

Hemodynamic instability in asphyxiated neonates: incidence, pathomechanism, treatment

Doctoral thesis

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Introduction

The incidence of hypoxic-ischemic encephalopathy (HIE) is 1.5 per 1,000 live births per year causing 0.7 million death worldwide in a year. Ten percent of the infants with moderate-severe HIE are likely to die in the neonatal period, another 10% will suffer from cerebral paresis, and 40% of survivors would live with neurologic and other disabilities. To date, only therapeutic hypothermia (TH) has shown to be clinically efficacious by reducing the rate of death or severe neurodevelopmental disabilities in patients with moderate-to-severe encephalopathy. Results of preclinical and clinical studies suggest that to be more effective, therapeutic hypothermia must be initiated as soon as possible after the hypoxic insult. TH has become the standard of care to improve morbidity and mortality in infants with HIE based on the results of three large, multi-center, international clinical trials (Total Body Hypothermia for Neonatal Encephalopathy (TOBY), CoolCap, National Institute of Child Health and Human Development (NICHD)). TH has been shown to produce clinically important improvements in neurodevelopmental outcome in survivors (number needed to treat, NNT=8) in patients with moderate or severe encephalopathy. Maintenance of normal heart function and systemic blood flow continues to be the cornerstone of critical care with the aim to restore adequate cerebral blood flow.

Asphyxiated neonates often present with multiorgan failure and systemic hypotension; TH could worsen the hemodynamic instability but there are limited data. Therefore, treatment of cardiovascular impairment represents a major challenge in this clinical setting.

The pathophysiology of hemodynamic instability in patients with HIE is complex; specifically, asphyxia-associated myocardial ischemia, vasoregulatory impairment and the direct effects of TH (sinus bradycardia, increased vascular resistance) may all play a role in its development. As a result, neonates undergoing TH frequently

present with decreased cardiac output and hypotension, in addition to hypovolemia, all of which may lead to systemic and brain hypoperfusion. Therefore, asphyxiated neonates often receive vasopressor-inotropic support, despite that cardiovascular response to catecholamine therapy is blunted during TH.

Relative adrenal insufficiency (RAI), a condition characterized by inadequately low ($<15 \mu\text{g/dL}$) cortisol concentration in an acute illness setting, is a biologically plausible underlying etiology in patients with refractory hypotension. Low-dose hydrocortisone supplementation was shown to improve blood pressure in other critically ill populations (preterm and term infants, pediatric patients and adults), however has not been studied in HIE infants.

In our study, we aimed to investigate the incidence of multiorgan failure, pathophysiology of hemodynamic instability and the effect of hydrocortisone supplementation on systemic hypotension of neonates with hypoxic-ischemic encephalopathy at the neonatal intensive care unit of the 1st Department of Pediatrics, Semmelweis University.

Aims

The general objective of my PhD thesis is to provide a description of hemodynamic instability of asphyxiated infants during hypothermia treatment with special focus on relative adrenal insufficiency as a possible underlying etiology in systemic hypotension. The specific aims are the following:

The incidence of multiorgan failure and hemodynamic instability:

- a. To describe the most common pathologic factors in our patients associated with hypoxic injury.
- b. To study the characteristics of hypothermia treatment in our patient population.
- c. To investigate the incidence of multiorgan failure and determine which organ systems are most frequently affected in cooled, asphyxiated newborns.
- d. To study the occurrence of hemodynamic instability and the possible therapeutic options during hypothermia treatment in neonates with HIE.

Retrospective analysis of relative adrenal insufficiency and hydrocortisone supplementation:

- a. To assess serum cortisol values during the first week of life in critically ill asphyxiated neonates with hypotension.
- b. To study whether there is an association between severity of illness and serum cortisol values in asphyxiated infants during hypothermia treatment.
- c. To describe the occurrence of low-dose hydrocortisone supplementation in our clinical practice in asphyxiated neonates with hypotension.
- d. To determine the long-term neurodevelopmental outcomes after hydrocortisone supplementation in patients with HIE.

Randomized controlled study of low-dose hydrocortisone therapy in hypotensive asphyxiated neonates undergoing hypothermia treatment:

- a. To study the blood pressure and heart rate change in hydrocortisone and control groups. To describe the primary outcome, defined as the proportion of patients who reached at least a 5 mmHg increase in mean arterial pressure (MAP) within two hours of randomization, in the treatment and control groups. To determine the possible clinical variables which influence blood pressure and heart rate during hypothermia.
- b. To investigate the dose and duration of standard dopamine therapy in the two study groups.
- c. To compare the secondary clinical outcome measures (cardiovascular, respiratory, renal, neurological and metabolic parameters) and short-term outcomes in patients receiving hydrocortisone supplementation and in the control group.
- d. To evaluate the serum cortisol levels from the baseline until the end of cooling in the two study groups.

Methods

All patients were outborn and admitted to the Neonatal Intensive Care Unit (NICU) at the 1st Department of Pediatrics, Semmelweis University. We recruited term neonates with moderate-to-severe hypoxic-ischemic encephalopathy who underwent 72 hours standard hypothermia treatment (as described in the TOBY trial).

Asphyxia registry

A new, web-based registry was developed with bioinformatical help to store and handle the clinical data of the asphyxiated neonates who were treated in our unit.

Patient populations

The incidence of multiorgan failure and hemodynamic instability

We conducted a retrospective cohort analysis between 2013-2015, including 97 asphyxiated neonates with HIE who received hypothermia treatment, using our in-house developed novel registry database. We analyzed the anamnesis of birth, the details of resuscitation, initial blood gas values, the details of hypothermia treatment, clinical parameters, incidence of multiorgan failure and hemodynamic instability.

Retrospective analysis of relative adrenal insufficiency and hydrocortisone supplementation

After the first descriptive study, we conducted a retrospective cohort study, including term neonates with moderate-to-severe hypoxic-ischemic encephalopathy who underwent standard hypothermia treatment between 2007-2016. Cortisol values were measured in 79 infants whenever hypotension occurred in the first week of life (between the 0-168th hours of life). For studying adrenal function during hypothermia treatment, we performed a subgroup analysis including patients whose cortisol values were measured between the 12-85th hours of postnatal life (n=58 patients). In this subgroup, we

excluded measurements that were made during the first 12 postnatal hours, based on prior knowledge that cortisol values are considerably higher due to the stress experienced during labor and delivery. Hypothermia treatment was started within the first 6 postnatal hours, lasted 72 hours, followed by 7 hours of rewarming phase, adding up to a maximum of 85 hours of postnatal life (6+72+7=85). For the subgroup analysis, we divided the patients into mild and moderate-severe groups based on the illness severity using the Score for Neonatal Acute Physiology (SNAP-II) recorded within 12 hours of the cortisol measurement. Long term outcome was registered in a subgroup of patients who were available to follow-up (n=35) at 18 to 42 months of age using the Bayley Scales of Infant Development, Second Edition (BSID II) mental and psychomotor developmental indices (termed MDI and PDI, respectively). Infants with congenital malformation, metabolic disorder and bilateral adrenal hemorrhage were excluded from the retrospective analyses. For the clinical data collection, ethical permission was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (11790-2/2016/EKU)

Randomized controlled study of low-dose hydrocortisone therapy in hypotensive asphyxiated neonates undergoing hypothermia treatment

This was a prospective, double-blind, randomized, placebo-controlled study that was conducted in a single center. A total of 35 asphyxiated neonates with hypotension during TH were recruited prospectively between February 2016 and November 2017. Ethical permission for the study was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (5705-1/2016/EKU). The study was registered with ClinicalTrials.gov, identification number NCT02700828.

Inclusion criteria were:

- Gestational age of ≥ 36 weeks
- Whole body hypothermia treatment
- Presence of systemic hypotension (defined as MAP less than the gestational age in weeks) despite administration of volume expanders (10-20 ml/kg)
- Written informed parental consent

Exclusion criteria were:

- Single or combined vasopressor-inotrope therapy before randomization
- Had a hematocrit level $\leq 35\%$
- Presented with congenital abnormalities.

Sample size calculation demonstrated that a total of 32 patients, 16 in each treatment arm, was needed to show the difference in MAP with hydrocortisone administration versus placebo, with a power of 80%, using a two-sided $p=0.05$. Sample size calculation was based on our previous observational data, which suggested a 5 mmHg increase in MAP in the presence of dopamine, 2 to 6 hours after hydrocortisone administration (0.5 mg/kg).

Management of systemic low blood pressure during TH

In asphyxiated neonates the diagnosis of systemic hypotension was defined as MAP less than the gestational age in weeks. The treatment of hypotension was the following:

1. fluid bolus: one or two doses (10 mL/kg per dose) over 15 minutes were given initially to correct presumed hypovolemia

If volume expansion deemed unsuccessful in maintaining blood pressure:

2. serum cortisol measurement
3. randomization and “study drug” preparation

4. dopamine infusion was started at a rate of 6 $\mu\text{g}/\text{kg}/\text{min}$, and simultaneously, 0,5 mg/kg hydrocortisone or placebo in every 6 hours until the end of rewarming

If necessary, the dopamine dose was increased in 2 $\mu\text{g}/\text{kg}/\text{min}$ increments up to 20 $\mu\text{g}/\text{kg}/\text{min}$. The use of dobutamine was reserved for patients with poor cardiac contractility on echocardiography, which was performed by a pediatric cardiologist. No other inotrope or vasopressor was used in this study. Weaning of inotropes was initiated based on the attending neonatologists' decision who were blinded to the study.

Serum cortisol levels were measured at randomization, and every 24 hours thereafter, by electrochemoluminescent immunoassays. In the present study, however, the clinical management was not influenced by the actual cortisol levels (the clinicians did not see the results until the end of the study).

Statistical analysis

Groups were compared with Student t-test, Mann-Whitney U-test, Wilcoxon signed rank test, Barnard's exact test or chi-square test as appropriate. A curve fitting method with automatic outlier elimination was used to describe the relationship between cortisol values and time, using the "ROUT" method. Regression modeling in the prospective, randomized trial was performed to predict MAP, heart rate (HR) and pulse pressure (systolic - diastolic blood pressure difference) using a repeated-measures linear mixed-effect model with first-order autoregressive within-group correlation structure fitted by maximizing the restricted log-likelihood.

Statistical tests were run by using IBM SPSS Statistics 22.0, SigmaPlot Version 11.0 or R Statistical Software, and graphs were plotted with GraphPad Prism Version 6.01. The level of significance was set at 0.05.

Results

The NICU of the 1st Department of Pediatrics, Semmelweis University has large patient load of asphyxiated newborns receiving TH which offers unique research opportunities. Our in-house developed Asphyxia registry currently contains the data of approximately 600 neonates who have been treated in the NICU of the 1st Department of Pediatrics, Semmelweis University since 2006. The registry enabled us to conduct comprehensive retrospective analyses in this patient cohort.

The incidence of multiorgan failure and hemodynamic instability

We started our research with a comprehensive survey of 97 neonates with moderate-to-severe HIE treated with TH between 2013 and 2015. In the descriptive analysis, we found that the meconium stained amniotic fluid, umbilical cord abnormalities (knot, nuchal cord, prolapse) and prolonged labor were the most common pathologies associated with the hypoxic injury in our patients. In this population, TH was started during neonatal transport in 94%, and neonates reached the target cooling temperature at 3 hours of age. Multiorgan failure associated with the perinatal asphyxia was present in 83% of the patients and 79% required circulatory support. Hydrocortisone supplementation was used in 55% of the neonates in the observed period used as a treatment for vasopressor-resistant hypotension and/or suspected RAI. Perinatal death occurred in 6% in this survey.

Retrospective analysis of relative adrenal insufficiency and hydrocortisone supplementation

Secondly, we aimed to investigate the serum cortisol levels and the incidence of relative adrenal insufficiency in asphyxiated newborns with hemodynamic instability between 2007 and 2016. Cortisol values displayed an exponential decay characteristic in the first week of postnatal life, with 89% of the measurements being less than 15 µg/dl, the threshold of RAI (Figure 1).

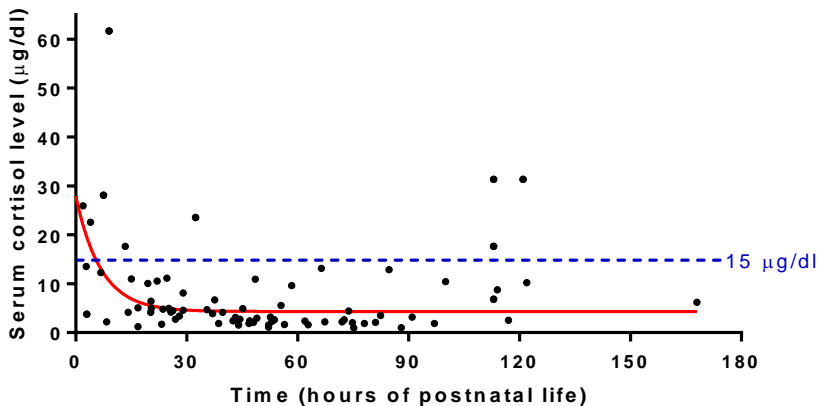


Figure 1: Serum cortisol values display an exponential decay characteristic after birth in asphyxiated neonates undergoing hypothermia treatment. (n=79)

Curve fitting method was used after automatic outlier elimination. The following equation describes the curve: $y = (27.9 - 4.315) * \exp(-0.1467 * x) + 4.315$. R^2 equals to 0.460, the plateau phase equals to a cortisol value of 4.3 µg/dl.

Infants with more severe condition measured on the SNAP-II scale had significantly higher cortisol values during hypothermia (moderate-severe 5.0 [3.9; 10.9] µg/dl vs mild condition 2.8 [2.0; 4.6] µg/dl; $p=0.002$). Eventually 57% of patients received low-dose hydrocortisone supplementation (HCS) at a median dose of 0.6 [0.5; 1.0] mg/kg due to hemodynamic instability and suspected RAI. Among those who were available for follow-up, patients with or without HCS scored similarly on the Bayley-II (HCS group vs non-HCS group: 103.0 ± 15.5 vs 94.1 ± 19.2 MDI; $p=0.14$ and 103.1 ± 12.5 vs 99.2 ± 9.4 PDI; $p=0.31$).

Randomized controlled study of low-dose hydrocortisone therapy in hypotensive asphyxiated neonates undergoing hypothermia treatment

After the retrospective analyses, we performed a randomized clinical trial in infants with HIE with hypotension during TH to compare the cardiovascular effects of low-dose hydrocortisone supplementation (0.5 mg/kg) versus placebo with standard dopamine therapy in both arms.

During the 22-month study period, of the 67 asphyxiated infants eligible for initial assessment, 35 HIE infants met the inclusion criteria and were enrolled prospectively. However, three infants from the placebo group were subsequently excluded from the study due to critical deterioration (severe complications included pulmonary hypertension, acute kidney failure treated with continuous venovenous hemofiltration and hypertrophic cardiomyopathy) and received hydrocortisone thus breaking the study protocol. Accordingly, we performed both a per protocol analysis on the dataset.

The primary outcome, defined as the proportion of patients who reached at least a 5 mmHg increase in MAP within two hours of randomization, was different between the treatment and control groups (94% in the cortisol group vs 63% in the placebo group; $p=0.04$). Furthermore, the duration of cardiovascular support, cumulative and peak inotrope dosage were all lower in the hydrocortisone group. The regression equation predicted that an increase of 4 mmHg in MAP, corresponding to the effect of hydrocortisone administration as per the study protocol, was comparable to 15 $\mu\text{g}/\text{kg}/\text{min}$ dopamine treatment (Figure 2). We also analyzed the systolic - diastolic blood pressure difference in the 2 treatment groups and found that time elapsed during the study period or the dosage of inotrope therapy had no effect ($p=0.09$ and $p=0.64$, respectively). The pressure gradient, however, was greater, by 2.2 mmHg in the hydrocortisone treatment group ($p=0.02$), a finding that was already present at baseline.

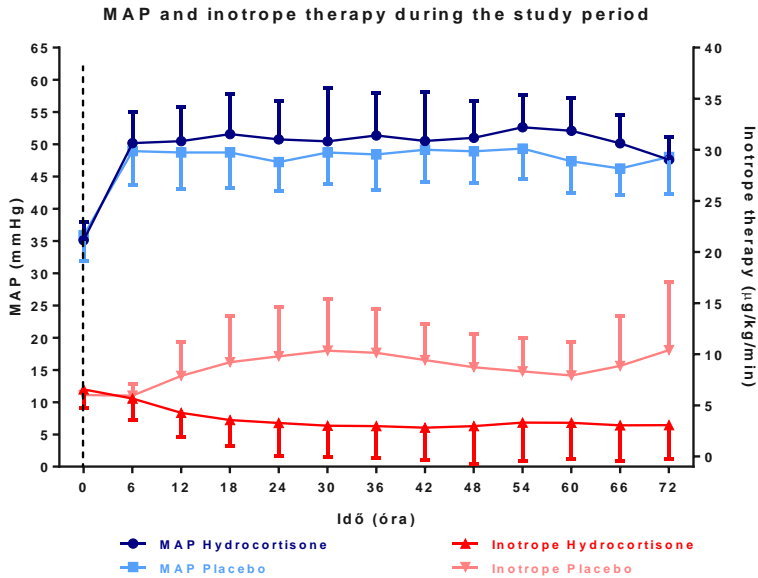


Figure 2: The trends of the MAP (left y axis, in blue color, mmHg, mean \pm SD) and inotrope therapy (right y axis, in red color, $\mu\text{g}/\text{kg}/\text{min}$, mean \pm SD) are shown in 6-hour epochs. Time “0” is the start of hydrocortisone or placebo treatment.

We analyzed the HR trends in the two treatment groups and found it to be higher (13 beats/min; $p < 0.001$) in the placebo group, probably due to higher dopamine doses.

Baseline median serum cortisol values upon enrollment were low in both groups (hydrocortisone vs placebo: 3.5 [2.2; 14.5] $\mu\text{g}/\text{dl}$ vs 3.3 [2.4; 11.3] $\mu\text{g}/\text{dl}$; $p = 0.87$) and 75% of patients in both treatment arms had serum cortisol levels < 15 $\mu\text{g}/\text{dl}$. Further cortisol concentrations were determined at 24-hour intervals until the end of TH. It is noteworthy, that the cortisol levels were very low in the placebo group and seemed to decrease further during the study period.

Short-term outcomes, including time to exclusive enteral feeding, hospitalization length and discharge data, were comparable in the two groups. Finally, the long-term neurodevelopmental follow-up results are still awaited in our patient population.

Conclusions

In our study, we aimed to investigate the incidence of multiorgan failure, pathophysiology of hemodynamic instability and the effect of hydrocortisone supplementation on systemic hypotension of neonates with hypoxic-ischemic encephalopathy at the neonatal intensive care unit of the 1st Department of Pediatrics, Semmelweis University.

Our results showed that 83% of our patients with moderate-severe hypoxic-ischaemic encephalopathy between 2013-2015 had multiorgan-failure during hypothermia treatment. Cardiovascular compromise as a part of multiorgan dysfunction was present in 79%.

In the next part of our study, we confirmed that serum cortisol values decrease rapidly in the first postnatal hours in asphyxiated newborns treated with hypothermia between 2007-2016. 89% of the cortisol values were below 15 µg/dL, the threshold of relative adrenal insufficiency. Eventually 57% of patients received low-dose hydrocortisone supplementation due to hemodynamic instability and suspected adrenal insufficiency. Patients receiving hydrocortisone supplementation scored similarly on the Bayley-II test of infant development when compared to the control group.

The results of our randomized controlled trial between 2016-2017 showed that hydrocortisone administration was effective in raising the blood pressure of patients with hypoxic-ischemic encephalopathy with hypotension during therapeutic hypothermia. A greater proportion of patients (94% vs 63%) reached at least 5-mmHg increase of mean arterial blood pressure within 2 hours of drug administration. In addition, adjunctive dopamine therapy was reduced and inotropes were weaned off sooner in the hydrocortisone treatment group, compared with the placebo group. The regression equation predicted that an increase of 4 mmHg in mean arterial blood pressure was corresponding to the effect of hydrocortisone administration. Lower heart rate in the hydrocortisone group may be favorable due to the decreased oxygen and energy requirement of the

hypoxic myocardium. In addition, higher pulse pressure may indirectly indicate improved left ventricular systolic function in the hydrocortisone group. Of note, 75% of the initial serum cortisol values were below the threshold of relative adrenal insufficiency and the levels decreased even further in the placebo group during the study period, confirming the initial hypothesis that hydrocortisone supplementation may be a causative therapy in this patient population.

Hydrocortisone supplementation may be used as a personalized therapy in hypotensive patients with birth asphyxia and RAI, contrary to vasopressor-inotropes that provide symptomatic treatment only. Steroid therapy stabilizes the cardiovascular status and improves endothelial integrity leading to better cerebral and peripheral perfusion, while undesired complications due to high inotrop demand may be avoided.

Based on our findings, a larger multicenter trial may be warranted to confirm or disprove the beneficial effects of hydrocortisone therapy in patients with hypoxic-ischemic encephalopathy with hypotension. On the long term, hydrocortison treatment may be the part of routine clinical practice in the treatment of hemodynamic instability of asphyxiated neonates.

Bibliography of the candidate's publications

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