Influence of Cooling duration on Efficacy in Cardiac Arrest Patients (ICECAP) – Clinical Trial Synopsis
A multicenter, randomized, adaptive clinical trial to identify the optimal duration of cooling in comatose survivors of cardiac arrest

Neurological death and disability are common outcomes in survivors of cardiac arrest. Therapeutic cooling of comatose patients resuscitated from shockable rhythyms has been shown in two randomized controlled trials to markedly increase the rate of good neurological outcome, but the optimal duration of induced hypothermia has not been investigated. ICECAP is a randomized adaptive clinical trial to characterize the duration-response curve of induced hypothermia in comatose survivors of cardiac arrest and to determine the optimal duration of cooling. Subjects will initially be randomized to 12, 24, or 48 hours of cooling. After 150 subjects have been enrolled, response adaptive randomization will allocate subjects to a shorter duration (6 hours) if the developing model suggests a flat duration-response curve, or to longer durations (60 or 72 hours) if the developing model suggests a positive but not yet plateauing duration-response curve, and to the original and interposed durations (18, 30, 36, 42 hours) as needed to refine the model. Comatose adult survivors of cardiac arrest from shockable rythyms that have already been rapidly cooled using a definitive temperature control method (endovascular or surface) will be enrolled. The primary outcome will be modified Rankin score at 90 days analyzed as a weighted score incorporating both the proportion of subjects achieving a good neurological outcome and degree of residual functional impairment among those with good neurological outcomes.

Objectives

The overarching goal of this project is to identify clinical strategies that will increase the number of patients with good neurological recovery from cardiac arrest. We hypothesize that longer durations of cooling may improve either the proportion of patients that attain a good neurological recovery or may result in better recovery among the proportion already categorized as having good outcome. Secondarily, we will determine if a dose response curve can provide evidence of efficacy of cooling itself to confirm previous RCT's for survivors of shockable rythyms and to provide first prospective controlled evidence of efficacy in those without initial shockable rythyms.

Primary objective:

to determine, in each of two populations of adult comatose survivors of cardiac arrest (those with initial shockable rythyms and those with PEA/asystole), the shortest durations of cooling that provides 95% of the maximal treatment effect as determined by 90 day modified Rankin score analyzed as a weighted average score.

Secondary objectives:

(i) to determine, in each of two populations of adult comatose survivors of cardiac arrest, whether a duration-response curve is sufficiently positive to imply confirmation of previously identified efficacy versus zero duration of cooling (normothermia),
(ii) to characterize the overall safety and adverse events associated with duration of cooling,
(iii) to characterize the effect of duration of hypothermia on neuropsychological outcomes,
(iv) to characterize the effect of duration of hypothermia on patient reported quality of life.

Design

The study is a randomized, response-adaptive, duration (dose) finding, comparative effectiveness clinical trial with blinded outcome assessment.

Study Population

Comatose adult survivors of out of hospital cardiac arrest that have already been rapidly cooled using a definitive temperature control method (endovascular or surface) will be enrolled in the emergency department or intensive care unit.

Clinical Sites

Hub and spoke hospitals from the NETT will be enriched with high potential ancillary Hubs. Approximately 50 hospitals are anticipated to each enroll an average of 6 subjects per year.

Randomization

Central computerized randomization by web-based interface will be used. Subjects will be potentially randomized over the course of the trial to following possible durations of cooling (in hours): 6, 12, 18, 24, 30, 36, 42, 48, 60, and 72. The randomization allocation ratio will initially be 0:1:0:1:0:0:0:1:0:0 for the first 150 subjects (i.e., 1:1:1 for 12, 24, and 48 hours). After this burn in period, a predetermined response adaptive algorithm based on a smoothing spline (NDLM) model and an imposed set of constraints will be used to adjust the randomization allocation ratio iteratively every 50 subjects. Separate allocation ratios will be developed for the two populations based on initial rythym.

Data Collection

The on-call study team will respond to the emergency department to screen survivors of cardiac arrest for eligibility, engage eligible patient's legally authorized representatives in an informed consent process, coordinate with the clinical care team, and randomize enrolled subjects. EMS and enrollment case report forms will be completed in the emergency department. In particular, study teams will determine and identify the source for the times of arrest and of initiation of cooling. Temperature and physiologic data collection may be augmented by a study data logger. The study team will follow each subject daily until subject end of study or day 9 for data collection and sheperding of clinical standardization. There will be additional data collection at discharge, and follow up assessment on day 90 and at 6 months. Telephone contact between discharge and day 90 will protect against loss to follow up. Computerized adaptive testing will be used at follow up to assess patient reported outcomes and neuropsychological performance at 90 days and 6 months.

Inclusion

- Coma after resuscitation from out of hospital cardiac arrest
- Witnessed arrest
- Cooled to <34 deg C with 240 minutes of cardiac arrest
- Definitive temperature control applied
- Age ≥ 18 years
- Informed consent from LAR including intent to maintain life support for 96 hours

- Enrollment within 6 hours of initiation of cooling

Exclusion

- Hemodynamic instability
- Pre-existing neurological disability or condition that confounds outcome determination
- Pre-existing terminal illness, unlikely to survive to outcome determination
- Planned early withdrawal of life support
- Presumed sepsis as etiology of arrest
- Prolonged down time, >10 min to CPR, >30 min to ROSC
- Known pregnancy
- Prisoner

Primary Outcome Measure

The primary outcome measure will be the modified Rankin scale at 90 days after return of spontaneous circulation. The mRS will be analyzed nonparametrically as a weighted score incorporating both the proportion of subjects achieving a good neurological outcome and degree of residual functional impairment among those with good neurological outcomes.

Consent

Eligible subjects in this trial will not have capacity to provide informed consent. An in-person informed consent process including written documentation from a legally authorized representative will be required. The process may be augmented by multimedia informational tools created for the study. In the absence of brain death or particularly malignant prognostic findings, it is consistent with common clinical practice to await signs of neurological improvement in comatose survivors of cardiac arrest over a period of 96 hours of life support if that is consistent with the wishes of a patient's family or LAR. An important element of the informed consent process will be to identify and only include patients for whom the family or LAR initially intend to pursue at least 96 hours of life support.

Intervention

The intervention will be random allocation to duration of cooling after cardiac arrest. Cooling in the study will be by a definitive temperature control method to a target temperature of 33 deg C. Any endovascular or surface cooling system with closed loop feedback will be allowed. Duration of cooling will be measured from the time that cooling is initiated. Cooling may be initiated by EMS or in the emergency department. Eligibility will require that a temperature of <34 degrees be obtained by 240 minutes after cardiac arrest. After the allocated duration of cooling is completed, controlled rewarming will be performed. Rewarming to a temperature of 36.5 deg C will occur over the shorter of 24 hours or a rewarming period equal to the allocated duration of cooling. Definitive cooling devices may be used for maintenance of normothermia after rewarming is complete.

A clinical standardization guideline will be followed to reduce the effects of practice variability. Key physiologic and practice variables will be tracked and compliance with clinical standardization and deviation from physiologic targets reported back to study teams. Clinical standardization guidelines will include but may not be limited to: avoiding hypotension, avoiding hypoxia, controlling rebound

hyperthermia, treatment of seizures, treatment of shivering, management of sedation and paralysis, prognostic testing, and defining and treating infections. Clinical standardization guidelines will include defined parameters for malignant prognostic findings. Early withdrawal of life support will only be clinically recommended when these parameters have been met.

Sample Size

1200 subjects (maximum)

Enrollment Period

4 years (estimated accrual rate of 25 subjects per month)

Statistical Analysis for the Primary Outcome Measure

The primary analysis will identify the duration of cooling that has the highest posterior probability of being the lowest duration with a treatment effect of at least 95% of the maximum identified treatment effect. This dose is designated the ED95, and it represents the beginning of the plateau of the duration response curve.

A secondary analysis will identify if the duration-response curve implies superiority of cooling versus "zero duration" normothermia. A positive analysis is defined as a posterior probability of >0.98 that the ED_{max} or the ED95 is better than any shorter duration.

Investigational New Drug

This trial is expected to require an IDE from the Food and Drug Administration.