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Original Research

Impact of a neuro-intensive care service for newborns

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Abstract.
BACKGROUND: Advances in treating the injured neonatal brain have given rise to neuro-intensive care services for newborns. This study assessed the impact of one such service in a cohort of newborns treated with therapeutic hypothermia.
METHODS: Our newborn neuro-intensive care service was started in November 2012. From January 2008 to October 2016, a cohort of 158 newborns was treated with therapeutic hypothermia, 29 before and 129 after the inception of the service. This study compared the outcomes of newborns treated by the service with those of newborns treated before. Multivariate regression analysis associating length-of-stay and treatment pre- or post-service was adjusted for five-minute Apgar score, time-to-target temperature, seizures, and mortality.
RESULTS: The neuro-intensive care service was also associated with a decrease in mortality (17% before service to 5.4% with the service, $p = 0.03$), though this association is likely multifactorial and reflects the application of therapeutic hypothermia to a wider variety of patients. However, the service was independently associated with decreased length-of-stay (mean 22 pre-service to 13 days with the service, $p < 0.0005$.)
CONCLUSIONS: The service educated referring hospitals in recognizing therapeutic hypothermia candidates, which increased the number of treated newborns, and created a number of procedures to streamline the delivery of treatment. While the increasing number and variety of patients treated could spuriously reduce length-of-stay, length-of-stay was still significantly reduced after adjustment, providing evidence that neuro-intensive care services for newborns can improve hospital outcomes.

Keywords: Newborn, neurology, NICU, hypothermia, encephalopathy

1. Introduction

Dedicated adult neuro-intensive care services are associated with improvements in mortality, hospital length-of-stay, and discharges to home instead of rehabilitation center [1–3]. Neuro-intensive care services for adults are now an established feature of most academic centers in the United States and adult neuro-intensive care is an accredited subspecialty [4]. In recent years neuro-intensive care services for neonates have been established, mostly due to the adoption of therapeutic hypothermia as the standard of care for the treatment of neonatal encephalopathy, as well as the increased use of 24-hour continuous electroencephalography (EEG) recording enabling treatment of both clinical and

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electroencephalographic neonatal seizures [5]. However, there is yet limited evidence for the clinical effect of these services for neonates, in contrast to those for adults. Wietstock and colleagues at the University of California San Francisco (where one of the first neonatal neuro-intensive care services was established) recently published data showing that their neonatal neurocritical care service was associated with significant reduction in cumulative phenobarbital dosage for neonates with hypoxic ischemic encephalopathy and seizures, fewer patients discharged on maintenance phenobarbital, and an unadjusted reduction in length of stay [6]. To date, this is the only literature associating neonatal neurocritical care services and improved outcomes.

Our neuro-intensive care for newborns service was established in November of 2012 after the center reached the benchmark of a minimum of two neuro-intensive care nurses in the neonatal intensive care unit (NICU) at all times. The initial aim of the service was to increase detection and expedite treatment of candidates for therapeutic hypothermia. This included educating physicians and staff not only at our own center, but at the hospitals that refer patients as well. The analysis of the clinical impact of our service is submitted herein.

2. Materials and methods

2.1. Subject identification

All subjects were admitted to the NICU at Sharp Mary Birch Hospital for Women and Newborns (SMBHWN) between January 2008 and October 2016. The center is a level-III NICU within a delivery hospital and accepts transfers from several community hospitals. De-identified data for all subjects were collected prospectively as part of the Vermont Oxford Network cohort study of neonatal encephalopathy. Inclusion criteria for subjects within this cohort were qualification for and treatment with therapeutic hypothermia, detailed in the section below. Exclusion criteria were: absence of perinatal depression (to exclude those who received therapeutic hypothermia for cardiopulmonary arrest well after birth), any disorder incompatible with survival, the presence of a surgical disorder unrelated to neonatal hypoxic ischemic encephalopathy, or transfer of the baby to another hospital (as accurate information about the remainder of the hospital course could no longer be obtained).

2.2. Therapeutic hypothermia

Therapeutic hypothermia (cooling) was initiated at our center in January 2008. Eligibility for hypothermia at our center requires the presence of: (1) gestational age $\geq$35 weeks, (2) moderate to severe encephalopathy, and (3) one or more of the following: ten-minute Apgar score $\leq$6, prolonged resuscitation at birth, severe acidosis as defined by cord, arterial, or venous pH < 7.1 within 60 minutes of birth, or a base deficit of –12 from cord or arterial sample within one hour of birth [7]. From 2008 to 2012 the base deficit was $\geq$16 to potentially qualify for treatment with therapeutic hypothermia and this was changed to a base deficit of $\geq$12 in 2012. This is why multivariate regression analysis was performed to ensure that the change in base deficit qualification was not responsible for the reduction in length of stay before and after the inception of the neuro-intensive care service. The institutional protocol requires initiation of cooling within six hours of birth. Children born at outside institutions were either passively or actively cooled (using the Tecotherm Neo, Inspiration Medical LTD, Leicester, UK) during transport as part of the California Transport Cooling Trial [8]. Upon arrival at SMBHWN, active whole-body cooling was accomplished via a blanket cooling device. The Cincinnati Sub-Zero Blanketrol II (Cincinnati, Ohio) was used from January 2008 to March 2011, and the Cincinnati Sub-Zero Blanketrol III (Cincinnati, Ohio) was used thereafter. Core temperatures were measured by esophageal probe and maintained at 33.5°C for 72 hours. Rewarming was done by increasing the target temperature by 0.5°C per hour for a total of six hours. Both 16-channel continuous video electroencephalography (EEG) and amplitude-integrated EEG were recorded throughout the duration of hypothermia and rewarming. Shivering was controlled with morphine, magnesium sulfate, and covering the hands and feet. The time-to-target temperature was defined as the amount of time (starting from time of birth) needed to achieve the first core temperature below 34°C.

2.3. Neuro-intensive care for newborns service

The neuro-intensive care service for newborns included neonatologists, pediatric neurologists, pediatric neuroradiologists, a placental pathologist, the neonatal resuscitation team, EEG technicians, and a neonatal nursing team with neurology training. The team of neonatal nurses received training in set-up, troubleshooting, and interpretation of amplitude-integrated EEG (specifically in identification of seizures) in newborns. The nursing team was also trained in expedited set-up and troubleshooting of the whole-body hypothermia equipment. A minimum of two neonatal neurology nurses were in the hospital at all times. The physicians of the service were responsible for training referring community centers in identification of possible candidates for therapeutic hypothermia and development of adjuvant protocols for administration of therapeutic hypothermia. Adjuvant protocols implemented as a result of the service included a dedicated order-set for therapeutic hypothermia admission, a step-wise protocol for shivering control, and a procedure for maintenance of target hypothermia temperature while in the magnetic resonance imaging scanner (which enabled an early abbreviated imaging sequence reserved for newborns with profound perinatal depression to provide prognostic information for parents who were considering withdrawal of care during therapeutic hypothermia.) After the establishment of the service, all physicians and nurses involved met routinely for review of recent hypothermia cases, identification and resolution of any issues, and ongoing training.

2.4. Data and outcome measures

This study was conducted with the approval of the hospital Institutional Review Board. Data collected for each subject included gestational age, birthweight, gender, mode of delivery, extent of resuscitation received at birth, Apgar scores, length-of-stay, mortality, diagnosis of seizures, and receipt of any surgeries that were not related to sequelae of hypoxic ischemic encephalopathy. A previously published scale for gauging extent of resuscitation was used, which was a 1-to-6 scale in which 1 represented "no intervention", escalating to a score of 6 which was defined as "endotracheal intubation with ventilation and medication (sodium bicarbonate with or without epinephrine)" [9]. The presence of seizures was confirmed via 16-channel continuous video EEG. All but five subjects received neuroimaging with magnetic resonance imaging (MRI) either during cooling or after cooling at four to five days after birth. (Subjects who underwent neuroimaging during cooling did so under an institutional protocol designed to maintain therapeutic hypothermia target temperature while in the scanner; the early MRI was obtained to guide parental decision-making in the cases of subjects who were at risk of profound brain injury beyond that treatable with therapeutic hypothermia.) All scans were read by an experienced pediatric neuroradiologist. Injury was classified by three regions: cortical injury, white matter injury, and injury to the deep gray nuclei.

2.5. Data analysis

Statistical analysis was performed using SPSS 22 (©IBM, Armonk, New York.) Means were compared using the *t*-test, proportions using the Pearson chi-squared test (or Fisher's exact test in cases where groups contained less than five subjects), and medians using the Mann-Whitney U test. Multiple regression analysis was used to study the relationship between length-of-stay and subjects treated before and after establishment of the neonatal neuro-intensive care service. Because more subjects were given therapeutic hypothermia as time elapsed and awareness increased, this relationship was likely to be confounded by severity of perinatal depression. Therefore, multivariate regression analysis associating length-of-stay and treatment pre- or post-service was adjusted for factors found to be significantly different before and after inception of the service.

3. Results

3.1. Clinical characteristics

166 newborns were treated with therapeutic hypothermia at the center during the study period. A total of eight subjects were excluded. Two subjects were excluded for being less than 35 weeks gestation at birth. Two other subjects were excluded from analysis for having disorders requiring surgical correction that were unrelated to neonatal hypoxic ischemic encephalopathy (one excluded subject required placement of ventriculo-peritoneal shunt for post-hemorrhagic hydrocephalus and the other required ostomy placement for gastrointestinal perforation.) Four subjects were transferred to another hospital.

The proportion of outborns did not change significantly after the inception of the service, nor did the proportion of gender. The rate of delivery via cesarean section declined after the inception of the service and did not quite reach significance (76% to 58%, $p = 0.08$). The five-minute Apgar score was significantly higher in the "after-service" portion of the cohort (median 3, IQR 1–5 pre-service to median 5, IQR 4–6 after service, $p = 0.001$), but the cord arterial pH did not differ (mean 6.90 ± 0.21 pre-service versus 6.97 ± 0.16, $p = 0.11$). The rise in Apgar score was paralleled by a decline in the extent of resuscitation needed per the scale described (median 5, IQR 5–6 pre-service to median 5, IQR 4–5 after service, $p < 0.0005$). The time-to-target temperature also increased in the after-service era (203 ± 110 minutes to 249 ± 115, $p = 0.05$).

3.2. *Hospital outcomes*

Before and after the establishment of the neuro-intensive care service for newborns, the incidence of parenchymal injury on post-hypothermia MRI did not significantly differ (34% before the service versus 29% with the service, $p = 0.34$, Table 2) and neither did the incidence of injury to more than two regions (24% before the service versus 16% with the service, $p = 0.21$). The rate of seizures detected did decrease significantly after establishment of the service (38% versus 14%, $p = 0.003$). Likewise, the mortality rate declined as well (17% before versus 5.4% after the service, $p = 0.03$.).

Lastly, length-of stay also significantly decreased after establishment of the service, after adjustment for time-to-target temperature, the presence of seizures, and five-minute Apgar score (22 ± 21 versus 13 ± 8.6, $p < 0.0005$.) A multiple regression was run to predict length-of-stay from treatment before or after the service, five-minute Apgar score, time-to-target temperature, and the presence of seizures. These variables statistically significantly predicted length-of-stay, $F(4, 135) = 6.566$, $p < 0.0005$, $R^2 = 0.163$. The only variables that added statistically significantly to the prediction were pre/post service ($p < 0.0005$) and the presence of seizures ($p = 0.008$).

4. Discussion

Recent evidence has shown a reduction in the total amount of phenobarbital needed to treat seizures in newborns with hypoxic ischemic encephalopathy, as well as fewer patients discharged on maintenance phenobarbital. This was the first evidence that neuro-intensive care services are associated with improved care for newborns at increased risk for brain injury.

This study corroborates this association and provides distinct evidence that such services can improve hospital outcomes for these newborns. For newborns requiring therapeutic hypothermia for neonatal encephalopathy in the setting of perinatal depression, length-of-hospital stay significantly and independently declined after the establishment of a dedicated neuro-intensive care service for newborns. This relationship remained significant after adjusting for factors that could affect length-of-stay, namely in-hospital mortality, gender, and the presence of seizures. The study by Wietstock and colleagues also documented a decrease in length of stay with the establishment of their service, although their reduction was unadjusted (though it should be noted that length-of-stay was not the primary outcome of that study and the significant reduction of cumulative phenobarbital dose was adjusted for seizure burden.) The other critical difference between their study and this one was that our respective cohorts were quite different; ours was a cohort of subjects with neonatal encephalopathy treated with therapeutic hypothermia and theirs assessed a cohort of subjects with seizures in the context of neonatal encephalopathy, a portion of which were treated with therapeutic hypothermia.

The expansion of the use of therapeutic hypothermia to treat less severe encephalopathy (a phenomenon known as "therapeutic drift") necessitates adjustment to assess the impact of a neonatal neuro-critical care service independently [10]. This cohort displayed marked therapeutic drift, as evidenced by the increase in five-minute Apgar scores, and decrease in extent of resuscitation in the portion of the cohort treated after inception of the service. Therefore the length-of-stay comparison required adjustment for five-minute Apgar score, as well as the burden of resuscitation. However, the reduction in length-of-stay remained significant after multivariate regression analysis. Though the rate of seizures also declined significantly after the initiation of the service, it is important to note that continuous video EEG recording was used for all the patients in this cohort, both before and after the service was begun. Given that the same measure was used to detect seizures both before and after inception of the service, it is unlikely that increased accuracy in detection of seizures is responsible for the reduction in length-of-stay.

Assuming a causal relationship between the neuro-intensive care service and reduction in length-of-stay, it is likely that there are multiple mechanisms for this association. Possible factors include dedicated funding from the hospital administration for the establishment of the service, increased availability of neurologists, increased and/or earlier recognition of newborns in need of therapeutic hypothermia,

Table 1
Clinical characteristics of cohort

	Before service ($n=29$)	After service ($n=129$)	P value
Outborn (n,%)	11, 38%	64, 50%	0.26
Male (n,%)	14, 48%	78, 60%	0.23
Gest. age (weeks, mean ± SD)	38.6 ± 1.3	39.1 ± 1.7	0.13
Birth weight (g, mean ± SD)	3373 ± 834	3258 ± 571	0.49
C-section (n,%)	22, 76%	75, 58%	0.08
5-minute Apgar (median, IQR)[1]	3, IQR 1–5	5, IQR 4–6	0.001
Cord arterial blood pH (mean ± SD)	6.90 ± 0.21	6.97 ± 0.16	0.11
Resuscitation score (median, IQR)	5, IQR 5–6	5, IQR 4–5	<0.0005
Time-to-target temperature (minutes, mean ± SD)	203 ± 110	249 ± 115	0.05

[1] IQR = interquartile range.

Table 2
Outcomes of cohort, before and after establishment of neurology service

	Before service ($n=29$)	After service ($n=129$)	P value
Seizures (n,%)	11, 38%	18, 14%	0.003
Abnormal post-cooling MRI (n,%)	10, 34%	37, 29%	0.34
≥2 areas of injury on MRI (n,%)	7, 24%	21, 16%	0.21
Mortality (n,%)	5, 17%	7, 5.4%	0.03
G tube placement before discharge (n,%)	2, 6.9%	2, 1.6%	0.15
Tracheostomy before discharge (n,%)	1, 3.4%	0, 0%	0.18
Length of stay (days, mean ± SD)	22 ± 21	13 ± 8.6	<0.0005[a]

[a] Adjusted.

increased training of neonatal intensive care nurses and delivery room staff, increased comfort level on the part of practitioners caring for patients treated with therapeutic hypothermia, and development of protocols ancillary to therapeutic hypothermia.

The primary limitation of this study is the lack of a direct measure of encephalopathy. Though a numeric scale for neonatal encephalopathy was not used in this study, all newborns treated had documented evidence of moderate encephalopathy per the Sarnat grading system of encephalopathy [11]. However, currently available scales of neonatal encephalopathy have yet to be associated with long-term neurodevelopmental outcomes now that therapeutic hypothermia has become standard-of-care for neonatal encephalopathy [12]. Therefore, other measures of perinatal depression (resuscitation score and five-minute Apgar score) were used in adjusting hospital outcomes.

It is clear that patients, newborn and adult alike, stand to benefit from neuro-intensive care services, though further research is needed to define precisely which aspects of the collaboration between intensive care and neurology provide the most benefit. Likewise, ours is only one model of how neurocritical care can be delivered in the neonatal intensive care unit. Another direction for useful future inquiry would be to describe the effectiveness of other models of neonatal neurocritical care, such as a telemedicine-based service. It remains to be seen how neuro-intensive care services for newborns could potentially affect long-term neurodevelopmental outcomes, as well as benefit newborns with other common neurological disorders, such as intraventricular hemorrhage or periventricular leukomalacia.

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References

[1] Suarez JI, Zaidat OO, Suri MF, et al. Length of stay and mortality in neurocritically ill patients: Impact of a specialized neurocritical care team. Crit Care Med. 2004;32(11): 2311-7.

[2] Varelas PN, Eastwood D, Yun HJ, et al. Impact of a neurointensivist on outcomes in patients with head trauma

treated in a neurosciences intensive care unit. J Neurosurg. 2006;104(5):713-9.

[3] Samuels O, Webb A, Culler S, Martin K, Barrow D. Impact of a dedicated neurocritical care team in treating patients with aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2011;14(3):334-40.

[4] Subspecialties UCfN. United Council for Neurologic Subspecialties 2017 [Available from: https://www.ucns.org/go/subspecialty/neurocritical.

[5] Glass HC, Bonifacio SL, Peloquin S, Shimotake T, Sehring S, Sun Y, et al. Neurocritical care for neonates. Neurocrit Care. 2010;12(3):421-9.

[6] Wietstock SO, Bonifacio SL, McCulloch CE, Kuzniewicz MW, Glass HC. Neonatal neurocritical care service is associated with decreased administration of seizure medication. J Child Neurol. 2015;30(9):1135-41.

[7] Shankaran S, Laptook AR, Ehrenkranz RA, et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med. 2005;353(15):1574-84.

[8] Akula VP, Joe P, Thusu K, et al. A randomized clinical trial of therapeutic hypothermia mode during transport for neonatal encephalopathy. J Pediatr. 2015;166(4):856-61.e1-2.

[9] Miller SP, Ramaswamy V, Michelson D, et al. Patterns of brain injury in term neonatal encephalopathy. J Pediatr. 2005;146(4):453-60.

[10] Massaro AN, Murthy K, Zaniletti I, et al. Short-term outcomes after perinatal hypoxic ischemic encephalopathy: A report from the Children's Hospitals Neonatal Consortium HIE focus group. J Perinatol. 2015;35(4):290-6.

[11] Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress. A clinical and electroencephalographic study. Arch Neurol. 1976;33(10):696-705.

[12] Miller SP, Latal B, Clark H, et al. Clinical signs predict 30-month neurodevelopmental outcome after neonatal encephalopathy. Am J Obstet Gynecol. 2004;190(1):93-9.