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Pre-hospital Induced Therapeutic Hypothermia Improves Neurological Outcomes

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Pre-hospital Induced Therapeutic Hypothermia Improves Neurological Outcomes

By

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PERMISSION

Title Pre-hospital Induced Therapeutic Hypothermia Improves Neurological Outcomes

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04/12/2012

COVER LETTER FOR SUBMISSION OF NEW MANUSCRIPT

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Subject: **SUBMISSION OF NEW MANUSCRIPT FOR EVALUATION**

I am enclosing herewith a manuscript entitled "Pre-hospital Induced Therapeutic Hypothermia Improves Neurological Outcomes" submitted to "JEMS" for possible evaluation.

With the submission of this manuscript I would like to verify that the above mentioned manuscript has not been published elsewhere, accepted for publication elsewhere or under editorial review for publication elsewhere.

Select Type of Submitted manuscript: Literature Review

For the Editor-in-Chief, I would like to disclose the following information about the project:

This literature review project was conducted under the supervision of Dr. Jody Ralph PhD, RN and the project was my MSN independent project.

Detail of each author with his/her contribution in this paper is as under:

Name of the author and e-mail ID	Types of contribution
Mark Kosten	Author
Dr. Jody Ralph	Advisor/editor

ABSTRACT

Early induction of therapeutic hypothermia may provide better neurological outcomes for survivors of an out-of-hospital cardiac arrest (OHCA). Some community based hospitals and emergency medical services are initiating early use of therapeutic hypothermia as standard protocol. The purpose of this review is to provide an overall description of current literature on the initiation of therapeutic hypothermia in a pre-hospital setting in OHCA. Electronic databases were searched using key terms: Out of hospital, cardiac arrest, cardiopulmonary arrest, hypothermia, therapeutic hypothermia, pre-hospital, induced, emergency medical services, neurological outcomes, improved and early implementation. The electronic databases that were searched are: MEDLINE, CINAHL, PUBMED and EMBASE. Therapeutic hypothermia practice in the pre-hospital setting is becoming more common but remains inconsistently implemented throughout communities. The American Heart Association recommended initiating therapeutic hypothermia in the updated 2005 standards, though the timing is not identified. Induced therapeutic hypothermia initiated pre-hospital can be done easily, safely and without severe side effects. Protocols should be developed in collaboration with a hospital and health system that will continue hypothermia care. Pre-hospital cooling may improve survival and neurological outcomes by early and effective cardiopulmonary resuscitation, initiating cooling procedures and continued hypothermia care in a hospital setting. To understand the timing and effectiveness of implementing TH in a pre-hospital setting more research is needed.

Introduction

Therapeutic hypothermia (TH) is a relatively new treatment used to preserve neurological outcome in persons that suffer a cardiac arrest. Out of hospital cardiac arrest (OHCA) is an increasing problem affecting approximately 295,000 persons each year, yet sadly of those who suffer OHCA, the median survival rate is only 8.4% (Nichol et al., 2010). For those who survive, one of the most devastating sequelae of cardiac arrest is cerebral anoxia and thus, permanent neurological injury. It has been suggested that if this treatment is started pre-hospital patients may have a better neurological outcome. TH has not been initiated in many hospitals let alone pre-hospital for various reasons. Some believe there is not enough data and that no treatment protocols have been developed. However, by providing accurate and up to date information on current TH research, agencies will be well informed regarding the use of pre-hospital TH. Patients that have a cardiac arrest episode with return of spontaneous circulation may have a better neurological outcome by implementing TH.

Purpose

This paper will examine early implementation of TH and how it relates to pre-hospital care. TH may be effective in preventing severe neurological injury, decrease in-patient stays, and reduce morbidity and mortality. Throughout this paper, support for the use of TH will be evidenced by supporting studies and recommended practices. Refer to Appendix A for an informational pamphlet which gives recommendation guidelines.

Background

Globally, sudden cardiac arrest is a significant health concern. In the United States approximately 295,000 OHCA occur each year. The outcome of these patients is poor even with the advances in health technology and resuscitation techniques. Many suggest that patient

mortality remains high due to secondary brain injury and multiorgan failure (Cabanas, Brice, De Maio, Myers & Hinchey, 2011).

With increased awareness of TH, post cardiac arrest therapies can improve patient outcomes. There have been many studies in laboratory animals which suggest that implementing hypothermia shortly after return of spontaneous circulation (ROSC) may improve neurological outcomes, but there have only been a few studies that support this. With various factors incorporated into studies done pre-hospital, there is much controversy on the lack of strong evidence based studies (Bernard et al., 2002).

Hypothermia was first introduced in the 1940's to treat cancer patients. Other studies suggested that hypothermia benefited those who suffered from cardiac arrest and was protective during cardiac surgery. This prompted the standard for intraoperative hypothermia during cardiac surgery but the use for cardiac arrest was not implemented by health professionals. "In 2002 a randomized controlled trial supported the use of induced hypothermia in postresuscitative care for a small group of patients" (Cady & Andrews, 2009, p. 403). "Post cardiac arrest care has significant potential to reduce early mortality caused by hemodynamic instability and later morbidity and mortality from multiorgan failure and brain injury" (Pederby et al., 2010, p. S768).

The American Heart Association (AHA) has developed guidelines to assist health care professionals in developing system protocols for the implementation of TH. According to the AHA, therapeutic hypothermia is the only intervention demonstrated to improve neurological recovery and should be considered on post-cardiac arrest patients with ROSC (Pederby et al., 2010, p. S768).

The AHA developed the "chain of survival" which has had a positive response from communities and may account for higher survival rates. Four links interlock the chain which comprises of: (1) early recognition and access to emergency medical services, (2) early cardiopulmonary resuscitation (CPR), (3) early defibrillation and (4) early advanced cardiac life support (Hinchey et al., 2010). All chains play a significant role and can substantially improve outcomes. From studies done using this chain of survival, urban/suburban emergency medical services showed a doubling of survival between pre- and postimplementation phases. In 2005, the AHA guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care were updated to recommend induction of hypothermia to improve neurological outcomes for patients with ROSC. They also emphasized on minimizing chest compression interruptions and avoidance of hyperventilation (Hinchey et al., 2010).

Although implementation barriers exist, examples of system wide adoption are appearing through press releases emphasizing the need for more wide spread implementation. An example of this was a letter written for Critical Care journal in 2008. It stated "the design of future trials on therapeutic hypothermia, however, seems challenged by the fact that withholding this treatment in a control arm might be considered unjustifiable from an ethical point of view" (Schefiold, Storm & Hasper, 2008, p. 413).

Review of Literature

TH Implementation Practices

There have been several studies that indicate or conclude that therapeutic hypothermia improves neurological outcomes. In 2011, Cabanas et al. conducted a systemic review of the literature which concluded that induced hypothermia improves neurological outcome and is not

associated with adverse effects (Cabanas et al., 2011). Another study in 2009 concluded that it is justifiable to implement prehospital cooling even in the absence of unambiguous evidence to support TH practice. It was suggested that this practice be implemented rather than withheld which may be beneficial while waiting for evidence (Kamarainen, Hoppu, Silfvast & Virkkunen, 2009). In 2002 the New England Journal of Medicine published a study by the Hypothermia After Cardiac Arrest Study Group which showed 55 percent of patients with hypothermia had a favorable outcome, compared to a 39 percent in a normothermia group. They concluded that mild hypothermia increased the rate of a favorable neurological outcome and reduced mortality (The Hypothermia After Cardiac Arrest Study Group, 2002). Ohio's Department of Safety showed a difference of 80% of patients discharged with good to moderate neurological function after initiating TH compared to 77% without TH (Sayre, 2008). Regardless of whether the studies show minimal or significant improvement, all agree; in the absence of adverse effects treatment should not be withheld.

Post Cardiac Arrest Neurological Outcomes

Studies on the effectiveness of TH in post-cardiac arrest patients define neurological outcomes in several ways. In the study by Bernard et al. (2002) the patients, when ready for discharge, were evaluated by a specialist in rehabilitation medicine who was blinded from the treatment group. Base on the results of the evaluation, the patients either had a good outcome, discharged to home or rehabilitation center or a poor outcome viewed as death in the hospital or discharged to a long-term facility (Bernard et al., 2002). Another study done by Kim et al. (2009), evaluated mortality and neurological outcomes by using cerebral performance category (CPC). The patients were divided into four groups. The groups consisted of survivors and non-survivors 1 month after admission and good and poor cerebral performance category 1 month

after admission. The Hypothermia After Cardiac Arrest Study Group defined neurological outcome by using the Pittsburg cerebral-performance category scale. This was rated by 1-good recovery, 2-moderate disability, 3-severe disability, 4-vegatative state and 5-death. At six months post cardiac arrest the patients were evaluated and assigned a category. Patients with a 1 or 2 were viewed as an improved neurological outcome as these patients had sufficient cerebral function to live independently and at least work part-time (The Hypothermia After Cardiac Arrest Study Group, 2002). In 2009, Hinchey et al. used the same CPC scale at time of discharge for evaluation (Hinchey et al., 2010).

TH Mechanism of Action

Patients who have a cardiac arrest may never awaken due to brain injury. Patients resuscitated from out-of-hospital ventricular fibrillation have shown to improve neurological recovery and survival with the implementation and combination of goal directed post-cardiac arrest care. The AHA has identified a post-cardiac arrest care guide. It begins with a patient that experiences a cardiac arrest with return of spontaneous circulation. The next goal is to optimize ventilation and oxygenation. This can be accomplished by maintaining oxygenation greater then 94%, consider advanced airway with capnography and do not hyperventilate. Treat hypotension and keep systolic blood pressure above 90 with intravenous or intraosseous fluid boluses, vasopressors and consider treatable causes of the hypotension. If the patient is unable to follow commands, consider inducing TH. "If the patient is able to follow commands, consider ST elevation myocardial infarct or high suspicion of acute myocardial infarct and hold therapeutic hypothermia" (Peberdy et al., 2010, p. S769).

The physiological effects of hypothermia play a role on the heart, cardiac output, blood pressure and intravascular volume. Hypothermia may cause presence of J waves, prolonged PR, QRS and QT intervals and atrial arrhythmias seen on electrocardiographs (Young et al., 1983). These adverse effects are typically seen when body temperatures are below 30°C. A study done by Gebauer et al. in 2006 concluded that mild to moderate hypothermia reduced cardiac output by 33% and stroke volume by 23%. Despite these reductions, no apparent clinical significance was noted (as cited by Marion & Bullock, 2009). We know that hypothermia in combination with major trauma or sepsis syndrome has increased mortality (Marion & Bullock, 2009). Some health care professionals have verbalized concern that hypothermia may cause adverse effects on coagulation, cardiac function, acid-base stability and the immune system. However, studies that induced hypothermia in patients with stroke and severe head injury show promising results. This is reinforced by a study by Bernard et al. (2010) which suggested that induced moderate hypothermia lasting 12 hours did not show any clinical significance in adverse effects. It did show that hypothermia decreases the pulse rate and increased systemic vascular resistance, but no cardiac arrhythmias were clinically significant. Bradycardia was reported as one side effect, but most suggest that this is a positive beta-blocking effect on the ischemic heart (Sunde & Soreide, 2011).

Studies Supporting the Use of TH

In 2011, the AHA provided data over a nine year period that showed patients who presented with ventricular fibrillation or pulseless ventricular tachycardia had a higher percentage of good outcomes but patients with pulseless electrical activity/asystole had a very low percentage of good outcomes (Whitefield, Coote & Ernest, 2009). From these findings the AHA recommends that patients with initial rhythms of ventricular fibrillation or pulseless

ventricular tachycardia, or patients with a shockable rhythm, with ROSC be considered for TH treatment. Patients with a non-shockable rhythm tend to have a worse prognosis (Dumas et al., 2011).

Potential Complications or Contraindications

Other studies have shown that hypothermia can have adverse effects on platelet and white cell counts with more prolonged periods of hypothermia. In one study, with hypothermia duration of 12 hours, no significant changes to platelet or white cell count were noted (Bernard et al., 2002). Cooled patients are at greater risk for infections due to the suppression of the immune system. This is particularly seen with cooling for several days or more. Bernard et al. (2002) did not show any clinically significant infections. In a recent review by Holzer it was concluded that TH is not associated with more complications than normothermia in comatose cardiac arrest survivors (as cited by Sunde & Soreide, 2011). It has also been shown that hypothermia causes an increase in potassium especially during the rewarming phase. With proper management, studies found that it was not considered to be clinically important (Bernard et al., 2002).

Special Considerations for TH in the Prehosptial Setting

Various methods of cooling out-of-hospital have been identified and several studies have been done on the efficiency. The American Heart Association published a study by Kim et al. (2007) which was a randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4°C normal saline. This study concluded that the infusion of up to 2 liters of 4°C normal saline in the field is feasible, safe and effective in lowering temperature (Kim et al., 2007, p. 3064). The effect of this cooling method on neurological outcome after cardiac arrest should be studied in larger numbers of patients,

especially those whose initial rhythm is ventricular fibrillation. Invasive cooling has been shown to provide rapid induction of hypothermia. This helps in reducing the temperature of target organs, such as brain and heart (Kim et al., 2007). Surface cooling is a non-invasive method of cooling but has shown to be not as effective as it requires more time to reach target temperatures. Although it is easy and simple to use, it may also be not as effective due to human protective mechanisms. Vasoconstriction, shivering and redirection of blood flow away from extremities or skin to prevent heat loss are all conditions that can influence the temperature of the body (Lee & Asare, 2010). Another study by Kamarainen et al. (2008) concluded that infusion of ice-cold fluids significantly reduce temperatures. They also concluded that this infusion during CPR did not negatively affect the chance of achieving ROSC (Kamarainen, Virkkunen, Tenhunen, Yli-Hankala & Silfvast, 2008). A pilot study done by Virkkunen, Yli-Hankala, and Silfvast (2004) found that pre-hospital induction of therapeutic hypothermia with peripheral infusion of ice-cold solution seems feasible. A study by Bruel et al. (2008) stated that "prehospital induction of therapeutic hypothermia using 2 liters of 4°C normal saline during advanced life support was feasible, effective and safe" (p. R31). Most recently, Sunde (2011) stated "Independent of the cooling method chosen, therapeutic hypothermia is easy to perform and without severe side-effects or complications associated with mortality" (p. 251).

Discussion

Many countries like the USA, UK, Austria, Italy and Germany have a low implementation rate of TH, whereas the Netherlands and Scandinavia report as high as 92 percent use. Recently the UK had a significant increase in use of TH due to worldwide effectiveness studies (Sunde & Soreide, 2011). Although recommendations from AHA and other international organizations exist, the general medical community continues to stall

implementation. Many surveys showed that the perceived lack of scientific evidence isn't the main reason for not using therapeutic hypothermia. The surveys indicated that clinicians are more concerned with the lack of staff and cooperation concerning hospital cooling protocols and the technical aspects (Soreide & Sunde, 2008). A survey of EMS directors in 2006 indicated that cooling is infrequent. The study done by Cady (2009) reinforces that any EMS agency should only be initiating TH only if that agency is in cooperation with a hospital program that is capable to continue the hypothermia treatment (Cady & Andrews, 2009). Studies have shown that re-warming these patients too early may be more harmful. Other factors that have influenced the slow implementation of TH in EMS systems include: short transport times, a perception that cooling will not be continued at the receiving facility, lack of refrigeration equipment, and health care providers being too overburdened with other tasks to implement TH (Suffoletto, Salcido & Menegazzi, 2008).

Studies have shown that the early implementation of TH have increased neurological outcomes after a cardiac event has occurred (The Hypothermia After Cardiac Arrest Study Group, 2002). No matter the specifics of each study and the patient population size, they all agree that the implementation of TH is safe with no adverse effects. As discussed, the feasibility and cost of implementing TH into pre-hospital protocols is easy and low cost. With the use of ice packs and ice-cold saline, the only equipment cost is related to a method of cooling the fluids. No special equipment or the necessity of teaching a special procedure to EMS is needed. With the collaboration of a well organized health system and guaranteed continuation of TH implementation, the possibility of improved neurological outcomes is good.

There is some confusion in the timing that TH is applied. Some researchers debate the application of TH can be delayed up to six hours after ROSC while others suggest the earlier

implementation lends itself to better outcomes. Animal studies suggest that early implementation of TH improves neurological outcomes. Some debate the initiation of TH in the pre-hospital environment versus waiting to start TH once arrived at the hospital in a system with short transport times. Others would state the pathophysiology is like a sprained ankle. The sooner ice is applied the better. In a post arrest situation, replacing room temperature fluids with ice-cold fluids and placing ice packs on the patient requires minimal time for the possible benefit of early initiation (Nozari et al., 2006).

The exact timing for optimal outcome is not known. Many believe that the earlier approach started by EMS gives the best chance for improved outcomes. With animal studies showing that cooling before reperfusion reduced mortality and improved myocardial function, further human studies are called for. Even though the exact timing is unknown, TH should only be started within a well-designed health system collaborated with pre-hospital agencies (Skulec et al., 2010).

Certain criteria must be met in order to initiate TH to optimize the results. The literature supports that TH initiated on patients with ventricular fibrillation and pulse-less ventricular tachycardia are the most benefited. Protocols that incorporate these criteria, along with pre-hospital implementation give the best chance for a good survival rate following a cardiac arrest. All the studies reviewed agreed that therapeutic hypothermia is not associated with any more complications than normothermia patients when cooled to an appropriate temperature.

All TH studies, whether animal or human, demonstrate the need for further studies. However, controversy remains if it would be unethical to withholding TH care in a control group. Does therapeutic hypothermia requires evidence base practice to implement? With past studies which give us a clear and biological rationale supporting the earliest possible induction,

would a prospective randomized trial be feasible and justifiable? Stated by Schefold and colleagues, "We may have reached another boundary of evidence-based medicine" (Schefiold, Storm & Hasper, 2008, p. 413). Hinchley et al. (2010) completed a study which looked at the AHA guidelines suggested in 2005. They concluded that "not only were more lives saved but also more patients survived with good neurological outcome" (p. 354). In the community of study, they estimated that an additional 25 lives would be saved annually or 3 lives per 100,000. It is believed that each year 375,000 people in Europe have a cardiac arrest. Using the criteria developed by the AHA recommendations, it is estimated that 30,000 of those people will meet criteria for TH. The Hypothermia After Cardiac Arrest Study Group "believes they are 95 percent confident that treatment with hypothermia would prevent an unfavorable neurological outcome in 1200 to 7500 of these patients" (2002, p. 555).

Recommendations

Although TH is gaining acceptance and implementation is increasing internationally, TH focus must include a strong established system of care. This system of care includes community education in CPR, access to EMS, in-hospital care, and appropriate follow-up following discharge. In order to achieve the ultimate outcome of survivability post cardiac arrest with acceptable neurological outcomes, it is essential that every step of the TH process be optimized. Focus should be placed on solid basics, CPR effectiveness, appropriate monitoring O_2 and CO_2, and continuity of care.

The most recent AHA guidelines from 2005, were developed by a panel of approximately 300 experts. These changes were focused on compression to ventilation ratio, 1-shock versus 3-shock defibrillation, compressions first before early defibrillation for unwitnessed cardiac arrest, minimal interruptions during chest compressions, and emphasis on post resuscitation care which

included therapeutic hypothermia. Implementing AHA guidelines into pre-hospital initiated TH may result in a multidisciplinary approach to improve OHCA. This will be made much more effective when included as part of a community wide approach starting with 911 dispatchers and continuing through the emergency and critical care departments (Hinchey et al., 2010).

Therapeutic hypothermia implemented pre-hospital alone will not improve neurological outcomes. It is crucial that TH protocols be established by a system of care through the continuing care of the patient until discharge. TH started pre-hospital needs to be supported and integrated into the care provided at the community hospital (Cabanas et al., 2011). Well defined implementation plans must be sensitive to local culture and organizational barriers through hospitals and health systems.

Studies done on induced therapeutic hypothermia conclude that hypothermia improves outcomes in patients that are comatose after resuscitation. The outcomes are varied from low to relatively high significance. No matter the size of the study, all call for further studies to determine the optimal time and method for cooling to maximize neurological outcomes (Hammer, 2008).

Is it ethical to withhold induced therapeutic hypothermia? With no known side effects, and no negative outcomes, why isn't this procedure seen done more often? With the medical communities statement of, do no harm, are we causing harm by not implementing? Some call for evidence based research that will support the scientific information to support hypothermia. In order to produce evidence based research, trials would need to knowingly withhold treatment which is unjustifiable from an ethical point of view (Schefiold, Storm, & Hasper, 2008).

Induced therapeutic hypothermia initiated pre-hospital can be done easily, safely and without severe side effects. The protocols should be developed in collaboration with a hospital and health system that will continue hypothermia care. With education focused on the chain link of survival, quality of CPR and hypothermia started pre-hospital, patients that suffer from a sudden cardiac arrest with a rhythm of ventricular fibrillation or pulseless ventricular tachycardia will have an optimal neurological outcome.

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Appendix A

Initiation of mild therapeutic hypothermia post-cardiac arrest: Mild therapeutic hypothermia during transport

INDICATIONS:

- 18 years or older
- Cardiac arrest (requiring CPR)
- Return of spontaneous circulation with systolic blood pressure greater than 90 mmHg. Blood pressure can be maintained either spontaneously or with fluid and vasopressors.
- Unresponsive with GCS less than 10 or motor score less than 4 if intubated.
- Core temperature greater than 34°C

CONTRAINDICATIONS:

- Expected to have a poor outcome due to a prolonged resuscitation attempt.
- Cardiogenic shock as evidenced by systolic blood pressure less than 90 mmHg despite resuscitation and use of high dose vasopressors.
- Uncontrolled bleeding
- Pregnancy
- Do no resuscitation code status
- Post arrest resuscitation from causes other than sudden cardiac death, such as head injury, drug overdose, CVA, pre-existing conditions and end stage diseases.

BEGIN COOLING PROCESS

- Administer 4°C 0.9% normal saline solution rapidly
    - Dose is 40 mg/kg.
    - Maximum dose is 2000 mL.
- Place ice packs in each axilla and the groin at the time of initiation. .
- Maintain core temperature between 32°C and 34°C
    - Record time when core temperature reaches 34°C.
    - If temperature goes below 32°C, remove peripheral ice packs and hold cold saline infusion.
    - Resume when temperature > 32°C.
- Transport to a hospital that will continue hypothermia therapy