Protocol for a multicentre randomised controlled trial of early and sustained prophylactic hypothermia in the management of traumatic brain injury

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ABSTRACT

Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Prophylactic hypothermia is effective in laboratory models, but clinical studies to date have been inconclusive, partly because of methodological limitations. Our Prophylactic Hypothermia Trial to Lessen Traumatic Brain Injury (POLAR) randomised controlled trial is currently underway comparing early, sustained hypothermia versus standard care in patients with severe TBI. We describe our study protocol and the challenges in conducting prophylactic hypothermia research in TBI.

Design: We aim to randomise 500 patients to either prophylactic 33°C hypothermia initiated within 3 hours of injury and continued for at least 72 hours, or standard normothermic management. Patients will be enrolled by paramedic services in the prehospital setting, or by emergency department staff at participating sites in Australia, New Zealand and Europe. The primary outcome will be the eight-level extended Glasgow outcome scale (GOSE), dichotomised to favourable and unfavourable outcomes at 6 months after injury. Secondary outcomes will include mortality at hospital discharge and at 6 months, ordinal analyses of 6-month GOSE outcomes, quality of life with health economic evaluations and the differential proportion of adverse events. We will predefine subgroup and interaction analyses.

Discussion: After a run-in phase, recruitment for our main study began in December 2010. When the study is completed, we aim to provide evidence on the efficacy of prophylactic hypothermia in TBI to guide clinicians in their management of this devastating condition.

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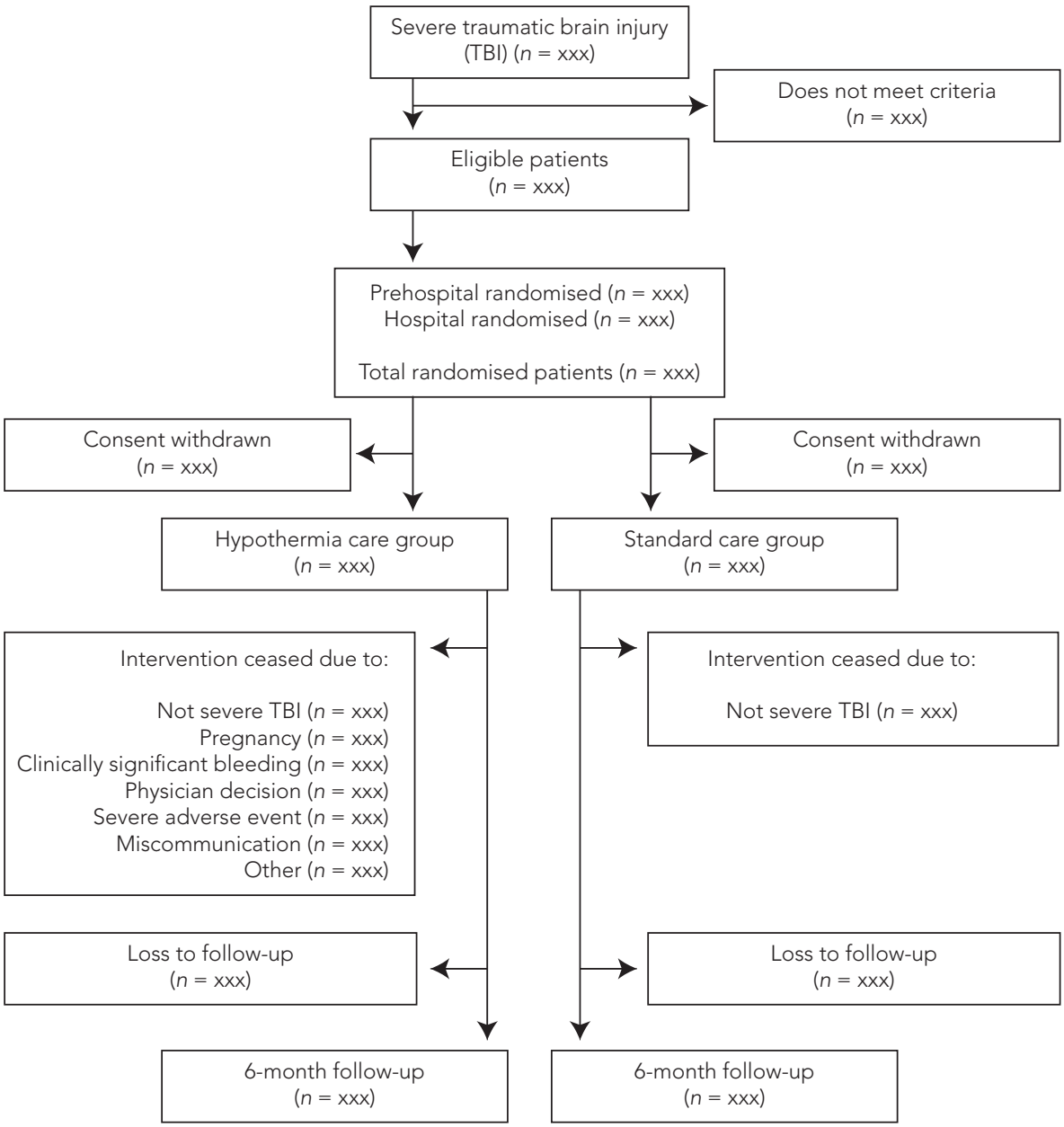
Traumatic brain injury (TBI) is a leading cause of death and long-term disability, particularly in young adults and children.[1] Globally, an estimated 10 million people are affected every year by a new TBI.[2] About 1.7 million people sustain a TBI in the United States annually, resulting in 275 000 hospital admissions and 52 000 deaths.[3] Lifetime costs, including health care costs and lost productivity, are estimated at US$60 billion annually.[4] The emotional toll on surviving victims and relatives is immeasurable. A therapy that provides even a small increase in the number of patients with a TBI having a favourable neurological outcome (ie, independent living) rather than an unfavourable one (ie, dead or requiring high-level support) would yield major societal and economic benefits.

Current treatment of established severe TBI is principally supportive and focuses on prevention and management of secondary brain injury using a combination of deep sedation, intravenous (IV) fluids,[5] and manipulation of oxygen delivery, intracranial pressure (ICP) and cerebral perfusion pressure (CPP).[6]

Induced moderate hypothermia (to 33°C) has been proposed as a therapy for severe TBI, either as a neuroprotectant against secondary brain injury ("prophylactic hypothermia"), or as a treatment for increased ICP that is refractory to first-tier therapies. The effects of hypothermia include a reduction in the metabolic rate, positive effects on cerebral blood flow, blockade of excitotoxic inflammatory cascades, a decrease in oedema, and modulation of apoptosis.[7] Experimental models also suggest that a therapeutic window exists when induction of hypothermia soon after the primary TBI may provide optimal neurological protection, leading to improved outcomes.[8]

In the past two decades, numerous clinical studies of varying methodological quality and with differing protocols have been performed to assess the effects of induced hypothermia in TBI.[9-11] Most have been underpowered to detect clinically significant outcome differences, and although some have shown significant benefit or trends toward benefit, none have shown worse outcomes in the hypothermic treatment group.[12-19] Post-hoc analysis of results from two large randomised controlled trials (RCTs) suggested that cooling before or soon after craniotomy, with maintenance at 33°C for 48 hours afterwards may improve outcomes for patients with severe TBI and intracerebral haematomas.[20] More recently, two systematic reviews

Figure 1. Trial design



of RCTs of primary therapeutic hypothermia for patients with TBI found an overall lower risk of both mortality and poor neurological outcome with cooling,[21,22] although both reviews noted that not all included trials were of high methodological quality.

In the largest multicentre RCT to date, there was an average delay of 8.4 hours (SD, 3 hours) in attaining the target temperature, due to suboptimal cooling technology.[15] Overall, there was no strong evidence of a treatment effect, but a long-term neurological advantage was associated with the subgroup of patients who were initially hypothermic and treated with continued induced hypothermia, raising the possibility that the other cooled patients may have missed a therapeutic window.[23] A subsequent multicentre trial was stopped early after enrolling fewer than half the planned number of patients due to slow recruitment.[19] At the time of the interim analysis there were no significant differences in outcomes and the authors concluded that their trial could not confirm the utility of prophylactic induced hypothermia. This trial succeeded in

Table 1. Inclusion and exclusion criteria

Prehospital setting	Emergency department
Inclusion criteria:	Inclusion criteria:
Blunt trauma, clinical diagnosis of severe TBI and GCS < 9	Blunt trauma, clinical diagnosis of severe TBI and GCS < 9
Estimated age ⩾ 18 and < 60 years	Estimated age ⩾ 18 and < 60 years
Patient is intubated or intubation is imminent	Patient is intubated or intubation is imminent
Exclusion criteria:	Exclusion criteria:
Clinical diagnosis of drug or alcohol intoxication predominant cause of coma	Clinical diagnosis of drug or alcohol intoxication predominant cause of coma
Randomisation unable to be performed within 3 hours of estimated time of injury	Randomisation cannot be performed within 3 hours of estimated time of injury
Estimated transport time to study hospital > 2.5 hours	Able to be intubated without drugs
Able to be intubated without drugs	Persistent SBP < 90 mmHg
SBP < 90 mmHg	Cardiac arrest at scene or in transit
Heart rate > 120 beats/min	GCS = 3 and unreactive pupils
Cardiac arrest at the scene or in transit	Clinically significant bleeding likely to require haemostatic intervention; eg,
GCS = 3 and unreactive pupils	➢ bleeding into chest, abdomen or retroperitoneum likely to require surgery, +/– embolisation
Penetrating neck or torso injury	➢ pelvic fracture likely to require surgery, +/– embolisation
Known or obvious pregnancy	➢ > 2 long bone fractures requiring operative fixation
Receiving hospital is not a study site	Penetrating neck or torso injury
Evidence of current anticoagulant treatment	Positive urine or blood pregnancy test
Carer-dependent due to pre-existing neurological condition	Evidence of current anticoagulant treatment
	Carer-dependent due to pre-existing neurological condition
	In the treating clinician's opinion, cooling is not in the patient's best interest

TBI = traumatic brain injury. GCS = Glasgow coma score. SBP = systolic blood pressure.

cooling patients to 33°C within a mean time of 4.4 hours (SD, 1.5 hours) but had other methodological limitations, in common with previous trials, that may have confounded the detection of a treatment effect. First, in severe TBI, the swelling of brain tissue frequently persists for more than 48 hours; therefore, the duration of induced hypothermia in these trials may have been insufficient for optimal therapy. This contention is supported by a previous meta-analysis finding that prophylactic induced hypothermia maintained for longer than 48 hours was associated with reduced mortality.[24] A recent human trial in full-term neonates with moderate or severe hypoxic ischaemic encephalopathy reported the lowest patient mortality in association with induced hypothermia at 33.5°C for 72 hours.[25] Second, patients were rewarmed at 0.5°C every 2 hours, irrespective of their ICP. During rewarming, patients with TBI may suffer rebound intracranial hypertension, and rapid rewarming has been shown to reverse the neuroprotective effects of hypothermia.[26] Therefore, rewarming may best be undertaken when intracranial hypertension has resolved, and may require temporary cessation if intracranial hypertension recurs. The investigators also reported higher rates of raised intracranial pressure in the hypothermic group, which may have been due to early rapid rewarming,[27] or to aggressive fluid resuscitation.[19,28]

Other ongoing multicentre RCTs of therapeutic hypothermia have used increased ICP as an inclusion criterion, or have allowed enrolment up to 10 days after injury.[29,30] These trials therefore will not address the efficacy of prophylactic hypothermia, but rather of hypothermia as a rescue therapy.

Study rationale

The question of whether early and sustained prophylactic induced hypothermia will benefit patients with severe TBI remains unanswered. To address this evidence gap we are undertaking a large, multicentre RCT comparing protocolised, early, prophylactic hypothermia (started within 3 hours of injury) in the management of severe TBI, compared with standard practice. Our study will be powered sufficiently to detect clinically relevant differences in mortality and neurological outcomes, as measured by the eight-level extended Glasgow outcome scale (GOSE)[31] at 6 months after injury, accounting specifically (by sample size inflation) for anticip-

Table 2. Primary and secondary outcome measures and additional analyses

Primary outcome
Proportion of favourable neurological outcomes (GOSE 5–8) at 6 months after injury
Secondary outcomes
Probability of an equal or greater GOSE level at 6 months compared to the probability of a lesser GOSE level, using a proportional odds model
Quality of life, assessed with:
EQ-5D
SF-12
Mortality (all-cause) at:
Hospital discharge
6 months
Incidence of adverse events:
Bleeding
Infection
Additional analyses
Health economic evaluation
Per-protocol analysis
Tests for interactions with GOSE outcomes at 6 months:
GCS at randomisation
Achievement of cooling to 33°C within 6 hours in the hypothermic group
Presence of intracranial mass lesions

GOSE = extended Glasgow outcome score. EQ-5D = EuroQol-5D. SF-12 = short form-12. GCS = Glasgow coma score.

ated levels of patient withdrawal from the study and crossover between treatment arms. By using a pragmatic study design, we will attempt to overcome some of the methodological limitations of other trials. We will mandate induction of hypothermia in the prehospital or emergency department (ED) setting, continuing hypothermia for at least 72 hours, and rewarming will be guided by ICP.

Study design and outcomes

The Prophylactic Hypothermia trial to Lessen Traumatic Brain Injury (POLAR) RCT is a multicentre trial comparing early and sustained induced hypothermia with standard normothermic care in the management of severe TBI (ClinicalTrials.gov, NCT00987688; Australian New Zealand Clinical Trials Registry, ACTRN12609000764235). The trial is designed to recruit 500 adult patients with severe (GCS ≤ 8) non-penetrating TBI from prehospital ambulance services and hospitals throughout Australia, New Zealand and Europe (see Appendix 1).

Participants

Patients who have experienced blunt trauma, aged between 18 and 60 years and with severe TBI, who are intubated, or have intubation planned, will be eligible for this study (see Figure 1). The inclusion and exclusion criteria are shown in Table 1.

Outcome measures

The primary outcome of our study is the proportion of patients with favourable neurological outcomes, conventionally defined according to a midpoint dichotomisation of the eight-level GOSE, at 6 months after injury (Table 2).

Our secondary end points include quality-of-life assessments, measured using the EuroQol-5D (EQ-5D) and short form-12 (SF-12) questionnaires,[32,33] and the probability of an improved GOSE level at 6 months according to a proportional odds ordinal logistic model.[34] We will also assess all-cause mortality at hospital discharge and 6 months after injury and the proportions of adverse events, including bleeding and infection. We will include a health economic evaluation using hospital and postdischarge estimates of costs.

Study treatments

The intervention we will examine is induction of moderate systemic hypothermia (33°C) started within 3 hours of injury and continued for at least 72 hours, compared with standard TBI management. Initial cooling will be undertaken using bolus infusion of cold IV fluids and exposure, and subsequent cooling will be with refrigerated water blankets and vests (Medi-Therm III, Stryker Corporation).

Paramedic enrolment — prehospital treatment

In the prehospital setting, we will achieve induced hypothermia to a target of 35°C by exposure and rapid infusion of 30 mL/kg ice-cold (4°C) 0.9% sodium chloride solution. To avoid fluid overload, a limited volume will be administered and will vary depending on the patient's intubation status. Patients randomised after intubation will receive no more than 1000 mL solution; patients randomised before intubation will receive no more than 2000 mL. If the patient's temperature is < 35°C at the time of paramedic assessment, the patient will not receive cold IV fluid.

Patients randomised to the standard-care arm of the trial will be managed according to usual clinical practice (core temperature, 36.5–37.5°C) and transferred to the nearest participating study centre. Standard attempts to achieve and maintain normothermia (with maintenance of ambient temperature and blankets) will be implemented if the patient's core temperature is < 36.5°C.

Table 3. Data collection

Period of study	Data collected
Prehospital	Patient identifiers, baseline demographics, timing and mechanism of injury, vital signs including baseline temperature, GCS, pupillary responses, date and timing of cooling intervention, any hypoxia or hypotension, volume of fluid therapy administered
Hospital admission	Vital signs including baseline temperature, GCS, pregnancy test, CT brain scan appearance and Marshall classification, time of application of surface temperature control vest and leg wraps, haematological and biochemical parameters, hourly core temperature, volume of fluid therapy administered, neurosurgical interventions including ICP or brain tissue oxygen monitor insertion, ISS, AIS
Intensive care stay	Vital signs, haematological and biochemical parameters, hourly core temperature, episodes of intracranial hypertension (ICP > 20 mmHg) and low cerebral perfusion pressure, ICP management, vasopressor or renal replacement therapy use, type and volume of fluid therapy including blood, urine output, feeding and delivery method (nasogastric or parenteral)
Hospital discharge	Duration of mechanical ventilation, ICU readmissions, lengths of ICU and hospital stays, hospital discharge destination, vital status at hospital discharge, treatment limitations
Outcome collection	6-month GOSE, EQ-5D, SF-12
Health economic evaluation	Clinical costing, duration of rehabilitation stay, duration of nursing home stay, level of home care, linkage to other health services and compensation scheme data
General data collection	Withdrawal from study protocol, adverse events and serious adverse events including arrhythmias, infections, bleeding (intracranial or elsewhere), intractable intracranial hypertension, death

GCS = Glasgow coma scale. CT = computed tomography. ICP = intracranial pressure. ISS = injury severity score. AIS = abbreviated injury scale. ICU = intensive care unit. GOSE = extended Glasgow outcome scale. EQ = EuroQol-5D. SF-12 = short form-12.

Paramedic enrolment — ED assessment

On arrival at the ED, patients enrolled by the ambulance service and randomised to the hypothermic arm will be assessed by ED staff to confirm ongoing suitability for cooling (see Table 1). If there is significant bleeding, further cooling will be withheld and the patient will be maintained at a core temperature of 35–37°C while haemostasis is achieved by blood component replacement, embolisation, or surgery with blood product replacement as needed. If hypothermia cannot be reinstituted within 48 hours of the injury, the patient will subsequently receive standard temperature management. Patients suspected of having drugs or alcohol as the predominant cause of their coma may also not proceed with allocated cooling if, on clinical assessment, they localise or obey (GCS motor score, 5–6) or if, in the treating clinician's opinion, they do not have a severe TBI nor require ICU admission.

Hospital enrolment — ED assessment

Patients not enrolled before being admitted to hospital and who fulfil inclusion criteria and have no exclusion criteria (see Table 1) will be enrolled and randomised during their stay in the ED.

Patients randomised to prophylactic cooling will have hypothermia induced by exposure and infusion of ice-cold (4°C) 0.9% sodium chloride solution, with volumes limited according to the prehospital enrolment procedures, to an initial target temperature of 35°C.

Patients randomised to standard care will have a target core temperature of 36.5–37.5°C. Active warming with blankets or cooling may be used to maintain temperature in this range.

All patients — ongoing management

Once significant bleeding, pregnancy and other causes of coma have been excluded, all patients allocated to the hypothermic arm will be cooled to or maintained at 33°C with surface temperature control using refrigerated jackets and blankets applied to about 40% of the body surface area.

Seventy-two hours after initiation of hypothermia, if the patient's ICP remains at < 20 mmHg, cautious rewarming according to our protocol (warming by 0.5°C every 3 hours) will start. If, at any time during the rewarming process, there is a sustained, unprovoked increase in ICP by > 20 mmHg for more than 5 minutes, the patient will be recooled to a temperature that controls the ICP (to a minimum of 33°C) until the treating clinician deems it appropriate to restart warming.

If a patient allocated to hypothermia develops clinically significant bleeding at any time, cooling will be withheld and they will be rewarmed to 35–37°C. Once bleeding is controlled, the hypothermic protocol will resume (cooling to 33°C), provided it can be reinstituted within 48 hours of injury.

Management of TBI

Patients in the hypothermic and standard-care arms will be managed according to current international evidence-based guidelines,[35] including ICP monitor insertion (unless de-sedation and clinical assessment is planned, or insertion is contraindicated). This protocolised care has been used in previous comparative TBI trials,[36,37] and includes a stepped regimen for management of raised ICP and severely reduced CPP (< 60 mmHg).

Patients in the normothermic group who develop a strong clinical indication for induced hypothermia, such as for refractory intracranial hypertension, will be permitted to receive a therapeutic reduction in core temperature below 37°C, down to a minimum of 35°C.

Randomisation, allocation concealment and blinding

As temperature is a key vital sign, it is not possible to blind clinical staff to patient treatment allocation. All staff at the coordinating centre will be blinded to treatment allocation, except for a nominated statistician who will conduct the interim analyses, two data managers responsible for the web-based data management system, and an independent medical safety monitor. Bias will be minimised by allocation concealment before randomisation, by protocolised treatment in both groups, by use of a robust primary outcome minimally susceptible to ascertainment bias, and by blinded assessment of the primary outcome by trained research staff external to the coordinating centre.

Centrally controlled, real-time electronic or telephone randomisation was not feasible for this multicentre, international trial involving prehospital ambulance-based randomisation in series with recruitment at hospital EDs. Sequentially numbered, opaque, sealed envelopes were chosen as a pragmatic, implementable solution for treatment assignment. These envelopes were printed at the Australian trial coordinating office according to an electronic randomisation schedule that allocated hypothermia and normothermia in a 1:1 ratio. Allocation is within a permuted block design stratified according to prehospital or ED enrolment, as well as the geographic location of enrolment (Victoria, New South Wales, Queensland, Western Australia, New Zealand and European countries).

Data collection and management

Data will be collected by trained staff at each study site and entered into a secure, password-protected, encrypted, web-based data collection form. Data will be checked for consistency, and queries will be generated automatically by the trial website so that immediate query resolution can occur.

Enrolled patients will be followed up to death or 6 months after randomisation. Details of data to be collected are shown in Table 3. At 6 months, neurological outcomes will be assessed using the 8-point GOSE, and quality of life will be assessed using the EQ-5D and SF-12 questionnaires. Full protocol data will be collected on all patients, including patients who were excluded at any stage. Patients allocated to the hypothermia group for whom hypothermia is subsequently withdrawn for any reason will be followed up according to our protocol.

Data management will be performed by the Clinical Informatics and Data Management Unit, Monash University, Melbourne, Australia.

Site monitoring will be performed at each participating hospital by the project manager to ensure the study is conducted according to the protocol and all applicable regulations, and to perform source data verification.

Ethics approval

This is a study of a time-critical therapy in patients who are unconscious and unable to consent to participation; therefore, a waiver of consent will be obtained for participants to be enrolled in the study and to receive the allocated study intervention. As soon as is appropriate, the participant's guardian or next of kin will be asked to provide consent to continue in the study. Patients who recover sufficient cognition to understand the explanation of the study will additionally be asked to consent to continue in the study.

Approval for this protocol has been obtained from appropriate regulatory authorities, and from the human research ethics committee at each participating hospital.

Sample size and power

The sample size of 500 is based on an estimated rate of 50% favourable neurological outcomes in Australian and New Zealand patients with severe TBI,[38] aiming for 80% power to detect an absolute difference of 15% (relative difference of 30%) in the trial primary outcome of 6-month neurological status. This sample size allows for an anticipated 5% loss to follow-up, a 12% withdrawal of hypothermia treatment in those randomised to this group (crossover), and two interim safety analyses.

Statistical analysis

We will perform a modified intention-to-treat analysis based on all randomly assigned patients except those

withdrawing consent for use of all trial data and those not fulfilling inclusion criteria and never receiving the intervention.[39] Baseline variables will be summarised using descriptive statistics and we will compare the primary outcome between treatments with an unadjusted risk ratio and 95% confidence interval. We will perform sensitivity analyses using logistic regression, adjusting for stratification factors and prognostic baseline covariates exhibiting substantial imbalance between randomisation arms. We will apply a proportional odds, cumulative logistic model,[34,40] adjusting for relevant covariates, as a secondary outcome to the eight-level vector of 6-month GOSE.

Other secondary analyses, including assessment of outcomes according to actual treatment received, quality-of-life assessment, mortality at hospital discharge and 6 months, and incidence of adverse events, will be compared between treatment groups using unadjusted and adjusted logistic regression as above. Prespecified subgroup analyses of differential intervention effects according to randomisation GCS, time to reaching target temperature, and the presence of an intracranial mass lesion will be obtained using interaction terms in logistic regression models. We will report adjusted effect estimates of the POLAR intervention derived from logistic and proportional odds ordinal logistic models as adjusted risk ratios averaged over the remaining covariates, as recently recommended.[41-43] We will analyse time-to-event data using Kaplan–Meier curves and unadjusted and adjusted Cox proportional hazards regression models.

Data and safety monitoring

An independent data safety and monitoring committee (DSMC), comprising experts in clinical trials, biostatistics, emergency medicine and intensive care, will monitor serious adverse events (SAEs) throughout the trial and predefined outcomes at designated interim analyses.

Planned interim safety analyses are scheduled by the DSMC at 6 months after 25% ($n = 125$) and 50% ($n = 250$) patient recruitment. There is no plan for early trial stopping for apparent futility. The first interim analysis examined all-cause mortality and the differential proportion of favourable neurological outcomes between treatment groups, and the DSMC recommended continuation of the trial. The second interim analysis will re-examine these two trial outcomes.

We will report all adverse events (AEs) and SAEs thought to be related to the study intervention to the study coordinating centre. As with other studies in critically ill patients, AEs already defined and reported as study outcomes will not be separately reported.[44]

Funding

The POLAR RCT is funded by the Australian National Health and Medical Research Council and the Victorian Transport Accident Commission. The cooling vests and blankets are purchased and maintained using project grant funds. Funding agencies and cooling device suppliers and manufacturers have not had and will not have any role in study design, data collection, data analysis or writing of manuscripts.

Current status

A pilot, run-in phase for the study was conducted at The Alfred Hospital, Melbourne, Australia in January 2010, to test the study procedures and data collection. The main study commenced in December 2010, and continues in Australia, New Zealand and France.

Summary

Severe TBI is a common and debilitating condition with few proven, specific therapies available. Early prophylactic induced hypothermia has the potential to reduce neurological damage and improve outcomes, and is supported by a scientific rationale and extensive laboratory data; however, clinical studies to date have been inconclusive, in part because of methodological limitations. The POLAR RCT aims to provide definitive guidance for clinicians on the utility of early and sustained prophylactic hypothermia in the management of severe TBI.

Competing interests

None declared.

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Appendix 1. Participating hospitals, prehospital organisations, investigators (Is) and research coordinators (RCs)

The Alfred Hospital, Melbourne: Prof. DJ Cooper, Prof. S Bernard, Dr O Roodenburg, Dr L Hocking, Prof. JV Rosenfeld, Prof. P Cameron (I), Mrs S Vallance, Ms J Broad (RC).

The Royal Melbourne Hospital, Melbourne: A/Prof. C MacIsaac, A/Prof. N Harley, Dr T Rechnitzer, Dr S Sriram, Dr R D'Costa, Dr C Karcher, Dr K Gorman, Dr R Citroni, Dr J Knott, Prof. R Judson (I), Mrs D Barge (RC).

Princess Alexandra Hospital, Brisbane: A/Prof. C Joyce, Dr L Nunnink, Dr H Fuentes, Dr E Burkett (I), Mr K Perkins, Mr J Meyer (RC).

Royal Perth Hospital, Perth: Prof. S Webb, Dr E Litton, Dr S Honeybul, Dr N Henry, Prof. S Brown (I).

Sir Charles Gairdner Hospital, Perth: Dr S Baker (I), Mrs B Roberts (RC).

Auckland City Hospital, New Zealand: Prof. C McArthur, Dr T Smith (I), Mrs L Newby (RC).

Waikato Hospital, New Zealand: Dr Robert Frengley (PI), Mr J Durning (RC), Mrs Mary LaPine (RC).

Hôpital Jean Minjoz, Besançon, France: Prof. G Capellier, Prof. S Pilifloury (I).

CHRU Besançon, France: Ms L Vetteroti, G Cottet-Emard (RC).

Hôpital Gabriel Montpied, Clermont-Ferrand, France: Dr R Chabanne.

Hôpital de Hautepierre, Strasbourg, France: Dr J Pottecher.

St John Ambulance (Western Australia): Prof. I Jacobs (I).

Ambulance Victoria: A/Prof. T Walker, Mr M Stephenson (I).

Queensland Ambulance Service: Dr S Rashford (I).

SAMU-SMUR 25: Dr L Fehner, Mr A Journot (I).

SAMU-SMUR 63: Dr F Dissait (I).

SAMU-SMUR 67: Dr L Tritsch, Dr H Arzouq (I).

Follow-up assessors: Dr H Waddy, Dr E Debustos Medeiros.