Manisha Gupte
CRC – IRB proposal
11/19/10

Effect of Adjunctive Therapeutic Hypothermia on Clinical Outcomes Following Catheter Based Therapy for Acute Ischemic Stroke.

A. Study Purpose and Rationale

Stroke is the third leading cause of death and the most common cause of adult disability [1]. ~~(Kissela et al.).~~ About 85% of strokes are ischemic, with approximately half due to large vessel occlusion secondary to a cardioembolic source [2]. ~~(Smith et al.).~~ In the US, ~~I~~less than 5% of patients with acute ischemic stroke (AIS) receive intravenous recombinant tissue-type plasminogen activator (rt-PA) [3]. ~~in the US~~ ~~(Kliendorfer).~~ Use of rt-PA is ~~generally~~ limited due to the fact ~~by~~ patients presenting outside the approved 3 hour window following symptom onset, or presenting with another contraindication do not qualify for this treatment. Endovascular intervention/catheter based therapy (CBT), which grants a larger window of time – up to 8 hours following symptom onset, is another option for treatment~~, which permits a longer window of time, up to 8 hours following symptom onset~~, but has not been shown to have as much success as systemic rt-PA [4]. This leaves a large margin for improvement in clinical outcomes following AIS.

The two defining studies to date looking at CBT are the PROACT and MERCI trials. The PROACT II trial~~,~~ was a randomized, controlled, multicenter study, published in 1999.~~,~~ ~~which~~ It looked at the efficacy of intra-arterial recombinant prourokinase (IA r-proUK) in patients with AIS of less than 6 hours~~²~~ duration caused by a middle cerebral artery (MCA) occlusion. The recanalization rate was 66% for the treatment group vs. 18% for the control group ($p < 0.001$). Favorable clinical outcomes, defined as a modified Rankin Scale (mRS) 0-2 (see scale in Appendix) at 90 days, was seen in 40% of those treated with IA r-proUK (n=121), compared to 25% of controls (n = 59), ($p = 0.04$). Mortality was 25% for the r-proUK group and 27% for the control group. A 50% decrease from baseline National Institutes of Health Stroke Scale (NIHSS) was seen in 41% (50/121) ~~in~~ of the treatment group and 75% (44/59) ~~in~~ of the control group [5]. ~~(Furlan).~~ While we do not use r-proUK in the US, this study ~~supported~~ led the current use of intra-arterial recombinant tissue-type plasminogen activator (IA rt-PA) within 6 hours of AIS for large vessel occlusions.

The ~~final results of the~~ Multi MERCI trial was~~,~~ a multicenter, international, prospective, single-arm ~~trail~~study, published in 2008.~~,~~ It showed thrombectomy (via the L5 retriever) within 8 hours of AIS achieved successful recanalization in 75 of 131 (57.3%) of treated large vessels and in 91 of 131 (69.5%) after adjunctive therapy with IA rt-PA~~,~~ or mechanical embolectomy. Overall, favorable outcomes, again defined as mRS ≤ 2 at 90 days, were found in 36% of all patients ~~,~~ with 49% of those with successful recanalization having a favorable outcome and 9.4% with unsuccessful recanalization having a favorable outcome ($p<0.001$). Overall mortality was 34% at 90 days, with 23%

Formatted: Font: Not Bold
Formatted: Not Highlight
Formatted: Not Highlight
Comment [S.G.1]: Cite
Formatted: Not Highlight

of the overall recanalized group dying and 52% in the overall not recanalized group. NIHSS decreased by 10 in 26% (38 of 146) of patients [6]. (Smith – MERCI).

Analysis of these studies reveal, despite successful recanalization in roughly ~65% of the subjects, ~ about 50% have mRS ≥ 3 at 90 days., with Aabout half of those the 50% being are mortalities and the other half having have moderate to severe disability. This difference can not be fully attributed to adverse events. The most common adverse event with CBT is intracranial hemorrhage. The Mmulti MERCI trial found 9.8% of patients to have symptomatic intracranial hemorrhage and a 2.4% device-related adverse events [6]. (Smith – MERCI). PROACT II reported symptomatic intracranial hemorrhage in 10% of treated patients and 2% of controls (p = 0.06) (Furlan). [5]. One possible explanation for worse clinical outcomes despite recanalization is reperfusion injury.

Therapeutic Hypothermia (TH), defined as core temperature cooling to 32-34°C for 12-24 hours, is now the standard of care, per the AHA, in the US for unconscious adult patients with spontaneous circulation following outside-of-hospital cardiac arrest when initial rhythm is ventricular fibrillation., because Iit has been shown to improve neurological outcomes and reduced mortality [7]. (AHA, HACA). Variations of TH are used by many institutions for a variety of cardiac presentations. TH is thought to provide neuroprotection via multiple mechanisms, including reducing brain metabolism, decreasing formation of reactive oxygen species during reperfusion, inhibiting excitatory amino acid release, decreasing the immune response during reperfusion, and inhibiting apoptosis. In addition, studies have shown TH to also reduce cerebral edema after ischemia [8]. (Janata). Taken together the benefits of TH in AIS could lead to prolonging the therapeutic time window, limiting reperfusion injury, and potentially reducing hemorrhagic conversion rates [9]. (Guluma). Small phase I trails of TH in AIS have shown it to be safe and feasible [(DeGeorgia10, Guluma9])]. However, these studies were not designed to analyze clinical outcomes. Neuroprotective strategies, including TH, are most effective in transient ischemia (Janata) and therefore the combination of TH and revascularization is an appealing concept, with a potentially synergistic effect [8].

Formatted: Not Highlight

Formatted: Not Highlight

In the Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L) trial, published last month, patients were randomized to receive rt-PA alone or rt-PA plus endovascular TH. Groups were stratified into treatment windows of 0-3hrs and 3-6hrs. Twenty-eight patients received TH, with 22 receiving rt-PA within 3hrs, 2 receiving rt-PA between 3-6 hrs, and 4 received TH alone. TH was started 30-180 minutes after completion of rt-PA infusion in fear of bleeding complications. The median time to target temperature of 33°C after catheter placement was 67 minutes. The incidence of pneumonia was significantly higher in the TH group (7/28 vs 2/30 p<0.0.5), symptomatic intracerebral hemorrhage occurred in 4 patients – all of which had received rt-PA within 3 hours, and only 1 was in the rt-PA plus TH group. While the TH group did have significantly more adverse events (p = 0.018), other than pneumonia, no other single adverse event was noted to be significantly different between groups,. At 90 days, neither the NIHSS, mRS, nor mortality differed significantly between groups. The study

specifically notes, delay in cooling may have diminished the neuroprotective benefit of TH [11]. (Hemmen).

Due to the small percentage of patients qualifying for rt-PA and concern for bleeding with systemic rt-PA and catheter placement for endovascular cooling, I think TH with CBT for AIS is worth investigating. In addition, cooling prior to reperfusion may show the most benefit in terms of clinical outcome by limiting reperfusion injury.

A number of cardiac trials have shown induction of TH prior to percutaneous coronary intervention (PCI) to be safe, feasible, and to not have an effect on door-to-balloon time (Wolfrum, Dixon, Batista, Kandzari [12, 13, 14, 15]).

Formatted: Not Highlight

Formatted: Not Highlight

B. Study Design and Statistical Analysis

Design: This is a prospective, multicenter, interventional 2-arm study. Patients meeting selection criteria will be randomized into two groups, CBT only or CBT with therapeutic hypothermia, with stratification of NIHSS at presentation and type of CBT received. Stratification based on NIHSS is necessary due to previous data illustrating NIHSS is a predictor of outcome (Adams et al, 1999). NIHSS score will be stratified into three two groups, NIHSS < 6, 6-16, >16. CBT is being defined as intra-arterial thrombolysis, mechanical thrombectomy, angioplasty, / and/or stenting, or combination therapy. Therapies used will be at the discretion of the neurointerventionalist. Therefore patients will be stratified into 8 total groups. The randomization sequence will then be generated by the Department of Medical Statistics for each site with the blocked randomization method.

Group assignment will be delivered in a sealed opaque envelope to the interventional suite, just prior to CBT. Patients assigned to the CBT only group will proceed with CBT and standard medical care.
CBT is being defined as intra-arterial thrombolysis, mechanical thrombectomy, angioplasty, and/or stenting. Therapies used will be at the discretion of the neurointerventionalist.

Patients assigned to TH, will be consented for cooling using the Celsius Control System. They will receive endovascular cooling via the Celsius Control System. They will also receive standard medical care in addition to the cooling protocol. The pProtocol derived is a combination of methods used by Gotberg et al. for TH prior to PCI, those used by Guluma et al. for TH in awake ischemic stroke patients, and institutional protocol [16, 9, 17]. All protocols used the Celsius Control System. Patients will have surveillance blood cultures drawn in addition to standard labs prior to initiation of cooling. They will be given 30mg of oral buspirone and a 1mg/kg loading dose of meperidine, followed by a continuous infusion of meperidine at 30 mg/h. Shivering will be assessed using the 4-point bedside shivering assessment scale (0 – no shiver; 1- mild shiver -head and neck only; 2- moderate shiver- intermittent upper extremity involvement; 3 – severe shiver – generalized whole body shiver [17]; derived by Badjatia et al.) Additional 25mg IV boluses of meperidine will be given if a patient's shiver score increases above 0 at any

Formatted: Not Highlight

Formatted: Not Highlight

point. A 14F introducer will be inserted into the right femoral vein. The 14F Celsius Control catheter (Innercool Therapies Inc) will be passed through the introducer into the inferior vena cava with the tip of the catheter at the level of the diaphragm. The target temperature will be set at 33°C. Core body temperature will be measured via the integrated temperature probe in the cooling catheter, with confirmatory peripheral measurements. Once core temperature is < 35°C, patients will undergo CBT. Patients will continue to be cooled for a total of 24 hours to limit reperfusion injury. Patients will be kept NPO with a nasogastric tube (NG) to low-wall suction to limit narcotic-related emesis. Surface counter warming will be accomplished using an air circulating blanket (BAIR Hugger, AZant Healthcare, Eden Prarie, MN) warmed to 43°C. Shivering will be continuously monitored with boluses of 10-25mg IV meperidine for scores above 0, followed by an increase in meperidine drip rate by 5mg/hr, with particular attention to sedation. If significant sedation is noted, drip rate will be lowered. At 8 and 16 hours following initiation of TH, patient will be given 15mg of buspirone orally or via NG. If severity of shivering continues to rise despite therapy, target temperature will be increased by 0.5°C on the console. After 24 hours of TH, patient will be rewarmed using the programmable console at a rate of 0.3°C per hour, to a target temperature of 36.5°C. This process will take 12 hours based on a starting temperature of 33°C. Once the target temperature is reached, the console will be shut off and the catheter and introducer sheath will be removed.

Just prior to discharge and at 90 days, all patients will be scored using the modified Rankin Scale, as a measurement of primary outcome, and NIHSS, as a measure of secondary outcome, by study neurologists blinded to group assignments.

Power:

The chi-square test will be used to determine the number of subjects needed in each group to power for analysis of the primary outcome measure of mRS. The chi-square test is chosen because we are interested in the proportion of patients in each group that have a mRS ≤ 2 at 90 days.

Using data from the Multi Merci trial, overall, 36% of patients had a mRS ≤ 2, therefore 0.36 will serve as "p1" [6]. Raising this proportion to 50% would be clinically significant, making 0.5, "p2." The effect size is then 0.14. To achieve this effect, 212 patients will be needed in each group.

Statistics:

Patients' baseline qualities will be analyzed. Subgroup analysis of primary outcome based on recanalization success will be performed. Secondary outcome of change in NIHSS will be analyzed.

C. Study Procedure

In addition to the protocol noted above, patients will receive standard medical care, and TH group will receive ~~chest xrays daily and~~ lower extremity dopplers following rewarming.

D. Study Drugs
No drugs in this study are investigational.

E. Medical Device
No devices in this study are investigational.

F. Study Questionnaires
N/A

G. Study Subjects
Inclusion criteria: Patients must be >18 years old, have a presenting NIHSS ≥ 6 and qualify for CBT per institutional protocol.

Exclusion criteria: Episode of sepsis in last 6 months, known coagulopathy, known arrhythmia other than atrial fibrillation, pregnancy, intolerance to buspirone or meperidine (including significant renal or liver dysfunction ~~as determined by pharmacist~~); treatment with monoamine oxidase inhibitors; life expectancy of < 6 months; baseline mRS ≥ 2; rapidly improving symptoms; intracerebral hemorrhage, mass, or aneurysm on head CT; conditions that could be worsened by TH - sickle cell, cryoglobulinemia, Raynaud's; hypothyroidism.

Patients who qualify for the study or their designated surrogate will sign an informed consent.

H. Recruitment of Subjects
Patients or surrogates will be approached in person for the study when the decision ~~is made~~ to pursue CBT for AIS is made.

An attempt will be made to contact a patient's primary care physician by phone; ~~,~~ however, given acuity of treatment, we ask that this requirement is waived.

I. Confidentiality of Study Data
Patients will be assigned a numerical ID for data analysis. Associated name and number will only be known to one individual on the team. Data will be stored on a password protected, encrypted, secure CPMC network, accessible only to investigators.

J. Potential Conflict of Interest
None

K. Location of Study
CPMC and other stroke centers with neurointerventionalists and capability for endovascular TH.
~~CPMC~~

L. Potential Risks

Infection, intracranial hemorrhage, arrhythmia, deep vein thrombosis, pulmonary embolus, femoral hematoma, respiratory depression, death.

M. Potential Benefits
Improved clinical outcome, with reduced long-term disability and improved quality of life.

N. Alternative Therapies
Patients may chose to not enroll in this study and still be treated with CBT at CPMC with standard medical care. They may also choose to enroll in a different study.

O. Compensation of Subjects
None. ~~Compensation will not be offered~~ in order ~~to eliminate~~ any ~~potential confounding factor of surrogates interested in financial gain over patients' wishes.~~

P. Costs to Subjects
None

Q. Minors as Research Subjects
N/A

R. Radiation or Radioactive Substances
N/A

References:

1. Kissela VB, Kittner S, Lloyd-Jones D, et al. Heart disease and stroke statistics—2008 update: A report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;117:e25–e147.

2. Smith WS, Lev MH, English JD, et al. Significance of large vessel intracranial occlusion
causing acute ischemic stroke and TIA. *Stroke* 2009;40:3834–3840.

3. Kleindorfer D, Kissela B, Schneider A. Eligibility for recombinant tissue plasminogen activator in acute ischemic stroke: A population study. *Stroke* 2004;35:27e–29e.

4. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* 2007 May;38(5):1655-711.

5. Furlan A, Higashida R, Wechsler L, Schultz G. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Journal of the American Medical Association.* 1999;282(21):2003–2011.

6. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the multi MERCI trial. *Stroke*. 2008;39(4):1205–1212.

~~Furlan A, Higashida R, Wechsler L, Schultz G. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. *Journal of the American Medical Association.* 1999;282(21):2003–2011.~~

7. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549–556.

8. Janata A, Holzer M. Hypothermia After Cardiac Arrest. *Prog Cardiovasc Dis.* 2009 Sep-Oct;52(2):168-79.

9. Guluma K.Z. Hemmen T.M., et al. A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. *Acad. Emerg. Med.* 2006;13:820–827.

10. De Georgia MA, Krieger DW, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (COOL AID): a feasibility trial of endovascular cooling. *Neurology*. 2004;63:312–317.

Formatted: Font: 12 pt

Formatted: Font: 12 pt, Italic

Formatted: Font: 12 pt

~~Guluma K.Z. Hemmen T.M., et al. A trial of therapeutic hypothermia via endovascular approach in awake patients with acute ischemic stroke: methodology. *Acad. Emerg. Med.* 2006;13:820–827.~~

11. Hemmen TM, Raman R, Guluma KZ et al. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. *Stroke.* 2010 Oct;41(10):2265-70.

12. Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med*. 2008;36:1780–1786.

13. Dixon SR, Whitbourn RJ, Dae MW, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol*. 2002;40(11):1928–1934. doi: 10.1016/S0735-1097(02)02567-6.

14. Batista LM, Lima FO, Januzzi JL Jr, et al. Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. *Resuscitation*. 2010 Apr;81(4):398-403.

15. Kandzari DE, Chu A, Brodie BR, et al. Feasibility of endovascular cooling as an adjunct to primary percutaneous coronary intervention (results of the LOWTEMP pilot study) *Am J Cardiol.* 2004;93:636–639.

16. Götberg M, Olivecrona GK, Koul S, et al. A pilot study of rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. *Circ Cardiovasc Interv*. 2010 Oct;3(5):400-7.

~~Adams HP, Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke : A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST) *Neurology*. 1999;53:126–131.~~

17. Badjatia N, Strongilis E, Gordon E, Prescutti M, et al. Metabolic impact of shivering during therapeutic temperature modulation: the Bedside Shivering Assessment Scale. *Stroke*. 2008 Dec;39(12):3242-7.

Appendix

Formatted: Font: 14 pt, Bold, Underline

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____
Rater Name: _____
Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

References

Rankin J. "Cerebral vascular accidents in patients over the age of 60." *Scott Med J* 1957;2:200-15

Bonita R, Beaglehole R. "Modification of Rankin Scale: Recovery of motor function after stroke." ***Stroke*** **1988 Dec;19(12):1497-1500**

Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J. "Interobserver agreement for the assessment of handicap in stroke patients." ***Stroke*** **1988;19(5):604-7**