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Original Article

Implementation of Neonatal Neurocritical Care Program Improved Short-Term Outcomes in Neonates With Moderate-to-Severe Hypoxic Ischemic Encephalopathy

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ABSTRACT

Background: Despite the introduction of therapeutic hypothermia, infants with moderate-to-severe hypoxic-ischemic encephalopathy remain at risk of mortality and morbidity. A dedicated service with standardized management protocols and improved communication may help improve care. We aimed to evaluate the impact of a dedicated neonatal neurocritical care service on short-term outcomes in infants with hypoxic-ischemic encephalopathy.

Methods: We performed a retrospective cohort study (July 2008 to December 2017) on term and near-term infants admitted to two tertiary neonatal intensive care units with moderate-to-severe hypoxic-ischemic encephalopathy, before and after neonatal neurocritical care service implementation. The primary outcome was brain magnetic resonance imaging findings consistent with those of hypoxic-ischemic encephalopathy. Secondary outcomes included the cooling initiation rate, hospital stay duration, antiseizure medication use, and inotrope use. Regression analysis and interrupted time series analysis were performed after adjusting for confounding factors.

Results: In total, 216 infants with moderate-to-severe hypoxic-ischemic encephalopathy were analyzed—109 before and 107 after neonatal neurocritical care implementation. After adjusting for confounding factors, there was a significant reduction in primary outcomes (adjusted odds ratio: 0.3, confidence interval: 0.15 to 0.57, $P < 0.001$) after neonatal neurocritical care implementation. Average hospital stay duration reduced by 5.2 days per infant ($P = 0.03$), identification of eligible infants for cooling improved ($P < 0.001$), antiseizure medication use reduced ($P = 0.001$), and early inotropes use reduced ($P = 0.04$).

Conclusion: Implementation of a neonatal neurocritical care service associated with decreased brain injury shortened the hospital stay duration and improved the care of infants with moderate-to-severe hypoxic-ischemic encephalopathy.

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Introduction

The first collective efforts to provide comprehensive care to a subset of critically ill patients at risk of neurological complications were undertaken in the 1980s.[1-3] Initially they were developed for neurosurgical patients, whose preoperative and postoperative management was found to be different when compared with that of other patients.[4] As new diagnostic and treatment modalities emerged, interest grew in a dedicated service to provide care over a wide spectrum of neurological conditions.

The concept of neurocritical care has recently expanded and transformed the management of life-threatening neurological disorders by bringing together intensive care, neurology, neurosurgery, and rehabilitative medicine.[5] By 2002, observational studies reported a dramatic reduction of mortality in addition to shorter hospital stay using this model of care in adult populations.[6-8] Neurological disorders are common in childhood and the neonatal period. Approximately one-fourth of the patients admitted to pediatric intensive care units are at risk of acute neurological injuries.[9] The incidence of brain injury is high among neonates (around five per 1000 live births) with hypoxic-ischemic encephalopathy (HIE) being the leading cause in term neonates.[10] Perinatal asphyxia comprises one of the most common neurological emergencies involving one to eight per 1000 live births in developed countries to 26 per 1000 live births in resource-limited countries. HIE has been identified as the cause in 14.5% cases of cerebral palsy, a disorder that has major social and economic impacts.[11] The lifetime expenditure for care of an individual with cerebral palsy is approximately US $1 million.[12] However, improved survival has been observed since the advent and widespread use of therapeutic hypothermia (TH) in the last decade.[13-16] Furthermore, although TH decreases mortality and improves long-term neurodevelopmental outcome in infants with HIE,[15] infants with severe HIE are still at high risk of significant morbidity and the accurate prognosis of outcome remains challenging.[13,17] Uniformity in diagnostic and management approaches may help reduce inconsistency in the approach to management and provision of services.[18]

The primary objective of this study was to describe the impact of a dedicated neonatal neurocritical care (NNCC) service on short-term outcomes in infants with HIE.

Materials and methods

We performed a retrospective cohort study of term and near-term infants with a diagnosis of moderate-to-severe HIE between July 1, 2008, and December 31, 2017, who were admitted to one of two Level III neonatal intensive Care Units (NICUs) in Calgary, Canada. Patients were divided into those admitted before the implementation of the NNCC program (July 1, 2008 untill December 2013) and those admitted afterward (January 2014 untill December 2017). There have been no changes in the catchment area and assigned levels of care to the NICUs in southern Alberta during the study period. Diagnosis of HIE was made at the time of admission by the attending physician using the following criteria: neonates of gestational age $\geq$ 35 weeks and birth weight greater than 1800 g who satisfied at least one of criteria A and Criteria B (Table 1), which is the presence of moderate-to-severe encephalopathy defined as seizures *or* presence of one or more signs in three of the six defined categories (level of consciousness, spontaneous activity, posture, tone, primitive reflexes, and autonomic system; Table 1)

Criteria A represents the need for resuscitation or perinatal insult. Criteria B represents the presence of moderate-to-severe encephalopathy based on modified Sarnat classification.

Exclusion criteria included major congenital anomalies, chromosomal abnormality (except for trisomy 21), severe disseminated intravascular coagulation, and severe persistent pulmonary hypertension of newborn.

Primary outcome

The primary outcome studied was brain magnetic resonance imaging (MRI) findings consistent with HIE. The attending neuroradiologist was unaware of the illness severity or clinical categorization of HIE and the treatment offered, to blind the results. All MRIs were performed after rewarming on days 4 to 5 of life. Brain injury was defined based on the presence of abnormalities on diffusion-weighted imaging sequence and apparent diffusion coefficient maps, or T1 signal shortening, and were categorized as follows (Fig 1)[19]:

1. Acute profound asphyxia with basal ganglia involvement
2. Partial prolonged asphyxia with bilateral subcortical white matter involvement
3. Total asphyxia with basal ganglia and white matter involvement
4. Multifocal: multiple small restricted diffusion areas

Severe brain injury was defined as the presence of acute profound (pattern 1) or total asphyxia (pattern 3).

Secondary outcomes

The rate of identification of eligible neonates for TH, time to TH initiation after birth, time to target temperature from birth, length of hospital stay, antiseizure medication use and its cumulative burden in total mg/kg/hospital stay, and any use of inotropes in the first 72 hours of life were also assessed.

Intervention

Although protocols for application of TH and seizure management were available before the NNCC program was initiated, there was a perceived lack of consistency in the initiation of cooling in infants born outside the tertiary centers and in the cooling process during transport. There was no outreach program for referring centers to facilitate the initiation of neuroprotective strategies on transport. In addition, the absence of an organized quality improvement (QI) data monitoring system and infant follow-up program impeded efforts to monitor outcomes and implement improved management protocols.

After implementation of the NNCC service, the following strategies were initiated:

1. A team consisting of pediatric neurology, neonatology, neuroradiology, and pharmacy was formed. A consultation model (Fig 2) was created with 24/7 referral coverage.
2. A long-term continuous video electroencephalographic (cvEEG) protocol was developed and implemented; all neonates with moderate-to-severe HIE who received TH were monitored using full montage video electroencephalography (EEG) for 72 hours plus the rewarming period.
3. Neonatal nurses were trained to set up full montage video EEG studies at any time with support from the EEG technologist during regular working hours.[20] A central system was available for remote access to the EEG studies. A neurophysiologist gave the initial feedback as soon as possible, whenever abnormalities were identified, and every 24 hours if no seizure was identified. A core group of nurses and on-call neonatology fellows were trained to read a reduced montage of the EEG screen. An HIE

TABLE 1.
HIE Diagnostic Criteria[14]

Criteria A (At Least One)	Criteria B
1. Apgar score ≤5 at 10 minutes 2. Ongoing resuscitation such as positive pressure ventilation at age 10 minutes 3. Cord pH or blood gas within 1 hour showing pH ≤ 7 or base excess ≤ −16	Seizure or moderate-to-severe encephalopathy based on modified Sarnat staging[14]

Abbreviation:
HIE = Hypoxic-ischemic encephalopathy

road map was created (Fig 3) to identify areas of focus and intervention. Furthermore, a training program was developed for nurses and medical trainees to improve knowledge on common neonatal neurological disease diagnosis, management, and neuroprotection strategies.[20]

4. An outreach program was established for referring centers, and servo-controlled cooling on transport was introduced.
5. Best practice and evidence-based protocols and neuroprotection bundles were developed and updated.
6. QI, practice monitoring working group, and database were set up.
7. A long-term outcome follow-up program was developed and implemented.

Approval

The Conjoint Health Research Ethics Board, ID REB17-1333, provided approval for this study, and the consent for file review was waived.

Statistical methodology

All statistical analyses were performed using IBM SPSS version 24. A two-tailed *t* test was performed, with significance defined as a P value < 0.05. Univariate and bivariate statistics were used to describe the sample. Baseline characteristics were expressed as count and percentages for categorical variables and mean and S.D.

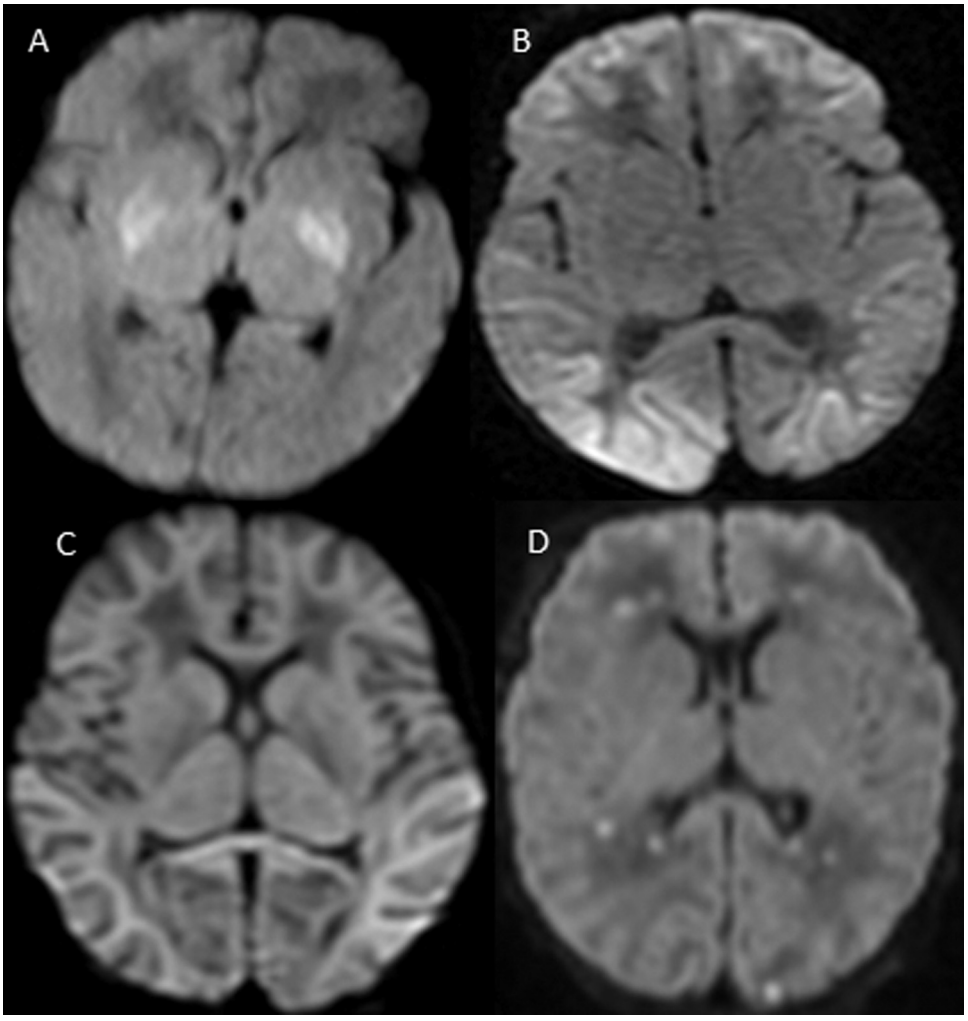

FIGURE 1. Hypoxic-ischemic encephalopathy patterns of brain injury on axial diffusion-weighted magnetic resonance imaging sequence where injured tissue is defined by restricted diffusion (hyperintense). (A) Acute profound asphyxia with basal ganglia involvement, (B) partial prolonged asphyxia with bilateral subcortical white matter involvement, (C) total asphyxia with basal ganglia and white matter involvement, and (D) multifocal, multiple small restricted diffusion areas.

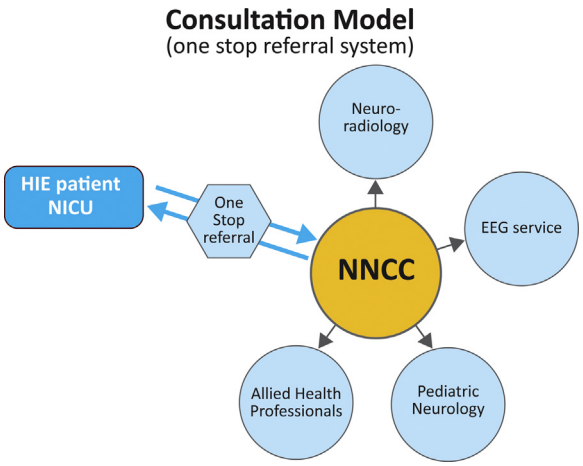

FIGURE 2. Consultation model of NNCC. A "one-stop" referral system was developed wherein the NICU team makes one referral call to the neurocritical care team (NCC) team. All NNCC required services such as neuroradiology, long-term cvEEG monitoring, and pediatric neurology, and allied health professionals are then notified and communicate directly with the NICU team. EEG, electroencephalography; HIE, hypoxic-ischemic encephalopathy; NICU, neonatal intensive care unit; NNCC, neonatal neurocritical care. The color version of this figure is available in the online edition.

or median and range for continuous variables. Categorical variables were compared using Fisher's exact test or chi-square test and continuous variables by Student *t* test (two-tailed) if normally distributed and Mann-Whitney U test if not normally distributed.

For our analyses, the outcome of interest was HIE brain injury on MRI. Logistic regression was performed to examine the association between NNCC implementation and brain injury adjusting for confounding factors such as gestational age, birth weight, gender, birth site status, Apgar score at 10 minutes, cord blood pH, and HIE clinical staging. As this study was exploratory in nature, we did not correct for multiple comparisons. Interrupted time series (ITS) analysis was performed to test change over time versus the impact intervention using autoregressive integrated moving average traditional forecasting model. Time intervals were set at six months.

Results

Patient characteristics

A total of 216 neonates with moderate-to-severe HIE were analyzed, 109 before neonatal NNCC implementation and 107 after. The basic characteristics of infants in each of the period are described in Table 2. Median gestational age was similar in both groups (40 weeks before versus 39 weeks after, $P = 0.4$) as was the mean birth weight (3238 g before versus 3317 g after, $P = 0.3$). Males comprised 52% and 57% of the two cohorts, respectively ($P = 0.4$). Most of the infants were born outside the tertiary centers (73% of the total cohort). In addition, moderate HIE comprised the bulk of the population (83%) when compared with severe (17%) with no difference before and after NNCC implementation. Mean cord pH was lower in the cohort before implementation of NNCC ($P = 0.04$).

A significant reduction in rate of HIE changes on MRI (adjusted odds ratio: 0.3, confidence interval: 0.15 to 0.57, $P < 0.001$) was observed after implementation of the NNCC service after adjusting for the confounding factors such as gestational age, birth weight, gender, outborn status, Apgar score at 10 minutes, cord blood pH, and HIE clinical staging. Although not statistically significant, a 49% reduction in mortality was observed (adjusted odds ratio: 0.38, confidence interval: 0.09 to 1.5, $P = 0.16$) (Table 3). A shorter average length of stay of 5.2 days per infant ($P = 0.03$), improved identification of eligible infants for TH ($P < 0.001$), reduced anti-seizure medication burden ($P = 0.001$), and reduced early inotrope use ($P = 0.04$) was also observed in the second time period.

ITS analysis

In the ITS analysis (Fig 4), we observed that the incidence of brain injury visible by MRI was significantly reduced after the implementation of the NNCC program (autoregressive integrated moving average model *P* value = 0.038).

Discussion

Our study underlines the importance of a dedicated NNCC service or program in improving short-term outcomes in infants

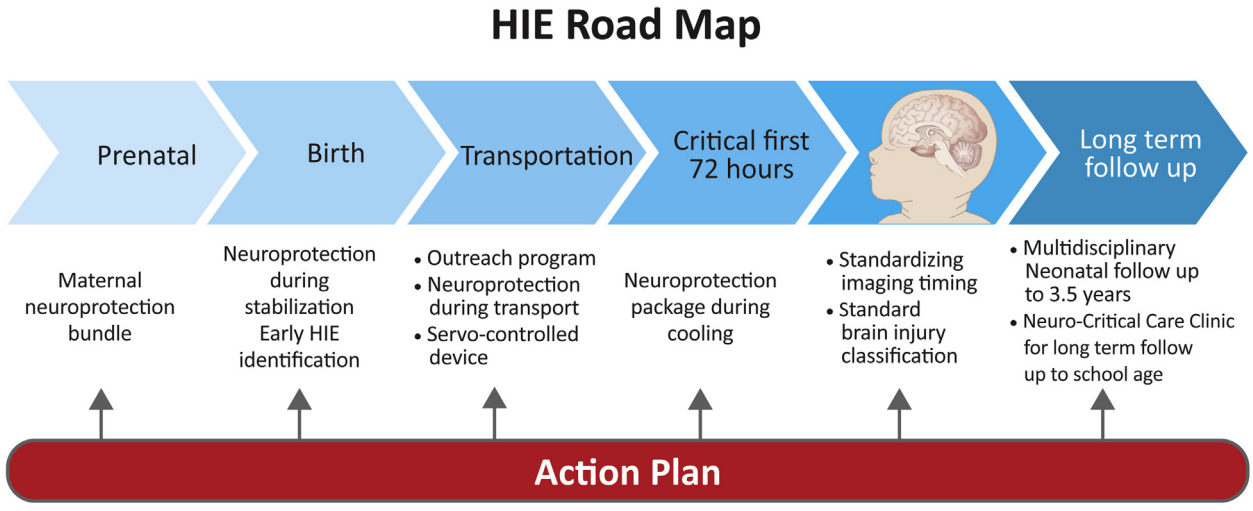

FIGURE 3. Hypoxic-ischemic encephalopathy (HIE) brain injury process map and action plan. A road map for potential brain injury in infants with HIE was created and broken down into distinct areas of intervention such as prenatal care, outreach and care during transportation, transition and stabilization, ongoing care in the NICU, and follow-up. Protocols and working QI working groups were created for each area. NCC, Neurocritical care; NFU, Neonatal follow-up. The color version of this figure is available in the on-line edition.

TABLE 2.
Baseline and Clinical Characteristics of Infants

Characteristics	Before NNCC N = 109	After NNCC N = 107	*P* value
Gestational age (weeks), (median IQR)	40 (38-41)	39 (37-40)	0.4
Birth weight (g), (Mean SD)	3238 (527)	3317 (565)	0.3
Male, N (%)	57 (52)	61 (57)	0.4
Outborn, N (%)	76 (70)	81 (76)	0.3
HIE stage, N (%)			0.5
Stage II	88 (81)	90 (84)	
Stage III	21 (19)	17 (16)	
Apgar at 10 minutes (median IQR)	5 (3-7)	6 (4-7)	0.6
Cord pH (mean S.D.)	6.96 (0.19)	7.02 (0.20)	0.04
Ventilated on day 1, N (%)	74 (68)	55 (51)	0.5
Use of opioids, N (%)	82 (75)	74 (69)	0.06

Abbreviations:
HIE = Hypoxic-ischemic encephalopathy
IQR = Interquartile range
NNCC = Neonatal neurocritical care
Outborn = Born outside the tertiary center

with moderate-to-severe HIE. Following implementation of the program we observed a significant reduction in morbidity in neonates with moderate-to-severe HIE. Our study results support the potential for developing more focused NNCC programs to improve outcomes for at-risk neonates. Furthermore, timely feedback of results within a center can inform on benefits and allow for adjustments to ensure quality control and improved outcome. For example, in a previous study, we observed a strong association between the early use of inotropes and death or brain injury in infants with HIE.[21] Based on these results we initiated a QI project to reduce the use of inotropes, where avoidable. The subsequent reduction of inotrope use, where clinically appropriate, was associated with reduction in brain injury and mortality. Thus, having closed-loop communication, in conjunction with clear treatment pathways and standardized protocols, as well as a robust follow-up program, proved to result in better outcomes, reduced length of hospital stay, and a lower burden on hospital resources.

With current advances in neonatology, there is a growing need to better understand the cause and extent of the morbidities associated with HIE, which despite the benefit of TH, can still cause a significant reduction in quality of life. NNCC has evolved over the last decade and has been augmented by improved neuroimaging, advances in cerebral function monitoring, use of continuous EEG, and clinical follow-up providing serial neurobehavioral examinations; this has led to more consistent predictions of outcome.[22,23] However, these technological advancements require a degree of familiarity and expertise, best provided by subspecialty services, thereby allowing for better implementation and application in clinical practice. Therefore the cornerstone of a dedicated service or program such as NNCC is a comprehensive and collaborative multidisciplinary effort to improve survival and reduce neurological injury.[24]

A significant improvement in the identification of babies eligible for TH and avoidance of unnecessary cooling has been achieved by establishing an outreach education program with NICU telehealth service. This outreach program provided on-site visits to referral centers to train health care professionals in performing neonatal targeted neurological examinations and the use of the HIE eligibility application on smartphones. The referring physician performed a targeted neurological examination, whereas the receiving neonatologist watched via telehealth system and a shared decision was made based on the examination to initiate or avoid cooling.

Another factor contributing to the success of our NNCC program and improvement in outcomes was the fact that bedside nurses played a key role in early intervention and implementation of neuroprotective care and provided a consistent observer of the infant's neurological status. NICU nurses and medical staff were trained to set up, initiate, and maintain the EEG monitoring system, as well as interpret reduced EEG montage on the bedside monitor. This facilitated timely initiation of monitoring and early reporting of abnormal findings to the medical team and helped with timely management.[20]

Concerns have been raised regarding antiseizure medication use; there is strong evidence from animal studies that such medications can cause neuronal cell apoptosis.[25] We recorded a reduction in the antiseizure medication burden due to early initiation of cvEEG monitoring by neonatal nurses, remote access and prompt feedback by epileptologists and neurologists, and education sessions for nurses and medical staff, which helped differentiate true clinical seizures from nonepileptic atypical movement.[26] Antiseizure medication was not initiated unless the abnormal movement was associated with corresponding electrographic changes or met specific clinical features (if no EEG was available at the time of the episodes). The net result was a significant reduction in cumulative antiseizure medication burden and a greater number of infants discharged without an antiseizure medication.

Studies have shown that consistent involvement with specialized neurological services or a neurointensivist may lead to effective resource utilization and reduced length of hospital stay. Patients are more likely to be discharged early, and there is a positive impact on the overall quality of life.[7,8,27] Moreover, establishing consistent management can reduce mortality and improve outcome.[28,29] Indeed, results from this study are in line with this hypothesis with demonstrable benefits in outcomes and reduced costs.

TABLE 3.
Impact of NNCC on Short-Term Outcomes

Short-Term Outcomes	Before NNCC N = 109	After NNCC N = 107	*P* value
Eligible and received therapeutic hypothermia, N (%)	80 (73)	100 (94)	<0.001
Electrographic seizures, N (%)	24 (22)	32 (30)	0.24
Cumulative burden of antiseizure medication, mg/kg/hospital stay (mean S.D.)	66.38 (128.63)	14.47 (46.54)	0.001
Inotropes use in the first 72 hours N (%)	58 (53)	36 (34)	0.004
Length of hospital stay (mean, S.D.)	16.8 (22)	11.6 (11)	0.03
Mortality, N (%)	16 (14.6)	8 (7.5)	0.09
Death or any HIE abnormality on MRI, N (%)	61 (56)	36 (34)	0.001
HIE abnormality on MRI, N (%)	55 (51)	31 (29)	0.001

Abbreviations:
HIE = hypoxic-ischemic encephalopathy
MRI = Magnetic resonance imaging
NNCC = Neonatal neurocritical care

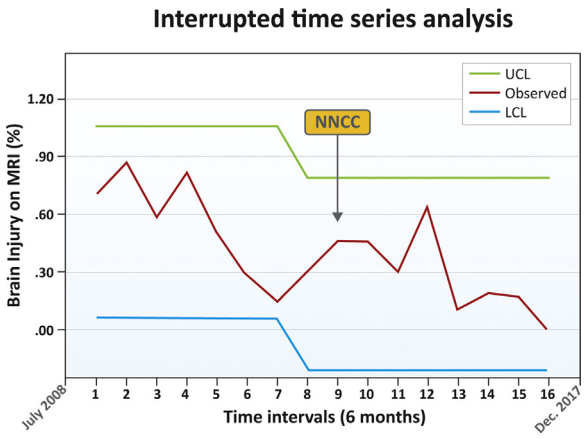

FIGURE 4. ITS showing the significant reduction after NNCC program implementation. Time intervals were set at six months. The arrow marks the time of NNCC program initiation. ITS, interrupted time series; LCL, lower confidence interval level; MRI, magnetic resonance imaging; UCL, upper confidence interval level. The color version of this figure is available in the online edition.

Challenges and lessons learned

Three different models of NNCC were considered: (1) a dedicated physical space for patients with neonatal neurointensive care at the outborn center, which was not feasible due to variability in the admission rate of such neonates over the year; (2) a neurocritical care team directly managing neonates requiring neurointensive care, which had logistic difficulties in terms of manpower and resources; and (3) a consultation model in which a separate NCC service was created by the pediatric neurology group, and was consulted by the NICU and pediatric intensive care unit house staff. The latter was easily adopted into the NICU, by developing and updating neonatal neurology protocols and guidelines, proper handling, and inservicing of the house staff and nurses on cvEEG monitoring.

Having the EEG studies initiated by the bedside nurses ensured a timely application, decision, and management. Having the support of EEG technologists ensured high-quality EEG tracings and helped maintain nurses' skills.

A separated clinical service for NCC care was created, and a "one-stop" referral system was developed to streamline the consults. The NCC neurologist served as the main point of contact for all specialties involved in the patient care.

Reading EEGs after working hours remained a challenge, although extending EEG technologist hours, having epilepsy fellows on call, and remote access by the pediatric neurologist on call helped to address the issue.

The compliance for all interventions was very high. For example, all infants with moderate-to-severe HIE received cvEEG, were cooled using the servo-controlled device on transport, and started feeding with mothers own milk or donor human milk during cooling. The reasons for high compliance were the engagement of bedside nurses and stakeholders, training and education before implementation, and close monitoring and follow-up after hospital discharge NNCC program initiation.

In conclusion, the implementation of NNCC service was associated with reduced mortality and brain injury and improved care in neonates with moderate-to-severe HIE. Our service model is feasible and applicable to both centers with more limited resources and larger centers.

Limitations

Because the data collected before the implementation of NNCC program was done retrospectively, it could be subject to selection bias. In addition, the different components of the program were introduced almost simultaneously, which precludes determining which specific combination or factor may have resulted in the improved outcomes. Moreover, this is a study of short-term outcomes, as the program is still in its nascent stage and long-term neurodevelopmental outcome data are currently being collected.

Although current practices in our center have conformed to international recommendations, the time span of study encompasses a decade (2008 to 2017). This period was one of the most complex ones in the history of HIE, where multiple trials were established to achieve the right therapeutic modalities to ameliorate the neurological injuries resulting from perinatal asphyxia. The changing practices of the decade could have implications. Finally, the science and clinical implementation of cooling also evolved during the evolution of our NNCC program from use of ice packs for transport to servo-controlled cooling devices during and after transport. This more tightly regulated early control of body temperature undoubtedly has been beneficial and could have an influence on our outcomes.

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