ADVANCED COOLING THERAPY

Prospective, interventional study evaluating the feasibility and safety of the Esophageal Cooling Device in patients suffering from traumatic brain injury and treated with targeted temperature management

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Abstract:

Controlling patient's body temperature, and in particular, reducing body temperature in a treatment referred to as targeted temperature management, has been shown to improve outcomes for many conditions, including neonatal hypoxic ischemic encephalopathy, cardiac arrest, and traumatic brain injury. However, available modalities for inducing targeted temperature management have a number of technical, logistical, and financial barriers. The Esophageal Cooling Device is a multi-chambered silicone tube placed in the esophagus that provides a highly efficient heat transfer to or from a patient. The Esophageal Cooling Device potentially improves the ability to treat patients with targeted temperature management by eliminating the risks and complexities of existing methods of inducing targeted temperature management while maintaining the functionality of the orogastric tube that it replaces. Initial mathematical and animal studies have shown strong support for the efficacy and safety of the Esophageal Cooling Device. Placement of a nasogastric or an orogastric tube is a standard of care for unconscious patients suffering from conditions typically treated with targeted temperature management. The present study will replace the usual orogastric tube with the Esophageal Cooling Device in order to evaluate the feasibility and safety of inducing targeted temperature management.

The aim of this prospective, interventional study is to assess the feasibility and safety of the Esophageal Cooling Device in 15 patients from the Ukraine suffering from traumatic brain injury who the treating physician is treating with targeted temperature management. Comparison of outcomes will be made to historical controls, and analysis will utilize a non-inferiority design. The primary outcome is the time to initiation of targeted temperature management, as measured from the time a decision is made to begin targeted temperature management, to the time the esophageal cooling device is in place.. The secondary endpoints: the feasibility of inducing, maintaining, and rewarming patients from targeted temperature management using the Esophageal Cooling Device (cooling rate, rewarming rate, and the percent of time within goal temperature during the goal-temperature maintenance period); evaluation of adverse events (including cardiac arrhythmias, severe bradycardia, myocardial infarction/re-infarction, dysphagia, odynophagia, aspiration pneumonia, non-aspiration pneumonia, reflux, esophageal injury, and esophagitis) will be closely monitored during the whole period of targeted temperature management

Background:

Current medical practice entails modifying or influencing the temperature of patients for a large and growing number of conditions. For example, temperature control (which includes reduction of body temperature below normal, maintenance of normal body temperature for the avoidance of febrile or hyperthermic states by cooling, and active warming of patients to avoid unintended reductions of body temperature) has been shown either preliminarily or definitively to be beneficial for:

- patients who remain comatose after resuscitation from cardiac arrest[1-5]
- neonatal hypoxic ischemic encephalopathy[6-10]
- certain subsets of traumatic brain injury[11, 12]
- spinal cord injury[13-15]
- certain subsets of stroke[16-20]
- acute myocardial infarction[21-24]
- traumatic/hemorrhagic cardiac arrest[25]
- surgical operations lasting longer than 1 hour[26-31]
- hepatic encephalopathy[32-34]
- severe heat stroke[35, 36]
- sepsis/septic shock[37]

Evaluations of temperature management in numerous other conditions are ongoing, including conditions such as spontaneous intracerebral hemorrhage, burns, sepsis, adult respiratory distress syndrome, acute subdural hematoma, pancreatitis, status epilepticus, necrotizing enterocolitis, and for organ preservation prior to donation. A recent search on ClinicalTrials.gov shows almost 300 open studies evaluating temperature management (hypothermia, normothermia, or targeted temperature management) for various clinical conditions. The strength of evidence for improved outcomes via modulating temperature of certain conditions (in particular, adults who remain comatose after resuscitation from cardiac arrest, neonates suffering from hypoxic ischemic encephalopathy, or patients undergoing general surgical procedures longer than one hour in duration) is such that it is now considered a standard of care, endorsed by the major resuscitative, cardiovascular, neonatal, and/or surgical standards groups (including the American Heart Association, the International Liaison Committee on Resuscitation, the European Resuscitation Council, the National Institute of Child Health and Human Development, the National Institute for Health and Care Excellence, the Centers for Medicare and Medicaid Services via the Surgical Care Improvement Project, and the American Society of Anesthesiologists).[38-45] The specific term applied to temperature modulation in the case of intentional reductions of body temperature to improve outcomes is generally referred to as therapeutic hypothermia (TH) or targeted temperature management (TTM). The use of TTM for traumatic brain injury (TBI) has been shown in a recent meta-analysis to be beneficial and associated with a significant reduction in mortality and a significant reduction in poor outcome.[11] In fact, while further randomized controlled studies are ongoing (in particular, the EuroTherm3235 trial), many institutions have adopted TH as a standard of care for TBI.[12, 46]

To date, however, available modalities for inducing TTM have a number of technical, logistical, and financial barriers, including difficulties in placement, risks of use (such as needle sticks, infections, blood clots, and skin damage), and high cost. The Esophageal Cooling Device is a disposable device that potentially improves the effectiveness of TTM while minimizing the risks

of other existing methods such as invasive methods.[47] The Esophageal Cooling Device (shown in Figure 1 and Figure 2) is a multichambered silicone heat exchanger that is placed in the esophagus to provide highly efficient heat transfer to/from a patient while simultaneously maintaining access to the stomach to allow gastric suctioning, decompression, and drainage, as usually performed in such patients in emergency departments, operating rooms, and intensive care units.

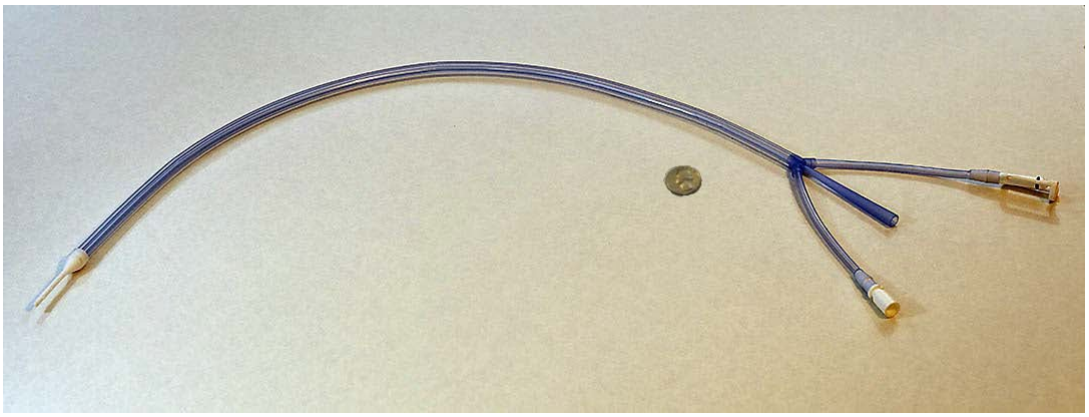

Figure 1. Photograph of the Esophageal Cooling Device (ECD).

The esophagus is in close proximity to blood flow from the heart and great vessels, and the Esophageal Cooling Device is designed to take advantage of this heat exchange environment. The Esophageal Cooling Device's ability to decompress the stomach and avoid distention of the esophagus away from the device ensures good contact with the esophageal mucosa, and thus maximizes heat transfer from the patient. The Esophageal Cooling Device replaces the standard orogastric tube which is placed in the target patient population as a routine standard of care, is made of standard medical-grade silicone, and is generally similar in size and shape to the orogastric tubes currently used. Initial mathematical and animal studies have shown strong support for the efficacy and safety of the Esophageal Cooling Device.[47-49]

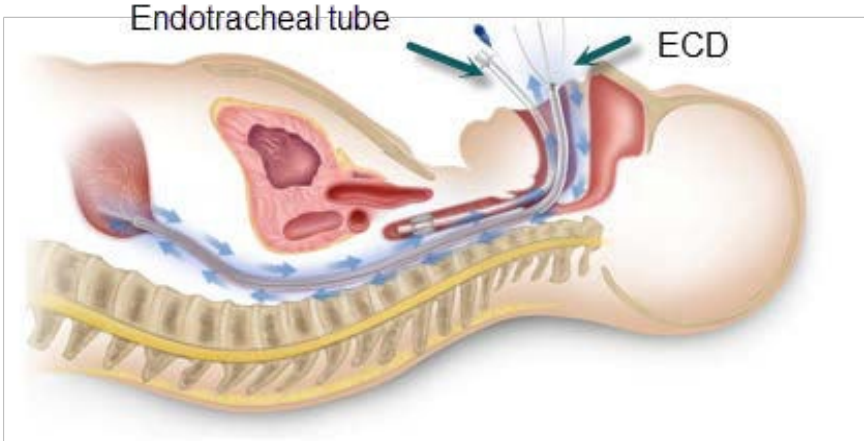

Figure 2. The Esophageal Cooling Device (ECD) shown in place in the esophagus (replacing the routine gastric tube placed in the target population as a standard of care), and located behind the trachea (containing the endotracheal tube which is placed in the trachea routinely to provide ventilation in the target patient population).

Study design:

Prospective, interventional study evaluating the feasibility and safety of the Esophageal Cooling Device in 15 patients suffering from traumatic brain injury and treated with targeted temperature management. Comparison of outcomes will be made to historical controls, and analysis will utilize a non-inferiority design.

Primary outcome:

Time to initiation of targeted temperature management, as measured from the time a decision is made to begin targeted temperature management, to the time the esophageal cooling device is in place.

Secondary outcomes:

Secondary performance outcomes include the feasibility of inducing, maintaining, and rewarming patients from targeted temperature management using the Esophageal Cooling Device. Specifically, cooling rate, rewarming rate, and the percent of time during the goal-temperature maintenance period within 1°C of goal temperature (typically 33°C, but with some centers using anywhere from 32°C to 36°C) will be measured.

Secondary safety outcomes include evaluation of adverse events including the following: cardiac arrhythmias, severe bradycardia, myocardial infarction/re-infarction, dysphagia, odynophagia, aspiration pneumonia, non-aspiration pneumonia, reflux, esophageal injury, and esophagitis.

Specific definitions of adverse events and the methods used to identify and diagnose each during the treatment and 30-day follow-up phases are as follows:

- Cardiac arrhythmias - recording of atrial or ventricular arrhythmias during course of treatment.
- Severe bradycardia - heart rate < 30/min and necessitating pacing and cessation of TH.
- Myocardial infarction - universal definition of myocardial infarction as per the joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction.[50]
- Dysphagia - report from patient of difficulty in swallowing for more than 24 hours after cessation of device use, diagnosed with a Modified Barium Swallow Study, Videofluoroscopic Swallow Study, or patient self-report.
- Odynophagia - report from patient of pain with swallowing for more than 24 hours after cessation of device use, diagnosed by subjective patient sensation.
- Aspiration pneumonia - demonstration by chest X-ray of evidence of aspiration pneumonia, as diagnosed by treating physician, within 24 hours of cessation of device use.

- Non-aspiration pneumonia - demonstration by chest X-ray of evidence of pneumonia within 24 hours of cessation of device use that is diagnosed by the treating physician as non-aspiration pneumonia.
- Reflux - report of symptoms from patient within 3 days of recovery, with diagnosis via esophageal pH monitoring or endoscopy.
- Esophageal injury - evidence of traumatic and/or ischemic esophageal injuries diagnosed by gastroenterologist evaluation via esophagogastroduodenoscopy as warranted or indicated, and describing the absence of necrosis or not according to the Zargar classification used for caustic injuries within 3 days of recovery .
- Esophagitis - evidence of esophageal inflammation diagnosed by gastroenterologist evaluation via esophagogastroduodenoscopy if warranted or indicated, and as defined by Savary-Miller and staged from 1 to 4 according to the severity of the disease within 3 days of recovery.

A serious adverse event (SAE) is defined as any adverse event that:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

Patient population:

Patient population will consist of 15 patients suffering from traumatic brain injury, in whom the treating clinician has determined that targeted temperature management will be initiated.

Duration of patient's participation in the study

The patient's duration of the participation should be considered as follows:

- From signing of consent form by patient's legal representative and until 30 days if the patient has recovered within 30 days from the consent's signature and is able to sign the ICF personally;
- From signing of consent form by patient's legal representative and until the patient's recovery – patient's ability to sign the consent form (either a full or at least sufficiently partial neurologic recovery that allows the patient to awaken, function, understand conversation, ability to sign personally);
- From signing of consent form by patient's legal representative to patient's death

Inclusion criteria:

Adult patients (age 18 years and over)

Exclusion criteria:

- Patients with known esophageal deformity or evidence of esophageal trauma (for example, known esophageal varices, cirrhosis, history of esophagectomy, previous swallowing disorders, achalasia, etc.).
- Patients with known ingestion of acidic or caustic poisons within the prior 24 hours.
- Patients with less than 40 kg of body mass.
- Patients known to be pregnant.
- Terminal disease or "do not resuscitate order" that could lead to early-onset therapeutic withdrawal (<48 hours after collapse).
- Unstable hemodynamic conditions (defined as intractable severe cardiogenic shock or ECLS requiring) that could lead to multi-organ failure and early-onset death (<48 hours after collapse).
- Pre-existing severe conductive disorder requiring pacing.

Informed consent and ethical considerations:

Written informed consent will be obtained from each patient's next of kin or patient's legal representative before inclusion. Surviving patients without severe neurological sequels will give their written informed consent. When a patient has recovered, and is able to do so, he/she has to sign the informed consent form personally.
This study will be conducted according to the principles of the Declaration of Helsinki (as amended October 2013) of the World Medical Association. The protocol will be submitted and approved by the local Ethics Committee of the institution.

Randomization:

Randomization: none

Esophageal Cooling Device:

The placement of the Esophageal Cooling Device will follow standard recommendations as per Instructions for Use. The Esophageal Cooling Device will beconnected to the appropriate console (Meditherm III, Blanketrol II, or Blanketrol III).

Other treatments:

Standard treatments for traumatic brain injury will follow local guidelines. Fluid and other management is left at the discretion of the attending physician.

Data collection:

All clinical and biological parameters will be recorded according to the Utstein-style recommendations for reporting resuscitation outcomes.[51] Neurologic outcome will be assessed according to the Cerebral Performance Category (CPC) score.[52] Initial temperatures will be measured via a tympanic or naso-pharyngeal temperature sensors in the prehospital field if available, or by other means used as standard of care. Continuous temperature measurement (specifically during cooling, maintenance, and rewarming) will be measured by bladder temperature sensors or rectal temperature sensors, and arterial temperature monitoring if available. Time of ECD placement in a patient will be recorded; the potential side effects (see above) will be recorded throughout the entire study..

Study assessments and procedures

Screening on Day 1

This visit includes the primary diagnostic procedures and the verification of the eligibility criteria. Subjects are eligible for the study will undergo the following procedures at this visit:

- Written informed consent (the form will be signed by a patients or legally acceptable representative);
- Previous medical history and co-morbidities;
- Physical examination including body weight, height and BMI, general appearance, heart, lungs, abdomen and extremities examinations;
- Demographics;
- Smoking habits;
- Alcohol consumption;
- Inclusion/exclusion criteria;
- Concomitant medications;
- Pre-hospital data: scene of injury (place of residence/public place/other), witness injury (yes/no), time from emergency call to arrival of EMS personnel, estimated time from injury to basic life support, estimated time from injury to advanced life support, location patient intubated (on scene/in ambulance/in emergency department);
- First recorded temperature and method of temperature measurement;
- Glasgow Coma Score;
- Presence of pupillary and corneal reflex;
- Any sign of spontaneous breathing/agonal breathing/gasping at admission;
- Blood gas and FiO2 (pO2, pCO2, BE, pH, lactate);
- Blood glucose;
- Troponin; (if obtained)
- BNP; (if obtained)
- ECG (normal/STEMI/LBBB/other);
- Echocardiogram (EF-normal, EF-moderately impaired, EF-severely); (if obtained)
- Head CT scan (at least the type of injury (subdural, epidural, subarachnoid, etc.) and relevant parameters for each (size, midline shift, volume of hematoma, etc.) should be recorded)
- Surgical interventions (if any)

After screening, subjects eligible for the study participation will undergo the following procedures during this time period:

- Temperature will be measured every hour from time point “0” to 39 hours. Time point “0” is the time either the patient or patient's legal representative, or close relatives signs the consent form. Method of temperature measurement should be recorded for each measurement. Two methods should be used for each time point measurement: 1) standard monitored route (rectal, Foley, intravascular, etc.); 2) temperature reported from the Blanketrol II
- Blood glucose and dose of insulin: 0 hr, 4 hr, 16 hr, 28 hr, 36 hr;
- Lowest and highest heart rate: 0 hr, 4hr, 16 hr, 28 hr, 36 hr;
- Lowest and highest mean arterial pressure: 0 hr, 4hr, 16 hr, 28 hr, 36 hr; (if arterial pressure is measured)

- Dose of vasopressor or other inotropic medication: 0 hr, 4hr, 16 hr, 28 hr, 36 hr;
- PaO2, FiO2 and mean airway pressure (MAP): 0 hr, 4hr, 16 hr, 28 hr, 36 hr;;
- Anti-shivering therapy administered, type and dose: 0 hr, 4hr, 16 hr, 28 hr, 36 hr;
- Central venous or mixed venous oxygen saturation: 0 hr, 4hr, 16 hr, 28 hr, 36 hr; (if measured)
- Arterial or venous lactate concentration: 0 hr, 4hr, 16 hr, 28 hr, 36 hr; (if measured)
- Blood gases (pH, pCO2, pO2, BE): 0 hr, 4hr, 16 hr, 28 hr, 36 hr; (if obtained as part of routine care)

After the first 24 hours from the admission of the patient to the hospital Simplified Acute Physiology Score (SAPS) III will be measured.

Daily during day 1-7 if ICU stay the following procedures and assessments will be performed and recorded in the CRFs:

- Sequential Organ Failure Assessment (SOFA) scores;
- GCS scores;
- Pupillary and corneal reflex check;
- Highest body temperature;
- Highest dose and type of vasopressor/inotropic medication;
- The need for pacing;
- Intracranial pressure monitor pressures will be recorded (if measured);
- Recording of a need for mechanical circulatory assistance;
- Mechanical ventilation (if necessary);
- Recording od daily net fluid balance;
- Recording of adverse events;

Daily from day 8 to ICU discharge or day 14 the following records will be made:

- Patient comatose (yes or no);
- Mechanical ventilation (yes or no);
- Renal replacement therapy (yes or no);
- Presence of pneumonia (aspiration/non-aspiration) and sepsis (yes or no)

CPC should be assessed and recorded daily with the last recording being either at discharge, or at the 30 day time point.

Daily from day 1 to day 14 “do not attempt resuscitation order” should be recorded in the CRFs.

Based on investigator’s discretion, the following procedures may be performed if a decision is being contemplated for withdrawal of patient care”:

- Results and time of SSEP, if performed (n20 present bilaterally/n20 present unilaterally/n20 absent);
- Results and time of EEG, if performed.

At ICU discharge or 30 days from admission the following procedures will be recorded if performed (only CPC and GCS are mandatory):

- EEG, MRI, CT (if performed)
- CPC and GCS;

- Esophagogastroduodenscopy (if performed)

Throughout the entire study:

- Concomitant medications;
- Adverse events

Statistical analysis

Sample size for primary outcome is calculated with an assumption of time to initiate cooling being approximately 5 minutes, with standard deviation of 4 minutes for the esophageal cooling device, and 20 minutes, with standard deviation of 15 minutes, for alternative devices. A power of 80%, and alpha of 5%, yields a sample size of 14 patients (with an equivalent size of historical controls). Sample size for secondary outcome is calculated for a non-inferiority test against the

current standard (cooling blankets or evaporative cooling). For the endpoint of percent of time over the study period within 1°C of goal temperature (33°C), the treatment effect of the active control is large, since non-treatment results in essentially no attainment of goal temperature. An estimate of effect of the active comparator (M_1) is therefore greater than would be acceptable to use as a base for a non-inferiority margin. Consequently, a more restrictive non-inferiority margin (M_2) is then proposed of 15% (i.e., if the standard maintains goal temperature +/-1°C for 60% of the time, and the ECD maintains goal temperature +/-1°C for 85% of the time, the lower bound of the 95% CI on the difference between percent time at goal temperature between standard and test device is greater than 70%).Setting the type I error rate to 5%, for an alpha of 0.05, and a power of 80%, for a beta of 0.2, yields a sample size estimate of 15 patients in the study (with another at least 15 patients coming from historical controls with available esophagogastroduodenoscopy evaluation).

Data analysis: as recommended by current FDA guidance documents, both per-protocol (as-treated) and intent-to-treat analyses will be performed.[53] Lower 95% confidence limit for difference between groups must exclude the non-inferiority margins for primary end point in both efficacy and safety.

Abbreviation

ACT - Advanced Cooling Therapy
AE – adverse event
BNP - brain natriuretic peptide
ECG - electrocardiogram
GCS – Glasgow Coma Score
CPC - Cerebral Performance Category
CT – computed tomography
ECD - Esophageal Cooling Device
ECLS - Extra-Corporeal Life Support
EEG – electroencephalogram
LBBB - left bundle branch block
MAP – mean airway pressure
MRI - Magnetic Resonance Imaging

OTC – over-the-counter
ROSC - Return of Spontaneous Circulation
SAE – Serious Adverse Event
SAPS – Simplified Acute Physiology Score
SOFA – Sequential Organ Failure Assessment
SSEP - Somatosensory evoked potentials
STEMI - ST-elevated myocardial infarction
TH - Therapeutic Hypothermia

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