THERAEUTIC HYPOTHERMIA IN TBI

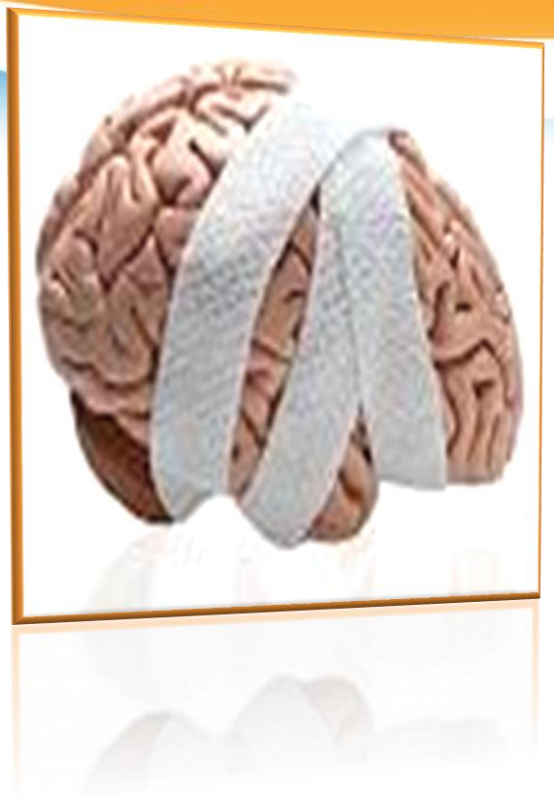
ALEXANDRIA EXPERIENCE

Abdallah ELATRASH, MD

Department of Critical Care Medicine

Alexandria University

OBJECTIVES



- TBI definition, burden on public health and pathophysiological classification .
- Neuroprotective mechanisms of therapeutic hypothermia in TBI.
- Alexandria study on therapeutic hypothermia in TBI.
- Some published data on therapeutic hypothermia in TBI.

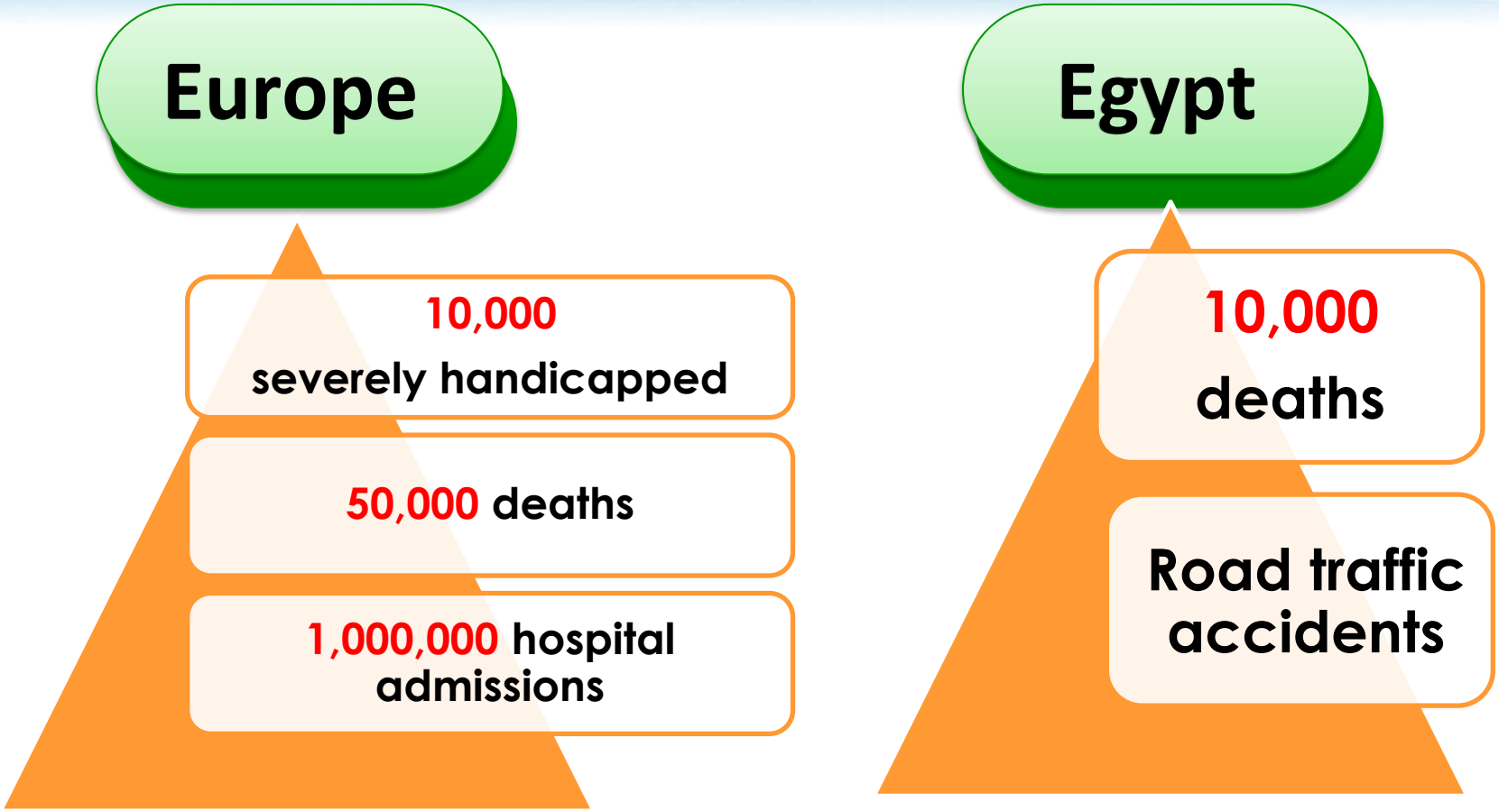
What Is a Traumatic Brain Injury (TBI)?

- The Centers for Disease Control and Prevention (CDC) defines TBI as:

  "Cranio-cerebral trauma associated with neurological or neuropsychological abnormalities, skull fracture, intracranial lesions or death".

Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.

Public Health Burden of TBI in Egypt compared to Europe

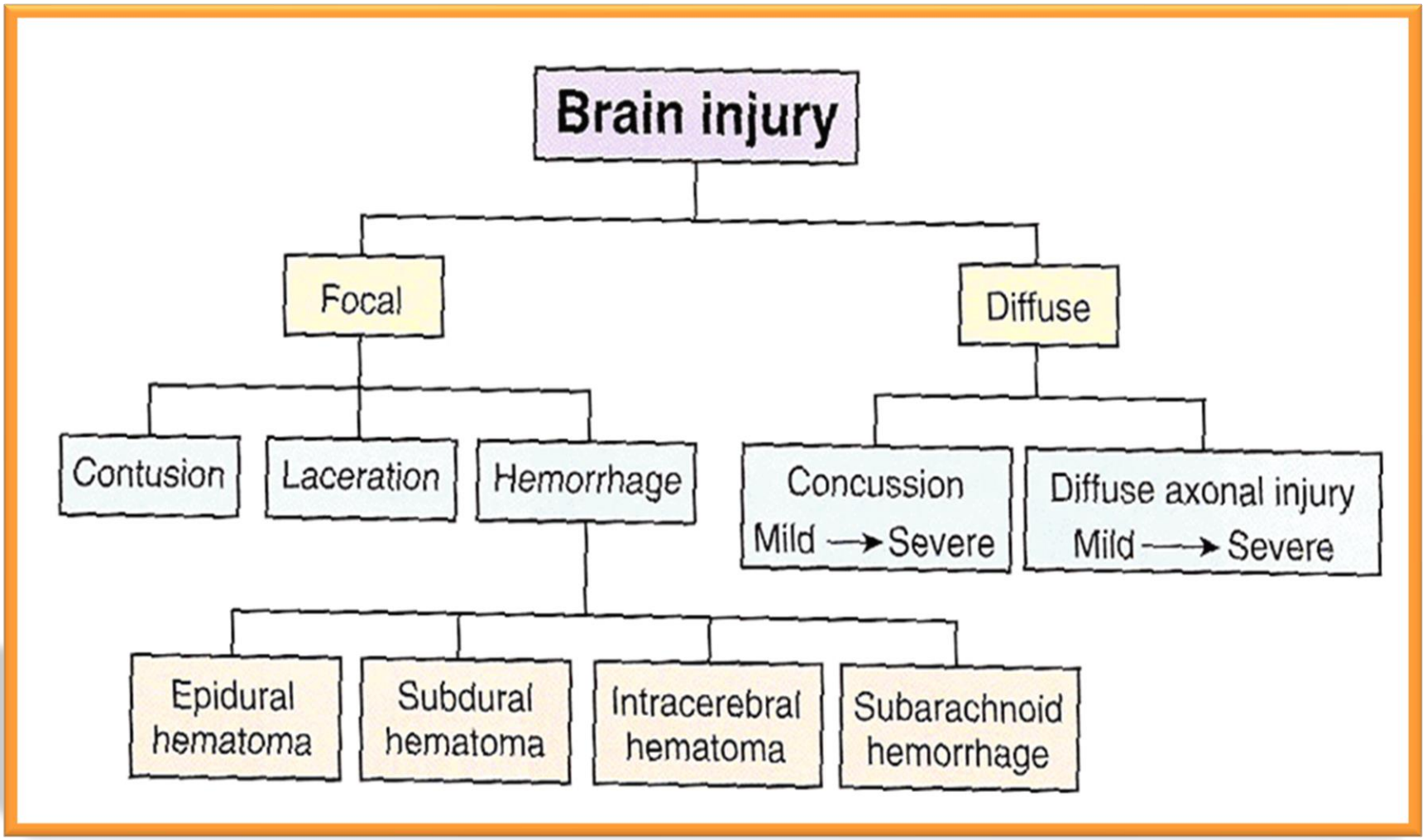


Sinclair HL, Andrews PG. Hypothermia in traumatic brain injury. Crit Care 2010.

El-Sayed F, et al. Road Traffic Injuries and Data Systems in Egypt: Addressing the Challenges. Traffic Injury Prevention 2012.

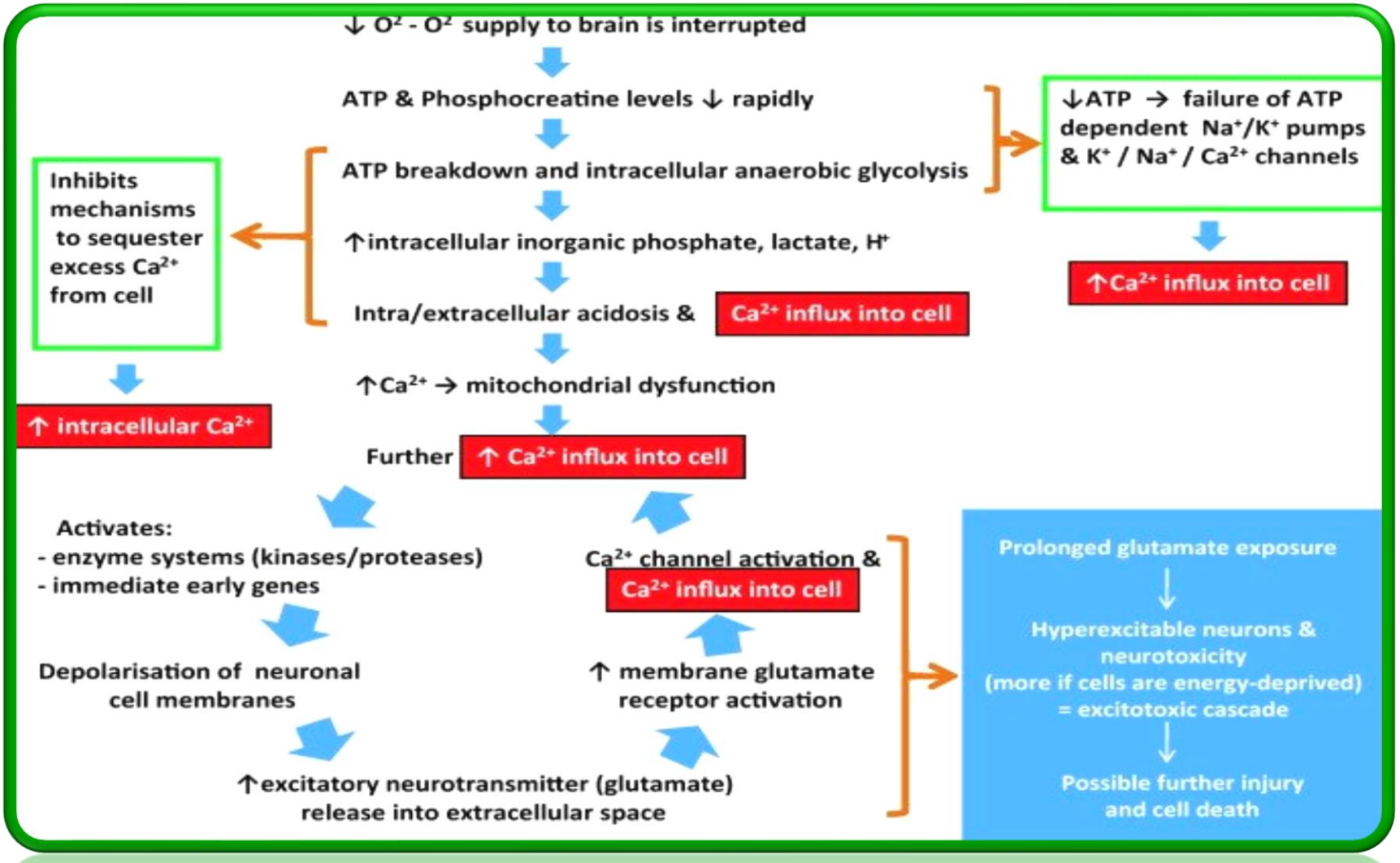
Primary Injury

- Occurs at the time of trauma.



Secondary Injury

- Begins immediately after the injury and lasts days to weeks.



Traumatic Brain Injury: From Guidelines to Novel Therapies

- Guidelines for management of traumatic brain injury focus on:
  - ICP and CPP optimization.
  - Hemodynamic and electrolyte and ventillatory optimization.
  - Prevention of infections and DVT.
  - Nutrition.

At Present There Are No Effective Drug Treatments for Traumatic Brain Injury

- Several novel treatment modalities are suggested and are under research:
  - Glutamate antagonists,
  - Antioxidants,
  - Caspase inhibitors and
  - Progesterone.
  - Therapeutic hypothermia.

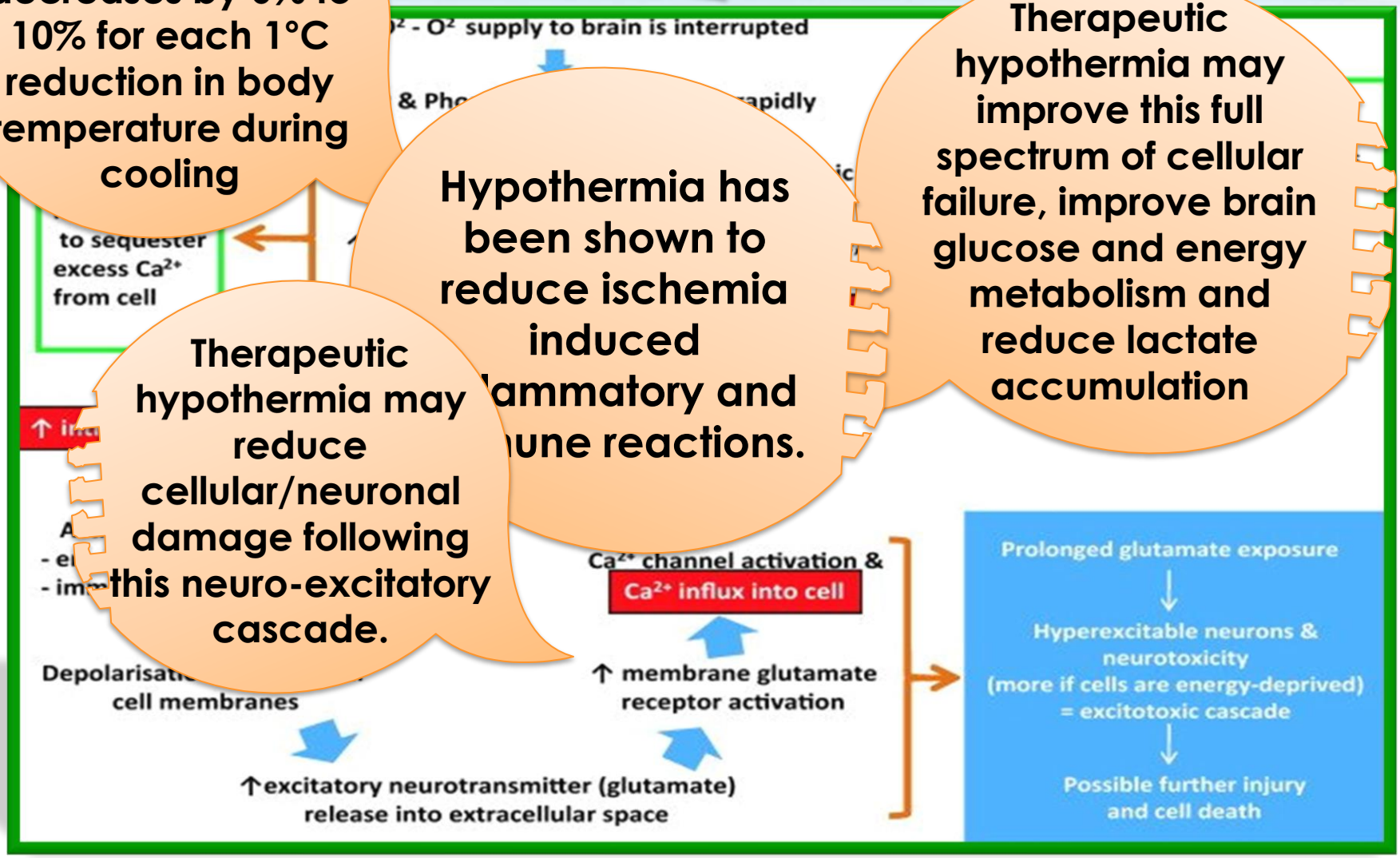
Therapeutic hypothermia
…oprotection

Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature during cooling

Hypothermia has been shown to reduce ischemia induced …lammatory and …une reactions.

Therapeutic hypothermia may improve this full spectrum of cellular failure, improve brain glucose and energy metabolism and reduce lactate accumulation

Therapeutic hypothermia may reduce cellular/neuronal damage following this neuro-excitatory cascade.



Therapeutic hypothermia

Hypothermia

- Is defined as core temperature less than 36.0°C regardless of the cause.

Therapeutic hypothermia

- Is an intentional reduction of a patients' core temperature below 36.0°C with the potentially deleterious effects, such as shivering, being controlled or suppressed.

Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008; 371: 1955– 69.

STUDY OF THE PROTECTIVE ROLE OF THERAPEUTIC HYPOTHERMIA IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY

Tamer A. Helmy[1], Wael M. Mosa[2], Abdallah F. Elatrash[1]
Alexandria University, [1]Department of Critical Care Medicine,
[2]Department of Neurosurgery Medicine, Alexandria, Egypt

- **In this study, we tried to answer three questions:**
  - **Does therapeutic hypothermia reduce mortality after TBI?**
  - **Does therapeutic hypothermia improve neurological outcome after TBI?**
  - **Is therapeutic hypothermia a safe intervention?**

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- 52 adult patients presented with severe traumatic brain injury, admitted to the Department of Critical Care Medicine at Alexandria University Main Hospital during 2012 were included.
- The patients were randomly divided (by sealed envelop method ten by ten) into 2 groups (normothermia group and therapeutic hypothermia group).
- Both groups received standard care for TBI according to BTF/AANS guidelines 2007 except for lack of invasive ICP monitoring.

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Inclusion criteria:

- **Age > 18 years.**
- **Primary closed non-surgical TBI.**
- **An abnormal CT scan of the brain. This is defined as one that shows hematoma, contusion, swelling or compressed basal cisterns.**
- **Glasgow Coma Score <9 pre-sedation after initial resuscitation.**
- **≤72 hours from the initial head injury.**

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Exclusion criteria:

- **Administration of barbiturate infusion prior to randomization.**
- **Temperature ≤34°C on hospital admission.**
- **Pregnancy**
- **Uncontrolled bleeding.**
- **Thrombocytopenia (platelets < 50,000 /cc) or other coagulopathy (INR >1.5**
- **Uncontrollable dysrhythmias.**
- **Refractory hypotension (MAP <60 mm Hg) despite preload optimization and use of vasoactive medications.**
- **Existing multi-organ dysfunction syndrome, sever sepsis, or comorbidities with minimal chance of meaningful survival independent of neurological status for the next 24 hours in the opinion of the ICU Consultant or Consultant Neurosurgeon treating the patient.**

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All patients were subjected to:

1. Complete history taking including.

2. Physical examination and baseline neurological evaluation.

3. Initial laboratories:

- **ABG.**
- **Random blood sugar.**
- **Blood urea nitrogen (BUN) / serum creatinine (Cr).**
- **CBC/ platelets / PT / PTT.**
- **Sodium/ potassium/ Calcium / Magnesium / Phosphorous.**
- **Lactate, CPK-MB, Troponin.**
- **Pan-culture.**
- **Toxicology screen when appropriate.**
- **Pregnancy test for females in child bearing period.**

4. Chest X ray on inclusion, Head CT on inclusion, Echocardiogram.

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Patient preparation:

1. Cardiovascular:

- Continuous ECG monitoring.
- Arterial-line in non-dominant side for continuous arterial blood pressure.
- Urinary catheter for continuous urine output measurement (in ml/hr).
- Central venous catheter (CVC) for central venous pressure (CVP in cmH2o) & central venous oxygen saturation (ScvO2) .
- A retrograde catheterization of the internal jugular vein (IJV) was used for SjvO2 monitoring. As the right IJV is usually dominant, it was commonly used for cannulation to reflect the global cerebral oxygenation. (102)

2. Pulmonary:

- Continuous SaO2 probe (in %).
- Frequent ABG's (temperature correction)..

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Patient preparation:

3. Temperature:

- Using tympanic membrane temperature probe (every 1 hr.).

4. Neurologic:

- Neuro checks q 2 hour (while paralyzed pupils were followed)

5. Additional monitoring and follow-up studies:

- If net fluid balance is > 5 liters in 24 hrs, intra-abdominal pressure (IAP) via Foley catheter was monitored (aiming to keep IAP is < 20 mmHg).
- CXR was repeated after 72 hours to rule out aspiration pneumonia.

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- **Cooling protocol in therapeutic hypothermia group:**
- **Goal:**

- Target temperature of 32° to 34 °C was achieved and maintained for 48 hours from time cooling initiated.

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- **Induction:**

- **Sedation and analgesia were initiated with Fentanyl (50 to 100 mcg IV bolus followed by 50 mcg/hour infusion) and Propofol (5-10 mcg/kg/min infusion) Midazolam was used as alternative to propofol in some selected patients.**

- **Paralysis with Cisatracurium (0.15-0.2 mg/kg IV bolus followed by 1-3 mcg/kg/min IV drip).**

- **Meperidine (0.25- 0.5 mg/ kg q4-6 hrs IVP but not to exceed 100 mg) was used to treat shivering once neuromuscular blockers (NMBs) have been stopped.**

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- **Induction:**

- **Infusion of 30 ml/kg of 4° C saline over 30 minutes. If target temperature was not achieved within 4 hours, additional 500 cc boluses of 4°C intra venous fluids was infused.**

- **Active external cooling with skin exposure, ice packs applied to groin and axilla (wrapped in sheet or pillow case) and occasionally fans started in parallel with iced saline infusion.**

- **If temp < 31°C, 250 ml boluses of warm 40°C IV normal saline solution was given.**

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- **Maintenance (Once core temp of 33 °C is achieved):**

- **Continue sedation, analgesia, and paralysis for 48 hours.**
- **Careful monitoring and adjusting of random blood sugar, electrolytes, and ventilator settings.**

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- **Rewarming (48 hrs after initiating cooling):**

- **Gradual rewarming (no faster than 0.25 ° C/hour or 1° C per 4 hours) by passive rewarming.**

- **Volume load aggressively with normal saline solution to compensate for reductions in central venous pressure (CVP).**

- **Discontinuation of all K+ containing fluids but always hypokalemia, and other electrolytes were corrected to the normal range.**

- **Paralysis was maintained until patient reached 36°C.**

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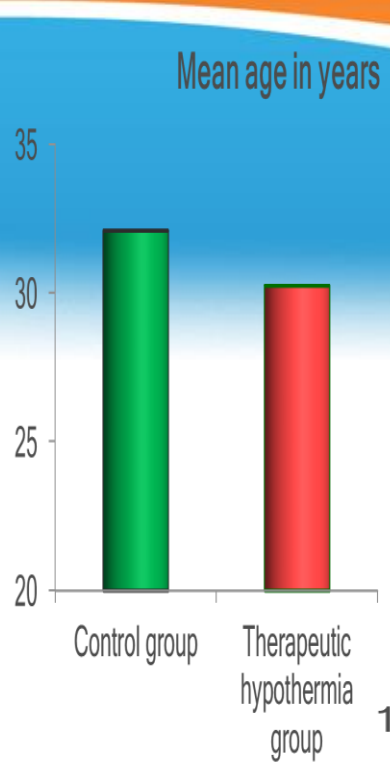
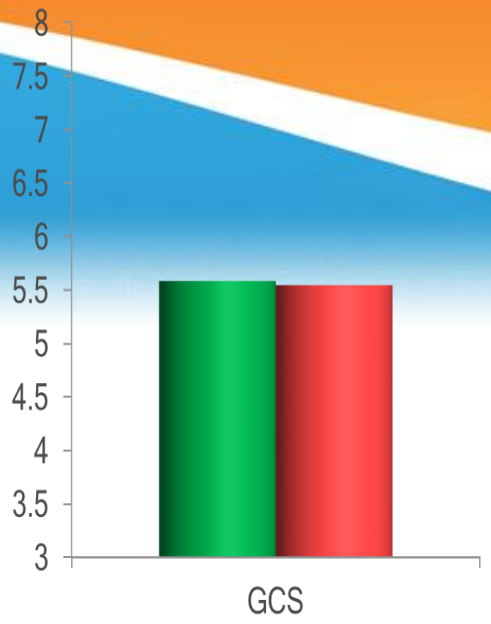
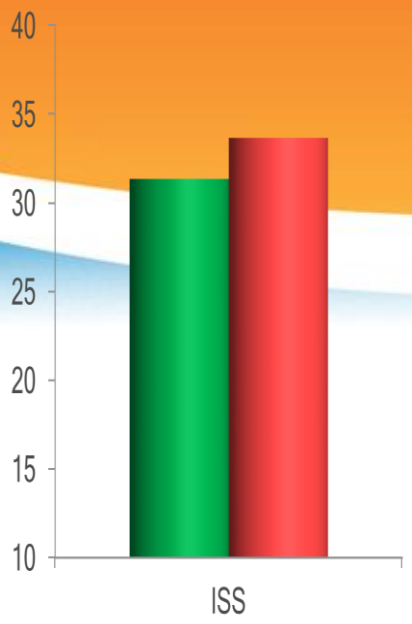
Patient management during therapeutic hypothermia:

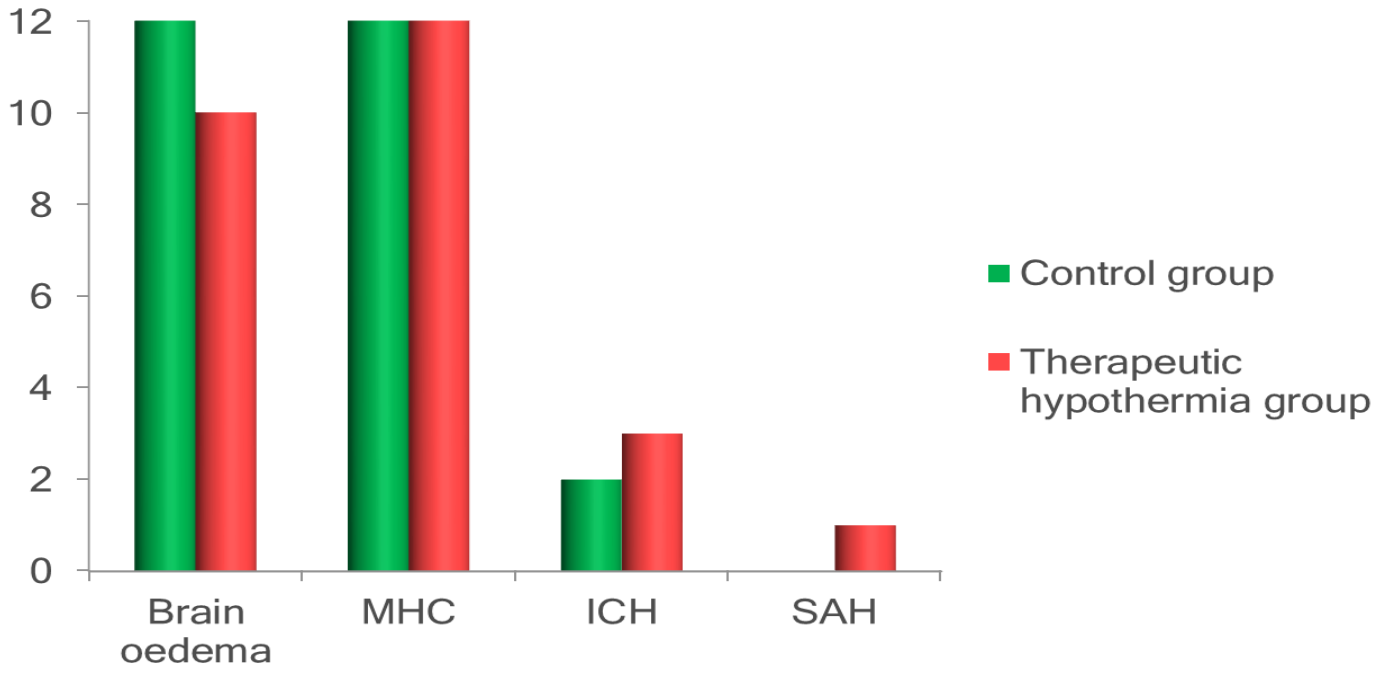
- **NPO**
- **Glucose Management Protocol to maintain RBS< 150 mg/dl.**
- **Prophylactic ampicillin-sulbactam IV q 6 (for PCN allergic Clindamycin 300 mg IV q 8 hours was used) within one hour to prevent aspiration pneumonia,**
- **Acetaminophen 1 gram per rectum or per NGT, then 500 mg q 6 hours during rewarming to prevent fever.**
- **GI and DVT prophylaxis with IV Ranitidine and SC Heparin or by the use of mechanical thromboprophylaxis using elastic stockings.**

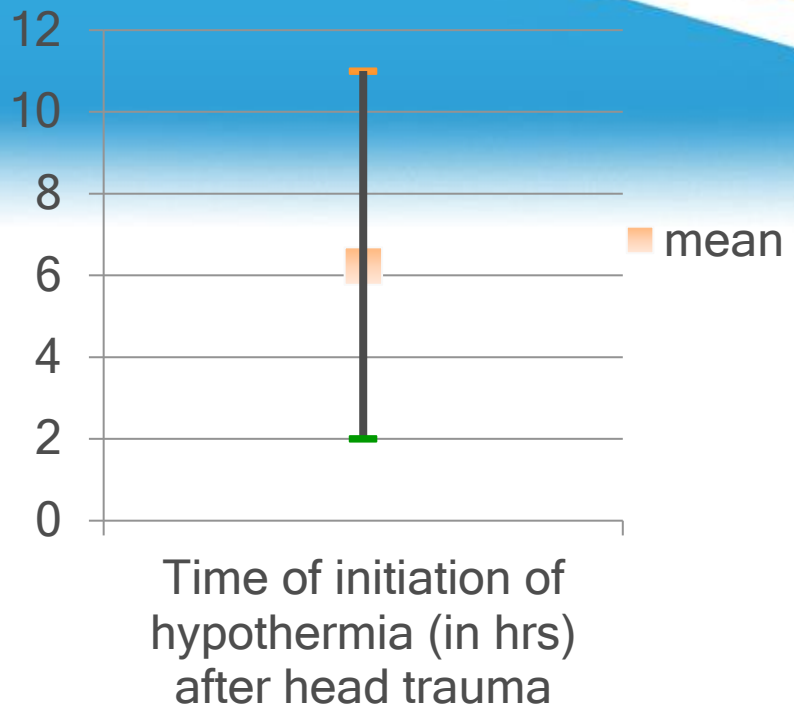
Results


Mean age in years
35
30
25
20
Control group
Therapeutic hypothermia group
Control group
Therapeutic hypothermia group

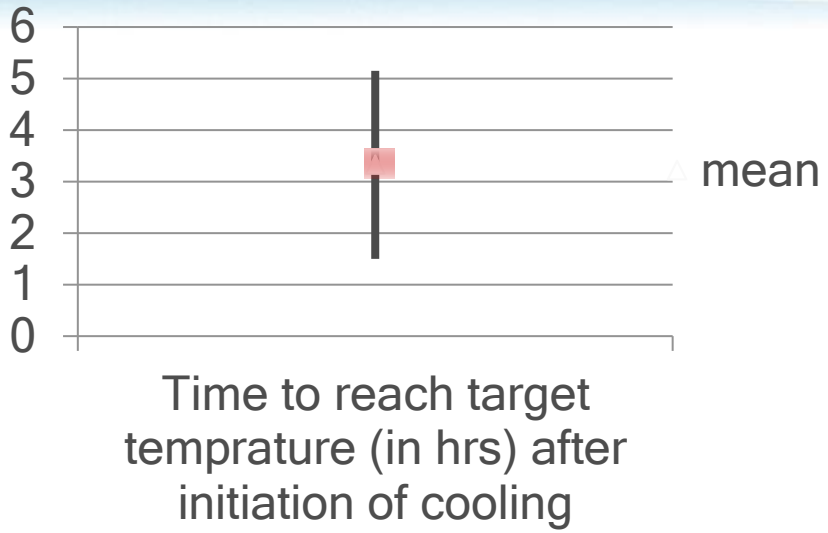

8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
GCS
Control group
Therapeutic hypothermia group


40
35
30
25
20
15
10
ISS
Control group
Therapeutic hypothermia group


12
10
8
6
4
2
0
Brain oedema
MHC
ICH
SAH
Control group
Therapeutic hypothermia group



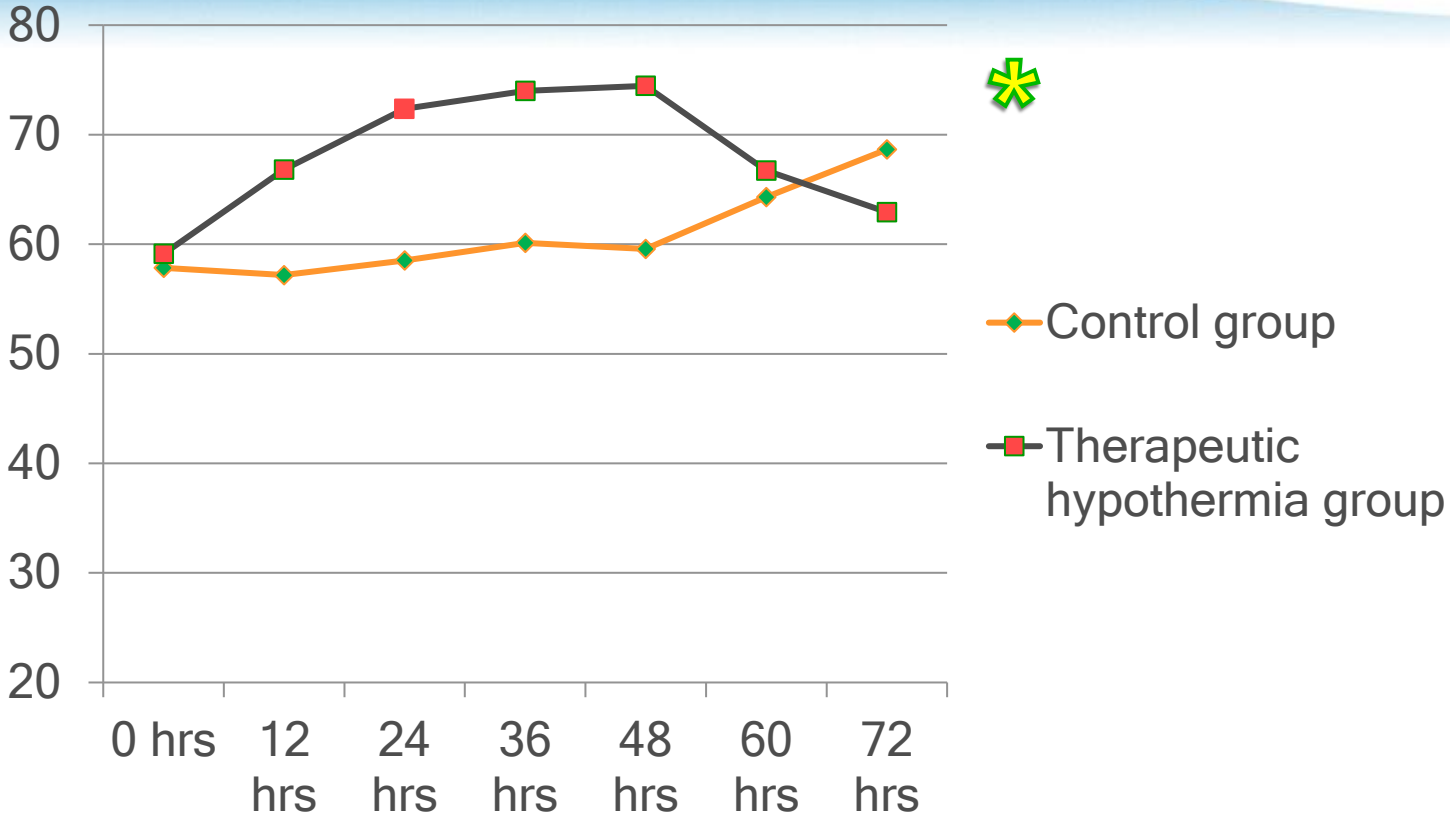
Time of initiation of hypothermia (in hrs) after head trauma



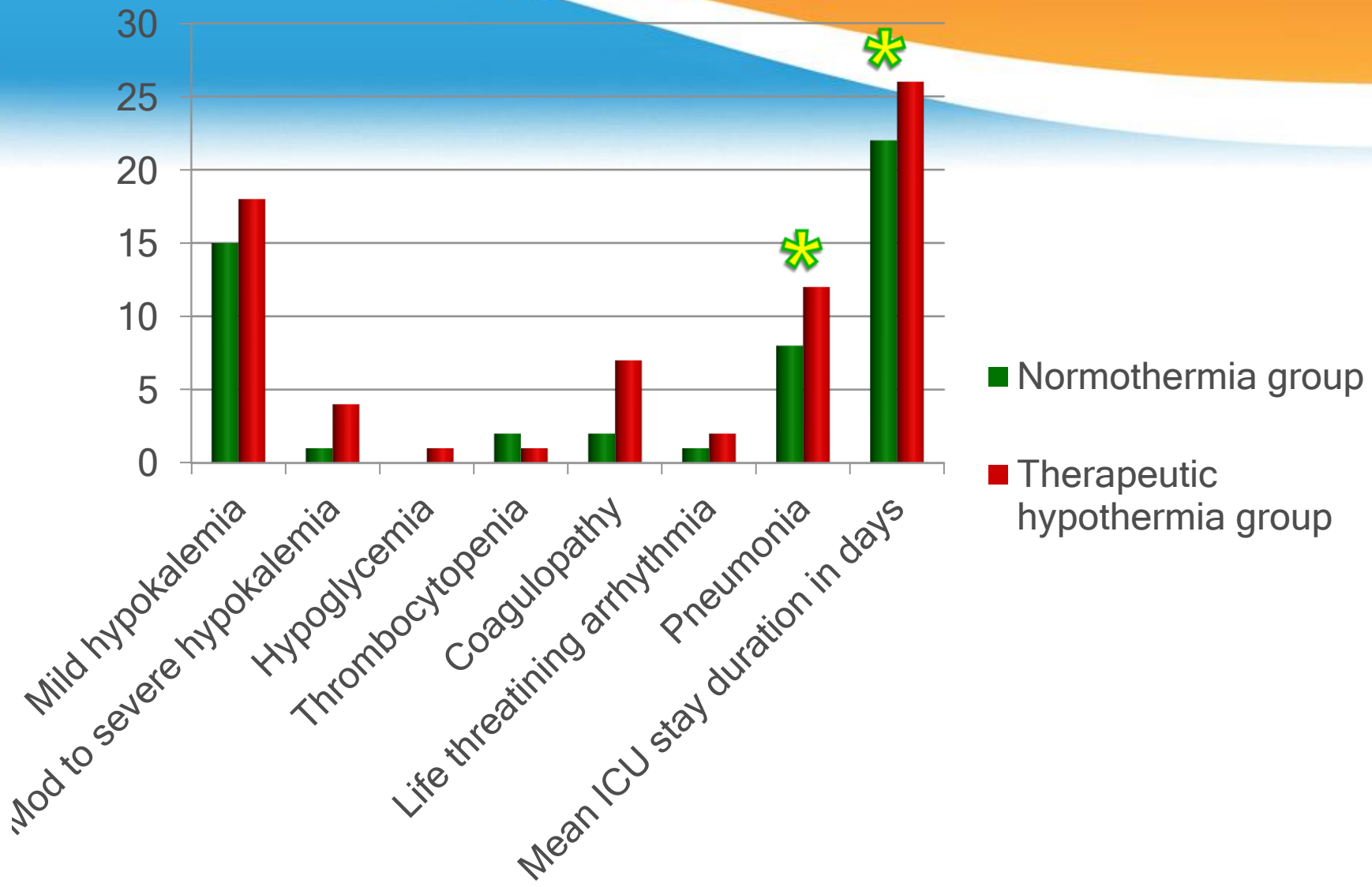
Time to reach target temprature (in hrs) after initiation of cooling

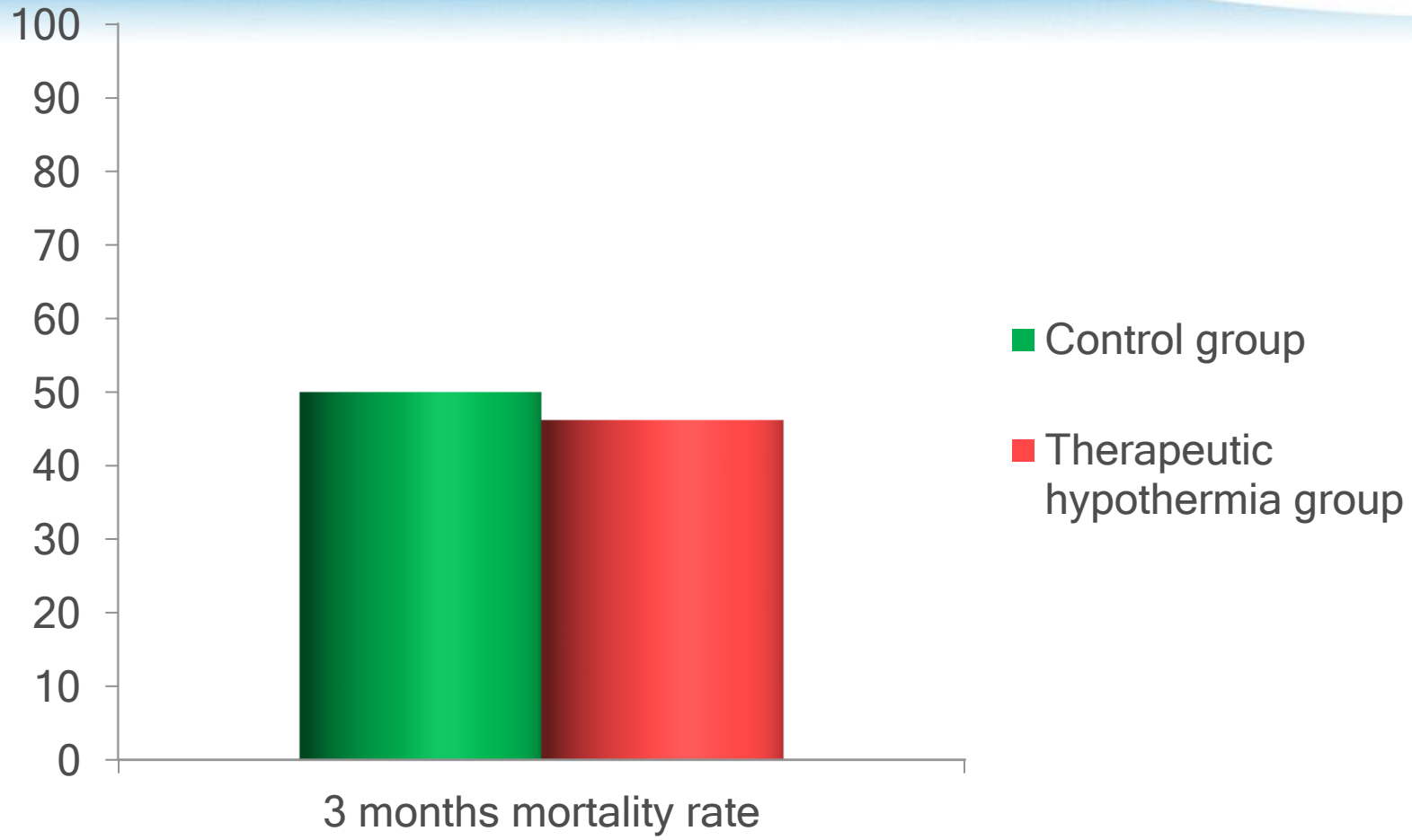
Temprature out of range time (%) during maintainence phase

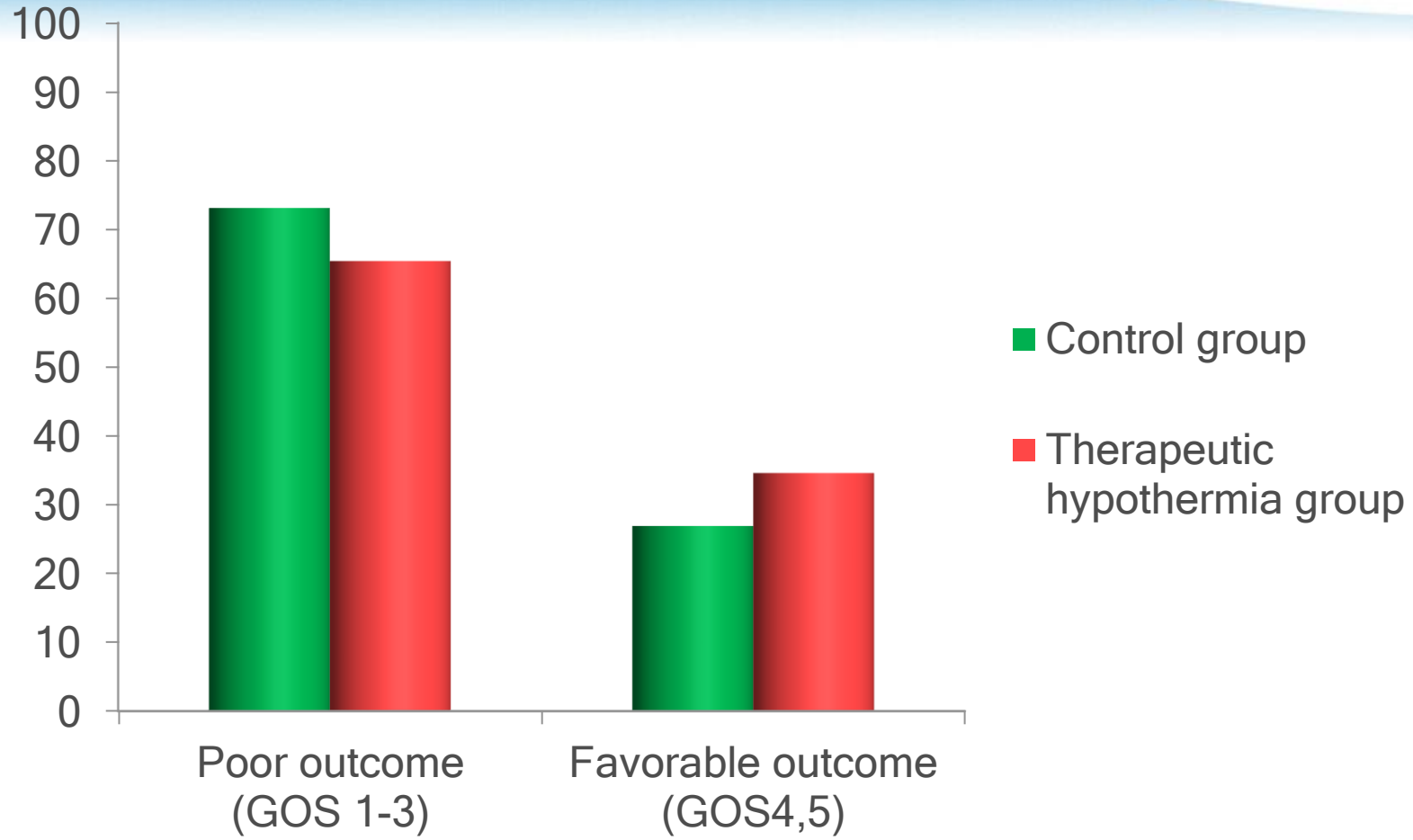
Mean arterial pressure

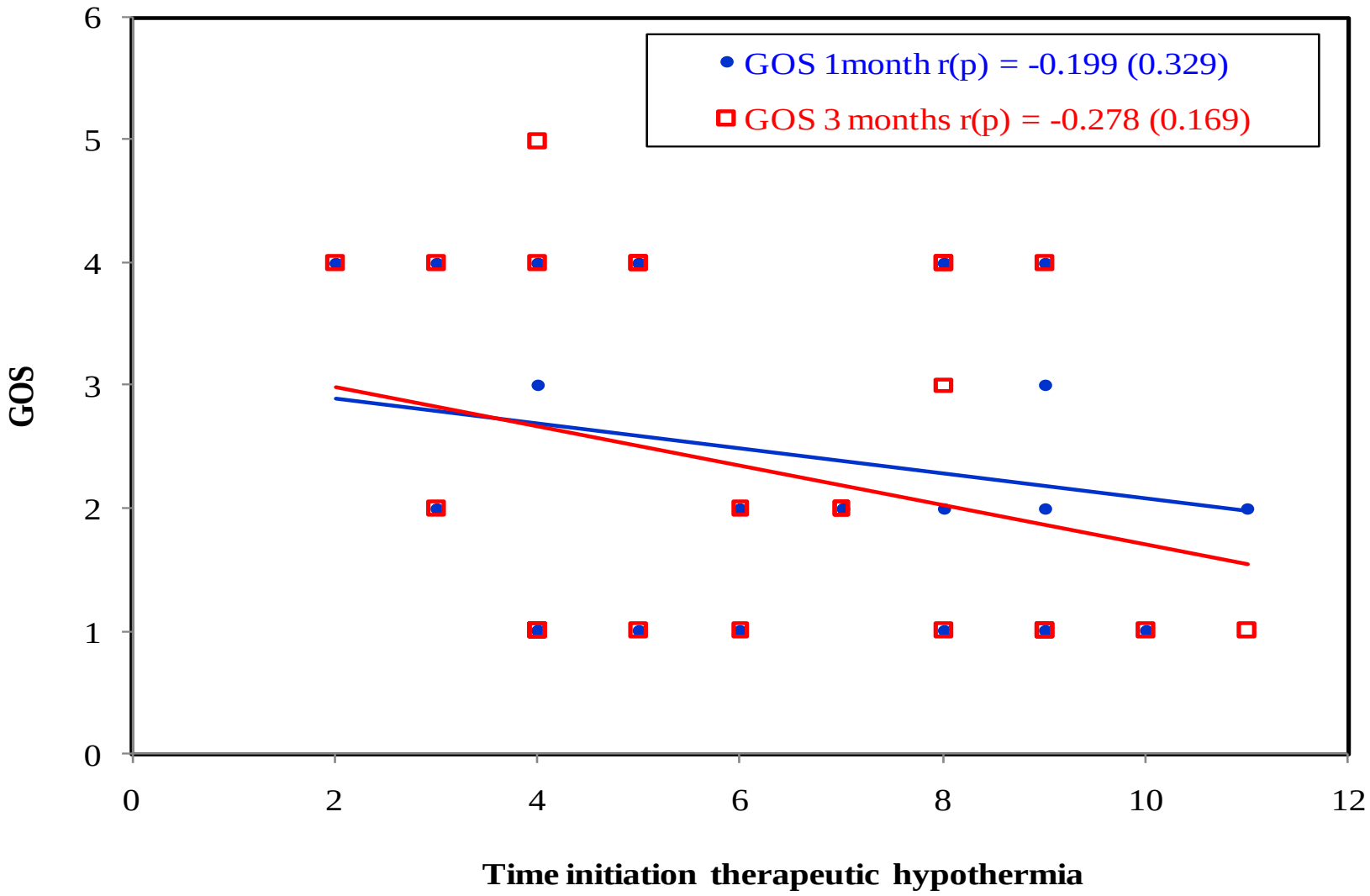


Jugular pulp venous oxygen saturation

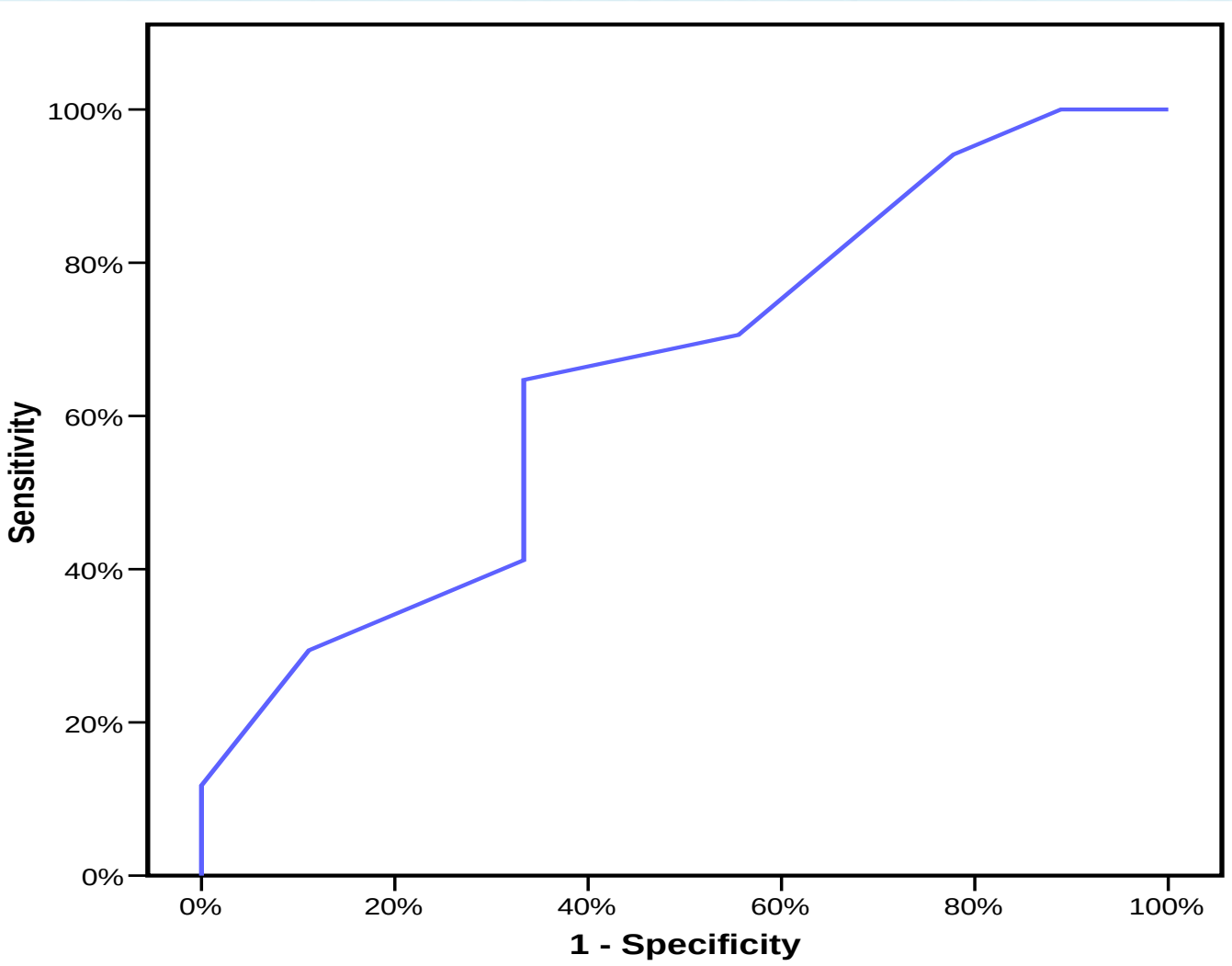

30
25
20
15
10
5
0
*
*
Mild hypokalemia
Mod to severe hypokalemia
Hypoglycemia
Thrombocytopenia
Coagulopathy
Life threatining arrhythmia
Pneumonia
Mean ICU stay duration in days
Normothermia group
Therapeutic hypothermia group


100
90
80
70
60
50
40
30
20
10
0
3 months mortality rate
Control group
Therapeutic hypothermia group


100
90
80
70
60
50
40
30
20
10
0
Poor outcome (GOS 1-3)
Favorable outcome (GOS4,5)
Control group
Therapeutic hypothermia group


GOS 1month r(p) = -0.199 (0.329)
GOS 3 months r(p) = -0.278 (0.169)
GOS
0
1
2
3
4
5
6
0
2
4
6
8
10
12
Time initiation therapeutic hypothermia

ROC curve for time of initiation of hypothermia and prediction of outcome.



Sensitivity, specificity and accuracy of time of initiation of therapeutic hypothermia for prediction of patient outcome.

		GOS AT ONE AND THREE MONTHS	
		Favorable outcome	Poor outcome
Time of initiation of hypothermia	< 5 hrs	6	6
	> 5 hrs	3	11
Sensitivity		66.67%	
Specificity		64.71%	
Positive predictive value		50.0%	
Negative predictive value		78.57%	
Accuracy		65.38%	

Conclusions

1. Patients treated with hypothermia were somewhat less likely to die than those in the control group, but this reduction in mortality was statistically insignificant.
2. Therapeutic hypothermia added a minimal statistically insignificant improvement in neurological outcome after severe TBI, this improvement is more with early cooling(within 5 hrs after head trauma).
3. Therapeutic hypothermia increased the incidence of pneumonia and the length of ICU stay duration.
4. Therapeutic hypothermia is a safe intervention with minimal non serious side effects.

Therapeutic hypothermia in TBI in clinical trials

June 11, 2003, Vol 289, No. 22 >

< Previous Article Next Article >

Review | June 11, 2003

Prolonged Therapeutic Hypothermia After Traumatic Brain Injury in Adults

A Systematic Review FREE

Lauralyn A. McIntyre, MD; Dean A. Fergusson, MHA, PhD; Paul C. Hébert, MD, MHSc; David Moher, MSc; James S. Hutchison, MD

JAMA. 2003;289(22):2992-2999. doi:10.1001/jama.289.22.2992.

Text Size: A A A

- 12 trials met eligibility criteria and were included in the analysis

Results:

- 19% reduction in the risk of death (95% confidence interval [CI], 0.69-0.96)
- 22% reduction in the risk of poor neurologic outcome (95% CI, 0.63-0.98) compared with normothermia.

Conclusions:

- Therapeutic hypothermia may reduce the risks of mortality and poor neurologic outcome in adults with TBI. Nonetheless, the evidence is not yet sufficient to recommend routine use of therapeutic hypothermia for TBI outside of research settings.

J Neurotrauma. 2008 Jan;25(1):62-71. doi: 10.1089/neu.2007.0424.

Hypothermia treatment for traumatic brain injury: a systematic review and meta-analysis.

Peterson K, Carson S, Carney N.

Oregon Evidence-Based Practice Center, Department of Medical Informatics and Clinical Epidemiology, Oregon Health and Science University, Portland, Oregon 97239, USA. peterski@ohsu.edu

- 13 trials met eligibility criteria, with a total of 1339 randomized patients.

Results:

- Reductions in risk of mortality were greatest (RR 0.51; 95% CI 0.33, 0.79) and favorable neurologic outcomes much more common (RR 1.91; 95% CI 1.28, 2.85) when hypothermia was maintained for more than 48 h.
- A significant increase in risk of pneumonia (RR 2.37; 95% CI 1.37, 4.10).

Conclusion:

- This meta-analysis supported previous findings that hypothermic therapy constitutes a beneficial treatment of TBI in specific circumstances. Accordingly, the BTF/AANS guidelines task force has issued a Level III recommendation for optional and cautious use of hypothermia for adults with TBI.

I. RECOMMENDATIONS

A. Level I

There are insufficient data to support a Level I recommendation for this topic.

B. Level II

There are insufficient data to support a Level II recommendation for this topic.

C. Level III

Pooled data indicate that prophylactic hypothermia is not significantly associated with decreased mortality when compared with normothermic controls. However, preliminary findings suggest that a greater decrease in mortality risk is observed when target temperatures are maintained for more than 48 h.

Prophylactic hypothermia is associated with significantly higher Glasgow Outcome Scale (GOS) scores when compared to scores for normothermic controls.

degree of clinical certainty. For Level III recommendations, the degree of clinical certainty is not established.

Brain Trauma Foundation, AANS, CNS. Guidelines for management of severe traumatic brain injury. 2007.

CJEM. 2010 Jul;12(4):355-64.

Prophylactic hypothermia for traumatic brain injury: a quantitative systematic review.

Fox JL, Vu EN, Doyle-Waters M, Brubacher JR, Abu-Laban R, Hu Z.

Department of Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada. jlrfox@gmail.com

- 12 trials with 1327 participants were selected for quantitative analysis.
- 8 of these studies cooled according to a long-term or goal-directed strategy, and 4 used a short-term strategy.
- When only short-term cooling studies were analyzed, neither mortality (RR 0.98, 95% CI 0.75-1.30) nor neurologic outcome (RR 1.31, 95% CI 0.94-1.83) were improved.
- In 8 studies of long-term or goal-directed cooling, mortality was reduced (RR 0.62, 95% CI 0.51-0.76) and good neurologic outcome was more common (RR 1.68, 95% CI 1.44-1.96).

Conclusion:

- To supports the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI as soon as possible after injury.
- The greatest benefit occurred with a long term or goal-directed cooling protocol, in which cooling was continued for at least 72 hours and/or until stable normalization of ICP for at least 24 hours was achieved.

British Journal of Anaesthesia 1[illegible] (3): 357–67 (2013)
Advance Access publication 25 January 2013 · doi:10.1093/bja/aes500

BJA

Role of therapeutic hypothermia in improving outcome after traumatic brain injury: a systematic review

A. P. Georgiou[1]* and A. R. Manara[2]

[1] Department of Anaesthesia and Intensive Care Medicine, Royal United Hospital, Combe Park, Bath BA1 3NG, UK
[2] Department of Anaesthesia and Intensive Care Medicine, Frenchay Hospital, Bristol BS16 1LE, UK
* Corresponding author. E-mail: andypgeorgiou@hotmail.com

- **Overall 18 randomized controlled trials, involving 1851 patients, were identified.**
- **In conclusion:**
  - **The pooled benefit of PTH on mortality and neurological outcome in TBI is lost when only high-quality data are analyzed.**
- **Recommendations for its use cannot be made outside of the realm of controlled clinical trials, particularly when the safety of the therapy is yet to be fully elucidated.**

The Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR-RCT)

This study is currently recruiting participants.

Verified April 2012 by Australian and New Zealand Intensive Care Research Centre

Sponsor:
Australian and New Zealand Intensive Care Research Centre

Collaborators:
Australian and New Zealand Intensive Care Society Clinical Trials Group
National Health and Medical Research Council, Australia
Victorian Neurotrauma Initiative

ClinicalTrials.gov Identifier:
NCT00987688

First received: September 29, 2009
Last updated: April 12, 2012
Last verified: April 2012
History of Changes

- **This project will determine if early, sustained cooling is safe and if it can improve the long term neurological outcomes of patients with traumatic brain injury.**
- **Lead Investigator: Prof David Cooper**
- **Co-Investigator(s): Prof Stephen Bernard; A/Pr Alistair Nichol; A/Pr Jeffrey Presneill; Prof Peter Cameron; Prof John Myburgh**
- **Total Grant Budget: $AUD 2,061,507**
- **Application Year: 2008**
- **Start Year: 2009**
- **End Year: 2013**

European society of intensive care medicine study of therapeutic hypothermia (32-35°C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm3235Trial)

Peter JD Andrews[1*], Helen Louise Sinclair[1], Claire G Battison[1], Kees H Polderman[2], Giuseppe Citerio[3], Luciana Mascia[4], Bridget A Harris[1], Gordon D Murray[5], Nino Stocchetti[6], David K Menon[7], Haleema Shakur[8], Daniel De Backer[9], the Eurotherm3235Trial collaborators

Methods/design: This is a pragmatic, multi-centre randomised controlled trial examining the effects of hypothermia 32-35°C, titrated to reduce intracranial pressure <20 mmHg, on morbidity and mortality 6 months after traumatic brain injury. The study aims to recruit 1800 patients over 41 months. Enrolment started in April 2010.

Participants are randomised to either standard care or standard care with titrated therapeutic hypothermia. Hypothermia is initiated with 20-30 ml/kg of intravenous, refrigerated 0.9% saline and maintained using each centre's usual cooling technique. There is a guideline for detection and treatment of shivering in the intervention group. Hypothermia is maintained for at least 48 hours in the treatment group and continued for as long as is necessary to maintain intracranial pressure <20 mmHg. Intracranial hypertension is defined as an intracranial pressure >20 mmHg in accordance with the Brain Trauma Foundation Guidelines, 2007.

Take Home Message

I. There have been a number of clinical research that suggests some benefit of therapeutic hypothermia in patients with severe TBI.

I. At the current time there is insufficient evidence to provide enough proof that cooling should be used routinely for patients with brain injury and like all treatments there can be some risks and side effects.


Thank You
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