Induced Hypothermia for Neuroprotection Following Cardiac Arrest: A Review of the Literature

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Abstract

Out-of- hospital cardiac arrests carry a mortality rate greater than 90%. Of those that survive the initial cardiac arrest, neurological injury remains a lasting morbidity. In recent years, randomized-control trials have proved the use of induced hypothermia in select patient populations effective at reducing mortality and improving neurological outcomes. This article provides an overview of the relevant literature and provides recommendations for advanced nursing practice.

BACKGROUND

Heart disease remains the leading cause of death among men and women in the United States. Each year an estimated eight-million people suffer a myocardial infarction. [1] Approximately 47% of people with cardiac arrests die before receiving medical assistance. [2] Of the patients that reach the hospital, 11-48% will have a favorable neurological outcome. The remaining patients die or remain in a persistent vegetative state. [3]

Once an individual sustains a cardiac arrest, depletion of cerebral oxygen stores rapidly ensues. Within 20 seconds, the patient loses consciousness. Within five minutes glucose and adenosine triphosphate stores are depleted. [4] During the period of cardiac arrest, membrane depolarization, the influx of calcium ions, metabolic acidosis, glutamate release, and the activation of numerous enzymes occurs. [4] Reperfusion injury occurs once cerebral perfusion has been restored, which causes the release of free radicals, calcium shifts, catecholamine release, and amino acid release that leads to mitochondrial damage. [5] Reoxygenation following cardiac arrest causes further neurological damage secondary to delayed necrosis of the tissue as well as apoptosis of the neuronal tissue. [3] Previous strategies for reducing neurological damage following cardiac arrest have been unsuccessful. Induced hypothermia is the only therapy that demonstrates improved neurological outcomes following cardiac arrest. [67]

The use of induced hypothermia following cardiac arrest was introduced in the 1950's. [89] In the 1990s, promising results in animal studies turned research to the feasibility of hypothermia in humans. Clinical feasibility studies in the late 1990's have proved the use of hypothermia in humans to be safe and effective. [11][1618] Several randomized clinical studies were conducted since that time. [67]

METHODS

A literature search was performed using three electronic databases, CINAHL (1960 to March 2008), SCOPUS (1950 to March 2008), and PubMed (1950 to March 2008). Key words were neuroprotection, cardiac arrest and induced hypothermia. Minimal search limits yielded 1796 citations. Further search limits included randomized or quasi-randomized controlled trials and systematic reviews of the literature. This search produced 939 citations. Citations excluded were those that did not contain original data, did not contain a control group, had historical controls, and used induced hypothermia for something other than cardiac arrest. Selected for review were three randomized control trials. [6710] The studies are summarized in Table 1.

Figure 1

Table 1: Study Comparison

Study	Study Design	Sample Size	Cooling Method	Outcomes		P Value (Difference in rates of good neurological outcomes between groups)
Hachimi-Idrissi [10]	RCT	N=30 HG=16 NT=14	Cooling helmet	Clinically feasible study		N/A
HACA[7]	RCT	N=275 HG=137 NT=138	Cooling mattress and ice packs	Hypothermia 55% good outcome 41% died	Normothermia 39% good outcome 55% died	P=0.009
Bernard et al.[6]	RCT	N=77 HG=43 NT=34	Ice packs	Hypothermia 49% good outcome 51% died	Normothermia 26% good outcome 6% severe disability 68% died	P=0.046

RCT, Randomized control trial; HACA, Hypothermia After Cardiac Arrest Study Group; HG, hypothermia group; NT, normothermia group

REVIEW OF THE LITERATURE

In 2001, Idrissi and colleagues published a clinical feasibility study for mild hypothermia using a helmet device. [10] Thirty study participants were prospectively randomized to the hypothermia group (HG) or normothermic group (NG). Sixteen patients were randomized to the HG and 14 patients were randomized to the NG. Inclusion criteria included patients with asystole or pulseless electrical activity (PEA) of cardiac origin that had return of spontaneous circulation (ROSC). Study participants were 18 years of age or older with a tympanic temperature of greater than 30° C at the time of arrival to the hospital. Other inclusion criteria included a Glasgow coma scale of seven or less, no known coagulopathy, no history of central nervous system depressant drug therapy prior to the cardiac arrest, participants could not be pregnant, and were hemodynamically stable. The researchers defined hemodynamic stability as a systolic blood pressure above 100 mm Hg and a mean arterial pressure of at least 60 mm Hg.

The researchers developed a comprehensive protocol to standardize all patient care for the duration of the study. The study participants received sedation and analgesia to optimize their respiratory status. Researchers utilized mechanical ventilation to maintain pre-determined respiratory parameters. Fluid resuscitation and vasopressor therapy prevented hypotension during the study period. Paralytics utilized for up to four hours during the study period prevented shivering. The researchers monitored bladder and tympanic temperatures every 15 minutes in all patients. Initiation of the study protocol began in the HG once the patient was stable. The helmet device was positioned on the head and neck of the patient's in the HG. This was the only therapy utilized to induce hypothermia. The helmet was replaced every hour to maintain adequate helmet temperatures. Study completion occurred once the bladder temperature reached 34° C or the study duration exceeded four hours. Once the study was complete, the patients in the HG were passively re-warmed over the next 8 hours.

Study results determined that utilization of the helmet device allowed the researchers to reach target temperature in a median time of 180 minutes. The HG had significantly higher mixed venous oxygen content and lower arterial lactate concentrations than the NG. Thirteen patients in each group died. Five deaths occurred due to refractory cardiogenic shock. The remaining 21 patients died secondary to neurological failure within 2 weeks of admission. None of the study participants died during the study. Three patients in the HG survived compared to one patient in the NG. The researchers contribute the low survival rate to the patient population included in the study. Individuals with PEA and asystole historically have a poorer prognosis.

The study results allowed the researchers to determine that the use of a helmet device to induce mild hypothermia post cardiac arrest is feasible, effective, inexpensive, and did not add common complications associated with hypothermia. Application of the helmet device can occur at any point in the resuscitative process and could lead to improvement in neurological outcomes in cardiac arrest patients.

Bernard and colleagues conducted a randomized control trial that included 77 patients randomized to a hypothermia group (43 patients) or a normothermia group (34 patients). [6] The primary study end point was survival to hospital discharge with good neurological recovery. The researchers described good neurological outcome as patients discharged to home or a rehabilitation facility. Inclusion criteria included patients with initial cardiac rhythm of ventricular fibrillation at the time of ambulance arrival, successful ROSC, persistent coma after ROSC, and ability to transfer to participating study center. Men less than 18 years of age and women less than 50 years of age were excluded from participation. Other exclusion criteria included patients in cardiogenic shock (defined by a systolic blood pressure of less than 90 mm Hg despite the use of vasopressor therapy), causes of coma other than cardiac arrest and the lack of an available intensive care unit bed at one of the four

participating study centers.

The day of the month determined patient assignment. Patients were assigned to the hypothermia group on odd days and the normothermia group on even days. Once eligible hypothermia patients were successfully resuscitated, field paramedics began the cooling process by removing the patients clothing and applying ice packs to the head and torso. Normothermia patients received usual pre-hospital treatment.

Once admitted to the emergency department all patients received an initial assessment. Initial treatment included mechanical ventilation for airway protection. Immediately following stabilization, patients received intravenous sedation and paralytics. Mechanical ventilation was adjusted to maintain a partial pressure of arterial oxygen of 100 mm Hg and partial pressure of arterial carbon dioxide of 40 mm Hg. A mean arterial blood pressure between 90 and 100 mm Hg was achieved using epinephrine or nitroglycerin. Unless contraindicated, all patients with electrocardiograms suggestive of acute myocardial infarction received intravenous thrombolytics. Patients with a past medical history or electrocardiogram suggestive of coronary ischemia received heparin. All study participants received a 1 milligram per kilogram bolus of Lidocaine followed by an infusion of 2 milligrams per minute for the first 24 hours in an effort to prevent ventricular arrhythmias. All study participants received aspirin. Serum potassium levels of 4.0 millimoles per liter were achieved with intravenous potassium administration. Subcutaneous insulin administration kept blood glucose levels below 180 milligrams per deciliter.

Initial patient assessment included a 12-lead electrocardiogram, arterial blood gases, serum electrolytes, lactic acid levels and creatine kinase. All testing was repeated 1-3 hours following admission and at hours six, twelve, eighteen and twenty-four. Complete blood counts were measured upon admission and every 12 hours for the first 24 hours. Preliminary temperature measurements were obtained using tympanic or bladder temperatures. Once admitted to the intensive care unit a pulmonary artery catheter was inserted in the majority of patients. In patients with a pulmonary artery catheter, hemodynamic parameters were measured in six-hour increments for 24 hours.

Ambulance personnel initiated cooling for patients randomized to the hypothermia group. Once admitted to the emergency department or intensive care unit patients had ice packs placed to the head, neck, torso, and extremities. Once the core temperature reached 33°C the ice packs were removed. A core temperature of 33°C was maintained for 12 hours. All patients received sedation and paralytics to prevent shivering. Eighteen hours after admission, warming blankets actively re-warmed patients for six hours.

Once the study was completed, patients continued to receive standard intensive care treatment. Patients who regained consciousness and tolerated ventilatory weaning were extubated and transferred out of the intensive care unit. The majority of patients that remained comatose had life support withdrawn. A rehabilitation physician examined all patients that survived to discharge. Patients discharged to home or rehabilitation facilities were considered to have a good outcome whereas patients that died or transferred to a long-term nursing facility were considered to have a poor outcome.

Patients in the hypothermia group had better neurological outcomes than those seen in the normothermia group. Forty-nine percent of patients in the hypothermia group had favorable neurological outcomes as described by the researchers compared to 26% in the normothermia group. The researchers identified two clinical correlations that negatively affected outcomes in the patient populations--age and time of collapse to ROSC. Each two-year increase in the patient's age correlated to a nine percent decrease in the likelihood of a favorable neurological outcome. For each one minute-thirty second delay in the ROSC, the likelihood of a negative neurological outcome increased by 14%. The principal cause of death in both groups was cardiac failure. The mortality rates between the groups (51% in the hypothermia group and 68% in the normothermia group) were not statistically significant (P=0.145).

In 2002, the Hypothermia After Cardiac Arrest Study Group (HACA) published a multicenter randomized control trial comparing mild hypothermia with standard therapy in patients with cardiac arrest secondary to ventricular fibrillation or non-perfusing ventricular tachycardia. The primary study end point was a favorable neurological outcome defined by a Pittsburgh cerebral performance category of 1 or 2 on a five point scale. A score of 1 identified patients with good recovery and a score of 2 was defined as moderate disability. Secondary end points were six-month mortality and complication rates within the first seven days following hospitalization. Two hundred seventy-five patients were randomly assigned to an induced hypothermia group (IH) or normothermia group (NT). [7] One-

hundred thirty seven patients were assigned to the IH group and 138 to the NT group.

Consecutive patients seen in the emergency department with ROSC following cardiac arrest were eligible for participation in the study. Inclusion criteria included patients 18-75 years old with a witnessed cardiac arrest from ventricular fibrillation or non-perfusing ventricular tachycardia and presumed cardiac cause of the initial arrest. The estimated interval from collapse to the first attempt at resuscitation had to be between five and 15 minutes and the ROSC had to be no longer than 60 minutes from the time of collapse. Patients excluded were pregnant, comatose prior to the arrest secondary to central nervous system depressant drugs or tympanic temperature of less than 30°C at the time of admission. Patients responsive to verbal commands following ROSC and prior to randomization were also excluded. Other excluding factors included hypotension (mean arterial pressure < 60 mm Hg) for greater than 30 minutes following ROSC, hypoxemia (arterial oxygen saturation less than 85%) for more than 15 minutes following ROSC. Patients with a terminal illness prior to the cardiac arrest, inability to follow up after hospital discharge, enrollment in another study, cardiac arrest after arrival of emergency medical services and patients with a known coagulopathy were also excluded.

Randomization to the IH or NT occurred by computer-generated assignments based on study location. Individuals involved in the direct care of the study participants were not blinded to the treatment group during the first 48 hours of the hospitalization. Physicians responsible for determining neurological recovery were blinded to treatment groups.

A standardized protocol was used to manage all study participants. Sedation and paralytics ensured comfort and prevented shivering in all patients. The initial body temperature was obtained using a tympanic thermometer. Subsequent temperatures were obtained with temperature sensing bladder catheters. An external cooling device cooled patients in the IH group to 32-34°C for 24 hours from the start of cooling. If the goal temperature was not achieved with the external cooling device within four hours of ROSC, ice packs were added to assist in cooling. Once the target temperature was maintained for 24 hours, patients were passively re-warmed over the next eight hours.

This study proved favorable outcomes in the hypothermia group. Fifty- five percent of patients in the hypothermia group had favorable neurological outcomes compared to 39% in the normothermia group. The researchers determined the number needed to treat to prevent one unfavorable neurological outcome was six patients. The six-month mortality rate was 14% lower in the hypothermia group. Based on the data, the number needed to treat with hypothermia to prevent one death was seven patients.

Complication rates among the groups did not differ significantly. The most common complications seen among the groups included bleeding, pneumonia, lethal or prolonged arrhythmias, and sepsis. Although sepsis was more likely to occur in the hypothermia group, the difference was not statistically significant.

DISCUSSION

A potential limitation of the research is the small sample size of the studies. Small sample sizes limit the power of the data. A second potential limitation observed among the studies included sample bias. Only patients with unstable ventricular arrhythmias were included in the larger Bernard et al. and HACA studies. [67] Although all three studies showed improved neurological outcomes, the HACA study was the only study that demonstrated a statistically significant reduction in mortality rates among the hypothermia group. Based on the morbidity and mortality associated with cardiac arrest, the research provided evidence that induced hypothermia reduces mortality and significantly improves neurological outcomes. Questions regarding the appropriate duration of hypothermia, accurate rates at which to re-warm patients, and whether hypothermia is effective in all types of cardiac arrest, and long-term effects of hypothermia remain unanswered. Larger, multi-center trials are needed to answer questions these questions.

CLINICAL INDICATIONS

In 2003, the International Liaison Committee on Resuscitation released an advisory statement recommending the use of induced hypothermia on unconscious adult patients that have sustained an out-of-hospital cardiac arrest secondary to ventricular fibrillation and have had ROSC. [11] The recommendation states hypothermia should be initiated immediately to achieve a core temperature of 32-34 °C for 12-24 hours. The advisory statement also recommends that induced hypothermia may also be beneficial in other types of cardiac arrest.

The American Heart Association (AHA) released revised advanced cardiac life support (ACLS) guidelines in 2005. The revised guidelines state the use of induced hypothermia

for neuroprotection following cardiac arrest may be beneficial. Based on the guidelines, the use of induced hypothermia may provide neuroprotection in unconscious adult patients that have had cardiac arrest due to ventricular fibrillation. Patients should be cooled to a core temperature of 32-34°C for 12-24 hours following ROSC. The AHA also states the use of induced hypothermia may be beneficial in patients with out of hospital cardiac arrest due to rhythms other than ventricular fibrillation and patients that suffer an in-hospital cardiac arrest. [12]

Although data show the use of induced hypothermia effective in reducing mortality and improving neurological outcomes following cardiac arrest, many physicians and advanced practice nurses are not comfortable ordering hypothermia. A 2005 survey of emergency physicians, critical care physicians, and cardiologists revealed that 87% of the responders had never utilized hypothermia for cardiac arrest. [13] Reasons physicians did not use hypothermia included a lack of significant data surrounding hypothermia, difficulty initiating and maintaining hypothermia, and the lack of mention of its use in previous ACLS guidelines. The literature details reviewed in this manuscript may allow advanced practice nurses to become more comfortable using induced hypothermia in practice.

The advent of improved technologies has made the implementation of induced hypothermia safe, effective and relatively uncomplicated. The advanced practice nurse (APN) must play an integral role in improving patient outcomes, providing quality patient care, and encouraging peers and nursing staff in the implementation of evidence based practice protocols. The APN may accomplish this mission through the development and implementation of treatment guidelines for induced hypothermia in collaboration with physicians and other health care providers.

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