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Characterization of Death in Neonatal Encephalopathy in the Hypothermia Era

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Abstract

This study aimed to characterize the circumstances of death in encephalopathic neonates treated with therapeutic hypothermia. Patients who died after or during treatment with therapeutic hypothermia between 2007-2014 were identified. Patient circumstance of death was characterized using an established paradigm. Thirty-one of 229 patients died (14%) at a median of 3 days of life. Most who died were severely encephalopathic on examination (90%) and had severely abnormal electroencephalographic (EEG) findings (87%). All those who had magnetic resonance images (n = 13) had evidence of moderate-severe brain injury; 6 had near-total brain injury. Cooling was discontinued prematurely in 61% of patients. Most patients (90%) were physiologically stable at the time of death; 81% died following elective extubation for quality of life considerations. Three patients (10%) died following withholding or removal of artificial hydration and nutrition. Characterization of death in additional cohorts is needed to identify differences in decision making practices over time and between centers.

Keywords

neonatal encephalopathy, death, decision making, therapeutic hypothermia, hypoxic-ischemic encephalopathy

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Despite the advent of therapeutic hypothermia, up to one-quarter of infants with neonatal encephalopathy will die. An additional 20% will survive, but experience moderate to severe disability.[1-3] How providers and parents consider, weigh, and value these outcomes is incompletely known. The majority of all deaths in the neonatal intensive care unit occur after the withdrawal of life sustaining interventions in physiologically stable infants. These decisions are typically based on provider and parent considerations of long-term prognosis and quality of life.[4,5] Understanding when, how, and why these decisions are made is necessary to accurately interpret information about infant mortality.[6]

It is not clear how new approaches to the care of infants with neonatal encephalopathy impact the circumstances of death for this population. Neonatal neurointensive care programs with specialized nursing, expertise in neonatal electroencephalography (EEG) and neuroimaging, and coordinated specialty care, are increasingly available.[7-9] Ancillary studies including continuous video EEG and magnetic resonance imaging (MRI) are widely used in prognostication; however, their role in parent and provider decision making is unknown. Furthermore, the impact of therapeutic hypothermia on decision making for providers and families is not well understood. To assess outcomes for these and other emerging interventions[10,11] it is important to characterize how infants with neonatal encephalopathy die in current clinical practice.

This study adapted the framework of Verhagen et al to characterize death in a cohort of infants with neonatal encephalopathy who were treated with therapeutic hypothermia.[12] The

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study aims to describe the clinical characteristics and ancillary findings of this cohort, to explore how information about an infant's long-term prognosis, as assessed soon after birth, is associated with choices regarding life-sustaining therapies in neonatal encephalopathy.

Patients and Methods

Subjects

Neonates admitted to the University of California, San Francisco Intensive Care Nursery from November 2007 to July 2014, and treated with therapeutic hypothermia, were prospectively enrolled into a database and considered for inclusion in this study.

Clinical criteria for therapeutic hypothermia included (1) ≥36 weeks gestational age at birth, (2) moderate to severe encephalopathy within 6 hours of birth, and (3) 1 or more of the following: 10-minute Apgar score <5, prolonged resuscitation (> 10 minutes) at birth, cord or first blood gas pH <7.0, cord or first blood gas base deficit >12. Neonates were excluded from hypothermia if they were less than 36 weeks of gestation, presented beyond 6 hours of life, had coagulopathy with active bleeding, or were prenatally diagnosed with conditions not compatible with survival. Additional exclusion criteria for this study included patients with congenital anomalies or genetic diagnoses known to be associated with developmental disabilities.

For outborn neonates, passive cooling was initiated at the referring hospital or during transport. During therapeutic hypothermia, active whole-body cooling was performed using a blanket device (Cincinnati Subzero Blanketrol III, Cincinnati, OH). Core temperatures were maintained at 33.5°C for 72 hours. Routine clinical care for neonates who undergo hypothermia at UCSF includes evaluation and management by a neurologist on the Neonatal Neurocritical Care service at the time of admission and daily at least until rewarming is complete.[8] A pediatric neurologist performed serial neurologic examinations throughout the infant's hospitalization. Conventional video EEG with bedside amplitude-integrated display was initiated upon admission and continued until rewarming according to national guidelines.[13] Morphine was administered to all patients and titrated as needed to prevent shivering. There were no substantive changes to the therapeutic hypothermia protocol over the course of the study period.

Measures

Most clinical and demographic data were compiled prospectively in a systematic manner using predetermined variable definitions. For the purpose of this study, medical records were reviewed for death category according to the framework developed by Verhagen et al,[12] as follows: (1) unstable patients who died while receiving CPR, (2) unstable ventilated patients who died while withholding CPR, (3) unstable patients who died after extubation to let the dying child die in parents' arms, and (4) elective extubation for quality of life considerations in stable patients. An additional category was identified in which infants were physiologically stable and died after withholding or withdrawal of artificial nutrition and hydration. Physiologic instability was defined as 2 of the following: persistent desaturation despite 100% oxygen on mechanical ventilation, hypotension despite volume infusion and inotropes, or protracted anuria for 24 hours. Protracted bradycardia, a criteria in previous studies, was not included as a criterion for instability in this cohort given the frequency of asymptomatic bradycardia that occurs in the setting of hypothermia.[12] Medical records were also reviewed for documentation of palliative care, ethics, and social work involvement.

The infant's final neurologic examination was extracted from the medical record and the level of encephalopathy was defined as mild, moderate, or severe using a modified Sarnat staging system, which relies on an infant's clinical exam alone.[14,15] The infant's final EEG background was classified as normal, moderately abnormal, or severely abnormal. Moderately abnormal was defined as discontinuous activity (interburst interval > 6 seconds and interburst amplitude > 5 microvolts) occupying over half of the recording with poor state changes. Severely abnormal was defined as (1) low voltage (between 5 and 15 microvolts) and undifferentiated activity, (2) burst-suppression (bursts of medium to high voltage activity lasting < 10 seconds followed by periods of marked voltage attenuation with amplitude < 5 microvolts, without state changes), or (3) extremely low voltage (< 5 microvolts) without state changes.[16] Clinical and subclinical seizures were also documented.

MRI of the brain was performed on a 1.5 or 3 T SignaEchoSpeed system (GE medical systems, Waukesha, WI). Imaging sequences included, at minimum, gradient echo volumetric T1 MRI, axial spin-echo T2 MRI, diffusion-weighted MRI, and MR spectroscopy with voxels over the basal ganglia and frontal white matter. A pediatric neuroradiologist blinded to infant clinical details independently scored all studies according to previously published criteria.[17,18] MRIs were considered to demonstrate moderate-severe brain injury if injury to the bilateral basal ganglia/thalamus or the watershed areas was present. Basal ganglia/thalamic injury was defined as abnormal signal in the lentiform nucleus and thalamus or more extensive injury (score ≥ 2). Watershed injury was defined as abnormal signal in the anterior or posterior watershed cortex and white matter or more extensive injury (score ≥ 3). If injury scores were maximal in both the watershed and basal ganglia regions, the MRI was also categorized as "near-total" brain injury, according to previously published criteria.[19] At the study institution, MRIs are typically performed on day 4-5 of life, after completion of therapeutic hypothermia when clinically able.

The University of California, San Francisco Committee on Human Research approved waiver of consent for data collection. Descriptive statistics were performed.

Results

Between July 2007-2014, 31 patients (14%) died out of the 229 patients who were treated with therapeutic hypothermia. The clinical characteristics of these patients are presented in Table 1. Most infants were born via emergent cesarean section at outside facilities and transferred to receive therapeutic hypothermia. Approximately half of infants (52%) who died had electrographic seizures. All patients had EEGs, and most (n = 27, 87%) were severely abnormal. Neurologic examination revealed severe encephalopathy in the majority of patients (n = 28, 90%).

MRIs were obtained in 13 (42%) patients who died, all of which revealed moderate-severe brain injury. Six (46%) of the patients with MRIs had evidence of near-total brain injury. Of those infants who did not have an MRI (n = 18), 3 were physiologically unstable. Most were severely encephalopathic (n = 16) on examination and/or had a severely abnormal EEG (n = 15). Fifteen physiologically stable infants did not have an MRI;

Table 1. Maternal, Infant, and Birth Characteristics of 31 Neonates Treated With Therapeutic Hypothermia Who Died in the Neonatal Period.

Characteristic	
Maternal and birth	
Maternal age: median (range)	30 (17-41)
Birth hospital: n outborn (%)	27 (87)
First pregnancy: n (%)	16 (52)
Mode of delivery: n (%)	
Vaginal delivery	5 (16)
Operative vaginal	5 (16)
Emergency C-section	21 (68)
Infant	
Sex: n female (%)	14 (45)
Gestational age: median (range)	39 (36-43)
10 minutes Apgar: median (range)	3 (0-7)

most (n = 11) of these infants died prior to the completion of therapeutic hypothermia, when an MRI is typically obtained.

Cooling was discontinued prior to 72 hours in 19 (61%) patients due to death or withdrawal of life sustaining therapy (Table 2). Death occurred most commonly (n = 28, 90%) in the neonatal intensive care unit. Ten patients (32%) died prior to 48 hours of life. Circumstances of death are presented in Table 3 according to the framework proposed by Verhagen et al. No ventilated patients died while actively receiving CPR or as a result of withholding CPR. A minority of infants (10%) died after extubation in the setting of physiologic instability in the first 72 hours of life. The majority of deaths (n = 25, 81%) occurred in physiologically stable infants who were extubated due to prognosis for poor quality of life (Table 3). Of these 25 patients, 16 did not complete the full 72 hours of therapeutic hypothermia. All patients who were electively extubated died; there were no unexpected survivors among neonates who were electively extubated.

Three infants (10%) were physiologically stable and died after withholding or withdrawal of artificial nutrition and hydration. Two died under hospice care. The third infant died in the neonatal intensive care unit and was followed by the palliative care service. Time to death after removal of artificial hydration and nutrition ranged from 2-12 days. All 3 infants had evidence of severe encephalopathy on neurologic examination and severely abnormal EEG findings. All 3 had an MRI performed; 1 had evidence of near-total brain injury, while 2 had evidence of moderate-severe brain injury. None had the ability to suck or feed orally. None of these 3 infants were intubated when decisions to redirect care were made.

Autopsy reports were available for 18 infants; 1 infant's report does not include central nervous system findings due to lack of parental consent. Of the 17 infants with description of brain pathology, all were given a pathologic diagnosis of hypoxic ischemic encephalopathy. All of these infants had evidence of widespread neuronal necrosis and/or astrogliosis in the cerebrum. Fifteen also had evidence of injury to the cerebellar cortex and/or white matter. Thirteen had additional evidence of brainstem injury.

Table 2. Clinical Characteristics of 31 Neonates Treated With Therapeutic Hypothermia Who Died in the Neonatal Period.

Characteristic	
EEG background: n (%)[a]	
Moderately abnormal	3 (10)
Severely abnormal	27 (87)
Electrographic seizures	16 (52)
Unable to be interpreted	1 (3)
MRI obtained: n (%)	13 (42)
Moderate-severe brain injury	13 (42)
Near-total brain injury	6 (19)
Severity of Encephalopathy: n (%)[a]	
Moderate	3 (10)
Severe	28 (90)
Hypothermia discontinued early: n (%)	19 (61)
Location of death: n	
NICU	28 (90)
Under hospice care	3 (10)

Abbreviations: EEG, electroencephalography; MRI, magnetic resonance imaging; NICU, neonatal intensive care unit.
[a]As determined at the time of final examination prior to discussion of withdrawal of life sustaining treatment.

A neurologist, neonatologist and a social worker were involved with discussions related to goals of care for all families. The pediatric palliative care service was consulted once. One ethics consult was obtained; the reason for this consult was to ensure clinician and family consensus around the treatment plan. All decisions to withdraw life sustaining treatment were made jointly by parents and clinicians.

Discussion

In a cohort of encephalopathic neonates without congenital anomalies who were treated with therapeutic hypothermia, 14% died. Most were physiologically stable and died at a median age of 3 days following withdrawal of mechanical ventilation and early termination of cooling due to parent and clinician concerns for long-term prognosis. A minority of infants died either after nutrition and hydration were withheld and/or withdrawn or in the setting of physiologic instability. The majority of patients who died had evidence of severe encephalopathy on neurologic examination and EEG. All who had brain imaging had evidence of moderate-severe brain injury. Most patients died in the neonatal intensive care unit. Utilization of the Pediatric Palliative Care Service was rare.

This study provides a detailed characterization of death in a clinical cohort of patients with neonatal encephalopathy. These results build on the results of previous clinical trials, which suggest that most neonates with encephalopathy die as a result of withdrawal of life sustaining treatment. The proportion of patients who died in this manner was higher in this cohort (90%) than in previous studies. In the initial National Institute of Child Health and Human Development (NICHD) trial of whole body cooling, 63% of patients in the hypothermia group who died in the neonatal intensive care unit died in the setting

Table 3. Characterization of Death in 31 Neonates Treated With Therapeutic Hypothermia Who Died in the Neonatal Period.

Circumstances of death	Physiology	Patients (n = 31)	Age at death (median, range)	Did not complete 72-hour hypothermia course (n = 19)
Category A Died while receiving CPR	Unstable	0	N/A	N/A
Category B Died on ventilator while withholding CPR	Unstable	0	N/A	N/A
Category C Extubation to let dying child die in parents' arms	Unstable	3	2 (1-3)	3
Category D Elective extubation for quality of life reasons	Stable	25	3 (2-17)	16
Category E Withholding/withdrawing nutrition and hydration	Stable	3	12 (8-18)	0

of withdrawal of life sustaining treatment.[1] In the Infant Cooling Evaluation trial, 82% of all deaths in the hypothermia cohort died after withdrawal of life sustaining treatment.[20] In the recent NICHD trial to assess the effect of longer (120 hours) and/or deeper (32°C) cooling, 75% of neonatal intensive care unit deaths in the 72-hour group (at either 32°C or 33.5°C) occurred as a result of withdrawal of life sustaining therapies.[20,21]

In this study cohort, most patients (61%) died prior to completion of therapeutic hypothermia. Similar results were seen in the initial NICHD trial of whole body cooling, in which 75% of patients in the treatment group died during the intervention.[1] In the more recent trial investigating longer and/or deeper cooling; however, only 10% of patients who died in the 72-hour group died during the intervention.[21] Taken together, the results of the current study and others highlight the potential for differences in circumstances of death among centers and over time.

Bioethicists and clinicians refer to the ''window of opportunity'' in severe brain injury as a period of time during which a critically ill neonate will die soon after removal from the ventilator.[22-24] The impact of therapeutic hypothermia on the ''window of opportunity'' is unknown; however, there has been concern that hypothermia treatment may increase the risk of delayed decision making.[25] In this study, there was no evidence to suggest delayed decision making for the majority of patients. Furthermore, the current results are similar to those reported in a cohort of encephalopathic infants in Spain who were studied prior to the advent of therapeutic hypothermia. In that cohort, in which only 1 infant was cooled, most infants (94%) died in the context of an end-of-life decision, at a mean age of death of 64 hours.[26]

If and how to incorporate the window of opportunity into clinical decision making is controversial, in part due to concerns over the accuracy of prognostication.[22,23] While prognostic uncertainty exists in neonatal encephalopathy, clinical history, neurologic examination, electrophysiologic data, and neuroimaging are often available early in the clinical course and can help guide clinicians and families.[27-30] Severe EEG abnormalities, including cerebral inactivity and burst suppression patterns, predict severe disability and death in cooled[31] and noncooled[32] infants. Although hypothermia attenuates the prognostic utility of early amplitude-integrated EEG, failure to return to normal background within 48 hours remains highly prognostic of death or moderate to severe disability.[33] Burst suppression and extremely low-voltage conventional EEG patterns have been shown to be predictive of moderate to severe brain injury on MRI, with a specificity of 81% in the first 24 hours of admission and 100% specificity at 24-30 hours.[34] Automated calculations of excessive discontinuity (mean discontinuity >30 seconds/minute-long epoch) predicts abnormal 2 year neurodevelopmental outcome with 100% specificity at 24 hours.[35] Basal ganglia and thalamic injury on MRI has been shown, in both cooled[36,37] and noncooled[17] infants, to be highly predictive of disability.

Verhagen et al provided a structured framework to characterize the ways in which infants die that has been used to compare end-of-life decision making between hospitals. This study identified an additional circumstance of death in which artificial nutrition and hydration was withheld/withdrawn for quality of life considerations in physiologically stable infants. This circumstance was reported as an independent category given the clinical and ethical complexity that often accompanies this decision.[38,39] While withholding or withdrawing artificial nutrition remains controversial in many neonatal intensive care units, professional guidelines support this practice in certain circumstances.[38-43] In this cohort, decisions to forgo nutrition and hydration were made by families with the support from hospice and/or palliative care involvement in all cases. Since the study period, the study institution has chosen to automatically involve palliative care in all cases in which a decision to forgo nutrition and hydration is considered.

This study is limited to a single institution's experience. Characterization of death should be explored in a larger cohort of newborns. There are inherent differences in this single-center cohort and those reported in clinical trials. The study cohort was a clinical cohort and included many critically ill infants, who may have been excluded as ''moribund'' in previous studies. The narrow criteria used to define physiologic stability in this study do not fully capture other systemic complications experienced by patients. The pediatric palliative care consultation service began in 2012 and, prior to that date, a

palliative care nurse practitioner provided bereavement support without formal consultative services and consistent documentation. Palliative care utilization prior to 2012 may be underrepresented. Furthermore, this sample is limited to those patients who received hypothermia. The circumstances of death in neonates with encephalopathy who were not treated with hypothermia are not captured in this sample. These data cannot answer the important ethical question of how to best balance decision timing with prognostic certainty; this study offers one institution's experience in an effort to prompt further exploration. Information regarding the content and process of discussion of treatment limitation was not well documented in the medical records and conversations were not recorded, which limited the ability to fully characterize decision making. An important next step will be prospectively characterizing how families make these difficult decisions with their medical team.

Death in neonatal encephalopathy is common and, in this cohort, typically occured in physiologically stable infants. These results show that providers and parents make decisions about withdrawal of life-sustaining treatment early in the treatment course with the aid of neurologic examination and ancillary testing, often prior to the completion of therapeutic hypothermia. This study also identified an important subset of infants in which artificial nutrition and hydration was withheld or withdrawn in the setting of profound neurologic injury and quality of life considerations. The current results highlight the potential for variability among centers; decision making practices should be studied at multiple centers and time intervals. There may be additional opportunities to study the incorporation of a pediatric palliative care service or communication interventions in this patient population. Future studies should include detailed information about the circumstances and nature of death.

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This study was performed at the University of California, San Francisco.

Author Contributions

MEL conceptualized and designed the study, analyzed and interpreted data, drafted the initial manuscript, and revised the manuscript. RDB contributed to study conception, interpreted data, and critically reviewed the manuscript. SLB conceptualized and designed the study and critically reviewed the manuscript. AFB conceptualized and designed the study and critically reviewed the manuscript. AJB analyzed and interpreted data and critically reviewed the manuscript. HCG conceptualized and designed the study, collected data, analyzed data, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: MEL has received compensation for medicolegal work.

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Ethical Approval

The University of California, San Francisco Committee on Human Research approved a waiver of consent for data collection.

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