PROTOCOL

Magnesium for Neuroprotection: Understanding Mechanisms

MagNUM

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CONTENTS

TITLE: ANTENATAL MAGNESIUM SULPHATE: MECHANISMS OF FETAL NEUROPROTECTION (MagNum)

PURPOSE OF THE MagNUM STUDY

To understand the mechanisms that underlie the neuroprotective effects of antenatal magnesium sulphate therapy in children born preterm. We will assess

a) the effect of magnesium sulphate on white matter structure when children born moderately preterm reach term-equivalent age; and

b) the relationship between white matter microstructure and neurological function at term and neurodevelopmental outcomes at 2 years' corrected age in the same cohort of children.

c) whether DTI measurements of white matter at term can provide a clinically meaningful biomarker for subsequent neurological development.

STUDY HYPOTHESES

Antenatal magnesium sulphate given to women at risk of preterm birth between 30 and 34 weeks' gestation when birth is imminent has neuroprotective effects that are apparent throughout the cerebral white matter on MRI at term equivalent age, specifically in the neural tracts that sub-serve motor and cognitive function.

BACKGROUND

Preterm birth and the burden of perinatal brain injury

Preterm birth (<37 weeks' gestation) with a global incidence of over 10% is a leading cause of cognitive impairment and educational under-performance (March of the Dimes 2012, Petrini 2009). Babies born preterm have a higher chance of dying in the first few weeks of life that those born at term (ANZNN 2009). Babies who survive have a greater risk of neurologic impairments, such as cerebral palsy, cognitive dysfunction, blindness and deafness, and a greater risk of substantial disability as a result of these neurologic impairments (Petrini 2009, ANZNN 2009).

In New Zealand in 2010 over 4,800 (7.4%) of live born babies were born preterm, with approximately half of these being born between 30 and 34 weeks' gestation (Tetzlaff 2012). Preterm birth rates are higher amongst Maori than in other New Zealand ethnicities (MOH 2010, ADHB 2012). Preterm birth is associated with 45% of all cases of cerebral palsy, a severe disorder of movement and posture (ACPR Group 2009). Moderate prematurity is responsible for as many cases of cerebral palsy as extreme prematurity (ACPR Group 2009). Cerebral palsy is eight times more likely for babies born at 30-34 weeks than for babies born at term and the relative risk for special educational needs is 1.32 (95% CI 1.1 to 1.58) for children born less than 32 weeks and 1.27 (95% CI 1.02, 1.57) for those born at 32 to less than 34 weeks (ANZNN 2009, Quigley 2012). These morbidities are associated with significant, long-term health, educational and societal costs (Mangham 2009, Petrou 2012).

At present there is no cure for cerebral palsy, which makes effective preventative interventions of paramount importance. To reduce the impact of cerebral palsy from preterm birth, efforts must be focused on understanding the pathological basis of cerebral palsy and primary prevention.

The predominant lesion in preterm brain injury is periventricular leucomalacia, a disease of the white matter, mediated by vulnerability of the premyelinating oligodendrocyte (pre-OL). Preterm birth is associated with pre-OL death, or survival with reduced capacity to differentiate into myelin forming mature OLs. The end result is hypomyelination accompanied by astrogliosis and microgliosis. Preterm infants are susceptible to cerebral ischaemia and infection/inflammation, which activate downstream mechanisms of microglial activation, glutamate-mediated excitotoxicity, and release of reactive oxygen and nitrogen species, that lead to pre-OL injury (Volpe 2011). The timing of these interacting pathogenic processes is around birth; the time when neuroprotective therapies are most likely to be effective.

Antenatal magnesium sulphate and fetal neuroprotection

In a landmark case-control study 18 years ago, antenatal magnesium sulphate was linked with a dramatic reduction in the risk of cerebral palsy (odds ratio 0.14; 95% confidence interval 0.05 to 0.51) (Nelson 1995). In humans, magnesium is essential for key cellular processes, including glycolysis, oxidative phosphorylation, protein synthesis, and plasma membrane integrity (Mildvan 1987).

Magnesium favourably affects mechanisms implicated in cell death by decreasing proinflammatory cytokines or free radicals produced during hypoxic-ischaemic reperfusion and inflammatory diseases of pregnancy (Shogi 2003). Magnesium prevents excitotoxic calcium-induced injury by a non-competitive voltage-dependent inhibition of the N-methyl-D-aspartate receptor to glutamate reducing calcium entry into the cell (Nowak 1984).

The Cochrane systematic review on use of magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Doyle 2009) has four neuroprotective trials (Mittendorf 2002, Rouse 2008, Marret 2008, Crowther 2003), and shows that antenatal magnesium sulphate is effective at reducing death or cerebral palsy after preterm birth (Doyle 2009). However, the optimal gestational ages for use are uncertain.

The recently published bi-national Australian and New Zealand Clinical Practice Guidelines recommend use of antenatal magnesium sulphate as a neuroprotective at less than 30 weeks' gestation, endorse the need for further randomised trials at 30 weeks' gestation or more, and have "identifying causes and causal pathways" as priority research questions (The Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010). There have been independent calls for investigations into the mechanisms underlying magnesium mediated neuroprotection using Diffusion Tensor Imaging (DTI) on magnetic resonance imaging (MRI) (Duerden 2013).

It remains uncertain exactly how magnesium exerts its protective effects and whether magnesium protects parts of the brain that are important for learning and behaviour as well as those areas that control movement and posture.

Opportunity to explore mechanistic pathways of neuroprotection for magnesium sulphate

The Magenta Trial is a multicentre, placebo controlled, randomised trial assessing the effect of antenatal magnesium sulphate between 30 and 34 weeks' gestation. The primary outcome is death or severe motor impairment at 2 years (Crowther 2013). Magenta is funded by the National Health and Medical Research Council in Australia, with a sample size of 1676 babies, and is recruiting at 28 hospitals in Australia and New Zealand, but is not designed to investigate mechanistic or cognitive effects of antenatal magnesium therapy.

The nested **MagNUM Study (Magnesium for Neuroprotection: Understanding Mechanisms)** will assess the effects of magnesium treatment on neonatal brain structure at term equivalent age. We will use magnetic resonance (MR) diffusion tensor imaging (DTI) to compare brain microstructure and white matter integrity between the babies who received magnesium and those who did not, to evaluate whether the intervention modifies brain injury.

DTI and Magnetic Resonance Imaging

DTI is an MR technique in which the molecular motion of water is the dominant contrast in the image. Because water motion is influenced by axonal thickness, density and degree of myelination, its measurement can be used to make inferences about underlying tissue microstructure (Basser 1996). Measures derived from DTI that have been used to study the developing brain include fractional anisotropy (FA, the fraction of diffusion attributed to anisotropic diffusion), axial diffusion (AD, the magnitude of diffusion parallel to fibres) and radial diffusion (RD, diffusion perpendicular to tracts).

In healthy, well-myelinated white matter tracts FA is high and RD is low as water molecules diffuse preferentially along the tracts. In the preterm brain, FA in white matter increases with postmenstrual age, driven mainly by a decrease in RD. FA is reduced in white matter disease and, at term equivalent age, is dependent on the degree of prematurity at birth and closely linked to neurological function (Ball 2010).

We will measure FA as our primary outcome as it reflects white matter microstructure and is objective, non-biased, spatially resolved and closely linked to neurodevelopmental function (Counsell 2008, Krishnan 2007, Pogribna 2013). In secondary analyses we will also explore the effects of magnesium sulphate on RD and AD. This will enable us to assess whether white matter tracts that support movement, learning and behaviour are altered by magnesium therapy and how these changes relate to later developmental outcomes.

The MagNUM study will also provide an opportunity to apply emerging DTI analysis techniques to neonatal data. Specifically, we will employ probabilistic neighbourhood tractography (PNT), an automated and objective tractography approach that allows for quantitative measurement of the integrity (FA, RD and AD) and shape of predefined white matter tracts. This exploratory analysis will harness cutting edge techniques for applying PNT to diffusion data from neonates (Anblagan 2013). The use of this technique will allow us to assess the neuroprotective effects of magnesium sulphate on entire white matter tracts, and will contribute to our understanding of whether the FA at term acts as a biomarker for subsequent neurological development.

RESEARCH PLAN

Study Design

A nested cohort study within the pre-existing Magenta Trial (Crowther 2013).

The Magenta Trial: Magenta is a multicentre, double blind, two-arm, parallel, randomised controlled trial, comparing the efficacy of magnesium sulphate with placebo for prevention of death or cerebral palsy when administered to women at risk of imminent preterm birth at 30 to 34 weeks' gestation (Crowther 2013). Women are eligible for Magenta if they are at risk of preterm birth between 30 to 34 weeks' gestation, birth is planned or definitely expected within 24 hours, they have a singleton or twin pregnancy, there are no contraindications to the use of antenatal magnesium sulphate and they give informed consent. Women are not eligible if they have already received magnesium sulphate or if magnesium sulphate therapy is considered essential for the treatment of pre-eclampsia.

The primary outcome for the Magenta Trial is the incidence of death or cerebral palsy, defined as stillbirth, death of a liveborn infant before hospital discharge, or death after hospital discharge before 2 years' corrected age or any cerebral palsy (abnormality of tone with motor dysfunction). Children will undergo neurodevelopmental assessment at 2 years of age corrected for prematurity by a developmental paediatrician and a psychologist trained to administer the Bayley III Scales.

Magenta is already recruiting in Auckland City Hospital, Middlemore and Christchurch Women's Hospital. Thus, it provides a unique opportunity to obtain the highest quality

evidence (that from a placebo-controlled randomised trial) about the mechanisms of action of magnesium sulphate and relate this to later developmental outcome in a timely fashion, at limited additional cost.

Entry Criteria

Inclusion Criteria: Babies born to mothers enrolled in the Magenta Trial at Auckland City Hospital, Middlemore and Christchurch Women's Hospital.

Exclusion Criteria: Known congenital or genetic disorders likely to affect brain structure.

Study Entry

Women enrolled in the Magenta trial and their partners at the above two hospitals will be invited to enrol their baby in the MagNUM Study. Written informed consent will be obtained. MR imaging, neurological assessment and anthropometry will be arranged at term equivalent age (38 to 42 weeks' post menstrual age). Many babies born at 30-34 weeks gestation will have been discharged home from the neonatal unit by term equivalent age. Their parents will be asked to bring them for the assessments.

MRI Acquisition

MR imaging will be conducted using a 3.0 Tesla Siemens Skyra system at the Auckland Centre for Advanced MRI and a 3.0 Tesla General Electric HDxt system at the Christchurch Centre by staff experienced in acquiring neonatal MR images. The babies will be fed, wrapped and settled in a vacuum extracted bean-bag pillow. General anaesthesia or sedation will not be used. Diffusion weighted, single shot, spin-echo, echo planar imaging volumes ($b = 750$ s/mm^2, 2 mm isotropic voxels) covering 64 non collinear directions will be acquired along with high resolution T1 - and T2 - weighted anatomical volumes.

A rigorous standardisation and quality control programme will be used to ensure the validity and robustness of inter-site DTI comparisons. This will involve standardising the MRI protocol to acquire axial whole brain imaging data with the same number of baseline and diffusion encoding gradient directions, b-values, slice locations and voxel dimensions. A volunteer will be scanned at both sites to finalise the protocol, and a detailed written protocol will be provided to the radiographers at both sites to ensure the data are compatible.

MRI Analysis

The majority of previous studies that have used DTI to assess white matter structure in the neonatal brain have used a region-of-interest-based analysis. In this approach, specific regions of white matter such as the corpus callosum and optic radiations are identified manually within each brain. The average FA, AD or RD values within each region are then determined separately for each brain and used for a group analysis. This approach has provided important contributions to our understanding of white matter injury in infancy Cheong 2009, Kaukola 2009, Partridge 2004). However, because it relies on manual identification of brain areas for each participant, it is susceptible to errors, inconsistencies between studies and is not ideal for studies with large numbers of participants.

An alternative approach is to perform a statistical analysis that includes all regions of white matter for all participants and allows for the detection of differences between groups that may be restricted to specific white matter tracts. This process is well established for the adult brain and can be conducted using the Tract-Based Spatial Statistics (TBSS) analyses package (Smith 2006) that is embedded within the FSL analysis software from Oxford University. TBSS is an observer independent method of aligning FA images from multiple subjects to make assessments of differences in FA in major white matter tracts. The output is a map where significant differences in mean FA between groups are viewed in anatomic brain space.

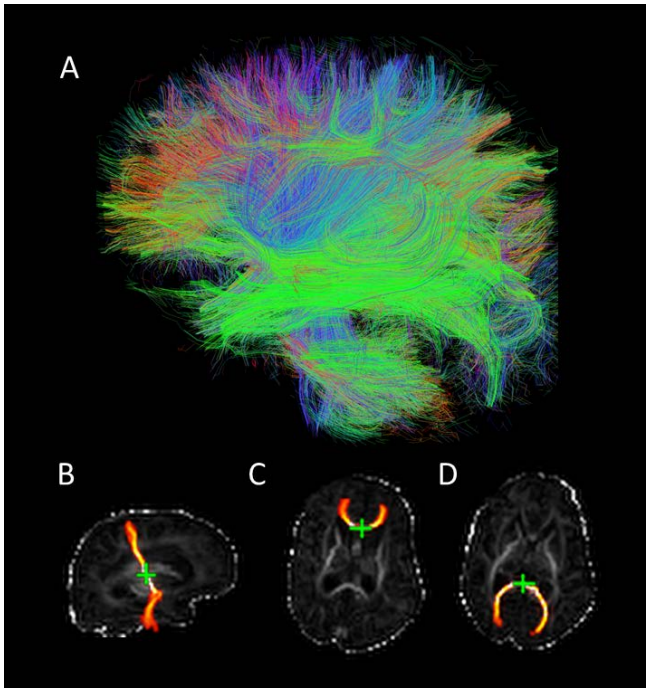
The first step in the analysis is the alignment of the individual FA maps to a template brain. A white matter "skeleton" is then generated that represents the white matter tracts that are common to the group. Individual datasets can then be projected onto this skeleton to allow for group voxel-wise analysis which can reveal general and/or specific differences in white matter microstructure between different groups of participants.

Until recently the use of approaches such as TBSS for neonatal brain imaging studies has been complicated by the fact that neonatal DTI data tend to have lower resolution and contrast than adult data. This combined with the large variability in brain size and structure that can occur in neonates born at risk of abnormal neurodevelopment can result in incorrect registration of individual brains to the template. This is important, as accurate alignment is crucial for group analysis of DTI data. This issue has recently been solved by our collaborators, Dr Boardman and his colleagues, who have developed a protocol for accurate co-registration and analysis of group DTI data from neonates (Figure 1). In collaboration with Dr Boardman we will establish and validate this analysis technique at the University of Auckland and use TBSS implemented in FSL (www.fmrib.ox.ac.uk/fsl) (Ball 2010) to assess the effect of antenatal magnesium sulphate therapy on white matter microstructure in term equivalent age infants.

Specifically, the DTI datasets will be registered to the baseline b0 image to minimise image artefacts due to eddy current distortions. The skull will be removed from the images with the Brain Extraction Tool of FMRIB. FA, AD, and RD maps will be calculated using the Diffusion Toolbox in FMRIB. All subjects' FA images will be aligned to a target in a common space using TBSS protocol for neonates (Ball 2010). Each subject's aligned FA, AD, and RD data will be projected onto this mean FA skeleton. Voxelwise cross-subject statistics will be performed to assess the relationship between FA, AD, and RD and treatment allocation group. The results will be corrected for multiple comparisons by controlling the family-wise error rate following threshold-free cluster enhancement.

In addition to TBSS we will employ PNT within a secondary analysis using the TractoR package for fiber tracking analysis (http://www.tractor-mri.org.uk). Guided by previous work in this area by our collaborators, eight tracts of interest will be identified; the genu and splenium of corpus callosum, the cingulum cingulate gyri (CCG), the left and right projections of the corticospinal tract (CST), and the inferior longitudinal (ILF) fasciculi. Once generated, the tract masks will be applied to the FA, RD and AD volumes to provide tract specific mean values for each participant. Examples of Fibre Tracking and PNT results for neonates are shown in Figure 1.

Figure 1. Fibre Tracking and PNT



(A) Sagittal view of whole brain white matter tracts from a neonate obtained using DTI. Tracts running predominantly in the anterior/posterior direction are coloured green, superior/inferior blue and right/left red.

(B, C and D) Two-dimensional sagittal and axial projections of the left corticospinal tract (B), and genu (C) and splenium (D) of the corpus callosum obtained using PNT in a neonate overlaid on maps of FA.

The colours represent the proportion of probabilistic streamlines generated from the seed point (green cross) passing through each voxel. Tract-averaged values of FA, AD and RD for each pathway, weighted by connection probability, can be obtained from these tractography masks.

In addition to these detailed TBSS analyses, a practising paediatric radiologist skilled in neonatal MRI acquisition and interpretation will provide a routine clinical report on each structural MRI scan. These reports, with which clinicians are familiar, will be compared with the more complex research analyses, to assess the extent to which clinical radiological assessment can be predictive and to help bridge the research findings into clinical practice if appropriate.

Neurological assessment

Babies will undergo standard neurological assessment at term equivalent age, including tone and reflexes, by an experienced paediatric registrar or paediatrician. They will also be videotaped for assessment of spontaneous movements. Sequential assessment of these movements in preterm babies has been shown to be highly predictive of later cerebral palsy (Ferrari 2002, Einspieler 2005) but there are no reports of the relationship between contemporaneous measures of neurological status, spontaneous movements and white matter microstructure quantified using FA, nor how well these will predict later motor, cognitive and behavioural outcomes.

Anthropomentry

Babies will be weighed (digital scales), and length (Harpenden neonatometer) and occipito-parietal head circumference measured (Seca 212 Teflon non-stretch head circumference measuring tapes). Head circumference correlates with brain volume and neonatal growth, particularly of head circumference, is related to developmental outcomes in babies born preterm (Cheong 2009). Thus, it will be important to be able to consider potential relationships between growth by term equivalent age, DTI findings and later developmental outcomes.

Neurodevelopmental Assessment at 2 years corrected age

As part of the Magenta Trial all of the children in the MagNUM study will be formally assessed at two years corrected age, by a developmental paediatrician and psychologist or other assessor trained to administer the Bayley Scales. All assessors will remain blinded to treatment group assignment. Assessments will be made of health, neurodevelopment, behaviour, growth and blood pressure (Crowther 2003, Crowther 2007). Although cerebral palsy may not remain a stable diagnosis before 5 years of age, (Stanley 1992) a diagnosis of severe cerebral palsy (defined below) at 2 years of age is unlikely to change after that time (Paneth 2008).

Gross Motor Function: The paediatric assessment will include a neurological examination to diagnose cerebral palsy (abnormality of tone with motor dysfunction) and other disability outcomes according to previously reported criteria (Doyle 2004). Gross Motor Function will be assessed using the Gross Motor Function Classification System (GMFCS) level 0 to 5 (Palisano 1997).

Psychological Assessments: The psychological assessment will include the cognitive, motor and language scales of the Third Edition of the Bayley Scales of Infant and Toddler Development (BSID-III) (Bayley 2006). This is well-standardised with demonstrated validity and reliability. Psychological test scores will be recorded as standardised scores [derived from raw test scores - mean/standard deviation (SD)]. Children with severe developmental delay who are unable to complete the psychological assessment will be given a standardised score of 4 SD below the mean.

Behaviour: The child's caregiver will be asked to complete the Child Behaviour Checklist (CBC) (Achenbach 1992) and the Behavior Rating Inventory of Executive Function – Preschool version (BRIEF-P) (Gioia 2000).

General Health, Health Resource Utilisation, Body Size and Quality Of Life: A general history and physical examination will determine the presence of any significant chronic illness, and data regarding hospital readmissions will be confirmed, where necessary, from the admitting hospital or doctor. Children whose vision has not previously been assessed will be referred to an ophthalmologist if they are considered to have abnormal vision. Children will be considered blind if visual acuity in both eyes is worse than 6/60. Hearing should have been assessed earlier in childhood. Those who have not been seen will be referred for audiological assessment if they are considered to have language delay or deafness is suspected. Children will be considered deaf if their hearing loss is sufficient to require hearing aids, or worse.

Questionnaires will be completed by the child's caregiver about any respiratory morbidity, history of illness or injury, use of health services since primary hospitalisation (Parent/Caregiver Questionnaire) and developmental progress (Squires 2009).

The child's height, weight, and head circumference will be measured, and values for the relevant centile, percent of median, and standard deviation scores (Z scores) specific for age and gender will be computed from the WHO Growth References (WHO Multicentre Growth Reference Study Group 2006).

Categorisation of Neurosensory Disability: Children will be considered to have a neurosensory impairment if they have cerebral palsy, GMFCS level 1 to 5, blindness, deafness or a standardised score more than 1SD below the mean (< -1SD). The

neurosensory disabilities imposed by the various neurosensory impairments will be classified as severe, moderate or mild (Doyle 2004), as follows:

Severe Disability comprises severe cerebral palsy (child non-ambulant and likely to remain so; GMFCS level 4 or 5), severe developmental delay (standardised score < -3SD) or blindness.

Moderate Disability comprises moderate cerebral palsy (child non-ambulant at 2 years of age but who is likely to ambulate subsequently; GMFCS level 2 or 3), or deafness, or moderate developmental delay (standardised score from -3SD to < -2SD).

Mild Disability comprises mild cerebral palsy (child walking at 2 years with only minimal limitation of movement (GMFCS level 1) or suspect development (standardised score from -2SD to < -1SD).

No Neurosensory Disability comprises children without any neurosensory impairment.

OUTCOMES

Primary Study Outcomes

The primary outcome is FA throughout the cerebral white matter on neonatal magnetic resonance imaging at term equivalent age.

Secondary Study Outcomes

Exploratory analyses will focus on relationships between white matter microstructre and neurological findings at term. In the planned follow up for the Magenta Trial we will assess motor, cognitive and neurobehavioural outcomes at 2 years' corrected age. The provides the unique opportunity for the MagNUM study to explore the relationships amongst the white matter microstructure and examination findings at term equivalent age, and neurodevelopment at 2 years' corrected age. Specific secondary outcomes are:

- Clinical interpretation of brain MRI at term equivalent age.
- Neurological examination at term equivalent age, including spontaneous movements.
- Neonatal morbidity: hypoglycaemia, IVH, sepsis, retinopathy of prematurity, periventricular leucomalacia, chronic lung disease, necrotising enterocolitis.
- Growth to 2 years corrected age corrected for prematurity; weight, length, head circumference.
- Motor, cognitive, neurobehavioural and neurosensory disability outcomes at 2 years' corrected age.

Sample size

Differences in white matter FA of 5-30% have been observed associated with clinically significant perinatal events, including extreme prematurity, chronic lung disease and therapeutic hypothermia (Ball 2010). This order of magnitude of difference in FA relates to neurodevelopmental outcome (Ball 2010).

A sensitivity analysis of TBSS using simulated data (Ball 2013) shows that an estimated 160 babies (80 per arm) are required to detect a 5% difference in FA in 75% of affected voxels with $p<0.05$. Assuming that significant voxels will be randomly distributed rather than clustered, a detailed assessment of spatial localisation of affected white matter tracts will be made possible by detecting 75% of affected voxels.

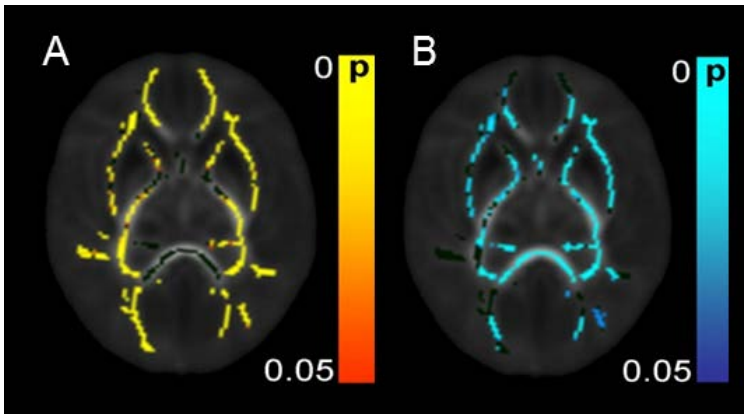
We plan to recruit 200 babies (100 per arm) to allow for any violations of Magenta Trial protocol (eg did not receive the study medication as intended) and babies from whom MR data amenable to TBSS cannot be obtained. This approach has been used to inform sample size calculations where TBSS is a primary outcome for other neonatal neuroprotective trials (TOBY ISRCTN 08886155; MINT ISRCTN 15119574).

STATISTICAL ANALYSES

DTI results will be presented as mean (standard deviation) FA, RD and AD for treatment and placebo groups, and maps highlighting voxels where there is a significant difference in mean FA between treatment and placebo groups ($p<0.05$), displayed in three dimensions in order to localise differences to specific tracts. Analysis will be by intention to treat, and will be adjusted for post-menstrual age at scan because this influences DTI measures (Ball 2010). One pre-specified subgroup analysis will be performed stratifying by gestational age when randomised (30 to 31+6 weeks and 32 to 33+6 weeks' gestation).

Figure 2. Examples of the use of regression analyses combined with TBSS in neonates to identify regions of white matter where stronger FA values are significantly associated with age at imaging (panel A) and gestational age at birth (panel B, corrected for age at imaging). FA skeletons are shown in dark green and the data (n = 93) are projected onto a mid-axial slice through the brain. Colour bars indicate p-values (Ball 2010).

The relationship between FA and neurological outcomes at term and at 2 years of age will be assessed using a regression model applied to the TBSS data. This will identify voxels within white matter tracts that are significantly associated with the neurological outcome variables (Bayley III cognitive, language and motor scores, cerebral palsy (Palisano 1997), CBC and BRIEF-P scores, and neurosensory disability (Crowther 2013) and allow us to pinpoint those tracts that are associated with neurodevelopmental outcomes. Examples of this approach are shown in Figure 2.



In secondary analyses mean FA, RD and AD values will be extracted from the TBSS skeleton for each participant and regression analyses will be used to assess the relationship between white matter microstructure and measures of neurodevelopment at term-equivalent age and at 2 years of age. Regression analyses will also be used to test for associations between neurological outcomes and the shape and FA of whole white matter tracts provided by PNT.

ETHICAL CONSIDERATIONS & CONFIDENTIALITY

Each woman with an infant eligible for recruitment into the MagNUM Study will be counselled about the study by a member of the research team and given a written information sheet to assist her in making an informed decision about the study. Informed, signed consent is obtained for each participant. The woman is free to withdraw herself or her child(ren) from the study at any stage, without prejudice to their future care.

Information about women and their babies recruited to the trial will be stored securely (locked filing cabinets and password protected computer files). Identifying details will be separated from other information and no identifying information will be published.

OUTCOMES AND SIGNIFICANCE OF THE MagNUM STUDY

The MagNUM Study provides a unique, time-limited opportunity to investigate the mechanisms underlying neuroprotection in the neonatal brain. We expect the results will

- Improve our understanding of the pathological basis of cerebral palsy and provide a significant advance in knowledge to improve our understanding of the mechanisms of action of antenatal magnesium sulphate as a neuroprotective therapy in preventing cerebral palsy and white matter damage related to preterm birth.
- Influence the focus of future research in fetal neuroprotection by identifying the mechanisms and location of effects of magnesium sulphate on the brain in the perinatal period.
- Help understand the mechanisms of neuroprotection in early infancy and advance our general understanding of neuroprotection within the human brain that could have implications for older children and adults.
- Contribute to the update of the bi-national practice guidelines about the use of magnesium for neuroprotection prior to preterm birth, and will influence the focus of future research in fetal neuroprotection.

STUDY COMMITTEE ORGANISATION

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Safety Monitoring Committee and Data Monitoring Committee:

A multidisciplinary adverse events committee for the Magenta Trial, blinded to treatment allocation, will review the cause of death for any maternal and infant deaths. These data will be made available to the Magenta Independent Data Monitoring Committee.

Publications

The MagNUM Steering Committee will be the writing committee for the study. Publications arising from the study will include the name of the MagNUM Study Group with all active collaborators acknowledged and not only members of the Steering Committee. The local collaborators will be responsible for providing a list of all people at their institution warranting acknowledgment for their contribution.

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