



TARGETED TEMPERATURE MANAGEMENT AFTER ACUTE BRAIN INJURY

*... Does normothermia reduce disability
and death after acute brain injury?*

OVERVIEW OF THE DAY

Teleologically, over millions of years, the pathophysiological response to tissue injury has been naturally selected to facilitate tissue repair and subsequent recovery. This complex response includes elevating body temperature.

More recently animal models of vascular and traumatic brain injury suggest that deliberate cooling improves outcome, when compared to deliberate heating. Additionally, observational clinical evidence appears to be supportive.

There are no high quality randomised clinical trials.

There is clinical uncertainty about which process provides most benefit with least harm: evolutionary adaptive pressure or modern evidence from the laboratory? This is a provocative and controversial area.

Today we focus on designing a feasibility study of two temperature targets within the normothermic range. This is needed before attempting the lofty ambition of a definitive clinical trial that answers the important question of whether normothermia reduces disability and death after acute brain injury.

Convener: Manoj Saxena

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Overview

- *Manoj Saxena*

11:05

Evidence for induced normothermia from animal models

- *Nicky Watts*

11:25

The relationship between temperature and outcome in observational clinical studies

- *Manoj Saxena (on behalf of Sophie Liang)*

11:45

Defining usual care in ANZ from observational studies

- *Naomi Hammond*

12:15

The efficacy and safety of interventions in reducing temperature

- *Manoj Saxena*

12:40

Results of a survey designed to understand temperature management and NSAID use after TBI

- *Kiran Deol*

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LUNCH

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A feasibility study evaluating protocols to deliver normothermia and usual care to patients with stroke/SAH

- *All Speakers*

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		Design	Data Collection	Data Analysis	Publication
Systematic reviews	Cochrane review Modest cooling (35-37.5C) interventions for TBI (2008)	✓	✓	✓	✓ Cochrane
	Systematic review of observational studies of the association between temperature and outcome after TBI	✓	✓	✓	Manuscript in progress
	Revision of Cochrane Review (2013-14)	✓	✓	✓	Published in the next edition of the Cochrane Hand
Observational Studies	A Point Prevalence study of Temperature Management after acute brain injury	✓	✓	✓	✓ CCR
	*A Multi-Centre Retrospective Cohort Study Of Normothermia After Traumatic Brain Injury	✓	✓	✓	Under Submission
	*The CLARITY Study: An audit of temperature regulation in intensive care patients with traumatic brain injury and stroke in Australia and New Zealand.	✓	✓	✓	Analysis complete, Manuscript preparation
	Early Temperature and mortality in critically ill patients with acute neurology: infection differs from trauma and stroke	✓	✓	✓	Under Submission
	The CELSIUS Study - Comparison Of Core And Peripheral Temperature Measurement In Adult Critically Ill Patients With Brain Injury.	✓	✓	✓	Manuscript preparation
The Association Between Body Temperature And Long-Term Outcome For Patients With Traumatic Brain Injury (SAFE- TBI post hoc analysis).	✓	✓	✓	Manuscript preparation	
Phase 2 RCT	*PARITY study: A phase 2b randomised, controlled clinical trial evaluating the safety and efficacy of intravenous paracetamol for traumatic brain injury.	✓	✓	SAP being finalized	
Survey	A Survey Of Temperature Management After Traumatic Brain Injury - Evaluating The Potential Role Of NSAIDs	✓	✓	In progress	Manuscript preparation

**Supported by the Honda – St George Critical Care and Trauma Fellowship*



Dr Kiran Deol

Dr Kiran Deol is a provisional fellow in intensive care medicine. After working as a senior registrar at St George Hospital and The Alfred, she has developed a strong interest in the management of complex multi-trauma and traumatic brain injury patients. Research aspirations include a plan to commence a PhD in the field of traumatic brain injury, with specific interests being the use of NSAIDs in brain injury and the use of imaging and monitoring techniques to assess regional blood flow and metabolism.



Naomi Hammond

Naomi is both a Research Fellow in the Critical Care and Trauma Division at the George Institute for Global Health and an Intensive Care Clinical Research Manager at Royal North Shore Hospital, Sydney. She is a trained intensive care nurse with a Master of Nursing (Critical Care) and a Master of Public Health and has been working in Critical Care for over 13 years with the majority of time spent in clinical research.

Naomi is an NHMRC postgraduate scholarship holder and is currently conducting her PhD in translational research of fluid resuscitation practices in critical care.

Naomi is the Australian Project Manager of the HEAT study and has also been a site Principle Investigator for the TTM Trial and the EUROTHERM 3235 Trial.



Sophie Liang

Sophie is a final year medical student at the University of Sydney. She has a bachelor's degree in statistics and is working towards a master's degree in clinical epidemiology. Sophie is actively engaged in critical care research. She recently completed an Honours research project on the effect of temperature elevation on long-term functional survival in patients with traumatic brain injury. Sophie aspires to be a clinician-researcher who is both a practitioner and producer of evidence-based medicine.

Dr Manoj Saxena

Manoj is currently an Intensive Care Physician at St. George Hospital (University of New South Wales), Sydney, Australia. He also has an appointment as a Research Fellow at The George Institute for Global Health and his main area of research interest is whether normothermia reduces death and disability after acute brain injury. Manoj is completing a PhD on this subject and has coordinated a series of observational studies, surveys and interventional studies with the aims of informing the study design and understanding the feasibility of a definitive clinical trial.

Manoj is the Australian Principle Investigator of the HEAT study and has also been a site Principle Investigator for the TTM Trial and the EUROTHERM 3235 Trial.

He is an Executive Member of the Australia and New Zealand Clinical trials Group, an examiner for the College of Intensive Care Medicine and Chair of the Scientific Program for the St. George and Sutherland Medical Research Symposium.



Dr Nicky Watts

Nicky is a Postdoctoral Research Fellow in the Critical Care and Trauma Division at The George Institute for Global Health. She has a background in basic research and completed a PhD in Neuroscience in 2011. Her research focused on neural precursor cell activity in the adult brain and its connection with brain function.

Nicky made the transition to clinical research in 2012, initially working as a research coordinator in the Departments of Paediatric Intensive Care and Anaesthesia at The Children's Hospital at Westmead. Nicky joined the Critical Care and Trauma division in 2013, and her current research interests include adult and paediatric fluid resuscitation practices, temperature regulation after brain injury, and cognitive and psychological outcomes in intensive care patients.



SPEAKERS

Evidence for induced normothermia from animal models

It is well established in animal models of stroke and traumatic brain injury that induced hyperthermia can increase the severity of neuronal injury relative to induced normothermia or hypothermia. However, little is known about natural temperature variation following stroke and TBI and whether controlled temperature interventions are neuroprotective under conditions of spontaneous hyperthermia. The experimental evidence for induced normothermia as a therapeutic intervention to correct spontaneous temperature variations will be reviewed.

The relationship between temperature and outcome in observational clinical studies.

Patients with traumatic brain injury commonly develop high temperatures within days after injury and this may adversely affect long-term outcomes. The aim of this talk is to provide a systematic review of the evidence from clinical observational studies.

We will also discuss a new analysis of the traumatic brain injury cohort of the SAFE study. This study provides high quality evidence on the relationship between temperature and long term functional outcome.

Defining usual care in ANZ from observational studies.

Maintaining normothermia is a recommended practice for patients with an acute brain injury treated in the intensive care unit (ICU). The literature, however, lacks a consistent definition of normothermia.

This session will provide the first presentation of the CLARITY study – a prospective audit of 308 adult patients with acute brain injury from 16 ANZ ICUs.

Understanding the spectrum of usual care is key to being able to define a feasibility study prior to a definitive clinical trial.

The efficacy and safety of interventions in reducing temperature.

We will review the phase 2 evidence on the safety and efficacy of pharmacological agents on reducing temperature after acute brain injury in the critically ill. This will include the first presentation of the PARITY study results, a phase 2b clinical trial evaluating the safety and efficacy of intravenous paracetamol in reducing temperature after TBI. In addition, we will review information regarding the efficiency of different techniques of physical cooling that could maintain normothermia.

Results of a survey designed to understand temperature management and NSAID use after TBI

Observational studies suggest non-steroidal anti-inflammatory drugs (NSAIDs) have antipyretic activity, anti-inflammatory activity and can reduce raised intracranial pressure in patients with TBI. However, NSAIDs appear to be rarely used in the management of patients with TBI in Australia and New Zealand.

In order to clarify the perceived role of NSAIDs in TBI, an online scenario-based survey was sent to Intensive Care Specialists working in trauma-receiving centres in Australia and New Zealand.

Kiran Deol will discuss the results of The SANITY survey.

Invited Attendees

John Myburgh
Jamie Cooper
Paul Young
Adam Deane
Oliver Flower
Colman Taylor
Anders Aneman
Andrew Chang
Ian Seppelt
Elizabeth Yarad
Deborah Inskip
Jennene Miller
Kelly Thompson
Manoj Saxena
Kiran Deol
Naomi Hammond
Nicky Watts
Sophie Liang

Apologies

Simon Finfer
Michael Reade
Ed Litton
Celia Bradford
David Gattas

20 AUGUST 14

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