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REGULAR ARTICLE

Asphyxiated neonates who received active therapeutic hypothermia during transport had higher rates of hypocapnia than controls

Eniko Szakmar[1], Kata Kovacs[1], Unoke Meder[1], Geza Bokodi[1], Andras Szell[2], Zsolt Somogyvari[2], Attila J. Szabo[1,3], Miklos Szabo[1], Agnes Jermendy (jermendy.agnes@med.semmelweis-univ.hu)[1]

1.1st Department of Paediatrics, Semmelweis University, Budapest, Hungary
2.Neonatal Emergency & Transport Services of the Peter Cerny Foundation, Budapest, Hungary
3.Paediatrics and Nephrology Research Group, MTA-SE, Budapest, Hungary

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Correspondence
A Jermendy, 1st Department of Paediatrics, Semmelweis University, 53 Bokay ut, Budapest 1083, Hungary.
Tel: +36-204600798 |
Fax: +36-13138212 |
Email: jermendy.agnes@med.semmelweis-univ.hu

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ABSTRACT

Aim: We investigated the association between active hypothermia and hypocapnia in neonates with moderate-to-severe hypoxic-ischaemic encephalopathy (HIE) transported after birth.

Methods: This was a retrospective cohort study of neonates with HIE born between 2007 and 2011 and transported to Semmelweis University, Hungary, for hypothermia treatment before and after we introduced active cooling during transport in 2009. Of these, 71 received intensive care plus controlled active hypothermia during transport, while the 46 controls just received standard intensive care. Incident hypocapnia was defined as a partial pressure of carbon-dioxide (pCO_2) that decreased below 35 mm Hg during transport. Multivariable logistic regression investigated the relationship between hypothermia and incident hypocapnia.

Results: Incident hypocapnia was more frequent in the actively cooled transport group (36.6%) than control group (17.4%; $p = 0.025$). pCO_2 decreased from a median of 45 to 35 mm Hg ($p < 0.0001$) in the intervention group, but remained unchanged in the controls. After adjusting for confounders, hypothermia remained an independent risk factor for hypocapnia with an odds ratio (OR) of 4.23 and 95% confidence interval (95% CI) of 1.30–13.79. Sedation was associated with a reduction in OR of hypocapnia, at 0.35 (95% CI 0.12–0.98).

Conclusions: Hypothermia increased the risk of hypocapnia in neonates with HIE during transport.

INTRODUCTION

Hypoxic-ischaemic encephalopathy (HIE) due to perinatal asphyxia continues to be one of the leading causes of neonatal mortality and morbidity (1), with long-term neurological sequelae occurring in one to two cases per 1000 live term-born infants in developed countries (2). Several studies have demonstrated that initiating whole-body moderate hypothermia (33–34°C) within six hours of birth reduced mortality and neurodevelopmental disability at 18 months of age and beyond (3).

Preclinical and clinical studies have established that, to be effective, hypothermia must be started during the latent phase of HIE before the secondary energy failure leads to ultimate cell death (4,5). The findings of a retrospective study suggested that initiation of hypothermia within three hours, rather than three to six hours after delivery, was associated with improved motor outcome in the surviving patients (6). These findings lend further support to the growing efforts to initiate hypothermia as soon as possible after the hypoxic insult.

Abbreviations
CBF, Cerebral blood flow; HIE, Hypoxic-ischaemic encephalopathy; IQR, Interquartile range; NICU, Neonatal intensive care unit; OR, Odds ratio; pCO_2, Partial pressure of carbon-dioxide.

Key notes

- This study examined the association between active hypothermia and hypocapnia in neonates with moderate-to-severe hypoxic-ischaemic encephalopathy before and after active cooling was introduced during transport.
- Of these, 71 received intensive care plus controlled active hypothermia during transport, while the 46 controls received standard intensive care.
- Incident hypocapnia was more frequent in the intervention than control group, and hypothermia was an independent risk factor for hypocapnia.

Many neonates who present with moderate-to-severe HIE are born in hospitals where neonatal intensive care units (NICU) do not offer hypothermia treatment (7). As these neonates need to be transferred to a NICU with an active hypothermia treatment programme, the accepted clinical approach is to start passive cooling immediately after delivery and, if possible, use a transport system that is capable of providing active cooling during transport (8). Importantly, clinical trials have not reported serious side effects of moderate whole-body hypothermia treatment, either during transport or in a hospital setting.

Several factors may jeopardise the beneficial effects of cooling in an asphyxiated neonate and these include inadvertent hypocapnia, which may play a significant role in worsening the brain injury (9–11). Multiple retrospective analyses have noted a high rate, of up to 88%, in the incidence of hypocapnia during the first 12 hours of postnatal life (10). Moreover, a dose-dependent association was found between hypocapnia and an adverse neurodevelopmental outcome, defined as death or disability at 18–22 months, in a mixed population of cooled and noncooled HIE infants (9,10).

Although therapeutic hypothermia has clearly proven to be beneficial, and early initiation of active cooling is desirable, there is still room for improvement in the critical care of neonates with HIE, especially with regard to optimal ventilation. Based on the theoretical consideration that hypothermia reduces the metabolic rate and lowers endogenous carbon-dioxide production (12), we hypothesised that therapeutic hypothermia treatment could add to the risk of incident hypocapnia in the first hours of life in asphyxiated neonates with HIE. To test this hypothesis, we conducted a retrospective cohort study using data from a single centre to examine any potential association between hypocapnia and active hypothermia at 33–34°C, provided when outborn asphyxiated, mechanically ventilated neonates were transported to our hospital.

PATIENTS AND METHODS

In this retrospective cohort study, the medical records of 126 asphyxiated neonates born between 2007 and 2011 were reviewed. Permission was obtained from the Scientific and Medical Research Council Ethics Committee of Hungary (11790-2/2016/EKU). All infants were outborn and transport was provided by the neonatal emergency and transport services run by the Peter Cerny Foundation, Budapest, Hungary. The infants were cared for in the tertiary NICU of the 1st Department of Paediatrics, Semmelweis University, Budapest. Between October 2009 and December 2011, all 72 infants with HIE transported to the centre underwent controlled active cooling during transport and this actively cooled transport group was compared to a historical control group of 54 infants with HIE that had received intensive care, but no cooling, when they were transported between January 2007 and September 2009. In the control group, therapeutic hypothermia was only started on arrival at the cooling centre. Thus, the study was designed to be a before and after study, divided by the introduction of active cooling during transport.

Infants were excluded if they died within 12 hours of postnatal life (n = 5), had congenital anomalies (n = 2), or if they presented with mild asphyxia and did not fulfil the criteria for hypothermia treatment (n = 2). Altogether, 117 patients met the criteria and were included in the analysis, with 71 patients in the actively cooled transport group and 46 patients in the control group.

The clinical criteria for the diagnosis of moderate-to-severe encephalopathy warranting hypothermia treatment were in accordance with the Total Body Hypothermia for Neonatal Encephalopathy Trial protocol (13). Hypothermia in the cooled group was induced and maintained using a water-filled thermo blanket, the Tecotherm Ts med 200 N (Inspiration Healthcare, East Midlands, UK) placed underneath the patients, targeting a rectal temperature of 33–34°C.

The protocols of the transport team and our NICU were that infants undergoing active hypothermia treatment needed to be mechanically ventilated by a Dräger Babylog 2000 ventilator (Dräger, Lübeck, Germany) and, if warranted, receive analgesia and sedation with fentanyl (2–5 μg/kg). The transport team routinely administrated 5–6 mg/kg of thiopental as premedication prior to endotracheal intubation. The ventilator parameters were set by the transport team based on the standards of clinical care.

In addition, according to the clinical protocols, infants had to have at least two blood gas samples taken and recorded: one before transport, to confirm the indication for initiating hypothermia treatment, and one on admission to the NICU. These were performed using the Abbott i-STAT1 blood gas analyser (Abbott Diagnostics, Princeton, NJ, USA). Additional blood gas samples were taken as required but were not analysed as part of this study.

We noted that 94% of the blood gas samples were of capillary origin and the values, including partial pressure of carbon-dioxide (pCO_2), base deficit and pH, were temperature corrected using the formula described by Ashwood et al. (14). This states that during hypothermia, pCO_2 decreases and pH increases compared with measurements that are made at a body temperature of 37°C. In a healthy newborn infant, a pH of 7.4 will rise to 7.5 and a pCO_2 of 40 mm Hg will decrease to 34 mm Hg, if the actual body temperature is reduced to 33°C by the hypothermia treatment (15).

Incident hypocapnia during transport was defined as a temperature-corrected pCO_2 value that was >35 mm Hg before transport and decreased to ≤35 mm Hg on arrival at the NICU. The cut-off value for hypocapnia was determined based on previous publications (10,16,17).

We performed a multivariable logistic regression analysis to detect possible relationships between incident hypocapnia and clinical predictors of interest, including five variables: hypothermia treatment (33–34°C), use of sedation, respiratory rate of the mechanical ventilator, base deficit and hours of age on admission to the NICU. Predictor variables were chosen based on *a priori* clinical

knowledge. Sedation is likely to decrease hypocapnia by reducing spontaneous respiratory activity. In contrast, base deficit reflects the degree of metabolic acidosis, which increases the risk of hypocapnia by triggering forced respiration as a compensatory mechanism for acidosis. Similarly, high respiratory rate settings on the mechanical ventilator could also increase the hypocapnia risk (18). To control for the effect of the rapid, time-dependent acidosis recovery, which is typically seen in asphyxiated infants during the first postnatal hours, their hours of age on admission to the NICU, which corresponded to the time of the second blood gas sampling, was also included in the model (19). Including additional variables in the regression model, such as pH or temperature, did not affect the association, which was mostly due to collinearity with other parameters that had already been included.

Neonatal clinical characteristics were compared between the study groups using Fisher's exact test for categorical variables and the Mann–Whitney *U*-test and Wilcoxon test for continuous variables.

We used SPSS version 23 (IBM Corp, Armonk, NY, USA) and GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA, USA) with significance set at $p < 0.05$ to analyse and plot the data. The data are presented as medians with interquartile ranges unless otherwise indicated.

RESULTS

The baseline characteristics of the 117 neonates with moderate-to-severe HIE that were included in this retrospective cohort study are summarised in Table 1. All of the 117 infants were transported from the referring hospitals to the regional centre by the same neonatal transport system detailed above.

As expected from the study design, controlled active cooling was initiated at a median of 3.59 hours earlier in infants who were actively cooled during transport than in controls, who only received therapeutic hypothermia when they arrived at the cooling centre. Cooling was commenced 1.24 hours after birth in the actively cooled transport group, with an interquartile range (IQR) of 0.7–1.8, versus 4.83 (IQR 3.1–6.7) hours after birth for the control group ($p < 0.0001$). In the actively cooled transport group, the median rectal temperature was 33.6 (IQR 33.1–36.2)°C on arrival at the cooling centre indicating the provision of appropriate hypothermia treatment during transport. In contrast, rectal temperature did not change in the control group during transport (Table 1). Although this was not an aim of this study, we did note that 10 (14%) babies in the actively cooled transport group were overcooled on admission.

The heart rate decreased among infants in the actively cooled transport group during the transport period due to their lower rectal temperature, (Table 2) and their mean arterial pressure was lower before the transport, compared to the controls, but still remained in the normal range. Furthermore, the use of inotropic support and the median dose of dopamine and dobutamine administrated were similar in both groups (Table 2).

In accordance with our protocol at the time of the study, more neonates in the actively cooled transport group were intubated and ventilated compared to the control infants (88.7% versus 73.9%, $p = 0.038$, respectively). The ventilator settings were similar in the two groups. Consistent with this finding, neonates in the actively cooled transport group were more likely to receive analgesia and, or, sedation (69.0% versus 39.1%, $p = 0.002$) (Table 2). Adverse events leading to pulmonary or circulatory failure were not recorded in either group during the transport period.

Blood gas values were evaluated before transport, at the referring hospital and after transport, on admission to the cooling centre in both groups. The initial pH in the actively cooled transport group was statistically significantly lower, but the difference was not clinically remarkable at 7.02 (IQR 6.90–7.18) versus 7.10 (IQR 6.89–7.26), respectively, ($p = 0.019$). Furthermore, the base deficit was comparable between the two groups (Table 2).

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 mm Hg during the study period. The rate of incident hypocapnia during transport, defined as a pCO_2 value of >35 mm Hg before and ≤35 mm Hg after transport, was significantly higher in the actively cooled

Table 1 Baseline clinical characteristics

	Actively cooled transport group (n = 71)	Control group (n = 46)	p values
Gestational age (weeks)	39 (38–40)	39 (38–40)	0.708
Birth weight (g)	3150 (2850–3490)	3200 (2800–3500)	0.562
Male, n (%)	37 (52.1)	27 (58.7)	0.485
Apgar 1′	2 (1–3)	2 (1–3)	0.969
Apgar 5′	5 (4–6)	4 (2–6)	0.078
Apgar 10′	6 (4–7)	6 (4–6)	0.111
Age when hypothermia was initiated (h of age)	1.24 (0.7–1.8)	4.83 (3.1–6.7)	<0.0001
Age on admission to NICU (h of age)	2.25 (1.9–3.5)	2.69 (1.7–3.8)	0.928
Rectal temperature (°C) (before transport)	35.2 (34.5–36.2)	35.6 (34.6–36.4)	0.237
Rectal temperature (°C) (after transport)	33.6 (33.1–36.2)	35.5 (34.9–36.2)	<0.0001
Death, n (%)	10 (14.1)	10 (21.7)	0.283

Data shown as median and interquartile ranges. See text for details.

Table 2 Blood gas values, vital signs, ventilatory parameters and use of medication during transport

	Actively cooled transport group (n = 71)	Control group (n = 46)	p values
Vital signs			
Heart rate (/minute) (before transport)	130 (116–142)	135 (122–150)	0.314
Heart rate (/minute) (after transport)	117 (105–132)	135 (127–146)	<0.0001
Mean arterial pressure (mm Hg) (before transport)	42 (34–49)	46 (40–54)	0.045
Mean arterial pressure (mm Hg) (after transport)	44 (36–52)	46 (40–53)	0.487
Inotropic support, n (%)	23 (32.4)	19 (41.3)	0.326
Dopamine (μg/kg/minute)	5 (3–6)	4 (3–5)	0.533
Dobutamine (μg/kg/minute)	7 (5–9)	6 (5–8)	0.624
Mechanical ventilation			
Conventional mechanical ventilation, n (%)	63 (88.7)	34 (73.9)	0.038
Respiratory rate setting (/minute)	34 (27–49)	41 (22–51)	0.469
Mean airway pressure (cm H_2O)	10 (9–11)	9 (8–10)	0.358
Delta pressure (mm Hg) (ΔP = PIP-PEEP)	15 (14–17)	16 (14–18)	0.344
FiO_2 (%)	40 (21–83)	30 (21–83)	0.559
Analgesia, n (%)	49 (69.0)	18 (39.1)	0.002
Anticonvulsive treatment, n (%)	12 (16.9)	3 (6.5)	0.156
Blood gas values			
pH (before transport)	7.02 (6.90–7.18)	7.10 (6.89–7.26)	0.019
pH (after transport)	7.21 (7.11–7.31)	7.26 (7.12–7.29)	0.921
pCO_2 (mm Hg) (before transport)	45 (36–68)	42 (32–63)	0.182
pCO_2 (mm Hg) (after transport)	35 (26–48)	41 (29–52)	0.184
Base deficit (mmol/L) (before transport)	15.5 (12.9–21.3)	14.6 (10.1–18.9)	0.105
Base deficit (mmol/L) (after transport)	11.4 (7.6–15.6)	12.0 (4.9–15.4)	0.434

ΔP = Delta pressure; PIP = Peak inspiratory pressure; PEEP = Positive end expiratory pressure.
Data shown as median and interquartile ranges. See text for details.
Respiratory rate is shown for patients on mechanical ventilator.

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 (IQR 36–68) mm Hg, to 35 (IQR 26–48) mm Hg (p < 0.0001) during transport. In contrast, pCO_2 did not change significantly during transport in the control group, from 42 (IQR 32–63) to 41 (IQR 29–52) mm Hg (p = 0.322). 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 (Table S1). Figure 1 shows the temperature-corrected pCO_2 values before and after transport in the actively cooled transport group and control group.

Multivariable logistic regression analysis was used to ascertain the effect of active therapeutic hypothermia (33–34°C), 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. Table 3 demonstrates the adjusted and unadjusted odds ratios for each variable. 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).

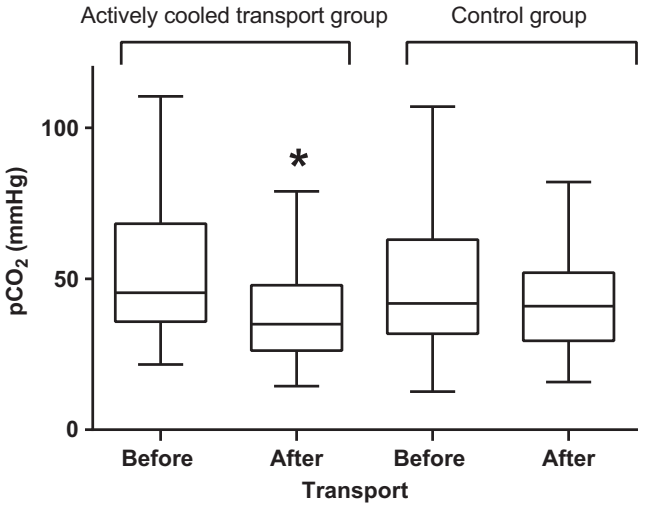

Figure 1 Box plot for temperature-corrected pCO_2 values before and after transport in the actively cooled transport group and the control group. In the actively cooled transport group, the median pCO_2 decreased from the normal range to hypocapnia [45 (IQR 36–68) versus 35 (IQR 26–48) mm Hg; p < 0.0001]. In the control group, pCO_2 did not change during transport [42 (IQR 32–63) versus 41 (IQR 29–52) mm Hg; p = 0.322]. Data are presented as median with interquartiles (boxes) and ranges (whiskers). *p < 0.0001.

Table 3 Logistic regression predicting likelihood of hypocapnia

	Unadjusted odds ratios			Adjusted odds ratios		
	OR	(95% CI)	p values	aOR	(95% CI)	p values
Hypothermia	2.74	(1.11–6.77)	0.028	4.23	(1.30–13.79)	0.017
Use of sedation	0.66	(0.27–1.47)	0.311	0.35	(0.12–0.98)	0.046
Respiratory rate setting (/minute)	0.99	(0.96–1.01)	0.312	0.98	(0.95–1.02)	0.305
Base deficit (mmol/L)	1.06	(0.97–1.06)	0.522	1.02	(0.96–1.07)	0.580
Age on admission to NICU (h)	1.04	(0.82–1.34)	0.734	0.98	(0.69–1.39)	0.915

OR = Odds ratio; aOR = Adjusted OR; CI = Confidence interval.
Logistic regression model predicting likelihood of incident hypocapnia based on hypothermia treatment (ref. category: none), use of sedation (ref. category: none), respiratory rate setting on mechanical ventilator, base deficit and hours of age on admission to NICU.

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.

DISCUSSION

In this retrospective cohort study, we investigated the development of hypocapnia in the early hours of life among neonates with moderate-to-severe HIE receiving active hypothermia treatment during neonatal transport. The introduction of active cooling during transport in late 2009 made it possible to compare groups before and after this procedure was used over a two-year period. We found that infants who were cooled during transport were more likely to develop hypocapnia than the historical control group of asphyxiated infants who only received hypothermia treatment after they arrived at the cooling centre. Even after adjusting for clinically relevant factors, hypothermia remained a strong independent predictor of hypocapnia with an OR of 4.23 (95% CI 1.30–13.79). This finding lends further support, albeit indirect, to the speculation that increased incidence of hypocapnia might be caused, at least partly, by the lower body temperature.

There are several physiologically plausible explanations for the frequently observed hypocapnia in asphyxiated cooled neonates. Severe metabolic acidosis leading to compensatory hyperventilation and severe brain injury causing decreased carbon-dioxide production may both lead to hypocapnia (18). In addition, hypothermia is associated with a reduction of up to 30% in metabolic rate, which could further increase the risk of hypocapnia (12). In fact, it is conceivable that all these unmodifiable factors may play a role in the occurrence of hypocapnia. Iatrogenic causes of hypocapnia in this patient population include the use of inappropriate ventilator settings. Hence, we adjusted our statistical model for this factor as well. On the other hand, sedation or muscle relaxation can diminish patients' respiratory efforts, thereby reducing the risk of hypocapnia due to spontaneous hyperventilation. In accordance with this notion, we found that sedation protected against incident hypocapnia in our study population when we used multivariable regression modelling.

The pCO_2 is the most potent regulator of cerebral blood flow (CBF), with hypocapnia causing vasoconstriction and decreased cerebral perfusion (18). The CBF reactivity to actual pCO_2 might be diminished or absent in infants with the most profound hypoxic-ischaemic insults (20). However, vasoparalysis had less effect on those infants who sustained mild-to-moderate injury, and, therefore, most patients with HIE were at risk of the undesired secondary effects of hypocapnia. Animal studies have also demonstrated that hypocapnic ventilation negatively affected the cellular energy metabolism of the brain, resulting in increased apoptosis (21), while moderate hypercapnia appeared to have protective effects, at least in a rat model of HIE (22). In human preterm neonates, hypocapnia during the first postnatal days has been associated with periventricular leukomalacia and, or, cerebral palsy (23,24). Although in healthy term neonates, hypocapnia-induced transient decreases in cerebral perfusion might be tolerated, the resulting decrease in oxygen delivery and the reduced removal of potentially toxic metabolites could be perilous to the injured brain (25,26). In support of this notion, three large studies showed an association between poor outcome in infants with postasphyxial HIE and hypocapnia, two of which were secondary analyses of the landmark CoolCap and National Institute of Child Health and Human Development Neonatal Research Network hypothermia trials (9,10).

Klinger et al. reported that severe hypocapnia and severe hyperoxaemia were associated with adverse outcomes, defined as death or cerebral palsy at 24 months of age in infants with postasphyxial HIE (11). In the National Institute of Child Health and Human Development Neonatal Research Network cohort, low pCO_2 values – namely a minimum pCO_2 or cumulative pCO_2 of <35 mm Hg – during the first 16 postnatal hours were associated with an increased risk of death or disability at 18–22 months of age (10). The association between hypocapnia and unfavourable outcome was confirmed in the CoolCap cohort as a dose-dependent effect for decreasing pCO_2 values (9). Subsequently, Sabir et al. reported no association between measures of hypocapnia and outcome in a smaller patient cohort (27). Finally, in support of the potential harmful effects of hypocapnia, the findings of large retrospective analyses of resuscitated adults following cardiac arrest suggested that normocapnia or mild hypercapnia was associated with better neurological function and a greater likelihood of discharge from the hospital among survivors (17).

It is noteworthy that the association between hypocapnia and poor outcomes in asphyxiated patients has not been

evaluated prospectively. As a result, it remains unclear whether hypocapnia is a risk factor or surrogate maker of unfavourable outcome. However, the consistent findings of an association between hypocapnia and poor outcomes in asphyxiated neonates and adults suggest that close pCO_2 monitoring and avoidance of hypocapnia might be a reasonable approach to enhance the chances of achieving optimal neuroprotection. Nevertheless, large, multicentre interventional trials are warranted to test this hypothesis in future.

Our study had several limitations that should be taken into consideration. First, this was a retrospective cohort study with the inherent disadvantages associated with that study design. Second, neonates with HIE were transported from different referring hospitals with possibly different resuscitation practices that could have influenced the initial patient characteristics. However, the neonatal transport team and the treatment protocol used for providing intensive care were the same throughout the study period, except for the hypothermia treatment during transport. This may be considered as a strength of our analysis. Third, our transport team used a manually controlled cooling device for hypothermia provision, instead of a servo-controlled method, and it is possible that this could have provided tighter temperature control. We note that 10 (14%) babies in the actively cooled transport group were overcooled on admission. However, it is unlikely that the observed relatively low rate of overcooling played a significant role in the high rate of hypocapnia among the infants actively cooled during transport. Fourth, continuous carbon-dioxide monitoring using transcutaneous or end-tidal CO_2, may have yielded a better real-time measurement of pCO_2 trends. However, the technical limitations and lack of experience in asphyxiated infants made these techniques problematic and unattainable in our cohort. Fifth, a major limitation of our study is that we could not include the severity of encephalopathy as a predictor of interest in our models. In the control group, neurological scoring was not performed routinely before transport, as the transport team did not have to evaluate the severity of the encephalopathy for decision-making on cooling. Finally, we have not reported on patient outcomes, although this was not the objective of the present study.

CONCLUSION

This study compared two groups of infants with HIE before and after active cooling was introduced during transport to our centre for hypothermia treatment. We report, for the first time, that hypothermia remained a strong predictor of hypocapnia after adjusting for potential confounding factors including provision of sedation, ventilatory settings and acidosis severity. We speculate that the advantage of initiation of hypothermia treatment shortly after delivery might be further enhanced by avoiding frequently observed hypocapnia. However, in the absence of randomised controlled trials, we only can suggest that it seems reasonable to avoid hypocapnia using rigorous monitoring and judicious ventilatory management in neonates with HIE undergoing therapeutic hypothermia.

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COMPETING INTERESTS

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Parameters of mechanical ventilation in hypocapnic and normo, - hypercapnic group.