Optimizing the intensive care of asphyxiated neonates

Doctoral thesis

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Introduction

Perinatal asphyxia is a devastating condition that may lead to hypoxic-ischemic encephalopathy (HIE) and permanent neurological deficit in the adulthood. HIE affects up to 3 infants per 1000 live birth every year in developed countries, placing a huge burden on families and the health care system. The magnitude of the problem is clear from both a personal and an economic perspective. To date, only therapeutic hypothermia (TH) has been shown to reduce mortality and adverse neurodevelopmental outcome in patients with moderate to severe HIE. The neuroprotective effect of TH continues to childhood. Even with hypothermia, nearly 40% of infants affected either die or develop severe disabilities such as cerebral palsy, mental retardation and learning difficulties. Over the last decade, several pharmacological agents have been tested in order to augment the hypothermic neuroprotection. To date none of the adjunctive therapies have been proven to be beneficial in the treatment of HIE. The optimization of TH and the provision of intensive care support to these infants have become the center of attention lately. First, it is well established that TH must be initiated as soon as possible after the hypoxic-ischemic insult to enhance the neuroprotective effect of cooling. Further, the optimal respiratory and cardiovascular management during TH has the ability to prevent the secondary progression of brain injury leading to improved outcomes. The consistent findings of the association between hypocapnia and adverse neurological outcome suggest that the avoidance of hypocapnia may be a reasonable approach to optimize long term outcomes in this high risk population.

Aims

The general objective of the present PhD thesis was to study the therapy optimization for hypoxic-ischemic encephalopathy specifically the intensive care during therapeutic hypothermia. The specific aims were the following:

1. **To evaluate the safety and feasibility of controlled active hypothermia compared to standard intensive care alone during neonatal transport.**

Since timing of TH has a key role in its neuroprotective effect, implementation of active hypothermia during neonatal transport is crucial. We hypothesized that controlled active TH during neonatal transport is safe and feasible. First, to confirm the safety we investigated the critical care needs of infants receiving active TH during neonatal transport compared to a historical control group with standard intensive care alone.

For safety analysis, we compared acid-base status and vital signs before and after transport in the two groups. We also compared the need for cardiac support and the rate of overcooling. In addition, we closely monitored for adverse events (severe hypotension, persistent hypoxemia, cardiac arrhythmias). In addition, we compared the in-hospital mortality rates (occurring after 12 h of postnatal life but before discharge).

Second, the feasibility of active TH during transport was assessed by comparing the temperature profile between the actively cooled group and historical controls: 1) the time when hypothermia treatment was initiated, and 2) the time when the upper limit of target temperature (34°C) was achieved , and 3) the rectal temperature at admission to the cooling center. Moreover, we compared the length of stabilization. Finally, we categorized the infants in the actively cooled group based on the temperature ranges on admission (< 33°C, ≤ 34°C and ≥ 33°C, and > 34°C) and compared the disease severity and the transport characteristics between the 3 groups.

2. **To investigate the incidence of hypocapnia in mechanically ventilated infants receiving hypothermia for HIE and to evaluate the association between hypothermia and developing hypocapnia.**

Based on the physiological phenomenon that TH reduces the metabolic rate, we hypothesized that the incidence of hypocapnia is higher during active TH compared to asphyxiated infants receiving standard care. Hypocapnia was defined as a temperature corrected PCO_2 that decreased below 35 mmHg during transport. Furthermore, low core temperature can add to the risk of developing hypocapnia during the early hours of postnatal life. To test our hypothesis, we compared infants undergoing active TH during neonatal transport to historical controls receiving intensive care alone.

3. **To test the safety and feasibility of adding low concentration CO_2 (5% CO_2 + 95% air) to the inhaled gas mixture in mechanically ventilated asphyxiated infants to achieve a desired range of PCO_2 of 40–60 mmHg.**

There is an increasing evidence in the literature that there is a dose-dependent association between hypocapnia and adverse neurodevelopmental outcome at 2 years of age. However, there are limited options to avoid the hypocapnia in asphyxiated infants. We hypothesized that adding 5% CO_2 to the inhaled gas is a reasonable approach to correct hypocapnia and maintain temperature corrected $PaCO_2$ level between 40 and 60 mmHg. **The primary outcome** was the percentage of time spent in the desired temperature corrected PCO_2 range of 40–60 mmHg during CO_2 inhalation.

The secondary outcomes were defined as: **1)** hours of life until base deficit (BD) decreased < 5 mmol/L; **2)** hours of life until pH increased > 7.25; **3)** severe hypotension (MABP < 25 mmHg), despite administration of more than one inotropic agent and volume replacement within the 72 h of life; **4)** number of seizures, either detected clinically or by aEEG monitoring within the 72 h of life; and 5) intracranial hemorrhage detected by MRI within the first week of life.

Methods

We enrolled term infants with the diagnosis of moderate to severe HIE in accordance with the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial protocol. All infants were outborn and admitted to the Level-III Neonatal Intensive Care Unit (NICU) of the 1st Department of Pediatrics, Semmelweis University. The transport was provided by the Neonatal Emergency &Transport Services of the Peter Cerny Foundation (NETS-PCA). Active TH has been adopted by the transport team since 2009 October. In general, infants were excluded if they had congenital disorders, presented with mild asphyxia not fulfilling the criteria for TH or died within 12 hours of life.

Ethical permission for the studies was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (11790–2/2016/EKU and 5705-1/2016/EKU).

Patients

1. Safety and feasibility of controlled active hypothermia during neonatal transport

Medical records of 214 asphyxiated infants treated with TH between 2005 and 2015 were retrospectively reviewed. Of those, 136 infants who received active TH during transport between 2009 October and 2015 were compared to a historical control group of 78 infants born between January 2005 and September 2009.

Control patients received standard intensive care alone without any type of cooling methods during transport and TH was initiated only after admission to the Level-III NICU.

2. **Risk of hypocapnia in asphyxiated infants treated with hypothermia**

A total of 126 infants, who received TH between 2007 and 2011 in our unit, were assessed retrospectively for study purposes. Five infants were excluded due to death within 12 hours of life related to severe asphyxia, 2 neonates presented with mild asphyxia and 2 patients had major congenital anomalies. Altogether, 117 patients were included in this cohort study. Patients who were cooled actively during neonatal transport (n=71) were compared to a historical control group (n=46) who received active TH only on arrival at the cooling center.

3. **Hypoxic-Ischemic Encephalopathy Therapy Optimization in Neonates for Better Neuroprotection with Inhalative CO2: the HENRIC feasibility and safety trial**

Between February 2016 and June 2017, 62 term infants with moderate or severe HIE were assessed for eligibility and a total of ten infants were enrolled in this open-label, single center interventional trial. Inclusion criteria were: 1) fulfilling criteria for TH based on the TOBY trial; 2) temperature corrected arterial $PCO_2 \leq 40$ mmHg at any time within 6 h of life; 3) presence of spontaneous respiratory efforts while being intubated and ventilated; and 4) presence of an indwelling arterial line; 5) written informed parental consent.
Exclusion criteria were the following: 1) meconium aspiration syndrome (MAS) or fraction of inspired oxygen (FiO_2) > 40%; 2) severe metabolic acidosis (pH < 6.8 and/or lactate levels > 15 mmol/L) on admission; 3) cardiovascular compromise requiring more than one inotropic agent; 4) anemia (hematocrit < 35%); and 5) >1 mmol/kg bicarbonate administration during initial stabilization; and 6) major birth defects. The study protocol was registered with ClinicalTrials.gov number NCT02700854.

In addition, an external Data and Safety Monitoring Committee consisting of four independent neonatologists reviewed the data after each patient enrolment and permitted the continuation of the study.

Clinical management during neonatal transport

Active TH has been adopted by our neonatal transport team since 2009 October using a manually regulated cooling device. Before this date TH was started only upon the arrival to the cooling center. Rectal temperature was monitored continuously to secure temperature stability. As per clinical guideline, all patients were intubated and ventilated while receiving TH. Actively cooled infants had at least two blood gas values recorded: one before transport, to confirm the indication of TH, and another one after arrival to the NICU. Additional blood gas samples were taken as needed.

Clinical management and study protocol during the HENRIC trial

Active hypothermia has been initiated within 6 hours of life and continued for 72 hours followed by a 6-hour rewarming period with a rewarming rate of 0.5 ^{o}C using a servo controlled cooling device. Per clinical practice guideline, morphine was used for sedation during TH with a loading dose of 50 μg/kg followed by 10 μg/kg/h for maintenance. Initial mode and parameters of mechanical ventilation were set uniformly based on our guideline.

If any time within 6 hours of life arterial PCO_2 dropped below 40 mmHg, inhalation of low concentration CO_2 (5% CO2 +95% air) was started. The gas mixture was administrated into the inspiratory arm of the ventilatory circuit. For safety reasons a CO_2 sampling line was built into the inhalation circuit to monitor CO_2 delivery continuously. The ventilator displayed the partial pressure of the inhaled 5% CO_2, which was equal to 36 mmHg at atmospheric pressure. In addition, arterial blood gas samples were taken initially every 30 minutes followed by a 2 hourly sampling rate after the stabilization of arterial PCO_2.

According to the study protocol, CO_2 inhalation was discontinued after 12 h or earlier, if the base deficit decreased to < 5 mmol/L. During the CO_2 exposition the targeted PCO_2 range was between 40 and 60 mmHg. The initial settings of the ventilation were changed if the $PaCO_2$ decreased below 35 mmHg or increased above 65 mmHg. PCO_2 administration had to be stopped if $PaCO_2$ raised above 85 mmHg. Vital signs were monitored routinely and recorded every 30 minutes before, during the CO_2 administration and for up to 6 hours after stopping the CO_2 inhalation.

Neurointensive monitoring during the HENRIC trial

Single-channel biparietal aEEG was used for continuous neurointensive monitoring and for seizure detection. The aEEG recordings were subsequently analysed by a trained neonatologist until the end of the rewarming, the reader was blinded to the time and duration of CO_2 exposition.

Transcranial Doppler ultrasound measurements of cerebral blood flow velocity (CBFV) in the anterior and middle cerebral arteries were performed before initiation of inhalative 5% CO_2 to record a baseline, during the CO_2 exposition every second hour and after the offset of 5% CO_2.

Brain MRIs were carried out within the first week of life on a 3 Tesla Philips Achieva MRI scanner and analyzed by a pediatric radiologist blinded to the clinical data.

Bayley Scales of Infant Development II examination was performed at 18–22 months of age by trained examiners. Moderate disability was defined as mental developmental index (MDI) and/or psychomotor developmental index (PDI) score 1 SD below the mean (70–84). Severe disability was defined as any of the following: severe cerebral palsy, hearing impairment, bilateral cortical visual impairment, MDI and/or PDI > 2 SD below the mean (<70).

Statistical analysis

Data are presented as mean (standard deviation), or median (interquartile ranges), or number (percentages), as appropriate. Differences were assessed by using Mann-Whitney U and Kruskal-Wallis test for nonparametric and Student's t test or one-way analysis of variance (ANOVA) for parametric variables. Paired t test and Wilcoxon signed-rank test were used to account for repeated measures when appropriate. For categorical variables, differences were assessed using Chi-squared or Fisher's exact test.

To investigate the association between TH and incident hypocapnia multivariable logistic regression model was built.

In the HENRIC trial we calculated the mean values for cardiorespiratory and CBFV values for each infant during the 3 time epochs of the study: before, during, and after the administration of 5% CO_2 and compared the means between the 3 epochs by Friedman test. Linear interpolation was used to estimate the time spent in the desired PCO_2 range throughout the CO_2 inhalation. Regression modeling was performed to predict the changes of BD, pH, and lactate over time during the CO_2 inhalation, using a repeated-measures linear mixed-effect model.

Matched control patients were selected from our cooling database. Patients were matched for HIE severity according to the Thompson encephalopathy score, $PCO_2 \leq 40$ mmHg any time within the first 6 h of postnatal life, and for birth weight (<3000 g; ≥ 3000 g and <4000 g; ≥ 4000 g).

Results

1. Safety and feasibility of active hypothermia during neonatal transport

The baseline patient characteristics of the asphyxiated infants in the actively cooled group (n = 136) and control group (n = 78) were comparable, with the exception of the 5- and 10-minute Apgar scores that were significantly lower in the control group.

However, there was no difference in the severity of acidosis at referral between the study groups. The pH, PCO_2, and BD values were similar in both groups before and after transport, suggesting that active cooling did not affect acidosis recovery during the transport period.

Heart rate was comparable before transport but decreased significantly among neonates who were cooled during transport, as expected due to the lower body temperature and metabolic rate. Interestingly, less neonates received inotropic support in the actively cooled group compared with the control group (23.5% vs 37.2%; p=0.033). The median of the maximum dose of dopamine and dobutamine administered and volume therapy were similar in both groups.

Newborns with active cooling were more likely to receive conventional mechanical ventilation and sedation/ analgesia treatment during transport, as the current protocol of the transport team and our NICU recommend respiratory support in patients with hypothermia treatment. Importantly, we did not notice any adverse events leading to pulmonary or circulatory failure during the transport period in the entire study population.

In-hospital death rate (occurred after 12 h of life) was found to be eventually higher in the control group.

Hypothermia treatment was initiated a median 2.58 hours earlier in the actively cooled group compared with the control group, and the upper limit of the target temperature of TH (34°C) was also achieved a median 1.83 hours earlier in the cooled group ($p < 0.0001$ for both comparisons). Rectal temperature at admission to the NICU was 33.8°C ± 0.81°C in the actively cooled group, indicating the provision of appropriate active hypothermia treatment during the transport. In contrast, rectal temperature did not change during the transport period and remained 35.3°C ± 1.4°C in the control group ($p < 0.0001$) (Figure 1).

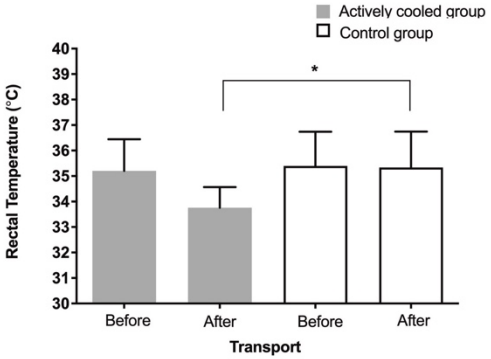

Figure 1. Bar graph for rectal temperature measurements before and after transport in the actively cooled and the control groups.
Before transport, rectal temperature was 35.2°C ± 1.24°C in the actively cooled group and 35.4°C ± 1.34°C in the control group. After transport, on admission to the NICU, the rectal temperature was 33.8°C ± 0.81°C in the actively cooled group and 35.3°C ± 1.4°C in the control group ($p < 0.0001$).

The stabilization time at the referring hospital was longer in the actively cooled group by a median 16 minutes. Accordingly, the duration of transport, calculated as the time from the arrival of the transport team to the referring hospital until their arrival to the NICU was a median 32 minutes longer in the actively cooled group. Consequently, infants in the actively cooled group were older when admitted to the NICU compared with controls; however, NICU admission still occurred before 3 hours of life in 69.16% of all patients.

Finally, to further examine the transport characteristics in the actively cooled group, we analyzed some variables of interest according to the temperature profiles on arrival to the NICU. Among the overcooled infants (rectal temperature < 33°C on admission to the NICU; n = 16) Apgar, pH, base deficit, and eventual death rate (7/16; 43.8%) indicated more severe disease, suggesting that patients with more profound HIE have poor temperature control.

2. Risk of hypocapnia in asphyxiated infants treated with hypothermia

The baseline characteristics of the actively cooled group and the control group did not differ. As expected from the study design, cooling was commenced significantly earlier in the actively cooled group compared to the control group.

We evaluated the PCO_2 levels in each group during transport and found that 54% of the total cohort had at least one PCO_2 value below 35 mmHg during the study period. The rate of incident hypocapnia during transport, defined as a PCO_2 value of > 35 mmHg before and ≤ 35 mmHg after transport, was significantly higher in the actively cooled transport group (26 of 71, 36.6%) compared to the control group (8 of 46, 17.4%, $p = 0.025$).

In addition, in the actively cooled transport group, PCO_2 decreased from the normal range, with a median of 45 [36–68] mmHg, to 35 [26–48] mmHg ($p < 0.0001$) during transport. In contrast, PCO_2 did not change significantly during transport in the control group (Figure 2). There were similar ventilatory parameters in both groups. We did not find any significant differences in the ventilator settings between the group of incident hypocapnic versus normocapnic and hypercapnic patients.

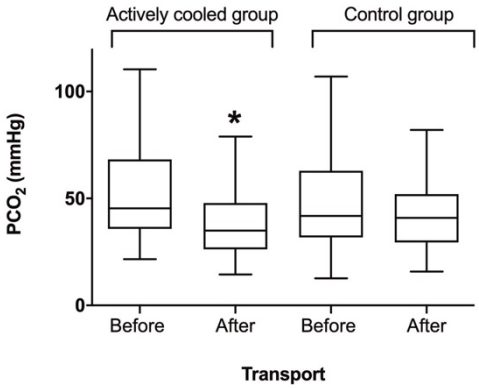

Figure 2. Temperature corrected PCO_2 values before and after transport in the actively cooled and the control groups.
In the actively cooled group, median PCO2 decreased from the normal range to hypocapnia (45 [IQR 36-68] versus 35 [IQR 26-48] mmHg; p<0.001). In the control group, PCO2 did not change during transport (42 [IQR 32-63] versus 41 [IQR 29-52] mmHg; p = 0.322).

Multivariable logistic regression analysis was used to ascertain the effect of active therapeutic hypothermia, on the likelihood that patients would develop incident hypocapnia, adjusting for other clinically relevant parameters, including sedation, the respiratory rate setting of the mechanical ventilator, base deficit and age of hours on admission to the NICU. The hours of age on admission to the NICU corresponding to the time of the second blood gas sampling was included in the model to control for the time-dependent acidosis recovery in asphyxiated infants. The model correctly classified 78.1% of cases. Of the five predictor variables, hypothermia and sedation were statistically significant. Infants who underwent hypothermia treatment during transport had 4.23 times higher odds (95% CI 1.30–13.79) of developing hypocapnia than patients in the control group, who received standard intensive care without cooling during transport. More frequent use of sedation was associated with a reduction in the likelihood of incident hypocapnia with an odds ratio (OR) of 0.35 (95% CI 0.12–0.98).

Based on these results, we can show that hypocapnia was common in asphyxiated infants and therapeutic hypothermia seemed to be an independent risk factor for developing hypocapnia in neonates with HIE.

3. The HENRIC feasibility and safety trial

Sixty-two term infants with moderate or severe HIE were assessed for eligibility, and a total of ten patients were enrolled prospectively into the trial. The median PCO_2 was 33 mmHg (range 26–40 mmHg) at the start of 5% CO_2 administration; which was commenced at a median 5.5 h of life (range 3.9–6.6). The CO_2 inhalation was stopped at a median 12.9 h of life (range 5.4–18.6). During the CO_2 administration, a total of 50 arterial blood gases were taken from the 10 patients. The temperature corrected arterial PCO_2 was between the targeted 40 and 60 mmHg in 96% (48/50) of the samples. All PCO_2 values were >40 mmHg, and the highest PCO_2 value detected was 64 mmHg (infant no. 6).

Calculating with a linear interpolation between the blood gas measurements, patients spent a median 95.1% (range 44.6–98.5%) of time in the desired PCO_2 range during the 5% CO_2 inhalation. In comparison, the patients in the control group spent significantly less time (median 45.3% ((range 0–91.7%), $p = 0.002$) in the target range (Figure 3).

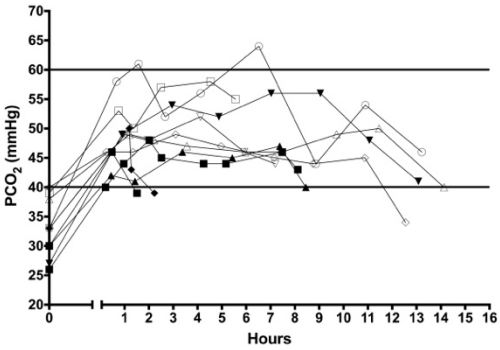

Figure 3. The trends of temperature corrected $PaCO_2$ values during CO_2 administration. Patients spent a median 95.1% (range 44.6–98.5%) of time in the desired PCO_2 range during the 5% CO_2 inhalation.

The 5% CO_2 exposure was continued for the predefined maximum of 12 h in 4 cases, while in 6 cases, the BD decreased <5mmol/L earlier and CO_2 administration was stopped accordingly. It is noteworthy that the latter 6 infants' BD normalized within 13 h of life, while in the former 4 cases the BD recovery was longer and normalized between 23.0 and 59.8 h of life. The end point of acidosis (defined as pH > 7.25) was median 9.1 h of life with a wide range of 1.5–59.8 h.

The regression equation predicted that BD decreased by 0.61 mmol/L and lactate decreased by 0.55 mmol/L per hour after the beginning of inhalation, whereas pH remained stable over time. The matched controls showed a similar tendency in recovery from acidosis.

Cardiovascular and respiratory parameters of the study population were analyzed at three time epochs: pre-inhalation, during, and post-inhalation. We detected a statistically significant decrease in heart rate during the study, which is a physiological response to reduced body temperature. Mean arterial blood pressure and peripheral oxygen saturation did not change. Severe hypotension or cardiovascular collapse did not occur.

Regarding respiratory parameters, the RR reduced significantly in the post-inhalation epoch of the study compared to the RR before and during CO_2 administration ($p = 0.008$, Friedman test). Furthermore, we detected an increased tidal volume during the 5% CO_2 inhalation, reflecting a physiological response to the intervention.
The temperature corrected arterial PO_2 was >100 mmHg in 40% (20/50) of the samples in 7 patients during the 5% CO_2 exposition while the oxygen requirement was 21% in all cases.

Continuous aEEG monitoring detected electrophysiological seizures in 3 patients during the 5% CO_2 exposition, 2 of them already had seizure activity before, and all 3 had seizures after the inhalation, resulting in permanent anticonvulsive treatment as per decision of the clinical team.
Brain MRI scans were carried out at a median of 3.5 (range 2–8) days of life. Diffusion-weighted imaging showed the presence of hypoxic–ischemic injury in 6/10 patients. Six neonates were noted to have intracranial hemorrhage in subdural, subarachnoid, and intraventricular (grade I) location, but none of them developed intraparenchymal bleeding.
We could not find differences in CBFV values measured in anterior and middle cerebral arteries when comparing the three epochs of the study. No death occurred during the perinatal period in our study population. One infant with severe HIE subsequently died in another hospital due to aspiration pneumonia. Severe disability (PDI and/or MDI <70) occurred in three cases; two infants were classified as moderate (PDI and/or MDI 70–84) on Bayley II scales at 18–22 months of age. One child had a total score of 88 (=6 percentile) on the behavior rating scale indicating a nonoptimal test behavior. Three infants had normal outcome (both PDI and MDI ≥85). The rate of severe and moderate disabilities did not differ between the treated and control groups.

Conclusions

Optimization of intensive care of infants with HIE might have the potential to prevent injury progression and further improve neurodevelopmental outcomes in this patient population.

First, we established that therapeutic hypothermia during transport is feasible and safe, allowing for significantly earlier initiation and achievement of target temperature, possibly providing the maximum possible effect of neuroprotection.

Second, we reported that the infants undergoing TH develop hypocapnia more frequently. Moreover, active cooling increases the risk of developing hypocapnia even after controlling for potential confounding factors including provision of sedation, ventilatory settings and acidosis severity. We speculated that the advantage of initiation of hypothermia treatment shortly after delivery might be further enhanced by avoiding frequently observed hypocapnia.

Since clinicians have limited options to lower the risk of hypocapnia in this patient population, we conducted a safety and feasibility trial to correct hypocapnia by adding CO_2 to the inhaled gas mixture in low concentration. The results of our interventional trial suggested that inhaled 5% CO_2 administration is a physiologically plausible, safe and straightforward intervention for correcting hypocapnia in mechanically ventilated, spontaneously breathing infants. Further studies are warranted to test the efficacy of CO_2 inhalation in providing better neurodevelopmental outcome in asphyxiated, hypocapnic neonates treated with HT. This pilot study could pave the way for such randomized trials investigating the efficacy of controlled normocapnia through 5% CO_2 administration.

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