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Hematopoietic stem cell transplantation for people with sickle cell disease (Review)

Oringanje C, Nemecek E, Oniyangi O

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[Intervention Review]

Hematopoietic stem cell transplantation for people with sickle cell disease

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ABSTRACT

Background

Sickle cell disease is a genetic disorder involving a defect in the red blood cells due to its sickled hemoglobin. The main therapeutic interventions include preventive and supportive measures. Hematopoietic stem cell transplantations are carried out with the aim of replacing the defective cells and their progenitors (hematopoietic (i.e. blood forming) stem cells) in order to correct the disorder. This is an update of a previously published review.

Objectives

To determine whether stem cell transplantation can improve survival and prevent symptoms and complications associated with sickle cell disease. To examine the risks of stem cell transplantation against the potential long-term gain for people with sickle cell disease.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Group's Haemoglobinopathies Trials Register complied from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and quarterly searches of MEDLINE.

Unpublished work was identified by searching the abstract books of major conference proceedings and we conducted a search of the website: www.ClinicalTrials.gov.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 06 October 2015.

Selection criteria

Randomized controlled and quasi-randomized studies that compared any method of stem cell transplantation with either each other or with any of the preventive or supportive interventions (e.g. periodic blood transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen) in people with sickle cell disease irrespective of the type of sickle cell disease, gender and setting.

Data collection and analysis

No relevant trials were identified.

Main results

Ten trials were identified by the initial search and none for the update. None of these trials were suitable for inclusion in this review.

Authors' conclusions

Reports on the use of hematopoietic stem cell transplantation improving survival and preventing symptoms and complications associated with sickle cell disease are currently limited to observational and other less robust studies. No randomized controlled trial assessing the benefit or risk of hematopoietic stem cell transplantations was found. Thus, this systematic review identifies the need for a multicentre randomized controlled trial assessing the benefits and possible risks of hematopoietic stem cell transplantations comparing sickle status and severity of disease in people with sickle cell disease.

PLAIN LANGUAGE SUMMARY

Transplantation of blood-forming stem cells for children with sickle cell disease

Review question

We reviewed the evidence about the cure rate and risks of hematopoietic stem cell transplantation for people with sickle cell disease.

Background

Sickle cell disease is a genetic disorder mainly characterized by the presence of deformed, sickle-shaped red blood cells in the blood stream. These cells deprive tissues of blood and oxygen resulting in periodic and recurrent painful attacks. Complications include acute chest syndrome and stroke. Although sickle cell disease is responsive to preventive and supportive measures such as the use of prophylactic antibodies and periodic blood transfusion, these do not provide a cure. The use of hematopoietic (blood forming) stem cell transplantation involves replacing the deformed red blood cells and its stem cells with stem cells from a healthy donor thereby producing normal red blood cells. These stem cells can be derived from either the bone marrow or blood (umbilical cord blood or peripheral blood) of a healthy individual. This is an update of a previously published review.

Search date

The evidence is current to: October 2015.

Key results

There are no randomized controlled trials assessing the benefits and risks; the most appropriate source of stem cells; or the most eligible participants (those who have experience severe complication or those who have not) of the procedure in people with sickle cell disease.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is a genetic hemoglobin disorder that can cause severe pain crises and dysfunction of virtually every organ system in the body, ultimately causing premature death. SCD occurs when the haemoglobin variant Haemoglobin S gene is inherited from both parents; the homozygous state (HbSS) is the most prevalent form of the disease (Serjeant 2001). Other clinically significant types of SCD are compound heterozygous conditions in which the sickle haemoglobin interacts with other abnormal haemoglobins, such as haemoglobin C (HbSC) or ß-thalassaemia (HbSb+ and HbSb0) (Lane 2001). Annually, worldwide, there are approximately 275,000 SCD affected conceptions or births (Modell 2008). Significant morbidity and premature death may result from SS disease with average life expectancy estimated at between 42 years and 53 years for men; and between 48 years and 58 years for women (Platt 1994). The disease is characterized by the presence of distorted, sickle-shaped red blood cells in the blood stream. These distorted cells can get trapped in small blood vessels, causing blockages depriving the tissues of blood and oxygen in turn leading to pain episodes known as vaso-occlusive crises. Blockages may even cause severe damage to major organs such as the brain, liver, kidneys and spleen.

Preventive and supportive measures such as periodic blood transfusion and use of prophylactic antibiotics are the main therapeutic interventions used. Long-term blood transfusion, although shown to be effective in preventing stroke and other complications of SCD (Adams 1998), is also associated with increased risk of iron overload, infection, and alloimmunization (Nietert 2000). Hydroxyurea, which is known to raise foetal haemoglobin and decrease cellular dehydration, has been shown to be both safe and effective in severely affected SS adults in reducing the number of SCD complications, but also has recognized side effects such as myelosuppression and nausea (Jones 2001).

Description of the intervention

Currently hematopoietic stem cell transplantation is an accepted form of treatment for various hematologic disorders. Its goal in sickle cell disease is to eliminate sickle red blood cells and progenitors (hematopoietic (blood forming) stem cells (HSCs). These are replaced with normal stem cells, to produce cells that expresses total or at least partial correction of the abnormal haemoglobin phenotype (Walters 2001). Sources of stem cells include bone marrow (bone marrow transplantation (BMT)); peripheral blood (peripheral blood cell transplantation (PBCT)); and umbilical cord blood (umbilical cord blood transplantation (UCBT)) (LHSC 2003).

Most hematopoietic stem cell transplantations (HSCTs) involve allogeneic transplant, where the individual receives stem cells from another person, related or unrelated. Ideally, the recommended donor is a sibling with an immunologic match (human leucocyte antigen (HLA) type match) (LHSC 2003). After identification of a suitably matched donor, a recipient undergoes extensive evaluations to confirm disease status, major organ functions and general health status. The individual then receives the preparative regimen, also called conditioning. For HSCT, the conditioning regimen must provide both myeloablation and effective immunosuppression in the recipient. Myeloblative regimens include busulfan, cytoxan with or without antithymocyte globulin or total lymphoid irradiation (Adamkiewicz 2004; Bernaudin 1993; Locatelli 2003; Vermylen 1998; Walters 2001). There are toxicities associated with myeloablative regimens; such as infertility and gonadal failure, chronic graft versus host disease (GVHD) (an immune reaction of donor cells against recipient tissues and a potential for secondary malignancies). In order to avert these, reduced intensity conditioning regimens were developed, which include a purine analog, an alkylating agent, or low-dose total-body irradiation. The purine analogs include fludarabine, cladribine, and pentostatin (Horan 2005; Iannone 2003; Jacobsohn 2004; van Besien 2000). With reduced-intensity preparative regimens, unfavourable outcomes are frequently reported, especially graft failure (the lack of sustained donor engraftment) (Iannone 2003; van Besien 2000). Immunosuppressants such as cyclosporine and methotrexate have also used to prevent GVHD (Atkins 2003).

Since its first successful use in 1968, HSCT has been used to treat a variety of malignant disorders. In 1984 the first case reported of HSCT for SCD involved an individual with acute myelogenous leukemia who was cured of both disorders after a bone marrow transplantation (Johnson 1984; Milpied 1988). This case illustrated the elimination of SCD upon engraftment of donor hematopoietic stem cells. Since then, several groups have studied HSCT for treating mostly children (under 16 years) with symptomatic SCD, showing severe complications such as stroke, recurrent vaso-occlusive painful crises, acute chest syndrome, sickle nephropathy and osteonecrosis of multiple joints (Johnson 1984; Walters 1995; Brichard 1996; Walters 1996; Walters 2001; Vermylen 2003; Jaing 2005). There is limited information about the outcome after HSCT amongst adults. However, adults might have a higher risk of death compared to younger patients (Lucarelli 1999; van Besien 2000), due in part to the increased frequency of GVHD (Sullivan 1991).

Why it is important to do this review

To date, approximately 250 people have undergone HSCT for SCD. Studies have reported an overall survival rate greater than 90% and event-free survival rate greater than 80% at two years, four years and further follow-up, suggesting that HSCT cures SCD (Walters 1996; Bernaudin 1997; Vermylen 2000; Walters 2000; Locatelli 2003). This chance for cure comes at the expense of an increased risk for adverse events, including death, GVHD, post-transplant neurologic complications, and late effects such as gonadal failure, sterility and reoccurrence of SCD (Giardini 1993; Bernaudin 1997; Vermylen 2000; Walters 2000; Walters 2002).

The use of HSCT in people with SCD is well established in developed countries. Current investigations are targeted at determining what population are best fitted for the procedure and improving conditioning regimens that greatly reduce graft rejection and graft versus host disease (GVHD). This systematic review aims to assess the cure rate and risks associated with HSCT. This is an update of previously published versions of this review (Oringanje 2009; Oringanje 2013).

OBJECTIVES

To examine the cure rate and risks of HSCT for people with SCD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomized controlled and quasi-randomized studies.

Types of participants

Children and adults with SCD of all phenotypes, either gender and in all settings*.

Post hoc change: the review has been expanded to include adults.

Types of interventions

Methods of stem cell transplantation compared with each other or with supportive care (e.g. periodic transfusion, use of hydroxyurea, antibiotics, pain relievers, supplemental oxygen).

Types of outcome measures

Primary outcomes

1. Event-free survival (individuals alive and free of SCD symptoms)

Secondary outcomes

1. Mortality (overall and at 100-days, and one-year post-HSCT)
2. Transplant-related (non SCD-related) mortality
3. Incidence of acute graft versus host disease
4. Incidence of chronic graft versus host disease
5. Incidence of neurological complications
6. Incidence of late complications related to SCD
7. Quality of life using a validated scale.
8. Graft rejection with recurrence or persistence of SCD
9. Other transplant-related morbidity (e.g. adverse drug reactions)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND (stem cell* OR bone marrow* OR gene therapy).

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Health Research Council Meetings; the National Sickle Cell Disease Program Annual Meeting. We also searched reference lists of articles. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group module.

Date of the most recent search of the Group's Haemoglobinopathies Trials Register: 06 October 2015.

We conducted a search of the website: www.ClinicalTrials.gov (Appendix 1). Date of last search: 11 December 2015.

Searching other resources

We searched the Meetings of the American society for Blood and Marrow Transplantation (1970 to December 2015); Center for the International Blood and Marrow Transplant Research (1972 to December 2015); and European Group for Blood and Marrow Transplantation (1970 to December 2015).

Data collection and analysis

Since no trials were included in the review, we are unable to carry out any analysis. For future updates, when studies are identified for inclusion in the review, the following methods will be applied.

Selection of studies

Two authors (CO and EN) independently screened the ten trials found by the initial search of all the databases and reference lists to identify papers with potential relevance to the review. We obtained the full text of selected articles. Two authors (CO and EN) independently selected trials for inclusion by applying the inclusion criteria to all potential trials. No relevant trials were found. Review authors were blinded to trial authors, institutions, journal of publication and study results. Disagreements concerning inclusion were resolved by discussion.

Data extraction and management

For future updates, when trials are found to be eligible for inclusion in the review, using data extraction forms designed specifically for this review, two authors (CO and EN) will independently perform data extraction. Information included on this form will include the number, age and gender of participants; type of SCD; type of HSCT; HLA status of the donor and recipient); the study design; duration of the study and the interventions; GVHD prophylaxis. The authors will extract data for all relevant outcome measures including death before transplant; and will resolve any disagreement about extracted data by discussion.

Unless otherwise stated above (Types of outcome measures), where possible, outcome data will be grouped into those measured at three months, at six months, then six monthly intervals (i.e. one year, eighteen months and so on). If outcome data are recorded at other time periods, then consideration will be given to examining these as well.

Assessment of risk of bias in included studies

Two authors (CO and EN), using a simple form, will independently assess the risk of bias of the included trials and will follow the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions 5.1* (Higgins 2011).

We will assess the following domains as having either a low, unclear or high risk of bias:

1. randomisation;
2. concealment of allocation;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting.

Measures of treatment effect

We will relate dichotomous variables to risk using the risk ratio (RR); we will relate continuous outcomes to risk using the mean difference (MD); we plan, if possible, to extract hazard ratios with their 95% confidence intervals for any time-to-event data (e.g. event-free survival and mortality).

Dealing with missing data

If possible, we will extract data by allocation intervention, irrespective of compliance with the allocated intervention, in order to allow an 'intention-to-treat' analysis; otherwise we will perform an 'as treated' analysis. We will include these variables in a meta-analysis using Review Manager 5.1 for the outcomes selected above (Review Manager 2011).

Assessment of heterogeneity

We will assess heterogeneity both by visual inspection of the forest plots and by a formal statistical test for heterogeneity using the chi-square test for interaction (or trend) (DerSimonian 1986). We will assess any detected heterogeneity and investigate reasons for this. If we are not able to explain any heterogeneity found, we will clearly state this in the review and apply appropriate caution in the interpretation of these data. If a cause for heterogeneity is apparent and justifies separate analyses of the studies, we will undertake these analyses and present the results.

Assessment of reporting biases

We will attempt to assess whether the review is subject to publication bias by using a funnel plot to graphically illustrate variability between trials and by using Egger's test (Egger 1997). If asymmetry in the funnel plot is detected, we will explore causes other than publication bias.

Data synthesis

Where meta-analysis is possible, we plan to use the fixed-effect model, however, If there is significant heterogeneity (I^2 > 50%), a random effects model will be considered.

Subgroup analysis and investigation of heterogeneity

We will also attempt to perform subgroup analysis by sickle status: 'severe genotypes' (HbSS and Sb0) and 'mild genotypes' (SC and Sb+); severity of disease (if an individual has experienced severe symptoms of the diseases such as stroke, acute chest syndrome, vaso-occlusive crises etc); age (children versus adults) and setting (developed versus developing countries). We will attempt to perform analysis by type of HSCT used (comparing BMT, PBCT and UBCT) and conditioning regimen if possible.

Sensitivity analysis

We plan to perform a sensitivity analysis based on the generation of the allocation sequence, including and excluding quasi-randomised trials.

RESULTS

Description of studies

No trials have been identified which are eligible for inclusion in the review.

The trials listed as 'Excluded studies' were not eligible for inclusion because they were neither RCTs nor quasi-RCTs (Walters 1995; Walters 1996; Vermylen 2000; Walters 2001; Weinberg 2001; Iannone 2003; Locatelli 2003; Hongeng 2004; Horan 2005; Bernaudin 2007).

Risk of bias in included studies

No trials eligible for inclusion in this review have been identified.

Effects of interventions

No trials eligible for inclusion in this review have been identified.

DISCUSSION

Over 30 years after the discovery of the use of hematopoietic stem cells to cure sickle cell disease (SCD), it is surprising that there are no randomized controlled trials to provide concrete evidence for its use in people with SCD. This could be attributed to the complexity of the patient condition (e.g. severity of condition, co-morbid conditions, and so forth) making it unfeasible to conduct randomized controlled trials in this area (transplant versus no transplantation or transplant versus standard care procedure such as the use of hydroxyurea), as this would be unethical. Therefore, this leaves observational studies to assess these interventions. These studies report that hematopoietic stem cell transplantations (HSCT) does improve survival and/or prevent symptoms and complications associated with SCD but there is the issue of risk which is still being investigated. In the absence of any relevant randomized controlled trial comparing HSCT to standard care or comparing the different methods of HSCT in SCD, this systematic review found no evidence for or against these interventions.

AUTHORS' CONCLUSIONS

Implications for practice

Due to lack of randomized controlled trials on HSCT for people with SCD, no findings can be made and as such no conclusions can be drawn at present. Though some studies have reported high event-free survival rate, this research evidence is currently limited to observational and other less robust studies. Clinicians should therefore inform people with SCD about the uncertainty surrounding this clinical procedure if it is to be used.

Implications for research

The absence of randomised controlled trials of HSCT in SCD as shown by this extensive literature search suggests the need for a well-designed prospective randomized controlled trial of HSCT in people with SCD in order to make necessary recommendations regarding its use.

While ideally, trials comparing HSCT to supportive care could be carried out, the high variability in the clinical course of SCD and characteristics of patient population hinders its feasibility and may be considered unethical. Thus, trials may compare the different types of HSCT with one another with subgroup analyses by sickle status, severity of disease, setting and age groups carried out to provide guidance on the optimal HSCT for each individual with SCD. Outcomes to be included in these trials should address the needs and concerns of patients, care-givers and health providers, in order to assess the risks and benefits of the procedure. Similar outcomes should be measured in trials to allow comparability of results and

future synthesis of data in a meta-analysis. Long-term follow up of participants is also necessary.

ACKNOWLEDGEMENTS

Dr. S. Shenoy for his comments.

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Cochrane Database of Systematic Reviews 2013, Issue 5. [DOI: 10.1002/14651858.CD007001.pub3]

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bernaudin 2007	Not a RCT/quasi-RCT
Hongeng 2004	Not a RCT/quasi-RCT
Horan 2005	Not a RCT/quasi-RCT
Iannone 2003	Not a RCT/quasi-RCT
Locatelli 2003	Not a RCT/quasi-RCT
Vermylen 2000	Not a RCT/quasi-RCT
Walters 1995	Not a RCT/quasi-RCT
Walters 1996	Not a RCT/quasi-RCT
Walters 2001	Not a RCT/quasi-RCT
Weinberg 2001	Not a RCT/quasi-RCT

RCT: randomised controlled trial

APPENDICES

Appendix 1. Search strategy: Clinicaltrials.gov

Date of latest search: 11 December 2015
Stem cell transplantation AND sickle cell

WHAT'S NEW

Date	Event	Description
31 March 2016	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any potentially eligible trials.
31 March 2016	New citation required but conclusions have not changed	Minor changes have been made throughout the review.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 1, 2009

Date	Event	Description
24 March 2014	Amended	Contact details updated.
15 March 2013	New citation required but conclusions have not changed	The review has been expanded to include adults as well as children. Minor changes to the text have been made throughout.
15 March 2013	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Haemoglobinopathies Trials Register did not identify any potentially eligible trials for inclusion in the review.
6 October 2010	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any potentially relevant trials for inclusion in the review.
9 September 2009	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any references potentially eligible for inclusion in this review.
28 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Chioma Oringanje conceived the idea for the review and drafted the original protocol with input on draft versions from Eneida Nemecek and Oluseyi Oniyangi.

DECLARATIONS OF INTEREST

Chioma Oringanje: none known.
Eneida Nemecek: none known.
Oluseyi Oniyangi: none known.

SOURCES OF SUPPORT

Internal sources

- Institute of Tropical Disease, Research & Prevention, University of Calabar Teaching Hospital, Calabar, Nigeria.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review has been expanded to include adults as well as children. Minor changes to the text have been made throughout.

INDEX TERMS

Medical Subject Headings (MeSH)

*Hematopoietic Stem Cell Transplantation; Anemia, Sickle Cell [*surgery]

MeSH check words

Child; Humans