Seminars in Fetal & Neonatal Medicine 20 (2015) 122–127

Contents lists available at ScienceDirect

Seminars in Fetal & Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Review

Impact of hypothermia on predictors of poor outcome: How do we decide to redirect care?

S.L. Bonifacio [a, *], L.S. deVries [b], F. Groenendaal [b]

[a] Division of Neonatology, Department of Pediatrics, University of California San Francisco, San Francisco, CA, USA
[b] Department of Neonatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Keywords:
Neonatal encephalopathy
Therapeutic hypothermia
Amplitude-integrated EEG
Magnetic resonance imaging
Redirection of care

SUMMARY

Therapeutic hypothermia is now considered the standard of care for neonates with neonatal encephalopathy due to perinatal asphyxia. Outcomes following hypothermia treatment are favorable, as demonstrated in recent meta-analyses, but 45–50% of these neonates still suffer major disability or die due to global multi-organ injury or after redirection of care from life support due to severe brain injury. The ability to determine which patients are at highest risk of severe neurologic impairment and death and those in whom redirection of care should be considered is limited. This is especially true in the first few days after birth and in situations where the brain might be more significantly affected than other organ systems, making it difficult to discuss redirection of care. Clinical history, neurologic examination, serum biomarkers, neurophysiology [amplitude-integrated electroencephalography (aEEG) or EEG], near-infrared spectroscopy, and magnetic resonance imaging have all been studied as predictors of severe neurologic injury and poor outcome, although none is 100% predictive. Serial evaluation over time seems to be an important element to facilitate discussion regarding anticipated poor prognosis and decision-making for transition to comfort care. Thus far, brain monitoring in the form of aEEG and conventional EEG seem to be the best objective tools to identify the highest-risk patients. A delay or lack of recovery of the aEEG background during hypothermia treatment is an established important predictor of poor outcome (death or disability). This paper highlights the prognostic indicators that have been considered and focuses on aEEG as an important predictor of death or severe disability, which may facilitate conversations regarding redirection of care.

1. Introduction

Therapeutic hypothermia (TH) for the treatment of neonatal encephalopathy due to perinatal asphyxia is now considered standard of care and should be offered to qualifying neonates [1]. Multiple randomized controlled trials have demonstrated efficacy in the reduction in the risk of death or moderate–severe disability at 18–24 months of age [2–4]. School age outcomes from the major trials are also now being published and demonstrate that treatment with hypothermia, in at least one of the major trials, has sustained benefit at 6–7 years of age [5,6]. Unfortunately, despite treatment with therapeutic hypothermia, in the randomized controlled trials (RCTs) and in clinical practice, a significant number of neonates do not survive (as high as 30%) and 45–50% suffer the composite outcome of death or major disability [7]. Identification of those neonates that are “too severe” to benefit is difficult. Clinicians have the arduous task of differentiating those who may survive with moderate impairments from those who will survive with severe impairments or who are unlikely to survive to hospital discharge. Discriminating these groups of newborns is complicated by the fact that hypothermia has impacted the ability of key markers of severity of encephalopathy (neurologic exam) to predict outcome and changes the time-frame in which tools such as amplitude-integrated electroencephalography (aEEG) are most predictive of outcome. Magnetic resonance imaging (MRI) is known to retain its predictive abilities but this is sometimes delayed – presumably due to clinical instability or poor access to imaging – by as much as two weeks after birth, which does not help in conversations about possible outcomes with parents in the first few days of life. Clinicians likely use these “predictive tools” as criteria for entering end-of-life discussions with parents, as neonates rarely die while actively receiving intensive care. Although poorly reported in the

* Corresponding author. Address: Neuro-Intensive Care Nursery, UCSF School of Medicine, 533 Parnassus Ave., Room U-585, San Francisco, CA 94143, USA. Tel.: +1 415 476 7242.
E-mail address: BonifacioS@peds.ucsf.edu (S.L. Bonifacio).

http://dx.doi.org/10.1016/j.siny.2014.12.011
1744-165X/

literature, it appears that the majority of deaths in the setting of severe hypoxic–ischemic encephalopathy (HIE) can be attributed to end-of-life decisions and redirection of the goals of care to comfort measures [8,9]. This article reviews the risk factors for poor outcome – including death in the newborn period, many of which the clinician considers during the course of treatment – and presents the findings of a subset of an international cohort study of newborns treated with hypothermia as part of standard of care in which these risk factors were evaluated as predictors of poor outcome and death in the newborn period.

2. Use of clinical examination as a predictor of outcome

Clinical examination is critical in properly identifying newborns who qualify for TH. All of the randomized trials used some form of the Sarnat staging system in order to identify eligible patients. In 1976, Sarnat and Sarnat published an article in which they serially evaluated a small cohort of 21 neonates with perinatal asphyxia and encephalopathy [10]. Using a standardized neurologic exam and EEG, initially performed at 12–24 h after birth, and then performed serially during the hospitalization, they were able to classify neonates into three stages, describe the duration and evolution of each stage of encephalopathy, and determine the association between stage and evolution of encephalopathy and outcome at 6–12 months of age. In this very small cohort, neonates with Stage 2 encephalopathy who normalized their neurologic exam and EEG within 5 days ($n = 8$) tended to have a good outcome at 6–12 months of age, and those with features of stage 3 ($n = 5$) all had a poor outcome of death or severe impairment. The neurologic exam used in this landmark paper was adapted/modified in order to select patients for enrollment into the RCTs of TH. In order to be eligible for enrollment in an RCT, the neurologic exam within 6 h of birth needed to be consistent with Stage 2 or 3 encephalopathy. However, it is important to note that the exact timing of the initial exam in the Sarnat paper was not presented but was stated to occur at the time of admission. There are two important and overlooked findings of the Sarnat paper: (1) Some neonates were in Stage 1 for >6 h and then progressed to Stage 2 encephalopathy. These neonates would not have been enrolled in the RCTs and it is unclear what their risk of long-term neurodevelopmental impairments would be. (2) The study had relatively short-term follow-up ranging from 6 to 12 months of age, but only two of the surviving subjects were seen at 12 months of age.

Hypothermia has impacted the ability of stage of encephalopathy at presentation to predict outcome. Secondary analyses of the National Institute of Child Health and Human Development (NICHD) trial and the CoolCap trial both identified that the predictive ability of the initial stage of encephalopathy was altered by treatment with hypothermia and that improvement in stage of encephalopathy during treatment was important in identifying patients who were likely to have a good outcome [11,12]. In addition there appears to be an interaction between encephalopathy stage at the end of treatment and treatment itself, as the predictability of moderate encephalopathy at the completion of treatment was altered by hypothermia with treated infants with persistent moderate encephalopathy on day 4 doing better than those who were not treated. Specifically, in the CoolCap trial, cooled neonates with a persistent moderate encephalopathy (HIE grade 2) at day 4 tended to have a favorable outcome as compared to non-treated infants (24 of 31 subjects vs 10 of 29 subjects, $P = 0.002$) (Fig. 1). Improvement in grade of encephalopathy from grade 2 to grade 1, regardless of treatment, seemed to confer a favorable outcome compared to those whose stage of encephalopathy deteriorated [11]. In an analysis of serial modified Sarnat staging of newborns enrolled in the NICHD trial, the initial stage at <6 h was predictive of death or disability, but, in those who survived to complete 72 h of treatment, initial stage at <6 h was no longer a statistically significant predictor of outcome when the stage at 72 h was accounted for [12], again suggesting that evolution of stage during treatment is more important than the initial stage of encephalopathy. In predictive models, time to improvement in stage and time to reaching no or mild HIE were important predictors of death/

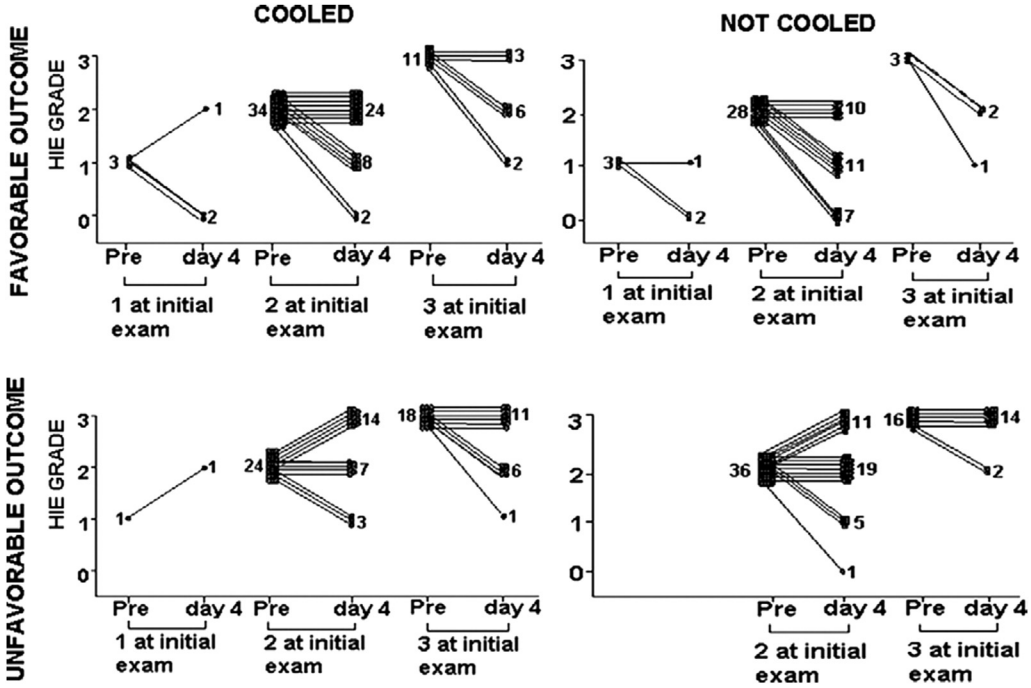

Fig. 1. Incidence of favorable and unfavorable outcome by stage of encephalopathy at pre-randomization and at day 4, in cooled and control neonates enrolled in the CoolCap Study. HIE, hypoxic–ischemic encephalopathy.