Early Human Development 90 (2014) 713–717

Contents lists available at ScienceDirect

Early Human Development

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

The importance of temperature on the neurovascular unit

Abbot Laptook *

Warren Alpert Medical School of Brown University, United States
Neonatal Intensive Care Unit, Women and Infants Hospital of Rhode Island, 101 Dudley Street, Providence, RI 02905, United States

ARTICLE INFO

Article history:
Received 19 June 2014
Accepted 23 June 2014

Keywords:
Neurovascular unit
Blood brain barrier
Hypoxia–ischemia
Hypothermia
Hypoxic–ischemic encephalopathy

ABSTRACT

Therapeutic hypothermia is the only treatment that has been shown to be of benefit to infant's ≥36 weeks of gestation with hypoxic–ischemic encephalopathy. The evidence for the benefit is based on multiple, well-designed randomized clinical trials. Based on this data, the use of therapeutic hypothermia has been widely disseminated throughout the neonatal community. An important concept in hypoxic–ischemic brain injury is the functioning of the neurovascular unit which links neurons, non-neuronal cellular elements and the capillary endothelial cells to promote optimal barrier maintenance between the brain and systemic circulation, regulation of blood flow and neuro-immunologic functioning. Hypoxic–ischemic injury can trigger increased permeability of the blood-brain-barrier via molecular events within the neurovascular unit and initiate pathways to brain injury. In addition, exposure of the brain to cellular elements from the systemic circulation can further propagate the neuro-inflammatory response. The influence of temperature on injury to the neurovascular unit has received relatively little attention. This review will focus on one component of the neurovascular unit, the blood-brain barrier and its constituents. Specifically, this review will address the effects of hypoxia–ischemia and temperature on the neurovascular unit and potential knowledge gaps which may serve as areas for further investigation.

1. Introduction

Neonatal encephalopathy is a clinical diagnosis to describe infants with manifestations of cerebral dysfunction and may be linked to serious adverse long term outcomes ranging from developmental and behavioral problems, cerebral palsy, sensory deficits, severe cognitive delay and potentially death [1]. Neonatal encephalopathy has multiple etiologies such as brain malformation, hemorrhage, infection, inflammatory response, toxin exposure, maternal medications and hypoxia–ischemia. Establishing an etiology for the encephalopathy is a high priority after birth since encephalopathy associated with hypoxia–ischemia (HIE) is potentially modifiable by the use of therapeutic hypothermia. Modest reductions in temperature (3–4 °C) are an efficacious neuroprotective treatment for HIE and have underscored the importance of temperature in the care of critically ill neonates. There have been tremendous advances in understanding the pathogenesis of hypoxic–ischemic brain injury including multiple pathways (excitotoxicity, oxidative stress, brain inflammation and accelerated apoptosis) potentially culminating in injury [2]. In contrast, there has been relatively little investigation of injury to the cerebrovasculature and the associated blood-brain barrier (BBB) which may also trigger or modulate the extent of tissue injury. This review will examine the effects of hypoxia–ischemia on the neurovascular unit and how temperature may modify these effects. The neurovascular unit is often used to characterize neuro-glial-vascular coupling and includes neurons, other supporting cell types (astrocytes, microglia, oligodendrocytes) and the vascular supply; its purpose is to integrate barrier integrity, regulation of blood flow, and neuro-immunologic functioning [3]. For this review the neurovascular unit will be limited to the components of the blood-brain barrier (capillary endothelial cells, tight junctions, pericytes, astrocytes and the basement membrane). As background, the effects of reduced and elevated temperature on the outcome of infants with HIE will be reviewed. The term hypoxic–ischemic encephalopathy (HIE) will be used although it is acknowledged that there are differing opinions regarding the appropriateness of this term [4,5].

2. Effects of hypothermia on newborns with HIE

Since 2005 there have been 6 large randomized trials to determine if therapeutic hypothermia reduces death or major disability among infants greater than or equal to either 35 or 36 weeks of gestation with HIE [6–11]. These trials have more features in common than differences and have facilitated meta-analysis of the results. A total of 1391 infants have been enrolled and 691 infants have undergone hypothermia therapy. All infants were enrolled at <6 h of age and inclusion criteria

Abbreviations: HIE, hypoxic–ischemic encephalopathy; BBB, blood-brain barrier; CSF, cerebral spinal fluid; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; LPS, lipopolysaccharide.

* Warren Alpert Medical School of Brown University, United States. Tel.: +1 401 274 1122 44721; fax: +1 401 453 7571.
E-mail address: alaptook@wihri.org.

http://dx.doi.org/10.1016/j.earlhumdev.2014.06.008
0378-3782/

of each study included a surrogate of impaired placental gas exchange (most commonly fetal acidemia on a cord blood gas or a blood gas within the first hour of life) and manifestations of moderate or severe encephalopathy on a neurological examination. Half of the trials used a cerebral function monitor to acquire electrophysiological confirmation of encephalopathy. Therapeutic hypothermia was achieved with either a combination of head and body cooling or whole body cooling alone. Core temperatures were a degree lower in the whole body cooling trials (33–34 °C) compared to combined head/body cooling (34–35 °C). Hypothermia treatment was used for 72 h followed by gradual rewarming. Control infants were cared for by usual care practices with goal core temperature at or near 37 °C.

The primary outcome in each trial was death or disability which was assessed between 18 and 24 months. Disability was typically severe and included any of the following: motor impairment (indicated by a Gross Motor Function Classification score), cognitive delay (using either the Bayley Scales of Infant Development, Griffiths assessment or the Gesell Child Development Age Scale) and neurosensory deficits (blindness or hearing impairment). A number of meta-analyses have been published to merge results across all large trials. The results of Tagin et al. assessed outcomes among 1214 patients which represented 87% of enrolled infants [12]. Death or disability was present in 63% of controls and 48% of hypothermic infants leading to a risk ratio of 0.76 (95% confidence intervals, 0.69–0.84). These trials demonstrated that HIE is a modifiable condition and established therapeutic hypothermia as the only evidenced based treatment available. It is not a perfect treatment since the number needed to treat to avoid one infant with death or a major disability is 7. Additional information regarding secondary outcomes can be reviewed in the meta-analysis of Tagin et al. [12].

3. Outcomes of infants with hyperthermia following HIE

There has been long standing concern about elevated temperatures at or soon after birth in neonatal medicine. Much of the literature on this issue does not report infant temperatures, and associations between temperature and infant sequalae often reflect maternal temperature. Infants exposed to maternal fever with or without epidural analgesia have a greater likelihood of a low 1 min Apgar score, poor respiratory effort, and the need for bag-mask ventilation in the delivery room [13,14]. A case–control study demonstrated that intra-partum fever, which was unlikely to be infectious in origin, was associated with a 3.4-fold risk of unexplained early onset seizures in term infants [15]. In a prospective cohort of 4915 low risk women in labor at 36–41 weeks, intra-partum fever occurred in 6.8% and encephalopathy was diagnosed in 3.2/1000 births [16]. After adjustment for covariates, fever was associated with neonatal encephalopathy (odds ratio, 4.7, 95% confidence interval 1.3–17.4). Similar associations were derived from a population based case–control study in Washington State [17]. In a case–control study comparing 46 children with disabling cerebral palsy and 378 randomly selected controls, maternal fever during labor was associated with an increased risk of cerebral palsy (odds ratio 9.3, 95% confidence interval 2.7–31.0) [18].

The non-cooled control group of the NICHD Neonatal Research Network whole body cooling trial provided an opportunity to examine if elevated infant temperatures are associated with worse outcomes at 18–22 months among infants with HIE [19]. Temperature control for non-cooled infants was by a radiant warmer initially servo-controlled to maintain abdominal skin temperature between 36.5 and 37.0 °C; subsequent adjustments of the servo control was done in response to higher or lower core temperatures (typically axillary) via each participating center's guidelines. All infants had an esophageal temperature probe positioned in the lower third of the esophagus and was used only to record a consistent core temperature among study infants. Each infant had up to 19 temperature measurements during the 72 h intervention (corresponding to the interval of hypothermia for the cooled group). A surprising observation was the frequency of elevated esophageal temperatures during the 72 hour intervention. The mean esophageal temperature of all control infants over 72 h was 37.2 ± 0.7 °C (25th and 75th percentiles; 36.9 °C and 37.5 °C, respectively). There were 1690 esophageal temperature values (191 missing values) and 63%, 22% and 8% were >37 °C, >37.5 °C and >38 °C, respectively. Temperature was analyzed as a predictor of death or neurodevelopmental outcome by determining the mean of the highest quartile, median, and mean of the lowest quartile of esophageal temperatures for each infant (Fig. 1). Using logistic regression and adjustment for co-variates, the odds of death or moderate/severe disability was increased 4-fold for each 1 °C increase in the mean of the highest quartile of esophageal temperature; similarly, the odds of death alone was associated with a 6.2-fold increase (Table 1). For the median esophageal temperature, the odds of death alone were increased 5.9-fold for each 1 °C increase. Associations between elevated temperature and greater odds of death or an IQ < 70 persist even at school age among infants who were followed to 6–7 years of age [20].

Parallel observations have been reported for the non-cooled control infants (n = 110) from the CoolCap trial [21]. Specifically 34 control infants had rectal temperatures ≥38 °C at any time during the 76 hour intervention and 28 had an unfavorable outcome. Among the 76 infants with all rectal temperatures <38 °C, 45 had an unfavorable outcome. These results lead to a 3.2-fold increase in the odds of an unfavorable outcome associated with a temperature ≥38 °C (95% confidence interval 1.2–8.4).

The association between elevated temperature and death or an adverse neurodevelopmental outcome during childhood could suggest

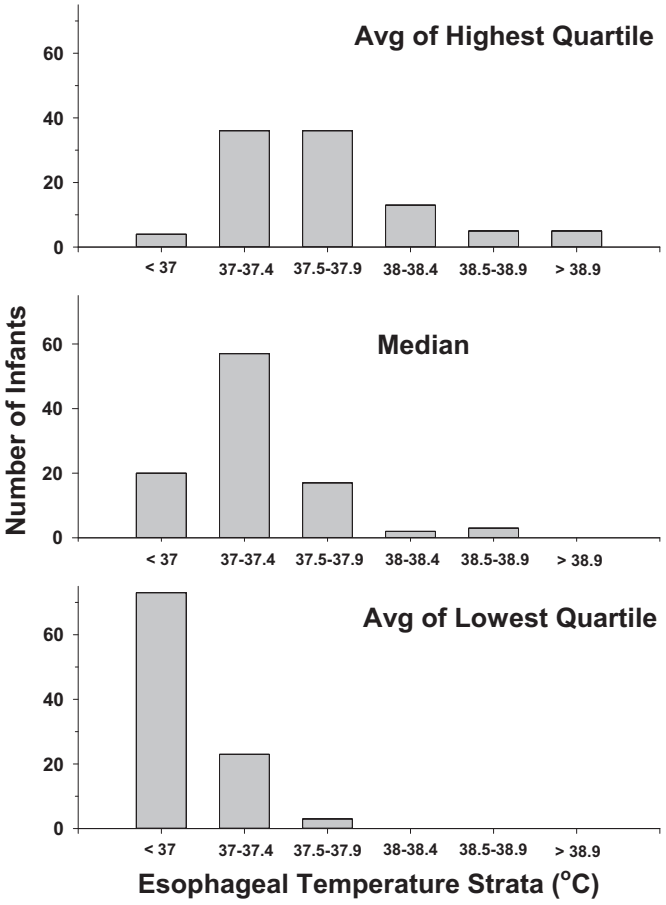

Fig. 1. Distribution of control infants among strata of esophageal temperatures for the mean of the highest quartile, median and mean of the lowest quartile of temperatures. The strata are in 0.5 °C increments to facilitate viewing of the distribution of the data. Reproduced with permission from Pediatrics, 122(3):491-499, Copyright 2008 by the AAP.