FAST-COOL

Pre-Hospital Hypothermia for Acute Ischemic Stroke

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FAST-COOL *Concept*

- FAST-COOL is a Phase 2/3 prospective randomized clinical trial of pre-hospital therapeutic hypothermia for patients who present acutely with moderate-to-severe acute ischemic stroke, with or without concurrent reperfusion therapy

FAST-COOL *Background*

- There is a compelling unmet need for rapid and effective neuroprotection for victims of AIS
- The recent success of the NETT RAMPART trial and the NIH FAST-MAG trial of magnesium for AIS have demonstrated that large-scale trials of pre-hospital therapies conducted by ambulance systems is feasible.

Key Treatment Intervals
(n=1470)

Stroke onset to study drug (median)	46 mins
Paramedic arrival on scene to drug (mean)	25 mins
Paramedic arrival on scene to ED (mean)	35 mins
Treated within 1 hour of onset	73%
Treated 1- 2 hr after onset	24%

NIH-NINDS

FAST-MAG

FAST-COOL *Background*

- A large phase 3 clinical trial of prehospital therapeutic hypothermia for AIS
  - Is the logical extension of these collective efforts
  - Is based on successful predicate experience with cardiac arrest
  - Will address a compelling unmet need

FAST-COOL *Hypothermia*

- In experimental models hypothermia is most effective when given **as early as possible**, and is much more effective for **temporary** than permanent occlusion.
- **Refrigerated intravenous saline** solution (30 ml/kg cooled to 5 °C) has been shown to be safe and effective for the induction of hypothermia after cardiac arrest in the ED and pre hospital setting.

FAST-COOL *Design*

- A major goal of FAST-COOL is to focus on a simple, easy to administer, and noninvasive cooling strategy based on nursing interventions.
- The protocol employs two phases
  - **Pre-hospital primary phase:** Refrigerated saline infusion to kick-start the cooling process
  - **Secondary in-hospital phase:** After further screening, cooling will continue in in the ED → ICU or stroke unit.
    - Surface-cooling
    - Magnesium infusion
    - Warm-air skin counter warming (BAIR Hugger)
    - Precedex or meperidine as rescue for shivering

FAST-COOL *Specific Aims*

1. *To evaluate the feasibility, safety, and efficacy of prehospital cooling with 2 liters of cold IV normal saline (over 1 hour) for stroke patients identified with the Los Angeles Motor Scale (LAMS)*

Aim 1 Main Outcome Measures

Proportion of patients who:

- Have cooling initiated within 1 hour of symptom onset
- Attain target temperature (≤35.5 °C) 1 hour after cooling
- Experience complications of special interest
  - Hypoxia (PF ratio <300)
  - Cardiac dysrhythmia (versus control).

Sensitivity and specificity of the LAMS for detecting patients with stroke (AIS or ICH) and an initial NIHSS score of 6 or more.

FAST-COOL *Specific Aims*

2. *To evaluate the feasibility, safety, and efficacy of 24 hours of surface cooling initiated in the ED (target temperature 32-34 °C) with the Arctic Sun Temperature Management System.*

Aim 2 Main Outcome Measures

Proportion of patients who

- Have surface cooling initiated within 1 hour of ED admission
- Attain target temperature (≤34 °C) within 3 hours of stroke onset
- Require pharmacological intervention to control shivering
- Are unable to complete the cooling intervention
- Experience complications of special interest (versus control)
    - Respiratory failure requiring intubation
    - Hypoxia (PF ratio <300)
    - Significant new-onset arrhythmia

FAST-COOL *Specific Aims*

3. To evaluate the effect of pre-hospital systemic cooling on vessel recanalization, hemorrhagic transformation, and brain edema.

Aim 3 Main Outcome Measures (by reperfusion subset)

Proportion of patients who experience

- Symptomatic hemorrhagic infarction
- TIMI 2b or 3 vessel recanalization (subset of those with documented LVO on admission angiography).

Mean infarct volume at 24 hours

Increase in CT infarct volume from 24 hours to day 5 (swelling)

FAST-COOL *Phase 3 Specific Aims*

4. *To evaluate the effect of pre-hospital systemic cooling on clinical outcome. outcomes will stratified by type of reperfusion therapy (IA, IV t-PA only, or none).*

Aim 4 Main Outcome Measures

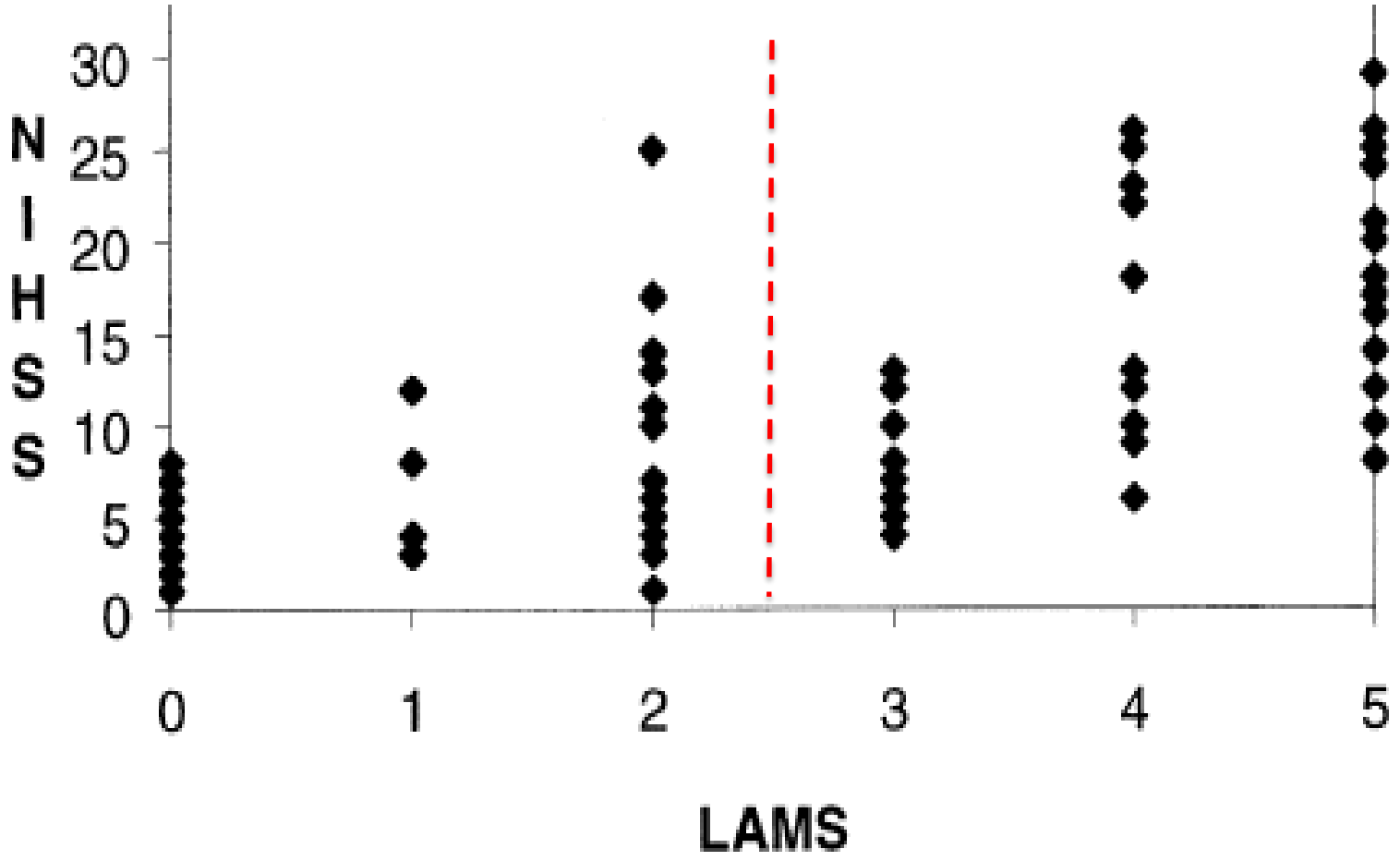
- Day 90 modified Rankin Scale (shift analysis)
- Day 90 mortality
- Day 7-9 NIHSS
- Neurological worsening (nonsedated NIHSS increase of ≥4 points from baseline)
- Neurological improvement (nonsedated NIHSS decrease of ≥4 points from baseline, or level 0-2)

FAST-COOL *Inclusion*

IN THE FIELD

- Age 18-80 years
- Focal neurological deficit with LAMS score 3-5
- Symptom onset or wake-up with new deficit within 2 hours
- Informed consent provided by patient or LAR

LAMS Predicts NIHSS



The Los Angeles Motor Scale (LAMS):

A New Measure to Characterize Stroke Severity in the Field

Jennifer N. Llanes, BA, Chelsea S. Kidwell, MD, Sidney Starkman, MD,
Megan C. Leary, MD, Marc Eckstein, MD, Jeffrey L. Saver, MD

FAST-COOL *Exclusion*

IN THE FIELD

- Respiratory failure or coma requiring intubation or BVM in the field
- Acute pulmonary edema or respiratory distress
- Witnessed seizure activity
- Acute myocardial ischemia (STEMI) on ECG
- Acute hypotension (SBP <100 mm Hg)
- Significant tachycardia or tachyarrythmia (HR <40, >120)
- Severe physical premorbid disability (unable to walk without assistance)
- End stage renal disease on dialysis
- Advanced COPD on home oxygen
- Advanced CHF (AHA 3 or 4)
- Known pregnancy
- Other concurrent serious illness or organ dysfunction (i.e. cancer, AIDS, cirrhosis) that would interefere with study procedures or outcome

FAST-COOL *Statistical Analysis*

The primary outcome for the phase 3 trial will be the overall proportion of subjects experiencing a favorable outcome at 12 weeks (90 days),

- Favorable is defined by the dichotomized mRS score as adjusted to the baseline NIHSS (stroke severity) as planned by the SHINE study.
- This proportion will be compared using a logistic regression model using covariates if they are found to significantly influence the main outcome measure (mRS)
  - Age,
  - Baseline NIHSS
  - Recanalization intervention (none, IV t-PA only, or endovascular ± IV t-PA)
  - Admission BP
  - Admission serum glucose level.