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Clinical paper

Effect of cardiac compressions and hypothermia treatment on cardiac troponin I in newborns with perinatal asphyxia☆

Xun Liu[a,*], Ela Chakkarapani[a], Janet Stone[b], Marianne Thoresen[a,c]

[a] Neonatal Neuroscience, School of Clinical Sciences, University of Bristol, Level D, Neonatal Neuroscience, St. Michael's Hospital, Bristol BS2 8EG, UK
[b] Department of Biochemistry, Bristol Royal Infirmary, Level 9, Department of Biochemistry, Bristol Royal Infirmary, Bristol BS2 8HW, UK
[c] Institute of Basic Medical Sciences, Department of Physiology, University of Oslo, Sognsvannsveien 9, PO Box 1103 Blindern, Oslo NO-0317, Norway

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ABSTRACT

Background: The American Heart Association, the European Resuscitation and the International Liaison Committee issued new neonatal resuscitation guidelines (2010) where therapeutic hypothermia is introduced after hypoxic-ischaemic encephalopathy (HIE) in term infants to prevent brain injury. Our study aimed to investigate whether hypothermia can reduce the release of a cardiac cellular marker, cardiac troponin I (cTnI), in HIE infants compared to normothermia care, if cTnI can be used as a prognostic marker for long term neuro-developmental outcome and if cardiac compression at birth affects the level of cTnI.

Methods: We retrospectively collected resuscitation data at birth and cTnI levels for the first 3 days in HIE infants who fulfilled cooling entry criteria. These infants received either normothermia care or induced hypothermia treatment in the neonatal period and were then followed up and tested by standard cognitive and motor assessments. The outcome is defined as death, disability or good.

Results: We confirmed an increase in cTnI after cardiac compressions ($p = 0.003$, Mann–Whitney test). We found that hypothermia significantly reduced the release of cTnI (peak level and area under the curve within 24 h of age), $p = 0.002$, linear regression. Receiver operating characteristic curves showed a level of cTnI at 24 h of age <0.22 ng/ml for normothermic and <0.15 ng/ml for hypothermic infants predicts a good outcome.

Conclusions: Our results suggest that hypothermia is cardio protective after HIE. The level of cTnI at 24 h of age is a good prognostic marker for neuro-developmental outcome at 18–22 months in both normothermia and hypothermia infants.

1. Introduction

Neonatal hypoxic-ischaemic encephalopathy (HIE) occurs in up to 6 per 1000 live births and accounts for one of the major causes of death and disability in the neonatal period. Those infants have either clinical or laboratory evidence of asphyxia due to hypoxia and ischaemia around the time of birth. Cardiac dysfunction is commonly seen (70%) in these newborns[1,2] and is associated with adverse neurological outcome.[3] In recent years, therapeutic hypothermia (HT) has been proven to improve neurodevelopmental outcome and is a recommended standard of care since 2010 by the National Institute for Health and Clinical Excellence (NICE) in the UK,[4] the American Heart Association, the European Resuscitation and the International Liaison Committee on Resuscitation (ILCOR).[5]

Cardiac troponin I (cTnI) is a specific cellular marker released by cardiomyocytes during cardiac injury (such as hypoxia or ischaemia) or can be released after a cardiac compression. Cardiac troponin I tests have become increasingly popular choices in assisting diagnostic and clinical intervention of acute coronary syndromes or other cardiovascular diseases in adults. However, despite the ever-increasing sensitivity and precision of the cTnI assays, the use and understanding of the cTnI levels in newborns is limited. cTnI is elevated after birth in newborn term infants with HIE compared to healthy controls[6] and associated with HIE severity[7] and a valid prognostic marker for short-term mortality.[8]

We have recently shown that immediate cooling reduces the release of cTnI in newborn pigs with HIE, compared to normothermia (NT) treatment,[9] where we found that cTnI levels 6 h after the insult correlated with brain injury examined after 3 days survival. In the current study we investigated if cardiac compression during resuscitation increased the level of cTnI shortly after birth

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* Corresponding author.
E-mail address: xun.liu@bristol.ac.uk (X. Liu).

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and if cooling treatment reduced cTnI release in newborn infants with HIE. We also studied if we can use cTnI (<3 days of age) as an early biomarker for long term neurodevelopmental outcome at 18–22 months of age in infants with moderate or severe perinatal asphyxia.

2. Patients and methods

This study was approved for a retrospective data collection project by our regional research committee (CH/2009/3091). Seventy-five infants fulfilled the entry criteria as used in the TOBY[10] trials and infants were either cooled or underwent NT management after moderate or severe perinatal asphyxia. Infants had repeated cTnI values measured during the first 72 h of life and outcome assessment by Bayley scale of infant development (BSID) second edition (II) score (BSID II) at 18–22 months of age. Normothermic management implied a rectal temperature at 37 ± 0.2 °C. Hypothermic infants were nursed at a rectal temperature of 33.5 ± 0.5 °C for 72 h followed by rewarming at 0.5 °C per hour to 36.5 °C. Infants were cooled using different cooling devices available at that time. Fifty-three infants were cooled with a servo-controlled whole body cooling device (Criticool, MTRE, Rehovot, Israel), 4 with a cool cap (Olympic Medical Ltd. USA) and 5 with a manual controlled body mattress (Tecotherm, Inspiration Health Care Ltd. Leicester, UK). Ten infants (6NT and 4HT) were a part of the TOBY trial[10]; 8 infants fulfilled the clinical and neurology cooling criteria but were older than 6 h at the time of admission hence only received NT treatment. From December 2006, babies were registered in the TOBY cooling registry and received cooling therapy as standard of care ($n = 57$).

2.1. Cardiac compression during resuscitation

Cardiac compression according to ILCOR guidelines were performed if an infant's heart rate (HR) was <60 bpm in the presence of adequate lung inflation and ventilation for 30 s. The infant's respiration, colour and HR were assessed every 30 s. The cardiac compression was discontinued if HR > 60 bpm. If an infant's HR remained <60 bpm despite good ventilation, oxygen supplementation, and cardiac compression, adrenaline was given at 0.01–0.03 mg/kg via endotracheal tube if an intravenous route (*i.v.*) was not established. As soon as an *i.v.* route was accessible, adrenaline was given *i.v.*

2.2. cTnI sampling and assay

Blood samples for cTnI analysis were obtained from an indwelling umbilical arterial line as a part of routine blood analysis. cTnI was analysed using an ACCESS assay (*Beckman* Coulter, Inc., Chaska, MN) with sensitivity at 0.03 ng/ml and defined as sensitive for clinical use.[11] The intra assay coefficient of variation (CV) is 1.4–3.9% and the inter assay CV of is 4.7–6.7%. The upper limit of cTnI in this study for healthy newborns was set to 0.06 ng/ml in keeping with published data.[7,12,13]

2.3. Correction of hypotension

A mean arterial blood pressure (MABP) of below 45 mmHg was first treated with two volume boluses of 10 ml/kg saline. If the hypertension persisted, a dopamine (5–20 μg/kg/min) infusion and then dobutamine (5–20 μg/kg/min) infusion were introduced. If MABP remained low, hydrocortisone (2.5 mg/kg, 3 times/day) was the third line drug after dopamine and dobutamine. A fourth line drug could be either adrenaline or noradrenaline infusion.

2.4. Developmental assessment

Bayley II scores at 18–22 months of age were used as the neurodevelopmental outcome in this study.[10] This scoring system is a standardised and validated measurement system widely used by clinicians for monitoring developmental assessment or as a primary outcome measurement in major international neonatal neuroprotection clinical trials.[10,14,15] It comprises a mental development index (MDI) and a psychomotor development index (PDI). The examination was carried out by trained research staff blinded to treatment groups. Disability was defined as MDI or PDI <70, or severe hearing or visual loss. The combined adverse outcome classification was death <18 months of age or disability. Six NT and 5 HT infants did not have full Bayley II examinations. Instead, clinical examinations were done at 24 months by a consultant neonatologist (MT) where a corresponding outcome measure (good or poor outcome) was given.

2.5. Statistical analysis

Non-parametric tests (Mann–Whitney) were used to compare baseline parameters and cTnI values of infants treated with NT or HT. The data is presented as median (interquartile range, IQR or 95% confidence interval, CI). If there was more than one cTnI value during the time period of interest, the highest value and corresponding time point were chosen. Kendall's Tau was used to test the correlations between the worst pH in the first hour of life and the peak cTnI level before 24 h of age. Pearson correlation was used to test the correlations between MDI or PDI and a cTnI value at the age of 24 ± 2 h. A receiver operating characteristic (ROC) curve was used to determine appropriate cTnI values at 24 h with a balanced sensitivity and specificity for a good neurodevelopmental outcome. A "N-1" chi square test was used to determine a statistical difference in 2 × 2 table.[16] Area under the curve (AUC) was calculated using trapezoidal rules for each day and before 36 h. The Statistical Package for the Social Sciences (SPSS software version 18.0, New York, USA) was used.

3. Results

3.1. Patient information

A total of 75 infants with moderate or severe HIE were enrolled in this study; 14 infants received standard intensive care at NT and 61 infants received HT treatment for 72 h. Patients' characteristics are summarised in Table 1. The need for cardiac compression, Apgar scores at 1 or 10 min and the worst pH within the first hour of life were not different between the two groups. Babies who were cooled had lower HR compared to those who were not cooled. More hypothermic infants (72%) received inotropic support than normothermic infants (25%) ($p = 0.01$, Mann–Whitney).

The relationship between the peak cTnI value (before 24 h) and the worst pH within the first hour of life is shown in Fig. 1. The worst pH and the peak cTnI value before 24 h was correlated ($r = -0.358$, $p = 0.078$ for NT; $r = -0.264$, $p = 0.003$ for HT, Kendall's Tau correlation).

3.2. Patients with normal cTnI values (<4 days)

Not all infants with perinatal asphyxia have cardiac compromise. The same proportion of NT (21%, 3/14) and HT (21%, 13/61) infants in this study had normal cTnI values ≤0.06 ng/ml throughout the first 4 days of life. Of these infants none of the NT infants but 8 (53%) HT infants received inotropic support. All infants with normal cTnI values survived and only 1 out of 16 had