Identifying Ways to Fix Outcome Disparities among Outborns Needing Therapeutic Hypothermia

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Abstract

Objective This study examined patterns of care after birth in newborns treated with therapeutic hypothermia to identify remediable causes for the poorer outcomes observed in outborn infants.

Study Design This was a secondary analysis of 150 newborns (68 outborn) prospectively enrolled at our center in the Vermont Oxford Neonatal Encephalopathy Registry from January 2008 to October 2016.

Results The 5-minute Apgar's score and cord pH value did not differ, but cord blood gases were obtained far less frequently in outborns ($p = 0.002$). Outborns needed more chest compressions ($p = 0.01$) and epinephrine ($p = 0.04$), and had more brain injury on neuroimaging ($p = 0.05$). Outborns took longer to reach target hypothermia temperature ($p < 0.0001$).

Conclusion The lack of cord gas values and longer time to reach target temperature observed in the outborns are two observed differences in care that can be potentially remedied by providing education and resources at delivering hospitals in rapid identification of hypothermia candidates, though further research is needed to define the effects of such measures. Possible solutions are also discussed here.

Keywords
- humans
- newborn
- hypothermia
- brain injuries
- induced hypothermia

Therapeutic hypothermia significantly reduces the risks of death and neurological disability in newborns with neonatal encephalopathy.[1] However, the majority of delivering hospitals do not perform therapeutic hypothermia, thus many newborns require transfer to hypothermia-enabled centers for treatment. The majority of randomized controlled trials of therapeutic hypothermia that have specifically evaluated outcome differences between newborns who need transfer (outborns) and infants born at centers capable of treating with therapeutic hypothermia (inborns) have found that outborns tend to have worse outcomes than inborns. Eicher and colleagues found that in both the hypothermia and normothermia arms of their trial, outborns were more likely to die than inborns ($p = 0.007$).[2] Outborns also reached target temperature sooner than inborns, though the authors noted that all patients who died reached target temperature in far less time than those who survived. Natarajan and colleagues conducted a secondary analysis of the NICHD hypothermia trial to specifically evaluate the effect of birth location and found that in both the hypothermia and normothermia treatment arms, outborns had a greater need for continued resuscitation at 10 minutes after birth and were more likely to have severe encephalopathy.[3] Within the hypothermia treatment arm, outborns started treatment later than inborns and reached the target temperature later as well. The Neo.nEURO trial also noted that the outborns within their hypothermia treatment arm started cooling later than the inborns (5.2 vs. 4.6 hours after birth, $p = 0.03$).[4] Lastly, the ICE trial did not find any differences between their inborns and outborns, though this trial had dedicated retrieval teams and/or a study investigator at the delivering hospital.[5]

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It is not known if the adverse outcomes observed among outborns reflect differences in clinical care between delivering hospitals and hypothermia-enabled centers or if milder cases of neonatal encephalopathy are being missed, and therefore are not being transferred within the 6-hour window after birth that is recommended for initiation of treatment with therapeutic hypothermia. As differences in the in-hospital outcomes for the inborns versus outborns at our own center were clinically apparent, we sought to evaluate this for our own center and referral network. In an effort to identify remediable reasons for poorer outborn outcomes, this study evaluated the heterogeneity in clinical practices across delivering hospitals that transfer newborns to a single hypothermia-enabled center using a single transport team.

Materials and Methods

Patient Identification

All patients were treated with therapeutic hypothermia at Sharp Mary Birch Hospital for Women and Newborns between January 2008 and October 2016, and prospectively enrolled in the Vermont Oxford Neonatal Encephalopathy Registry.[6] Inclusion criteria were qualification for and treatment with therapeutic hypothermia. Newborns born at <36 weeks of gestation were excluded. Data were collected with the approval of the Sharp Mary Birch Institutional Review Board.

All inborn patients were born at Sharp Mary Birch Hospital. All outborn patients were transferred to Sharp Mary Birch Hospital via emergency ground transport. Most of the outborn patients were transferred from one of four referring hospitals ranging from 11 to 17 highway miles from the center. The remainder of the outborns were either transferred from having been born at home or were passed over the border between the United States and Mexico (22 miles from the center) to an emergency ground transport team (►Fig. 1).

Therapeutic Hypothermia

Eligibility for treatment with therapeutic hypothermia required the presence of (1) gestational age ≥36 weeks, (2) initiation of therapy at ≤6 hours of age, (3) one or more of the following: Apgar's score of ≤6 at 10 minutes, continued need for mechanical ventilation or resuscitation at 10 minutes after birth, cord or arterial pH ≤7.1, or base deficit of ≥12 within 60 minutes of birth, (4) no congenital abnormalities or disorder incompatible with survival, and (5) presence of moderate-to-severe encephalopathy or presence of electroencephalography (EEG) abnormality (seizure or abnormal background activity). Eligible candidates received whole-body hypothermia using a blanket-cooling device. The Cincinnati Sub-Zero Blanketrol II (Cincinnati, OH) was used until March 2011, and the Cincinnati Sub-Zero Blanketrol III (Cincinnati, OH) was used thereafter. Patients were cooled by maintaining the core temperature at 33.5°C for 72 hours. Rewarming was staged over six hours, targeting an increase in 0.5 °C per hour. All patients had continuous video EEG from initiation of treatment with therapeutic hypothermia (for the inborns) or from arrival at our center (for the outborns) to at least 6 hours after completion of rewarming. Some of the outborn patients were actively cooled during transport as a part of the California Transport Cooling Trial using the Tecotherm Neo (Inspiration Medical LTD, Leicester, United Kingdom).[7] When the Tecotherm was not available, we typically recommended initiation of passive cooling prior to transport arrival.

Data and Outcome Measures

For each patient, the following data were collected: gender, gestational age, birth weight, mode of delivery, resuscitation measures received at birth, Apgar's scores, cord gas pH (if available), and whether or not cord gases were obtained. We also calculated the time to achievement of the target hypothermic temperature for each patient; this was calculated from the time of birth, as the time of initiation of active cooling was

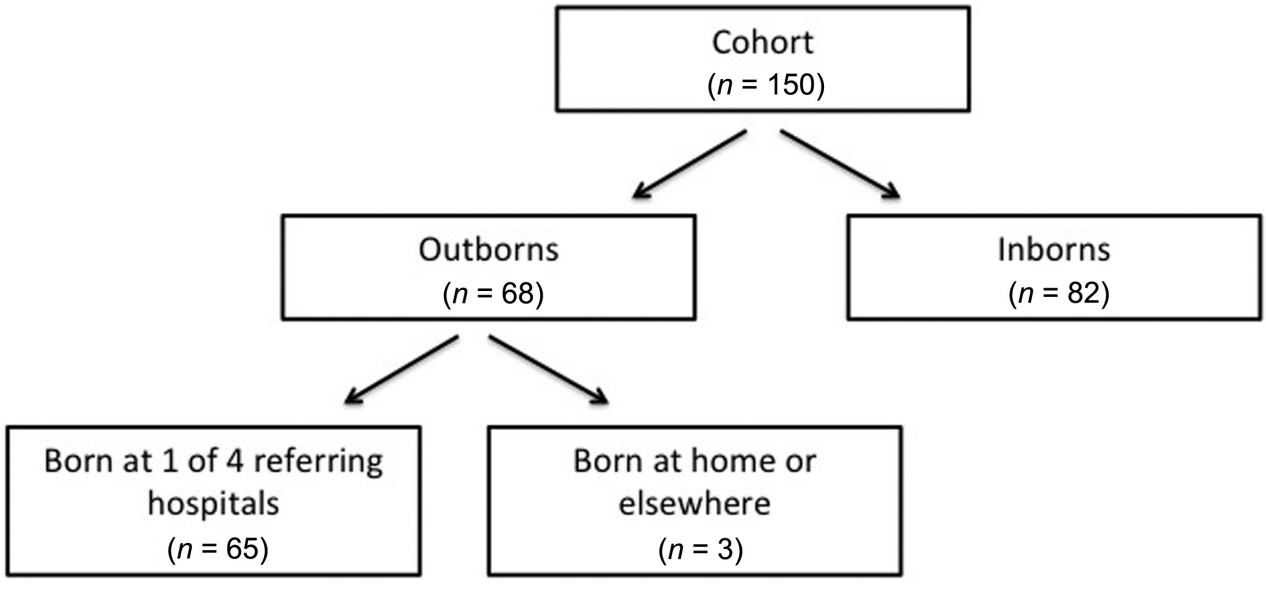

Fig. 1 Flow diagram of our referral network.

frequently not noted for the outborn population. In-hospital outcomes study included the presence of seizures, brain injury seen on neuroimaging, placement of a gastrostomy tube prior to discharge, and mortality. The presence of seizures was confirmed by EEG. Both amplitude-integrated EEG and raw-trace EEG were performed and analyzed in full for each patient, with all seizures confirmed on raw-trace EEG. Patients received neuroimaging via magnetic resonance imaging (MRI) on a 1.5-Tesla magnetic resonance scanner (GE Healthcare, Chicago, IL) between 4 and 5 days after birth, except in patients deemed insufficiently stable for transport to the scanner (usually cases of respiratory status too tenuous to tolerate prolonged imaging or transport off the unit), MRI scans were all read by experienced pediatric radiologists and/or neuroradiologists and were characterized as abnormal by the presence of diffusion-weighted abnormality. MR spectroscopy was not routinely performed for this cohort.

Data Analysis

Statistical analysis was performed using SPSS 22 (IBM, Armonk, NY). Means were compared using the *t*-test, proportions using the Fisher's exact test (used when comparison of groups involved fewer than five patients in any group) or Chi-square test, and medians using the Mann–Whitney *U*-test.

Results

Description of the Cohort

A total of 150 newborns were treated with therapeutic hypothermia and met criteria for inclusion, 68 (45%) of whom were outborn. The inborn and outborn groups did not differ with respect to gender or gestational age. The outborn group's mean birth weight was significantly higher than the inborn group (3,437 ± 667 vs. 3,188 ± 527, $p = 0.01$), though the inborn group was more likely to have been delivered via cesarean section ($p = 0.02$; ►Table 1).

Differences in Resuscitation

Outborns were no more likely than inborns to receive common resuscitative measures for newborns such as blow-by oxygen, continuous positive airway pressure, positive-pressure ventilation, and intubation (►Table 2). Outborns received extreme means of resuscitation more frequently than did inborns; outborns were more likely to receive chest compressions ($p = 0.01$) and epinephrine ($p = 0.04$). The median Apgar's score at 5 minutes after birth was the same among both inborns and outborns (both groups' median, 5; interquartile range [IQR]: 3–6, $p = 0.54$).

Table 1 Clinical characteristics of inborn versus outborn infants

	Inborns ($n = 82$)	Outborns ($n = 68$)	*p*-Value
Male gender (*n*, %)	48 (59)	39 (57)	0.88
Gestational age in wk (mean ± SD)	39.1 ± 1.4	39.3 ± 1.4	0.24
Birth weight in g (mean ± SD)	3,188 ± 527	3,437 ± 667	0.01
Delivery via cesarean section (*n*, %)	57 (70)	35 (51)	0.02
10-minute Apgar's score (median, IQR)	5 (3–6)	5 (3–6)	0.54

Abbreviations: IQR, interquartile range; SD, standard deviation.

Table 2 Differences in hospital care and outcomes between inborns and outborns

	Inborns ($n = 82$) *n* (%)	Outborns ($n = 68$) *n* (%)	*p*-Value
Blow-by oxygen	9 (11)	11 (16)	0.35
Continuous positive airway pressure	18 (22)	21 (31)	0.21
Positive-pressure ventilation	75 (91)	56 (82)	0.10
Intubated for meconium	22 (27)	14 (21)	0.37
Intubated	60 (73)	45 (66)	0.35
Compressions	11 (13)	21 (31)	0.01
Epinephrine	8 (10)	15 (22)	0.04
Cord gas obtained	75 (91)	49 (72)	0.002
Cord arterial pH (mean ± SD)	6.97 ± 0.16	6.99 ± 0.18	0.35
Minutes to target temperature (mean ± SD)	195 ± 109	294 ± 92	<0.001
Seizures	11 (13)	16 (24)	0.11
Brain injury on neuroimaging	19 (23)	26 (38)	0.05
Required gastrostomy tube placement prior to discharge	0 (0)	3 (4)	0.09
Died	7 (9)	5 (7)	0.79

Abbreviation: SD, standard deviation.

Differences in Clinical Practice

Outborns were far less likely to have had cord blood gas values obtained. Cord gas values were obtained for only 72% of outborns versus 91% of inborns ($p = 0.002$). When cord gases were available, cord arterial pH did not differ between the groups ($p = 0.35$). From the time of birth, outborns took almost 2 hours longer than inborns to achieve the target temperature for therapeutic hypothermia (294 vs. 195 minutes, $p < 0.001$).

Differences in Neurological Outcomes

During treatment, 24% of outborns had seizures confirmed on EEG compared with 13% of inborns, though this difference was not statistically significant. More outborns had evidence of parenchymal injury on posthypothermia neuroimaging (38% of outborns vs. 23% of inborns, $p = 0.05$). Mortality did

not differ between outborns and inborns, and neither did the number of newborns requiring gastrostomy placement prior to discharge.

Discussion

Findings of this Study in the Context of What is Already Known

Of the four randomized controlled trials of therapeutic hypothermia for neonatal encephalopathy that specifically analyzed differences between outborn and inborn infants, the NICHD and Neo.nEURO trials both found that outborns have treatment initiated later and take longer to reach target temperature, and the study by Eicher et al found that outborns had a higher mortality rate.[2–4] The ICE trial, the only study that did not observe significant differences between outborns and inborns, had dedicated transport teams that initiated therapeutic hypothermia at the referring hospital.[5] This suggests that the provision of education and resources for identifying candidates for therapeutic hypothermia at delivering hospitals can ameliorate poorer outcomes among outborns. In an effort to describe what such interventions might specifically entail, this study evaluated differences in clinical practices between delivering hospitals and their hypothermia-enabled referral center. Similar to the majority of the previous studies, the outborns in this study reached the target temperature for hypothermia much later than the inborns. This study adds the following findings that have not been previously reported: outborns had a higher incidence of brain injury on neuroimaging, received more extreme measures of resuscitation, and were also less likely to have cord gases ordered.

In-hospital Outcomes

Outborn infants were more likely to have evidence of acute parenchymal injury on neuroimaging. This observation has not been documented before and the reasons for these observations are unclear. It may be that outborns have a higher incidence of brain injury because of potential selection bias for newborns with worse encephalopathy, though later initiation of hypothermia and later achievement of target temperature are also possibilities. This study was not equipped to evaluate for selection bias, as a direct measure of neonatal encephalopathy was not used, which was a significant limitation of this study. Another alternative explanation for our findings was the lack of information detailing the prenatal care of the mothers of the outborns in this sample, preventing comparison with that of the inborns. There was no difference in mortality among outborns and inborns, though this may be due to sample size limitation.

Differences in Resuscitation and Management Practices after Birth

Outborns in this study received chest compressions and epinephrine more frequently than inborns. More extreme resuscitation measures in the outborn population could be a result of differences in resuscitation practices at delivering hospitals, or could reflect the aforementioned selection bias for more severe cases of neonatal encephalopathy at referring hospitals. Selection bias can be remedied by increasing awareness and education at delivering hospitals in the timely recognition of candidates for therapeutic hypothermia, which would likely result in an increase in the number of outborns observed to have moderate encephalopathy. It is also possible that the outborn differences observed in this study could be reflective of demographic differences such as socioeconomic status, parental education level, and ethnicity. It seems unlikely that demographic differences would be directly causative of needing more resuscitation at birth, but these differences could affect factors that are not easily assessed, such as access to medical care or parental refusal of physician recommendations such as urgent cesarean or instrumented delivery.

Most importantly, the remediable findings of this study were that outborns reached target temperature later than the inborns and were much less likely to have had cord gases obtained. These findings acutely define the need for education at delivering hospitals in identification of and rapid initiation of treatment in hypothermia candidates. There is reliable evidence from animal studies that earlier initiation of therapeutic hypothermia is more likely to confer neuroprotective benefit.[8–10] This has also been noted in the human newborn; Thoresen and colleagues recently demonstrated that neonates who were treated with therapeutic hypothermia starting at less than 3 hours after birth had a higher median psychomotor developmental index than neonates for whom therapy was initiated at more than 3 hours after birth (median, 90; IQR: 77–99 vs. Median, 78; IQR: 70–90; $p = 0.03$).[11] Employing a servoregulated cooling device during transport can help newborns to reach target hypothermia temperature earlier, as evidenced by Akula and colleagues in a recent randomized controlled trial of servoregulated device cooling during transport versus standard practice for cooling during transport.[12] It is not yet clear what the effect of increasing the frequency of cord blood gas analysis would be, if any. However, as cord gas values are part of the qualification criteria for treatment with therapeutic hypothermia, educating our referring hospitals in the need for cord gases is a fast and cost-effective measure that may be of assistance to evaluate cooling candidates from outside hospitals.

Though not assessed for this study, one potential source of clinical differences between outborns and inborns is the unknown number of outborns who are not identified at all as hypothermia candidates, or who are transferred too late to initiate treatment with therapeutic hypothermia. This is a compelling area of future research.

Educational Measures Taken and Future Directions

Realistically, instating a broad educational effort at the vast number of delivering hospitals, not to mention birthing centers, to improve detection of candidates for therapeutic hypothermia in the United States, is a daunting idea. This study suggests that simple measures, such as emphasizing the value of obtaining cord gases in newborns at risk for neonatal encephalopathy and enabling all neonatal transport teams with servocontrolled cooling devices, may be high-yield methods of improving identification and rapid treatment of candidates for therapeutic hypothermia. For the network of

referring hospitals in this study, we started an educational program for all newborn resuscitation nurses at each site in which we reviewed appropriate circumstances for obtaining cord gases, went over how to examine a newborn for evidence of encephalopathy, and discussed our center's criteria for treatment with therapeutic hypothermia. The two largest referring hospitals purchased their own servoregulated cooling devices so that initiation of therapeutic hypothermia would not be delayed while waiting for the transport team to arrive. We recognize that such an approach may not be feasible for hypothermia-enabled centers that have a large network of referring hospitals, so to that end, we have placed our educational curriculum into a free mobile application for smartphones called NeoCool that is available for free in the iOS Application Store. The NeoCool application is designed to assist nurses and physicians who are "first-line" in assessing newborns at risk for neonatal encephalopathy to determine if the newborn may qualify for treatment with therapeutic hypothermia. We also recommend online resources, such as the guidelines from the California Perinatal Quality Care Collaborative, which has published instructions for the assessment of newborns at risk for neonatal encephalopathy.[13]

Conclusion

There are several significant clinical differences in newborns requiring transport for treatment with therapeutic hypothermia compared with newborns treated at their hospital of birth, in case a referral center for therapeutic hypothermia. Many of these differences suggest opportunities to potentially remedy these disparities through education and changes in clinical practice.

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Conflict of Interest

M.J.A.H. reports grants from The Hartwell Foundation during the conduct of the study.

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