

BMJ Open Single group multisite safety trial of sibling cord blood cell infusion to children with cerebral palsy: study protocol and rationale

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ABSTRACT

Introduction Cerebral palsy (CP) is the most common physical disability of childhood but has no cure. Stem cells have the potential to improve brain injury and are proposed as a therapy for CP. However, many questions remain unanswered about the most appropriate cell type, timing of infusions, dose required and associated risks. Therefore, human safety and efficacy trials are necessary to progress knowledge in the field.

Methods and analysis This is a single group study with sample size n=12 to investigate safety of single-dose intravenous 12/12 human leucocyte antigen-matched sibling cord blood cell infusion to children with CP aged 1–16 years without immune suppression. The study is similar to a 3+3 design, where the first two groups of participants have severe CP, and the final six participants include children with all motor severities. Children will be monitored for adverse events and the duration that donor cells are detected. Assessments at baseline, 3 and 12 months will investigate safety and preliminary evidence of change in gross motor, fine motor, cognitive and quality of life outcomes.

Ethics and dissemination Full approval was obtained from The Royal Children's Hospital Human Research Ethics Committee, and a clinical trial notification was accepted by Australia's Therapeutic Goods Administration. Participant guardian informed consent will be obtained before any study procedures. The main results of this study will be submitted for publication in a peer-reviewed journal.

Trial registration number ACTRN12616000403437, NCT03087110.

INTRODUCTION

Cerebral palsy

Cerebral palsy (CP) describes a group of permanent non-progressive motor and postural disorders arising from damage to the developing brain while in utero, during birth or in the first years of life,^{1 2} and affects around 2 per 1000 live births across the world.³ Depending on the location and severity of brain damage, different regions of the body may be affected. The main types

Strengths and limitations of this study

- This is a rigorous safety study of a potential stem cell intervention for children with cerebral palsy.
- An advantage of the study is the investigation to determine cell persistence in immune-competent patients' circulation, which is relevant to many patient groups.
- However, as this is a safety study, the sample size is small, using a heterogeneous participant population.

of motor disorder found in CP include spasticity (stiffness of muscles accounting for around 80% of all diagnoses), dyskinesia (abnormal involuntary movements) and ataxia (unsteadiness) which result from lack of normal nervous control of muscles.¹

CP may be classified by the distribution of impairment: hemiplegia indicates that one side of the body is affected, diplegia that the legs greater than arms are affected and quadriplegia involves all four limbs and often the trunk. The degree of motor impairment is often defined using the Gross Motor Function Classification System (GMFCS), with GMFCS I describing a mildly impaired child able to walk independently, increasing in severity to GMFCS V indicating limited motor function and wheelchair use with poor head control.⁴ CP is often associated with epilepsy, difficulties in speech, sight, hearing, sensation, perception, behaviour or cognition. There is currently no cure for CP.

Cord blood for CP

Recent interest in stem cell therapy for intractable neurological disorders has led to a large number of preclinical studies of brain injuries related to CP that show evidence of therapeutic potential. Human umbilical cord blood (UCB) was used as the source of stem

cells as it is less ethically complex than other sources. UCB has been shown to be therapeutically useful and contains a variety of multipotent stem cells and other active cell types. The stem cells in UCB do not lead to cancers and present a lower risk of graft-versus-host disease (GvHD) than bone marrow stem cells.⁵ Transplantation of UCB cells in acute animal models of CP such as excitotoxic white matter injury⁶ and neonatal hypoxia-ischaemia^{7–12} has shown significant neurofunctional improvement, as have models of adult stroke,^{13–18} spinal cord injury^{19–23} and traumatic brain injury.²⁴ While some studies involve transplanting umbilical cord blood cells (UCBC) directly to the injured area of the brain, there is evidence that the minimally invasive intravenous infusion to the periphery is equally as effective.^{6 25} Because peripherally administered human (xenogeneic) stem cells do not engraft to replace lost brain cells in immune-suppressed animal models, such stem cell treatment is conceptualised best as a transfusion, not a transplant.

Investigations into the mechanism of action of UCBC infusion reveal (A) decreased astrogliosis and neuronal apoptosis^{26 27}; (B) increased white matter injury repair^{8 28 29}; (C) angiogenesis^{12 30}; and (D) enhancement of endogenous neural stem cell proliferation.^{31 32} CP is a heterogeneous condition with varied brain pathology, and stem cell infusion may act through different mechanisms for different children.^{31 33 34} Preclinical work has focused mainly on acute brain injury, which involves inflammation, primary and secondary cell death and chemical signalling, and it is unknown if these transfusion mechanisms will operate in the same way in the chronic phase of disease.

Safety considerations

Autologous blood transfusions are immunologically safe, while allogeneic cell infusions introduce the risk of an immune response. The first use of allogeneic UCBC infusion was a transplant in 1989,³⁵ and after optimising the technique in immune-depleted conditions for 25 years, there is still a risk of mortality from GvHD, whereby the donor cells attack the immune-suppressed recipient. This risk is at its lowest when using fully human leucocyte antigen (HLA)-matched related donors.⁵ Generic HLA matching examines six HLA genes and requires a minimum of 4/6 HLA match depending on clinical context, however technology allows examination of additional HLA genes.

The preclinical data behind stem cell therapy as a possible treatment for CP demonstrate that donor UCBCs may not need to persist or engraft to mediate functional benefit.⁷ Given the risks and side effects, and little expected benefit, this protocol does not use a conditioning regimen or immune suppression. Without immune suppression, the recipient's immune system is expected to easily reject infused cells, further reducing the risk of GvHD.

There is a risk of nausea, anaphylaxis and cardiovascular side effects when a cryopreservant such as dimethyl

sulfoxide is required which will be mitigated by 'washing' the cord blood unit before infusion.³⁶ There is also a risk as with any intravenous cell infusion that pulmonary capillaries may temporarily become blocked,³⁷ although this is less likely with cord blood or bone marrow mononuclear cells than larger types of stem cell.³⁸ These adverse events (AE) are considered temporary and treatable.^{36 37}

Rationale for phase I study

Despite the lack of conclusive evidence, UCBC infusion for CP is already in use in some parts of the world. Moreover, Australian children with CP are travelling to different parts of the world to undergo UCBC therapy in an unregulated environment and at a great financial cost.³⁹ Therefore, well-designed and properly administered trials evaluating the safety and efficacy of UCBCs in CP are necessary to guide clinicians and to inform patients and their families; and if successful, to develop treatment programmes in Australia. Such treatments would ideally involve cells that are available to any child with CP, yet this must be balanced against the increasing risk profile of cells taken from unrelated donors when there is as yet little evidence of benefit. For the same reasons, the method of administration must be designed to reduce risk wherever possible. A recent systematic review and meta-analysis of controlled trials of stem cells used for children with CP found five trials that met criteria, studying four different types of stem cells (fetal and bone marrow-derived neural stem cells, olfactory ensheathing cells and allogeneic UCBCs; all cryopreserved) at doses ranging from 2×10^6 cells in total to $\geq 3 \times 10^7$ cells/kg. The analysis indicated an acceptable risk-benefit ratio of 3% AEs in CP stem cell recipients and 2% AEs in controls and a small intervention effect on gross motor skills.⁴⁰ This study aims to investigate safety in cryopreserved washed 12/12 HLA-matched sibling UCBCs, intravenously infused without immune suppression.

METHODS

Aims and objectives

Primary objective

The primary objective of this study is to gain preliminary information on the safety of 12/12 HLA-matched sibling UCBC infusion in children with CP.

Secondary objectives

The secondary objectives of this study are:

- To gain preliminary information on the treatment effect of 12/12 HLA-matched UCBC infusion relative to baseline.
- To better understand the length of time that infused matched sibling UCBCs remain within recipients.
- To gather information and samples for future studies into the mechanistic activity of UCBCs.

Table 1 Participant cohorts within 3+3 type design

Cohort	Participants, n	Burden of disease
1	3	Severe CP
2	3	Severe CP
3	6	CP of any severity

CP, cerebral palsy.

Study design

Multisite single group investigator-initiated safety study conducted in tertiary hospitals. Rather than dose escalation, a 3+3 type design, with independent safety review by an independent Data Safety Monitoring Board (DSMB) between each group of 3 to assess the ongoing ethical acceptability of the study. After the first 3+3 participants with severe CP, the DSMB will decide whether the study can include a reduced burden of disease and continue with the final six participants having CP of any severity (see [table 1](#)). Any indication of GvHD severe enough to require intervention will stop the study.

Safety

The role of the DSMB is to safeguard the interests of trial participants by monitoring safety throughout the trial, trial feasibility and, together, advise Trial Steering Committee and Human Research Ethics Committee (HREC) on continuing ethical acceptability. The five-member DSMB will comprise transplant, paediatric, rehabilitation, biostatistical and clinical trials expertise and will require a minimum of three members to make decisions according to the trial DSMB Charter.

AEs will be recorded from the time of infusion until the last visit (12 months after infusion) regardless of their association with the study. The study team will estimate the likelihood that the AE was the result of the study intervention as unrelated, possible, probable or definite, according to the timing of the AE relative to the cell infusion, whether the AE is a known response to infusion, or could have occurred as part of the participant's clinical status or environment.

Serious adverse events (SAEs) will be reported to the DSMB within 72 hours of notification regardless of relatedness. The DSMB will provide independent advice on relatedness and evaluate the study team's response to the SAE (designation as suspected unexpected serious adverse reaction or significant safety issue, or requirement of urgent safety measure, all of which will be reported to the local HREC within 72 hours). The DSMB has the power to suspend or cease the trial, and detection of GvHD of a severity that requires treatment will automatically stop the trial.

Subject/study population

Inclusion criteria

To be eligible for this study, the following criteria must be fulfilled:

- ▶ Aged older than 1 year and younger than 16 years at the time of enrolment.
- ▶ Diagnosis of CP as confirmed by paediatrician and physiotherapist study team members.
- ▶ 12/12 HLA-matched sibling cord blood unit (CBU) in storage at a Therapeutic Goods Administration (TGA) licensed private cord blood bank.
- ▶ Ability to travel to one of the trial centres and participate in assessments.
- ▶ Informed consent by parent/guardian and an indication of willingness/compliance by the children.

Exclusion criteria

Patients will be unable to participate in the trial if:

- ▶ They show presence of progressive neurological disease.
- ▶ They have a known genetic disorder.
- ▶ They have a known brain dysplasia.
- ▶ They have ever been diagnosed with an immune system disorder or immune deficiency syndrome.
- ▶ They have infectious disease markers on virology screen (HIV 1 and 2 antibody and nucleic acid testing (NAT), hepatitis B core antibody, surface antigen and NAT, hepatitis C antibody and NAT, human T-cell lymphotropic 1 and 2 antibody, cytomegalovirus (CMV), syphilis).
- ▶ The intended cord blood unit shows evidence of contamination or has fewer than 10^7 nucleated cells per kilogram of body mass.
- ▶ They require ventilator support.
- ▶ They are unwell, or if the participant's medical condition does not allow safe travel.
- ▶ They have previously undertaken any form of cell therapy.
- ▶ They have had, or are scheduled for, treatment with botulinum toxin A within 3 months before or after infusion.
- ▶ They have had, or are scheduled for, surgery within 3 months before or after infusion.
- ▶ They cannot obtain parental or guardian consent.

Enrolment and screening

The study will be advertised through private Australian cord blood banks, clinical trial registries, CP professional and community organisations and institutional websites. When families of children with CP approach the study team with evidence of sibling cord blood unit in storage, they are provided with full information and invited to an informed consent discussion. Once written parent/guardian consent is obtained, and optional consent for extended use of biological samples is considered (sample consent form in online supplementary material), screening for HLA match is undertaken. A 75% screen fail rate is expected due to HLA mismatch, and no other eligibility screening is undertaken until this result is available (see [table 2](#)).

Intervention

The intervention will take place as a day procedure within a tertiary hospital paediatric haemopoietic stem cell

Table 2 Schedule of assessments

Study phase	Screening	Baseline	Infusion	Follow-up					
Timing	>8 weeks prior to infusion	28 days prior to infusion	0	1 day	1 week	1 month	3 months	6 months	12 months
Informed consent	X								
Medical history, CP assessment		X							
Medical examination, adverse events		X	X	X	X	X	X	X	X
Motor function assessment		X					X		X
Upper limbs assessment		X					X		X
Quality of life assessment		X					X		X
Cognition assessment		X							X
Infusion of UCBCs			X						
Peripheral blood collection	X	X	2X	X	X	X	X		

CP, cerebral palsy; UCBC, umbilical cord blood cell.

transplant ward to ensure appropriate expertise. After peripheral venous cannulation, the patient will receive intravenous normal saline for 2 hours along with hydrocortisone, antihistamine, paracetamol and ondansetron to reduce risk of adverse infusion reactions.

Cryopreserved UCBCs previously collected, tested for standard infectious disease markers (HIV, hepatitis B and C, human T-cell lymphotropic virus, CMV, syphilis), aerobic and anaerobic microbiology contamination/sterility and cell count, and stored in the gaseous phase of liquid nitrogen by a licensed cord blood bank are pilot thawed by the storage facility before shipment, checked on arrival at the Cell Therapy Laboratory and washed and resuspended in dextran/albumin to a volume of 100 mL. Cell viability, characterisation of CD34+ and CD45+ fraction and sterility are assessed on both pilot thaw and the final product. Infusion must be completed within 1 hour of thaw: infusion by gravity for 5 min, then paused to assess immediate safety before continuing. Minimum cell dose of 10^7 total nucleated cells/kg is based on pilot thaw cell counts and was selected based on preclinical data and international trials at the time of ethics submission. Normal saline is provided for an additional 4 hours after infusion, and intramuscular rhesus D immunoglobulin provided if donor/recipient is a rhesus mismatch. Vital signs and AEs will be monitored, and the patient discharged if medically stable.

Treatment discontinuation

Treatment administration is a single dose; therefore, interruption or discontinuation will only occur in response to immediate infusion reactions. Infusion will initially be interrupted, and continued if safe, but discontinued if reactions cannot easily be treated.

Endpoints

Safety

The primary safety endpoint will be assessed through the number of AEs possibly related to UCBCs or infusion procedure by 36 hours, 3 months and 12 months after

infusion. AEs will be elicited during observation, study visit medical reviews with transplant specialist and developmental paediatrician, laboratory tests (full blood examination, liver function tests, inflammatory markers) and between-visit reports from families. Relationship of AEs to study intervention will be assessed based on expectedness, timing relative to infusion, ongoing presence of donor DNA in the circulation, the patient's clinical state and environment.

Preliminary efficacy

Motor function will be assessed using the gold standard for CP, the Gross Motor Function Measure-66, which is valid, reliable and responsive to change⁴¹ and has population norms available. Upper limb movement will be assessed with the Quality of Upper Extremity Skills Test (QUEST), which measures each upper limb separately, then combines limb scores for each of four domains: disassociated movements, grasp, weight-bearing and protective extension. The QUEST is limited by measuring impairment reduction rather than functional activity but is one of the few bimanual assessment tools for CP with appropriate psychometric properties.⁴² See [table 2](#) for the schedule of assessments.

Cognitive assessment for CP is known to be challenging due to the motor requirements, yet there is anecdotal evidence of improvements in attention and learning following stem cell transplants. The direct cognitive assessments will be age appropriate (Bayley Scales of Infant Development, Second Edition, for children aged 1–2 years; Wechsler Preschool Primary Scale of Intelligence, Fourth Edition, for children aged 2–6 years; and Wechsler Intelligence Scale for Children, Fifth Edition, for children aged 6–16 years). Additionally, the Beery-Buktenica Developmental Test of Visual-Motor Integration will be used, along with parent report versions of the Vineland Adaptive Behaviour Scales, Second Edition, Behaviour Rating Inventory of Executive Function, and the Strengths and Difficulties Questionnaire.

Donor cell persistence

Because there is no direct evidence of the longevity of matched sibling cord blood cells after infusion to an immune-competent recipient, donor cell persistence will be examined using a highly sensitive surrogate chimerism analysis of donor DNA. The donor and the recipient will be genotyped to detect copy number deletions; then digital droplet PCR will be used to quantify the fraction of donor DNA, sensitive to 20 genome equivalents/mL.⁴³

Patient and public involvement

A Delphi study of research priorities for CP found that stem cell research was the third highest research priority⁴⁴ for the community. The CP Quest community reference group will be consulted before communication of study outcomes to ensure the messages and distribution are appropriate. No attempt was made to assess the burden of the intervention by patients themselves.

Statistical analysis

As the primary aim of this study is to assess safety, the sample size of 12 participants was selected to allow sequential groups of three participants. We will compare group characteristics with population data from the Australian Cerebral Palsy Register to assess the generalisability of the results obtained. Given the pilot nature of this trial, the results from this study will be presented descriptively. Safety data will be summarised as the proportion of participants who have an SAE and an AE within either of the three safety periods: within 36 hours, within 3 months or within the 12-month study period. The change in lab results at each time point will be presented relative to baseline on an individual participant basis, with comparison to published minimal clinically important difference of the tool.^{45 46} Change in motor and cognitive function will be presented relative to baseline. Donor cell persistence data will be categorised as 'immediate rejection' to indicate return to baseline fraction of donor DNA within 24 hours; 'rejection' to indicate a return to baseline fraction of donor DNA by 1 month; 'slow rejection' to indicate the presence of between 200 donor genome equivalent/mL and engraftment at 3 months, and 'engraftment'.

Data management and administrative aspects

Study data will be collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Murdoch Children's Research Institute (MCRI). REDCap is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Hard copy documents will be stored in locked files, and electronic files will be password protected and accessible by the study team only. Final data collection is predicted to occur in mid-2020. Records will be securely stored until

the youngest participant turns 25 years of age, although records of biobanked samples and their consent conditions may be retained longer.

Neuroscience Trials Australia will independently verify source data and adherence to Good Clinical Practice. The study may be audited or inspected by representatives of regulatory organisations.

Data statement

The deidentified data set collected for this analysis of the trial will be available 6 months after publication of the primary outcome. The study protocol, analysis plan and consent forms will also be available. The data may be obtained from the MCRI. Prior to releasing any data the following are required: a data access agreement must be signed between relevant parties, the SCUBI-CP Trial Steering Committee must see and approve the analysis plan describing how the data will be analysed, there must be an agreement around appropriate acknowledgement and any additional costs involved must be covered. Should the Trial Steering Committee be unavailable, this role is delegated to the MCRI. Data will only be shared with a recognised research institution which has approved the proposed analysis plan.

ETHICS AND DISSEMINATION

This study received initial approval from The Royal Children's Hospital HREC in late 2015, as have all changes to participant documents and protocol amendments. The current protocol is version 10, approved on 6 March 2017. A clinical trial notification was submitted to the TGA, Australia, in March 2016. The study is registered on both the Australian and New Zealand Clinical Trials Registry and ClinicalTrials.gov with all items from the WHO Trial Registration Data Set and regularly updated. Recruitment is complete. Publication in a peer-reviewed journal is planned regardless of the outcome. The decision of what to publish and when, along with authorship according to Vancouver guidelines, will be made by the Trial Steering Committee. No participant will be identifiable from the data reported.

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Contributors All authors provided substantial contribution to design and drafting of the manuscript. KEC: coordination of the study. FMH, NE, IN: content expertise. KL: biostatistical study design. DR, MCF, NB, EV, PBC, FMH, IN, KL, PE and KEC: members of the Steering Committee. DR: study lead at coordinating centre (The Royal Children's Hospital). PE: study lead at subsite (Queensland Children's Hospital).

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Competing interests Cell Care Australia is a private cord blood bank with a representative on the Trial Steering Committee. There is, therefore, a potential conflict of interest which has been declared to HREC and Steering Committee and is well recognised. No one affiliated with Cell Care Australia will be involved in data analysis or interpretation.

Patient consent for publication Not required.

Ethics approval This study received initial approval from The Royal Children's Hospital Human Research Ethics Committee.

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