



Intracranial pressure monitoring with and without brain tissue oxygen pressure monitoring for severe traumatic brain injury in France (OXY-TC): an open-label, randomised controlled superiority trial

Jean-François Payen, Yoann Launey, Russell Chabanne, Samuel Gay, Gilles Francony, Laurent Gergele, Emmanuel Vega, Ambroise Montcriol, David Couret, Vincent Cotteceau, Sebastien Pili-Floury, Clement Gakuba, Emmanuelle Hammad, Gerard Audibert, Julien Pottecher, Claire Dahyot-Fizelier, Lamine Abdennour, Tobias Gauss, Marion Richard, Antoine Vilotitch, Jean-Luc Bosson, Pierre Bouzat for the OXY-TC trial collaborators*

Summary

Background Optimisation of brain oxygenation might improve neurological outcome after traumatic brain injury. The OXY-TC trial explored the superiority of a strategy combining intracranial pressure and brain tissue oxygen pressure (PbtO₂) monitoring over a strategy of intracranial pressure monitoring only to reduce the proportion of patients with poor neurological outcome at 6 months.

Methods We did an open-label, randomised controlled superiority trial at 25 French tertiary referral centres. Within 16 h of brain injury, patients with severe traumatic brain injury (aged 18–75 years) were randomly assigned via a website to be managed during the first 5 days of admission to the intensive care unit either by intracranial pressure monitoring only or by both intracranial pressure and PbtO₂ monitoring. Randomisation was stratified by age and centre. The study was open label due to the visibility of the intervention, but the statisticians and outcome assessors were masked to group allocation. The therapeutic objectives were to maintain intracranial pressure of 20 mm Hg or lower, and to keep PbtO₂ (for those in the dual-monitoring group) above 20 mm Hg, at all times. The primary outcome was the proportion of patients with an extended Glasgow Outcome Scale (GOSE) score of 1–4 (death to upper severe disability) at 6 months after injury. The primary analysis was reported in the modified intention-to-treat population, which comprised all randomly assigned patients except those who withdrew consent or had protocol violations. This trial is registered with ClinicalTrials.gov, NCT02754063, and is completed.

Findings Between June 15, 2016, and April 17, 2021, 318 patients were randomly assigned to receive either intracranial pressure monitoring only (n=160) or both intracranial pressure and PbtO₂ monitoring (n=158). 27 individuals with protocol violations were not included in the modified intention-to-treat analysis. Thus, the primary outcome was analysed for 144 patients in the intracranial pressure only group and 147 patients in the intracranial pressure and PbtO₂ group. Compared with intracranial pressure monitoring only, intracranial pressure and PbtO₂ monitoring did not reduce the proportion of patients with GOSE score 1–4 (51% [95% CI 43–60] in the intracranial pressure monitoring only group vs 52% [43–60] in the intracranial pressure and PbtO₂ monitoring group; odds ratio 1.0 [95% CI 0.6–1.7]; p=0.95). Two (1%) of 144 participants in the intracranial pressure only group and 12 (8%) of 147 participants in the intracranial pressure and PbtO₂ group had catheter dysfunction (p=0.011). Six patients (4%) in the intracranial pressure and PbtO₂ group had an intracerebral haematoma related to the catheter, compared with none in the intracranial pressure only group (p=0.030). No significant difference in deaths was found between the two groups at 12 months after injury. At 12 months, 33 deaths had occurred in the intracranial pressure group: 25 (76%) were attributable to the brain trauma, six (18%) were end-of-life decisions, and two (6%) due to sepsis. 34 deaths had occurred in the intracranial pressure and PbtO₂ group at 12 months: 25 (74%) were attributable to the brain trauma, six (18%) were end-of-life decisions, one (3%) due to pulmonary embolism, one (3%) due to haemorrhagic shock, and one (3%) due to cardiac arrest.

Interpretation After severe non-penetrating traumatic brain injury, intracranial pressure and PbtO₂ monitoring did not reduce the proportion of patients with poor neurological outcome at 6 months. Technical failures related to intracerebral catheter and intracerebral haematoma were more frequent in the intracranial pressure and PbtO₂ group. Further research is needed to assess whether a targeted approach to multimodal brain monitoring could be useful in subgroups of patients with severe traumatic brain injury—eg, those with high intracranial pressure on admission.

Funding The French National Program for Clinical Research, La Fondation des Gueules Cassées, and Integra Lifesciences.

Copyright © 2023 Elsevier Ltd. All rights reserved.

Lancet Neurol 2023; 22: 1005–14

See [Comment](#) page 973

*Study group members are listed in the appendix

Department of Anaesthesia and Intensive Care (Prof J-F Payen MD, G Francony MD, T Gauss MD, M Richard MSC, Prof P Bouzat MD) and Department of Public Health (A Vilotitch MSC, Prof J-L Bosson MD), Centre Hospitalier Universitaire Grenoble Alpes, Grenoble, France; INSERM U1216, Grenoble Institut Neurosciences, Grenoble, France (Prof J-F Payen, G Francony, T Gauss, M Richard, Prof P Bouzat); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Rennes, Rennes, France (Prof Y Launey MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Clermont-Ferrand, Clermont-Ferrand, France (R Chabanne MD); Department of Intensive Care, Centre Hospitalier Ancey Genevois, Ancey, France (S Gay MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Saint-Etienne, Saint-Etienne, France (L Gergele MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Lille, Lille, France (E Vega MD); Department of Intensive Care, Hopital Instruction des Armées Saint-Anne, Toulon, France (A Montcriol MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Sud, Reunion, France (Prof D Couret MD);

Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Bordeaux, Bordeaux, France (V Cottencau MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Besançon, Besançon, France (Prof S Pili-Floury MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Caen Normandie, Caen, France (C Gakuba MD); Department of Anaesthesia and Intensive Care, Hôpital Nord, Assistance Publique des Hôpitaux de Marseille, Marseille, France (E Hammad MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Nancy, Nancy, France (Prof G Audibert MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Strasbourg, Strasbourg, France (Prof J Pottecher MD); Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Poitiers, Poitiers, France (Prof C Dahyot-Fizelier MD); Department of Anaesthesia and Intensive Care, Hôpital Pitie-Salpetriere, Assistance Publique des Hôpitaux de Paris, Paris, France (L Abdenmour MD)

Correspondence to: Prof Jean-François Payen, Department of Anaesthesia and Intensive Care, Centre Hospitalier Universitaire Grenoble, Universitaire Grenoble Alpes, F-38000 Grenoble, France jfpayen@univ-grenoble-alpes.fr

See Online for appendix

Research in context

Evidence before this study

We assessed evidence for the usefulness of brain tissue oxygen pressure (PbtO₂) monitoring in changing outcome following severe traumatic brain injury with a MEDLINE search of papers published in English between Jan 1, 1998, and Jan 1, 2023, using the terms “severe traumatic brain injury”, “brain tissue oxygen pressure”, “brain hypoxia”, “adult” and “outcome”. Most studies were single-centre, observational, or retrospective, and indicated a possible association between low PbtO₂ and poor neurological outcome after severe traumatic brain injury. In these studies, brain tissue hypoxia was viewed as an independent contributor to poor outcome despite normalisation of intracranial pressure. One randomised trial showed that the information given by PbtO₂ monitoring could help to reduce the time spent in brain hypoxia. Two meta-analyses suggested that the combination of intracranial pressure and PbtO₂ monitoring to guide treatment might improve neurological outcome, but the certainty of evidence from analysed data was considered low quality. However, according to PET data, uncertainties existed on whether focal measurements of PbtO₂ could reflect the diffuse vascular changes found after brain trauma.

Added value of this study

To our knowledge, the OXY-TC trial is the first randomised trial to compare a dual strategy of intracranial pressure and PbtO₂ monitoring with a strategy of intracranial pressure monitoring only in patients after severe traumatic brain injury. The primary objective of our study was to test the hypothesis that early dual brain monitoring would be superior to intracranial pressure monitoring alone at reducing poor neurological outcome (ie, extended Glasgow Outcome Scale [GOSE] score 1–4 at 6 months).

Implications of all the available evidence

Our study indicates that, after severe traumatic brain injury, during the first 5 days of admission to an intensive care unit, a dual strategy combining intracranial pressure and PbtO₂ monitoring was not superior to intracranial pressure monitoring only to reduce the proportion of patients with GOSE score 1–4 at 6 months. However, the dual strategy might reduce the proportion of patients with poor neurological outcome who have high intracranial pressure on admission and a targeted approach to management therefore deserves further investigation.

Introduction

Severe traumatic brain injury, as defined by an initial Glasgow Coma Scale (GCS) score of less than 9 on admission, is a condition from which 25–40% of patients will die, and only 20% of patients avoid long-lasting disabilities.^{1,2} A cascade of biochemical events including excitotoxicity, changes in calcium homeostasis, oxidative stress, and inflammation leads to secondary brain damage and exacerbates the primary injury. Despite large clinical and structural heterogeneity in the presentation of severe traumatic brain injury, the reduction of secondary brain damage is the focus of modern traumatic brain injury management.

Early recognition of secondary brain damage relies on neuromonitoring in critically ill patients. Because intracranial hypertension is an independent risk factor for mortality and neurological disabilities,³ international guidelines emphasise the use of intracranial pressure monitoring following severe traumatic brain injury.^{4,5} Intracranial pressure monitoring is associated with higher therapy intensity, lower mortality, and better functional outcome at 6 months compared with no intracranial pressure monitoring.⁶ However, maintaining intracranial pressure at 20 mm Hg and lower does not guarantee improved neurological outcome, as shown by findings of clinical trials of prolonged hyperventilation⁷ and secondary decompressive craniectomy.^{8,9} Brain tissue hypoxia can develop independently of high intracranial pressure, and might be independently associated with poor neurological outcome.^{10–12}

Brain tissue oxygen pressure (PbtO₂) probes are used to monitor cerebral oxygenation at the bedside. PbtO₂ reflects brain perfusion and diffusion of dissolved plasma oxygen across the blood–brain barrier.¹³ A PbtO₂ value that is lower than 15 mm Hg for more than 30 min is an independent predictor of unfavourable outcome and death.¹⁰ In a phase 2 randomised controlled trial, Okonkwo and colleagues¹⁴ compared intracranial pressure monitoring with both intracranial pressure and PbtO₂ monitoring to guide treatment. PbtO₂ monitoring reduced the time spent in brain hypoxia.¹⁴ However, uncertainty remains about the effect of a strategy guided by focal measurements of PbtO₂ on global brain oxygenation.¹⁵ In two meta-analyses,^{16,17} a dual strategy of intracranial pressure and PbtO₂ monitoring to guide treatment indicated a potential benefit on outcome, but the certainty of evidence from the analysed data was considered low quality.

In view of the sparse evidence base, the OXY-TC trial group designed a randomised controlled trial to explore the hypothesis that a therapeutic strategy based on early intracranial pressure and PbtO₂ monitoring would be superior to a strategy of intracranial pressure monitoring only, to reduce the proportion of patients with poor neurological outcome at 6 months after severe traumatic brain injury.

Methods

Study design

The OXY-TC trial was a multisite, open-label, randomised superiority trial at 25 tertiary referral centres in France;

these centres had experience in the management of patients with severe traumatic brain injury and had constant availability of neurosurgery (appendix pp 12–47). The Institutional Review Board of Sud-Est V (Grenoble, France; (ref 14-CHUG-48), and Agence Nationale de Sécurité du Médicament et des produits de santé (ref 141435B-31) approved the published trial protocol.¹⁸

Participants

Individuals (aged 18–75 years) were screened for inclusion if they were admitted to one of the tertiary centres for a severe non-penetrating traumatic brain injury, had a best pre-hospital GCS of 3–8 and motor component of 1–5, and required intracranial pressure monitoring. Patients were included if sedation and mechanical ventilation were expected to exceed 48 h with a stable condition (the partial pressure of oxygen in the arterial blood [PaO_2] to the fraction of inspiratory oxygen concentration [FiO_2] ratio >150 and mean arterial blood pressure >70 mm Hg). Intracerebral monitoring (intracranial pressure with or without PbtO_2) had to be initiated within 16 h after the injury for inclusion.

Patients were excluded if they had any of the following criteria: penetrating head injury; pre-hospital GCS score of 3 with bilateral fixed dilated pupils; decompressive craniectomy before enrolment; quadriplegia; coagulation disorders contraindicating intracranial pressure or PbtO_2 monitoring; body temperature less than 34°C ; anticipated life expectancy of less than 24 h; post-traumatic cardiac arrest; neuropsychiatric comorbidities that could interfere with the outcome assessment at 6 months and 12 months; ischaemic stroke after traumatic internal carotid artery dissection; participation in an ongoing interventional trial; follow-up not possible; incapacitated in accordance with article L1121-5 to L1121-8 of the French public health code; and, according to French law, no health insurance.

Investigators obtained written informed consent from a next of kin or a legal surrogate. If next of kin or a legal surrogate were unable to provide written consent, the onsite investigator approved enrolment of the patient in accordance with French law (ie, procedural authorisation).¹⁹

Randomisation and masking

Participants were randomly allocated (1:1) to receive either intracranial pressure monitoring alone or both intracranial pressure and PbtO_2 monitoring. Randomisation was done through a dedicated password-protected, encrypted website created and implemented by Medsharing (Fontenay-sous-Bois, France), with blocks of variable size and stratification by centre and age (<50 years and ≥ 50 years). This study was open label due to the nature of PbtO_2 monitoring. Statisticians and assessors were masked to group allocation for the central assessment of the outcome and the statistical analyses.

Procedures

Before initiation of the trial, specific training was provided to local clinicians to interpret PbtO_2 monitoring and adapt patient management accordingly. All patients had intracranial pressure monitoring through an intracranial pressure probe (Codman Microsensor intracranial pressure transducer, Codman, Saint Priest, France; or Sophysa Pressio, Sophysa, Orsay, France). For patients in both groups, clinical management during the first 5 days in the intensive care unit followed international guidelines,^{4,5} using tier-one therapies—eg, continuous sedation and analgesia, and mechanical ventilation—to obtain normocapnia (partial pressure of carbon dioxide in arterial blood [PaCO_2] 35–40 mm Hg) and normoxia (PaO_2 80–140 mm Hg) and to maintain cerebral perfusion pressure of 60–70 mm Hg (with the equation: cerebral perfusion pressure = mean arterial blood pressure – intracranial pressure), serum glucose of 6–10 mmol/L and sodium of 140–150 mmol/L, haemoglobin of 7–10 g/dL, a body temperature of 36 – 38°C , and head elevation at 15° . The therapeutic objectives were to maintain intracranial pressure at 20 mm Hg or lower, and to keep PbtO_2 (for those in the dual-monitoring group) above 20 mm Hg, at all times.

For patients allocated to intracranial pressure monitoring only, if intracranial pressure exceeded 20 mm Hg, tier-two treatments were introduced—eg, a deep level of sedation or analgesia, use of vasopressors to maintain cerebral perfusion pressure above 70 mm Hg, moderate hyperventilation (PaCO_2 30–35 mm Hg), bolus osmotherapy, external ventricular drainage, neuromuscular blockade, or interventions for strict normothermia or mild hypothermia (35 – 37°C). For refractory intracranial hypertension in patients allocated intracranial pressure monitoring only, tier-three treatments were initiated,^{4,5} which consisted of moderate therapeutic hypothermia (33 – 35°C), secondary decompressive craniectomy, and barbiturate coma.

For patients allocated both intracranial pressure and PbtO_2 monitoring, an intraparenchymal catheter combining oxygen and temperature probes (Licox PMO catheter, Integra Lifescience, Saint Priest, France) was inserted at 20–25 mm below the dura mater, which was located either in an area unaffected by the traumatic brain injury or in the right frontal lobe (in the case of diffuse brain injury). A FiO_2 challenge was done within 2 h after probe placement, to assess the probe's functionality (with a goal of 100–300% increase in PbtO_2 with 100% FiO_2). The tier-two intracranial pressure management principles that were used in the intracranial pressure only group were also used in the dual-monitoring group. Additionally, for the dual-monitoring group, if PbtO_2 dropped below 20 mm Hg, even with intracranial pressure lower than 20 mm Hg, interventions were initiated to reach the following parameters in this predefined order (which was derived partly from Adamides and colleagues' observational study):²⁰ PaO_2 of 100–150 mm Hg; PaCO_2 of 35–45 mm Hg; temperature

of 35–37°C; cerebral perfusion pressure of 60–100 mm Hg; a cardiac index higher than 2.5 L per min per m²; haemoglobin of 9–12 g/dL; and PaO₂ higher than 150 mm Hg. In the dual-monitoring group, management followed four distinct clinical scenarios—ie, when PbtO₂ was either 20 mm Hg or greater or lower than 20 mm Hg, and when intracranial pressure was 20 mm Hg or lower or greater than 20 mm Hg; appendix pp 2–3).^{14,21}

At every study centre, trained research associates—under the supervision of the principal site investigator—collected patients' data using a web-based electronic case report form (Medsharing). Data obtained were baseline demographic information, intracerebral monitoring parameters (ie, intracranial pressure, cerebral perfusion pressure, and PbtO₂) every hour (days 1–5), extracerebral information on vital signs and therapies every 6 h (days 1–5), standard laboratory parameters every 12 h (days 1–5), adverse events during the entire stay in the intensive care unit, duration of stay in the intensive care unit, and survival status at day 28. The International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (TBI-IMPACT) score was calculated at randomisation (core and CT variables only) for the assessment of unfavourable outcome at 6 months.

A coordinating team from Grenoble Alpes University Hospital (Grenoble, France) did central data management and safety monitoring, including regular on-site visits. The sponsor safety department (Leo L, Centre Hospitalier Universitaire Grenoble Alpes) monitored continuously all serious adverse events. An independent and masked Data and Safety Monitoring Committee advised the trial management committee after inclusion of every 50 randomised patients.

Outcomes

The primary outcome was the proportion of patients with an extended Glasgow Outcome Scale (GOSE) score of 1–4 (death to upper severe disability) at 6 months after traumatic brain injury.²² Trained outcome assessors masked to group allocation did a central, structured telephone interview to assess GOSE at 6 months. The original primary outcome—early MRI quantification of brain injury volume between day 6 and day 10 after injury—was changed on Feb 7, 2018, due to major technical difficulties.¹⁸ The French legal authorities (International Review Board Sud-Est V and National Agency for Medicines and Health Products Safety, ref 2014-A01674-43/5) approved the change in primary outcome.

Secondary outcomes were the proportion of patients with a GOSE score of 1–4 at 12 months; GOSE scores at 6 months and 12 months; scores on the disability rating scale (DRS) at 6 months and 12 months; quality of life at 6 months and 12 months; survival at 28 days; therapeutic intensity during the first 5 days in the intensive care unit; and the proportion of critical events. GOSE is measured on an eight-point scale, with a score of 1 representing death

and a score of 8 representing no disability. DRS scores range from 0 (ie, no disability) to 29 (ie, extreme vegetative state). Quality of life was assessed at 6 months and 12 months after trauma using the functional independence measure (FIM) to assess cognitive and motor independency, ranging from 18 points (ie, complete dependence) to 126 points (ie, complete independence). During the first 5 days of stay in the intensive care unit, investigators recorded the number of patients receiving at least one tier-two and tier-three treatment, which allowed the calculation *a posteriori* of the daily therapeutic intensity level score (TIL₂₄) and the highest TIL₂₄ score during the 5-day monitoring period (TIL_{max}).²³ Critical events in both groups during the first 5 days of stay in the intensive care unit were defined as intracranial pressure higher than 30 mm Hg lasting for more than 30 min and intracranial pressure higher than 40 mm Hg lasting for more than 5 min. Critical events in the intracranial pressure and PbtO₂ group also included PbtO₂ below 10 mm Hg for at least 30 min. Deaths were monitored for 12 months, with survival reported at day 28 and for 12 months after trauma.

Statistical analysis

According to available literature at the time of study design (Sept 23, 2013),¹⁸ the proportion of patients with unfavourable neurological outcome after severe traumatic brain injury—ie, GOSE score of between 1 (ie, death) and 4 (ie, upper severe disability)—was expected to be around 55% in the intracranial pressure only group. To obtain a 30% reduction in the relative risk of GOSE 1–4 at 6 months in the intracranial pressure and PbtO₂ group, we aimed for a target sample size of 300 patients, including a possible 14 patients lost to follow-up. This target corresponds to an absolute reduction of 17%, with 80% power and a two-sided α of 0.05. No interim analysis was performed. After approval from the International Review Board of Sud-Est V (ref 2014-A01674-43/8), an additional group of 20 patients was enrolled during the study period, an amendment that was deemed necessary due to a higher than expected number of erroneous inclusions that would have otherwise impaired the statistical power of the trial.

Independent statisticians masked to group allocation did all data handling and analyses (appendix pp 48–54). Results were expressed as median (IQR) and n (%). Odds ratios (ORs) were expressed as means with associated 95% CIs. The primary analysis was reported in the modified intention-to-treat population, which included all patients who were randomly assigned, except those who withdrew consent or had protocol violations. Protocol violations corresponded to non-inclusion criteria detected between randomisation and planned probe insertion. Multiple imputation by chained equations (MICE) was used to estimate missing data for the primary outcome in patients who were lost to follow-up; the resulting data were exclusively used in the sensitivity analysis.

For the TBI-IMPACT score see
<http://www.tbi-impact.org/?p=impact/calc>

The primary outcome was analysed using logistic regression, with GOSE scores 1–4 at 6 months as the dependant variable and the allocated group as the independent variable. ORs and 95% CIs for unfavourable outcomes at 6 months were calculated using the intracranial pressure group as the reference, after adjustment for age as a fixed effect and for centres as a cluster. For secondary outcomes, GOSE at 12 months was analysed according to the same strategy. A linear regression model analysed data from DRS and FIM at 6 months and 12 months. Kaplan-Meier and Cox analyses, adjusted for age and centre, compared survival rates over the 12 months after trauma. The number of patients with tier-three treatments, and the incidence of critical events, were analysed using logistic regression after adjustment for age and centre. The TIL_{24} was analysed using a mixed linear regression model and the TIL_{max} compared groups using linear regression. The changes in mean intracranial pressure and cerebral perfusion pressure values between the two groups over each 6 h period were analysed using a mixed linear regression model.

All analyses were repeated in the per-protocol population in a sensitivity analysis. This population included all patients who were randomly assigned, except those with consent withdrawal, protocol violations, and protocol deviations (ie, no neuromonitoring within the first 16 h after traumatic brain injury; inability to measure intracranial pressure for either group or PbtO₂ for the intracranial pressure and PbtO₂ group for at least 48 consecutive h in living patients; or erroneous use of PbtO₂ in the intracranial pressure only group). In post-hoc analyses, we assessed the effect of PbtO₂ monitoring on the proportion of patients with unfavourable outcomes at 6 months in the most severe subgroups at baseline (ie, intracranial pressure ≥ 20 mm Hg; Marshall CT classification 3, 4, and 6; GCS motor score 1–2; and patients with major extracranial injuries [ie, abbreviated injury severity score ≥ 3]). In case of a significant difference between groups regarding any of these criteria, a search for an interaction was done between the most severe patients versus the other patients on outcome (GOSE 1–4 vs GOSE 5–8) at 6 months.

Serious adverse events were assessed from data collected by the sponsor safety department on all randomly assigned patients. Analyses were done using Stata version 15.0. This trial is registered at ClinicalTrials.gov, NCT02754063.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 15, 2016, and April 17, 2021, 2578 patients were screened for eligibility, and 318 patients with severe

traumatic brain injury were randomly assigned to study groups. 160 patients were assigned to the intracranial pressure only group and 158 patients were assigned to the intracranial pressure and PbtO₂ group. Of these, 16 patients in the intracranial pressure only group and 11 patients in the intracranial pressure and PbtO₂ group were not included in the primary analysis due to consent withdrawals (n=8) and protocol violations (n=19). 20 individuals with missing data had analyses using MICE imputation. 291 patients were available for the primary analysis (modified intention-to-treat population): 144 patients in the intracranial pressure only group and 147 patients in the intracranial pressure and

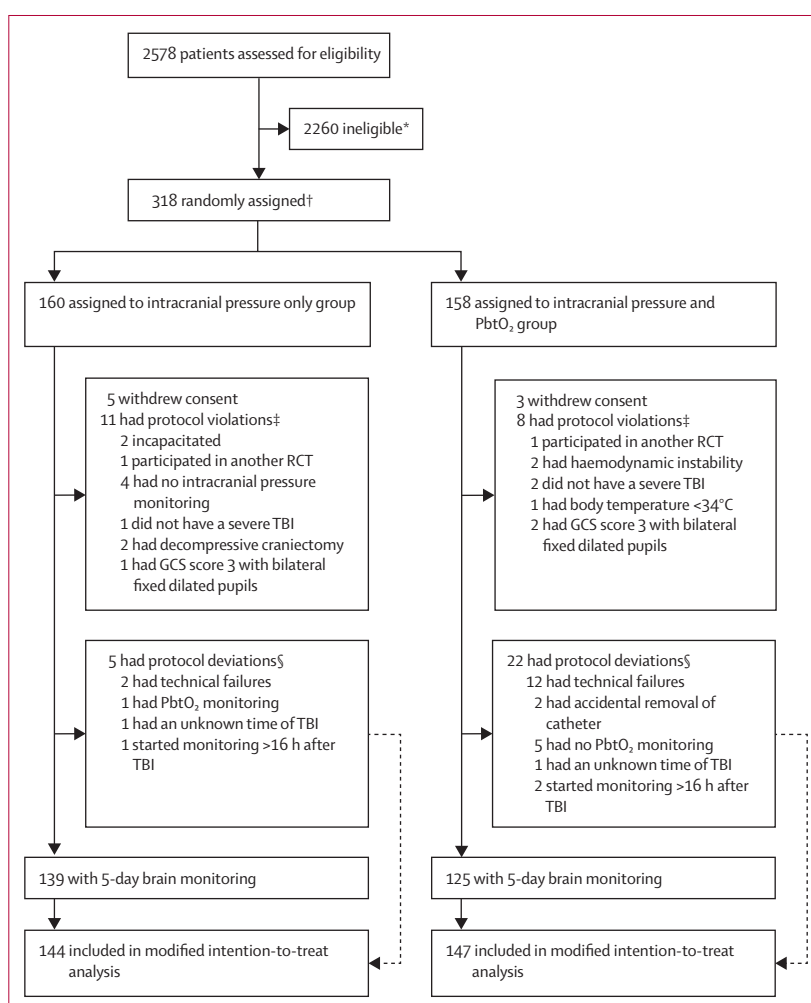


Figure 1: Trial profile

GCS=Glasgow coma scale. PbtO₂=brain tissue oxygen pressure. RCT=randomised controlled trial. TBI=traumatic brain injury. *533 did not have a severe TBI; 336 had no indication for intracranial pressure monitoring; 266 were not aged 18–75; 253 begun monitoring >16 h after TBI; 226 had a life expectancy <24 h; 146 had decompressive craniectomy; 97 had no indication for sedation for >48 h; 73 had screening failure; 51 had GCS score 3 with bilateral fixed dilated pupils; 36 had cardiac arrest at presentation; 34 had penetrating TBI; 27 had persistent haemodynamic instability; 22 had no insurance; 17 had consent withdrawn; 143 for other reasons. †Randomisation was stratified by age and centre. ‡Protocol violations of inclusion criteria detected between randomisation and planned probe insertion led to exclusion of these patients. §Protocol deviations did not preclude inclusion in the primary analysis because these patients were considered to have met all other inclusion criteria.

	Intracranial pressure only	Intracranial pressure and PbtO ₂
Age, years	38 (26–55)	40 (26–55)
Male	107/144 (74%)	108/147 (74%)
Female	37/144 (26%)	39/147 (27%)
Cause of injury		
Road traffic accident	92/144 (64%)	92/147 (63%)
Fall	34/144 (24%)	36/147 (25%)
Violence or assault	2/144 (1%)	0/147
Suicide attempt	2/144 (1%)	1/147 (1%)
Other	14/144 (10%)	18/147 (12%)
Best prehospital GCS score		
3–4	42/144 (29%)	51/145 (35%)
5–8	102/144 (71%)	94/145 (65%)
Best prehospital GCS motor score		
1–2	43/128 (34%)	53/128 (41%)
3–5	85/128 (66%)	75/128 (59%)
Prehospital mechanical ventilation	135/144 (94%)	139/145 (96%)
Pupillary reactivity on admission		
Both pupils reacting	87/132 (66%)	95/132 (72%)
One pupil reacting	8/132 (6%)	11/132 (8%)
No pupils reacting	37/132 (28%)	26/132 (20%)
Norepinephrine at admission	90/144 (63%)	106/145 (73%)
ISS score	31 (21–43)	29 (21–41)
Major extracranial injuries	78/140 (56%)	73/145 (50%)
SAPS II score	46 (37–53)	45 (39–55)
TBI-IMPACT probability of poor outcome at 6 months	0.57 (0.39–0.74)	0.57 (0.38–0.71)
Marshall classification on initial CT		
Diffuse injury I	8/141 (6%)	5/141 (4%)
Diffuse injury II	49/141 (35%)	52/141 (37%)
Diffuse injury III	8/141 (6%)	7/141 (5%)
Diffuse injury IV	3/141 (2%)	4/141 (3%)
Evacuated mass lesion	11/141 (8%)	8/141 (6%)
Non evacuated mass lesion	62/141 (44%)	65/141 (46%)

(Table 1 continues in next column)

PbtO₂ group (figure 1). The per-protocol population comprised 264 patients who received monitoring during the first 5 days of their admission to the ICU: 139 patients in the intracranial pressure only group and 125 patients in the intracranial pressure and PbtO₂ group.

No difference was found between the two groups regarding variables at baseline (table 1), except that the proportion of patients who had been given norepinephrine at admission was visibly higher in the intracranial pressure and PbtO₂ group. The PaO₂:FiO₂ ratio on admission was well above 150 in both groups, indicating no change in pulmonary gas exchange in the study population. Intracranial pressure, cerebral perfusion pressure, and PbtO₂:PbtO₂ values remained within the predefined ranges for therapeutic outcomes during the 5-day monitoring period in both groups (appendix pp 4–6). The median duration of stay in the intensive

	Intracranial pressure only	Intracranial pressure and PbtO ₂
(Continued from previous column)		
Traumatic subarachnoid haemorrhage on initial CT*	120/144 (83%)	115/145 (79%)
Acute subdural haematoma on initial CT*	77/135 (57%)	84/140 (60%)
Intraventricular haemorrhage on initial CT*	54/144 (38%)	50/145 (35%)
Epidural haematoma on initial CT*	22/135 (16%)	28/140 (20%)
Body temperature at randomisation, °C	36.5 (35.9–37.5)	37.0 (36.1–37.6)
Blood glucose at randomisation, mmol/L	7.5 (6.3–8.4)	7.3 (6.2–8.7)
Blood sodium at randomisation, mmol/L	141 (138–144)	141 (139–143)
Haemoglobin at randomisation, g/dL	12.5 (11.4–13.7)	12.8 (11.5–13.9)
PaO ₂ :FiO ₂ at randomisation	400 (260–470)	390 (270–520)
Intracranial pressure on intensive care unit admission, mm Hg	11 (6–19)	12 (8–16)
Cerebral perfusion pressure on intensive care unit admission, mm Hg	69 (62–77)	72 (66–79)
Mean arterial blood pressure on intensive care unit admission, mm Hg	83 (75–90)	84 (78–93)
PbtO ₂ on intensive care unit admission, mm Hg	..	14 (8–21)

Data are median (IQR) or n/N (%). Data for some variables were not available for all patients. FiO₂=fraction of inspired oxygen. GCS=Glasgow coma scale. ISS=injury severity score. PaO₂=partial pressure of oxygen in arterial blood. PbtO₂=brain tissue oxygen pressure. SAPS=simplified acute physiology score. TBI-IMPACT=International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury. *Denominators vary due to available information for brain lesions.

Table 1: Baseline characteristics in the modified intention-to-treat population

care unit was similar between the two groups: 20 days (IQR 10–32) in the intracranial pressure only group versus 22 days (12–35) in the intracranial pressure and PbtO₂ group (p=0.18).

Primary outcome data were available for 271 patients. The proportion of patients with a GOSE score of 1–4 at 6 months did not differ between the intracranial pressure only group (70 [53%] of 132 patients) and the intracranial pressure and PbtO₂ group (72 [52%] of 139 patients; OR 0.9, 95% CI 0.6–1.6, p=0.83; figure 2, table 2). After imputing primary outcome data for the 20 patients who were lost to follow-up, the proportion of patients with a GOSE score of 1–4 at 6 months did not differ between the two groups: 51% (95% CI 43–60) in the intracranial pressure only group versus 52% (43–60) in the intracranial pressure and PbtO₂ group (OR 1.0, 95% CI 0.6–1.7, p=0.95).

With respect to secondary outcomes, GOSE scores of 1–4 at 12 months (appendix p 7), DRS at

6 months and 12 months, FIM at 6 months and 12 months, and survival at day 28 did not differ between groups (table 2). All patients received at least one tier-two treatment; around a third of patients in each group required at least one tier-three treatment to control intracranial pressure. Of note, 101 (74%) of 137 patients in the intracranial pressure and PbtO₂ group received at least one treatment to correct brain hypoxia. 38 (29%) of 132 patients in the intracranial pressure and PbtO₂ group had at least one critical event of PbtO₂ less than 10 mm Hg during the 5-day monitoring period. TIL₂₄ decreased similarly between groups over the 5-day monitoring period (appendix p 8). The incidence of high intracranial pressure events was similar between groups. Information about survival at 12 months was available for 275 (95%) of 291 patients. There was no difference in survival between groups (hazard ratio 1.09, 95% CI 0.67–1.77); p=0.72; figure 3). At 12 months after injury, 33 deaths had occurred in the intracranial pressure

group: 25 (76%) were attributable to the brain trauma, six (18%) were end-of-life decisions, and two (6%) due to sepsis. 34 deaths had occurred in the intracranial pressure and PbtO₂ group at 12 months: 25 (74%) were attributable to the brain trauma, six (18%) were end-of-life decisions, one (3%) due to pulmonary embolism, one (3%) due to haemorrhagic shock, and one (3%) due to cardiac arrest.

Investigators repeated all analyses in the per-protocol population as a sensitivity analysis. No differences from the primary analysis were noted with respect to the primary and secondary outcomes (appendix p 10).

In a post-hoc analysis of the subgroup of patients with high intracranial pressure (≥20 mm Hg) on admission, a significant reduction in the proportion of patients with GOSE scores of 1–4 occurred in the intracranial pressure and PbtO₂ group at 6 months: 14 (52%) of 27 patients, versus 25 (89%) of 28 patients in the intracranial pressure group (OR 0.13, 95% CI 0.02–0.86, p=0.034; appendix p 11). There was an interaction between

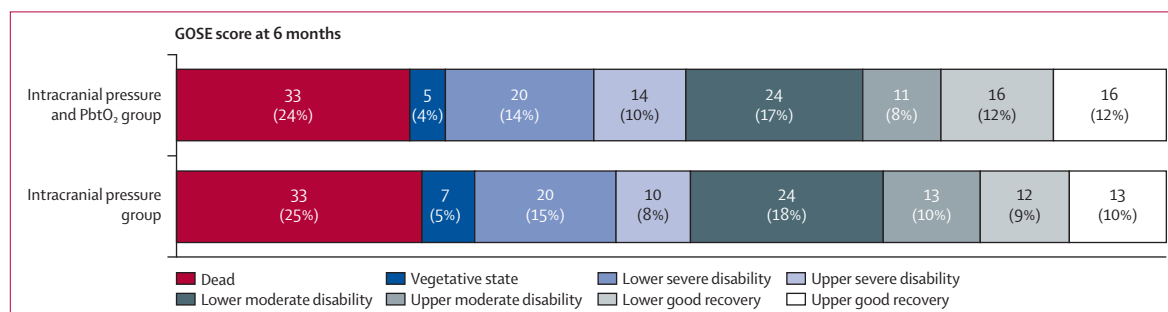


Figure 2: Distribution of GOSE scores at 6 months
Missing data were not imputed. Each cell corresponds to a score on the scale and the length of each cell represents the proportion of patients with equivalent scores. GOSE=Extended Glasgow Coma Scale. PbtO₂=brain tissue oxygen pressure.

	Intracranial pressure only (ref)	Intracranial pressure and PbtO ₂	Regression coefficient or OR (95% CI)	p value
Primary outcome				
GOSE 1–4 at 6 months	70/132 (53%)	72/139 (52%)	0.9 (0.6 to 1.6)*	0.83
Secondary outcomes				
GOSE 1–4 at 12 months	61/126 (48%)	58/135 (43%)	0.8 (0.5 to 1.3)*	0.34
DRS at 6 months†	3 (0–5)	3 (0–6)	0.0 (–2.6 to 2.7)‡	0.98
DRS at 12 months§	3 (0–5)	3 (0–5)	–0.3 (–2.8 to 2.1)‡	0.77
FIM at 6 months¶	122 (112–126)	123 (113–126)	0.6 (–10.3 to 11.5)‡	0.91
FIM at 12 months	124 (110–126)	124 (115–126)	3.5 (–6.8 to 13.8)‡	0.49
Tier-three treatment	49/142 (35%)	48/141 (34%)	1.0 (0.6 to 1.6)*	0.94
TIL _{max} **	10 (7–16)	11 (7–16%)	0.2 (–1.1 to 1.6)‡	0.74
Patients with critical events				
Intracranial pressure >30 mm Hg for 30 min	54/144 (38%)	58/135 (43%)	1.3 (0.7 to 2.2)*	0.43
Intracranial pressure >40 mm Hg for 5 min	41/144 (29%)	39/135 (29%)	1.0 (0.5 to 1.9)*	0.95
PbtO ₂ <10 mm Hg for 30 min	..	38/132 (29%)
Deaths at day 28	28/144 (19%)	25/145 (17%)	0.8 (0.5 to 1.5)*	0.53

Data are n/N (%), n/N (%), n/N (%), 95% CI, or median (IQR) unless otherwise indicated. RCs and ORs are adjusted for age and centre. DRS=disability rating scale. FIM=functional independence measure. GOSE=Extended Glasgow Outcome Scale. OR=odds ratio. PbtO₂=brain tissue oxygen pressure. RC=regression coefficient. TIL_{max}=highest therapy intensity level score. *OR. †177 patients. ‡Regression coefficient. §182 patients. ¶200 patients. ||192 patients. **287 patients.

Table 2: Trial outcomes in the modified intention-to-treat population

intracranial pressure values on admission (≥ 20 mm Hg vs < 20 mm Hg) and neurological outcome at 6 months ($p=0.054$). Patients with high intracranial pressure (ie, ≥ 20 mm Hg) received at least one tier-three treatment: 15 (56%) of 27 in the intracranial pressure and PbtO₂ group versus 18 (67%) of 27 in the intracranial pressure only group (0.6, 0.2–2.1, $p=0.45$). Furthermore, 22 (88%) of 25 patients in the intracranial pressure and PbtO₂ group received specific treatments to correct brain hypoxia. Other post-hoc analyses of subgroups of the most severely affected patients did not show any difference between groups.

In the intracranial pressure only group, two (1%) of 144 patients had serious adverse events related to the trial, whereas in the intracranial pressure and PbtO₂ group,

seven (5%) of 147 patients did (OR 3.5, 95% CI 0.8–15.5, $p=0.090$; table 3). Technical failures and intracerebral haematomas were significantly more frequent in the intracranial pressure and PbtO₂ group than in the intracranial pressure group (table 3). No significant difference in the intensive care unit-related complications was found between the two groups (table 3).

Discussion

The findings of the open-label, randomised controlled superiority OXY-TC trial, do not support the superiority of a strategy of combined intracranial pressure and PbtO₂ monitoring over one of intracranial pressure monitoring alone to reduce the proportion of patients with poor neurological outcome at 6 months after severe traumatic brain injury. Post-hoc results, however, suggest that an intracranial pressure and PbtO₂-guided strategy could reduce the number of patients with poor neurological outcomes in the case of high intracranial pressure on admission.

Although intracranial pressure monitoring in patients with severe traumatic brain injury can mitigate tissue damage, evidence suggests that brain hypoxia might still develop, even if intracranial pressure is within the normal range, thereby causing a deterioration in outcome.^{10–12} In people with traumatic brain injury, systemic factors such as arterial hypotension, hypocapnia, hypoxaemia, and anaemia can compromise brain oxygenation. Brain hypoxia can also result from local causes such as microthrombosis, microvascular collapse, and perivascular oedema, which decrease cellular oxygen delivery, even in the absence of macrovascular ischaemia.^{24,25} For these reasons, PbtO₂ monitoring is a promising method to improve brain oxygenation in real-time at the bedside. In patients with traumatic brain injury, PbtO₂ monitoring can assess the effects of anaemia or hypoxaemia on brain oxygenation and detect cerebral areas in hypoperfusion.²⁶ Information from PbtO₂ monitoring has been shown to reduce the duration and depth of brain hypoxia.^{14,20} However, the small volume of brain tissue that can be assessed with a PbtO₂ probe (< 10 mm³) has raised concerns about the accuracy of this method to reflect global brain hypoxia in heterogeneously affected brain regions. Accordingly, PbtO₂ values have been shown to correlate poorly with abnormalities in flow-metabolism coupling and cerebral vasoregulation in patients with traumatic brain injury.¹⁵ Notwithstanding these limitations, the Seattle Brain Injury Consensus Conference guidelines recommend a strategy of monitoring intracranial hypertension, brain hypoxia, or both.²¹ The OXY-TC trial shares this specific rationale—ie, to assess the effect of brain oxygenation monitoring on neurological outcome—with two large ongoing trials: BOOST-3 (NCT03754114)²⁷ and the Brain Oxygen Monitoring in Australia and New Zealand Assessment (BONANZA; ACTRN12619001328167).

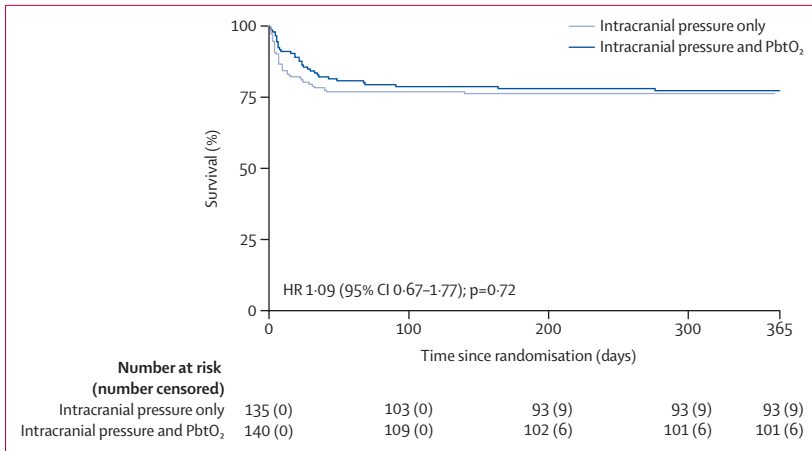


Figure 3: Survival at 12 months
Data are adjusted for age and centre. Time from randomisation was to 12-month follow-up or death. HR=hazard ratio. PbtO₂=brain tissue oxygen pressure.

	Intracranial pressure only (n=144)	Intracranial pressure and PbtO ₂ (n=147)	p value
Technical failures related to intracerebral catheter			
Catheter dysfunction	2 (1%)	12 (8%)	0.011
Accidental removal	0	2 (1%)	0.050
Serious adverse event related to the trial			
Severe hypoxaemia during MRI	1 (1%)	0	0.49
Intracerebral haematoma	0	6 (4%)	0.030
Cardiorespiratory arrest during MRI	1 (1%)	0	0.49
Intracranial pressure increased	0	1 (1%)	1.00
Intensive care unit-related serious adverse event			
Ventilator-acquired pneumonia	45 (31%)	62 (42%)	0.067
Septic shock	6 (4%)	5 (3%)	0.77
Seizure	6 (4%)	9 (6%)	0.60
Meningitis	4 (3%)	0	0.059
Pulmonary embolism	5 (4%)	12 (8%)	0.13

Data are n (%). PbtO₂=brain tissue oxygen pressure.

Table 3: Serious adverse events and intensive care unit-related complications in the modified intention-to-treat population

Despite the strong rationale, OXY-TC investigators did not find any difference in neurological outcome at 6 months between patients having intracranial pressure monitoring only and those undergoing intracranial pressure and PbtO₂ monitoring. In the OXY-TC trial, groups were balanced with respect to baseline characteristics. Moreover, all patients needed tier-two treatments, and around a third in each group needed at least one tier-three treatment to maintain the recommended therapeutic outcomes. These data show that clinical teams successfully applied the management protocols with a high level of compliance. The stepwise escalation in therapy intensity—ie, exhausting tier-two treatment before considering tier-three treatment—has not always been observed among European centres, according to findings from the Collaborative European NeuroTrauma Effectiveness Research (CENTER-TBI) study.²⁸

Findings of a post-hoc analysis of patients with intracranial pressure of 20 mm Hg or higher on admission suggested that, in this subgroup of patients, a strategy of both intracranial pressure and PbtO₂ monitoring could be more effective than a strategy of intracranial pressure monitoring alone to reduce the incidence of poor neurological outcome. Moreover, an interaction between intracranial pressure on admission and outcome at 6 months was noted, which supports the finding. This observation did not occur in other subgroups, such as patients with extended brain tissue damage documented on the initial CT scan, those with major extracranial injuries, and people with a low GCS motor score. Therefore, additional PbtO₂ monitoring might successfully correct brain hypoxia, intracranial hypertension, or both, within the first hours of admission, with a potential benefit for this subgroup of very severe patients. These results require validation in a larger sample.

The findings of the OXY-TC trial also indicate that baseline GCS score does not reflect the heterogeneity of patients with severe traumatic brain injury. Similar to this finding, a CENTER-TBI dataset identified three endotypes of patients with severe traumatic brain injury based on six specific features,²⁹ and the risk of intracranial hypertension varied according to injury types.³ The results of the OXY-TC trial advocate for a targeted multimodal brain monitoring approach in patients with severe traumatic brain injury.

Although no difference between groups in neurological outcome was recorded, intracerebral catheter-related adverse events and technical failures were significantly more frequent in the intracranial pressure and PbtO₂ group. A risk–benefit evaluation should guide indications for invasive brain monitoring in patients with traumatic brain injury.

The OXY-TC trial has several limitations. First, the trial was done in France only; considering the diversity in the management of traumatic brain injury patients across

countries,²⁸ these findings require confirmation in international trials. However, the therapeutic algorithms for intracranial pressure monitoring and PbtO₂ monitoring followed international guidelines^{4,5} and published protocols.^{14,21} Moreover, we controlled for various sources of bias via centralised randomisation and allocation concealment, and primary endpoint assessment was done by assessors masked to group allocation. Second, the OXY-TC investigators hypothesised that management in the first 5 days would most affect neurological outcome. In traumatic brain injury, the highest therapeutic intensity is usually observed during the first week and can rapidly decrease, as shown by TIL₂₄ scores collected over the first 5 days in this trial (appendix p 8). Since patients with severe traumatic brain injury are expected to stay in the intensive care unit for about 10–20 days, we believe that our focus on the first 5 days was an acceptable compromise to ensure high protocol compliance while maximising outcome effect. Third, the OXY-TC group estimated a 30% relative reduction in unfavourable outcome in the intracranial pressure and PbtO₂ monitoring group compared with intracranial pressure monitoring only, which required inclusion of 300 patients for suitable power. This hypothesis might appear optimistic but was in line with retrospective cohort studies at the time of trial design, and such an effect size was suggested in two meta-analyses.^{16,17} Fourth, due to the absence of high-resolution intracranial pressure monitoring data, investigators were unable to calculate the magnitude and duration of high intracranial pressure (ie, the cumulative dose of intracranial pressure, in the two groups).³⁰ Therefore, we cannot ascertain whether PbtO₂ monitoring reduces the cumulative dose of intracranial pressure. Finally, due to patients lost to follow-up, the target sample size could not be reached, implying a potential lack of statistical power for the primary outcome analysis. However, after imputation of missing data from these patients, no difference in the primary outcome was observed, suggesting that the effect of missing data was negligible.

In conclusion, a therapeutic strategy based on the combination of intracranial pressure and PbtO₂ monitoring did not reduce the proportion of patients with poor neurological outcome at 6 months after severe traumatic brain injury. Further research to ascertain the role of PbtO₂ monitoring in patients with high intracranial pressure on admission is required.

Contributors

J-FP, PB, GF, LG, GA, and CD-F developed the protocol. J-FP, PB, GF, LG, GA, CD-F, AV, and J-LB designed the study. GF, LG, GA, CD-F, YL, RC, SG, EV, AM, DC, VC, SP-F, CG, EH, JP, and LA did the data collection. AV and J-LB did the statistical analysis. J-FP, PB, GF, LG, GA, CD-F, YL, RC, SG, EV, AM, DC, VC, SP-F, CG, EH, JP, LA, and TG did the data interpretation. J-FP and PB wrote the first draft of the report. TG drafted the final version of the report. GF, LG, GA, CD-F, YL, RC, SG, EV, AM, DC, VC, SP-F, CG, EH, JP, LA, AV, and J-LB reviewed the report. MR was the principal clinical research associate of the study. All authors attest to have full access to all the data in the study and had

final responsibility for the decision to submit for publication. All authors approved the final manuscript. J-FP, AV, J-LB and PB have directly accessed and verified the underlying data reported in the manuscript.

Declaration of interests

J-FP reports honoraria from Integra Lifesciences, Sedana Medical, and IDD CDM-Lavoisier. PB and TG report honoraria from Laboratoire du Biomédicament Français. RC reports consulting fees from Roche Diagnostics and Sophysa, and receives support for attending meetings from UCB. LG reports grants from La Fondation des Gueules Cassées, Ramsay Santé, and Sophysa; consulting fees from Sophysa; honoraria for lectures from Sophysa and Fresenius; support for attending meeting from Pfizer and Sophysa; and receipt of equipment from Atys Medical. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data, data dictionary defining each field in the set, and study protocol will be made available to others upon reasonable request. Data will be communicated as deidentified participant data according to French law, and will be available after publication of the manuscript. Data will be made available at the Direction de la Recherche Clinique, Grenoble Alpes University Hospital, Grenoble, France (drci@chu-grenoble.fr), with investigator support, after approval of a proposal with a signed data access agreement.

Acknowledgments

We thank patients and their relatives, physicians, and caregivers for their active participation with this study. We thank the French National Program for Clinical Research, La Fondation des Gueules Cassées, and Integra Lifesciences as sources of funding for this study. The Neurocritical Care and Neuro Anaesthesiology French Speaking Association (ANARLF) supported the study. The French National Program for Clinical Research (13–0119), and the Fondation des Gueules Cassées (49–2015) supported the trial with a dedicated grant. Integra Lifesciences graciously provided PbtO₂ catheters to participating centres.

References

- Roozenbeek B, Maas AI, Menon DK. Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol* 2013; **9**: 231–36.
- Maas AIR, Menon DK, Manley GT, et al. Traumatic brain injury: progress and challenges in prevention, clinical care, and research. *Lancet Neurol* 2022; **21**: 1004–60.
- Stocchetti N, Carbonara M, Citerio G, et al. Severe traumatic brain injury: targeted management in the intensive care unit. *Lancet Neurol* 2017; **16**: 452–64.
- Carney N, Totten AM, O'Reilly C, et al. Guidelines for the management of severe traumatic brain injury, fourth edition. *Neurosurgery* 2017; **80**: 6–15.
- Geeraerts T, Velly L, Abdennour L, et al. Management of severe traumatic brain injury (first 24hours). *Anaesth Crit Care Pain Med* 2018; **37**: 171–86.
- Robba C, Graziano F, Reborna P, et al. Intracranial pressure monitoring in patients with acute brain injury in the intensive care unit (SYNAPSE-ICU): an international, prospective observational cohort study. *Lancet Neurol* 2021; **20**: 548–58.
- Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg* 1991; **75**: 731–39.
- Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011; **364**: 1493–502.
- Hutchinson PJ, Koliass AG, Timofeev IS, et al. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med* 2016; **375**: 1119–30.
- van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. *Neurosurgery* 2000; **46**: 868–76.
- Maloney-Wilensky E, Gracias V, Itkin A, et al. Brain tissue oxygen and outcome after severe traumatic brain injury: a systematic review. *Crit Care Med* 2009; **37**: 2057–63.
- Oddo M, Levine JM, Mackenzie L, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. *Neurosurgery* 2011; **69**: 1037–45.
- Rosenthal G, Hemphill JC 3rd, Sorani M, et al. Brain tissue oxygen tension is more indicative of oxygen diffusion than oxygen delivery and metabolism in patients with traumatic brain injury. *Crit Care Med* 2008; **36**: 1917–24.
- Okonkwo DO, Shutter LA, Moore C, et al. Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. *Crit Care Med* 2017; **45**: 1907–14.
- Launey Y, Fryer TD, Hong YT, et al. Spatial and temporal pattern of ischemia and abnormal vascular function following traumatic brain injury. *JAMA Neurol* 2020; **77**: 339–49.
- Gouvêa Bogossian E, Diosdado A, Barrit S, et al. The impact of invasive brain oxygen pressure guided therapy on the outcome of patients with traumatic brain injury: a systematic review and meta-analysis. *Neurocrit Care* 2022; **37**: 779–89.
- Hays LMC, Udy A, Adamides AA, et al. Effects of brain tissue oxygen (PbtO₂) guided management on patient outcomes following severe traumatic brain injury: a systematic review and meta-analysis. *J Clin Neurosci* 2022; **99**: 349–58.
- Payen JF, Richard M, Francony G, et al. Comparison of strategies for monitoring and treating patients at the early phase of severe traumatic brain injury: the multicentre randomised controlled OXY-TC trial study protocol. *BMJ Open* 2020; **10**: e040550.
- Toulouse E, Granier S, Nicolas-Robin A, et al. The French clinical research in the European Community regulation era. *Anaesth Crit Care Pain Med* 2023; **42**: 101192.
- Adamides AA, Cooper DJ, Rosenfeld FL, et al. Focal cerebral oxygenation and neurological outcome with or without brain tissue oxygen-guided therapy in patients with traumatic brain injury. *Acta Neurochir (Wien)* 2009; **151**: 1399–409.
- Chesnut R, Aguilera S, Buki A, et al. A management algorithm for adult patients with both brain oxygen and intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med* 2020; **46**: 919–29.
- Weir J, Steyerberg EW, Butcher I, et al. Does the extended Glasgow Outcome Scale add value to the conventional Glasgow Outcome Scale? *J Neurotrauma* 2012; **29**: 53–58.
- Zuercher P, Groen JL, Aries MJ, et al. Reliability and validity of the therapy intensity level scale: analysis of clinimetric properties of a novel approach to assess management of intracranial pressure in traumatic brain injury. *J Neurotrauma* 2016; **33**: 1768–74.
- Menon DK, Coles JP, Gupta AK, et al. Diffusion limited oxygen delivery following head injury. *Crit Care Med* 2004; **32**: 1384–90.
- Veenith TV, Carter EL, Geeraerts T, et al. Pathophysiologic mechanisms of cerebral ischemia and diffusion hypoxia in traumatic brain injury. *JAMA Neurol* 2016; **73**: 542–50.
- Bouzat P, Marques-Vidal P, Zerlauth JB, et al. Accuracy of brain multimodal monitoring to detect cerebral hypoperfusion after traumatic brain injury*. *Crit Care Med* 2015; **43**: 445–52.
- Bernard F, Barsan W, Diaz-Arrastia R, Merck LH, Yeatts S, Shutter LA. Brain Oxygen Optimization in Severe Traumatic Brain Injury (BOOST-3): a multicentre, randomised, blinded-endpoint, comparative effectiveness study of brain tissue oxygen and intracranial pressure monitoring versus intracranial pressure alone. *BMJ Open* 2022; **12**: e060188.
- Huijben JA, Dixit A, Stocchetti N, et al. Use and impact of high intensity treatments in patients with traumatic brain injury across Europe: a CENTER-TBI analysis. *Crit Care* 2021; **25**: 78.
- Åkerlund CAI, Holst A, Stocchetti N, et al. Clustering identifies endotypes of traumatic brain injury in an intensive care cohort: a CENTER-TBI study. *Crit Care* 2022; **26**: 228.
- Güiza F, Depreitere B, Piper I, et al. Visualizing the pressure and time burden of intracranial hypertension in adult and paediatric traumatic brain injury. *Intensive Care Med* 2015; **41**: 1067–76.