Is It Still "Cool" to Use Hypothermia following Pediatric TBI?

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Director, Barrow Neurological Institute
at Phoenix Children’s Hospital
Diane and Bruce Halle Endowed Chair for Children’s Neuroscience
Chief, Pediatric Neurosurgery
“Insanity is doing the same thing over and over again and expecting a different result.”

Benjamin Franklin (1706-1790)
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Disclosures

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• **Scientific Advisory**
  - Traumatec
Introduction

• Trauma and TBI are the leading cause of death and disability in the young in the United States and around the world
• Mortality from trauma, particularly TBI greater than all other pediatric diseases combined
• Leading cause of death and disability in young adults and geriatric population
• Improvements in our understanding have come mostly from single institution series and cohorts
Introduction (cont’d)

- Hypothermia has much experimental evidence and clinical studies.
- Long history for management for stroke, hypoxic ischemic injury, etc.
- Challenge has been in translation of experimental to clinical application in TBI.
NEURAL INJURY 101
Factors Involved In Outcome

Etiology of complications or worsened outcome

- Known v. Unknown?
- Primary mechanism v. Secondary mechanism?
- Primary Injury v. Secondary Injury?
- Disease/Disorder v. iatrogenic?
- Passive v. Aggressive?
- Individual v. Population?
- Physiologic? Biochemical? Molecular?
Key Issues in Acquired Neural Injury and Contemporary Approach to Management

- Age-related differences in neurobiology
- Age-related differences to injury (Primary Mechanisms)
- Age-related differences in pathobiology and response to injury (Secondary Mechanisms)
- Age-related differences in response to treatment (Pediatric approach to treatment)
- Age-related differences in recovery and rehabilitation
ANI 101: Terminology

Definitions:

• Primary Mechanism – the etiologic cause of the injury

• Primary Injury - tissue injury that is as a direct result of the mechanical forces applied at the time of the trauma

• Second/ Secondary Insult - additional injury following the primary injury due directly or indirectly to the trauma (e.g.) hypotension, hypoxia, hyperthermia, etc.

• Secondary Mechanism - pathophysiologic response as a result of the primary injury and/or an additive second insult leading to further injury/damage (e.g.) excitotoxicity, inflammation, dysautoregulation, etc.

• Secondary Injury - injury as a result of the secondary mechanisms
1° Mechanism

Impact/Insult

TBI

(Primary Injury)

2° TBI

(Secondary Injury)

Secondary Mechanisms

Excitotoxicity

Inflammation

Lipid Peroxidation

Apoptosis

2° Insult

2° Insult
Types of Second Insults

- Hypoxia
- Hypotension
- Hematoma
- Ischemic event (i.e.) vascular dissection, MI, etc.
- Second primary injury (i.e.) second concussion/ mild TBI
- Iatrogenic
Secondary Mechanisms

- Seizures
- Hyperthermia
- Impaired CBF/ autoregulation (decreased perfusion)
- Metabolic Failure/ Oxidative Stress
- Cytotoxic vs. Vasogenic Edema - capillary compression
- Biochemical Disruption - Excitotoxicity, inflammatory response, free radical formation, lipid peroxidation/ membrane dissolution, Apoptosis
- Brain Swelling/ Herniation - arterial compression
- Vasospasm

Secondary injury can also be a Second Insult!
Severe TBI

Mediators of Secondary Injury

- Glutamate
- Aspartate
- Glycine
- Inflammation
- IL-2
- IL-4
- IL-6
- IL-8
- IL-10
- IL-12
- sP-Sel
- sICAM-1
- QUIN

Endogenous Neuroprotectants

- Adenosine
- Adrenomedullin
- Procalcitonin
- BCL-2

CBF - Related

- Endothelin-1
- Nitrate / Nitrite

Cell Death Markers

- Nucleosomes
- sFas
- sFasL
- NSE
- S-100B
APPROACH TO CONTEMPORARY MANAGEMENT
Time is Brain!!
What do we know about the Management of TBI?

Supportive care and early intervention based on Adult and Pediatric Guidelines - Avoidance of second insults

Some treatments for intracranial hypertension - Response to secondary injury mechanisms

Medical and or surgical intervention in select cases - Avoidance of second insults and response to secondary injury
Hypothermia

My feet are just freezing!

BLIMEY!!
You think you've got troubles!
TRAUMATIC INJURIES OF THE BRAIN AND ITS MEMBRANES

WITH A SPECIAL STUDY OF PISTOL-SHOT WOUNDS OF THE HEAD IN THEIR MEDICO-LEGAL AND SURGICAL RELATIONS

BY
CHARLES PHELPS, M.D.
SURGEON TO BELLEVUE AND ST. VINCENT'S HOSPITAL

WITH FORTY-NINE ILLUSTRATIONS

NEW YORK
D. APPLETON AND COMPANY
1897

“What is new is old....

... and what is old is new!”
“The shaving of the head, which has been advised as a means of facilitating diagnosis, is at the same time a measure of treatment. ... its removal in some degree aids in the reduction of temperature. The essential advantage, however, ... is that it permits the effective application of the ice-cap, which next to trephination, under indicated conditions, is not nearly a directly curative resource.”

“The topical use of cold in this manner is serviceable in those cases in which cerebral hyperaemia or meningeal inflammation is manifested by pain, high temperature, and active delirium.”

“It is contraindicated in hemorrhages and cerebral lacerations when uncomplicated by serious contusion; but, as those lesions are constantly thus complicated, it may be held a proper resort when such symptoms are manifest, without regard to exact diagnosis.”

“There is the history of a case, ... which ended in recovery, in which the mind was clear and the temperature approximately normal whenever the ice-cap was applied, and in which the temperature rose markedly and delirium recurred whenever it was removed. These interchangeable conditions were made the subject of frequent observation for several days.”

Charles Phelps, MD, 1897
Experimental Evidence Favoring Hypothermia

Hypothermia:
- Reduced the amount of brain tissue damage in a number of adult animal and pediatric models of hypoxia and/or ischemia and TBI
- Even brief periods after ANI resulted in better functional outcome
- More effective if begun earlier rather than later post-injury
- Neuronal protection in typically vulnerable brain regions (e.g.) hippocampus and striatum, even when reduction of only 2°C.
Experimental Evidence (cont’d)

• Longer periods resulted in less histologic damage, less apoptosis, delayed neuronal death, decreased infarct size
• Decreased cell signal survival pathways
• Partially or completely inhibited the release of high levels of EAA that typically occur following injury to the brain
• The shorter the post-ischemic intervention delay and the greater the degree of hypothermia, the better the neuroprotective effect seems to be.
• Even delay of onset resulted in greater neuroprotection when a greater duration of cooling used after an ischemic event
• Long term effect dependent on length and timing of intervention
Experimental Evidence Favoring Hypothermia

• The mechanism(s) for the beneficial effect of HYPO in humans (both adult and pediatric) remains unknown though likely multi-factorial.

• Experimental models of TBI demonstrated positive effects of HYPO:
  – Reduced mediators of secondary injury including excitotoxicity, reduced inflammation, reduced apoptosis.

• Experimental evidence has provided insight but not definitive understanding.
WHAT ‘S NEW SINCE THE 2003 GUIDELINES? CLINICAL EVIDENCE
Clinical Evidence for Hypothermia

Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension
Biswa et al., Critical Care Medicine 2002

Description of Study
RCT of 21 children with severe TBI treated with hypothermia (32-33°C) within 6 h of injury for 48 h followed by re-warming within 12 h vs normothermia

Study of effect on ICP though outcomes reported on GOS, PCPC, and the POPC

Conclusion
Positive impact on ICP during cooling but no significant impact on outcome in any of the functional outcome scales used
Clinical Evidence for Hypothermia

Treatment of acute traumatic brain injury in children with moderate hypothermia improves intracranial hypertension
Biswa et al., Critical Care Medicine 2002

Rated a class III study
Unclear reporting of randomization and allocation; baseline differences in GCS; differential attrition

Supports beneficial effect on ICP during moderate hypothermia when applied within 6 h and continued for 48 h

Conclusion
Positive impact on ICP during cooling but no significant impact on outcome in any of the functional outcome scales used
P. David Adelson, M.D.
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John Ragheb, M.D.
Department of Neurosurgery, University of Miami, Miami, Florida

J. Paul Muizelaar, M.D.

PHASE II CLINICAL TRIAL OF MODERATE HYPOTHERMIA AFTER SEVERE TRAUMATIC BRAIN INJURY IN CHILDREN

OBJECTIVE: To determine whether moderate hypothermia (HYPO) (32–33°C) begun in the early period after severe traumatic brain injury (TBI) and maintained for 48 hours is safe compared with normothermia (NORM) (36.5–37.5°C).

Adelson et al. 2005
Clinical Evidence for Hypothermia

Phase II clinical trial of moderate hypothermia after severe TBI in children
Adelson et al, 2005

Description of Study
RCT of 75 children with severe TBI (GCS 3-8) cooled to 32-33°C within 8 h of injury for 48 h as compared to normothermia.
Slow re-warming at a rate of 0.5-1.0 °C per 12-24 h

Conclusion
No difference between groups in mortality or 3- and 6-month GOS

Rated a class II study
Supports beneficial effect of moderate hypothermia (32-33°C) on ICP and Safety when used for 48 h duration and initiated within 8 h

No difference between groups in complication rates
Hypothermia Therapy after TBI in Children

Description of Study

RCT of 225 children with severe TBI (GCS score 3-8) that were randomized to cooling to 32-33°C within 8 h of injury for 24 h vs. normothermia.

Re-warming at a rate of 0.5-1.0°C per h.

Conclusion

No difference between groups on functional outcomes at 6 mo.

Trend towards increased mortality and morbidity in the hypothermia group.

Higher ICP in hypothermic group during re-warming.

Significant increase in hypotension and pressor requirements in the hypothermia groups.

Rated a class II study—deficiencies between groups at baseline.

Supports two positions:

1) Moderate hypothermia (32-33°C) initiated within 8 h of severe TBI and applied for 24 h should be avoided.

2) If hypothermia is induced, re-warming at a rate of >0.5°C per h should be avoided.

<table>
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<tr>
<th>Adverse events — no. (%)</th>
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<tbody>
<tr>
<td>Hypotension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-24 hr</td>
<td>27 (25)</td>
<td>18 (15)</td>
<td>0.07</td>
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<tr>
<td>25-72 hr</td>
<td>49 (45)</td>
<td>38 (32)</td>
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Comparison of hypothermia and normothermia after severe traumatic brain injury in children (Cool Kids): a phase 3, randomised controlled trial

Summary
Background: On the basis of mixed results from previous trials, we assessed whether therapeutic hypothermia for 48–72 h with slow rewarming improved mortality in children after brain injury.

Methods: In this phase 3, multicenter, multinational, randomised controlled trial, we included patients with severe traumatic brain injury who were younger than 18 years and could be enrolled within 6 h of injury. We used a computer generated randomisation sequence to randomly allocate patients (1:1; stratified by site and age [<6 years, 6–15 years, 16–17 years]) to either hypothermia (rapidly cooled to 32–33°C for 48–72 h, then rewarmed by 0·5–1·0°C every 12–24 h) or normothermia (maintained at 36·5–37·5°C). The primary outcome was mortality at 3 months, assessed by intention-to-treat analysis; secondary outcomes were global function at 3 months after injury using the Glasgow outcome scale (GOS) and the GOS-extended pediatrics, and the occurrence of serious adverse events. Investigators assessing outcomes were masked to treatment. This trial is registered with ClinicalTrials.gov, number NCT00222742.

Findings: The study was terminated early for futility after an interim data analysis on data for 77 patients (enrolled between Nov 1, 2007, and Feb 28, 2011): 39 in the hypothermia group and 38 in the normothermia group. We detected no between-group difference in mortality 3 months after injury (6 [15%] of 39 patients in the hypothermia group vs two [5%] of 38 patients in the normothermia group; p=0·15). Poor outcomes did not differ between groups (in the hypothermia group, 16 [42%] patients had a poor outcome by GOS and 18 [47%] had a poor outcome by GOS-extended paediatrics; in the normothermia group, 16 [42%] patients had a poor outcome by GOS and 19 [51%] of 37 patients had a poor outcome by GOS-extended paediatrics). We recorded no between-group differences in the occurrence of adverse events or serious adverse events.

Interpretation: Hypothermia for 48 h with slow rewarming does not reduce mortality of improve global functional outcome after paediatric severe traumatic brain injury.
RESULTS: ICP

• During the 5-day ICP monitoring period, TH patients had lower average ICP, 2.1 mm Hg ± 2.0 though not statistically significant (p=0.23).

• There were group differences with regard to 2nd Tier therapy treatment in that NORM patients underwent decompressive craniectomy for control of their ICP more frequently than TH patients (17 (44.7%) vs. 7 (17.9%), respectively).
Conclusions

• TH was not shown to be efficacious as a primary neuroprotective strategy from mortality or early global outcome in children with severe TBI

• TH was effective in lowering ICP as part of 2nd Tier therapy.

• Multiple issues related to CKT study and clinical trials in TBI and in children
Critiques of CKT

1. Poor accrual
   • Decrement in actual patient numbers
     – Decreased traumas
     – Decreased consent
     – Increased exclusions - abuse, age
   • Waiver and/or Emergency Waiver of consent
Critiques of CKT

2. Select patient population
   - Select patient population (< 6 h from injury) but also diverse
     - High number of transfers
     - Limited population
   - Exclusion of:
     - Abuse, GCS=3, Unknown time of injury
   - Heterogeneous patient population
     - Variable pathologies
Critiques of CKT

3. Center Recruitment Issues
   • Prolonged center recruitment
     – Identification
     – Obtaining of data to determine potential as a site
     – Approval by all necessary personnel
   • Prolonged time to get a center screening and recruiting
     – IRB submission and approval
     – Contract approval
     – Training of personnel
     – Initiation of screening
Critiques of CKT

4. Design and protocol variation

- Initially up to 48 h of cooling with variable time of initiation of rewarming, then change to up to 72 h

- Inclusion of up to 16 years then change to up to 18 years of age

- Abuse with known time of injury

- Despite strict protocol delineation:
  - Variable treatment paradigms as part of protocol
  - Variability in practice conformity
5. Relevance

- Mortality as a primary outcome measure
- Differences in treatment groups
  - Hypothermia vs. Normothermia
  - Hypothermia vs. Decompressive Craniectomy
- Validity of secondary outcome measures
  - Global function
  - Neuropsychological measures
  - ICP
- Improved outcomes with involvement in clinical trials
Multicenter and Multinational

Added dimension of complexity

• Protocol development and “buy in”
• IRB’s
  – Central vs. Local
  – Waiver of consent
• Contracts
  – Contracted service agreements/ per patient vs. Fixed center support
FUTURE OF HYPOTHERMIA?
Present Day Situation TBI

Present lack of:

• Understanding of the unique aspects of brain and response to injury
• Preclinical studies and experimental models with re: to mechanisms of injury and therapeutic interventions
• Clinical studies in traumatic brain injury
• Clinical trials in TBI
• Infrastructure to institute large scale TBI clinical trials
Acquiring Adequate Current Best Evidence

PubMed Search (2014)  

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<tr>
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Glioblastoma Survival: Progress To Date

1980: median survival of 10 months
2010: median survival of 14 months
Survival following Pediatric TBI

5 Year Epochs


Survival

% Survival

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
Art of Medicine (Now?)

“One practices the ‘art of medicine’ when science does not (yet) provide the answer.”

PD Adelson, 2009
Complexity of Disease

• One practices the “art” when evidence lacking for best quality care

• Multiple “optimal” approaches to disease when certainty does not exist

GOAL!!: Decrease uncertainty, increase probability
Keys to Management: Present and Future

Goal: Create an environment of neural recovery

- Understand that injury differs on an individual basis, personalized approach to dx and rx
- Understand the mechanisms of injury
- Measure in real time the injured brain
- Minimize second insults
- Minimize secondary mechanisms of injury
- Improved capability and understanding to measure responses to treatments
Conclusions (to date)

• Efficacy of hypothermia treatment following TBI? Age, mechanism of injury, etc.?
• Mechanisms of action?
• Timing of initiation, length of cooling, rewarming protocol, and multimodality approach?
• Measure of outcome?
• Global application?
  – Minimizing complications
  – Optimizing outcome