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JOURNAL READING

Hypothermia for the treatment of ischemic and hemorrhagic stroke

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Introduction

- "Gold standard" for neuroprotection
- In hypoxic-ischemic brain injury after cardiac arrest (Anoxic brain injury)
- ↓ brain edema and intracranial pressure (ICP) in traumatic brain injury (TBI)

✓ Few studies for ischemic and hemorrhagic stroke

In stroke

- Antiplatelet, TPA for ischemic
- Elusive for ICH and SAH
- Hypothermia in neuroprotection
  -The Stroke Therapy Academic Industry Roundtable
- Save "penumbra"
- Minimize secondary injury

- However, with complication and different methods

Table 1. Mechanisms of action by which hypothermia can limit ischemic damage

Reduced metabolic demand
Reduced proteolysis
Cell membrane stabilization
Inhibits spreading depolarizations
Decreased excitotoxic damage
Reduces lactate and tissue acidosis
Reduced free radical and reactive oxygen species formation
Reduced disruption of blood brain barrier
Preserves cerebral autoregulation

Table 1. Mechanisms of action by which hypothermia can limit ischemic damage

Reduced metabolic demand
Reduced proteolysis
Alters apoptotic signals
Reduction in neuronal calcium influx and toxicity
Reduces ischemia-associated gene expression
Inhibits inflammation and cytokine production
Reduced disruption of blood brain barrier
Preserves cerebral autoregulation
Inhibits inflammation and cytokine production
Reduced disruption of blood brain barrier
Preserves cerebral autoregulation

Initiation, Duration, and Depth

- Animal models
- strong, time-dependent
- Favor within 120~180 mins
- >3 hrs is serious doubt
  (Except for hippocampus and cerebellum after global hypoxia)
- Prolong→ ↑ protection and complication
- ↓ temperature → ↑ protection
- <33 ℃ → ↑ ↑ complications

Methods

- Pharmacological and physical
- ETT and mechanical ventilation
- opioids and sedatives
  - → ↓ Shivering and discomfort
  - → ↓ respiratory drive
  - → ↓ the neural mechanisms and hemodynamic instability of airway protection

Methods

- Ice packs and cold infusions→ in ER
- Automated surface cooling systems
  → less IV line and complication
- Endovascular heat exchange catheters
- Monitors: bladder, esophagus, rectum, or pulmonary artery

Management of Shivering

- opioids, and central α-2 agonist
- Meperidine → increasing shivering threshold without causing major side effects
- buspirone, propofol, dexmedetomidine, fentanyl, and magnesium sulfate

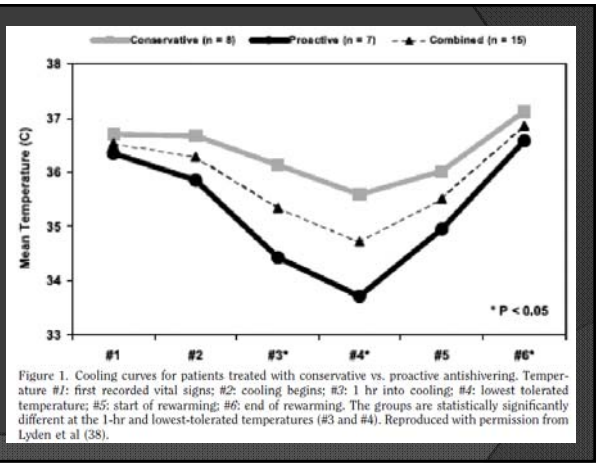


Figure 1. Cooling curves for patients treated with conservative vs. proactive antishivering. Temperature #1: first recorded vital signs; #2: cooling begins; #3: 1 hr into cooling; #4: lowest tolerated temperature; #5: start of rewarming; #6: end of rewarming. The groups are statistically significantly different at the 1-hr and lowest-tolerated temperatures (#3 and #4). Reproduced with permission from Lyden et al (38).

Complications

- Cardiac→ arrhythmias, ↓ LV function and hypotension
- Immunologic→ immunosuppression
- Hematologic→ ↓ Plt and coagulopathy
- Metabolic→ stress related to shivering, hyperglycemia, hypokalemia, ileus, cold-induced diuresis, and a variety of other problems

Complications

- Ventricular arrhythmias→ <28°C, and almost never >32°C
- Rewarming

→ Most dangerous period (SIRS like, hypotension and IICP)

→ Slow rewarming rate in IICP patients

Complications

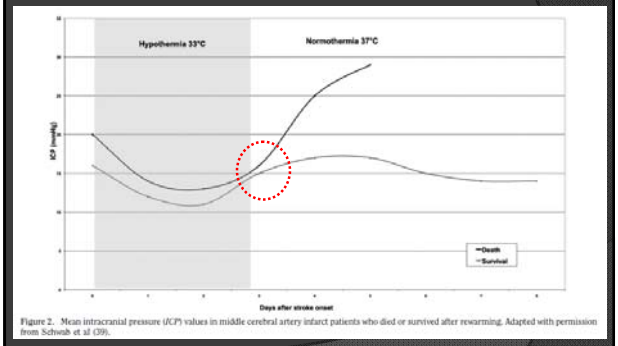
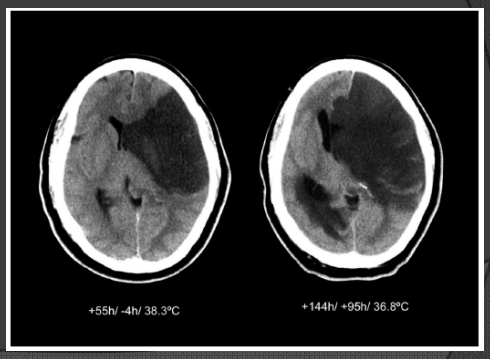


Figure 2. Mean intracranial pressure (*ICP*) values in middle cerebral artery infarct patients who died or survived after rewarming. Adapted with permission from Schwab et al (39).

Complications



Studies in Ischemic Stroke

- *Hypothermia in Spontaneously Breathing Stroke Patients*

✓ No endotracheal tube insertion

✓ aircirculating blankets, IVC cooling catheter (better results)

✓ Meperidine and buspirone for antishivering (good response)

Studies in Ischemic Stroke

- *Hypothermia Plus IV Thrombolysis*

✓ Major stroke, surface cooling for 12~72 hrs→ worse outcome

- Krieger et al, 2001

✓ Within12hrs after onset, IVC catheter for 24hr, 33℃→ ↓ DWI surface

- De Georgia et al, 2004

Studies in Ischemic Stroke

- *Hypothermia and Postischemic Edema*

✓ Morphometric CT, 33°C for 12 or 24 with endovascular system→ ↑ CSF

- Guluma et al, 2008

- *Hypothermia as Salvage Therapy for MCA Infarction*

✓ Surface cooling, ICP monitor→ ↓ ICP, but rebound IICP in fast rewarming

- Schwab and Mayer, 2001

Studies in Ischemic Stroke

- *Hypothermia Plus Hemicraniectomy*
  - ✓ >2/3 of hemisphere, hemicraniectomy alone, or in combination with hypothermia→ better outcome

  - Els et al, 2005
- *Ongoing Trials*
  - ✓ 6-hr window for TPA coupled with hypothermia in intravascular device

Studies in SAH

- *Mild Hypothermia After Poor-Grade SAH*
  - ✓ Severe brain edema, long vs. short term hypothermia (72 hrs)→ no diff.

  - Gasser et al, 2003
- *Intraoperative Hypothermia for SAH*
  - ✓ 33℃ vs. 36.5℃→ better outcome, more postoperative infection

  - Todd et al, 2005

Studies in ICH

- Animal medols
  - ✓ Striatal hypothermia
- *Selective brain hypothermia*
  - ✓ "Brain-protecting Freezer" for 48hrs→ edematous volume decreased

  - Feng et al, 2002

Conclusion

- Considerable potential in stroke
- Feasible widespread application
- Need for high-quality critical care (ICP, rewarming rate, image…..)