

Temperature management in patients with acute neurological lesions: an Australian and New Zealand point prevalence study

Manoj K Saxena, Colman B Taylor, Naomi E Hammond, Paul J Young, Ian M Seppelt, Parisa Glass, John A Myburgh on behalf of George Institute for Global Health and the ANZICS Clinical Trials Group

In-vivo and in-vitro studies suggest that induced hyperthermia (39.0°C) increases interleukin (IL)-10 levels,¹ glutamate levels^{2,3} and neutrophil activity⁴ following experimental models of neurological injury, compared with induced normothermia (normal body temperature) in control animals (37.0°C). Other data suggest that inflammatory mediators (tumour necrosis factor, IL-1 β) may be unaffected.⁵⁻⁷ Although there is an observational association between temperature above certain thresholds (> 37.9°C,⁸ > 38.5°C,⁹ 38.3°C¹⁰ and > 38.0°C¹¹) and adverse outcomes in critically ill patients with acute neurological lesions, the relationship between a raised body or brain temperature and intracranial pressure (ICP) remains clinically uncertain.^{7,11-15} In stroke and traumatic brain injury (TBI), which globally are the two most common forms of neurological injury, the evidence for the intervention of maintaining normothermia is based largely on experimental and clinical observational studies, rather than on randomised controlled trials (RCTs). Systematic reviews, expert opinions and consensus group opinions have highlighted the clinical uncertainty in this area.¹⁶⁻²² Therefore, the practice of maintaining a normal body temperature after both stroke and TBI remains underpinned by inconclusive evidence with uncertain effects on safety and efficacy.

There are limited data about how temperature is managed in patients with acute stroke and TBI in the critical care setting and it remains unclear what temperatures are sought and attained in routine clinical practice. We hypothesised that among this group, body temperature would be intensively monitored, and normothermia, defined as temperature < 37.5°C, would be achieved. This definition was pragmatic and consensus-based, given the heterogeneity of definitions used previously^{8-11,23,24} (Table 1), and was also consistent with the definition of normothermia in the control arm of an Australian and New Zealand trial evaluating systemic hypothermia for TBI.²⁵

Methods

We conducted an observational, multicentre, single-day point-prevalence study (PPS) on one of 3 study days in May

ABSTRACT

Background: Given the scientific uncertainty of the efficacy and safety of normothermia (36.0°C to 37.5°C) on disability and death after acute neurological lesions, we sought to understand how temperature is managed in usual clinical care for this patient population in Australia and New Zealand.

Objective: To describe temperature management in patients with acute neurological lesions.

Design: Prospective, observational, multicentre, single-day point-prevalence study.

Participants, setting and methods: Observational data of usual practice were recorded for all patients with an intensive care admission diagnosis of acute neurological lesions and who were present in 33 intensive care units at 10:00 on the study day. Data were collected prospectively for the ensuing 24-hour period.

Main outcome measures: Achieved temperature, interventions used to modify temperature and target temperature.

Results: There were 106 patients with acute neurological lesions (61% with either stroke or traumatic brain injury) with a mean APACHE (Acute Physiology and Chronic Health Evaluation) II score of 19.3 \pm 7.4, age of 53.5 \pm 19.0 years and median time from intensive care admission to data capture of 3 days (interquartile range, 1–9). A target temperature was specified in 24% of patients. Although paracetamol was commonly used (56%), it was infrequently used at the maximum licensed dose and there was no use recorded of non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors. Physical cooling was used in 25% of patients and core temperature was measured in 32%. Measured temperature often exceeded 37.0°C (62% of readings), 37.5°C (43%) and 38.0°C (22%).

Conclusions: Temperature readings above 37.5°C are common. Further cohort studies are required to validate these preliminary, exploratory findings.

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Table 1. Summary of observational studies reporting temperature in patients with acute neurological lesions

Author (year)	Study design	Study population	Study period	Definition of fever	Temperature measurement technique	Proportion of patients with fever	Data on physical cooling
Jeremitsky et al (2003) ³⁰	Retrospective	All patients with TBI	First 24 hours	> 38.5°C	Not stated	35/81 (43%)	No
Geffroy et al (2004) ³²	Retrospective	Patients with TBI, and those with ICP monitoring	First 48 hours	> 38.5°C	Tympanic	44/101 (44%)	Yes
Jiang et al (2002) ³¹	Retrospective	Patients with TBI and GCS score < 8	First 72 hours	> 37°C	Not stated	567/840 (68%)	No
Stocchetti et al (2002) ¹¹	Retrospective	All patients with TBI	First week	> 38.4°C	Axillary, rectal and bladder	80/110 (73%)	Yes
Natale et al (2000) ²⁹	Retrospective	Patients with TBI (paediatric)	From admission to emergency department to first 24 hours of intensive care admission	> 38.5°C	Oral, axillary and rectal	26/117 (22%)	No
Diringer et al (2004) ⁹	Retrospective	Mixed brain injury	Intensive care admission	37.5–38.4°C (low fever category), 38.5–39°C (moderate fever category) and > 39°C (high fever category)	Oral (90%)	1591/4295 (37%) (low fever category), 719/4295 (17%) (moderate fever category) and 717/4296 (17%) (high fever category)	No
Oliveira-Filho et al (2001) ¹⁰	Prospective	Subarachnoid haemorrhage	Neurologic intensive care admission	> 38.3°C for 2 days	Tympanic	38/92 (41%)	No
Jørgensen et al (2001) ⁴⁵	Prospective	Stroke	Stroke unit admission temperature	> 37.5°C	Tympanic	97/390 (25%)	No
Azzimondi et al (1995) ⁸	Prospective	Stroke	Stroke unit, maximum temperature in first week after stroke	> 37.2°C	Not stated	79/183 (43%)	No

GCS = Glasgow Coma Scale. ICP = intracranial pressure. TBI = traumatic brain injury.

and June 2009 to understand temperature management practices in patients with acute neurological lesions in Australia and New Zealand. This occurred within the Point Prevalence Program (PPP) of the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS CTG): at that time, there was a total of 182 adult intensive care units (35 tertiary, 39 metropolitan, 49 rural and regional, and 59 private) in both countries.²⁶ The PPP study included all patients occupying a bed in participating ICUs in Australia and New Zealand at the census point of 10:00 am on the study day and allows a description of usual care in the 24 hours before or after the census point. We collected demographic data and data related to temperature management in this 24-hour period in all patients with an intensive care admission diagnosis consistent with acute neurological lesions, defined as a diagnosis of TBI, stroke, intracerebral haemorrhage, subdural or extradural haemorrhage, subarachnoid haemorrhage, central nervous system

infection, metabolic encephalopathy or hypoxic encephalopathy after cardiac surgery or cardiac arrest (corresponding to APACHE [Acute Physiology and Chronic Health Evaluation] III diagnostic codes 102, 203, 301, 401–410, 601, 701, 1206, 1207, 1501–1506 and 1601). The demographic data included age, sex, APACHE II score,²⁷ admission diagnosis and the time from both initial neurological injury and admission to ICU until the start of the period of data capture. The main outcome measures were specification of a target temperature (recorded from the medical notes or intensive care chart, or directly from the bedside nurse), measured temperature (including technique and location of the temperature measurement) as recorded during usual clinical care, and interventions used to modify temperature. Core temperature measurements were defined as temperature measurements taken by oesophageal, naso- or oropharyngeal, bladder, rectal or intravascular routes. Non-core temperature measurements were

Table 2. Demographics of 106 patients admitted to intensive care with stroke or traumatic brain injury (TBI)

Patient characteristics	All patients (n = 106)	Time in ICU		ICP monitoring at admission*	
		< 72 hours (n = 52)	> 72 hours (n = 54)	Yes (n = 46)	No (n = 58)
Mean age in years (SD)	53.5 (19.0)	56.7 (19.2)	50.4 (18.6)	46.3 (19.4)	58.8 (17.0) [†]
Sex, n (%)					
Male	65 (61%)	29 (56%)	36 (67%)	31 (67%)	32 (55%)
Female	41 (39%)	23 (44%)	18 (33%)	15 (33%)	26 (45%)
Hours since injury, median (IQR)	84 (33–215) [‡]	33 (22–62)	185 (137–356) [§]	153 (64–231)	59 (31–193)
Hours in ICU, median (IQR)	76 (31–208) [¶]	26 (15–45)	192 (126–349)**	116 (56–208)	58 (22.5–187)
Mean APACHE II score (SD)	19.3 (7.4)	19.4 (8)	18.9 (5.9)	18.7 (5.1)	19.8 (8.9)
Mean GCS score (SD) ^{††}	8.8 (4.0)	10.3 (4.4)	8.0 (3.7)	7.6 (6.0)	11.6 (3.7)
Source of admission to ICU, n (%)					
Emergency department	34 (32%)	15 (29%)	19 (35%)	12 (26%)	22 (38%)
Hospital floor	11 (10%)	6 (12%)	5 (9%)	1 (2%)	10 (17%)
Another ICU	8 (8%)	3 (6%)	5 (9%)	4 (9%)	4 (7%)
Another hospital	10 (9%)	2 (4%)	8 (15%)	3 (7%)	6 (10%)
Emergency surgery	33 (31%)	20 (38%)	13 (24%)	23 (50%)	9 (16%)
Elective surgery	10 (9%)	6 (12%)	4 (7%)	3 (7%)	7 (12%) ^{‡‡}
Postoperative admission, n (%)					
Yes	42 (40%)	29 (56%)	17 (31%)	25 (54%)	15 (26%)
No	61 (58%)	23 (44%)	36 (67%)	20 (43%)	41 (71%)

APACHE = Acute Physiology and Chronic Health Evaluation. GCS = Glasgow Coma Scale. ICP = intracranial pressure. ICU = intensive care unit. IQR = interquartile range. * Two patients had missing data. [†] $t = -3.51$; $P = 0.0007$. [‡] Forty-eight patients had missing data.

[§] $z = -5.74$; $P < 0.0001$. [¶] Three patients had missing data. ^{**} $z = -8.73$; $P < 0.0001$. ^{††} For patients with TBI only, $n = 35$. ^{‡‡} $\chi^2(5) = 17.9$; $P = 0.0031$.

defined as temperature measurements taken by tympanic, axillary, groin or oral routes. In situations where the location of temperature measurement was not known or not recorded, we imputed the location based on most of the temperature reading locations in patients from the same hospital. In situations where the patient with a missing temperature measurement location was the only patient from a site, we recorded the location as “missing”. The use of pharmacological interventions (paracetamol, non-steroidal anti-inflammatory drugs [NSAIDs] and cyclooxygenase-2 [COX-2] inhibitors; total daily dose and route) and physical interventions with potential effects on temperature was also recorded. Physical interventions included fans, ice packs, cooling blankets, vests and wraps, intravascular cooling catheters, internal cavity lavage and the specific use of extracorporeal circuits. Sepsis on the study day was defined as the presence of a defined focus of infection and two or more of the criteria for systemic inflammatory response syndrome.²⁸

To examine differences in lead-time and illness severity, we investigated differences in temperature management in two a-priori defined subgroups. We compared patients with

< 72 hours of admission to intensive care with patients with > 72 hours of admission, and patients with ICP monitoring at admission with those without ICP monitoring. Differences between means were tested using the Student *t* test for normally distributed data and the Wilcoxon signed-rank test for non-normally distributed data. Differences in proportions were tested using χ^2 tests. Data were collected prospectively on paper and electronic case report forms (CRFs) by research coordinators at participating hospitals, and statistical analysis was performed at the George Institute for Global Health using SAS version 9.2 (SAS Institute). Ethical and research governance approval was obtained at all sites and included a waiver of consent.

Results

Demographics

There were 106 patients with acute neurological lesions in 33 ICUs (Table 2). The mean age of the cohort was 53.5 ± 19.0 years, with a mean APACHE II score of 19.3 ± 7.4 . The admission diagnosis was stroke or TBI in 61% (65/106) of the patient population. The median time

Table 3. Proportion of temperature measurements above defined thresholds according to patient group

Patient group	Proportion of temperature measurements above each threshold		
	≥ 37.0°C	≥ 37.5°C	≥ 38.0°C
All patients	61%	43%	22%
< 72 hours of admission	51%	33%	19%
> 72 hours of admission	70%	52%	25%
ICP monitoring	66%	49%	23%
No ICP monitoring	58%	36%	21%

ICP = intracranial pressure.

from onset of illness or injury to the start of the data capture period was 3.5 days (interquartile range [IQR], 1–9), and the median time from admission to intensive care to the start of the data capture period was 3 days (IQR, 1–9). ICP monitoring was present in 44% of patients (46/104), and two patients had missing data on ICP monitoring. Twenty-five per cent (27/106) had sepsis on the study day.

Temperature measurement technique

The most common technique of temperature measurement was axillary (40%; 42/106), followed by bladder (13%; 14/106), tympanic and nasopharyngeal (10%; 11/106), other (26%; 28/106) and not known or not stated (10%; 11/106). After imputation, 68% of patients (71/104) were classified as having non-core temperature readings, 32% (33/104) were classified as having core temperature readings and two patients were classified as having missing data. A small proportion of patients had more than one temperature measurement technique (18 patients had two techniques and four patients had three techniques; we used data from the most common technique for analyses).

There were 1291 temperature measurements made in 106 patients (median, 11 readings per patient; IQR, 6–20) during the 24-hour study period. Of the patients with < 72 hours of admission, 15/52 (29%) had core temperature measurements (median, 23; IQR, 14–24), and of the patients with > 72 hours of admission, 18/54 (33%) had core measurements (median, 24; IQR, 23–24). Of the patients with an ICP monitor, 17/46 (37%) patients had core temperature measurements (median, 24; IQR, 23–24), and in patients without an ICP monitor, 16/57 (28%) had core measurements (median, 23; IQR, 16–24).

Specification of target temperature

A target temperature was specified in 24% of patients in the total cohort (25/104; two patients had missing data).

Nine out of 104 patients (9%) had a specified target temperature of 36.0–37.5°C. Of the patients with < 72 hours of admission, 26% (13/50) had a specified target temperature, compared with 22% of patients (12/54) with > 72 hours of admission ($\chi^2[1]=0.20$; $P=0.6524$). Patients with an ICP monitor had a specified target temperature in 35% of cases (16/46), compared with 14% (8/57) of those without an ICP monitor ($\chi^2[1]=6.13$; $P=0.0133$).

Interventions used to modify temperature

Paracetamol was the most common pharmacological agent used during the period of data capture (59/106 patients; 56%) — there was no recorded use of either NSAIDs or COX-2 inhibitors, except low-dose aspirin (one patient). The route of administration of paracetamol was enteral in 51 patients and intravenous in 12, and the total daily dose was variable (0.5 g, one patient; 1 g, 11 patients; 1.5 g, one patient; 2 g, 12 patients; 3 g, 12 patients; 4 g, 21 patients; and 5 g, one patient). For those patients who received paracetamol, the mean dose was 2.7 g ± 1.2 g (median, 3 g; IQR, 2–4). Physical interventions were used in 27/106 patients (25%) and included fans (one), ice packs (eight), cooling blankets (12) and intravascular cooling (one). Seventy-eight patients (74%) were treated with at least one of either a pharmacological or a physical agent. Among other factors that may affect temperature measurement, 17 patients received steroids, one patient received a neuromuscular blocking agent and six patients had recorded use of an extracorporeal circuit.

Temperature measurements

Overall, 62% of temperature measurements (799/1291) were ≥ 37.0°C, 43% (561/1291) were ≥ 37.5°C, and 22% (290/1291) were ≥ 38.0°C, (Figure 1 and Table 3). In addition, 9% (116/1291) of temperature readings were ≥ 38.5°C, and 3% (39/1291) were ≥ 39.0°C. Adjustment by lead-time bias or illness severity did not appreciably alter these findings. The mean temperature in patients with < 72 hours of admission was 36.7°C ± 1.5°C, compared with 37.3°C ± 1.3°C in patients with > 72 hours of admission ($t[952]=6.66$; $P<0.0001$). The mean temperature in patients with an ICP monitor was 37.1°C ± 1.4°C, compared with 36.9°C ± 1.4°C in patients without an ICP monitor ($t[940]=1.47$; $P=0.1413$).

Discussion

Key findings

In a mixed cohort of critically ill patients with acute neurological lesions in Australia and New Zealand, 75% of whom had data captured within 9 days of onset of illness or

Table 4. Contemporary randomised controlled clinical trials investigating hypothermia in patients with acute neurological lesions: summary of temperature target in the control arm

Study title	Participating countries and regions	Temperature target for control arm (normothermia) (°C)
The prophylactic hypothermia trial to lessen traumatic brain injury ²⁵	Australia and New Zealand	36.5–37.5°C
European Society of Intensive Care Medicine study of therapeutic hypothermia (32–35°C) for intracranial pressure (ICP) reduction after traumatic brain injury ³⁴	Europe	Usual practice
Hypothermia in traumatic brain injury in children ³⁵	Australia and New Zealand	36.0–37.0°C
Hypothermia in children after trauma ³⁶	America	37.0–38.0°C
Target temperature management after cardiac arrest ³⁷	Europe, Australia	Target 36.0°C (to avoid temperatures above 37.0°C)
Mild intraoperative hypothermia during surgery for intracranial aneurysm ³⁸	America, Australia, Canada, Europe, New Zealand	36.0–37.0°C

injury, we have shown that although intensive temperature monitoring is a component of clinical care, non-core temperature measurements are commonly used, temperature readings above 37.5°C are common, and there appears to be the potential to increase the use of physical and pharmacological interventions.

Relation to previous work

Our results are consistent with previous observational studies which have demonstrated that a raised body temperature is common after acute neurological lesions (43%–73%) (Table 1).^{9–11,29–32} Factors that affect the reported incidence or prevalence of a raised body temperature after acute neurological lesions include variations in the definition of normothermia (definitions of a raised temperature vary between >37.0°C and >38.5°C), temperature measurement technique, the duration over which temperature is assessed, the severity of injury of the study population and the use of antipyretic and physical cooling interventions.^{8–11,24,29–33}

In their Italian retrospective cohort study, Stocchetti and colleagues reported that 66/110 patients received antipyretic interventions and the intervention used was the NSAID diclofenac (63/66), with 23 patients treated with both physical cooling and diclofenac.¹¹ In a French retrospective study, Geffroy and colleagues reported that 50/101 patients in their retrospective cohort received paracetamol (mean dose, 3.5 g ± 1.5 g in the first 48 hours after injury), but no information was given on the use of physical cooling interventions.³² In our cohort, the only pharmacological agent used was paracetamol (56%), with a maximum daily dose of 5 g (in one patient), with no use of NSAIDs or COX-2 inhibitors to intentionally reduce temperature — therefore, these classes of drug are additional pharmacological tools that could potentially be employed to reduce temperature. The proportion of physical cooling

interventions used in our study population was similar to that in the Italian study. Increasing the use of physical interventions may also have the potential to reduce temperature.

Clinical implications and significance

In the context of varied definitions of normothermia that are used for the control arm of contemporary RCTs of hypothermia (Table 4), a key implication from our data appears to be the need for an agreed definition of normothermia. In clinical trials evaluating hypothermia, definitions of the “normothermic” control arm vary from maintaining temperature below 36.0°C to maintaining temperature below 38.0°C.^{25,34–38} Similarly, in experimental studies, the threshold for defining fever remains contentious,^{22,39} with few animal data examining the effect of spontaneously occurring hyperthermia in models of neurological injury against induced normothermia.⁴⁰ We searched clinical trial registries (the World Health Organization International Clinical Trials Registry Platform, the Australian New Zealand Clinical Trials Registry and ClinicalTrials.gov) for ongoing studies evaluating normothermia, and found four studies: one observational study evaluating the feasibility of maintaining body temperature below 36.5°C (Table 5), two randomised studies evaluating the efficacy of pharmacological agents (paracetamol or diclofenac) on temperature reduction compared with usual care, and one study comparing mixed pharmacological and physical cooling with usual care.

It is possible that non-core temperature measurements do not reliably estimate core temperature and may differ from core measurements by 0.3–0.5°C,⁴¹ although this relationship is contentious.⁴² Given the use of non-core measurements in our cohort, it remains possible that the reported temperatures may not accurately reflect the

Table 5. Studies evaluating normothermia that are currently recruiting (World Health Organization Registry of International Clinical Trials, Australia and New Zealand Clinical Trials Registry and ClinicalTrials.gov)

Title	ClinicalTrials.gov identifier	Study design	Intervention	Estimated study completion date
Normothermia protocol for traumatic brain injury patients	NCT01354509	Observational	Physical cooling	May 2013
The paracetamol after traumatic brain injury study	ACTRN12609000444280	Randomised, placebo-controlled.	Paracetamol	December 2013
Outcomes associated with application of a normothermia protocol in patients with severe neurological insult and fever	NCT00890604	Randomised, controlled	Pharmacological (paracetamol and ibuprofen) and physical cooling	July 2010
Normothermia in patients with acute cerebral damage	NCT00491192	Randomised, placebo-controlled	Diclofenac	June 2009

proportion of temperature measurements that are actually above 37.0°C, 37.5°C and 38.0°C. If temperature control is considered clinically important, it may be optimal to use core temperature measurements preferentially, facilitating continuous and accurate monitoring of temperature rather than intermittent surface temperature monitoring.

Our study suggests that in Australia and New Zealand, NSAIDs and COX-2 inhibitors are not used to modify temperature. Although paracetamol use was relatively common, dosing was inconsistent, with a small proportion receiving the maximum licensed dose of paracetamol. In part, this may reflect a lack of demonstrated antipyretic efficacy of paracetamol, 4 g per day, in patients with acute neurological lesions.⁴³ However, doses of 6 g per day reduce temperature by 0.3°C (95% CI, 0.1–0.5) and may improve outcomes in a subgroup of stroke patients with an admission body temperature between 37.0°C and 39.0°C without an increase risk of hepatotoxicity.⁴⁴ There are therefore opportunities to optimise the use of pharmacological agents to control temperature after acute neurological lesions.

There was a discrepancy between the observed use of interventions to reduce temperature and the recorded use and specification of a target temperature by clinicians. This may be due to the use of paracetamol as an analgesic agent, or this may be a limitation of our method of capturing specified target temperature.

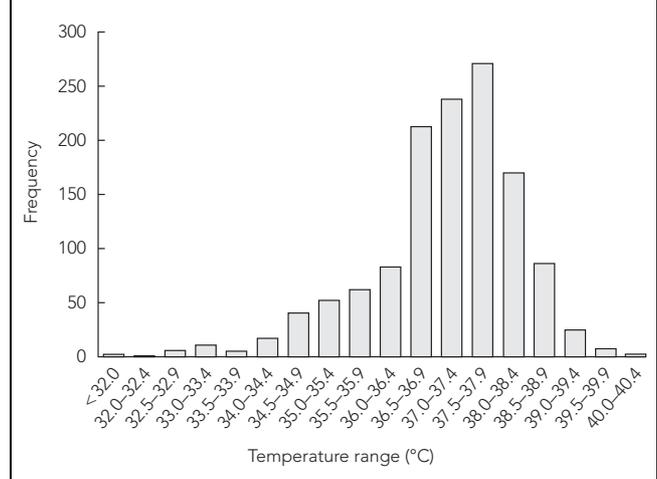
Our study highlights that in a heterogeneous cohort of critically ill patients with acute neurological lesions, temperatures of less than 37.5°C are often not achieved. There are many possible explanations for this finding, including the lack of robust efficacy data that controlling temperature to less than 37.5°C reduces death and disability, concern about toxicity of the interventions used

to reduce temperature, uncertain efficacy of the interventions at actually reducing temperature, lack of resources and equipment and other issues being given clinical priority (eg, the competing risk between reducing sedation to allow neurological assessment and the need for sedation to facilitate physical cooling).

Strengths and limitations

The main strength of our study is that it provides contemporary, prospective, multicentre, binational observational data on the management of body temperature after acute neurological lesions, with information on actual measured temperature in the context of pharmacological and physical interventions and specification of target temperatures.

Figure 1. Frequency of measured temperature in 106 intensive care patients (1291 measurements)



The limitations of our study include the following: first, our observational data are limited to a single 24-hour period during intensive care admission, and we are unable to infer how temperature management may vary longitudinally over the extended period of emergency admission and hospitalisation. Second, we described practice in a mixed convenience sample of patients with acute neurological lesions and it may be that the temperature management varies depending on the specific type of neurological injury (ischaemic, traumatic, metabolic or infective) and the severity of the neurological injury. Third, by studying prevalence we may have introduced bias towards patients with a longer length of stay. Fourth, we are not able to reliably demonstrate an effect attributable to lead-time bias or illness severity because of a lack of statistical power. However this study was primarily designed to be an exploratory, preliminary investigation and we plan to further explore these initial findings by performing subsequent cohort studies.

Future studies

We plan to conduct cohort studies (retrospective and prospective) to further explore baseline practice in Australia and New Zealand and to validate these preliminary, exploratory findings. Particular data of interest include longitudinal data on the measured temperature and temperature measurement technique, the use of physical interventions and the time from injury admission to initiation of pharmacological and physical interventions, adjusting for illness severity. Additional survey methodology may be appropriate to understand clinician preferences. Depending on these findings, appropriately designed RCTs may be warranted to rigorously understand the balance between efficacy and toxicity for the intervention of maintaining normothermia compared with usual practice after acute neurological lesions.

Conclusion

In mixed cohort of patients in Australia and New Zealand in the early phase after acute neurological lesions, there was low use of target temperature specification and physical cooling, paracetamol was infrequently used at the maximum licensed dose or effective maximum dose (NSAIDs were not used), and measured temperatures often exceeded 37.5°C. Further observational data from cohort studies are required to validate these exploratory observations. Understanding baseline practice may inform the feasibility and design of subsequent Phase II and Phase III RCTs, which are needed to ascertain whether maintaining a normal temperature in patients

with acute neurological lesions improves patient-centred clinical outcomes.

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Competing interests

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Author details

Manoj K Saxena, Intensive Care Physician^{1,2,3}

Colman B Taylor, Research Fellow²

Naomi E Hammond, Research Fellow²

Paul J Young, Intensive Care Physician^{4,5}

Ian M Seppelt, Senior Staff Specialist^{2,6,7}

Parisa Glass, Divisional Manager²

John A Myburgh, Director^{1,2,3}

On behalf of George Institute for Global Health and the ANZICS Clinical Trials Group

1 Department of Intensive Care Medicine, St George Hospital, Sydney, NSW, Australia.

2 George Institute for Global Health, Sydney, NSW, Australia.

3 St George Clinical School, University of New South Wales, Sydney, NSW, Australia.

4 Medical Research Institute of New Zealand, Wellington, New Zealand.

5 Intensive Care Unit, Wellington Regional Hospital, Wellington, New Zealand.

6 Australian and New Zealand Intensive Care Society Clinical Trials Group, Melbourne, VIC, Australia.

7 Sydney Medical School, University of Sydney, Sydney, NSW, Australia.

Correspondence: m.saxena@unsw.edu.au

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Appendix 1. Site-based contributors

We would like to acknowledge the following site-based contributors to data acquisition (listed in alphabetical order, with all in Australia unless specified as New Zealand [NZ]): Alfred Hospital, Melbourne: V Bennett, J Board, A Davies, S Vallance; Auckland City Hospital Cardiovascular Intensive Care Unit, Auckland, NZ: V Cocharne, S McGuinness, R Parke; Auckland City Hospital Department of Critical Care Medicine, Auckland, NZ: C McArthur, L Newby, C Simmonds; Austin Health, Melbourne: R Bellomo, G Eastwood, L Peck; Bendigo Hospital, Bendigo: J Fletcher, J Smith; Blacktown Hospital, Sydney: G Reece, T Sara; Box Hill Hospital, Melbourne: S Elliott, D Ernest, J Sidhu; Cabrini Hospital, Melbourne: F Hawker; Calvary Mater Newcastle Hospital, Newcastle: K Ellem, S Meakes; Canberra Hospital, Canberra: R Ashley, I Mitchell, E Taylor; Christchurch Hospital, Christchurch, NZ: S Henderson, J Mehrtens; Concord Hospital, Sydney: D Milliss, H Wong; Epworth Eastern Hospital, Melbourne: C Giannellis, S Ho; Flinders Medical Centre, Adelaide: E Matheson, S Verghese; Frankston Hospital, Melbourne: J Botha, D Lewis, J Vuat; Fremantle Hospital, Fremantle: D Blythe, A Palermo; Geelong Hospital, Geelong: C Catterton, T Elderkin, M Fraser; Gold Coast Hospital, Southport: B Richards, M Tallott, R Whitebread; Gosford Hospital, Gosford: R Cameron, S Hatter; Hawke's Bay Hospital, Hastings, NZ: L Chadwick, R Freebairn; John Hunter Hospital, Newcastle: M Hardie, P Harrigan, D Whitaker; Liverpool Hospital, Liverpool: S Micallef, M Parr; Lyell McEwin Hospital, Adelaide: R Ramadoss, J Wood; Mater Adult Hospital, Brisbane: K Gregory, J Morgan, J Presneill, J Sutton;

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