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Is Hypothermia Therapy An Effective Treatment In Improving Survival Rates In Pediatrics Patients That Have Suspected Brain Injuries?

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Abstract

Objective: The objective of this selective EBM review is to determine whether or not therapeutic hypothermia is an effective treatment in improving survival rates in pediatric patients that have suspected brain injuries.

Study Design: Two randomized control trials and one cohort analysis published in 2015 to 2016 were selected based on their relevance to the clinical question.

Data Sources: Studies were obtained by searching PubMed, OVID, Medline databases. All articles were published in English and peer viewed journals.

Outcome Measured: The outcome measured was survival rates at 12-month post injury compared between the groups that received therapeutic hypothermia or normotherapy in pediatric patients.

Results: All three studies reviewed did not find a statistically significant improvement in survival rates at 12 months with the use of therapeutic hypothermia in pediatric patients with brain injuries. There was a variation between studies on therapeutic hypothermia technique and duration utilized, injury to treatment times, as well as type of brain injury sustained.

Conclusions: The results of the systematic review of the three studies showed that therapeutic hypothermia does not improve survival rates at the 12-month mark following an acute brain injury in pediatric patients at this time. However, it should be stated that further investigation in the subject matter should include similar hypothermia therapy techniques, faster injury to treatment times, and larger sample sizes.

Keywords: Therapeutic hypothermia, randomized, pediatric, traumatic brain injury, drowning, pediatric cardiac arrest.

Introduction

It's cool to be cold, or at least that is the thinking with therapeutic hypothermia. Targeted temperature management (TTM) or hypothermia therapy is the intentional lowering of the core body temperature from its normal temperature of 37°C to a range of 32° to 34°C in an effort to improve brain injury outcomes[1]. Hypothermia has been used to manage problems that arise from global ischemia and reperfusion injuries[2]. Brain injuries can be considered such events and are defined as non-degenerative non-congenital insults to brain tissue that can possibly cause permanent or temporary impairment of cognitive, physical, psychosocial functions with an associated diminished or altered state of consciousness[1].

Brain injuries can be divided into two categories, primary and secondary. Primary brain injuries include direct impacts with the brain such as a concussion, contusion, coup-contrecoup, and diffuse axonal injury. Primary injuries also involve insults to brain tissue such as hypoxia or anoxic injuries either due to an illness, disease process, or cardiac arrest. Secondary brain injuries refer to the changes that occur within hours to days after a primary brain injury. These changes include endogenous cascade of cellular and biochemical events that trigger excessive amounts of the excitatory amino acid glutamate[3]. This excessive amount triggers neuronal cell death and is termed "excitotoxicity"[3]. The destructive cascade appears to be not only dependent on severity, but also age-dependent in which immature cells are more susceptible making pediatric patients more at risk[3].

The severity of a brain injury is also clinically calculated during a neurological assessment called the Glasgow Coma Scale (GCS) where a patient's motor, verbal, and eye response are all rated and scored. A score is ranged between 3 and 15, with 15 being normal. A score of 13-16 is considered a mild injury, 9 to 12 moderate, and 3 to 8 being severe[3].

Brain injuries are the most common cause of morbidity and mortality in children and encompass 90% of all pediatric injury related deaths[4]. In a 2013 study by Robertson et al, it was discovered that across 24 pediatric intensive care units the average bill in treating brain injuries was $46,784 for an average 5.3 day stay[4]. Hospital stays ranged from 1 to 5,324 days and the most expensive bill costing $7.8 million[4].

The issue with managing brain injuries in pediatrics is appropriately treating the secondary injury. Currently, there is no standard of therapy for this secondary process or halting the excitatory process associated with neuronal cell death[3]. However, hypothermia has been shown in experimental trials to be neuroprotective against secondary brain injury by decreasing cerebral metabolism, inflammation, and excitotoxicity[3]. The only absolute contraindication to hypothermic therapy is situations in which aggressive treatment is not warranted[2.] It has been suggested that therapeutic hypothermia be utilized in pediatric brain injuries to protect developing brains and decrease the economic burden associated with these injuries.

Objective

The objective of this selective EBM review is to determine whether or not "therapeutic hypothermia is an effective treatment in improving survival rates in pediatric patients that have suspected brain injuries."

Search Strategy Methods

This investigation looked at two randomized controlled trials (RCT) and one cohort study. Selection for the studies used were based on several factors. The population was any pediatric patient, ages 48 hours old to 18 years old that had suspected brain injuries. The brain injuries included both hypoxic events and physical head trauma. Within the studies reviewed this was demonstrated as children who required chest compressions for at least 2 minutes and were

mechanically ventilated, had a GCS less than 9, or an abnormal CT scan. The interventions in all three studies included the use of therapeutic hypothermia. Typically, this included an array of techniques that centered on cooling a patient's body temperature to between 32°and 34°C for a period of time. This group was compared to patients who underwent normothermic treatment. These patients kept a strict body core temperatures of 36°to 37° C and were strictly monitored. The outcomes addressed in reviewing the studies included individual 12-month post injury survival status.

Studies were obtained by searching PubMed, OVID, Medline Database during 2016. Key words used were "therapeutic hypothermia", "randomized", "pediatrics", "traumatic brain injury", "drowning", and "pediatric cardiac arrest". All articles were published in English and were peer reviewed. The author conducted all the appropriate research on the subject and ultimately articles were selected based on relevance to clinical questions with patient oriented outcomes. Inclusion criteria for articles included pediatric patients ages 18 years old or younger and therapeutic use of hypothermia for a brain injury. Exclusion criteria were absent survival rates at the 12-month mark, older population, and absence of suspected brain injury. The inclusion and exclusion criteria for each article is listed below (see Table 1). Statistical analysis for this review included calculations concerning the control event rate (CER), experimental event rate (EER), relative risk reduction (RRR), absolute risk reduction (ARR), and numbers needed to treat (NNT). All which were calculated by the author using dichotomous data found in each study.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	Number of Patients	Age	Inclusion Criteria	Exclusion Criteria	Withdrawn	Interventions
Beca[5]	RCT	55	1 to 15 y.o.	Children who could be randomized, mechanically ventilated, GCS less than 9, and who had a abnormal CT scan	Children who could not be randomized within 6 hours, who had penetrating brain injury, who had fixed dilated pupils with GCS of 3, had a cervical spinal cord injury, had a disability prior to injury, acute epidural hematoma, refractory shock, or suspected non-accidental trauma (NAT).	5	Induced therapeutic hypothermia 32-33◦C for 72 hours, rewarmed after 72 hours. Rate of rewarming 0.5◦C every 3 hours
Moler[6]	RCT	295	48 hours old to 18 y.o.	Children with cardiac arrest that required chest compressions for at least 2 minutes and remained on dependent on mechanical ventilation	Inability to randomize within 6 hours, GCS score of 5 or 6, decision by clinical team to with withhold aggressive treatment, or sustained major trauma	8	Hypothermia 32.0 - 34.0◦C for 48 hour, rewarmed over 16 hours or longer to 36.8◦C for a total of 120 hours TTM
Moler[7]	Cohort	74	48 hours old to 18 y.o.	Children who sustained chest compressions for at least 2 minutes and remained comatose on a mechanical ventilation, and was a victim of drowning.	Inability to randomize within 6 hours, GCS score of 5 or 6, motor response subscale 1 to 6 score, lack of commitment or aggressive care, associated major trauma, or drowning in ice covered water	5	Hypothermia 32.0 - 34.0◦C for 48 hour, rewarmed over 16 hours or longer to 36.8◦C for a total of 120 hours TTM

Outcomes Measured

The outcome measured in this review was survival at the 12-month post injury mark. Mortality was compared between the groups that received therapeutic hypothermia to normothermic therapy in pediatric patients with brain injuries.

Results

All three studies gave insight on survival rates of pediatric patients with brain injuries with the use of therapeutic hypothermia versus normothermia. The articles reviewed provided dichotomous data that could be used for calculations of RRR, ARR, and NNT at the desired time frame of 12 months status post injury per individual patient.

In the Beca et al study 92 patients were eligible and 55 were recruited for randomization from 8 pediatric intensive care units (PICU) in Australia, New Zealand, and Canada[5]. This study utilized temperature control through a cooling blanket and IV fluid bolus and monitored via a temperature probe in the esophagus. Hypothermia was maintained for a minimum of 72 hours and rewarming was induced at a rate of 0.5°c every three hours[5]. During the course of treatment 5 had management protocol violations and were removed from the study's results[5]. Of the remaining 50 patients, 24 patients were randomized to therapeutic hypothermia and 26 patients to normothermia[5]. The trial reported that at 12 months 4% of the normothermia group and 13% of the hypothermia group had died. The results were not significantly different ($p = 0.34$)[5]. Extracted information for use of therapeutic hypothermia demonstrated a RRR of 2.25% and an ARR of 9%. The numbers needed to treat was 12, meaning that 12 patients needed to be treated with therapeutic hypothermia in order to see a benefit in survival compared to control (Table 2). Additionally, this study found no difference in complication rates between the two groups of

treatment over the course of 12 months, but did cite that rewarming is a difficult process with hypotension as a common issue[5].

In the Moler et al study in 2015, 295 patients enrolled in the randomized controlled study at 38 children's hospitals across United States and Canada[6]. The therapeutic hypothermia group was managed for a total of 120 hours and achieved 48 hours of temperatures at 33ºC using Blanketrol III cooling units applied anteriorly and posteriorly[6]. Patients were rewarmed over 16 hours or longer to 36.8°C[6]. Temperature was monitored via esophageal, rectal, or bladder device. 3 patients achieved temperature management through extracorporeal membrane oxygenation (ECMO). The normothermia group was aggressively monitored for 120 hours at 36.8°C[6]. At 12 months post incident mortality was assessed amongst 287 patients. Survival was reported as 38% of the therapeutic hypothermia patients and 29% of the normothermia with a relative likelihood of 1.29, a 95% confidence interval (CI) 0.93 to 1.79, (P = 0.13)[6]. Therefore, there was no significant difference between groups. Additionally, obtained information from the study provided a RRR of -12.7% and an ARR of -9.0%. The numbers needed to treat was -11 (Table 2). A negative number means that for every 11 patients who were treated with therapeutic hypothermia there was one fewer incidence of survival in the normothermia group. The study reports that mortality at 28 days status post incident did not significantly differ between the groups, 57% hypothermia vs 67% normothermia (P=0.08)[6]. The primary cause of death for both groups of these patients were brain death or withdrawal of life sustaining therapy due to poor neurological prognosis[6]. The incidence of complications such as bleeding, infection, and arrhythmias were similar among both groups[6]. However, hypokalemia and thrombocytopenia occurred more frequently in the hypothermia group, and renal replacement therapy more

common in the normothermia group[6]. Overall, this study fails to prove that therapeutic hypothermia is beneficial in improving survival rates.

The Moler et al cohort study of 2016 was conducted selectively on pediatric drownings. At 24 PICUs 74 patients were reviewed[7]. This study used 48 hours of temperatures at 33ºC using Blanketrol III cooling units applied anteriorly and posteriorly[7]. Patients were rewarmed over 16 hours or longer to 36.8°C[7]. Temperature was monitored via esophageal, rectal, or bladder device. No ECMO was used. At the individual 12-month status post incident mark, 5 patients' status was unknown. Of the remaining 69 patients, 49% of the hypothermia group and 42% of the normothermia group were alive at 12 months with a 95% CI, 0.68-1.99 (p=0.58) that demonstrate the results were not statistically significant[7]. Extracted data gave a RRR of -11%, an ARR of -6.5%, and a -15 NNT (Table 2). The negative number to treat indicates that for every 15 patients treated with hypothermia there was one fewer incident in the normothermia group. Conversely, this study is limited by the relative small sample size. As with the other studies it coincides to the belief that therapeutic hypothermia does not appear to improve survival rates at 12 months.

Table 2: Comparison of outcomes measured of included studies

Study	Number of Patients	CI	P-value	RRR (%)	ARR (%)	NNT
Beca[5]	50	N/A	0.34*	2.25%	8.70%	12
Moler[6]	287	0.93 - 1.79	0.13	-12.70%	-9.00%	-11
Moler[7]	69	0.68 - 1.99	0.58	-11.00%	-6.50%	-15

*Data based off deaths rather than survival

Discussion

The goal of this systematic review was to determine if therapeutic hypothermia improved survival rates. Therefore, it should be noted that the above studies have their own limitations to proving a true benefit of therapeutic hypothermia. Sample size is a crucial factor for creating statistically significant data. Both Beca et al and Moler et al 2016 contained small sample sizes respectfully. Each had under 70 total participants that were available for review at the end of 12 months[5,7]. Among studies reviewed there was also insight that a variation of conducting therapeutic hypothermia may have occurred and different hospitals might have used different protocols. The time of total TTM varied, methods of conducting the reduced body temperature, method of monitoring, and rewarming process differ just among the three studies reviewed.

Another limitation to the studies in review was time to treatment. The goal of medical therapy is to reduce the secondary injuries associated with a brain injury. In reviews of the Beca et al study the median time from injury to target temperature for hypothermia patients was 9.3 hours[5]. The average timeframe for Moler et al 2016 cohort study was 5.8 hours from return of circulation to treatment initiation[7]. The suspected area of delay to treatment is obtaining consent during a very critical and emotional timeframe. Medical treatment requires providers to obtain consent before initiating treatment. The Beca et al study mentions foregoing consent by mentioning that emergency care research meets criteria to override or defer consent when there is a delay. The study included this type of thinking with 8 patients at 4 of the research sites, as patients were randomized without consent[5]. The deferred consent proved no problems later for both researchers and ethic committees. Initiating therapy sooner could have a positive effect and slow the secondary brain injury destructive process. In turn this could improve survival of these pediatric patients and should be sought after in future studies.

Conclusions

The articles included in this systematic review justify the conclusion that therapeutic hypothermia in pediatric brain injuries does not improve survival rates. However, since the research supports use in the adult population further investigation can be justified. Additional studies are warranted, especially with a reduction in injury to treatment times. Standardized hypothermic techniques in a larger sample could show similar results in pediatric use when compared to adults. The current use of therapeutic hypothermia in children doesn't work as hoped, but it would be a lot cooler if it did in the future.

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