Protocol Synopsis*

ARCTIC (Acute Rapid Cooling for Traumatic Injuries of the Cord)

A prospective, multi-center trial of moderate intravascular hypothermia for the treatment of acute traumatic cervical spinal cord injury.

** This synopsis is based on the initial grant application for this study and is subject to the ongoing revisions in response to peer review and other input. It is provided for internal informational purposes.*

Background and Rationale

Traumatic spinal cord injury (SCI) affects an estimated 11,000 people in the United States every year. Advances in the medical and surgical management of this patient population have resulted in substantial improvements in the survivability of these injuries, with a large majority of patients having a near-normal life expectancy. Because of its devastating consequences but likelihood of long-term survivability, SCI exerts a disproportionate medical, social and economic toll with an estimated cost of $8 billion/year in the United States. Basic research has proven that secondary injury mechanisms contribute substantially to the neurological dysfunction that follows SCI. Secondary injury evolves in the hours following the primary trauma, but to date no emergent neuroprotective therapy has proven effective at improving clinical outcome after traumatic SCI. Significant pre-clinical evidence has demonstrated that moderate hypothermia administered early following injury can reduce the extent of neural damage in experimental SCI, and hypothermia is the only neuroprotective therapy that has been proven effective in clinical trials in other forms of CNS injury. We conducted a pilot trial to evaluate the safety of intravascular cooling to 33.0°C in patients with complete SCI. In that study a 42.8% conversion to incomplete injuries was identified with rates of complications and sequelae from SCI similar to those found in historical cohorts. We propose a large multicenter randomized clinical trial, built upon the existing pre-clinical and pilot studies, to definitively determine the efficacy of early induction of moderate hypothermia in patients with SCI.

Primary objective

This study will assess the efficacy of moderate induced hypothermia (33.5 + 0.2° C) for improving the ASIA motor score. Significant improvement will be determined by a greater than 10 point difference between the two treatment arms in the mean change in ASIA motor score as determined at 12 month follow-up.

Secondary objectives

Secondary objectives of this study include assessing the safety of moderate hypothermia following SCI, and the effect of induced hypothermia on sensory recovery as determined by the ASIA sensory score, on functional recovery as measured by the Spinal Cord Independence Measure (SCIM-3) score, and on neuropathic pain following spinal cord injury as measured by the International Spinal Cord Injury Pain

Basic Data Set (ISCIPDS:B) instrument. Additional secondary endpoints including patient reported outcomes will also be assessed.

Study Design / Intervention

This is a randomized controlled clinical trial with blinded outcome assessment of subjects with acute traumatic cervical spinal cord injury at C4 to C8 and no motor function below the injury level (AIS grades A & B). Individual patient consent is required. Because the timeliness of intervention is critical, baseline ASIA motor assessment, consent, and randomization must be performed early enough to ensure initiation of study treatment within 6 hours of the injury.

After randomization, study treatment is initiated by infusion of cold or room temperature intravenous fluids rapidly followed by placement of an endovascular temperature control catheter. Core body temperature will be actively controlled in all subjects with an endovascular temperature control catheter for 72 hours. Subjects will be randomized to receive either: (1) maintenance of normothermia at 37º C for 72 hours, or (2) cooling to 33.5º C + 0.2 C for 48 hours followed by 24 hours of controlled re-warming.

All of the other aspects of treatment will be according to standard patient care, and in accordance with consensus guidelines. Compliance of experimental therapy with the protocol, and of standard therapy with established care guidelines, will be carefully tracked daily. Protocol deviations and guideline transgressions will be rapidly reported to allow remediation in real time as previously implemented in the NETT for neurotrauma trials. Outcome measures will be assessed at 6 weeks, 6 months, and 12 months.

Active control of body temperature using endovascular temperature control catheters ensures highly accurate and precise control. Endovascular temperature control is required to reliably prevent fever in subjects randomized to normothermia, as hyperthermia has confounded results in previous trials of hypothermic neuroprotection. In subjects randomized to cooling endovascular temperature control allows rapid cooling and highly controlled rewarming. Shivering will be managed through a standardized protocol including meperidine and skin counter-warming.

Patient Recruitment / Eligibility

Subjects will be recruited by an on-call rapid response study team in the ED of the receiving participating hospital or at the time of transfer by the critical care transfer service of the participating receiving hospital.

Patients eligible for inclusion will be 15 to 65 years old with complete motor (ASIA grade A/B) deficits below a cervical spinal cord injury between C4 and C8 inclusive.

Patients will be excluded from this trial if they have a rapidly improving exam, severe non-CNS injury, significant traumatic brain injury, penetrating or pre-existing SCI, are pregnant, or are unable to provide informed consent. Prisoners, patients with an unknown time of injury, history of cardiac arrhythmia, and those in whom a baseline motor score cannot be obtained are also excluded.

Outcomes

Primary outcome measures

Primary Efficacy Outcome - ASIA Motor Score: The absolute change from baseline in the 12-month ASIA motor score will be utilized as the primary outcome measure in this study. The baseline measure of the ASIA motor score will be obtained prior to administration of the assigned treatment by trained assessors. The average change score will be compared in cooled versus normothermic subjects, with a greater than 10 point difference between groups determined as a clinically relevant difference between the two treatment arms. Recognizing that improvements in motor function can manifest in different patterns, this threshold of a 10 point change in the ASIA motor score has been recognized by the ICCP Panel as a clinically relevant and measurable change in neurologic function for interventional SCI trials.

The ASIA motor score will also be compiled separately as an upper extremity motor score (UEMS) and lower extremity motor score (LEMS) for secondary analyses of the primary outcome. This will allow for the assessment of large change scores due to substantial recovery in a zone of partial preservation versus recovery of neurological function through long tracts.

Primary Safety Outcome – Mortality: The primary safety outcome is all cause mortality at 12 months. Mortality was selected as the primary determinant of safety of treatment because of the severity of the injuries in the subjects of this study, and because it is an objective metric of obvious clinical importance. Furthermore, the clinical outcomes of most of the anticipated or potential adverse effects of the study intervention, including cardiac effects, venous thrombus, and infectious complications are generally well partitioned between death and full recovery. That is, these are complications that do not usually cause any lasting morbidity, disability, or persistent risk if they are not fatal at the time of occurrence.

Secondary outcome measures

Secondary Efficacy Outcomes: Additional outcome measures will be used to assess for concordant efficacy across a broad range of domains of recovery from acute SCI. Additional neurological assessment includes the ASIA sensory score. Functional disability will be assessed with the Spinal Cord Independence Measure (SCIM-Version III). The SCIM-III specifically measures the "…ability of persons with SCI to perform everyday tasks based on the relative value (of that task) to that individual patient." Neuropathic pain, an important source of ongoing morbidity in patients with SCI, will be measured using the International Spinal Cord Injury Basic Pain Data Set (ISCIPDS:B). Health-related quality of life (HRQOL) will be assessed using the SCI-QOL/SCI-CAT, a comprehensive, SCI-specific QOL measurement system based upon and validated using state of the art methodology including item banking, Item Response Theory (IRT), and Computerized Adaptive Testing (CAT).

Secondary Safety Outcomes: in addition to routine adverse event and safety monitoring, four rigorously pre-defined safety outcomes will be tracked as specific secondary safety outcomes. These are (1) neurological worsening, (2) thromboembolism, (3) sepsis, and (4) malignant arrhythmia.

Statistical Considerations / Power

Clinical experience and controlled studies have estimated that a 10-point difference in the mean change score between the two treatment arms is clinically relevant. If the hypothermia group does not have at least a 10 point or higher mean change score than the normothermia group, then hypothermia will not be considered a worthwhile therapy for SCI patients. Based on Sygen data the estimated standard deviation of the change score is 15 points for AIS A cervical patients and 25 points for AIS B cervical patients. The estimated standard deviation of the change in ASIA motor score used for sample size estimation is 20 points. Taking into consideration one planned interim analysis for futility and a two-sided type I error of 0.05, the study is powered to assure greater than 90% likelihood of identifying a 10 point difference between the mean change scores of the two treatment arms if a difference truly is present. Sample size estimation is based on the comparison of independent means. Although every attempt will be made to avoid drop outs and losses to follow up, the required sample size is inflated for a 10% non-adherence rate. The maximum sample size required for randomization is 212 subjects.

Web-based central randomization will prevent possible selection bias by providing random treatment assignment to each subject, and will prevent accidental treatment imbalances for the known prognostic variables through a combination of minimization and weighted coin algorithms.

The analysis of the primary outcome of change (Month 12–Baseline) in the ASIA motor score will use a multiple linear regression model that will include entry AIS Grade (A versus B), gender, level of injury (C4-C8), and age (continuous) as model covariates. Two secondary analyses of the primary outcome will be conducted following the primary analysis. One analysis will evaluate the change in ASIA motor score over time using a mixed effects model repeated measures analysis which will include the covariates listed above plus covariate*time and covariate*time*treatment interactions effects. The second analysis will evaluate the ASIA motor change score separately for upper extremity motor score and for lower extremity motor score using the primary model defined above. All tests will be two-sided and performed under the intent-to-treat (ITT) principle at the significance level of 0.05.

In addition to the continual monitoring of adverse events by the safety monitor and DSMB and the planned statistical monitoring of specific events, final analyses of specified safety outcomes will be conducted and specific serious adverse event rates will be compared between the two treatment arms, given their high potential for affecting clinical outcome.