and Objective: Stem cell therapy has emerged as a potential therapy for the treatment of stroke. We performed a systematic review and meta-analysis of published randomized controlled studies using various types of stem cell therapies in patients with ischemic stroke (IS). **Method:** Literature search was carried out using PubMed, Google Scholar, Cochrane library, and clinicaltrial.gov to identify studies on stem cell therapy in IS from its inception till January 2020. Data were extracted independently by two reviewers. STATA version 13 was used for carrying out meta- analysis. We included only randomized controlled trials (RCTs) if any of the stem cell therapy was used to treat patients with IS in any phase after the index stroke. **Results:** We included a total of eight randomized controlled studies involving 459 subjects (217 intervention and 242 controls) in the meta-analysis. We did not observe statistically significant reduction in mean NIHSS score in the intervention group (SMD - 0.34, 95% CI - 0.76 to 0.08) in patients with acute or sub-acute stroke. However, a statistically significant reduction (SMD - 1.57, 95% CI -2.22 to -0.92) was observed in patients with chronic ischemic stroke. Statistically non-significant reduction in mean mRS in the intervention group (SMD 0.04, 95% CI -0.20 to 0.28) in patients with acute or sub-acute ischemic stroke was observed, however a statistically significant reduction (SMD - 1.07, 95% CI - 1.94 to -0.19) was noted in patients with chronic stroke. We did not observe statistically significant reduction in mean Barthel index score (SMD 0.24, 95%CI -1.69 to 2.17) in chronic stroke. Statistically non-significant lower mortality rate was observed in intervention group compared to controls (Risk Ratio 0.84, 95% CI 0.43 to 1.66) among acute or sub-acute, as well as in the chronic stroke group (Risk Ratio 0.47, 95% CI 0.20 to 1.09). **Conclusion:** Our meta-analysis provides no clinically important evidence for efficacy of stem cells in reducing neurological deficit compared to control group. Well-designed large randomized controlled trials are required to provide more information on the efficacy of stem cell therapy in patients with IS.

Keywords: Ischemic stroke, randomized control trial, stem cells, stem cell therapy

Introduction

Stroke has emerged as the second most leading causes of death and disability worldwide but unfortunately, there are limited therapeutic options. Although thrombolysis and thrombectomy are promising therapeutic options in the acute phase of stroke, it caters to only a limited number of patients owing to the lack of availability and performance ability in the low to middle income countries. The past four decades of preclinical research has demonstrated that stem cells posses various properties and abilities like survival, homing into the affected areas of brain, secretion of molecule to promote neurogenesis, angiogenesis and synaptogenesis. These functional integration and behavioral effects of infused stem cells have formed the basis for conducting clinical trials on stem cell therapy in stroke. Despite the fact that safety of stem cell has been well established in clinical trials, its effectiveness to improve the outcome is yet to be proven. Several types of stem cells like bone marrow mononuclear stem cells, mesenchymal stem cells, umbilical cord blood stem cells have been used in clinical research. Genetically modified stem cells like SB623, multipotent adult progenitor cells (MAPCs), and neural stem cells have been used to prove its efficacy in improving the neurological outcome after the stroke. However, the studies have been conducted with smaller sample size and

contain substantial heterogeneity due to the differences with respect to the types of stem cell used, route of administration and dosages. For justifying and panning future trials, it is necessary to combine and contrast the studies to determine if there is any overall benefit with the use of stem cells and whether the benefit is a function of a particular type of stem cell. Meta-analysis is a powerful tool for combining the results to estimate the overall effects of an intervention and permits determination of factors influencing the effect through meta-regression. As the most reliable method to determine the safety and efficacy of any intervention is randomized controlled trial; therefore, we have conducted

Address for correspondence: Prof. Kameshwar Prasad,
Department of Neurology, Room No. 602, 6th Floor, Neurosciences Centre,
Ansari Nagar, AIIMS, New Delhi - 110 029, India.
E-mail: kp0704@gmail.com

a meta-analysis to determine the safety and efficacy of stem cell therapy in patients with ischemic stroke elucidated in randomized controlled trials.

METHODS

We followed the preferred reporting items for systematic review and meta-analysis (PRISMA) statement for conducting meta-analysis.

Search strategy

We searched the PubMed, Google Scholar, Google, Web of Sciences, Clinical Trial Registry, Cochrane Library from inception until January 2020 for randomized controlled trials dealing with stem cell therapy for patients with ischemic stroke. The following search terms were used.

(#1) "Stroke" or "ischemic stroke" or "CVD" or "cerebral infarct" or "ischemic stroke" or "Brain Stroke".

(#2) "Stem cell" or "stem cells" or "Cellular Therapy" or "Regenerative medicine" or "Bone marrow mononuclear cells" or "Mesenchymal Stem cell" or "Peripheral blood cell" or "Induced Pluripotent stem cell" or "Embryonic stem cell" or "Neural stem cell" or "mononuclear cell".

(#3) "intervention" or "infusion" or "transplantation" or "therapy".

(#4) #1 AND #2 AND #3 AND #4 (filters: "Human" AND "randomised controlled trial")

Apart from the above-mentioned strategy, further manual search was done to identify any further published study via screening the reference lists of relevant papers and reviews.

Selection criteria

The studies were included if they fulfilled the following criteria.

Inclusion criteria

a. Studies conducted on autologous bone marrow mesenchymal stem cell, mononuclear stem cells; multipotent adult progenitor cells; peripheral blood stem cells.
b. Studies that defined the ischemic stroke in accordance with the World Health Organisation criteria including both acute/subacute and chronic stroke
c. Sufficient outcome data were available to be extracted for pooled analysis
d. Studies used randomized controlled trial as study design.

Exclusion criteria

a. Studies which used methods other than randomized controlled trial as study design
b. Meta-analysis, case report or case series
c. Studies conducted on animals
d. Multiple reports from the same study in which earlier reports were excluded.

Data extraction

Two independent investigators AK and DR searched the literature according to the inclusion/exclusion criteria of the study and extracted the relevant baseline and outcomes data. Relevant data for the present study as for example author name, year of publication, study design, type of stroke, sample size, mean age, route of stem cell therapy, type of stem cell, follow-up duration and dose were extracted. Risk of bias assessment was done using the Cochrane Systematic Review Guidelines.

Statistical analyses

The effect measure used in the meta-analysis was risk ratio. Pooled risk ratio with 95% confidence interval was computed using the Mantel Hansel statistics for the categorical variables. Pooled standardized mean difference with 95% confidence interval was used for the continuous variables. Heterogeneity was assessed using the I^2 statistics. Fixed-effect model was used if heterogeneity was less than 50% otherwise random effects model was used. Meta-regression analysis was done to examine the source of heterogeneity. Publication bias was not assessed as number of studies was not more than ten in any of the outcome to meet the assumptions for assessing the publication bias. Methodological quality of studies was assessed by the Guidelines recommended by the Cochrane guidelines. All the statistical analyses were conducted using the RevMan version. 5.1 and STATA software version 13.
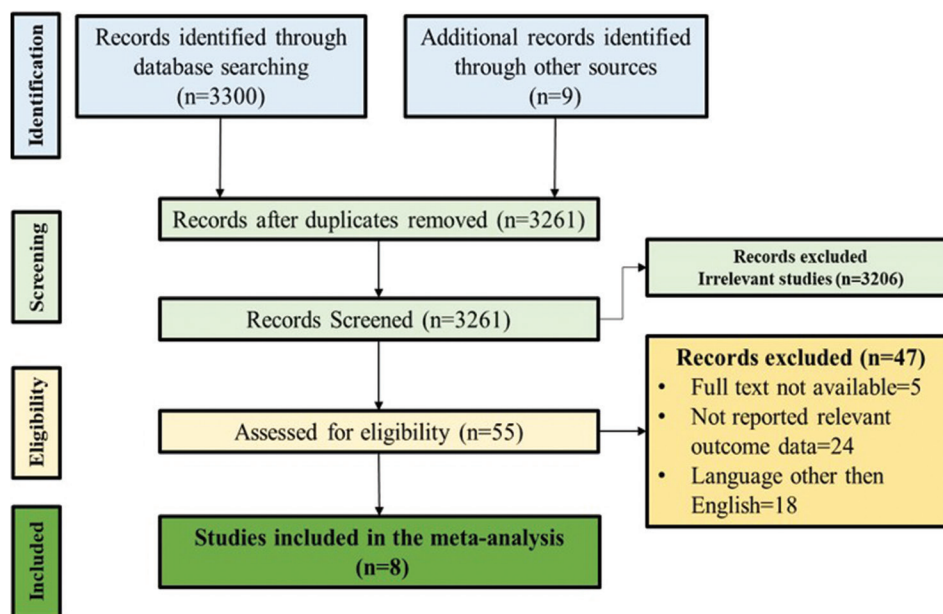
RESULTS

Study Characteristics

For the present meta-analysis our initial search identified 3309 studies using the database searching and thorough manual search strategies. Forty-Eight duplicate references to the same papers were removed manually. After reading the titles and abstracts of remaining articles with irrelevant topics or not fulfilling the selection criteria were excluded, resulting in a potential total of 55 articles.

After reading full text of all available articles among 55, eight articles were eventually included. Hence, the present meta-analysis is based on that eight studies that were ultimately included [Figure 1].

In the present meta-analysis two studies from India[1,2] two from Korea,[3,4] three from China[5–7] and one study from USA[8] are included. Among all included studies, four studies[1,2,5,7] used mononuclear stem cells; two studies[3,4] used mesenchymal stem cells, one study[8] used multipotent adult progenitor cell and one study[6] used peripheral blood stem cells. In addition, one of the eight interventions were performed in patients with acute stroke[8]; three with sub-acute stroke[1,2,7] and four with chronic stroke.[3–6] Furthermore, four of eight treatments were administered via the Intravenous route[2–4,8] followed by three subarachnoid[5–7] and one with intra-arterial.[1] The duration of follow-up ranged from three-month[7] to 7 years.[5] Different number of doses were given to the intervention group in the studies included in the present meta-analysis ranging from 10 million to 15 µg/kg/day. Detailed characteristics have been given in Table 1.

Figure 1: Study Flow Diagram (Results of data base searches)

Methodological quality of study

Summary of each risk of bias item for each included study is given in Figure 2. Each risk of bias item presented as percentages across all the included studies is given in Figure 3.

Random Sequence generation

All trials stated randomized-controlled trial as study design. Among all included trials, six[2–4,6,7,8] specified the randomization method and hence we judged them at low risk of bias. Two studies[1,5] were classified as unclear risk of bias for the random sequence generation because they did not report which method of randomization was used.

Allocation concealment

In six trials[1,2,5–8] allocation was concealed adequately and were judged at low risk of bias. Two studies[3,4] did not report the information about the allocation concealment, therefore classified as unclear risk of bias for allocation concealment [Figure 2].

Blinding of participants and personnel (Performance bias)

Two trials[7,8] were blinded to both participants and trial personnel hence, judged at low risk of bias for performance bias. All the other studies[1,2,3–6] included in the meta-analysis were judged high risk of performance bias because of blinding of participants and personnel were not performed.

Blinding of outcome assessment (detection bias)

Among all eight trials, only one trial[5] did not report whether outcome was assessed by blind assessor and hence it was judged at high risk of bias.

Incomplete outcome data

All eight trials stated the data of lost to follow-up. In Bang 2005,[4] 40% of controls were lost, and hence judged at high risk of bias, and remaining seven trials at low risk of bias.

Selective reporting

Among eight trials, three[1,8,5] were considered at high risk of bias, as two trials[1,8] did not report, primary outcomes in the published study whereas, in one trial[5] the outcomes listed in the method section were different from those reported in the results.
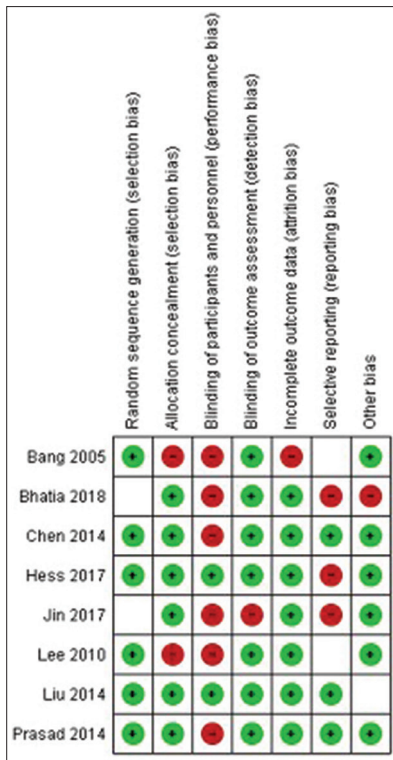
Other risk of bias

One study[1] classified as high risk of bias due to data for 22 subjects randomized between day 15 and 28 days was not available in the published study.

Efficacy Outcomes

Heterogeneity

We used random-effects model because significant clinical and statistical heterogeneity was observed in the pooled analysis ($I^2 = 67\%$, $P = 0.03$) for outcome NIHSS among acute or sub-acute [Figure 4a], however a fixed-effect model was used because no significant heterogeneity was observed in the pooled analysis ($I^2 = 0\%$, $P = 0.68$) among chronic stroke [Figure 4b]. For outcome mRS, no significant heterogeneity was observed in the pooled analysis ($I^2 = 0\%$, $P = 0.43$) among acute or sub-acute hence, a fixed-effect model was used [Figure 4c]; however, a random-effects model was used for chronic stroke because significant heterogeneity was observed ($I^2 = 72\%$, $P = 0.03$; Figure 4d). To determine the difference in Barthel Index between the intervention and control group, we used random-effects model because significant heterogeneity was observed in the pooled analysis ($I^2 = 93\%$, $P < 0.001$) for subjects with chronic stroke [Figure 4e]. For mortality, we used fixed-effect model for acute/sub-acute and chronic stroke due to non-significant heterogeneity ($I^2 = 20\%$, $P = 0.29$) [Figure 4f and 4g].
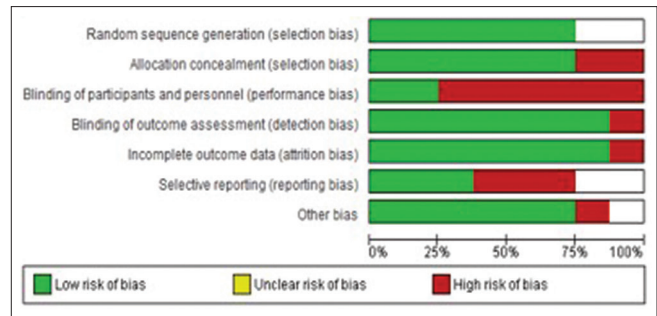
Figure 2: Risk of bias summary based on Cochrane Systematic Review Guidelines for each included study (green for low risk of bias, blank for unclear risk of bias and red for high risk of bias)

Figure 3: Risk of bias graph review authors judgements about each risk of bias item presented as percentages across all included studies

Functional outcome NIHSS: Six studies reported the NIHSS outcomes at the end of follow up involving 377 participants (191 intervention group and 186 in control group). Among all six studies, four studies were on acute or sub-acute stroke involving 327 participants (166 intervention group and 161 in control group) which did not show a statistically significant reduction in follow up NIHSS in the intervention group as compared to control group (SMD - 0.34, 95% CI -0.76 to 0.08, $P = 0.11$) [Figure 4a]. However, two studies which were on chronic stroke involving 50 participants (25 intervention group and 25 in control group) showed a statistically significant reduction in follow up NIHSS in the intervention group compared to controls (SMD -1.57, 95% CI -2.22 to -0.92, $P < 0.001$) [Figure 4b].

Functional outcome mRS: Six studies reported the mRS outcome at the end of follow up involving 371 participants (178 intervention group and 193 in control group). Among all six studies, three studies were on acute or sub-acute stroke involving 269 participants (137 intervention group and 132 in control group) and they did not show statistically significant difference in mRS outcome at the end of last follow up between the intervention group and the control group (SMD 0.04, 95% CI -0.20 to 0.28, $P = 0.76$) [Figure 4c]. Three studies conducted on chronic stroke involving 102 participants (41 intervention group and 61 in control group), showed statistically significant reduction in the mRS in the intervention group compared to control (SMD -1.07, 95% CI -1.94 to -0.19, $P = 0.02$) [Figure 4d].

Barthel Index: In the present meta-analysis only four studies reported the BI outcomes at the end of the follow up period involving 200 participants (95 intervention group and 105 in control group). Among four studies, three were on chronic stroke involving 80 participants (35 intervention group and 45 in control group), which did not show a statistically significant improvement in the intervention group compared to control (SMD 0.24, 95% CI -1.69 to 2.17, $P = 0.81$) [Figure 4e].

Mortality outcome: Mortality was reported in six studies, at the end of follow up period involving 371 participants (178 intervention group and 193 in control group). Among six studies, three studies were on acute or sub-acute stroke involving 269 participants (137 intervention group and 132 in control group). Meta-analysis showed a statistically non-significant lower mortality rate in intervention group compared to controls among acute/subacute stroke (Risk Ratio 0.84, 95% CI 0.43 to 1.66, $P = 0.62$) [Figure 4f], as well as in studies conducted on chronic stroke involving 102 participants (41 intervention group and 61 in control group) with a Risk Ratio 0.47, 95% CI 0.20 to 1.09, $P = 0.08$) [Figure 4g].

Subgroup Analysis
We did a subgroup analysis to determine the variation in the effect size associated with moderator variables on ischemic stroke outcomes using meta-regression analysis. We observed the significant effect of moderator variable (route of stem cell intervention) on NIHSS outcome in favor of subarachnoid route (r = -0.56, t = -4.39, $P = 0.012$) [Figure 5a]. The similar trend was also observed for the outcome mRS, favoring the subarachnoid route of intervention ($P = 0.010$) Figure 5b. Meta regression analysis was performed keeping time of stem cell intervention as a moderator variable suggested that better outcome in chronic stroke subjects for outcome NIHSS (r = -0.79, t = -3.16, $P = 0.034$) [Figure 5c]. However, for outcome mRS we did not observe the significant effect in time to intervention of stem cells [Figure 5d]. We did not observe the significant effect of moderator variable (types of stem cell infusion) on outcome NIHSS and mRS [Figure 5e and 5f].

Summary results
We did not observe the statistically significant effect of stem cells intervention in improvement of neurological outcome measured by NIHSS and mRS for acute/subacute stroke,

Table 1: Summary of the published Randomized control clinical trial on stem cell therapy in Ischemic Stroke

Author and year	Country	Study Design	Type of stroke	Sample Size (Intervention/Control)	Mean Age (Intervention/Control)	Route	Stem Cell	Follow-up	Outcome	Dose	Time Window (Post Stroke)
Bhatia 2018[1]	India	Open-label, blinded-end point	Subacute	10/10	57±12.2 and 66±7.3	Intra-Arterial	BM-MSCs	6 months	mRS, BI, NIHSS	5 X 10⁸ cells	8-15 days
Hess 2017[8]	USA	Double-blind, placebo-controlled, RCT	Acute	67/62	61.8±11.4 and 62.6±11.4	Intravenous	MAP	12 months	mRS, BI, NIHSS	12 X 10⁷ million total cells	24-36 hours
Jin 2017[5]	China	RCT	Chronic	10/10	ND	Subarachnoid	BM-MSCs	7-year	mRS, BI, NIHSS	~10⁷ cell	3 weeks to 3 months
Chen 2014[6]	China	Single blinded, RCT	Chronic	15/15	50.1±7.7 and 52.8±9.0	Subarachnoid	PBSCs	12 months	NIHSS, mRS European Stroke Scale, and European Stroke Scale Motor Subscale	15 μg/kg/day for 5 consecutive days	6 months to 5 year
Liu 2014[7]	China	RCT	Subacute	29/29	55.3±3.6 and 56.9±4.4	Subarachnoid	BM-MSCs	3 months	CNS, NIHSS, FMA	1×10⁷/kg (4 cycles)	1 day to 4 weeks
Prasad 2014[2]	India	Single blinded, RCT	Subacute	60/60	50.7±11.6 and 52.5±12.1	Intravenous	BM-MSCs	12 months	NIHSS, BI and mRS	280.75 million	7 days to 30 days
Lee 2010[3]	Korea	Single blinded, RCT	Chronic	16/36	64.0±11.6 and 64.9±14.5	Intravenous	MSCs	12 months	mRS	5×10⁷ (2 cycles)	4 weeks to 5 weeks
Bang 2005[4]	Korea	Single blinded, RCT	Chronic	10/20	63.0±7.5 and 59.3±11.5	Intravenous	MSCs	12 months	NIHSS, BI, mRS	5×10⁷ (2 cycles)	32 days to 61 days

RCT-Randomized Control Trial; mRS-Modified Rankin Scale; BI-Barthel Index; NIHSS-National Institutes of Health Stroke Scale; BM-MSCs-Bone marrow mononuclear stem cells; MAP-Multipotent adult progenitor cells; PBSCs-Peripheral blood stem cells; MSCs- Mesenchymal stem cells; ND-Non determined; CNS-Clinical nerve function limitation scores; FMA-Fugl Meyer assessment
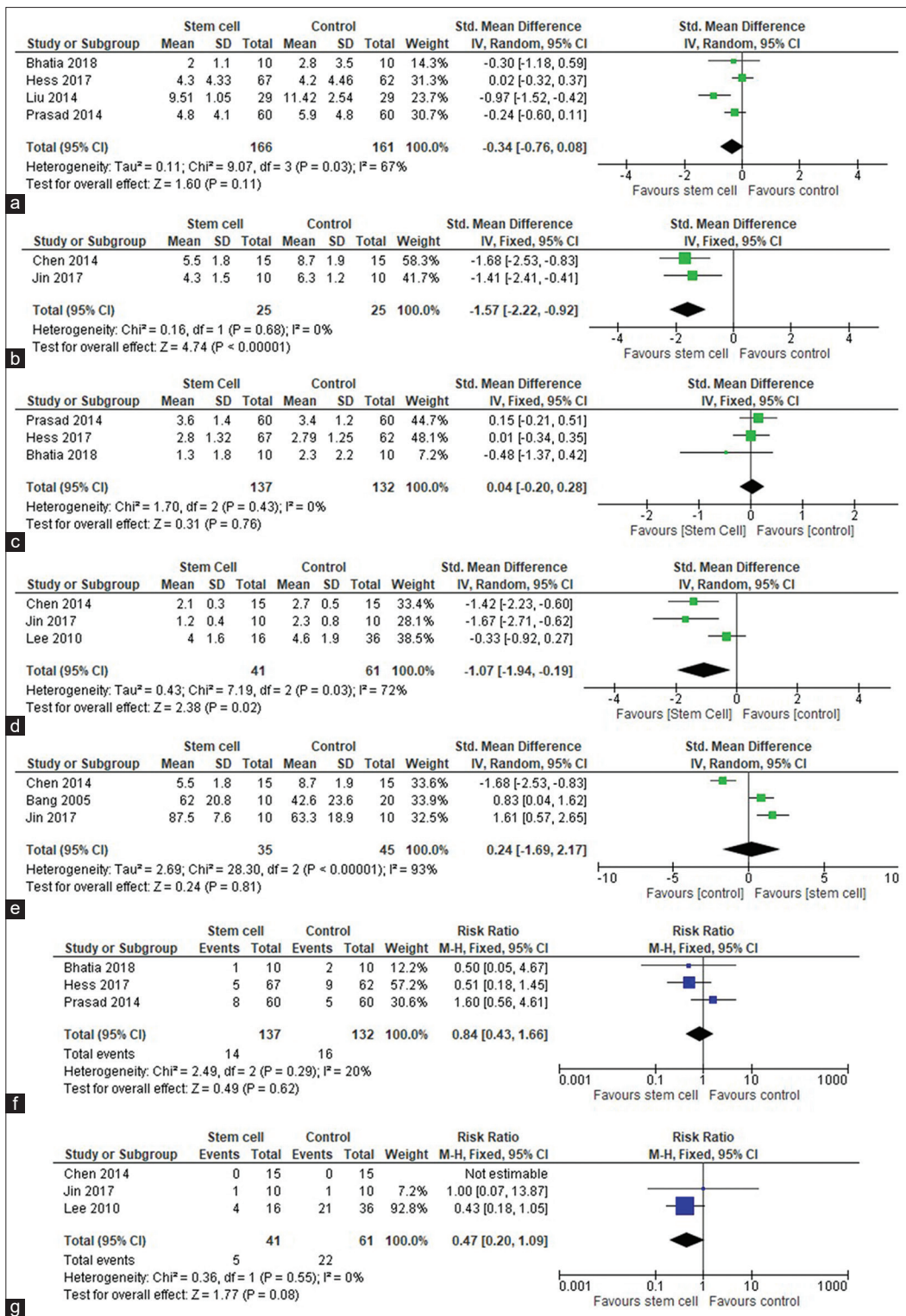
Figure 4: (a) Forest plot of NIHSS, fixed-effect model at last follow up between Intervention group (stem cell therapy) and control group in Acute or Sub-acute Stroke. (b) Forest plot of NIHSS, fixed-effect model at last follow up between Intervention group (stem cell therapy) and control group in Chronic Stroke. (c) Forest plot fixed-effect model, comparing standardized mean difference for mRS at last follow up between Intervention group (stem cell therapy) and control group in Acute or Sub-acute Stroke. (d) Forest plot, random-effects model, comparing standardized mean difference for mRS at last follow up between Intervention group (stem cell therapy) and control group in Chronic Stroke. (e) Forest plot, random-effects model, comparing standardized mean difference of Barthel Index at last follow up between the Intervention group (stem cell therapy) and control group in Chronic Stroke. (f) Forest plot, fixed-effect model, comparing mortality at last follow up between Intervention group (stem cell therapy) and control group in Acute or Sub-acute Stroke. (g) Forest plot, fixed-effect model, comparing mortality, at last, follow up between Intervention group (stem cell therapy) and control group in Chronic Stroke
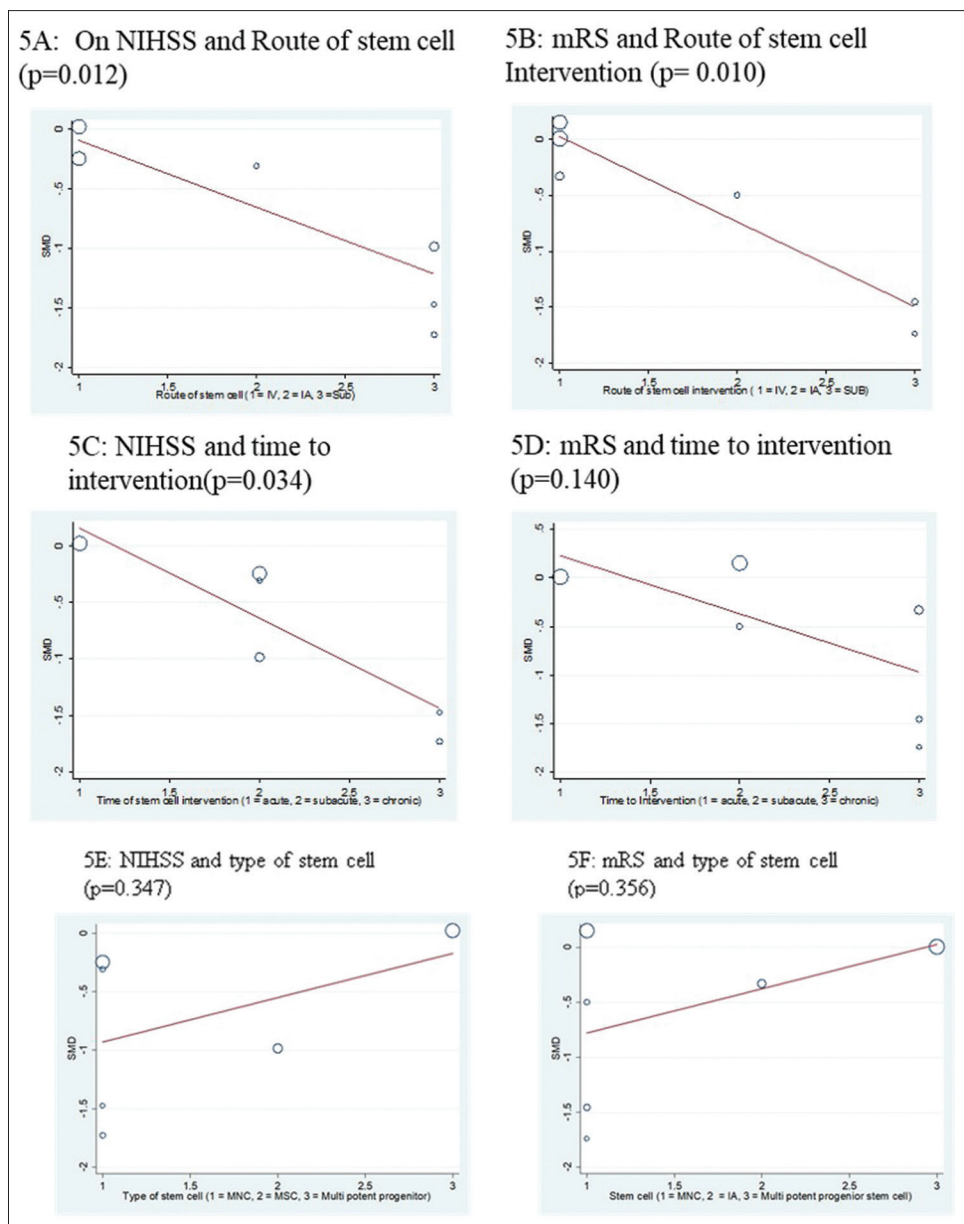
Figure 5: (a-f) Meta-regression Analysis to assess the heterogeneity explained by the different independent variables

however, a significant improvement was noted in case of chronic stroke. Barthel index score did not differ significantly between both the groups for chronic stroke. Statistically non-significant lower mortality rate was observed in the intervention group compared to controls among patients with acute or sub-acute stroke, as well in chronic stroke.

Discussion

We have conducted a meta-analysis involving reported RCTs to determine the precise evidence associated with Stem cell therapy for treatment of Ischemic Stroke. Stem cell therapy is emerging as a potential therapeutic option for treatment of Ischemic stroke.

Pre-clinical studies have shown the consistent efficacy of stem cell for treatment of stroke. A meta-analysis involving 64

studies on preclinical studies strongly supports the translational potential of stem cell therapy for ischemic stroke.[9]

The first stem cell therapy using neuroterocarcinoma cells that transformed into postmitotic neurons infused in patients with stroke conducted by Kondziolka *et al.* in 1998, provided the preliminary data on safety, feasibility, and tolerability of stem cell therapy in human following which, several studies reported in this direction. More than six thousand trials are registered with online clinical registry trial website (https://clinicaltrials. gov/) involving several types of stem cells, addressing many types of disorders and diseases. Out of which 44.5% have been completed[10]

A pilot study published by our group consisting of 11 patients showed intravenous bone marrow mononuclear cell therapy

is feasible and safe without having any tumor formation at one year follow up period. A meta-analysis involving single arm studies which included 14 studies have shown that stem cell therapy has potential to improve outcome after stroke. However, the finding of this meta-analysis should be read with caution as there was no control group. We need a control group to determine the efficacy as recovery from stroke is well recognized in its natural disease history. There are several types of effects like Hawthorne effect, placebo effect that may lead to biases which may result in false positive effect associated with intervention. The most reliable method to determine the efficacy and safety of interventional products is a randomized controlled trial. Our largest randomized controlled trial using intravenous infusion of autologous bone marrow derived stem cells therapy appeared safe and feasible but did not improve neurological outcome compared to control group.[2] A double blind, placebo-controlled, phase II randomized controlled trial (MASTER) showed that multipotent adult progenitor cells is safe and well tolerated in patients with acute ischemic stroke, however it, did not demonstrate any beneficial effect in improvement of neurological outcome compared to control. Another randomized controlled trial which included 48 subjects within 8-15 days of stroke, noted that intra-arterial infusion does not improve the outcome at 12 months after stem cell infusion.[1] A large phase III trial (PISCES) on genetically neural modified stem cells is ongoing in which, multi countries are expected to be involved to determine the efficacy of neural stem cell in patients with ischemic stroke.[11] Another, Phase II study using genetically modified stem cells (SB623) in ischemic stroke was recently completed and results are awaited.[12]

Our meta-analysis involving eight studies have not shown any significant difference in NIHSS, mRS, BI scores, and mortality between the stem cell and control group in acute or subacute stroke category. In case of chronic stroke, NIHSS was statistically significantly lower in the stem cell group compared to control group [Figure 4b], however, this finding is based on only two studies which were conducted in the Chinese population. Significant improvement was also noted for the outcome mRS in the intervention group as compared to control group in the studies conducted on chronic stroke. However, we cannot exclude the type I error associated with this finding. There is clear need to conduct more studies to obtain the precise estimate of evidence in order to determine the efficacy of stem cell therapy in patients with ischemic stroke whereas, earlier reported meta-analysis included non-randomized clinical trials, we included only randomized controlled trial in order to improve the overall quality of studies to determine the precise evidence associated with stem cell intervention. The findings of this meta-analysis will help in designing the future randomized controlled trials in this direction. There are several points need to be discussed in this direction.

Route of stem cell infusion: Our meta-regression analysis suggests that sub-arachnoid route is superior in improving the outcome [Figure 5a,5b], however, we cannot exclude the false positive finding (Type 1 error) in this observed effect as sample size was small in the subgroup analysis. While intravenous route is easy and less invasive, most of the infused stem cells are trapped in internal organs such as lungs and kidney, limiting the homing of stem cells to brain area and thus, requires higher cell volume. On the other hand, other routes like intra-arterial/sub-arachnoid allow more localized delivery in order to home the stem cells to the vascular territory and infarcted area and therefore affords the use of lower cell volumes. Safety of intra-arterial delivery of bone marrow derived mononuclear stem cell in patients with ischemic stroke has been shown in earlier published study.[1] Small size stem cell like bone marrow mononuclear cell which range from 7 μm associated with less risk for vascular obstruction. On the contrary, bigger size stem cells like neural stem cells (size 13–15 μm), mesenchymal stem cells (size over 25 μm) impose risk for vascular obstructions.[13] A preclinical study noted that safety concern (e.g., micro thrombi formation, decreased cerebral blood flow) and concluded that both infusion velocity and cell dose is associated with complication following stem cell infusion via intra-arterial route.[14] It cannot be denied that although the intra-arterial infusion of cells is an invasive method, it helps in homing of stem cell in the infarcted area with less risk compared to direct intra-cerebral transplantation. Intracerebral route is difficult to execute during acute phase due to risk of hematoma formation, which further increases the risk for bleeding in brain. The most effective route of intervention still needs to be explored.

Types of stem cells: We did not observe any obvious effect of any particular type of stem cell and outcome in our meta-regression analysis [Figure 5c,5f] although we could not exclude the Type II error due to insufficient sample size for subgroup analysis. No beneficial effect of bone marrow derived mononuclear cell therapy on stroke outcome has been noted in large multicentric randomized controlled trial.[2] There are various types of stem cells through various routes are underway that may shed a light on potential types of stem cells for improving outcome after stroke. A phase-II randomized, double blind, placebo controlled multi-center study involving 33 centers in UK and USA conducted by Hess *et al.* showed that multi-potent adult progenitor cells injected through intravenous route appeared safe and well tolerated in patient with acute ischemic stroke. A phase 1/2a open label single arm study on chronic stroke showed two-year safety and improvement in clinical outcome at 12 months after infusion of genetically modified bone marrow derived mesenchymal stem cells (SB623). A recently completed phase II double blind, sham surgery randomized controlled trial conducted by same group would provide more insight about efficacy of SB623 cells in patients with chronic stroke.[4] Another promising single arm study conducted on 13 subjects using CTX-DP a drug product of immortalized human neural stem cell line showed that single intracerebral doses up to 20 million has no safety concern and were associated with improved neurological function. Based on this observation a further phase II randomized controlled multi-center study with an

estimated enrolment of 110 participants is underway to test its efficacy on stroke outcome.[11]

Timing of stem cell infusion: Our subgroup analysis did observe statistically significant effect in improvement assessed by mRS and NIHSS on trials conducted at chronic phase of stroke, however number of studies were inadequate for any conclusive findings. Preclinical studies support the early infusion of stem cell to achieve the maximum benefit as indicated by a study which demonstrated that significant reduction in the neurological deficit after using the bone marrow mononuclear cells when infused within the 72 hours, but not at 7 days.[15] A preclinical study observed the dose response gradient between stem cell infusion and structural outcome, decrease in infarct size, with 1.5% decline in efficacy with each day delay in infusion, however it did not observe the same relationship with functional outcome.[16] More clinical trials are required to determine the optimal time for stem cell infusion in patient with ischemic stroke.

Safety: Finding of this meta-analysis suggests that there is no significant difference in the mortality between stem cell infusion group and control group. Adverse events between stem cell and control group were also similar as noted by an earlier systemic review and meta-analysis.[17]

Large number of clinical trials with different type of stem cells and different routes are underway and their results may provide the further precise evidence for role of stem cell therapy on efficacy for patients with ischemic stroke. The results of a recently completed phase II double blinded RCT used modified stem cells SB623[12] is awaited which may show further evidence on efficacy of stem cell treatment is patient with ischemic stroke. An ongoing phase III randomized placebo controlled multi-centric study with an aim to test the efficacy of neural stem cells through intracerebral (stereotactic) route may provide further information on role of stem cell infusion for treatment of ischemic stroke.[11] A meta-analysis published by Kumar A *et al.*, concluded that well-designed randomized controlled trials are required to determine the efficacy of stem cell therapy for patients with ischemic stroke.[18]

Limitation of study

Significant number of Chinese studies published in Chinese language were not included in the meta-analysis due to language barrier and relevant data could not be extracted. Total number of studies were not >10 for any of the outcome measures, limiting us from using funnel plot to determine the publication bias in the present meta-analysis.

Conclusion

The majority of studies included in the meta-analysis are with low to moderate quality of evidence, hence at best provide preliminary efficacy of stem cell therapy in chronic stroke however, small sample size limits our ability to draw any clear conclusion. Therefore, well designed randomized controlled

trials are warranted to determine the efficacy of stem cell for treatment of ischemic stroke.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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