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Acute brain injury and therapeutic hypothermia in the PICU: A rehabilitation perspective

Ericka L. Fink[a,*], **Sue R. Beers**[b], **Mary Louise Russell**[c], and **Michael J. Bell**[a]

[a]Department of Critical Care Medicine, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Faculty Pavilion, 2nd floor, Pittsburgh, PA, USA

[b]Department of Psychiatry, University of Pittsburgh, Oxford Building, Rm. 724, Pittsburgh, PA, USA

[c]Department of Children's Rehabilitation Services, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, 2nd floor, Pittsburgh, PA, USA

Abstract

Acquired brain injury from traumatic brain injury, cardiac arrest (CA), stroke, and central nervous system infection is a leading cause of morbidity and mortality in the pediatric population and admission to inpatient rehabilitation. Therapeutic hypothermia is the only intervention shown to have efficacy from bench to bedside in improving neurological outcome after birth asphyxia and adult arrhythmia-induced CA, thought to be due to its multiple mechanisms of action. Research to determine if therapeutic hypothermia should be applied to other causes of brain injury and how to best apply it is underway in children and adults. Changes in clinical practice in the hospitalized brain-injured child may have effects on rehabilitation referral practices, goals and strategies of therapies offered, and may increase the degree of complex medical problems seen in children referred to inpatient rehabilitation.

Keywords

Cardiac arrest; traumatic brain injury; hypothermia; child

1. Introduction

Acquired brain injury from traumatic brain injury (TBI), cardiac arrest (CA), stroke, and central nervous system (CNS) infection is a leading cause of morbidity and mortality in the pediatric population and admission to inpatient rehabilitation [22,81,112,125,126,140]. The epidemiology of acute brain injury and frequency of hospital mortality and morbidity in children are summarized in Table 1.

Neurological morbidity in survivors is varied in severity, can be long-lasting, and includes deficits in motor, speech, cognition, sensory, and behavior domains [90]. Initial injury and patient characteristics including injury severity, etiology, type (focal vs. diffuse), location, patient age and sex, socioeconomic status, and factors related to resuscitation, critical care, and rehabilitation all may affect outcome [6,14,89]. Developmental stage at the time of injury has large effects on outcome with regard to capability to gain or re-gain skills and

[*]Corresponding author: Ericka L. Fink, MD, Department of Critical Care Medicine, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Faculty Pavilion, 2nd floor, Pittsburgh, PA 15224, USA. finkel@ccm.upmc.edu.

potential for neuroplasticity [10,71,80,87,109,123]. With the exception of pediatric TBI, which has evidenced-based medical treatment guidelines, clinical care remains supportive for children with acute brain injury [2].

Mild (32–34°C), induced hypothermia (HT) has been presumed to be effective in mitigating secondary injuries after cerebral ischemia and trauma because it can influence multiple pathways that may be injurious. In contrast, more targeted therapies (e.g., excitatory amino acid receptor blockade, steroids) have failed in clinical trials, presumptively because pathological aspects of injury cascades are redundant. HT affects multiple cell death pathways known to occur after traumatic injury. HT decreases inflammation, cellular metabolism, oxidative and nitrosative stress, edema formation, and can down regulate effectors of apoptosis. HT has shown efficacy in decreasing neurological injury in a variety of experimental acute brain injury models [21,47,106,137]. In the early 2000s, landmark randomized, controlled trials (RCTs) have raised the profile of HT as a neuroprotectant after CA [19,91] such that mild HT is recommended by the American Heart Association and used increasingly in clinical practice in adults who remain comatose after resuscitation from ventricular-arrhythmia-induced CA to decrease neurological morbidity [99]. The neonatalogy community has embraced the positive findings of HT for 72 h in full-term infants with hypoxic-ischemic encephalopathy presenting at the time of birth [53,118] The neuroprotective potential of mild HT in children with acute brain injury is under evaluation in TBI and CA [4,62,63] and is virtually the only therapy currently in Phase III trials. Current recommendations for the clinical use of HT in children with acute brain injury are summarized (Table 2).

Therapeutic HT is not without risk to the patient. The risks of adverse events with HT are dose-dependent (lower temperature and greater duration of hypothermia lead to increased risk), and include electrolyte disturbance, arrhythmia, coagulopathy, infection, prolonged drug metabolism effects (e.g., sedatives, neuromuscular blockade), over-cooling below target temperature, rapid re-warming, and shivering [107]. Over-cooling increases the risk of adverse events during HT, and rapid re-warming can negate the neuroprotective benefit received during HT and increase the risk of hyperthermia, which has been shown to be detrimental in acute brain injury [56,76,96]. Deep (< 20°C) HT, employed in surgery for correction of congenital heart disease, results in a profound leftward shift of the oxygen dissociation curve (thereby making hemoglobin less likely to release oxygen to tissues) which may be associated with movement disorders observed later in the hospital course or during rehabilitation [35,50,74,78,88]. Finally, the application of HT to critically ill children often requires the use of neuromuscular blockade for varying durations, which increases the likelihood of weakness [34,52,54,97].

The objective of this article is to review the contemporary clinical use of HT in children with severe acute brain injury and discuss potential effects on rehabilitation and outcome.

2. Clinical use of HT

2.1. TBI

In experimental models of TBI, HT can decrease brain edema, intracranial pressure (ICP), cell death, and improves outcome [27,38] with the degree of effectiveness of HT dependent upon the injury model, timing of HT initiation, temperature target, duration, and re-warming characteristics [82,111]. Events such as hypoxia, hypotension, fever, and seizure may render treatment with HT ineffective [3,111]. In clinical practice, HT has universally been associated with decreased ICP in all studies [4,28,129]. Yet, conflicting results have been found in its ability to improve neurological outcome and/or survival. In a single center randomized-controlled trial, adults with severe TBI and presenting Glasgow coma scale

(GCS) 5–7 had improved outcomes after 24 hours of mild HT versus the normothermia group, but there was no difference in outcome for subjects presenting with GCS 3–4 [83]. Disappointingly, a subsequent multicenter RCT failed to demonstrate a benefit with 48 hours HT [28]. Systematic reviews conclude that there may be a benefit providing HT in severe TBI in adult victims, and that discrepant results in available clinical trials may reflect differences in patient injury severity, etiology of TBI, occurrence of secondary insults, details in the application of HT, and differences in the inter-facility execution of care [5,26,32,68,85,86,104]. Ensuing studies are underway to answer this important question in the US and Europe.

A phase II multi-center RCT in children with severe TBI using 48 hours mild HT found that in comparison to the normothermia group, children receiving HT had decreased mean ICP but a tendency to have increased ICP during re-warming, increased arrhythmias (possibly due to electrolyte and volume depletion), and a trend toward improved cognitive ability at 6 months (Adelson et al.) [4]. Subsequently, a multi-center RCT of mild HT for 24 hours in children with severe TBI reported a trend toward increased mortality in the intervention group (Hutchison et al.) [63]. This study highlighted some of the risks associated with HT. Authors found that the normothermia group had increased use of hypertonic saline versus the HT group for ICP control, wide variation in time to target temperature in the HT group, and increased prevalence of hypotension in HT patients during re-warming [63]. Both studies had similar target temperatures (32.5°C) and re-warming rates (1°C every 4 h) but actual time to target temperature ranged from 10–14 h from injury and re-warming duration averaged 16–18 h with a large variation seen in the Hutchison et al. trial. Passive re-warming was used in the phase II trial while it was unclear what re-warming method was used in the phase III trial. Questions remain – would HT be effective in severe TBI if it was applied for longer durations, shorter durations to target temperature are achieved, and slower re-warming rates were used and rigorous prevention of hypotension and aggressive treatment of increases in ICP that may accompany re-warming were considered. A multi-center RCT using 48 hours of mild HT versus normothermia in children with severe TBI is underway, powered to detect a significant difference in mortality. Strict entry criteria (e.g., children with significant hypoxia, hypotension, prolonged time to enrollment, or inflicted (or intentional) TBI (iTBI) are excluded) as well as a more conservative re-warming plan are in place. HT for patients with iTBI has not been studied, but a RCT is planned (personal communication, Rachel P. Berger, MD, MPH). iTBI has a unique pathophysiology that often combines TBI with global hypoxia-ischemia and seizures, which are thought to contribute to the particularly poor outcomes seen in these patients [12].

3. Global hypoxia-ischemia

Children with global hypoxic-ischemic injury from CA have dismal survival to hospital discharge (13% for out-of-hospital and 24% for in-hospital) and survivors have less potential for recovery with rehabilitation than children with severe TBI [44,141]. The pathophysiology of 90% of CA in children is asphyxia, and involves the sequence of hypoxia, bradycardia, acidosis and then ischemia (or no blood flow) [141]. Pre-clinical studies using HT after asphyxial CA have been encouraging in terms of providing neuroprotection [60,136]. Although somewhat different pathophysiologically, HT has shown efficacy in decreasing brain injury and improving survival after birth asphyxia in neonates and arrhythmia-induced CA in adults. In full-term newborn infants, whole body mild HT for 72 hours decreased the combined outcome of mortality and moderate or severe neurological injury versus normothermia after birth asphyxia from various etiologies including CA, stroke, and maternal hemorrhage [118]. Similarly, localized head cooling for 72 hours decreased mortality and severe neurological injury in moderately but not severely injured neonates [53]. In two multicenter RCTs, adults remaining comatose after ventricular

arrhythmia-induced CA, 12 and 24 hours of mild HT decreased neurological morbidity in survivors [19,91]. Re-warming in the adult CA and neonatal asphyxia studies was faster than in the TBI trials, most commonly using a rate of 0.5°C/h. Both passive and active re-warming (increasing the set point on the cooling blanket) were used.

The American Heart Association recommendations from 2005 state that consideration of mild HT for 12–24 h in children comatose after return of spontaneous circulation [1,98]. Two retrospective studies found that clinicians were applying HT in the sickest children surviving CA without clinical benefit [39,46]. A prospective multi-center RCT comparing mild HT and normothermia after CA is now enrolling children and has support from the pediatric community (personal communication, Frank Moler MD, MS) [58].

4. Congenital heart disease surgery

Children with congenital heart disease (CHD) are at increased risk of brain injury pre-, peri-, and postoperatively [40,92] with studies demonstrating increased risk of learning disabilities, behavior problems, and attention deficit hyperactivity disorder in survivors [132]. Preoperatively, newborns with CHD have increased evidence of stroke, white matter injury, and abnormal brain metabolism compared to newborns without heart disease [93]. Intraoperatively, deep hypothermic circulatory arrest (DHCA) (15–20°C) is required for some complex surgical procedures and has been implicated as a source of brain injury, seizures, and abnormal long-term neurodevelopmental outcome [17,18,69,100,135]. During deep HT, hemoglobin affinity for oxygen is increased and there is impaired oxygen delivery to tissues and decreased cerebral blood flow[8,55,101,130]. Duration of deep HT with or without circulatory arrest and increased age at surgical correction have been associated with injury to the basal ganglia resulting in movement disorders [35,36,43,74,88,134]. Postoperatively, secondary neurologic injury may occur from hypoxic-ischemic insults (e.g., low cardiac output syndrome), fever, or seizure [41]. Children have increased risk of stroke post-operatively that is associated with older age at surgery, longer duration of cardiopulmonary bypass, and need for re-operation [40].

5. Stroke

Stroke occurs in children less frequently than adults, with half presenting with primary ischemia and the other half with primary hemorrhage, and occurs more frequently in neonates than older children [20,70]. Only one-third of children with stroke experience good recovery of neurological function. However, neurologic morbidity and mortality rates are 55% and 10% [81]. Poorer outcome has been associated with younger age, size of ischemic stroke, hemorrhagic vs. ischemic stroke, and altered mental status or seizure at presentation [61,81]. In comparison, adults experience 14–20% mortality and up to 71% have impaired speech and 31% require assistance with activities of daily living [24].

Experimentally, HT decreases brain injury from stroke by affecting injury-initiated cascades, leading to preservation of energy reserves, and decreased glutamate release, free radical generation, inflammation, blood – brain barrier permeability, and cell death [72, 142]. Pilot studies in adults with ischemic stroke have demonstrated feasibility of using HT for neuroprotection [33,57,73,117,120]. Similar to TBI, HT may have a role in treating increased ICP if ICP monitoring is employed [98].

6. Other uses of therapeutic HT in the ICU

Therapeutic HT is being studied in other disease states associated with brain injury including meningitis, encephalitis, and liver failure-related cerebral edema [108,127]. For example, HT decreased inflammation in experimental models of meningitis as evidenced by decreased

serum nuclear factor-kB (a marker of increased inflammation) and cerebrospinal fluid C-tau, and CNS white blood cell response. HT also attenuated oxidative stress, brain edema and ICP [7,65,66,103,113]. Case reports exist in humans but there have been no prospective studies [31,94,139]. Intracranial hypertension in liver failure occurs secondary to cytotoxic edema from abnormal cellular osmoregulation, with the accumulation of ammonia and glutamine in astrocytes [23,77,128]. In addition, vasogenic edema transpires from increased cerebral blood flow due to impaired cerebral autoregulation, which is hypothesized to originate from increased circulation of nitric oxide, endotoxin, and inflammatory cytokines [128]. HT attenuates these events and has been used in humans to decrease ICP, possibly extending the patient's window of opportunity for transplantation [67]. The U.S. Acute Liver Failure Study Group recommended the consideration of mild HT for refractory intracranial hypertension that fails to respond to mannitol based on promising observational but not interventional studies [121]. Moreover, patients with hepatic encephalopathy from liver failure have varying degrees of altered mental status, cerebral edema, and intracranial hypertension. Those who successfully receive transplants may require rehabilitation secondary to malnutrition, de-conditioning, and neurological deficits [30,37,105].

7. How might hypothermia affect specific rehabilitation needs?

There are no studies in children with acute brain injury randomized to HT or normothermia that have set out to answer this question. However, preliminary imaging studies in neonates with hypoxic-ischemic encephalopathy who were randomized to HT or normothermia demonstrated regional variation in neuroprotection that may be dependent on the method of cooling and severity of initial injury. One study compared infants with whole body HT, head-only cooling, and normothermia. They found that both cooling methods decreased the number of basal ganglia and thalamic lesions as compared with normothermic controls on magnetic resonance imaging (MRI), but only in the moderate injury group vs. severe injury group [116]. Conversely, Inder et al. found that whole body HT preferentially protected cortical gray matter but not the basal ganglia or cortical white matter as seen on MRI performed within the first week after birth [64]. Birth asphyxia has various etiologies including CA and infection, and some infants in these studies were premature, who are known to have similar (basal ganglia and thalamus) and different (premature infants are more susceptible to intraventricular hemorrhage and leukomalacia) regions of brain especially vulnerable to hypoxia-ischemia as well as developmentally-related differences in baseline brain imaging findings compared to older infants and children [45]. Infants and children surviving CA frequently have basal ganglia and cortical injury, and prospective imaging studies that examined patterns of injury and longer-term neurological outcome are needed in children with acute brain injury [25,59].

Finally, we speculate that improved neurological outcomes in adults with CA from ventricular arrhythmia who received HT may also be the result of improved quality of CPR and implementation of protocols for patient care [110,122]. It is unknown if advances in resuscitation and post-resuscitation care will result in more survivors and what long term outcomes they will attain. Pediatric neurologists and physiatrists generally defer final classification of a child's long term outcome after brain injury for up to one year. Parents and clinicians frequently request the supportive care necessary for a severely brain-injured child to attain readiness for rehabilitation, such as feeding tubes and tracheostomy with or without mechanical ventilation. This has led to more children requiring therapy for spasticity, dysautonomia, and coma awakening, for which there is little research in children. Such patients may require relatively longer time periods for paralyzation and sedation in the acute phase of injury. These children would be at increased risk for complications of immobility-contracture and decubitii formation.

8. Implications of HT on longer term outcome after TBI

Rehabilitation interventions for patients surviving TBI in the acute care setting include complication prevention, positioning, and cognitive and communication remediation [115]. Complications to be prevented include contracture and decubiti formation. Early institution of physical therapy and other treatments (e.g., Botulinum toxin injection to affected limbs, baclofen administration) can limit disability from contractures and frequent changes in the positioning of the child can prevent decubiti formation. Placing the child in side lying or prone may inhibit primitive posturing patterns. Bed and mattress modifications include the use of modified beds, such as Clinitron beds and modified mattresses, such as alternating air pressure mattresses. To assist with cognitive and communication remediation, family members and staff personnel can orient the child to his/her surroundings. In the acute care setting, an attempt is made to determine the patient's rehabilitation needs. Criteria exist to ascertain inpatient rehabilitation needs of children after TBI including injury severity, previous medical conditions, cognitive functioning, and need for caregiver training [114].

The cognitive deficits that remain after TBI in a child discharged from rehabilitation are now well characterized in the literature [15]. Apart from severity of injury, age younger than five years and an adverse family environment are related to persistent sequelae of head injury. Within the cognitive domain, intellectual ability as measured by conventional, standardized tests, frequently shows a trend of recovery after severe head injury and eventually approximates the normal range in most children. However, deficits in explicit memory and learning, attention, and executive functions such as planning and self-regulation frequently persist despite the apparent recovery of intellectual ability. Residual memory problems also contribute to reduced academic achievement in children following severe head injury. Finally, executive functions, as measured by laboratory tasks such as planning, metacognitive measures such as estimating one's learning and retention, and self-regulation of behavior in daily activities as rated by parents and teachers, are frequently impaired over long intervals after severe head injury. Importantly, some studies have reported unexpected late declines in cognitive skills such as working memory and attention. Adaptive functioning in relation to age expectation can also decline following severe head injury [15].

To date researchers have proposed such interventions such as medications [16] or rehabilitation programs to mitigate disability after head injury in children, but evidence for their efficacy is generally limited to case reports and group studies that lack randomized, placebo-controlled designs [13,84,102,138]. RCTs that measure the longer term outcome after HT have not been completed and the results of preliminary findings are mixed. In the Hutchison study of HT vs. normothermia for pediatric TBI [63], results suggested a trend to poorer outcome in the HT group based on a comparison of the gross outcome measure Pediatric Cerebral Performance Category score (PCPC) results [48,49]. However, upon careful review one notes several weaknesses in the Hutchison trial with the most significant being that the PCPC was completed over the telephone by the child's parents who were not blinded to the child's treatment arm. In addition, standardized, performance-based cognitive testing, including the Wechsler intelligence scale and Children's memory scale, were completed by only 50% of the subjects in the trial [29,131]. The results of Hutchinson et al. contrast with the results of the HT Pilot Trial completed by Adelson et al. [4]. In addition to the gross measure, Glasgow outcome score (GOS), this trial used comprehensive cognitive testing administered by blinded technicians to assess longer term outcome using the Vineland Adaptive Behavior Scales and the Child Health Questionnaire [75,119,133]. When examining the outcome of children across study time points, there were no significant differences at the 3 month time point, but children in the normothermia group improved faster than that children in the HT group. By the end of the outcome period (6 months), the

HT group exhibited an advantage on tests measuring memory. A description of neuropsychological measures used to characterize cognitive deficits after TBI is beyond the scope of the paper and we refer the reader to a recent publication [79].

For conditions other than TBI, few HT studies have assessed outcome using performance-based instruments, and instead rely on subjective clinician or parents reports to complete categorical outcome measures such as the GOS or the PCPC. The adult CA RCTs employed similar gross outcome measures. One exception is the ongoing TOBY Study, a RCT that investigates the use whole body HT to treat perinatal asphyxia and ensuing hypoxic-ischemic encephalopathy [9]. In addition to mortality, neurodevelopmental impairment will be assessed using a standardized scale of infant development, providing a more fine-grained and objective measure of outcome. A multicenter RCT of HT versus normothermia after pediatric CA is currently enrolling subjects with the primary outcome survival with good neurobehavioral outcome at 12 months.

9. Summary

HT is being used more commonly as a therapy in the ICU for the prevention of secondary neurological injury after acute brain injury in children, although without prospective study it remains unclear if HT will improve longer-term outcomes and mortality. Brain-specific rehabilitation is essential to attain maximum benefit of HT since patient outcome is not often conclusive until up to one year in the developing child with brain injury.

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3. Beers

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Table 1

Epidemiology of pediatric brain injury

	Incidence in children (per 100,000/yr)	Mortality rate[a]	Morbidity rate[b]
Cardiac arrest	OOH: 2.6–19.7 [42] IH: 21–1900 [126]	OOH: 8% [141] IH: 24–34% [126,141,95]	59% [141]
CNS infection	9.5[c]	4–8 [51,11]	18–26% [11]
Stroke	1.3–13 [81]	5–20% [81]	50% [81]
TBI	918–1188 [22]	33% [89]	69% [89]

CNS, central nervous system; TBI, traumatic brain injury; OOH, out-of-hospital; IH, in-hospital.

[a] Mortality at hospital discharge.

[b] Neurological morbidity present at hospital discharge.

[c] National Center for Immunization and Respiratory Diseases / Division of Bacterial Diseases.

Table 2

Summary level of recommendation of mild (32–34°C) HT for neuroprotection in pediatric acute brain injury

	Recommendation	Evidence level [124]
Cardiac arrest	Consider the use of HT for 12–24 h in children comatose after CA [1].	7
CNS infection	No recommendation.	
Stroke	No recommendation.	
TBI	Therapeutic options include the avoidance of hyperthermia and the consideration of HT for refractory intracranial hypertension [3].	7

CNS, central nervous system; TBI, traumatic brain injury; HT, hypothermia; CA, cardiac arrest.

Level 1: Randomized clinical trials or meta-analysis of multiple clinical trials with substantial treatment effects.
Level 2: Randomized clinical trials with smaller or less significant treatment effects.
Level 3: Prospective, controlled, nonrandomized cohort studies.
Level 4: Historic, nonrandomized cohort or case-control studies.
Level 5: Case series: patients compiled in serial fashion, control group lacking.
Level 6: Animal or mechanical model studies.
Level 7: Extrapolations from existing data collected for other purposes, theoretical analyses.
Level 8: Rational conjecture (common sense); common practices accepted before evidence based guidelines.