Stem cell transplantation for ischemic stroke (Protocol)

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TABLE OF CONTENTS

Stem cell transplantation for ischemic stroke

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A B S T R A C T

This is the protocol for a review and there is no abstract. The objectives are as follows:

The review aims to assess the efficacy and safety of stem cell transplantation, compared with conventional treatments, in patients with ischemic stroke.

BACKGROUND

Acute stroke is one of the leading causes of morbidity and mortality worldwide. In industrialised countries, stroke is the second or third most common cause of death and the primary cause of morbidity and long-term disability (Hack 2003).

Some thrombolytic interventions given in the acute phase of ischemic stroke, such as intravenous recombinant tissue plasminogen activator (rtPA), improve outcomes, including survival and residual disability (Kwiatkowski 1999). However, despite significant clinical benefit, only a minority of eligible patients receive thrombolysis within the required three hours. When aspirin is administered within 48 hours of stroke onset, the resulting small but significant decline in morbidity and mortality seems to be due to a reduction of early recurrent stroke rather than limitation of neurological consequences (Adams 2007). Therefore, once stroke-induced cell damage has occurred, little can be done to improve functional outcome, except for rehabilitation therapy and pharmacological management of co-morbidities.

A growing number of studies highlight the potential of stem cell transplantation as a novel therapeutic approach for stroke. Studies in animal models of ischemic stroke have shown that stem cells transplanted into the brain not only survive, but also lead to functional improvement (Chopp 2002). Although many experimental studies have shown that cell transplantation improves stroke recovery, the mechanisms responsible for this are largely unknown. It is hypothesised that the cell grafts provide trophic factors that enhance cell survival and function, establish local connections that enhance synaptic activity, or provide a bridge for host axonal regeneration (Chopp 2002; Wechsler 2003).

Following these results, clinical trials of stem cell transplantation in patients with ischemic stroke have commenced (Savitz 2004; Pluchino 2005; Bliss 2007). However, effective therapies will depend on strategies that increase the survival of the new neurons and enhance their incorporation into the reorganising neural circuitries (Lindvall 2006). Many factors may be critical for transplantation success: the localisation and extension of the infarct area; the time window (acute or chronic phase); the source of stem cells (human or animal; embryonic, fetal, or adult; from brain or other tissues); the need for immunosuppression; and the route of administration (local or systemic).

To date, evidence for the benefits of stem cell transplantation in ischemic stroke patients is lacking. The safety of these interventions also requires careful evaluation (Bliss 2007). A systematic review of the available clinical trials is needed to assess the benefit-to-risk profile of this type of intervention.

OBJECTIVES

The review aims to assess the efficacy and safety of stem cell transplantation, compared with conventional treatments, in patients with ischemic stroke.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include randomized controlled trials (RCTs).

Types of participants

We will include patients 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 allows for the inclusion of studies investigating both the acute neuroprotective and non-acute neurorestorative effects of transplanted stem cells.

Types of interventions

We will compare stem cell transplantation with conventional treatments. All types of stem cell transplantation will be included 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.

Types of outcome measures

Primary outcomes

Efficacy (functional outcome or disability/dependency, or both) at longer follow up will be assessed using clinical outcome measures or validated international scales (e.g. National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale, Barthel Index), or both. The minimum follow-up period accepted is six months.

Secondary outcomes

The following post-procedure safety outcomes will be evaluated.
(1) Any cause of death within 30 days of the procedure and thereafter.
(2) Severe worsening of neurological deficit (increase of 4 points on NIHSS scale or equivalent) within 30 days of procedure and thereafter.
(3) Infections within 30 days of the procedure and thereafter.
(4) Neoplastic transformation of ischemic lesion at longer follow up.

We will also consider the following subgroups.

(1) Type of participant:

(a) phase of disease: acute and subacute (within three months of ischemic stroke) versus chronic (more than three months after ischemic stroke).

(2) Type of treatment:

(a) source of stem cells: human versus non-human, embryonic and fetal versus adult, neural versus non-neural;

(b) route of administration: neurosurgery versus intra-arterial versus intravenous.

Search methods for identification of studies

See: 'Specialized register' section in Cochrane Stroke Group

We will search the Cochrane Stroke Group Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, latest issue), MEDLINE (1966 to present) (Appendix 1), EMBASE (1980 to present), Science Citation Index (1985 to present), and BIOSIS (1985 to present).

In an effort to identify further published, unpublished, and ongoing trials we will handsearch potentially relevant conference proceedings, screen reference lists, and search ongoing trials and research registers (from www.controlled-trial.com, www.strokecenter.org, http://www.stemcellforum.org/). We will also contact individuals active in the field and stem cell manufacturers (from http://www.stem-cell-companies.com/).

Data collection and analysis

Selection of studies

Two review authors (GB and AB) will read the titles and abstracts (if available) of the identified references and eliminate obviously irrelevant studies. Two review authors (GB and AB) will independently examine potentially relevant studies using the predetermined criteria of whether:

- the study is an RCT;
- the participants have had an ischemic stroke and the intervention is stem cell transplantation;
- functional impairment or disability/dependency, or both, are measured at entry and at the minimum follow-up period of six months using validated international scales.

We will rank studies as excluded, included, or uncertain using a checklist. Any disagreements will be resolved through discussion with a third review author (LC).

Assessment of methodological quality of included studies

Two review authors (GB and AB) will independently assess the methodological quality of the trials using standard Cochrane criteria: method of randomisation (true or quasi-randomisation), concealment of allocation (adequate, inadequate, or unclear), blinding of outcome evaluators, analysis by intention-to-treat, and losses to follow up. We will rank methodological quality as high, low, or ambiguous. Any disagreements will be resolved through discussion with a third review author (LC).

Data extraction and analysis

Two review authors (GB and AB) will independently extract data from publications on quality parameters (as above); source, route, and timing of stem cell transplantation; the number of events; and status within 30 days after the treatment, at six months, and at the end of the follow-up period.

We will combine the results using a meta-analytic approach. We will calculate the weighted treatment effect and 95% confidence intervals across trials using a random-effects model. For proportions (dichotomous outcomes), we will calculate the relative risk (RR). We will convert continuous data to the mean difference (MD) and calculate an overall MD.

To quantify between-study heterogeneity, we will use the I-squared (I^2) statistic. If there is substantial heterogeneity ($I^2 > 75\%$), we will explore the reasons for this.

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

If there are sufficient RCTs, we will conduct a subgroup analysis using meta-regression techniques, otherwise we will use the chi-square test. We will compare:

- acute and subacute with chronic transplantations;
- human with non-human transplantations;
- embryonic and fetal with adult transplantations;
- neural with non-neural transplantations;
- and local with systemic transplantations.

We will use Review Manager 5 for all data entry and analysis.

REFERENCES

Additional references

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy

The following search strategy will be used for MEDLINE and modified to suit the other databases.

1. cerebrovascular disorders/ or exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or carotid stenosis/ or cerebrovascular accident/ or exp brain infarction/ or exp hypoxia-ischemia, brain/ or intracranial arterial diseases/ or cerebral arterial diseases/ or intracranial arteriosclerosis/ or exp "intracranial embolism and thrombosis"/

2. ((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.

3. (isch?emi$ adj6 (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or attack$)).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. 4 and 12
14. limit 13 to humans

H I S T O R Y

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C O N T R I B U T I O N S   O F   A U T H O R S

Giorgio Boncoraglio drafted the protocol and approved the final manuscript. He will search electronic databases and conference proceedings, contact trialists about unpublished data, screen titles and abstracts of references identified by the search, select and assess trials, extract trial and outcome data, and draft and approve the final manuscript of the review.

Anna Bersano contributed to the conception and design of the protocol and approved the final manuscript. She will search electronic databases and conference proceedings, contact trialists about unpublished data, screen titles and abstracts of references identified by the search, select and assess trials, extract trial and outcome data, contribute to the analysis and interpretation of the data, and contribute to and approve the final manuscript of the review.

Livia Candelise contributed to the conception and design of the protocol and approved the final manuscript. She will guide trial selection and assessment, as well as the statistical analysis and the interpretation of the data. She will contribute to and approve the final manuscript of the review.

Brent Reynolds contributed to the conception and design of the protocol and approved the final manuscript. He will contribute to the search of unpublished data and interpretation of the data. He will contribute to and approve the final manuscript of the review.

Eugenio Parati contributed to the conception and design of the protocol and approved the final manuscript. He will contribute to the search of unpublished data and interpretation of the data. He will contribute to and approve the final manuscript of the review.

D E C L A R A T I O N S   O F   I N T E R E S T

None known