Selective Cerebral Cooling Effectively Achieves Mild Therapeutic Hypothermia In Healthy Volunteers

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Objective

To determine the ability of the Excel® Cryo Cooling System to achieve a rapid reduction of cerebral temperature into mild Therapeutic Hypothermia in healthy adult volunteer subjects.

Study Design

Twenty (20) consecutive healthy adult volunteers were enrolled in the study. The Excel Cryo Cooling System (Cryothermic Systems, Inc., Cleveland, Ohio), consisting of a uniquely designed cervical immobilization collar and cooling element, was used to cool subjects. The study protocol called for a recording of baseline tympanic temperature and additional temperature readings every five (5) minutes over a period of eighty (80) minutes. The device used for tympanic temperature measurement was the Kendall Genius™ 2 Tympanic Thermometer. Heart rate was measured several times throughout the study. Heart rate and oxygen levels were monitored using a pulse oximetry device. The EXCEL Cryo Cooling Element was replaced every 20 minutes per manufacturer's suggested protocol.

Results

Of the twenty subjects participating, five were excluded for protocol compliance issues. Fifteen subjects enrolled for data analysis reached an average temperature drop of 1.73°C, with the average time to reach Mild TH of 31.7 minutes. We conclude that the Excel Cryo Cooling System is a safe and effective method for selective cerebral cooling and reaching mild Therapeutic Hypothermia, necessary for neuro-protection in cardiac arrest patients.

Introduction

Sudden Cardiac Arrest (SCA) is known to affect over 380,000 people in the United States each year, and survival to hospital discharge is reported to be just over 11%[1]. The majority of SCA incidences occur out-of-hospital. The high mortality rate can be linked to those patients initially resuscitated from out-of-hospital cardiac arrest, who are admitted to the hospital but die before discharge, where the cause of death is related to the severe neurologic injury attributable to the prolonged period of brain ischemia during cardiac arrest and the reperfusion injury subsequent to return of spontaneous circulation[2].

Hypothermia has been utilized medically for centuries. Numerous clinical studies have demonstrated its use and great benefit during brain trauma. In 2002, the New England Journal of Medicine published two landmark studies, a study conducted in Australia, by Bernard[3], and Hypothermia After Cardiac Arrest Study Group (HACA), by Holzer[4], a study conducted in Europe. These studies proved that inducing therapeutic hypothermia improved outcomes and reduced mortality rates. This was accomplished through in-hospital systemic cooling methods, whereby the body is cooled to between 32-34°C for 12 to 24 hours and then rewarmed.

Mild hypothermia is generally accepted as reducing the brain temperature 0.8° to 3°C. The benefits of cooling are similar within the mild Therapeutic Hypothermia temperature range[5]. Inducing mild cerebral hypothermia as soon as possible post-cardiac arrest provides the following benefits to the brain:

- Reduces the risk of ischemic injury to brain tissue following a period of insufficient blood flow.
- Encourages cell membrane stability during periods of oxygen deprivation
- Helps to reduce reperfusion injury caused by oxidative stress when blood flow is restored
- Reduces intracranial pressure
- Reduces or eliminates free radical production

Studies have shown that although achieving therapeutic hypothermia (TH) in the ICU is beneficial, outcomes can be improved by achieving cooling earlier in the care process, as close to the incident as possible. In 2005, the American Heart Association (AHA) adopted its first recommendation, a Class II recommendation, to cool patients who were resuscitated following cardiac arrest. Cooling is now the standard of care for post-resuscitation patients in the intensive care unit (ICU) setting.

Recent studies show an association between time to cooling and mortality with a 1-hour delay in time to cooling increasing the risk of death by 20%[6], and positive outcomes when therapeutic hypothermia was combined with return of spontaneous circulation within 25 minutes of cardiac arrest[2]. This clearly establishes the need to develop an effective method for achieving consistent, safe and rapid cerebral cooling in the pre-hospital and emergency department settings. In 2010 the AHA increased the strength of its recommendation to a Class 1A, to cool patients as soon as possible post-cardiac arrest and after return of spontaneous circulation (ROSC). The use of cooling is quickly moving to pre-hospital and emergency department applications as recent studies show that early initiation of cooling significantly improves neurologic outcomes and survival rates versus waiting until the patient arrives in the ICU.

The use of TH has also been studied in the settings of acute ischemic stroke and traumatic brain injury (TBI). Both animal[7-14] and human[15] trials have demonstrated benefits from the induction of TH included with the use of thrombolytic therapy. The number of patients suffering from acute ischemic stroke annually is significantly greater than the incidence of survival from cardiac arrest[16], making cooling a very important clinical application. Cerebral cooling also appears to be beneficial in patients with severe TBI. A recently published meta-analysis of 12 studies with 1327 participants supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (Glasgow Coma Scale score ≤ 8) to decrease mortality and improve rates of good neurologic recovery. The report recommended that cerebral cooling be

commenced as soon as possible after injury regardless of initial ICP, or even before ICP is measured.[17] Furthermore, in studying effectiveness of cooling methods and outcomes, selective brain cooling (SBC) was compared to mild systemic hypothermia (MSH) in a TBI study of 66 patients randomized into 3 groups including SBC, MSH and control group. It was shown that the percentage of patients with a good neurological outcome after two years after injury was 72.7%, 57.1% and 34.8% in the SBC, MSH and control groups' respectively.[18]

Three currently available methods for early cooling in the pre-hospital and ED settings are the Excel® Cryo Cooling System, application of ice/chemical ice packs on the groin and axilla, and IV infusion of chilled saline. Ice/chemical packs have known issues of movement and unreliable placement; inconsistent cooling based upon patient size/weight; local skin irritation; and shunting of blood from peripheral vessels to the central circulation, thereby preserving core brain temperature. IV infusion of chilled saline, while shown to be effective in some cases, has numerous side effects, including hemodilution, potential fluid overload in patients with heart failure, coagulopathy, increased infection rates, reduced drug effectiveness, and patient excessive body hypothermia, resulting in shivering. Furthermore, cooling effectiveness has been shown to be variable due to patient-to-patient body mass and is severely limited by the maximum solution that can be infused greatly limiting the amount of time that cooling can be maintained. This is significant in light of transport times and the period necessary to arrive at, and achieve, hypothermia target temperature in the ICU. The Excel Cryo Cooling System was designed to provide consistent cooling regardless of patient size or weight, by cooling of the blood traveling through the carotid triangles to the brain. The carotid triangles are generally superficial to the surface of the skin. By cooling the brain through the extraction of heat from carotid blood flow, the Excel System provides consistency from patient to patient, provides long term uninterrupted cooling, and avoids the undesired systemic side effects seen with use of the other cooling methods.

Materials and Methods

The EXCEL Cryo Cooling System consists of a unique cervical immobilization collar and a cooling element. Once activated, the cooling element achieves a temperature of -3.0°C to -5.0°C within seconds. The collar is fitted around the patient's neck and the cooling element is applied to the front of the neck over the carotid arteries and secured in place by the collar. By cooling the blood traveling directly through carotid arteries, the system induces selective cooling of the brain. The investigators appropriate personnel were trained in proper application of the Excel Cryo Cooling System. Prior to the Excel cervical collar being placed on the neck, a tympanic temperature was recorded and logged as the baseline and heart rate was recorded. The Excel collar was fitted on the subject, and the Cryo cooling element was activated and placed in position within the cervical collar as designed. The tympanic temperature was recorded at 5 minute intervals after placement of the first cooling element. After placement of the initial cooling element, the cooling element was replaced every 20 minutes per the manufacturer's recommendation, for a total of 80 minutes of cooling.

Results

Of twenty healthy volunteers, fifteen were enrolled for data analysis and five subjects were disqualified. The reasons for disqualification were due to inaccurate initial baseline temperature

readings and reported correlation, and other errors related to 1) delayed temperature recordings 2) incorrect tympanic temperature reading and 3) improper placement of cooling elements over subjects clothing creating insulation between the cooling element and the skin.

Of the 15 patients included in the study, all reached a temperature drop into the mild therapeutic hypothermia range. We noted the following results (see tables 1 and 2):

- The average temperature drop was 1.73°C
- Average time to Mild TH was 31.7 minutes
- 5 quickest to cool subjects dropped temperature between 0.90°C and 1.7°C in 20 minutes
- 53% (8 of 15) of subjects reached Mild TH within 25 minutes
- 60% (9 of 15) of subjects dropped temperature 1.5°C or more
- 7 subjects dropped from .9 – 1.5°C
- 6 subjects dropped from 1.6 – 2.5°C
- 2 subjects dropped temperature 3.0°C and 3.6°C, respectively

TABLE 1

Result	Time to Mild TH (min.)	Max Temp Drop (Celsius)
1	20	2.0
2	10	3.0
3	75	1.0
4	35	1.1
5	35	2.1
6	50	0.9
7	25	1.1
8	40	1.7
9	25	1.9
10	25	1.7
11	20	2.0
12	35	1.0
13	20	1.5
14	15	3.6
15	45	1.3
Average	**31.7**	**1.73**

TABLE 2

Drop Range	.9 - 1.5	1.6 - 2.5	2.6 - 3.6	Total
Δ Start-Low	7	6	2	15

Statistical Analysis

The temperature improvement for the 15 patients was analyzed in two ways:

1. The temperature improvement for each patient was compared to a random improvement between 0.1° and 0.4°, which is the normal temperature range over the course of several hours. An unpaired t-test was used to compare the p-value between the test group and a randomized group. Results are given in Table 3 below.

2. The temperature improvement for each patient was analyzed looking at the change from the start of the treatment to the lowest temperature observed during the treatment, and compared to the temperature change from the start of the treatment to the end of the study. A paired t-test was used to compare the p-value between the test group change in temperature during treatment and the change in temperature after treatment. Results are given in Table 4 below.

TABLE 3

	Treatment Group	Control Group
Mean	1.727	0.26
Std Deviation	0.766	0.099
Std Error Mean	0.198	0.025
N	15	15
Difference of Means	1.467	
95% Confidence Interval	1.058 - 1.875	
t-value	7.3573	
Degrees Freedom	28	
p-value	<0.0001	

TABLE 4

	Temp Change Due To Treatment	Temp Change Start To Completion
Mean	1.727	1.113
Std Deviation	0.766	0.59
Std Error Mean	0.198	0.152
N	15	15
Difference of Means	0.613	
95% Confidence Interval	0.401 - 0.826	
t-value	6.1966	
Degrees Freedom	14	
p-value	<0.0001	

Both differences are considered to be statistically significant.

Discussion

The University Hospitals EMS Training & Disaster Preparedness Institute in northeast Ohio has medical oversight for emergency medical services for 77 municipalities and/or agencies in the region, comprising of over 200 first response vehicles. In our attempt to target improvement in patient care, specifically for incidences of out-of-hospital cardiac arrest, we have implemented protocols and training for high performance CPR, airway management, and therapeutic hypothermia. It is well known that in such cardiac arrest incidences, and with corresponding lack of blood flow, brain cells begin to die with 3 – 6 minutes. The use of therapeutic hypothermia to lower a patient's brain temperature has been proven effective in giving the patient the best opportunity for survival and good neurological outcome. In 2010, the AHA revised its recommendation for treatment of post-cardiac arrest. The revision stresses cooling as soon as possible after return of spontaneous circulation. Until the creation of the Excel Cryo Cooling System, the only methods available to first responders and EMS providers included ice/chemical cold packs and/or the infusion of chilled saline. The Excel Cryo Cooling System was designed to safely, effectively, and non-invasively cool patients for use by EMS and hospital first responders. The system was adopted as part of our EMS resuscitation protocol and implemented on over 200 vehicles in 2012. We studied the Excel Cryo on fifteen health volunteer subjects to provide ourselves and our emergency medical community colleagues with additional data

validation of the effectiveness of the product. The results show that Mild TH can be attained quickly and safely. We did not witness any side effects (such as shivering or skin irritation) on our subjects during the 80 minute cooling period, although several subjects reported significant cooling of core body and/or extremities. We do also note, given the subject variation in time to Mild TH and temperature drop, that compromised patients may, in fact, cool faster and with a more significant temperature drop versus non-compromised volunteer subjects who potentially have a normal thermo-regulatory response to cooling. Importantly, the debate over the reliability of tympanic temperature readings has been well documented, and was noted as an issue during our study. We noted challenges acquiring readings that were due to use and position placement of the temperature probe in the ear canal, and not device related. We recommend that future studies include actual brain temperature from compromised patients and correlation of those readings to both tympanic and core body temperatures. We also believe intra-arrest cooling (before ROSC) may provide earlier neuro-protective benefit and recommend future studies be conducted to explore the impact on survival and neurological outcome.

Conclusion

This study demonstrated the cooling effectiveness of the Excel Cryo Cooling System in its ability to achieve a rapid reduction of brain temperature into mild Therapeutic Hypothermia, supporting the use of the product by our first response personnel.

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