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[Intervention Review]

Stem cell transplantation for ischemic stroke

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ABSTRACT

Background

Stroke is a leading cause of morbidity and mortality worldwide, with very large healthcare and social costs, and a strong demand for alternative therapeutic approaches. Preclinical studies have shown that stem cells transplanted into the brain can lead to functional improvement. However, to date, evidence for the benefits of stem cell transplantation in people with ischemic stroke is lacking. This is the first update of the Cochrane review published in 2010.

Objectives

To assess the efficacy and safety of stem cell transplantation compared with control in people with ischemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched August 2018), CENTRAL (last searched August 2018), MEDLINE (1966 to August 2018), Embase (1980 to August 2018), and BIOSIS (1926 to August 2018). We handsearched potentially relevant conference proceedings, screened reference lists, and searched ongoing trials and research registers (last searched August 2018). We also contacted individuals active in the field and stem cell manufacturers (last contacted August 2018).

Selection criteria

We included randomized controlled trials (RCTs) that recruited people with ischemic stroke, in any phase of the disease (acute, subacute or chronic), and an ischemic lesion confirmed by computerized tomography or magnetic resonance imaging scan. We included all types of stem cell transplantation, regardless of cell source (autograft, allograft, or xenograft; embryonic, fetal, or adult; from brain or other tissues), route of cell administration (systemic or local), and dosage. The primary outcome was efficacy (assessed as neurologic impairment or functional outcome) at longer term follow-up (minimum six months). Secondary outcomes included post-procedure safety outcomes (death, worsening of neurological deficit, infections, and neoplastic transformation).

Data collection and analysis

Two review authors independently applied the inclusion criteria, assessed trial quality and risk of bias, and extracted data. If needed, we contacted study authors for additional information. We performed random effects meta-analyses when two or more RCTs were available for any outcome. We assessed the certainty of the evidence by using the GRADE approach.

Main results

In this updated review, we included seven completed RCTs with 401 participants. All tested adult human non-neural stem cells; cells were transplanted during the acute, subacute, or chronic phase of ischemic stroke; administered intravenously, intra-arterially, intracerebrally, or into the lumbar subarachnoid space. Follow-up ranged from six months to seven years. Efficacy outcomes were measured with the

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National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), or Barthel Index (BI). Safety outcomes included case fatality, and were measured at the end of the trial.

Overall, stem cell transplantation was associated with a better clinical outcome when measured with the NIHSS (mean difference [MD] -1.49, 95% confidence interval [CI] -2.65 to -0.33; five studies, 319 participants; low-certainty evidence), but not with the mRS (MD -0.42, 95% CI -0.86 to 0.02; six studies, 371 participants; very low-certainty evidence), or the BI (MD 14.09, 95% CI -1.94 to 30.13; three studies, 170 participants; very low-certainty evidence). The studies in favor of stem cell transplantation had, on average, a higher risk of bias, and a sample size of 32 or fewer participants.

No significant safety concerns associated with stem cell transplantation were raised with respect to death (risk ratio [RR] 0.66, 95% CI 0.39 to 1.14; six studies, participants; low-certainty evidence).

We were not able to perform the sensitivity analysis according to the quality of studies, because all of them were at high risk of bias.

Authors' conclusions

Overall, in participants with ischemic stroke, stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. No obvious safety concerns were raised. However, these conclusions came mostly from small RCTs with high risk of bias, and the certainty of the evidence ranged from low to very low. More well-designed trials are needed.

PLAIN LANGUAGE SUMMARY

Stem cell transplantation for ischemic stroke

Review question

Is stem cell transplantation safe and more effective than conventional treatments in improving recovery after ischemic stroke?

Background

Stroke represents a leading cause of death and disability worldwide, with very large healthcare and social costs. Available therapies, targeted to restore patency of the blood vessel, consist of intravenous thrombolysis (the breakdown of blood clots formed in blood vessels, using medication) and endovascular mechanical thrombectomy (surgical removal of clot), administered within a few hours of stroke onset, to just a few selected patients. Preliminary studies of stem cell transplantation (injecting cells that may save or replace damaged nerve tissue) could be safe and effective in ischemic stroke. However, information in humans is lacking. This review updates the previous Cochrane Review on this topic ([Boncoraglio 2010](#)).

Study characteristics

We included randomized trials that recruited adults with ischemic stroke, at any time after onset. We included any kind of stem cell or method of administration.

Key results

We identified seven randomized trials, involving 401 participants. Overall, stem cell transplantation was associated with a reduced neurological impairment, but not with a better functional outcome. No safety concerns were raised.

Certainty of the evidence

The certainty of the evidence ranged from low to very low because of the risk of bias in the included studies, the lack of precision of the results, and different designs. More well-designed randomized controlled trials are needed.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Stem cell transplantation compared to conventional treatments for ischemic stroke

Stem cell transplantation compared to conventional treatments for ischemic stroke

Patient or population: ischemic stroke
Setting: hospital
Intervention: stem cell transplantation
Comparison: conventional treatments

Outcomes	Anticipated absolute effects (95% CI)			Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Without stem cell transplantation	With stem cell transplantation	Difference				
Neurologic impairment (measured by NIHSS; 0 to 42; higher = worse)	Median score = 5.9	-	MD 1.49 lower (2.65 lower to 0.33 lower)	-	319 (5 RCTs)	⊕⊕⊕⊕ Low ^{a,b}	Four studies were at high risk of bias for blinding of participants and personnel at high risk of bias. Heterogeneity: Tau ² = 1.13; Chi ² = 11.68, df = 4 (P = 0.02); I ² = 66%
Disability (measured by mRS; 0 to 6; higher = worse)	Median score = 2.75	-	MD 0.42 lower (0.86 lower to 0.02 higher)	-	371 (6 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}	Five studies were at high risk of bias for blinding of participants and personnel at high risk of bias. Heterogeneity: Tau ² = 0.19; Chi ² = 18.12, df = 5 (P = 0.003); I ² = 72%. The confidence interval was wide.
Dependency (measured by BI; 0 to 100; higher = better)	Median score = 63.39	-	MD 14.09 higher (1.94 lower to 30.13 higher)	-	170 (3 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}	All studies were at high risk of bias for blinding of participants and personnel at high risk of bias. Heterogeneity: Tau ² = 154.96; Chi ² = 9.04, df = 2 (P = 0.01); I ² = 78%. The confidence interval was wide and crossed the line of no difference.
Any cause of death	Study population			RR 0.66 (0.39 to 1.14)	371 (6 RCTs)	⊕⊕⊕⊕ Low ^{a,c}	Five studies were at high risk of bias for blinding of participants and personnel at high risk of bias. The confidence interval was wide and crossed the line of no difference.
	19.7%	13.0% (7.7 to 22.4)*	6.7% fewer (12 fewer to 2.8 more)				

Severe worsening of neurological deficit	8.9%	12.4% (4.6 to 33.8)	3.5% more (4.4 fewer to 24.9 more)	RR 1.39 (0.51 to 3.79)	321 (4 RCTs)	⊕⊕○○ Low ^{a,c}	Three studies were at high risk of bias for blinding of participants and personnel at high risk of bias. The confidence interval was wide and crossed the line of no difference.
Infections	23.2%	18.6% (12.5 to 27.2)	4.6% fewer (10.7 fewer to 3.9 more)	RR 0.80 (0.54 to 1.17)	321 (4 RCTs)	⊕⊕○○ Low ^{a,c}	Three studies were at high risk of bias for blinding of participants and personnel at high risk of bias. The confidence interval was wide and crossed the line of no difference.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

BI: Barthel Index; **CI:** confidence interval; **mRS:** modified Rankin Score; **MD:** mean difference; **NIHSS:** National Institutes of Health Stroke Scale; **RR:** risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aBlinding of participants and personnel at high risk of bias in almost all studies

^bHigh heterogeneity

^cImprecision

BACKGROUND

This review is the first update of a previously published review (Boncoraglio 2010).

Description of the condition

After ischemic heart disease, stroke is the leading cause of morbidity and mortality worldwide (Hankey 2017). About 85% of strokes are ischemic, caused by the interruption of blood flow in a brain-supplying artery; this leads to irreversible cell damage in the ischemic core, surrounded by a penumbra of surviving neurons. The rescue of the ischemic penumbra influences the functional recovery and represents the target of the available therapies (Hankey 2017; Powers 2018). In the last two decades, with the widespread adoption of organized stroke units, some reperfusion interventions given in the acute phase of ischemic stroke, such as intravenous recombinant tissue plasminogen activator and endovascular mechanical thrombectomy for large artery occlusion, have improved outcomes, including survival and residual disability (Hankey 2017; Powers 2018). However, due to the restricted treatment window and the selection criteria, only a minority of people can benefit from these therapies (de Los Rios la Rosa 2012; Kim 2017). Therefore, once brain damage has occurred, little can be done to improve functional outcome, except for rehabilitation therapy and pharmacological management of comorbidities, with very large healthcare and social costs. To date, the case fatality rate at five years is 50%, and 40% of stroke survivors are disabled (Hankey 2017), which leads to a strong demand for alternative therapeutic approaches.

Description of the intervention

Following a large number of experimental studies that highlighted the potential of stem cell transplantation as a novel therapeutic approach for stroke (STEPS 3 2014; Zhang 2009), over the past 15 years, a series of small, safety and feasibility-focused studies have investigated the use of stem cell therapies in people with stroke (Muir 2016). Various sources (xenogeneic, allogenic, or autologous) and types (embryonic or fetal neural, umbilical mesenchymal, bone marrow-derived mesenchymal, or peripheral blood hematopoietic) of stem cells have been evaluated, in different phases of disease (acute, subacute, or chronic), and with different routes of administrations (intravenous, intra-arterial, or intracerebral [Nagpal 2017]). STEPS 3 (Stem cells as an emerging paradigm in stroke 3) provides suggestions to develop phase II/III clinical trials in acute and chronic stroke (STEPS 3 2014), but currently, exact recommendations about patient selection, cell type and dosing, time window, end-points, and follow-up duration, do not exist.

How the intervention might work

Preclinical studies have demonstrated that various types of cell-based therapies substantially improve stroke recovery (Zhang 2009). However, during the last 15 years, the understanding of mechanisms of action has significantly advanced: rather than cell replacement, the benefit of stem cell treatments in stroke seems to result from indirect mechanisms, such as immunomodulation, intended to suppress the postischemic inflammatory response, and enhancement of the endogenous repair (Goldman 2016; Janowski 2015; Muir 2016; Zhang 2009). Trial paradigms are now focused on two different approaches: neuroprotection in the acute phase, and neurorestoration in the chronic phase (Borlongan 2016).

The early delivery of cells reduces acute tissue injury, modifying the tissue environment, basically with a paracrine mode of action, for example suppressing oxidative stress, inflammation, mitochondrial impairment, and apoptosis. In acute stroke, patients may be in a critical state, and the minimally invasive intravenous or intra-arterial delivery of stem cells is preferred. Pooled allogenic cells manufactured by the industry are ready to use, and will migrate close to the infarcted area due to peripheral chemoattractants (Borlongan 2016; Muir 2016). Cells with a higher immunomodulating potential, such as mesenchymal stem cells, are usually preferred (Janowski 2015).

A later delivery of cells during the recovery phase, when the chemokine signaling has waned, requires a direct intracerebral implantation close to the damaged areas. Neural stem cells have a higher potential of engraftment within the brain, and are usually preferred in this phase (Janowski 2015). The engraftment is intended to initiate brain remodeling by stimulating quiescent stem cells to mount reparative processes, including angiogenesis, vasculogenesis, neurogenesis, and synaptogenesis (Borlongan 2016; Muir 2016).

Why it is important to do this review

Stroke is a leading cause of morbidity and mortality worldwide, with very large healthcare and social costs, and there is a strong demand for alternative therapeutic approaches. To date, evidence for the benefit and safety of stem cell transplantation in patients with ischemic stroke is lacking. A systematic review of the available clinical trials is needed to assess the benefit-to-risk profile of stem cell transplantation in people with ischemic stroke compared with control.

OBJECTIVES

To assess the efficacy and safety of stem cell transplantation compared with control in people with ischemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We only included published and unpublished randomized controlled trials (RCTs).

Types of participants

We included people with ischemic stroke, with an ischemic lesion confirmed by computerized tomography (CT) or magnetic resonance imaging (MRI) scan, in any phase of the disease, from acute to chronic. This long time period allowed for the inclusion of studies investigating both the neuroprotective and neurorestorative effects of transplanted stem cells.

Types of interventions

We included all types of stem cell transplantation, regardless of cell source, cell type, route of administration, or dosage. We excluded studies with combined treatments.

Types of outcome measures

Primary outcomes

Efficacy (neurologic impairment or functional outcome – disability or dependency, or both) at longer-term follow-up, assessed using clinical outcome measures or validated international scales, for example the National Institutes of Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), or the Barthel Index (BI). We set six months as the minimum follow-up period.

Secondary outcomes

We evaluated the following postprocedural safety outcomes:

- any cause of death within 30 days of the procedure, and thereafter;
- severe worsening of neurological deficit (increase of four points on the NIHSS scale or equivalent) within 30 days of procedure, and thereafter;
- infections within 30 days of the procedure, and thereafter;
- neoplastic transformation of ischemic lesion at longer follow-up.

Search methods for identification of studies

See the Cochrane Stroke Group's [search methods](#). We searched for trials in all languages and arranged translation of relevant research where necessary.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Information Specialist on 13 August 2018; the Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 7) in the *Cochrane Library* (searched August 2018; [Appendix 1](#)); MEDLINE Ovid (1966 to August 2018; [Appendix 2](#)); Embase Ovid (1980 to August 2018; [Appendix 3](#)); and BIOSIS Citation Index (1926 to August 2018; [Appendix 4](#)).

We also searched the following ongoing trials and research registers in (last searched August 2018):

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch);
- Internet Stroke Center Stroke Trials Registry (www.strokecenter.org/trials/).

Searching other resources

In an effort to identify further published, unpublished, and ongoing trials we:

- handsearched the conference proceedings;
- screened reference lists of relevant papers;
- contacted individuals active in the field and stem cell manufacturers (Athersys, Celgene Cellular Therapeutics, ReNeuron, SanBio); we last contacted them in August 2018.

Data collection and analysis

Selection of studies

Two review authors (AB and MR) independently read titles and abstracts (if available) of the identified references and eliminated obviously irrelevant studies. We retrieved full-text articles for the references that remained, and two review authors (AB and MR) independently examined potentially relevant studies, using the predetermined criteria of whether:

- the study was a RCT;
- the participants had an ischemic stroke with an ischemic lesion confirmed at neuroimaging, and the intervention was stem cell transplantation;
- neurologic impairment, or disability or dependency, or both, were measured at entry and at the minimum follow-up period of six months, using validated international scales.

We ranked studies as excluded, included, or uncertain, using a checklist. We resolved any disagreements through discussion with a third review author (GBB).

We collected multiple reports on the same study, so that each study, not each reference, was the final unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram ([PRISMA 2009](#)).

Data extraction and management

Two review authors (AB and MR) independently extracted data from the included studies. We resolved discrepancies by discussion. We used a standard data extraction form based on the one recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* to extract the following information: first study author; year of publication; recruitment period; phase of the disease; sample size; source and type of stem cell transplantation; route of administration; timing of stem cell transplantation; outcome data; and the follow-up period ([Higgins 2011](#)).

Assessment of risk of bias in included studies

Two review authors (AB and MR) independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We resolved disagreements by discussion, or by consultation with another review author (GBB). We assessed risk of bias according to the following domains:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting;
- other bias.

We graded the risk of bias for each domain as high, low, or unclear, and provided information from the study report, together with justification of our judgment, in the 'Risk of bias' tables.

Measures of treatment effect

For continuous outcome, we calculated the mean difference (MD) and relative 95% confidence interval (CI) for studies using the same scales, and the standardized mean difference (SMD) with its relative 95% CI if different scales were used; for dichotomous outcomes, we calculated the relative risk (RR) and 95% CI.

Unit of analysis issues

The unit of analysis was the participant; we did not include cluster-randomized trials.

Dealing with missing data

When we found data were missing or identified discrepancies in study publications, we contacted the study authors to request further information. Where intention-to-treat analyses were not possible from the published and unpublished data, we did on-treatment (per protocol) analyses.

Assessment of heterogeneity

To quantify between-study heterogeneity, we used the I^2 statistic. If we found substantial heterogeneity ($I^2 > 75\%$), we explored the reasons.

Assessment of reporting biases

If we had identified at least 10 studies for each outcome, we would have assessed reporting bias using funnel plots.

Data synthesis

We combined the study results using a random-effects meta-analysis. We estimated the weighted treatment effect and 95% CI across trials for continuous outcomes, and pooled RR with its 95% CI for dichotomous outcomes. We used Review Manager 5 for all data entry and analysis ([RevMan 2014](#)).

Subgroup analysis and investigation of heterogeneity

For the primary outcomes, we considered the following prespecified subgroups.

- Type of participant:
 - * phase of disease: acute (within seven days of ischemic stroke), subacute (between eight days and three months), or chronic (more than three months after ischemic stroke).
- Type of treatment:
 - * source of stem cells: human or nonhuman; embryonic and fetal; or adult, neural, or non-neural;

- * route of administration: neurosurgery, intra-arterial, or intravenous.

We considered heterogeneity to be significant if I^2 was greater than 75%; if so, we sought the potential reasons, e.g. different follow-up period.

Sensitivity analysis

To test the robustness of the results, we had intended to undertake a sensitivity analysis by incorporating or removing studies that we assessed to be of lower or ambiguous methodological quality.

Summary of findings table

We presented the overall certainty of the evidence for efficacy outcomes (neurologic impairment, disability, dependency), any cause of death, severe worsening of neurological deficit, and infections. We evaluated the overall certainty of the evidence according to the GRADE approach ([GRADE Working Group 2004](#)). We created the 'Summary of findings' table using GRADEpro GDT ([GRADEpro GDT](#)).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#); [Characteristics of studies awaiting classification](#); [Characteristics of ongoing studies](#).

We included seven randomized trials of 401 participants with acute, subacute, and chronic ischemic stroke, who had been treated with stem cell transplantation.

Results of the search

We identified 6398 references from electronic databases and through handsearching. [Figure 1](#) shows the PRISMA study flow diagram. Of the 6398 records identified, we removed 751 duplicate references to the same papers. We excluded a further 5560 references because they were not relevant. After full-text review of the remaining 87 references, referring to 74 studies, we excluded 43 studies that did not meet the eligibility criteria (see [Excluded studies](#)). For 12 studies that met the inclusion criteria, we were unable to obtain published relevant data; therefore, we contacted authors to obtain additional unpublished data, but we did not receive any replies (see [Studies awaiting classification](#)). Twelve studies met the inclusion criteria, but are currently ongoing (See [Ongoing studies](#)). Therefore, we included six new studies in this version of the review, along with one trial already included in the previous version, involving 401 participants ([Boncoraglio 2010](#)).

Figure 1. Results of database searches

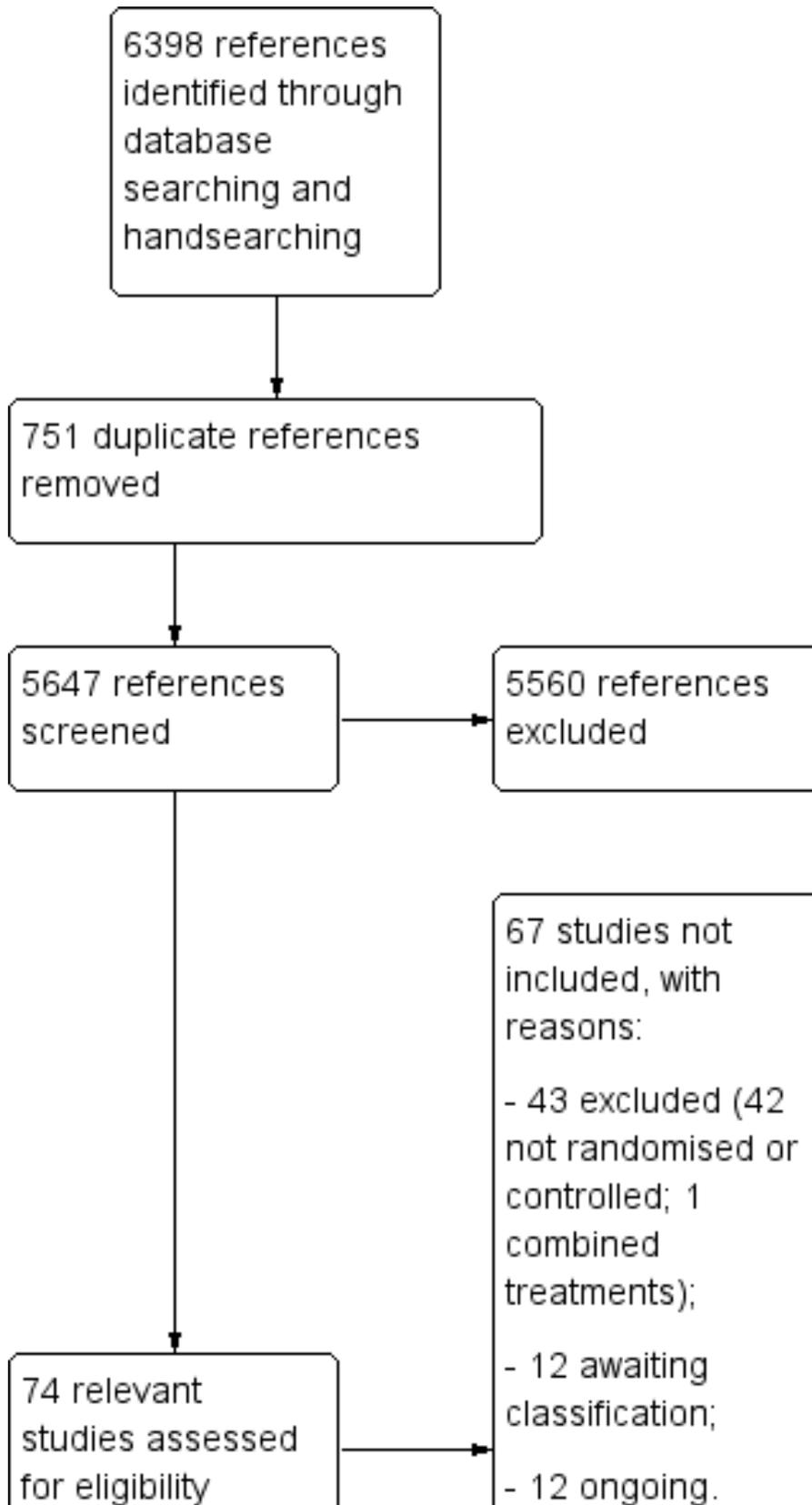
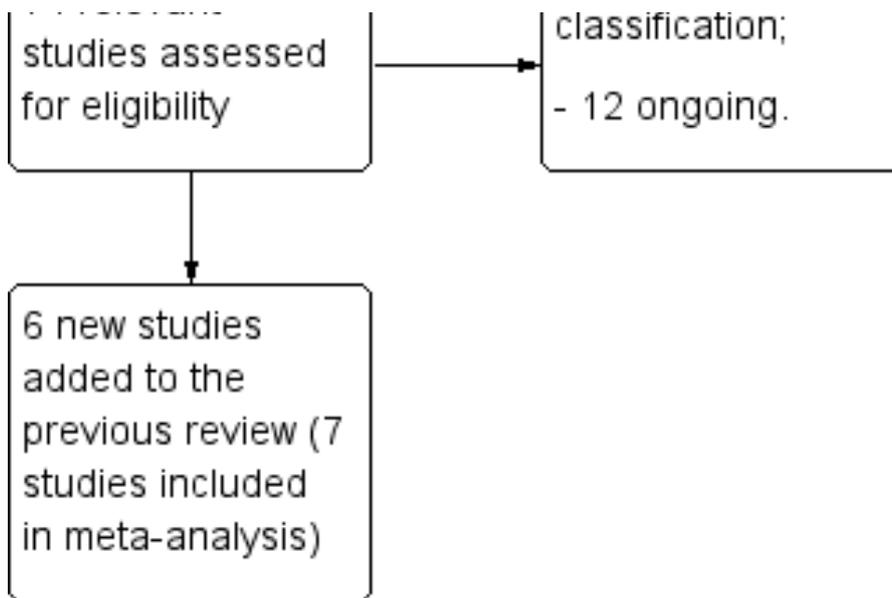


Figure 1. (Continued)



Included studies

We identified seven trials that fulfilled the inclusion criteria (Bang 2005; Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Lee 2010; Prasad 2014).

All seven trials used adult human non-neural stem cells: five bone marrow-derived mesenchymal/mononuclear cells (Bang 2005; Bhatia 2015; Jin 2016; Lee 2010; Prasad 2014), one peripheral blood stem cells (Chen 2014), and one multipotent adult progenitor cells (Hess 2014).

In five studies, during the subacute phase, cells were transplanted intravenously (Bang 2005; Lee 2010; Prasad 2014), intra-arterially (Bhatia 2015), or into the lumbar subarachnoid space (Jin 2016). In one study, cells were transplanted intravenously during the acute phase (Hess 2014), and in one study, cells were transplanted intracerebrally during the chronic phase (Chen 2014).

Follow-up ranged from six months (Bhatia 2015), to one year (Bang 2005; Chen 2014; Hess 2014; Prasad 2014), five years (Lee 2010), or seven years (Jin 2016).

Efficacy outcomes were reported using the National Institutes of Health Stroke Scale (NIHSS) in five studies (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Prasad 2014), the modified Rankin Scale (mRS) in six studies (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Lee 2010; Prasad 2014), and the Barthel Index (BI) in three studies (Bang 2005; Jin 2016; Prasad 2014). Safety outcomes included case fatality at end-of-trial in cases and controls in six studies (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Lee 2010; Prasad 2014), neurological deterioration in four studies (Bhatia 2015; Hess 2014; Lee 2010; Prasad 2014), infections in four studies (Bhatia 2015; Hess 2014; Lee 2010; Prasad 2014), and new neoplastic disease in two studies (Bhatia 2015; Lee 2010).

We reported detailed description of the included studies in the [Characteristics of included studies](#).

Excluded studies

We excluded 43 studies for the reasons described in the [Characteristics of excluded studies](#): 42 were not randomized controlled trials (Banerjee 2014; Battistella 2011; Bhasin 2011; Bhasin 2013; CoBIS 2015; Friedrich 2012; Ghali 2016; Honmou 2011; ISRCTN15677760; Kondziolka 2000; Li 2007; Lin 2008; Lu 2013; Man 2006; Mendonça 2006; Mohamed Ibrahim 2016; Moniche 2012; Napgal 2016; NCT01297413; NCT02397018; NCT02795052; NCT03296618; NCT03384433; PISCES 2016; PISCES II 2017; Prasad 2012; Qiao 2014; Rabinovich 2005; Savitz 2005; Savitz 2011; Sharma 2014; Sinden 2009; Steinberg 2014; Suarez-Monteagudo 2009; Taguchi 2015; Vahidy 2012; Wanamaker 2015; Wang 2007; Wang 2013; Yang 2005; Yang 2007; Zhang 2006), and one evaluated combined treatments (Meng 2009). We did not exclude any study because of the lack of neuroimaging or measurement of the neurological impairment at baseline.

Twelve studies did not publish or provide data relevant for this review (see [Characteristics of studies awaiting classification](#) [ChiCTR-INR-16008908; Kondziolka 2005; NCT01310114; NCT01468064; NCT01518231; NCT02378974; NCT02564328; NCT02605707; NCT03176498; NCT03186456; Sych 2012; Yavagal 2015]).

A further 12 studies met the inclusion criteria, but are currently ongoing, and are expected to enroll over 1300 participants (see [Characteristics of ongoing studies](#) [Bhasin 2016; Detante 2013; Diez-Tejedor 2014; Honmou 2016; Kim 2013; Moniche 2015; NCT02448641; NCT02580019; NCT03004976; NCT03545607; RESSTORE 2015; TREASURE 2018]).

Risk of bias in included studies

For full details, see the corresponding 'Risk of bias' tables in [Characteristics of included studies](#), and [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

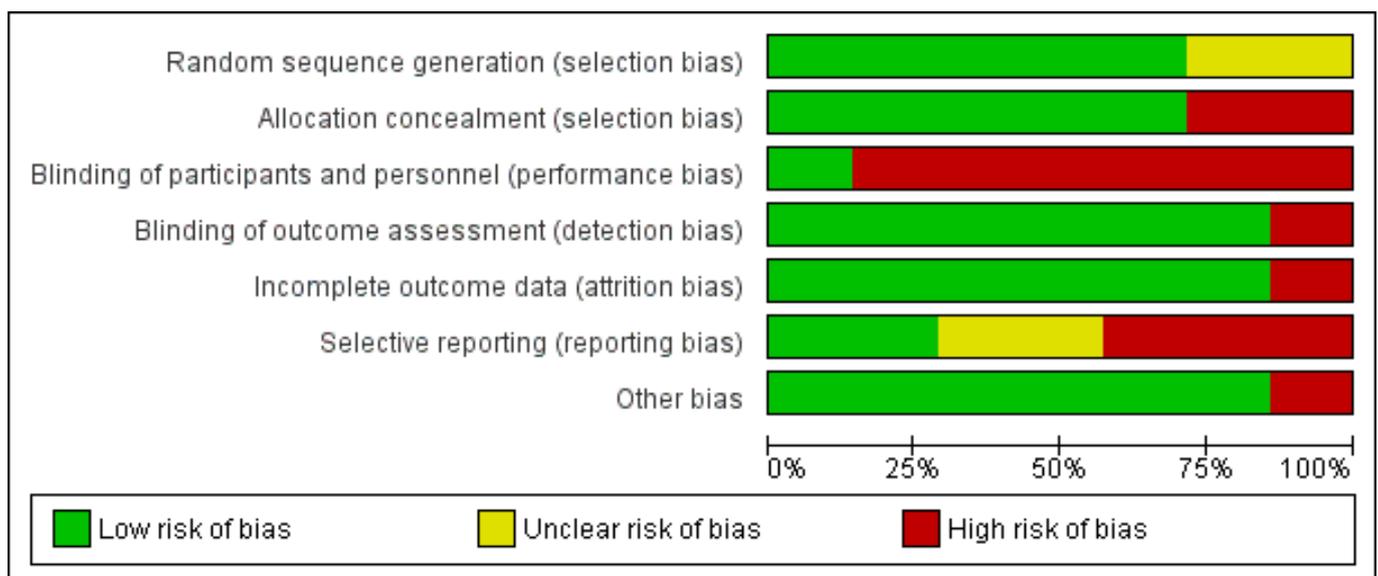


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (green for low risk of bias, yellow for unclear risk of bias, and red for high risk of bias)

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bang 2005	+	-	-	+	-	?	+
Bhatia 2015	?	+	-	+	+	-	-
Chen 2014	+	+	-	+	+	+	+
Hess 2014	+	+	+	+	+	-	+
Jin 2016	?	+	-	-	+	-	+
Lee 2010	+	-	-	+	+	?	+
Prasad 2014	+	+	-	+	+	+	+

Allocation

All included trials explicitly stated that randomization occurred. Five trials reported the method of randomization, and we judged them at low risk of bias (Bang 2005; Chen 2014; Hess 2014; Lee 2010; Prasad 2014); two did not report how participants were random-

ized, and we judged them at unclear risk of bias (Bhatia 2015; Jin 2016).

Allocation was adequately concealed in five trials, and we judged them at low risk of bias (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Prasad 2014). In one trial, after initial randomization to the

treatment group, five of 15 participants refused, and were allocated to the control group (Bang 2005). In one study, after initial randomization, 33 of 85 participants were not included in the study (11 participants died early or underwent hopeless discharge within four weeks after randomization, before the first boosting of stem cells; and 22 were unwilling to participate) without mentioning allocation (Lee 2010). We judged these two trials at high risk of bias.

Blinding

One trial was blinded to both participants and outcome assessors, and we judged it at low risk of bias (Hess 2014). Due to the invasive procedures required for autologous stem cell transplantation (i.e. bone marrow aspiration or stereotaxic intracerebral implantation), most of the included trials were blinded only to outcome assessors, and not to participants (Bang 2005; Bhatia 2015; Chen 2014; Lee 2010; Prasad 2014). Although this limitation cannot be avoided for ethical reasons, given its possible effect on participants, we assessed these studies at high risk of bias. One trial did not report blinding procedures for either the participants or for the assessors, and we judged it at high risk of bias (Jin 2016).

Incomplete outcome data

All seven trials reported the numbers lost to follow-up. In one study, 40% of controls were lost, and we judged the study at high risk of bias (Bang 2005); we judged the remaining six trials at low risk of bias.

Selective reporting

In two of the included trials, primary outcomes listed in published protocols were adequately reported in the results, and we judged them at low risk of bias (Chen 2014; Prasad 2014). In two trials, the primary outcomes listed in published protocols or interim publications were different from those reported in the results, and we judged them at high risk of bias (Bhatia 2015; Hess 2014). In one trial, the outcomes listed in the methods section were different from those reported in the results, and we judged it at high risk of bias (Jin 2016). In two of the trials, selective reporting bias was not clear because the protocols were not available (Bang 2005; Lee 2010).

Other potential sources of bias

In one trial, relevant results of 22 participants randomized between day 15 and 28 were not available (Bhatia 2015); the study authors concluded that in this group, intra-arterial infusion of stem cells was safe but without beneficial effect on stroke outcome. However, we considered this a potential bias and judged it at high risk of bias.

In one trial, granulocyte-colony stimulating factor (G-CSF) was used to increase the number of CD34+ peripheral blood stem cells; since G-CSF may be neuroprotective in the acute phase, and this trial included only participants with chronic stroke, this was not considered a potential bias. Therefore, we judged it at low risk of bias (Chen 2014). We did not identify any other potential sources of bias for the remaining five trials, so judged them at low risk of bias.

Effects of interventions

See: [Summary of findings for the main comparison Stem cell transplantation compared to conventional treatments for ischemic stroke](#)

See: [Summary of findings for the main comparison](#)

Primary outcomes

Neurologic impairment

Five trials, with a total of 319 participants, used the NIHSS to measure this outcome at the end of follow-up (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Prasad 2014). Participants randomized to stem cell transplantation had a significantly better outcome compared with controls (mean difference [MD] -1.49, 95% confidence interval [CI] -2.65 to -0.33; $I^2 = 66%$; low-certainty evidence; [Analysis 1.1](#)). In subgroup analysis by phase of disease and route of administration, treatment in the chronic phase of stroke was more effective than in the acute or subacute phase ([Analysis 1.2](#)), and neurosurgery (intracerebral or lumbar subarachnoid administration) was more effective than intravenous or intra-arterial administration ([Analysis 1.3](#)). However, only one RCT, with 30 or fewer participants, was included in each of these subgroup analyses.

Disability

Six trials, with a total of 371 participants, used the mRS to measure this outcome at the end of follow-up (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Lee 2010; Prasad 2014). Results for participants randomized to stem cell transplantation were inconclusive compared with controls (MD -0.42, 95% CI -0.86 to 0.02; $I^2 = 72%$; very low-certainty evidence; [Analysis 1.4](#)). In subgroup analysis by phase of disease and route of administration, treatment during the chronic phase was more effective than treatment during the acute and subacute phase ([Analysis 1.5](#)), and neurosurgery (intracerebral or lumbar subarachnoid administration) was more effective than intravenous or intra-arterial administration ([Analysis 1.6](#)). However, only one RCT, with 30 or fewer participants, was included in each of these subgroup analyses.

Dependency

Three trials, with a total of 170 participants, used the BI to measure this outcome at the end of follow-up (Bang 2005; Jin 2016; Prasad 2014 - [Analysis 1.7](#)). The results were inconclusive between stem cell transplantation and controls, but the heterogeneity across trials was high (MD 14.09, 95% CI -1.94 to 30.13, $I^2 = 78%$; very low-certainty evidence; [Analysis 1.7](#)). We found inconclusive results between groups in subgroup analysis by route of administration ([Analysis 1.8](#)). In all three trials, participants were treated in the subacute phase.

Secondary outcomes

Any cause of death

Death was reported in six trials, with a total of 371 participants (Bhatia 2015; Chen 2014; Hess 2014; Jin 2016; Lee 2010; Prasad 2014). The results were inconclusive between stem cell transplantation and controls (risk ratio [RR] 0.66, 95% CI 0.39 to 1.14, $I^2 = 0%$; [Analysis 1.9](#)).

Severe worsening of neurological deficit

This outcome was reported in four trials, with a total of 321 participants (Bhatia 2015; Hess 2014; Lee 2010; Prasad 2014). The results were inconclusive between stem cell transplantation and controls (RR 1.39, 95% CI 0.51 to 3.79, $I^2 = 41%$; [Analysis 1.10](#)).

Infections

This outcome was reported in four trials, with a total of 321 participants (Bhatia 2015; Hess 2014; Lee 2010; Prasad 2014). The results

were inconclusive between stem cell transplantation and controls (RR 0.80, 95% CI 0.54 to 1.17, $I^2 = 0\%$; [Analysis 1.11](#)).

Neoplastic transformation

This outcome was reported in two trials, with a total of 72 participants ([Bhatia 2015](#); [Lee 2010](#)). The results were inconclusive between stem cell transplantation and controls (RR 1.13, 95% CI 0.11 to 11.53; [Analysis 1.12](#)).

Sensitivity analysis

We did not perform any sensitivity analyses according to the quality of studies, because all of them were at high risk of bias.

DISCUSSION

Summary of main results

We identified seven RCTs, involving 401 participants with ischemic stroke, 188 of whom were treated with stem cell transplantation and 213 of whom were controls. Overall, stem cell transplantation was associated with a better clinical outcome when measured with the National Institutes of Health Stroke Scale (NIHSS), but not with the modified Rankin Scale (mRS) or the Barthel Index (BI). These results could be consistent with a small benefit of stem cell transplantation, which could only be detected when we considered neurological impairment, not when we considered functional outcome. In subgroup analysis by phase of disease and route of administration, treatment during the chronic phase was more effective than treatment during the acute and subacute phase, and neurosurgery (intracerebral or lumbar subarachnoid administration) was more effective than intravenous or intra-arterial administration. However, only one RCT, with 30 or fewer participants, was included in each of these subgroup analyses. The high heterogeneity that we found in the primary outcome analysis could be explained by the average high risk of bias (most of the included studies had two or more sources of potential bias) and the different designs (phase of disease, route of administration, and duration of the follow-up) of the included studies.

Of note, two of the included trials, both with the lower risk of bias, treated 60 or more participants each with stem cells ([Hess 2014](#); [Prasad 2014](#)), whereas the remaining five trials, with higher risk of bias on average, treated 16 or fewer participants with stem cells. In both larger trials, stem cell transplantation did not significantly influence clinical outcomes, whereas in three of the five smaller trials, it did.

No significant safety concerns associated with stem cell transplantation were raised.

Overall completeness and applicability of evidence

Our review was deliberately broad, and we sought to include trials in which stem cells were transplanted in people with ischemic stroke so that the review would inform future research. The trials we identified were relevant to our review question. All seven trials used adult human non-neural stem cells, and the results of this review should not be extrapolated to other types of stem cells.

Quality of the evidence

Overall, five trials reported the method of randomization, five trials adequately concealed the sequence of randomization, and six tri-

als reported that the treatment was blinded to outcome assessors; only one was also blinded to participants. Five trials reported complete outcome data. Selective reporting bias was excluded in only two trials.

Using the GRADE approach, we assessed the certainty of the evidence as low to very low for the primary outcomes. The main reasons for downgrading the certainty of the evidence included risk of bias in included trials, inconsistency, and imprecision.

Potential biases in the review process

We attempted to limit bias in the review process. This review incorporated extensive literature searches guided by the Cochrane Stroke Group, and we sought unpublished and ongoing work by contacting authors of included studies and other experts in the field. Two review authors independently decided whether studies should be included, and two review authors independently extracted data. During the review process, we did not have any significant disagreement.

In the included studies, there were few missing data, probably with a minimum impact on our conclusions. However, the ongoing trials aim to enroll over 1300 participants, and are likely to have an important influence in future. In the next update, we intend to combine the three types of primary outcome measure into a single primary outcome.

Finally, the mRS is not usually analyzed as a continuous measure, and so the results based on this statistic may be very insensitive.

Agreements and disagreements with other studies or reviews

Another systematic review, which also included studies without a comparator arm and non-randomized controlled studies, had similar results ([Nagpal 2017](#)). Our findings are consistent with previously published papers calling for more research to determine the effectiveness of stem cell transplantation for ischemic stroke.

AUTHORS' CONCLUSIONS

Implications for practice

Currently there is insufficient evidence to support or refute the use of stem cell transplantation to treat ischemic stroke.

Implications for research

Given the high prevalence of long-term disability after stroke, more research is urgently needed to identify new treatments. Stem cells appear promising in animal models, but more well-designed clinical trials are needed ([STEPS 3 2014](#)).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]

Bang 2005

Methods	Single-blind, randomized, controlled, phase I/II clinical trial
Participants	30 participants with subacute cerebral infarction in the MCA territory and severe neurological deficit Treatment 10, control 20 Treated between 32 and 61 days from stroke onset
Interventions	Intravenous infusion of 2 boosts of 50 million culture-expanded autologous bone marrow mesenchymal stem cells
Outcomes	NIHSS score as an index of neurological deficit and BI and mRS as indices of functional recovery at the end of the 12-month follow-up
Notes	Corresponding author provided individual level data for BI at 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated by a blinded, independent co-ordinator, using a randomization table
Allocation concealment (selection bias)	High risk	After initial randomization, 5 participants allocated to the mesenchymal stem cell group 'refused' and were allocated to the control group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures, such as bone marrow aspiration, were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Neurological and functional outcomes were checked by a neurologist who was blind to the group allocation and radiological data
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants from the control group were lost to follow-up at 6 months
Selective reporting (reporting bias)	Unclear risk	Protocol was not available

Stem cell transplantation for ischemic stroke (Review)

Bang 2005 (Continued)

Other bias	Low risk	Control participants were significantly younger than those of the mesenchymal stem cell group
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Bhatia 2015

Methods	Single-blind, randomized, controlled clinical trial	
Participants	20 participants with subacute ischemic stroke in the MCA territory and NIHSS > 7 Treatment 10, control 10 Treated between 8 and 15 days from stroke onset	
Interventions	Intra-arterial infusion of bone marrow-derived mononuclear cells (mean 6.1 million) into the ipsilateral MCA	
Outcomes	Primary safety outcomes and secondary efficacy endpoints as combined mRS, BI, and NIHSS score at the end of the 6-month follow-up	
Notes	Corresponding author provided individual level data for NIHSS and mRS at 6 months In a second arm of the study, 22 participants were randomized between day 15 and 28; for these participants, relevant results were not available and therefore, were excluded from the analysis	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized, but the method of the random sequence generation was not specified
Allocation concealment (selection bias)	Low risk	Participants were correctly allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures, such as bone marrow aspiration, were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An experienced neurologist, blinded to the nature of intervention, did the clinical evaluations
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	High risk	Primary outcomes listed in interim publications were different from those reported in the results
Other bias	High risk	Relevant results of the 22 participants randomized between day 15 and 28 were not available

Chen 2014

Methods	Single-blind, randomized, controlled clinical trial
Participants	30 participants with chronic MCA infarction and neurological deficits of intermediate severity Treatment 15, control 15 Treated between 6 months and 5 years from stroke onset
Interventions	Subcutaneous granulocyte-colony stimulating factor injections (15 µg/kg/day) for 5 consecutive days, followed by stereotaxic implantation of autologous 3 to 8 million CD34+ immunosorted peripheral blood stem cells
Outcomes	Improvements in stroke scales (NIHSS, European Stroke Scale, and European Stroke Scale Motor Sub-scale) and functional outcomes measure (mRS) from baseline to the end of the 12-month follow-up
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned randomly (1:1) via SAS software to either the peripheral blood stem cells or the control groups
Allocation concealment (selection bias)	Low risk	Participants were correctly allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures (such as stereotaxic implantation) were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All clinical information was assessed by clinician raters in a single-blinded fashion (at clinical evaluation, each participant wore a hat to mask the surgical scar on their skull)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	Low risk	Primary outcomes listed in published protocols were adequately reported in the results
Other bias	Low risk	Granulocyte-colony stimulating factor may be neuroprotective in the acute phase, but this trial included participants treated between 6 months and 5 years from stroke onset

Hess 2014

Methods	Double-blind, randomized, placebo-controlled, phase II multicenter dose-escalation clinical trial. Analysis was by intention-to-treat
Participants	After safety assessments in 8 participants (6 treated with 400 million intravenous multipotent adult progenitor cells, 2 with placebo), 129 participants with acute ischemic stroke involving MCA territory, with NIHSS score 8 to 20, and infarct size between 5 and 100 cc ³ , were enrolled

Stem cell transplantation for ischemic stroke (Review)

Hess 2014 (Continued)

Treatment 67, control 62
 Treated between 24 and 48 hours from stroke onset

Interventions	Intravenous infusion of 1.200 million multipotent progenitor cells or placebo
Outcomes	The primary efficacy endpoint combined the mRS, the BI, and change in NIHSS score from baseline, and was evaluated at day 90, and at the end of the 12-month follow-up
Notes	Corresponding author provided summary statistics for NIHSS and mRS at 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization, interactive voice and web-response system
Allocation concealment (selection bias)	Low risk	Participants were correctly allocated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and all trial personnel were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Primary outcomes within day 90 were complete; at 1-year follow-up, 24 participants were lost (9 treatment and 15 placebo)
Selective reporting (reporting bias)	High risk	Primary outcomes listed in published protocols were different from those reported in the results
Other bias	Low risk	Intravenous tissue-plasminogen activator and endovascular thrombectomy were more frequent in the placebo group; mean baseline infarct size was larger in the placebo group

Jin 2016

Methods	Randomized, controlled clinical trial
Participants	20 participants with subacute cerebral infarction and NIHSS score between 5 and 30 Treatment 10, control 10 Treated between 3 weeks and 5 months from stroke onset
Interventions	Subarachnoid infusion of a cell suspension containing 10 million autologous bone marrow mononuclear cells
Outcomes	Various safety and efficacy outcomes through a 7-year follow-up

Stem cell transplantation for ischemic stroke (Review)

Jin 2016 (Continued)

Notes None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized, but the method of the random sequence generation was not specified
Allocation concealment (selection bias)	Low risk	Participants were correctly allocated
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures, such as bone marrow aspiration, were not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	High risk	Outcomes listed in the methods section did not correspond with those reported in the results, and NIHSS score reported in text and tables were different
Other bias	Low risk	None

Lee 2010

Methods	Single-blind, randomized, controlled clinical trial
Participants	52 participants with MCA territory infarct and severe neurological deficit Treatment 16, control 36 Treated between 4 and 9 weeks from stroke onset
Interventions	Intravenous infusion of 2 boosts of 50 million culture-expanded autologous bone marrow mesenchymal stem cells
Outcomes	mRS for functional recovery at the end of the 12-month follow-up
Notes	None

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated by a blinded, independent co-ordinator, using a randomization table

Lee 2010 (Continued)

Allocation concealment (selection bias)	High risk	After initial random allocation of 85 participants to treatment groups, 11 participants died or underwent hopeless discharge, and 22 refused, without reporting allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures, such as bone marrow aspiration, were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The outcome was evaluated separately, by one of the authors who was blinded to clinical information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcome data were complete
Selective reporting (reporting bias)	Unclear risk	Protocol was not available
Other bias	Low risk	None

Prasad 2014

Methods	Single-blind, randomized, controlled clinical trial
Participants	120 participants with anterior circulation ischemic stroke Treatment 60, control 60 Treated between 7 and 30 days from stroke onset
Interventions	Intravenous infusion of a mean of 280 million autologous bone marrow mononuclear stem cells
Outcomes	The primary efficacy endpoint were the mRS and the BI at day 180; NIHSS at day 365 was a secondary outcome. The safety outcomes included death, adverse events (serious and non-serious), epileptiform discharges in electroencephalography, and evidence of any new growth on PET scan at day 365
Notes	Corresponding author provided data for NIHSS and mRS at 12 months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned by a central computer, using permuted block randomization in a 1:1 ratio
Allocation concealment (selection bias)	Low risk	After initial randomization, 2 participants allocated to bone marrow mononuclear stem cell group were not treated (1 participant withdrew and 1 participant was missed because of logistical difficulty)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Experimental procedures, such as bone marrow aspiration, were not blinded

Stem cell transplantation for ischemic stroke (Review)

Prasad 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Follow up for all participants was done from the co-ordinating center, by a trained and blinded assessor, unaware of participant group
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 treated participant and 1 control were lost at longer follow-up
Selective reporting (reporting bias)	Low risk	Primary outcomes listed in published protocols were adequately reported in the results
Other bias	Low risk	Infarct volume at baseline was higher in control arm than in bone marrow mononuclear stem cell arm

BI: Barthel Index

MCA: middle cerebral artery

mRS: modified Rankin Score

NIHSS: National Institutes of Health Stroke Scale

PET: positron emission tomography

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Banerjee 2014	Not RCT
Battistella 2011	Not RCT
Bhasin 2011	Not RCT
Bhasin 2013	Not RCT
CoBIS 2015	Not RCT
Friedrich 2012	Not RCT
Ghali 2016	Not RCT
Honmou 2011	Not RCT
ISRCTN15677760	Not RCT
Kondziolka 2000	Not RCT
Li 2007	Not RCT
Lin 2008	Not RCT
Lu 2013	Not RCT
Man 2006	Not RCT
Mendonça 2006	Not RCT

Study	Reason for exclusion
Meng 2009	Combined treatments (conventional therapy, filgrastim, MSCs, filgrastim + MSCs)
Mohamed Ibrahim 2016	Not RCT
Moniche 2012	Not RCT
Napgai 2016	Not RCT
NCT01297413	Not RCT
NCT02397018	Not RCT
NCT02795052	Not RCT
NCT03296618	Not RCT
NCT03384433	Not RCT
PISCES 2016	Not RCT
PISCES II 2017	Not RCT
Prasad 2012	Not RCT
Qiao 2014	Not RCT
Rabinovich 2005	Not RCT
Savitz 2005	Not RCT
Savitz 2011	Not RCT
Sharma 2014	Not RCT
Sinden 2009	Not RCT
Steinberg 2014	Not RCT
Suarez-Monteagudo 2009	Not RCT
Taguchi 2015	Not RCT
Vahidy 2012	Not RCT
Wanamaker 2015	Not RCT
Wang 2007	Not RCT
Wang 2013	Not RCT
Yang 2005	Not RCT
Yang 2007	Not RCT

Study	Reason for exclusion
Zhang 2006	Not RCT

RCT: randomized controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

ChiCTR-INR-16008908

Methods	Randomized parallel controlled trial
Participants	62 participants with NIHSS scores between 15 and 25, 1 to 3 months after onset of ischemic stroke
Interventions	Intrathecal injection of allogenic bone marrow-derived mesenchymal stem cells
Outcomes	Efficacy evaluated with mRS scale, NIHSS, infarct volume and mortality within 13 months after treatment
Notes	

Kondziolka 2005

Methods	RCT
Participants	18 participants with fixed motor deficits, 1 to 6 years following a basal ganglia ischemic or hemorrhagic stroke
Interventions	Stereotactic implantation of cultured neuronal cells produced from the NT2/D1 cell line derived from a human teratocarcinoma
Outcomes	Efficacy evaluated with European Stroke Scale motor score, Fugl-Meyer, Action Research Arm Test, Stroke Impact Scale scores and the results of other motor, neuropsychological and functional tests at 6 months
Notes	Separated results for ischemic and hemorrhagic stroke participants were not available from the publications

NCT01310114

Methods	Randomized controlled dose-escalation trial
Participants	44 participants with acute ischemic stroke
Interventions	Intravenous infusion of human placenta-derived cells (PDA001)
Outcomes	Safety and tolerability up to 2 years
Notes	

NCT01468064

Methods	RCT
Participants	20 participants with acute cerebral infarct within the MCA territory and severe neurological deficit
Interventions	Intravenous infusion of autologous transplantation of ex vivo expanded bone marrow stromal cells and endothelial progenitor cells
Outcomes	Safety and efficacy up to 1 year
Notes	

NCT01518231

Methods	RCT
Participants	40 participants with ischemic stroke in the internal carotid artery territory during the previous year
Interventions	Intrararterial infusion of autologous Peripheral Hematopoietic Stem Cell
Outcomes	Safety and efficacy up to 1 year
Notes	

NCT02378974

Methods	Randomized controlled dose-escalation trial
Participants	18 participants within 7 days of onset of ischemic stroke
Interventions	Intravenous infusion of Cordstem-ST
Outcomes	Safety and efficacy up to 6 months
Notes	

NCT02564328

Methods	RCT
Participants	40 participants with chronic ischemic stroke (between 6 and 60 months after stroke)
Interventions	Intravenous infusion of autologous bone marrow mesenchymal stem cells
Outcomes	Safety and efficacy up to 1 year
Notes	

NCT02605707

Methods	RCT
Participants	30 participants with chronic ischemic stroke (between 6 and 60 months after stroke)
Interventions	Intravenous infusion of autologous endothelial progenitor cells
Outcomes	Safety and efficacy up to 1 year
Notes	

NCT03176498

Methods	RCT
Participants	40 participants with ischemic stroke, in the convalescent period
Interventions	Intravenous infusion of allogeneic umbilical cord mesenchymal stem cells
Outcomes	Efficacy up to 6 months
Notes	

NCT03186456

Methods	RCT
Participants	40 participants with acute ischemic stroke
Interventions	Intravenous infusion of allogeneic umbilical cord mesenchymal stem cells
Outcomes	Safety and efficacy up to 26 weeks
Notes	

Sych 2012

Methods	RCT
Participants	27 participants with brain infarction, 11 in the treatment group and 16 in the control group, treated 3 months after onset of stroke
Interventions	Transplantation of hematopoietic and non-hematopoietic mesenchymal and ectodermal fetal stem cells, harvested from germ layers of internal organs of 4 to 8 week-old fetuses
Outcomes	Evaluation of cognitive status (MMSE), frontal lobe dysfunction (FAB), and brain perfusion (transcranial doppler)
Notes	

Yavagal 2015

Methods	Randomized, sham-controlled clinical trial
Participants	Participants with anterior circulation ischemic stroke, treated between 9 and 19 days after onset of stroke
Interventions	Intracarotid infusion of autologous bone marrow cells (ALD-401)
Outcomes	Safety, efficacy and reduction in stroke volume at 1 year
Notes	

FAB: Frontal Assessment Battery

MCA: middle cerebral artery

MMSE: Mini Mental State Examination

mRS: modified Rankin Score

NIHSS: National Institutes of Health Stroke Scale

RCT: randomized controlled trial

Characteristics of ongoing studies [ordered by study ID]
Bhasin 2016

Trial name or title	Intravenous bone marrow-derived mononuclear stem cells in chronic ischemic stroke
Methods	Randomized, controlled clinical trial
Participants	20 participants with chronic motor deficit from ischemic stroke
Interventions	Intravenous infusion of bone marrow derived mononuclear stem cells (mean 60 to 70 million) or placebo
Outcomes	Efficacy evaluated with Fugl Meyer scale, modified BI, Medical Research Council Grade, Ashworth Tone Scale
Starting date	2014
Contact information	Prof MV Padma Srivastava, Department of Neurology, All India Institute of Medical Sciences, New Delhi, India
Notes	Interim analysis of safety, feasibility and efficacy at 8 weeks was published; follow-up is ongoing

Detante 2013

Trial name or title	Intravenous Stem cells after Ischemic Stroke (ISIS)
Methods	Randomized, controlled, open clinical trial
Participants	31 participants with subacute ischemic stroke
Interventions	Intravenous injection of low dose (100 million) or high dose (300 million) of autologous bone marrow mesenchymal stem cells; control group without intervention nor placebo

Detante 2013 (Continued)

Outcomes	Functional recovery and neuroradiological outcome by multimodal MRI (anatomic, activation, vasoreactivity, functional, and structural connectivity)
Starting date	2010
Contact information	Dr Olivier Detante, University Hospital, Grenoble, France
Notes	3 participants did not receive the treatment because of karyotype abnormalities during cell culture; recruitment is complete, 2-year follow-up is ongoing

Diez-Tejedor 2014

Trial name or title	AMASCIS-01
Methods	Double-blind, randomized, controlled, phase II clinical trial
Participants	19 participants with acute or subacute ischemic stroke, and NIHSS between 8 and 20
Interventions	Intravenous administration of allogeneic mesenchymal stem cells from adipose tissue (1 million / kg) within the first 2 weeks after the onset of stroke symptoms
Outcomes	Safety and efficacy analysis (mRS, NIHSS, size of infarct, and biochemical markers)
Starting date	2014
Contact information	Dr Exuperio Diez-Tejedor, University Hospital La Paz, Madrid, Spain
Notes	

Honmou 2016

Trial name or title	Phase III clinical trial using autologous mesenchymal stem cells for stroke patients
Methods	Double-blind, randomized, controlled clinical trial
Participants	Participants with subacute supratentorial cerebral infarction
Interventions	Intravenous infusion of auto-serum expanded bone marrow derived-autologous mesenchymal stem cells within 40 days from onset
Outcomes	Feasibility, safety, and efficacy of cell therapy
Starting date	2016
Contact information	Dr Osam Honmou, Research Institute for Frontier Medicine, Sapporo Medical University, Japan
Notes	

Kim 2013

Trial name or title	STARTING-2
Methods	Single-blind, randomized, open clinical trial
Participants	60 participants with acute, subacute, or chronic ischemic stroke, and moderate to severe neurologic deficit
Interventions	Intravenous transplantation of autologous mesenchymal stem cells, expanded with autologous serum
Outcomes	Functional endpoints, based on categorical shift in mRS, and neurologic deficits
Starting date	2012
Contact information	Dr Oh Young Bang, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
Notes	

Moniche 2015

Trial name or title	IBIS Trial
Methods	Single-blind, randomized, controlled, phase II, multicenter, open clinical trial
Participants	76 participants with acute ischemic stroke of moderate to severe intensity (NIHSS 6 to 20), involving the MCA
Interventions	Intra-arterial infusion of 2 or 5 millions/kg mononuclear autologous bone marrow stem cells
Outcomes	Functional outcomes evaluated with mRS and BI
Starting date	2015
Contact information	Dr Francisco Moniche, Hospitales Universitarios Virgen del Rocío, Seville, Spain
Notes	

NCT02448641

Trial name or title	ACTISIMA
Methods	Double-blind, randomized, controlled (interventional, sham-surgery), phase IIB clinical trial
Participants	156 participants with chronic motor deficit from ischemic stroke in subcortical region of MCA or lenticulostriate artery
Interventions	Stereotactic intracranial injection of 2.5 or 5 million modified stem cells (SB623) or placebo
Outcomes	Proportion of participants whose Fugl-Meyer Motor scale improved by ≥ 10 points at month 6 from baseline

Stem cell transplantation for ischemic stroke (Review)

NCT02448641 (Continued)

Starting date	January 2016
Contact information	Study Sponsor: SanBio, Inc Principal Investigator: Gary Steinberg, Stanford Hospital and Clinics, School of Medicine
Notes	

NCT02580019

Trial name or title	Umbilical cord derived mesenchymal stem cells treatment in ischemic stroke
Methods	Randomized, controlled, phase IIa, open clinical trial
Participants	Participants with subacute ischemic stroke and NIHSS < 24
Interventions	Intravenous injection of a single dose of 2×10^7 human umbilical cord mesenchymal stem cells once a week for 4 weeks
Outcomes	Safety and efficacy assessed as comparison of NIHSS and mRS
Starting date	2016
Contact information	Prof Duan Lian, Affiliated Hospital (307 Hospital), Academy of Military Medical Science, Beijing, China
Notes	

NCT03004976

Trial name or title	Study of allogeneic umbilical cord blood infusion for adults with ischemic stroke (CoBIS 2)
Methods	Double-blind, randomized, controlled, phase II, multicenter clinical trial
Participants	100 participants with acute ischemic stroke
Interventions	A single intravenous infusion of umbilical cord blood or placebo
Outcomes	Safety and efficacy analysis
Starting date	2017
Contact information	Dr J Kurtzberg, Robertson Clinical and Translational Cell Therapy Program, Duke University, North Carolina, US
Notes	Stem cells are supposed to be responsible, at least in part, for the mechanism of action of the umbilical cord blood

NCT03545607

Trial name or title	MASTERS-2
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Stem cell transplantation for ischemic stroke (Review)

NCT03545607 (Continued)

Methods	Double-blind, randomized, placebo-controlled, phase III, multicenter clinical trial
Participants	300 participants with acute ischemic stroke
Interventions	Intravenous infusion of 1200 million multipotent progenitor cells or placebo within 18 to 36 hours from onset of stroke
Outcomes	Efficacy endpoint, assessed with mRS, or combined mRS, BI, and NIHSS
Starting date	2018
Contact information	Athersys Clinical Trials Group
Notes	

RESSTORE 2015

Trial name or title	RESSTORE
Methods	Randomized, controlled, phase IIb, multicenter clinical trial
Participants	400 participants with ischemic stroke
Interventions	Intravenous infusion of allogenic adipose tissue derived mesenchymal stem cells
Outcomes	Safety and efficacy (functional recovery) using clinical rating scales, multimodal MRI, and blood biomarkers
Starting date	2015
Contact information	Dr Olivier Detante, University Hospital, Grenoble, France
Notes	

TREASURE 2018

Trial name or title	TREASURE
Methods	Double-blind, randomized, controlled, multicenter, phase II/III clinical trial
Participants	220 participants with acute ischemic stroke
Interventions	Intravenous infusion of 1200 million multipotent progenitor cells or placebo within 18 to 36 hours of onset of stroke
Outcomes	Safety and efficacy (the primary efficacy endpoint combines the mRS, BI, and NIHSS)
Starting date	2017
Contact information	Dr Kiyohiro Houkin, Hokkaido University Hospital, Sapporo, Japan
Notes	

Stem cell transplantation for ischemic stroke (Review)

BI: Barthel Index
 MCA: middle cerebral artery
 MRI: magnetic resonance imaging
 mRS: modified Rankin Score
 NIHSS: National Institutes of Health Stroke Scale

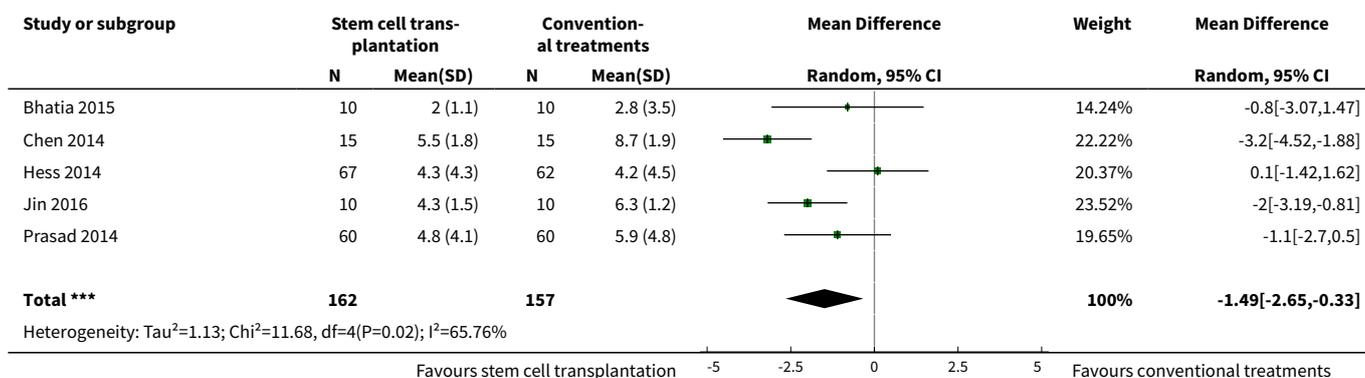
DATA AND ANALYSES

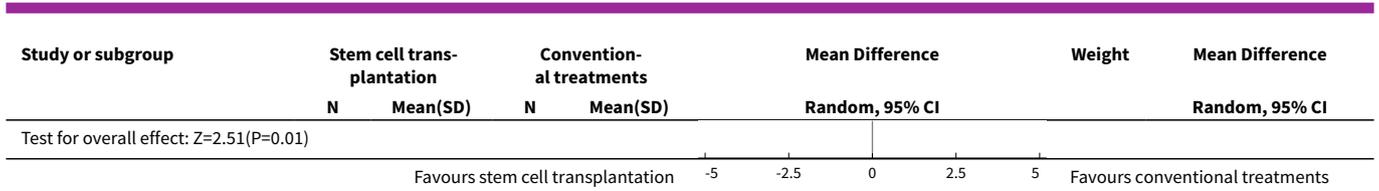
Comparison 1. Stem cell transplantation versus conventional treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Neurologic impairment (measured by NIHSS)	5	319	Mean Difference (IV, Random, 95% CI)	-1.49 [-2.65, -0.33]
2 Neurologic impairment (measured by NIHSS, by phase of disease)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Acute and subacute	4	289	Mean Difference (IV, Random, 95% CI)	-1.05 [-2.03, -0.07]
2.2 Chronic	1	30	Mean Difference (IV, Random, 95% CI)	-3.20 [-4.52, -1.88]
3 Neurologic impairment (measured by NIHSS, by route of administration)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 Intravenous	2	249	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.65, 0.70]
3.2 Intracerebral	1	30	Mean Difference (IV, Random, 95% CI)	-3.20 [-4.52, -1.88]
3.3 Lumbar subarachnoid space	1	20	Mean Difference (IV, Random, 95% CI)	-2.0 [-3.19, -0.81]
3.4 Intra-arterial	1	20	Mean Difference (IV, Random, 95% CI)	-0.80 [-3.07, 1.47]
4 Disability (measured by mRS)	6	371	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.86, 0.02]
5 Disability (measured by mRS, by phase of disease)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 Acute and subacute	5	341	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.97, 0.19]
5.2 Chronic	1	30	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.90, -0.30]
6 Disability (measured by mRS, by route of administration)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only

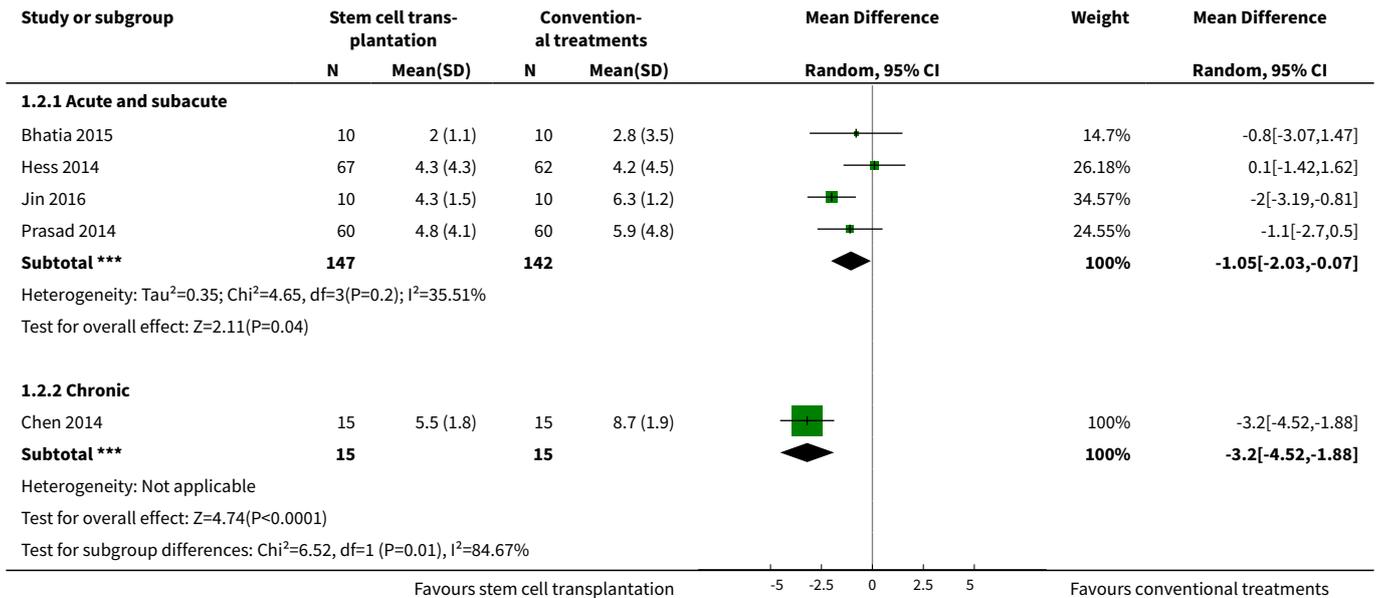
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Intravenous	3	301	Mean Difference (IV, Random, 95% CI)	0.03 [-0.28, 0.34]
6.2 Intracerebral	1	30	Mean Difference (IV, Random, 95% CI)	-0.60 [-0.90, -0.30]
6.3 Lumbar subarachnoid space	1	20	Mean Difference (IV, Random, 95% CI)	-1.10 [-1.65, -0.55]
6.4 Intra-arterial	1	20	Mean Difference (IV, Random, 95% CI)	1.00 [-2.76, 0.76]
7 Dependency (measured by BI)	3	170	Mean Difference (IV, Random, 95% CI)	14.09 [-1.94, 30.13]
8 Dependency (measured by BI, by route of administration)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Intravenous	2	150	Mean Difference (IV, Random, 95% CI)	8.75 [-9.84, 27.35]
8.2 Lumbar subarachnoid space	1	20	Mean Difference (IV, Random, 95% CI)	24.20 [11.57, 36.83]
9 Any cause of death	6	371	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.39, 1.14]
10 Severe worsening of neurological deficit	4	321	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.51, 3.79]
11 Infections	4	321	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.54, 1.17]
12 Neoplastic transformation of ischemic lesion at longer-term follow-up	2	72	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.11, 11.53]

Analysis 1.1. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 1 Neurologic impairment (measured by NIHSS).

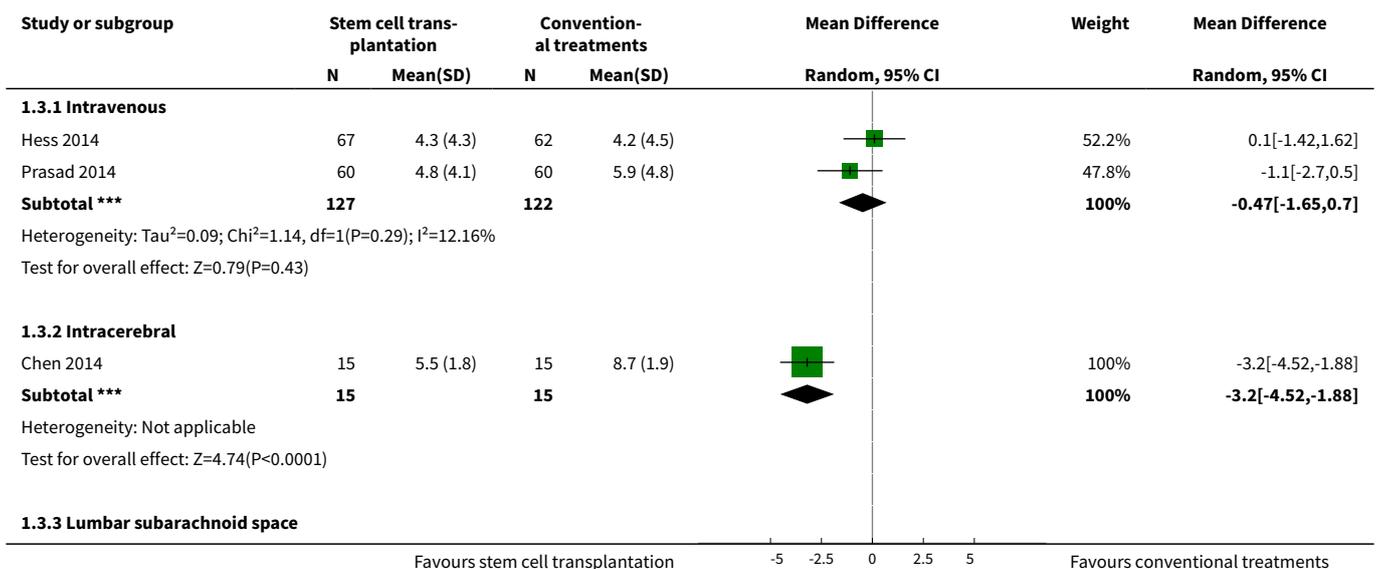


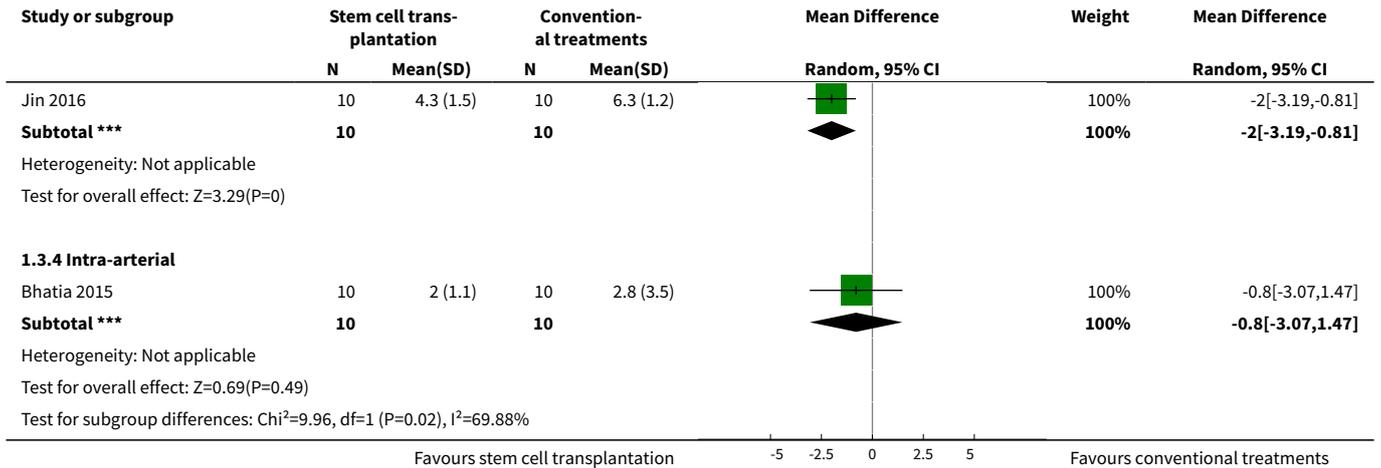


Analysis 1.2. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 2 Neurologic impairment (measured by NIHSS, by phase of disease).

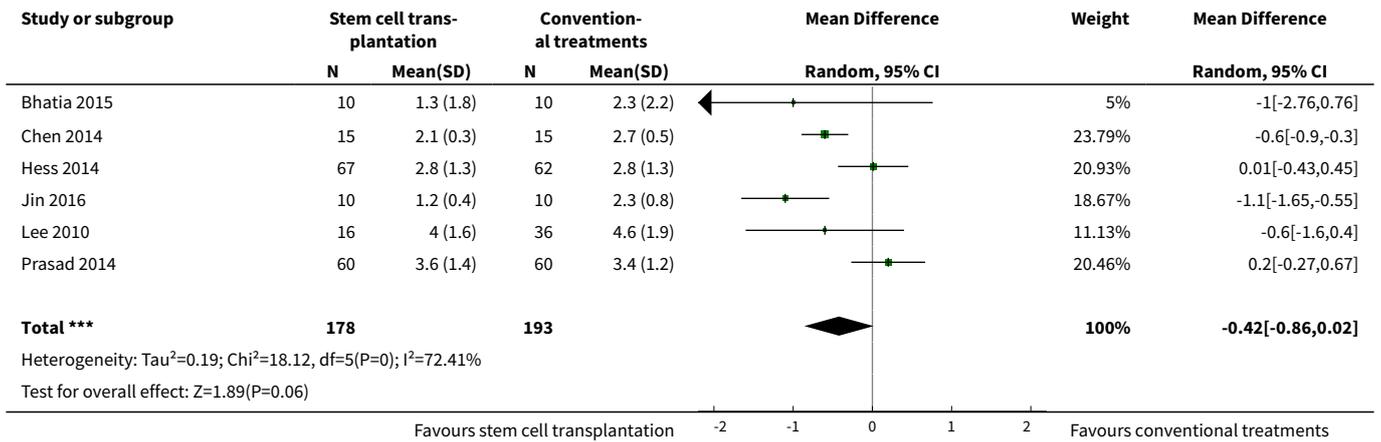


Analysis 1.3. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 3 Neurologic impairment (measured by NIHSS, by route of administration).

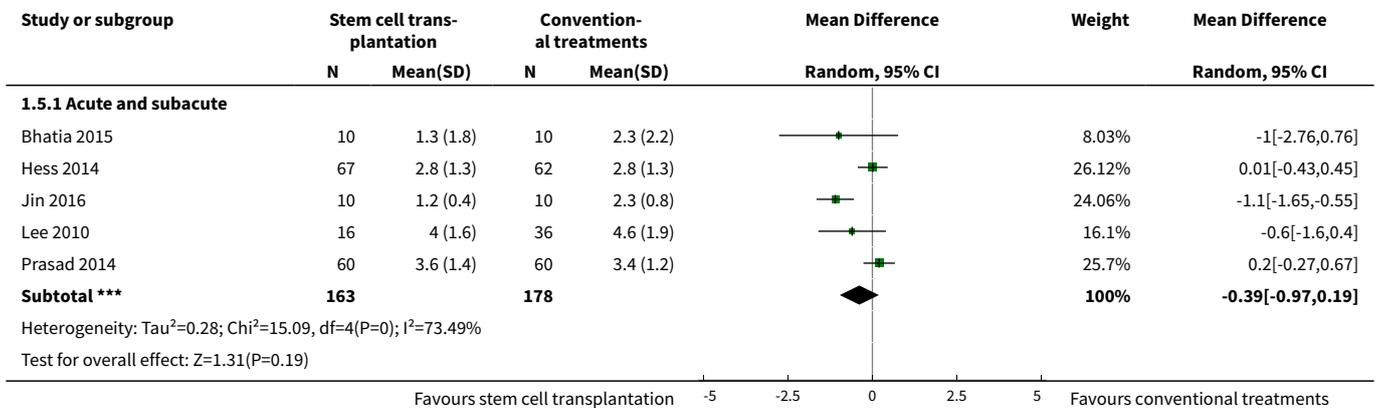


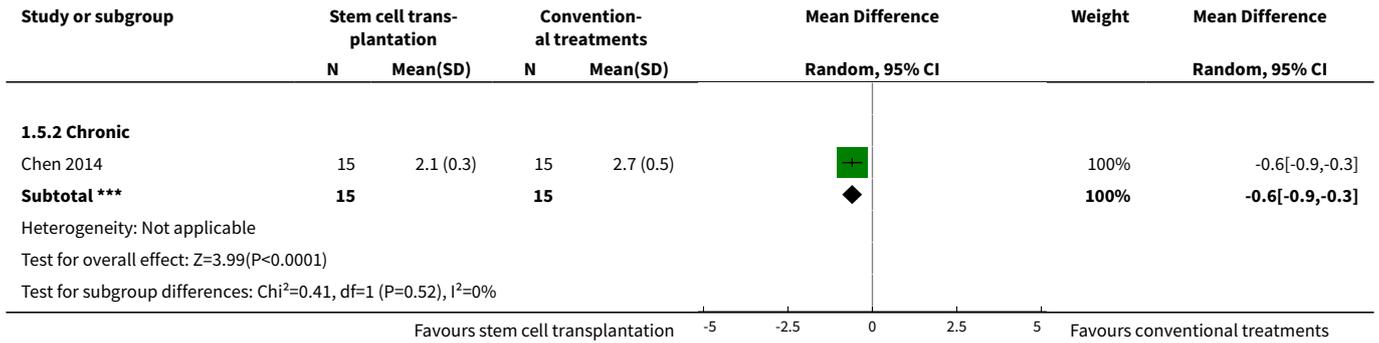


Analysis 1.4. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 4 Disability (measured by mRS).

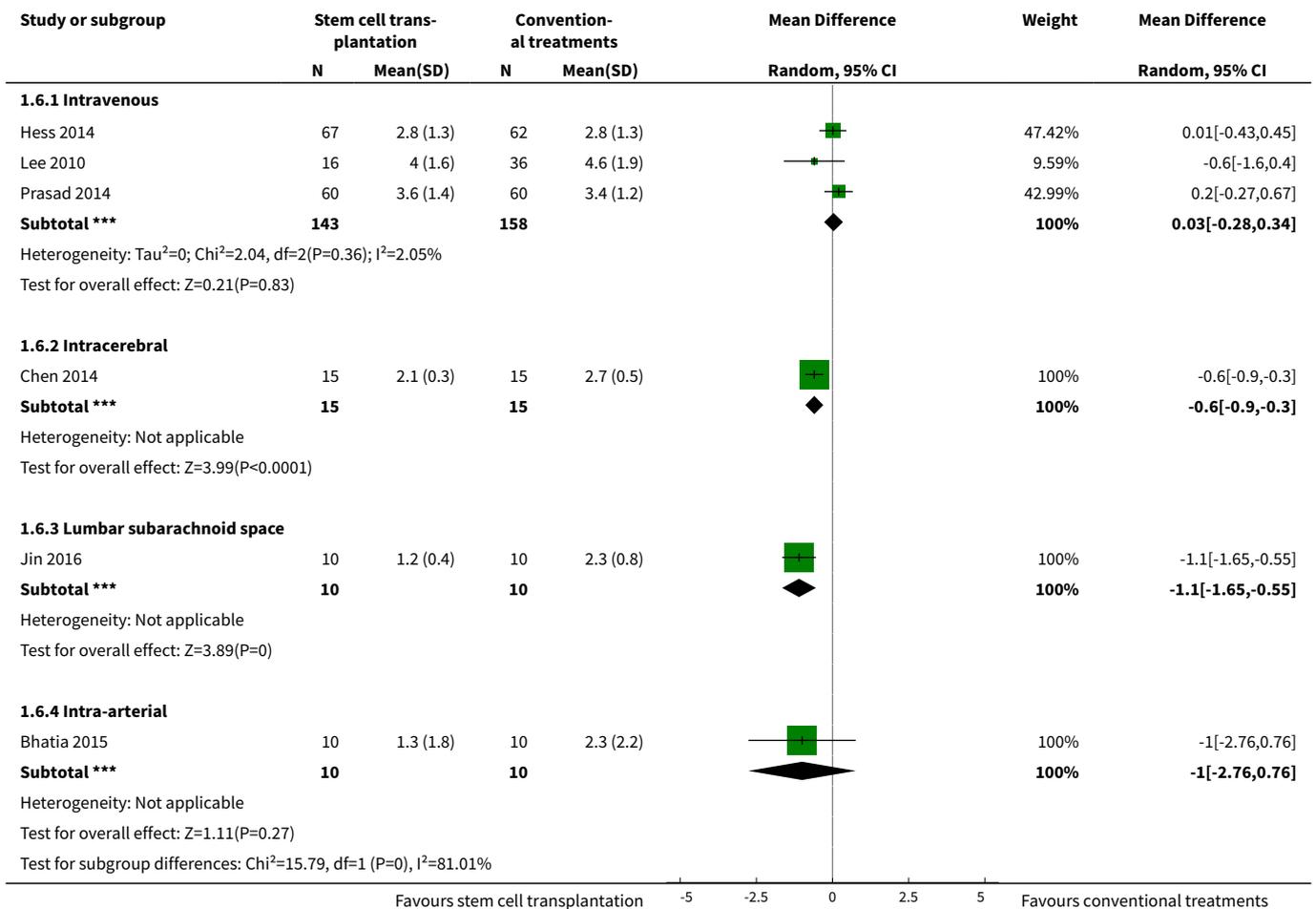


Analysis 1.5. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 5 Disability (measured by mRS, by phase of disease).

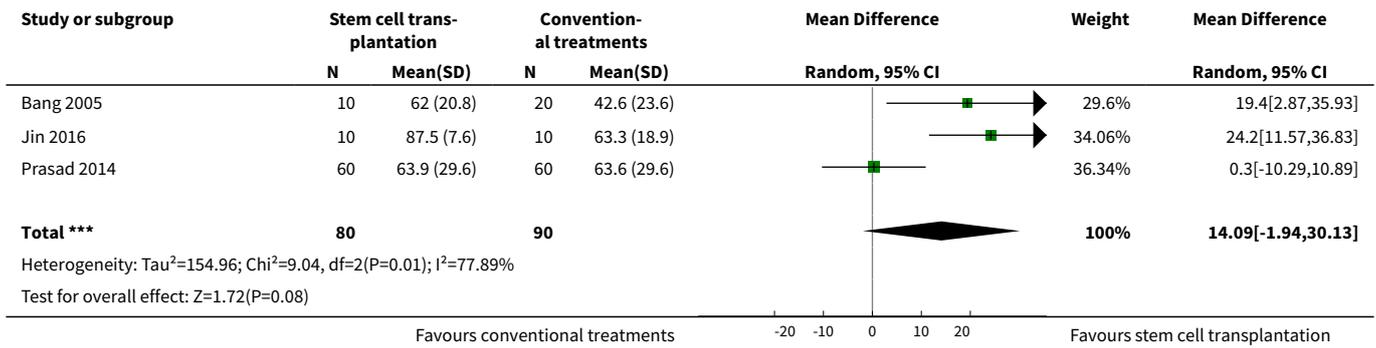




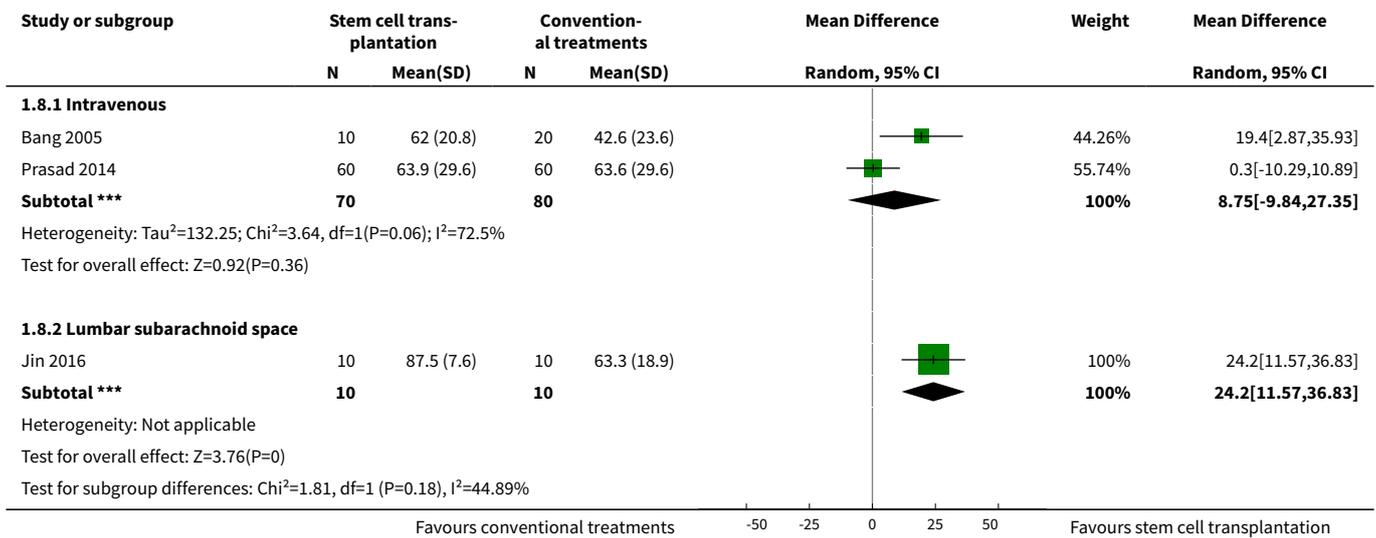
Analysis 1.6. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 6 Disability (measured by mRS, by route of administration).



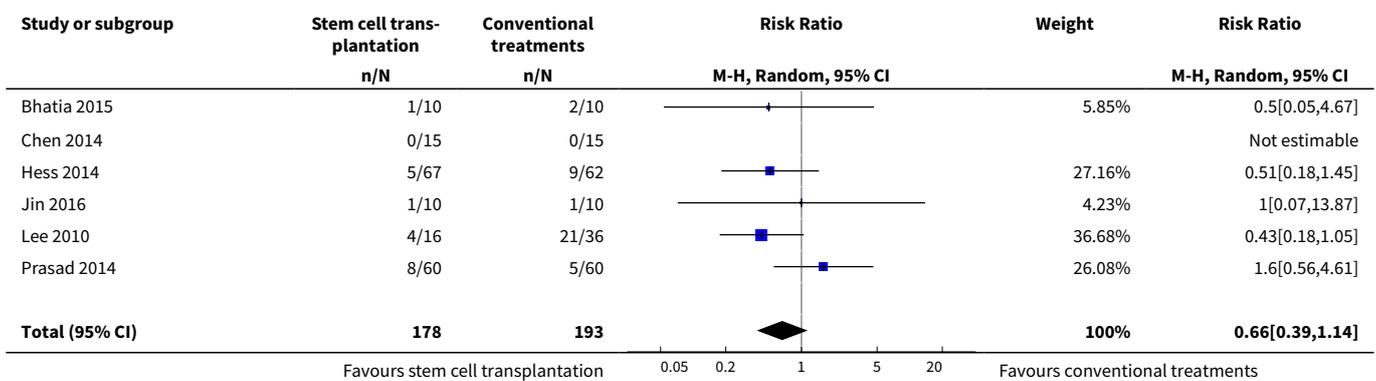
Analysis 1.7. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 7 Dependency (measured by BI).

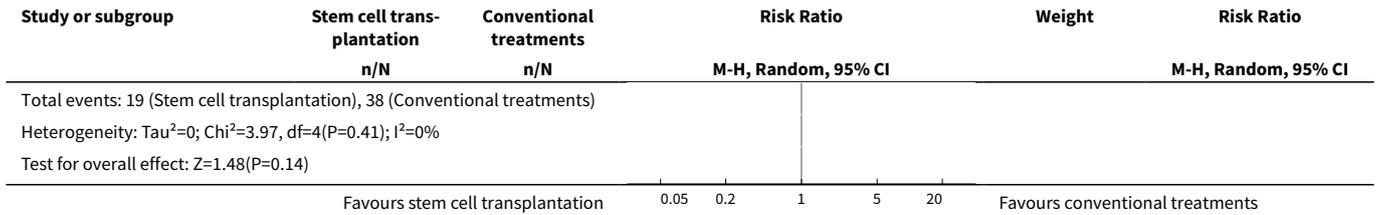


Analysis 1.8. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 8 Dependency (measured by BI, by route of administration).

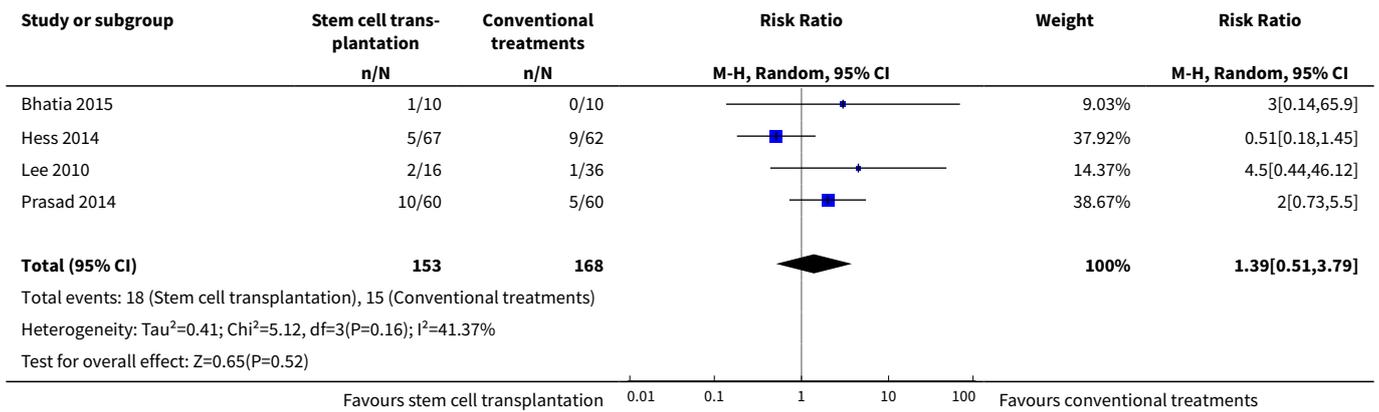


Analysis 1.9. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 9 Any cause of death.

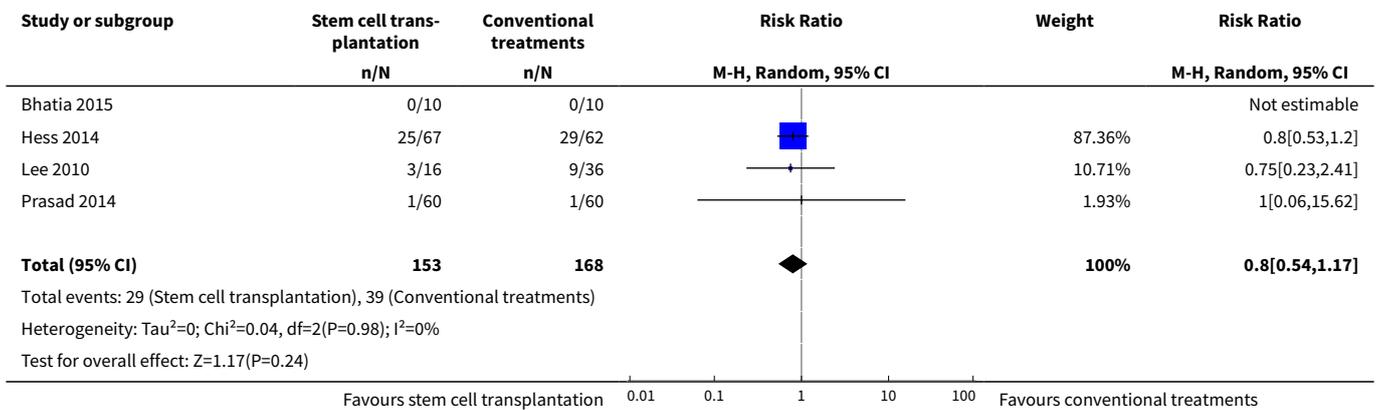




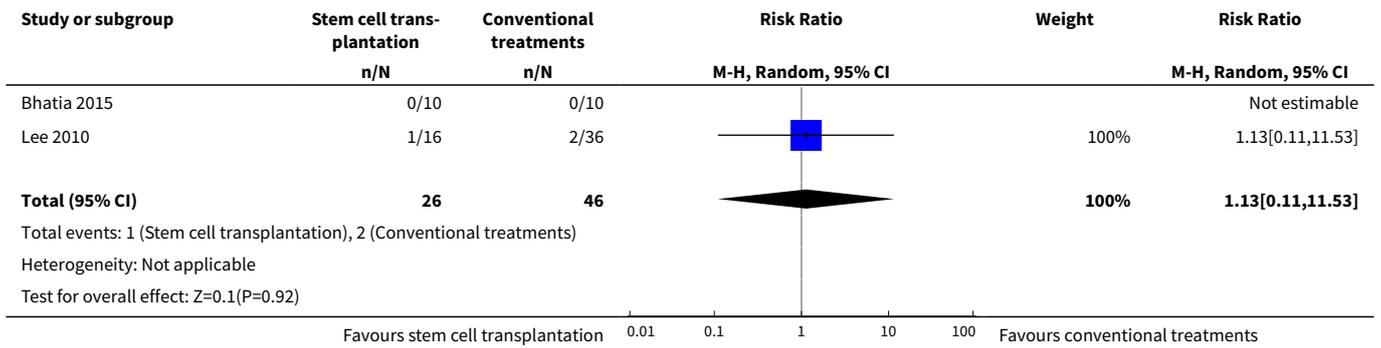
Analysis 1.10. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 10 Severe worsening of neurological deficit.



Analysis 1.11. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 11 Infections.



Analysis 1.12. Comparison 1 Stem cell transplantation versus conventional treatments, Outcome 12 Neoplastic transformation of ischemic lesion at longer-term follow-up.



APPENDICES

Appendix 1. CENTRAL search strategy

We used the following search strategy for CENTRAL.

ID Search Hits

- #1 [mh ^"cerebrovascular disease"] or [mh ^"cerebral artery disease"] or [mh ^"cerebrovascular accident"] or [mh ^stroke] or [mh ^"vertebrobasilar insufficiency"] or [mh ^"carotid artery disease"] or [mh "carotid artery obstruction"] or [mh "brain infarction"] or [mh "brain ischemia"] or [mh "occlusive cerebrovascular disease"]
- #2 [mh ^"stroke patient"] or [mh ^"stroke unit"]
- #3 (isch?emi* NEAR/6 (stroke* or apoplex* or cerebral vasc* or cerebrovasc* or cva or attack*)):ti,ab,kw (Word variations have been searched)
- #4 ((brain or cerebr* or cerebell* or vertebrobasil* or hemispher* or intracran* or intracerebral or infratentorial or supratentorial or middle cerebr* or mca* or anterior circulation) NEAR/5 (isch?emi* or infarct* or thrombo* or emboli* or occlus* or hypoxi*)):ti,ab,kw (Word variations have been searched)
- #5 {or #1-#4}
- #6 [mh ^"cell therapy"] or somatic cell therapy"] or [mh ^"cell transplantation"] or [mh "stem cell transplantation"]
- #7 [mh "stem cell"]
- #8 ((stem or progenitor or embryo* or fetal or foetal or umbilical or bone marrow or cord blood) NEAR/5 (cell or cells)):ti,ab,kw (Word variations have been searched)
- #9 (cell NEAR/5 (transplant* or graft*)):ti,ab,kw (Word variations have been searched)
- #10 (fibroblast* or myoblast*):ti,ab,kw (Word variations have been searched)
- #11 [mh ^"cell transplantation"]
- #12 {or #6-#11}
- #13 #5 and #12

Appendix 2. MEDLINE search strategy

We used the following search strategy for MEDLINE.

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
3. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
4. 1 or 2 or 3
5. cell transplantation/ or stem cell transplantation/ or cord blood stem cell transplantation/ or hematopoietic stem cell transplantation/ or mesenchymal stem cell transplantation/ or peripheral blood stem cell transplantation/
6. stem cells/ or adult stem cells/ or embryonic stem cells/ or fetal stem cells/ or fibroblasts/ or hematopoietic stem cells/ or myeloid progenitor cells/ or erythroid progenitor cells/ or mesenchymal stem cells/ or multipotent stem cells/ or exp myoblasts/ or pluripotent stem cells/ or totipotent stem cells/ or tumor stem cells/
7. exp cells/tr

8. ((stem or progenitor or embryo\$ or fetal or foetal or umbilical or bone marrow or cord blood) adj5 (cell or cells)).tw.
9. (cell adj5 (transplant\$ or graft\$)).tw.
10. (fibroblast\$ or myoblast\$).tw.
11. cell transplantation.jn.
12. 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Randomized Controlled Trials as Topic/
14. Random Allocation/
15. Controlled Clinical Trials as Topic/
16. control groups/
17. clinical trials as topic/ or clinical trials, phase i as topic/ or clinical trials, phase ii as topic/ or clinical trials, phase iii as topic/ or clinical trials, phase iv as topic/
18. double-blind method/
19. single-blind method/
20. Placebos/
21. placebo effect/
22. Drug Evaluation/
23. Research Design/
24. randomized controlled trial.pt.
25. controlled clinical trial.pt.
26. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv).pt.
27. (random\$ or RCT or RCTs).tw.
28. (controlled adj5 (trial\$ or stud\$)).tw.
29. (clinical\$ adj5 trial\$).tw.
30. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
31. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseud or random\$).tw.
32. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
33. placebo\$.tw.
34. controls.tw.
35. exp animals/ not humans.sh.
36. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
37. exp animals/ not humans.sh.
38. 4 and 12 and 36
39. 38 not 37

Appendix 3. Embase search strategy

We used the following search strategy for Embase.

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/
2. stroke patient/ or stroke unit/
3. (isch?emi\$ adj6 (stroke\$ or apoplex\$ or cerebral vasc\$ or cerebrovasc\$ or cva or attack\$)).tw.
4. ((brain or cerebr\$ or cerebell\$ or vertebrobasil\$ or hemispher\$ or intracran\$ or intracerebral or infratentorial or supratentorial or middle cerebr\$ or mca\$ or anterior circulation) adj5 (isch?emi\$ or infarct\$ or thrombo\$ or emboli\$ or occlus\$ or hypoxi\$)).tw.
5. 1 or 2 or 3 or 4
6. cell therapy/ or somatic cell therapy/ or cell transplantation/ or exp stem cell transplantation/
7. exp stem cell/
8. ((stem or progenitor or embryo\$ or fetal or foetal or umbilical or bone marrow or cord blood) adj5 (cell or cells)).tw.
9. (cell adj5 (transplant\$ or graft\$)).tw.
10. (fibroblast\$ or myoblast\$).tw.
11. cell transplantation.jn.
12. 6 or 7 or 8 or 9 or 10 or 11
13. Randomized Controlled Trial/
14. Randomization/
15. Controlled Study/
16. control group/
17. clinical trial/ or phase 1 clinical trial/ or phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or controlled clinical trial/
18. Crossover Procedure/
19. Double Blind Procedure/
20. Single Blind Procedure/ or triple blind procedure/
21. latin square design/
22. Parallel Design/

23. Placebo/
24. Multicenter Study/
25. experimental design/ or experimental study/ or quasi experimental study/
26. experimental therapy/
27. drug comparison/ or drug dose comparison/
28. drug screening/
29. EVALUATION/ or "EVALUATION AND FOLLOW UP"/ or evaluation research/ or clinical evaluation/
30. METHODOLOGY/
31. "types of study"/
32. research subject/
33. Comparative Study/
34. "systematic review"/
35. Meta Analysis/
36. random\$.tw.
37. (controlled adj5 (trial\$ or stud\$)).tw.
38. (clinical\$ adj5 trial\$).tw.
39. ((control or treatment or experiment\$ or intervention) adj5 (group\$ or subject\$ or patient\$)).tw.
40. (surgical adj5 (group\$ or subject\$ or patient\$)).tw.
41. (quasi-random\$ or quasi random\$ or pseudo-random\$ or pseudo random\$).tw.
42. ((multicenter or multicentre or therapeutic) adj5 (trial\$ or stud\$)).tw.
43. ((control or experiment\$ or conservative) adj5 (treatment or therapy or procedure or manage\$)).tw.
44. ((singl\$ or doubl\$ or tripl\$ or trebl\$) adj5 (blind\$ or mask\$)).tw.
45. (coin adj5 (flip or flipped or toss\$)).tw.
46. latin square.tw.
47. versus.tw.
48. (cross-over or cross over or crossover).tw.
49. placebo\$.tw.
50. sham.tw.
51. (assign\$ or alternate or allocat\$ or counterbalance\$ or multiple baseline).tw.
52. controls.tw.
53. (treatment\$ adj6 order).tw.
54. (meta-analy\$ or metaanaly\$ or meta analy\$ or systematic review or systematic overview).tw.
55. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
57. 5 and 12 and 55
58. 57 not 56

Appendix 4. BIOSIS search strategy

We used the following search strategy for BIOSIS.

You searched for: TOPIC: (stroke or cerebr*) AND TOPIC: (stem cell* or cell transplant*) AND TOPIC: (trial* or random* or placebo* or blind*)

Timespan: All years.

Indexes: BCI.

WHAT'S NEW

Date	Event	Description
23 February 2019	New citation required but conclusions have not changed	Conclusions not changed
13 August 2018	New search has been performed	Search strategy updated. Six new trials with 371 participants with ischemic stroke added. Meta-analysis of data from RCTs completed when at least two studies were available for each outcome.

CONTRIBUTIONS OF AUTHORS

Giorgio B Boncoraglio drafted the protocol, guided trial selection and assessment, contacted trialists about unpublished data, guided extraction of trial and outcome data, and drafted and approved the final manuscript of the review.

Michela Ranieri screened titles and abstracts of references identified by the search, searched electronic databases and conference proceedings, selected and assessed trials, extracted trial and outcome data, and contributed to and approved the final manuscript of the review.

Anna Bersano contributed to the conception and design of the protocol, screened titles and abstracts of references identified by the search, searched electronic databases and conference proceedings, selected and assessed trials, extracted trial and outcome data, and contributed to and approved the final manuscript of the review.

Eugenio A Parati contributed to the conception and design of the protocol, contributed to the search of unpublished data and interpretation of the data, and contributed to and approved the final manuscript of the review.

Cinzia Del Giovane analyzed the extracted data, and contributed to and approved the final manuscript of the review.

DECLARATIONS OF INTEREST

Giorgio Battista Boncoraglio: none known.

Michela Ranieri: none known.

Anna Bersano: none known.

Eugenio A Parati: none known.

Cinzia Del Giovane: none known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None

INDEX TERMS

Medical Subject Headings (MeSH)

*Stem Cell Transplantation [methods]; Brain Ischemia [*therapy]; Randomized Controlled Trials as Topic; Stroke

MeSH check words

Humans