Feasibility and Safety of Controlled Active Hypothermia Treatment During Transport in Neonates With Hypoxic-Ischemic Encephalopathy

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Objectives: To evaluate the feasibility and safety of controlled active hypothermia versus standard intensive care during neonatal transport in patients with hypoxic-ischemic encephalopathy.

Design: Cohort study with a historic control group.

Setting: All infants were transported by Neonatal Emergency & Transport Services to a Level-III neonatal ICU.

Patients: Two hundred fourteen term newborns with moderate-to-severe hypoxic-ischemic encephalopathy. An actively cooled group of 136 newborns were compared with a control group of 78 newborns.

Interventions: Controlled active hypothermia during neonatal transport.

Measurements and Main Results: Key measured variables were timing of hypothermia initiation, temperature profiles, and vital signs during neonatal transport. Hypothermia was initiated a median 2.58 hours earlier in the actively cooled group compared with the control group (median 1.42 [interquartile range, 0.83–2.07] vs 4.0 [interquartile range, 2.08–5.79] hours after birth, respectively; $p < 0.0001$), and target temperature was also achieved a median 1.83 hours earlier (median 2.42 [1.58–3.63] vs 4.25 [2.42–6.08] hours after birth, respectively; $p < 0.0001$). Blood gas values and vital signs were comparable between the two groups with the exception of heart rate, which was significantly lower in the actively cooled group. The number of infants in the target temperature range (33–34°C) on arrival was 79/136 (58.1%) and the rate of overcooling was 16/136 (11.8%) in the actively cooled group. In the overcooled infants, Apgar scores, pH, base deficit, and eventual death rate (7/16; 43.8%) indicated more severe asphyxia suggesting poor temperature control in this subgroup of patients. Adverse events leading to pulmonary or circulatory failure were not observed in either groups during the transport period.

Conclusions: Therapeutic hypothermia during transport is feasible and safe, allowing for significantly earlier initiation and achievement of target temperature, possibly providing further benefit for neonates with hypoxic-ischemic encephalopathy. (*Pediatr Crit Care Med* 2017; 18:1159–1165)

Key Words: asphyxia; emergency medical service; hypothermia; hypoxic-ischemic encephalopathy; newborn

The incidence of hypoxic-ischemic encephalopathy (HIE) is 1–2 per 1,000 live births per year (1). Twenty percent of the infants with HIE are likely to die in the neonatal period, and another 40% of survivors would live with neurologic and other disabilities (2).

To date, only therapeutic hypothermia has shown to be clinically efficacious by reducing the rate of death or severe neurodevelopmental disabilities in patients with moderate-to-severe encephalopathy (3). 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. Multiple animal studies established that moderate cooling started 1.5–3 hours after reperfusion reduced neuronal loss; however, neuroprotection decreases linearly with increasing delay, and cooling started beyond 6 hours provided no benefit (4, 5). Furthermore, a recent clinical study reported that hypothermia treatment started before 3 hours of life is associated with significantly better motor outcome (6).

Asphyxial insult is an unexpected event in the perinatal period, and 45–78 % of the neonates who meet the criteria for the diagnosis of asphyxia are born out of hospitals where

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the neonatal ICUs (NICUs) provides hypothermia treatment. These neonates must be transported during the first hours of postnatal life (7).

Ideally, hypothermia is started already at the referring hospital and maintained during neonatal transport to obtain the maximum possible effect of neuroprotection. However, cooling of infants on transport presents a particular challenge (8, 9). Studies with active cooling using servo-controlled devices during neonatal transport showed the best thermal control as opposed to passive cooling (cessation of active warming) or active cooling with adjuncts (7, 10–13). However, most of the trials were retrospective with relatively small patient cohorts and mainly focused on passive cooling. Detailed analysis of the critical care needs for neonates with active hypothermia treatment during transport is still awaited to confirm the safety and feasibility of this approach.

Our retrospective cohort study presents a single-center experience with intensive care plus active cooling versus intensive therapy alone to describe the feasibility and safety of active hypothermia treatment during transport in neonates with HIE.

METHODS

Medical records of asphyxiated neonates treated in the Level-III NICU of the 1st Department of Paediatrics, Semmelweis University, between 2005 and 2015 were retrospectively reviewed with ethical permission of the Scientific and Medical Research Council Ethics Committee of Hungary (11790–2/2016/EKU).

We included infants who met the eligibility criteria for diagnosing moderate-to-severe encephalopathy in accordance with the Total Body Hypothermia for Neonatal Encephalopathy trial protocol (14). Infants were excluded if they had congenital disorders, presented with mild asphyxia, and hypothermia was discontinued earlier than 72 hours or if they died within 12 hours of postnatal life.

All infants were outborn and transported to our center for hypothermia treatment by the Neonatal Emergency & Transport Services of the Peter Cerny Foundation (NETS-PCA). The NETS-PCA provides five Level-III NICUs in Budapest and six Level-III NICUs in the central part of Hungary (140 km surrounding of Budapest), transporting more than 4,000 neonates per year.

The dedicated neonatal mobile NICU-III transport team has been using controlled active hypothermia treatment for infants with HIE since 2009 October. In the present study, an "actively cooled group" of infants ($n = 136$, born between October 2009 and 2015) who received intensive care plus underwent controlled active cooling during neonatal transport was compared with a historic "control group" ($n = 78$, born between January 2005 and September 2009), who had received intensive care alone without any type of cooling methods during stabilization and transport. Control patients were transported in incubators with the warmer on and not allowed to cool, and therapeutic hypothermia was initiated only after arrival to our Level-III NICU. The rectal temperature was measured by the transport team upon arrival to the referral hospital and at admission to the NICU. In case of temperature instability, the rectal temperature was monitored continuously during the transport period.

In the cooled group, active hypothermia treatment was initiated by the transport team upon their arrival to the referring hospital and was maintained during transport with a manually regulated device (Tecotherm Ts med 200 N; Inspiration Healthcare, Leicester, United Kingdom). The thermo blanket was placed underneath the patients, targeting a rectal temperature of 33–34°C. Rectal temperature was monitored continuously to avoid over or undercooling. According to the protocols of the transport team and our NICU, neonates who underwent active hypothermia treatment were mechanically ventilated as per standard of care, using a Dräger Babylog 2000 ventilator (Dräger, Luebeck, Germany). For intubation, thiopental (5–6 mg/kg) was administered, and muscle relaxants were not used routinely. Sedation and analgesia was provided with fentanyl (2–5 μg/kg) if necessary. Protocols recommended against prophylactic antiepileptic drug administration, and phenobarbital was used only if clinical seizures were noted.

Feasibility of controlled active cooling during transport was assessed by comparing the length of stabilization (defined as the time that was spent at the referring hospital by the NETS-PCA to prepare the patient for transport), the time when hypothermia treatment was initiated, and the rectal temperature at admission to the Level-III NICU. For safety analysis, we compared acid-base status and vital signs (heart rate, blood pressure) before and after transport in the two groups. We also compared the need for cardiac support and the rate of overcooling in the two groups. In addition, we closely monitored for three adverse events: 1) severe hypotension (mean arterial pressure less than 25 mm Hg) despite full inotrope support and volume replacement. Blood pressure was monitored noninvasively and registered every 15 minutes. 2) Persistent hypoxemia (peripheral oxygen saturation < 90%) despite adequate ventilation, and 3) cardiac arrhythmias leading to circulatory failure. Routine electrocardiogram electrodes and cardiac monitoring were used to detect arrhythmias.

In the actively cooled group, all infants had at least two blood gas values recorded: one before transport, to confirm the indication for initiating hypothermia treatment, and another one after arrival to the NICU. Additional blood gas samples were taken as needed but were not analyzed in the current study. Blood gas samples were of capillary origin in 93% of cases, and pH, P_{CO_2}, and base deficit values were temperature corrected based on the method described by Ashwood et al (15). In addition, in the actively cooled group, we compared the indicators of the disease severity and the transport characteristics among the three temperature ranges (< 33°C, ≤ 34°C and ≥ 33°C, and > 34°C) after the transport. Finally, we compared death rates in the two groups by evaluating in-hospital mortality data (death occurring after 12 hr of postnatal life but before discharge).

Differences were assessed by using Mann-Whitney *U* and Kruskal-Wallis test for nonparametric and Student's *t* test and one-way analysis of variance (ANOVA) for parametric variables. Paired *t* test was used to account for repeated measures when appropriate. A two-way mixed ANOVA procedure was used to test

for interaction between time (before-after transport) and intervention (hypothermia or control treatment). The data were analyzed with chi-square or Fisher exact test for categorical variables.

We used SPSS version 22 (IBM Corp., Armonk, NY) and GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA) with significance set at p value of less than 0.05 to analyze and plot the data. Data are presented as median with interquartile ranges or mean with SD.

RESULTS

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 (**Table 1**).

Importantly, 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 therapeutic hypothermia (34°C) was also achieved a median 1.83 hours earlier in the cooled group ($p < 0.0001$ for both comparisons, see details in Table 1) 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 (= stabilization time + transit time), was a median 32 minutes longer in the actively cooled group (1.67 [1.33–2.17] vs 1.13 [0.89–1.46] hr; $p < 0.0001$). Consequently, infants in the actively cooled group were older when admitted to the NICU compared with controls (Table 1); however, NICU admission still occurred before 3 hours of life in 69.16% of all patients (66.91% of actively cooled neonates and 73.07% of controls).

The pH, P_{CO_2}, and base deficit values were similar in both groups before and after transport, suggesting that active cooling did not affect acidosis recovery during transport period (Table 1). Mean arterial blood pressure was similar in the actively cooled and control groups before and after transport. 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 (Table 1).

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 ($p < 0.0001$). In addition, there was a statistically significant interaction between the time elapsed during transport and the intervention (active cooling or standard care) on rectal temperature (two-way mixed ANOVA model, $F[1,209] = 103.3$; $p < 0.001$; effect size $\eta^2 = 0.331$).

Figure 1 shows the rectal temperature values before and after transport in the two groups. Temperature profiles were similar before transport; however, the proportion of infants in the target temperature range (33–34°C) was higher in the actively cooled group after transport compared with controls (58.0% vs 10.3%, respectively; $p < 0.0001$). The rate of overcooling (< 33°C) did not differ significantly between the two groups (11.8% vs 5.1%; $p = 0.1440$) (**Table 2**).

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 at 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. On the other hand, patients who remained warmer than the target temperature (rectal temperature > 34°C at admission to the NICU; $n = 41$) had a shorter distance and duration of the transport than those who reached the target temperature range (**Table 3**).

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 hr of life) was found to be eventually higher in the control group (Table 1).

Deaths occurred on a median 4.3 (1.7–7.6) postnatal day in the actively cooled group and on 2.4 (0.9–3.9) postnatal day in the control group (p= 0.1035). In seven of 14 cases (50.0%) in the actively cooled group and nine of 18 (50.0%) in the control group, the cause of death was severe hypoxic-ischemic encephalopathy. In further three cases in the actively cooled group and six cases in the control group, the severe encephalopathy was associated with multiple organ failure, predominantly with acute renal failure. In another three cases ($n = 2$ in the cooled group and $n = 1$ in the control group), the encephalopathy was complicated with septicemia. In the remaining four cases, the cause of death was disseminated intravascular coagulation combined with bilateral pneumothorax, twin-to-twin transfusion syndrome in the control group, and aspiration pneumonia and fetomaternal transfusion syndrome in the actively cooled group.

DISCUSSION

To the best of our knowledge, this is one of the largest cohort studies which reports on the provision of hypothermia with a manually regulated device versus standard intensive care, focusing on the detailed analysis of the critical care needs of neonates with HIE during transport. We found that active hypothermia treatment appears to be feasible and safe during

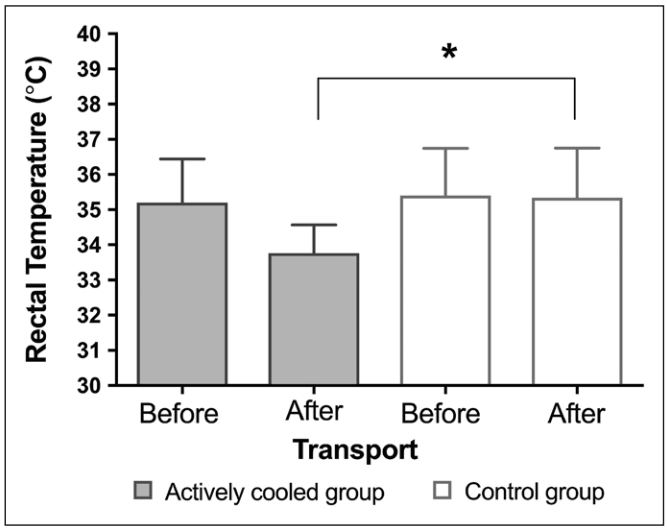

Figure 1. Bar graph for rectal temperature measurements before and after transport in the actively cooled and the control groups. Before transport, rectal temperature was 35.2°C ± 1.24°C in the actively cooled group and 35.4°C ± 1.34°C in the control group. After transport, at admission to the neonatal ICU, 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 ($p < 0.0001$). There was a statistically significant interaction between the intervention (actively cooled vs control group) and time on rectal temperature (two-way mixed analysis of variance model, $F[1,209] = 103.3$, $p < 0.001$, effect size $\eta^2 = 0.331$). Data are presented as mean ± SD. *$p < 0.0001$ (Student's *t* test).

neonatal transport, allowing for a significantly earlier initiation and achievement of target temperature of hypothermia treatment even in relatively short transport distances. Although temperature control has been studied extensively (7, 9–13, 16), our study provides a detailed analysis on physiologic parameters and critical care needs of transported neonates suggesting the safety of the hypothermia treatment during transport.

Early initiation of hypothermia is desirable to achieve based on both animal and human studies. Gunn et al (4) reported in a series of experiments that moderate, selective head cooling in near-term fetal lambs started 90 minutes after reperfusion reduced neuronal loss and was associated with near baseline amplitude-integrated electroencephalography activity; however, delayed cooling started at 5.5 hours was less effective and at 8.5 hours provided no benefit. Similarly, time-dependent results were obtained in neonatal rats (5). In addition, latent phase duration seems to be inversely related to insult severity (17). In line with this hypothesis, Thoresen et al (6) reported that motor outcome was improved in surviving asphyxiated newborns if hypothermia was initiated within 3 hours of life versus 3–6 hours. Taken together, timing seems to have an outstanding role in enhancing the neuroprotective effect of hypothermia treatment. Asphyxial insult is an unexpected event in the perinatal period, thus most of the affected infants born out of institutes with Level- III NICUs offering hypothermia treatment (7). Consequently, an increasing number of neonatal transport teams have started to adopt hypothermia treatment during transportation.

Early attempts on a small patient cohort with passive and active cooling with gel packs were less successful because many patients, as high as 34% of asphyxiated newborns, had core body temperatures below the target range of 33–34°C, predisposing them to the detrimental effects of overcooling (11). Hallberg et al (16) published similar results regarding overcooling with passive initiation of hypothermia. However, Kendall et al (9) reported that 67% of the infants who were cooled passively were in the target temperature range on arrival at the cooling center, and only 11% of the newborns were below 33°C. Recent retrospective and prospective randomized trials have shown that servo-controlled active cooling provides more temperature stability, and a similar approach was used in the present study. Chaudhary et al (10) reported that 100%, whereas Akula et al (7) found that 80% of actively cooled asphyxiated newborns have reached the target temperature during transport using a servo-regulated cooling device. In these trials, most of the infants had cooling initiated prior to arrival of the transport team. We observed that 58.1% of our cooled infants were in the target temperature range at admission to the NICU, and the rate of overcooling was 11.8%. The significantly lower success rate in our study compared with the other reports is explained by the relatively short transport period among the infants who

TABLE 2. Temperature Profiles in the Actively Cooled and Control Groups

Temperature Profiles	Actively Cooled Group, *n* = 136	Control Group, *n* = 78	*p*
Rectal temperature before transport (°C), mean ± SD	35.2 ± 1.24	35.4 ± 1.34	0.2883
Rectal temperature after transport (°C), mean ± SD	33.8 ± 0.81	35.3 ± 1.40	< 0.0001
Temperature range before transport (°C), *n* (%)			
< 33	6 (4.4)	2 (2.6)	0.4929
≤ 34 and ≥ 33	17 (12.5)	8 (10.3)	0.6229
> 34	113 (83.1)	68 (87.2)	0.4251
Temperature range after transport (°C), *n* (%)			
< 33	16 (11.8)	4 (5.1)	0.1440
≤ 34 and ≥ 33	79 (58.1)	8 (10.3)	< 0.0001
> 34	41 (30.1)	66 (84.6)	< 0.0001

See text for details.

TABLE 3. Patients of the Actively Cooled Group Divided According to Temperature Ranges Achieved by the Time of Admission to Neonatal ICU

Temperature range after transport (°C)	< 33 °C, *n* = 16	≤ 34 °C and ≥ 33 °C, *n* = 79	> 34 °C, *n* = 41	*p*
Apgar 1', median (IQR)	1 (0–3)	2 (1–3)	2 (1–4)	0.0491
Apgar 5', median (IQR)	5 (2–6)	4 (3–6)	5 (4–7)	0.2006
Apgar 10', median (IQR)	3 (2–7)	6 (4–7)	7 (6–8)	0.0057
Neurologic score, median (IQR)	16 (11–20)	14 (8–17)	13 (8–18)	0.1850
Rectal temperature before transport (°C), mean ± SD	34.0 ± 1.62	35.1 ± 1.16	35.8 ± 0.81	< 0.0001
pH, median (IQR)	6.9 (6.73–7.09)	7.1 (6.92–7.21)	7.1 (6.94–7.18)	0.0349
Base deficit (mmol/L), median (IQR)	18.2 (25.2–16.2)	15.3 (22–12)	14.9 (18.8–12.6)	0.0123
Duration of transport (hr), median (IQR)	1.66 (1.18–2.38)	1.70 (1.40–2.33)	1.43 (1.10–1.79)	0.0210
Distance of transport (km), median (IQR)	8 (1–56)	18 (9–81)	8 (5–12)	0.0004
Death, *n* (%)	7 (43. 8)	4 (5.06)	3 (7.32)	< 0.0001

IQR = interquartile range.

See text for details. Apgar and neurologic scores, rectal temperature and acid-base parameters shown were registered before the transport, at the referring hospital. The neurologic score was determined based on the criteria described in the Total Body Hypothermia for Neonatal Encephalopathy trial (https://www.npeu.ox.ac.uk/toby/protocol).

did not reach the target temperature until the admission to the NICU. In addition, the lack of any kind of cooling method before the arrival of the transport team may also contribute to the relatively high percentage of patients remaining above the target temperature by the end of the transport.

It has been known for over 50 years that asphyxiated infants lose temperature at a higher rate than healthy newborns, and this might be more pronounced in severe asphyxia (18). This presumption is consistent with our findings. The overcooled infants had deeper acidosis, lower Apgar scores, and a tendency for lower neurologic scores, all of which could indicate a more severe asphyxial insult. There are multiple risks for overcooling in this subgroup of patients with greater perinatal injury: 1) they experience an extended period of being unwrapped or lying on wet surfaces during resuscitation, 2) they have decreased metabolism and heat production due to the severe asphyxial insult, 3) they may have seizures prompting treatment with anticonvulsants or muscle relaxation for intubation that counteracts natural shivering and causes loss of muscle tone, and 4) addition of active cooling without adequate temperature control (19, 20). Therefore, a special attention is needed to ensure the proper temperature control in neonates with the most severe brain injury, including the use of overhead heater during resuscitation, and addition of active cooling only after stabilization, continuous rectal temperature monitoring, and the use of servo-controlled cooling devices.

The stabilization time of our transport team varied between 16.2 minutes and 3.08 hours, and it was a median 16 minutes longer in the actively cooled group compared with the controls. The longer stabilization time occurred probably due to the longer decision-making on hypothermia treatment, the procedural time for the premedication, intubation and initiation of mechanical ventilation, and equipment assembly for cooling. We believe that the somewhat extended stabilization time has relatively small clinical importance, outweighed by the advantage of early initiation of hypothermia. The overall stabilization time of 1 hour is still considerably shorter than the average time of 2.5 hours reported in the literature (10).

Finally, and importantly, no serious adverse events were observed, underscoring the safety and feasibility of providing active cooling during transport.

It is noteworthy that in-hospital mortality was higher in the control group than in those who received active cooling during transport, even though both groups received 72-hour standard hypothermia treatment after neonatal transport. One explanation might be that with increasing clinical experience with therapeutic hypothermia, it is likely that less severe cases have become routinely referred and transported throughout the study period, resulting in less mortality in recent years. In addition, it has been shown previously that hypothermia itself reduces death (3); and based on our results, the hypothermia treatment which started 2.58 hours earlier in the actively cooled group during transport may provide additional survival benefit. However, this finding should be interpreted with caution, because control neonates were born with a median 1 point lower Apgar scores, and needed more inotropic support. Apgar score has its own limitation, and 1 point difference might not carry a huge clinical impact; however, these differences may imply that perhaps more severe cases were selected for 72-hour hypothermia treatment in the past when control neonates were born. On the other hand, both groups had comparable acid-base status and vital signs; therefore, markedly different clinical conditions between actively cooled and control neonates were unlikely.

Our study has limitations that should be taken into consideration. First, our study is a retrospective analysis, with its inherent disadvantages. However, this is one of the largest patient cohort with controlled active cooling during neonatal

transport. Second, as the promising results of the large hypothermia trials were published around 2010, patient selection for transport and hypothermia treatment might have slightly changed, and neonates with less severe asphyxial insult also have received cooling therapy. Importantly, the dedicated neonatal transport team was the same throughout the study period, which may be considered as a strength of our analysis. Finally, we could not report on patient neurodevelopmental outcomes; however, it was not the main objective of the present study to assess long-term effects of active cooling.

We believe that cooling during transport is necessary to provide the best possible treatment for outborn infants who suffered perinatal asphyxia and present with moderate-to-severe HIE because neonatal transport is a time-consuming procedure and the efficacy of hypothermia is time dependent. The method of cooling and the experience of the transport team may influence temperature stability during transport. More importantly, the time of hypothermia initiation could affect neurologic outcome, and subsequent studies are needed to confirm that early cooling could indeed provide additional benefit.

CONCLUSION

To conclude, active hypothermia treatment with a manually regulated device during transport appears to be feasible and safe, allowing for initiation and achievement of target temperature of cooling significantly earlier compared with controls, possibly providing further benefit for neonates with HIE.

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