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Effects of brain tissue oxygen ($PbtO_2$) guided management on patient outcomes following severe traumatic brain injury: A systematic review and *meta*-analysis

Leanne M.C. Hays [a], Andrew Udy [b,c], Alexios A Adamides [d,e], James R. Anstey [f], Michael Bailey [b,g], Judith Bellapart [h], Kathleen Byrne [f], Andrew Cheng [i], D. Jamie Cooper [b,c], Katharine J. Drummond [d,e], Matthias Haenggi [j], Stephan M. Jakob [j], Alisa M. Higgins [b], Philip M. Lewis [k], Martin K. Hunn [l,m], Robert McNamara [n], David K. Menon [o], Lynne Murray [b], Benjamin Reddi [p,q], Tony Trapani [b,c], Shirley Vallance [b,c], Paul J. Young [r,s], Ramon Diaz-Arrastia [t], Lori Shutter [u], Patrick T. Murray [v,w], Gerard F. Curley [x,y], Alistair Nichol [a,b,*]

[a] *University College Dublin Clinical Research Centre, St. Vincent's University Hospital, Dublin, Ireland*
[b] *Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Victoria, Australia*
[c] *Department of Intensive Care and Hyperbaric Medicine, The Alfred Hospital, Melbourne, Victoria, Australia*
[d] *Department of Neurosurgery, Royal Melbourne Hospital, Parkville, Victoria, Australia*
[e] *Department of Surgery, The University of Melbourne, Parkville, Victoria, Australia*
[f] *Intensive Care Unit, Royal Melbourne Hospital, Parkville, Victoria, Australia*
[g] *Department of Medicine and Radiology, University of Melbourne, Victoria, Australia*
[h] *Department of Intensive Care, Royal Brisbane and Women's Hospital, Herston, QLD, Australia*
[i] *Intensive Care Unit, St George Hospital, Gray St, Kogarah, Sydney, NSW, Australia, 2217*
[j] *Department of Intensive Care Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland*
[k] *Department of Electrical and Computer Systems Engineering, Monash University, Melbourne, Victoria, Australia*
[l] *Department of Neurosurgery, Alfred Hospital, Melbourne, Victoria, Australia*
[m] *Central Clinical School, Monash University, Melbourne, Victoria, Australia*
[n] *Department of Intensive Care, Royal Perth Hospital, Curtin University, Perth, WA, Australia*
[o] *Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK*
[p] *Intensive Care Unit, Royal Adelaide Hospital, Port Road, Adelaide, SA, 5000, Australia*
[q] *School of Medicine, University of Adelaide, Adelaide, SA, Australia*
[r] *Medical Research Institute of New Zealand, Wellington, New Zealand*
[s] *Intensive Care Unit, Wellington Regional Hospital, Wellington, New Zealand*
[t] *Department of Neurology and Center for Brain Injury and Repair, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA*
[u] *Department of Critical Care Medicine, University of Pittsburgh School of Medicine / UPMC Health System, Pittsburgh, PA, USA*
[v] *School of Medicine, University College Dublin, Dublin, Ireland*
[w] *Clinical Research Centre, University College Dublin, Ireland, Division of Nephrology, Mater Misericordiae University Hospital, Ireland*
[x] *Department of Anaesthesia and Critical Care, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland*
[y] *Department of Neurosurgery, Royal College of Surgeons in Ireland, Dublin, Ireland*

ARTICLE INFO

ABSTRACT

Abbreviations: RCT, Randomized Controlled Trial; TBI, Traumatic Brain Injury; ICU, Intensive Care Unit.

* Corresponding author at: Alistair Nichol, University College Dublin Clinical Research Centre, St. Vincent's University Hospital, Dublin, Ireland.
E-mail addresses: leanne.hays@ucd.ie (L.M.C. Hays), andrew@udy.com (A. Udy), Alexios.Adamides@mh.org.au (A.A. Adamides), James.Anstey@mh.org.au (J.R. Anstey), michael.bailey@monash.edu (M. Bailey), Kathleen.Byrne@mh.org.au (K. Byrne), Andrew.Cheng@health.nsw.gov.au (A. Cheng), jamie.cooper@monash.edu.au (D. Jamie Cooper), Kate.Drummond@mh.org.au (K.J. Drummond), Matthias.Haenggi@insel.ch (M. Haenggi), Stephan.Jakob@insel.ch (S.M. Jakob), lisa.higgins@monash.edu (A.M. Higgins), Philip.Lewis@monash.edu (P.M. Lewis), M.Hunn@alfred.org.au (M.K. Hunn), Robert.Mcnamara@health.wa.gov.au (R. McNamara), dkm13@cam.ac.uk (D.K. Menon), lynnette.murray@monash.edu (L. Murray), benjamin.reddi@adelaide.edu.au (B. Reddi), tony.trapani@monash.edu (T. Trapani), Shirley.Vallance@monash.edu (S. Vallance), Paul.Young@ccdhb.org.nz (P.J. Young), Ramon.Diaz-Arrastia@pennmedicine.upenn.edu (R. Diaz-Arrastia), shutterla@upmc.edu (L. Shutter), patrick.murray@ucd.ie (P.T. Murray), gercurley@rcsi.ie (G.F. Curley), alistair.nichol@ucd.ie (A. Nichol).

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Keywords:
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Multimodality monitoring

Monitoring and optimisation of brain tissue oxygen tension ($PbtO_2$) has been associated with improved neurological outcome and survival in observational studies of severe traumatic brain injury (TBI). We carried out a systematic review of randomized controlled trials to determine if $PbtO_2$-guided management is associated with differential neurological outcomes, survival, and adverse events. Searches were carried out to 10 February 2022 in Medline (OvidSP), 11 February in EMBASE (OvidSP) and 8 February in Cochrane library. Randomized controlled trials comparing $PbtO_2$ and ICP-guided management to ICP-guided management alone were included. The primary outcome was survival with favourable neurological outcome at 6-months post injury. Data were extracted by two independent authors and GRADE certainty of evidence assessed. There was no difference in the proportion of patients with favourable neurological outcomes with $PbtO_2$-guided management (relative risk [RR] 1.42, 95% CI 0.97 to 2.08; p = 0.07; I2 = 0%, very low certainty evidence) but $PbtO_2$-guided management was associated with reduced mortality (RR 0.54, 95% CI 0.31 to 0.93; p = 0.03; I2 = 42%; very low certainty evidence) and ICP (mean difference (MD) − 4.62, 95% CI − 8.27 to − 0.98; p = 0.01; I2 = 63%; very low certainty evidence). There was no significant difference in the risk of adverse respiratory or cardiovascular events. $PbtO_2$-guided management in addition to ICP-based care was not significantly associated with increased favourable neurological outcomes, but was associated with increased survival and reduced ICP, with no difference in respiratory or cardiovascular adverse events. However, based on GRADE criteria, the certainty of evidence provided by this *meta*-analysis was consistently very low.

MESH:

Brain Ischemia; Intensive Care; Glasgow Outcome Scale; Randomized Controlled Trial; Craniocerebral Trauma.

1. Introduction

1.1. Description of the condition

With an annual incidence of 17.3 per 100,000 population worldwide [1]), severe traumatic brain injury (TBI) is a key public health issue, and is a major cause of death and disability in young adults [2,3]. After the primary insult, secondary brain injury can occur via a number of pathways, including; ischaemia, oxidative stress, increased vascular permeability, exocitotoxic damage and inflammation [4]. Current management of severe TBI aims to reduce this secondary brain injury by treating contributing factors [5].

Traditionally, severe TBI care has focused on reducing ICP (target < 22 mmHg) and maintaining an adequate cerebral perfusion pressure (CPP; as a marker of cerebral blood flow and oxygen delivery, usual target 60–70 mmHg). The benefit of ICP/CPP-guided management has not been determined in a randomized clinical trial and some studies question its utility [6,7]. In some ICUs, the partial pressure of brain tissue oxygen ($PbtO_2$) is also monitored and optimised, but evidence of benefit from this approach has yet to be established.

Brain ischaemia is considered a major cause of secondary brain injury [8] with low $PbtO_2$ values (less than the normal range 25–35 mmHg) often reported following severe TBI [9–12]. Most of these hypoxic episodes would not have been detected with traditional ICP/CPP monitoring [10]. Critically, brain tissue hypoxia (low $PbtO_2$ values) is associated with poor patient outcomes [12–15]. Interventions such as ventilator adjustments to raise the partial pressure of oxygen (PaO_2) and/or carbon dioxide ($PaCO_2$) in blood, haemoglobin (Hb) augmentation through transfusion of red blood cells (RBC) [16], and increasing the CPP have all been shown to increase low $PbtO_2$ values [9,17–22].

1.2. Description of the intervention

In observational, historical matched case-controlled and non-randomized studies, $PbtO_2$ monitoring and subsequent optimisation, in addition to conventional ICP-guided management has been associated with reduced mortality [20,22,23] and improved neurological outcome or trends towards this [21–24]. A small number of randomized controlled trials (RCTs) [25–28] indicate potential benefits of $PbtO_2$-guided management in neurological outcome and survival. To date, systematic reviews conducted on this topic have included observational, case-control, cohort and historical control studies [29,30] and have concluded that $PbtO_2$-guided management is associated with improved neurological outcome. $PbtO_2$-guided management may however be associated with increased respiratory and/or cardiovascular adverse events, as some of the main interventions used to optimise $PbtO_2$ include ventilator adjustment and haemodynamic interventions (e.g. increase in CPP).

1.3. Why it is important to do this review

RCTs of $PbtO_2$-guided management have not yet been systematically reviewed. We conducted this review to assess whether $PbtO_2$-guided management in addition to ICP-guided management improves patient outcomes, including functional status and mortality, and whether it is associated with respiratory or cardiovascular adverse events. This is important, as current international guidelines make no recommendation as to whether $PbtO_2$ monitoring should be employed in this setting. We also sought to determine if there remains equipoise for prospective randomised trials comparing these approaches to TBI management.

1.4. Objectives

The primary objective of this review was to assess, in patients with severe TBI, whether $PbtO_2$-guided management in addition to ICP-based care has an effect on neurological outcome. Secondary objectives were to assess if $PbtO_2$-guided management in addition to ICP-based care affects mortality, and respiratory and/or cardiovascular adverse events, in comparison to traditional ICP-guided management alone.

2. Methods

2.1. Registration

This systematic review and *meta*-analysis is registered on PROSPERO (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220661).

2.2. Data sources and searches

Eligible studies were identified by searches to 10 February 2022 in Medline (OvidSP), 11 February 2022 in EMBASE (OvidSP) and 8 February 2022 in the Cochrane library using MeSH terms “brain injuries, traumatic”, “Oxygen”, “Glasgow Outcome Scale” and “intracranial pressure” and keywords “TBI”, “multimodality monitoring”, “PbtO2”, “monitoring”, “neurocritical care” and “intensive care”. Reference lists of extracted studies were searched to identify additional studies. Ongoing trials were identified by searches to 8 February 2022 on

ClinicalTrials.gov (https://clinicaltrials.gov/), ISRCTN registry (http://www.isrctn.com/), EudraCT (https://eudract.ema.europa.eu/) and WHO International Clinical Trial Registry Platform (http://www.who.int/ictrp/). There were no limitations on year or publication status.

2.3. Study selection

Citations and abstracts retrieved using the search strategy were initially screened for relevance by two independent reviewers (LH and AU) and any clearly irrelevant articles were discarded. Potentially eligible studies were reviewed in full by two independent reviewers for inclusion/exclusion criteria. Any disagreement as regards eligibility among the two reviewers was resolved by a third reviewer (AN).

Studies were considered eligible if they were RCTs comparing $PbtO_2$ in addition to ICP-guided management to ICP-guided management alone in patients with moderate or severe TBI defined as a Glasgow Coma Scale (GCS) of 9–12 or ≤ 8, respectively. Studies were excluded from the review if they were not RCTs, were paediatric studies or if the article was not available in English.

The primary outcome of this review was the proportion of participants with a favourable neurological outcome at 6 months post injury, as measured by a score of ≥ 4 on the Glasgow Outcome Scale (GOS) and/or ≥ 5 on the Glasgow Outcome Scale Extended (GOSE). The GOS and GOSE measure survival and degree of disability and recovery. Other outcomes assessed were mortality at 6 months, mean ICP, and respiratory and cardiovascular adverse events. Mean ICP, respiratory and cardiovascular adverse events were included as defined by the individual trials.

2.4. Data extraction

Data extraction from eligible studies was carried out by two independent reviewers using a standard data extraction form (LH and AU). Disagreements were resolved by a third author (AN). Data extracted included trial design, location, number of sites, dates of recruitment, number of participants, clinical setting, inclusion and exclusion criteria, participant demographics, trial interventions, study procedures, relevant outcome data and any identified bias or issues that may affect bias or GRADE criteria. For each outcome, the number of participants in each treatment group, the number of participants with outcome data, the associated time point, unit of measure, point estimate and measure of spread and statistical methods used, were recorded.

2.5. Risk of bias and GRADE quality of evidence

All studies were assessed for risk of bias by two independent reviewers (LH and AU) following the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [31]. Risk of bias was assessed in the following areas as either low risk, unclear risk or high risk; random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and any other bias. Disagreements were resolved by a third reviewer (AN).

GRADE methods were used to assess the certainty of evidence as either very low, low, moderate or high [32] using GRADEpro GDT software (GRADEpro GDT:GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 [developed by Evidence Prime, Inc]. Available from gradepro.org). Risk of bias, inconsistency, imprecision, indirectness and publication bias were considered for the GRADE assessment.

2.6. Data synthesis

Data were analysed both qualitatively and quantitatively where possible. Meta-analysis was conducted on outcomes where sufficient data from two or more studies were available. Meta-analysis was carried out using Review Manager (RevMan) Version 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Fixed-effects models were used due to the similarity in patient population and interventions and the small number of studies. Data were analysed using the Mantel-Haenszel test. Dichotomous outcomes are reported as relative risks (RR) with 95 % confidence intervals (CIs). Continuous outcomes were analysed by inverse variance and are reported as mean difference (MD) with 95 % CIs. Results were considered statistically significant if they had a p-value < 0.05.

Chi-squared tests were used to measure statistical heterogeneity of intervention effects between studies and I^2 used to quantify the extent of heterogeneity (<40%: might not be important; 30% – 60%: may represent moderate heterogeneity; 50% – 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity). Planned subgroup analyses (based on presenting GCS, the requirement for evacuation of a mass lesion) were not performed due to the low number of participants, studies and the similarities between patient groups. Sensitivity analyses were performed, excluding data from specific studies, where appropriate. Evaluation for publication bias was not possible due to the small number of identified studies.

3. Results

3.1. Results of the search

A summary of the literature search is shown in the PRISMA flowchart (Fig. 1). Eight-hundred and fifty-one (n = 851) records were screened for

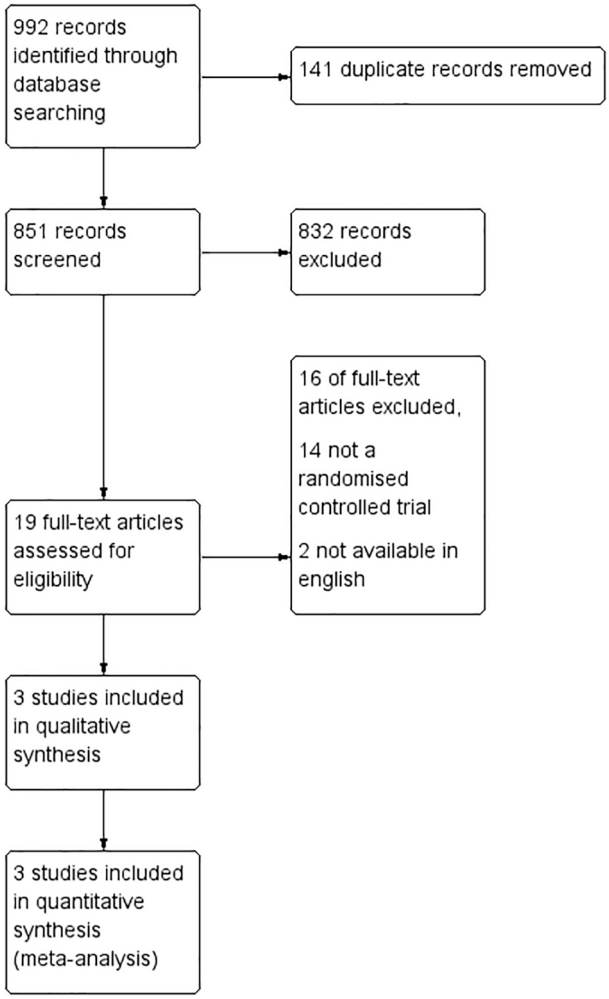

Fig. 1. Study flow diagram.

eligibility following removal of duplicates. Following removal of irrelevant studies (those assessing different interventions, not assessing $PbtO_2$, review articles, not in TBI, animal studies, etc), 19 articles were screened for full eligibility. Of these, three studies were suitable for inclusion [25–27]. We also identified three ongoing trials [33–35] and one completed trial with no associated published results available [36].

3.2. Included studies

The characteristics of the three included trials are outlined in Table 1. One trial was a single-centre study [25] and two studies were multicentre trials carried out in a single country [26,27]. Recruitment numbers were relatively low with only one study recruiting >100 participants [27]. All studies were conducted in intensive care units and included either adult [26] or adult and adolescent patients [25,27]. Two studies included only severe TBI patients (GCS $\leq$ 8) [25,27] and one study included both moderate (GCS 9–12) and severe (GCS $\leq$ 8) TBI [26]. However, ~70 % of the patients included in the latter study had severe TBI (GCS $\leq$ 8). All studies compared ICP-guided management with ICP/$PbtO_2$-guided management. One study compared three groups of patients (ICP/CPP-guided, ICP/CPP-guided and mild hypothermia and ICP/CPP and $PbtO_2$-guided and mild hypothermia) [25]. For this review the latter two groups were included with the only difference between the groups being the addition of $PbtO_2$-guided management. In all studies intracranial hypertension was treated if the ICP was $\geq$ 20 mmHg and brain hypoxia treated if $PbtO_2$ was < 20 mmHg.

The interventions to treat intracranial hypertension (ICP $\geq$ 20 mmHg), brain hypoxia ($PbtO_2$ < 20 mmHg) or a combination of both had similarities but also differed between the trials. [27] was particularly detailed with a clear hierarchical approach of less aggressive manoeuvres attempted before more aggressive ones. These interventions are outlined in Table 2. $PbtO_2$ was measured only in the $PbtO_2$-guided group in two studies [25,26] but was measured in both groups in the other study allowing comparison of the effects of ICP-guided therapy alone or ICP and $PbtO_2$-guided therapy on $PbtO_2$ values and cerebral hypoxic episodes [27]. Treating clinicians were not blinded to treatment allocation in any of the included studies. Only one study specified blinding within the study ($PbtO_2$ measurements in the ICP group were blinded and outcome assessors were blinded) [27].

3.3. Risk of bias in included studies

Risk of bias assessment was performed for each study and is shown in Fig. 2. The studies were considered in most categories to be at low risk of bias. All studies were considered to be at high risk of performance bias as participants and personnel were not blinded (not possible considering the intervention). Two studies were considered to be at unclear risk of selection bias as it was not specified how random sequence generation and allocation concealment were carried out, although both studies were RCTs [25,26]. Both studies were also considered to have unclear risk of detection bias as it was not specified if outcome assessors were blinded [25–26]. Lin et al. [26] was also considered to have unclear risk of bias for selective reporting, as numerical data were not always reported and ranges rather than exact values were reported in some cases.

3.4. Effects of interventions

3.4.1. Neurological outcome at 6 months

Data on neurological outcome at 6 months were recorded in all three trials and included in the analysis [25–27]. One study used the GOS [25], another used the GOSE [27] and the final trial measured both [26]. The proportion of favourable outcomes and the mean scores varied across the studies. There was no difference in favourable neurological outcomes between the treatment groups; RR of 1.42 (95% CI 0.97 to 2.08; p = 0.07; participants = 185; studies = 3; I^2 = 0%) (Fig. 3).

3.5. Mortality

All studies reported on mortality at 6 months and were included in the analysis [25–27]. One study also reported mortality at 1 and 3 months post injury, with the reduction in mortality at 3 and 6 months being statistically significant [26]. In pooled analysis, $PbtO_2$ and ICP-guided management was associated with a significantly reduced risk of mortality; RR 0.54 (95% CI 0.31 to 0.93; p = 0.03; participants = 185; studies = 3; I^2 = 42%) Fig. 4.

3.6. Respiratory adverse events

All studies reported on respiratory adverse events or complications

Table 1
Characteristics of Included Studies.

Study and Year	Setting	Methods	Participants	Interventions	Outcomes
Lee, 2010	Single ICU in Taiwan recruiting Sept 2006-August 2007	Single centre randomised controlled trial	45 participants (16 ICP/CPP, 15 ICP/CPP and mild hypothermia, 14 $PbtO_2$, ICP/CPP and mild hypothermia) with severe non-penetrating TBI after craniotomy (GCS 4–8) aged 12–70 years	Group A: ICP/CPP-guided management Group B (Control): ICP/CPP-guided management and mild hypothermia Group C (Intervention): $PbtO_2$ and ICP/CPP-guided management and mild hypothermia	-Glasgow Outcome Scale at 6 months (mean and favourable defined as $\geq$ 4) -Mortality -Length of ICU Stay -Length of Hospital Stay -Healthcare Cost -Complications -ICP (mean) -Cpk (medical treatment process capability)
Lin, 2015	6 neurosurgical ICUs in Taiwan recruiting Jan 2009-Dec 2010.	Prospective, multi-centre phase III Randomised Controlled Trial	50 participants (27 ICP, 23 ICP/$PbtO_2$) with moderate (GCS 9–12) and severe (GCS < 8) TBI aged 17–70 years ~ 70 % severe TBI (initial GCS 3–8).	Control: ICP-guided management Intervention: ICP and $PbtO_2$-guided management	-Glasgow Outcome Scale (1, 3 and 6 months) -Glasgow Outcome Scale Extended (1, 3 and 6 months) -Mortality (1, 3 and 6 months) -ICP (mean and hypertensive events) -Physiologic data: CPP, $PaCO_2$, GCS, PaO_2 -Pulmonary complications
Okonkwo, 2017	10 ICUs in level 1 trauma centres in US. Dates of recruitment not stated.	Two-arm, single-blind, prospective randomized controlled multicenter phase II trial	119 participants (ICP 62, ICP and $PbtO_2$ 57) with non-penetrating severe TBI (GCS 3–8) aged > 14 years	Control: ICP-guided management Intervention: ICP and $PbtO_2$-guided management	-Glasgow Outcome Scale Extended at 6 months (mean and favourable outcome GOSE 5–8) -Disability Rating Scale at 6 months -Mortality at 6 months -Serious adverse events -Brain hypoxia (burden, depth, proportion of time) -ICP (hypertension burden, depth, proportion of time)

Table 2
Comparison of Trial Interventions.

Study	ICP ≥ 20 mmHg and $PbtO_2$ ≥ 20 mmHg	ICP < 20 mmHg and $PbtO_2$ < 20 mmHg	ICP ≥ 20 mmHg and $PbtO_2$ < 20 mmHg
Lee 2010	Elevating the head end of the bed Sedation Paralysis Mannitol	Increase CPP until $PbtO_2$ values reach 20 mmHg through fluid and vasopressors *found that increasing FiO_2 did not increase $PbtO_2$	Elevating the head end of the bed Sedation Paralysis Mannitol Increase CPP until $PbtO_2$ values reach 20 mmHg through fluid and vasopressors *found that increasing FiO_2 did not increase $PbtO_2$
Lin 2015	Mannitol Glycerol Colloid Sedatives Decompressive craniectomy	100% FiO_2 challenge If 100% FiO_2 needed for > 5 h or $PbtO_2$ not increased by FiO_2 challenge: CPP increased to 80 mmHg $PaCO_2$ increased to 40 mmHg	Normalization of $PbtO_2$ considered most important strategy
Okonkwo 2017	Tier 1: 1. Adjust head of bed 2. Ensure temperature < 38 °C 3. Adjust pharmacologic analgesia and sedation 4. CSF drainage (if EVD available) 5. Standard dose Mannitol (0.25–1.0 g/kg) as bolus infusion 6. Hypertonic saline Tier 2: 1. Adjust ventilatory rate to lower $PaCO_2$ to 32–35 mmHg. 2. High dose Mannitol > 1 g/kg 3. Repeat CT to determine if increased size of intracranial mass lesions 4. Treat surgically remediable lesions with craniotomy according to guidelines 5. Adjust temperature to 35–37 °C, using active cooling measures Tier 3 (optional): 1. Pentobarbitol coma, according to local protocol 2. Decompressive craniectomy 3. Adjust temperature to 32–34.5 °C using active cooling measures 4. Neuromuscular blockade	Tier 1: 1. Adjust head of bed 2. Ensure temperature < 38 °C 3. Increase CPP to 70 mmHg with fluid bolus 4. Optimize hemodynamics 5. Increase PaO_2 by increasing FiO_2 to 60% 6. Increase PaO_2 by adjusting PEEP 7. Add EEG monitoring 8. Consider adding AED's, either Dilantin or Keppra, for 1 week only. Tier 2: 1. Increase PaO_2 by increasing FiO_2 to 100% 2. Increase PaO_2 by adjusting PEEP 3. Increase CPP up to a max of 70 mmHg with vasopressors 4. Adjust ventilatory rate to increase $PaCO_2$ to 45–50 mmHg. 5. Transfuse PRBCs to goal Hgb > 10 g/dL 6. Decrease ICP to < 10 mmHg. 6a. CSF drainage 6b. Increased sedation	Tier 1: 1. Adjust head of bed 2. Ensure temperature < 38 °C 3. Pharmacologic analgesia and sedation 4. CSF drainage (if EVD available) 5. Increase CPP to a max of 70 mmHg with fluid bolus 6. Standard dose Mannitol (0.25–0.5 mg/kg) as bolus infusion 7. Hypertonic saline 8. Increase PaO_2 by increasing FiO_2 to 60% 9. Increase FiO_2 by increasing PEEP 10. Consider EEG monitoring 11. Consider adding AED's, either Dilantin or Keppra, for 1 week only. Tier 2: 1. High dose Mannitol 1 g/kg or frequent boluses standard dose mannitol 2. Increase CPP up to a max of 70 mmHg with vasopressors 3. Increase PaO_2 by increasing FiO_2 to 100% 4. Increase FiO_2 by increasing PEEP 5. Transfuse to goal Hgb > 10 g/dL 6. Repeat CT to determine if increased size of intracranial mass lesions 7. Treat surgically remediable lesions with craniotomy according to guidelines 8. Adjust temperature to 35–37 °C, using active cooling measures Tier 3 (optional): 1. Pentobarbitol coma 2. Decompressive craniectomy 3. Adjust temperature to 32–34.5 °C using active cooling measures 4. Neuromuscular blockade

AED = anti-epileptic drugs, CPP = cerebral perfusion pressure, CSF = cerebrospinal fluid, CT = computed tomography, EEG = electroencephalogram, EVD = external ventricular drain, FiO_2 = fraction of inspired oxygen, ICP = intracranial pressure, $PaCO_2$ = partial pressure of carbon dioxide, $PbtO_2$ = partial pressure of brain tissue oxygen, PEEP = positive end-expiratory pressure, PRBCs = packed red blood cells.

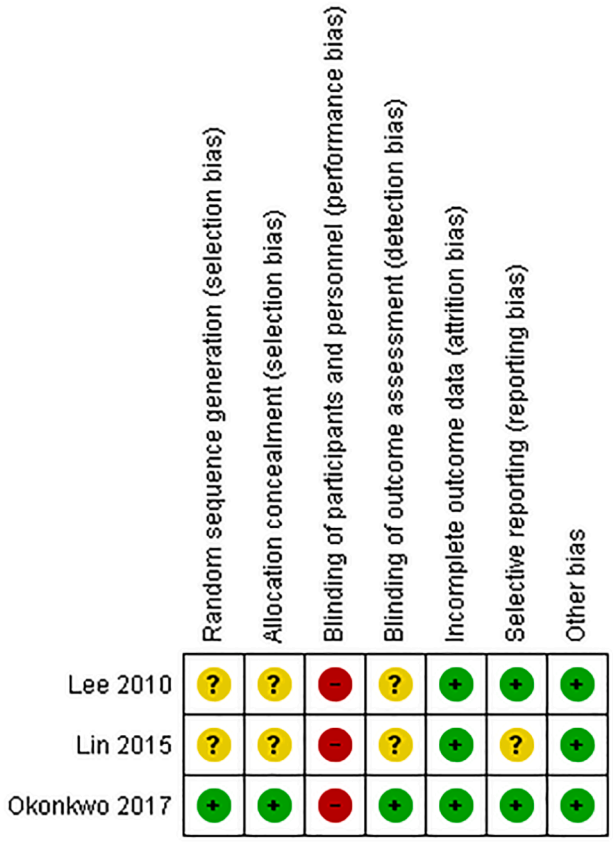

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

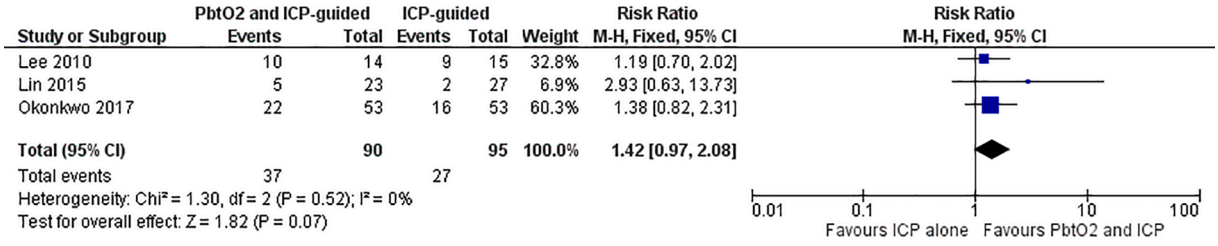

Fig. 3. Forest plot of comparison; $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Favourable neurologic outcome at 6 months.

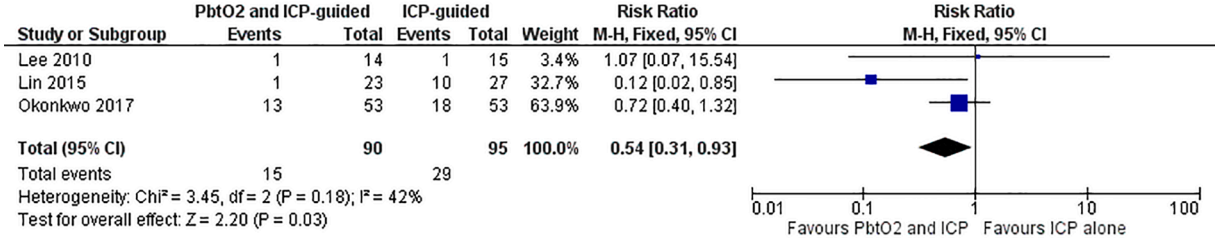

Fig. 4. Forest plot of comparison: $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Mortality.

and were included in pooled analysis [25–27]. The relative risk for respiratory adverse events was 1.37 (95% CI 0.59 to 3.21; p = 0.46; participants = 198; studies = 3; $I^2 = 15\%$) Fig. 5. The respiratory serious adverse events in the $PbtO_2$-guided group in [27] were pneumonia (2/4) and respiratory failure (2/4). [26] did not specify what the pulmonary complications were and in [25], only pulmonary infections were recorded.

3.7. Cardiovascular adverse events

[25]) reported on the incidence of arrhythmia and [27] reported on cardiovascular adverse events. These were included in pooled analysis [25,27]. The relative risk for cardiovascular adverse events was 1.44 (95% CI 0.65 to 3.20; p = 0.37; participants = 148; studies = 2; I^2 = 10%) Fig. 6.

3.8. Mean ICP

ICP was reported and measured in all three studies, albeit not in a consistent manner. Two studies reported the mean ICP [25-26], which was used in pooled analysis. Mean ICP was collected from ICU admission through the period of intracranial hypertension by Lee *at al.*, 2010 and the first five days in the ICU by [26]. The addition of $PbtO_2$ guided management was associated with lower mean ICP, with a mean difference of − 4.62 (95% CI − 8.27 to − 0.98; p = 0.01; participants = 79; studies = 2; $I^2 = 63\%$) Fig. 7.

3.9. Sensitivity analysis

We conducted a sensitivity analysis concerning favourable neurological outcome at 6 months excluding data from [26], as these data were extrapolated from figures, and therefore unconfirmed. There was no difference in favourable neurological outcome between the groups in our sensitivity analysis RR of 1.31 (95% CI 0.89 to 1.93; p = 0.17; participants = 135; studies = 2; $I^2 = 0\%$) Fig. 8.

3.10. GRADE assessment for certainty of evidence

The GRADE assessment for certainty of evidence for favourable neurological outcome, mortality, mean ICP, respiratory and cardiovascular adverse events was considered very low (Table 3). These were downgraded as all studies did not blind participants and personnel (although this is impossible given the intervention), two studies did not specify blinding of outcome assessors and lacked sufficient information on allocation concealment and random sequence generation (risk of bias) and for imprecision due to the very small sample sizes, small number of studies, small number of events and confidence intervals which include both potential harm and benefit. Mortality and ICP were also downgraded for inconsistency due to the moderate and substantial heterogeneity, respectively, detected in analysis.

4. Discussion

4.1. Summary of main results

This systematic review and *meta*-analysis of three RCTs found that

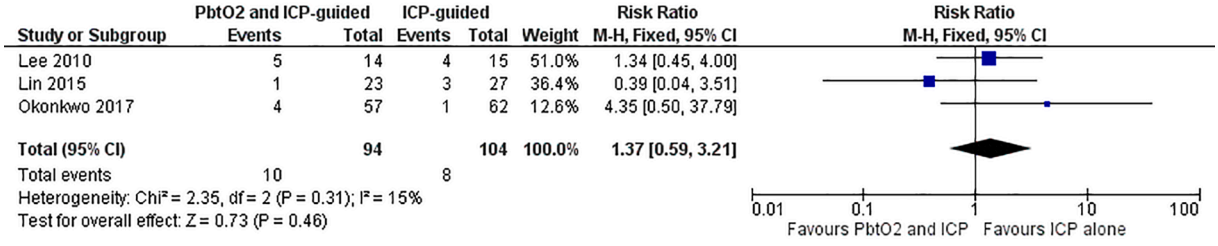

Fig. 5. Forest plot of comparison: $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Adverse Respiratory Events.

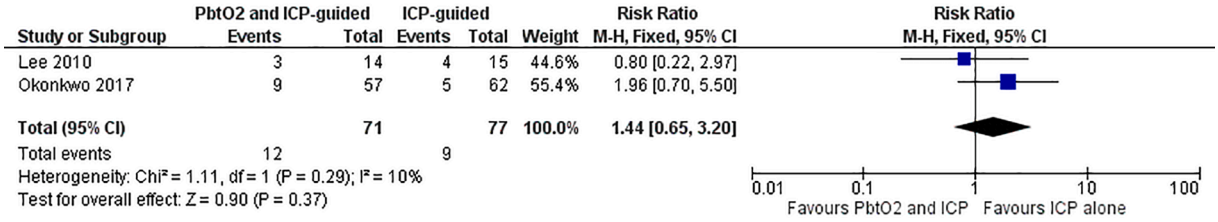

Fig. 6. Forest plot of comparison: $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Cardiovascular Adverse Events.

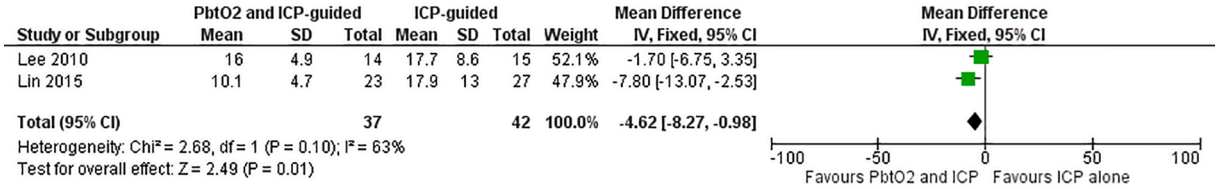

Fig. 7. Forest plot of comparison: $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Intracranial Pressure (ICP).

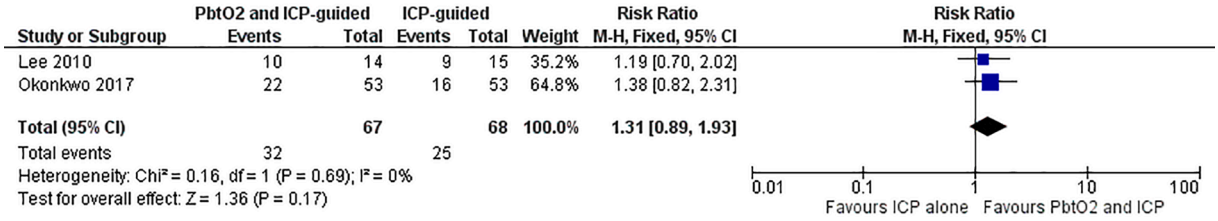

Fig. 8. Sensitivity Analysis: $PbtO_2$ and ICP-guided management versus ICP-guided management, outcome: Favourable neurologic outcome at 6 months.

the inclusion of $PbtO_2$-guided management was not associated with increased favourable neurological outcome at 6 months, although the certainty of evidence was considered very low. Sensitivity analysis, with removal of extrapolated data from Lin *et al.*, did not alter this conclusion. The addition of $PbtO_2$-guided management was associated with significantly reduced mean ICP and mortality at 6 months, although the certainty of the evidence available was also very low. Finally, $PbtO_2$-guided management was not associated with an increased risk of respiratory or cardiovascular adverse events. Of note, all evidence was considered very low certainty mainly due to the low number of RCTs in this area, the small sample sizes of the studies to date, the low number of events, confidence intervals including both potential harm and benefit, risk of bias, and moderate to significant heterogeneity. Thus, this *meta*-analysis lacked precision to detect an intervention effect with a high certainty.

4.2. Agreements and disagreements with other studies or reviews

$PbtO_2$ monitoring and subsequent treatment of low $PbtO_2$ in addition to conventional ICP-guided management may improve neurological outcome and survival of patients, by reducing the duration of cerebral hypoxic episodes and subsequent secondary brain injury. $PbtO_2$ and ICP-guided management has been found in observational series or studies with historical matched controls to reduce brain hypoxia [9,21,22] and has been associated with reduced mortality [20,22,23]. Improved neurological outcome or trends towards this have been observed in similar studies [21–24]. Other cohort studies suggest the addition of $PbtO_2$-guided management may have no effect [37] or may result in worse functional status [38]. McCarthy et al. [24] found a trend towards improved neurological outcome at 3 months but no effect on mortality or length of stay [24]. Previous reviews have primarily included observational studies, cohort studies, case control studies and historical controls [29,30], and have reported an association between $PbtO_2$-guided management and increased favourable neurological outcomes.

Xie et al., [30] included one RCT along with cohort studies, and also examined mortality, length of stay, and ICP, but found no significant association. Our review and *meta*-analysis is in agreement with much of this prior work, finding that $PbtO_2$-guided management may improve mortality, but the available evidence does not permit treatment recommendations. Furthermore, our review did not find a significant association between $PbtO_2$-guided management and favourable neurological outcome, although the evidence was of very low certainty. While the point estimate suggested benefit, our data do not exclude the possibility that $PbtO_2$-guided therapy may increase the number of disabled survivors, and as such, future research focusing on functional outcomes, rather than simply mortality, is a high priority.

The effect of $PbtO_2$-guided management on ICP remains uncertain. One observational study reported a reduction in mean ICP with the addition of $PbtO_2$-guided management [9], although some observational or historical-matched controlled studies and one RCT found no difference in ICP between groups with $PbtO_2$ and ICP-guided versus ICP-guided management alone [20,21,23,28,37]. Our review suggests an association between better ICP control, and use of $PbtO_2$-guided management, although the evidence provides very low certainty, and the mechanism remains uncertain. Finally, we did not find a significant association between $PbtO_2$-guided management and an increased risk of respiratory or cardiovascular adverse events, although the certainty of evidence is considered very low.

4.3. Limitations of this review

This review has several limitations. Firstly, the number of studies and number of participants in each study is extremely small. There is significant heterogeneity in some of the outcomes (mortality and ICP) and

Table 3
Summary of findings and GRADE quality of evidence.

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PbtO2 and ICP-guided management	ICP-guided management	Relative (95% CI)	Absolute (95% CI)	
Favourable neurologic outcome at 6 months											
3	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	37/90 (41.1%)	27/95 (28.4%)	**RR 1.42** (0.97 to 2.08)	**119 more per 1,000** (from 9 fewer to 307 more)	⊕○○○ VERY LOW
Mortality											
3	randomised trials	serious [a]	serious [c]	not serious	very serious [b]	none	15/90 (16.7%)	29/95 (30.5%)	**RR 0.54** (0.31 to 0.93)	**140 fewer per 1,000** (from 211 fewer to 21 fewer)	⊕○○○ VERY LOW
Intracranial Pressure (ICP)											
2	randomised trials	serious [a]	serious [c]	not serious	very serious [b]	none	37	42	–	MD **4.62 lower** (8.27 lower to 0.98 lower)	⊕○○○ VERY LOW
Adverse Respiratory Events											
3	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	10/94 (10.6%)	8/104 (7.7%)	**RR 1.37** (0.59 to 3.21)	**28 more per 1,000** (from 32 fewer to 170 more)	⊕○○○ VERY LOW
Cardiovascular Adverse Events											
2	randomised trials	serious [a]	not serious	not serious	very serious [b]	none	12/71 (16.9%)	9/77 (11.7%)	**RR 1.44** (0.65 to 3.20)	**51 more per 1,000** (from 41 fewer to 257 more)	⊕○○○ VERY LOW

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio.
Explanations: a. No blinding of participants and personnel, unclear if blinding of outcome assessors in two studies, allocation concealment and random sequence generation not described in two studies although they were randomized. b. Small sample sizes, small number of studies, small number of events, confidence intervals include both potential harm and benefit. c. Potential heterogeneity.

in some cases the confidence intervals are large including both harm and benefit (adverse events). There are significant risks of bias and the primary outcome of two of the studies included in the analysis [25,27] was not to detect clinical effects of PbtO2-guided management (which was the primary outcome of this review). Furthermore, the quality of evidence provided in this review is very low and insufficient to make treatment recommendations.

There are also potential limitations in the use of this intervention. Invasive $PbtO_2$ monitoring only measures a very focal area of cerebral oxygenation, while severe TBI can be more heterogeneous, with varying patterns of diffuse and focal injury. Moreover, optimal positioning of the probe is also uncertain, albeit current RCTs favour placing the device in normal appearing tissue, contra-lateral to the side of maximal injury, so as to obtain a value that most accurately reflects global oxygenation. Like any monitoring device, such catheters are also subject to technical and/or procedural complications, which can limit their reliability, particularly in naïve centres. Finally, the algorithms utilised to optimise $PbtO_2$ involve a variety of therapeutic options (from the use of hyperoxaemia to RBC transfusion), and it is unclear which strategy is the most effective and/or safest. To mitigate this potential confounding, future RCTs should be multicentre, stratified by site, and *apriori* sub-group analyses planned, that explore any heterogeneity in the treatment effect, based on case volume, and the specific treatments applied. Individual patient data *meta*-analyses are likely to be required to achieve this.

5. Implications for research

This review did not find an association between the addition of $PbtO_2$-guided management and improved neurological outcome, but found an association with increased survival. However, there are major shortcomings in the available data and the certainty of existing evidence is insufficient to support any treatment recommendations. As such, larger RCTs are needed to establish whether $PbtO_2$ monitoring and optimisation improves rates of survival with favourable neurological outcome when added to standard ICP monitoring. We note the BONANZA (ACTRN12619001328167), BOOST-3 (NCT03754114) and OXY-TC (NCT02754063) trials are ongoing, which will provide valuable future data.

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Declaration of Competing Interest

Authors include the Principal Investigator and management committee of BONANZA (Brain Oxygen Neuromonitoring in Australia and New Zealand Assessment Trial) and two Principal Investigators of BOOST-3 (Brain Oxygen Optimization in Severe Traumatic Brain Injury - Phase 3). BONANZA has been supported in-kind (trial consumables) by Integra Lifesciences.

Appendix

Search strategies

Medline (OvidSP)

1. Brain injuries, traumatic AND Oxygen AND Monitoring.
2. TBI AND multimodality monitoring.
3. $PbtO_2$.
4. Glasgow Outcome Scale AND Brain injuries, traumatic AND Oxygen.
5. Neurocritical care AND Oxygen.

EMBASE (OvidSP)

Using the 'Search as broadly as possible function'

Traumatic brain injur* AND oxygen AND monitoring AND intracranial pressure AND intensive care.

Cochrane library

Traumatic brain injur* AND oxygen AND monitoring AND intensive care AND intracranial pressure.

Clinical Trial Registries (ClinicalTrials.gov (https://clinicaltrials.gov/)), ISRCTN registry (http://www.isrctn.com/), EudraCT (https://eudract.ema.europa.eu/) and WHO International Clinical Trial Registry Platform (http://www.who.int/ictrp/)).

Traumatic brain injury AND Oxygen monitoring.

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