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Selective Cerebral Hypothermia For Term Infants Following Hypoxic Ischaemic Injury

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Abstract

Perinatal hypoxic ischaemic injury is an important cause of both neonatal death and long-term disability. The sequence of resuscitation followed by a latent phase then a secondary cascade of injury is well documented. This thesis covers key steps toward the utilization of selective hypothermia as an intervention during the latent phase to ameliorate the secondary injury and improve subsequent outcome.

The technique was shown to be both feasible and well tolerated. Specifically, a rectal temperature of 35 °C and 34.5 °C, in term infants with neonatal encephalopathy, was not associated with an excessive requirement for cardio-respiratory support. Although a decrease in heart rate occurred during cooling, this was expected and there was no significant change in blood pressure during either the cooling or rewarming phase. Additional reassuring findings were that neither major electrolyte disturbance; hypoglycaemia or haematological changes, including excessive haemorrhage, were observed during hypothermia.

The study of neurodevelopmental outcome established that selective cerebral hypothermia was not associated with late adverse effects and, in infants with moderate to severe encephalopathy, the combined cooled groups demonstrated a trend towards better outcome. These data confirmed the potential for selective cerebral hypothermia to provide neuroprotection following perinatal asphyxia. In further chapters cerebral CT scan was confirmed as a helpful adjunct to clinical staging in predicting neurodevelopmental outcome and important clinical experience was reported including rebound seizures following rewarming; sclerema neonatorum associated with hypothermia; and abnormal flow in the superior sagittal sinus, associated with perinatal asphyxia.

Lastly a review of infants assessed but not recruited to the CoolCap trial based on aEEG criteria was performed. As these aEEG criteria could be applied to future clinical use it was considered important to ensure large numbers of infants
with potential to benefit were not excluded from intervention. Neurodevelopmental status for those infants excluded by the aEEG criteria was largely favourable but a small number had adverse outcome and the majority manifested short term morbidity.

In conclusion, the work presented in this thesis suggests that intervention with selective hypothermia offers the potential to change disease progression and improve subsequent outcome following perinatal asphyxia at term.
Preface

There can be no greater motivating force than the sad experience of witnessing the evolving consequences of severe perinatal neurological injury; the newborn infant starts perfectly formed but by some tragic event, or events, is left devastated with cerebral palsy, seizures and microcephaly. Such misfortune is indeed a heavy loss for them, their families and society.

I came to New Zealand in 1997 to work as a neonatologist at National Women’s Hospital and very quickly became involved in the work on selective hypothermia as an intervention following perinatal asphyxia. The chance to offer some hope to families of affected babies was compelling in itself but the added opportunity to work with local and international collaborators and to be the site investigator for a large multicentre randomized controlled trial of selective cerebral hypothermia was truly an enlightening and rewarding experience. However, the true measure of the work will be in the transfer of the technique to routine clinical practice and hopefully the subsequent improvement in outcome for future infants.
Dedication

To my family: Paula, Georgia, Lydia and Toby who have missed me while I have been writing.
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List of Abbreviated Terms

Alpha-Amino-3-Hydroxy-5-Methyl-4-Isoxazole Propionate (AMPA)
Amplitude integrated EEG Recording (aEEG)
Anti Diuretic Hormone (ADH)
Beats per minute (BPM)
Brain Specific Proteins (BSPS)
Brainstem Auditory Evoked Responses (BAER)
Cerebral Blood Flow (CBF)
Cerebral Blood Flow Velocity (CBFV)
Cerebral Function Monitoring (CFM)
Cerebrospinal Fluid (CSF)
Computer Tomography (CT)
Concentration Ratio Of Phosphocreatine To Inorganic Phosphate ([Pcr]/[Pi])
Corrected QT (QTc)
Disseminated Intravascular Coagulation (DIC)
Electroencephalography (EEG)
Gamma Amino Butyric Acid (GABA)
Glial Fibrillary Acidic Protein (GFAP)
Glycine-Proline-Glutamate (GPE)
Grams (g)
Hypoxic Ischaemic Encephalopathy (HIE)
Hypoxic-Ischaemic (HI)
Insulin-Like Growth Factor-L (IGF-I)
International Normalised Ratio (INR)
Intracranial Pressure (ICP)
Lower Segment Caesarean Section (LSCS)
Magnetic Resonance imaging (MRI)
Magnetic Resonance Spectroscopy (MRS)
Mean Arterial Blood Pressure (MAP)
Negative Predictive Value (NPV)
Neonatal Encephalopathy (NE)
Neuronal Nitric Oxide Synthetase (Nnos)
Neuron Specific Enolase (NSE)
Partial Pressure of Oxygen (Pao2)
Persistent Pulmonary Hypertension (PPHN)
Poly(ADP-Ribose) Polymerase (PARP)
Positron Emission Tomography (PET)
Posterior Limb of the Internal Capsule (PLIC)
Proton (1H)
Resistive Index (RI)
Sclerema neonatorum (SN)
Somatosensory Evoked Potentials (SSEPS)
Standard Deviation (SD)
Subcutaneous fat necrosis of the newborn (SCFN)
Superior Sagittal Sinus (SSS)
Troponin T (TnT),
Visual Evoked Potentials (VEPS)
Weeks (Wks)
Years (Yrs)