

BMJ Open Early diagnosis of mortality using admission CT perfusion in severe traumatic brain injury patients (ACT-TBI): protocol for a prospective cohort study

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ABSTRACT

Introduction Severe traumatic brain injury (TBI) is a catastrophic neurological condition with significant economic burden. Early in-hospital mortality (<48 hours) with severe TBI is estimated at 50%. Several clinical examinations exist to determine brain death; however, most are difficult to elicit in the acute setting in patients with severe TBI. Having a definitive assessment tool would help predict early in-hospital mortality in this population. CT perfusion (CTP) has shown promise diagnosing early in-hospital mortality in patients with severe TBI and other populations. The purpose of this study is to validate admission CTP features of brain death relative to the clinical examination outcome for characterizing early in-hospital mortality in patients with severe TBI.

Methods and analysis The Early Diagnosis of Mortality using Admission CT Perfusion in Severe Traumatic Brain Injury Patients study, is a prospective cohort study in patients with severe TBI funded by a grant from the Canadian Institute of Health Research. Adults aged 18 or older, with evidence of a severe TBI (Glasgow Coma Scale score ≤ 8 before initial resuscitation) and, on mechanical ventilation at the time of imaging are eligible. Patients will undergo CTP at the time of first imaging on their hospital admission. Admission CTP compares with the reference standard of an accepted bedside clinical assessment for brainstem function. Deferred consent will be used. The primary outcome is a binary outcome of mortality (dead) or survival (not dead) in the first 48 hours of admission. The planned sample size for achieving a sensitivity of 75% and a specificity of 95% with a CI of $\pm 5\%$ is 200 patients.

Ethics and dissemination This study has been approved by the University of Manitoba Health Research Ethics Board. The findings from our study will be disseminated through peer-reviewed journals and presentations at local rounds, national and international conferences. The public will be informed through forums at the end of the study.

Trial registration number NCT04318665

Strengths and limitations of this study

- This prospective cohort study hopes to improve clinical practice by establishing CT perfusion (CTP) as a diagnostic triage tool which could assist in diagnosing brain death in patients with severe traumatic brain injury (TBI) on admission.
- Our study is the first of its kind where CTP is done at the time of the standard imaging on arrival to hospital.
- This study includes a diversified population of severe TBI patients who are treated at our Provincial Trauma Centre (Health Sciences Centre, Winnipeg).
- Patients receive institutional standard of care after CTP.
- CTP is compared with a reference standard clinical assessment for brainstem function.

INTRODUCTION

Globally, over 50 million people are estimated to suffer a traumatic brain injury (TBI) annually.¹ The global economic burden of TBI is estimated at approximately US\$400 billion per annum.¹ Primarily affecting healthy individuals with an excellent quality of life, TBI can result in a catastrophic injury, which makes it a huge public health challenge.² In Canada, it is anticipated that TBI will be the most prevalent and costly neurological condition through the year 2031, as it will account for a total indirect cost of over US\$8 billion.³ Furthermore, TBI represents a substantial expenditure for Canadian insurance companies dealing with medical insurance for rehabilitation therapy.³

Severity of TBI is classified into mild, moderate, and severe categories using the Glasgow Coma Scale (GCS), with 'severe TBI' defined as a GCS score ≤ 8 .³ Known as



the deadly killer or silent epidemic, severe TBI is believed to be the primary cause of postinjury hospitalisation, disability and death throughout the world.^{3,4} Severe TBI is a life-threatening clinical emergency, during which trauma teams work swiftly in tandem to provide high-level trauma care. Despite very resource-intensive care, which may include multiple complicated surgeries, the mortality rate for severe TBI patients within the first 48 hours post-admission remains at 50%.^{2,5} Early in-hospital mortality (<48 hours) is likely dependent on the 'preinjury' and more likely on the 'injury' factors.^{1,6} It is plausible that a significant percentage of these patients have permanent brain damage at the time of hospital admission, including brain death.

Clinical examination for confirmation of brain death

The clinical examination is the gold standard for diagnosing brain death.⁷ In patients with severe TBI, it can be complicated to elicit because of the nature of the injury itself, and the fact that most patients are on life support and/or sedative medications. Therefore, patients often receive elaborate resource-intensive treatment despite a lack of clear prognoses. Adding to the quandary of the clinical exam is the fact that there are several outcome scales proposed for the final neurological outcome.¹ The sheer existence of numerous outcome scales reflects the complexity of long-term outcome assessments in patients with severe TBI. The most used outcome scale is an eight-point extended Glasgow Outcome Scale (GOSE).⁸

A poor neurological outcome is characterized by a GOSE score of 1 (death), 2 (vegetative state), 3 (severe disability) or 4 (moderate disability).⁸ This outcome assessment is further complicated by preinjury and injury factors as well as patients' response at various stages. The absence of a definitive, reliable, validated, and timely triage tool to predict the higher in-hospital mortality of patients with severe TBI, warrants the urgent need of research in this field. This research may help reduce resource intensive and sometimes futile care in those who are already dead at the time of hospital admission. This may also facilitate the precious gift of organ donation.

Imaging for confirmation of brain death

Recent systematic reviews and recommendations have found that standard diagnostic imaging techniques (plain CT (CT) and CT angiography (CTA)) currently used to diagnose brain death have inadequate sensitivity.^{9–11} This strengthens the need for advanced techniques to facilitate the early diagnosis of brain death.

Standard of care imaging performed on admission and during the hospital stay of a severe TBI patient is the plain head CT.¹² Plain CT accurately and promptly diagnoses structural abnormalities but does not provide any functional information including information on brain death.^{12–17}

CTA is a readily available, practical, and omnipresent imaging test. However, the CTA protocol for confirmation of brain death varies considerably among different

centres, which makes it difficult for it to be accepted as the gold-standard test.¹⁸ Systematic reviews of the literature have concluded that the sensitivity of CTA is inadequate to confirm brain death and that clinicians should be wary when using it as an ancillary test.^{9,10} Moreover, CTA provides anatomic, but not functional, information about the brain.¹⁹

CT perfusion (CTP) is an advanced CT scan that provides both functional and anatomic information about the brain, and it is mainly used to triage patients with acute stroke.^{20–25} In this technique, the temporal change in contrast density is used to quantify perfusion parameters such as cerebral blood flow (CBF) and cerebral blood volume (CBV), which indicate areas of ischaemic or infarcted brain (areas of 'dead brain'). CTP is very sensitive in detecting CBF and can detect decreased perfusion as low as 2%–3% in CBF and 2% in CBV.²⁶ CBF <5 mL/100 g/min is consistent with clinical diagnosis of brain death.^{27,28} If CTP is unable to detect CBF, or if CTP shows markedly decreased CBF (<5 mL/100 g/min), brain death can be confirmed because cellular viability is not possible at such a low CBF. Moreover, CTP with approximately whole-brain coverage can also provide data for CTA.

CTP has rarely been used for patients with severe TBI due to lack of reliable evidence on the efficacy of CTP in this patient population. One of the first uses of CTP in patients with severe TBI on hospital admission, was described by Wintermark *et al.*^{29,29} They found a favourable outcome, which was assessed at 90 days postadmission in patients with normal or high brain perfusion on admission CTP and an unfavourable outcome in patients with low perfusion. Bendinelli *et al.*³⁰ performed CTP in patients with severe TBI who did not improve neurologically during the first 48 hours after trauma. They found low perfusion in one third of their patients. Additionally, they discovered that CTP altered clinical management in 10% of their patients who were diagnosed with massive and fatal strokes despite minimal changes on plain CT of head. Of importance, both studies used CTP with limited brain coverage due to technological limitations at the time; this may have missed key findings in other parts of the brain. These two studies addressed the neurological outcome at the end of the hospital stay, but failed to specify any association of CTP results with in-hospital mortality. We were the first to describe the CTP features of brain death as the most sensitive and specific imaging test for confirmation of brain death in intensive care unit (ICU) patients.^{2,5} Furthermore, we provided the evidence of using CTP to predict in-hospital mortality in comatose cardiac arrest patients.³¹

A triage tool to facilitate early, if not immediate, decision making is imperative as most deaths occur within 48 hours of hospital admission.^{19,31} The first 48 hours of hospitalization involves the most resource-intensive medical and surgical care activities. Some patients with severe TBI may be dead by neurological definition at the time of their hospital admission. Since, an accurate clinical diagnosis

is obscured by anaesthetic and neuromuscular blockade agents, a validated admission CTP triage tool could assist in diagnosing brain death in these patients. In a small pilot study, our group has shown that CTP could show mortality in 25% of patients at the time of their hospital admission.³² We hypothesize that in severe TBI patients, the CTP scan done at the time of hospital admission, can diagnosis brain death reliably as opposed to the current clinical examination which is routine practice.

The primary objective of the Early Diagnosis of Mortality using Admission CT Perfusion in Severe Traumatic Brain Injury Patients (ACT-TBI) study is to validate admission CTP features of brain death, relative to the clinical outcome of death versus survival, in the first 48 hours of hospital admission, among patients with severe TBI. Secondary objectives include: (1) to establish the safety of admission CTP; (2) to establish the inter-rater reliability of features of brain death on admission CTP.

METHODS AND ANALYSIS

The ACT-TBI study, is a prospective cohort study in patients with severe TBI, which builds on previous work by our team.³² The study design was conceptualized by experts in content (trauma/critical care neurosurgery, neuroradiology, emergency medicine and critical care), epidemiology, and clinical trials to ensure a high-quality study. The ACT-TBI study is under way at the Health Sciences Centre, which is the provincial trauma centre.

Study population

Our study population of interest are patients with severe TBI who meet the following inclusion criteria: (1) at least 18 years old; (2) severe head injury; (3) GCS score ≤ 8 after initial resuscitation and (4) on mechanical respiratory ventilation at the time of imaging. Study exclusion criteria include: (1) no known GCS after initial resuscitation; (2) known pregnancy; (3) known contraindication to CT contrast agent, for example, allergy or anaphylactic reaction and (4) known end-stage renal disease.

Patient and public involvement

Survivors of TBI and their families were involved in the planning, design, recruitment and conduct of the study.

Study Intervention-

All eligible consecutive patients will be screened and enrolled by the treating emergency department (ED) physician during the initial hospital admission resuscitation, and then undergo a standard imaging protocol, (whole body CT scan, including the plain head CT) as well as the study CT-perfusion protocol of the whole head (figure 1). Images will be acquired following our previously published protocol.³² In brief, a total of 40 mL of CT contrast media will be injected at a rate of 5 mL/s. A set of axial images with a slice thickness of 5 mm for the perfusion analysis will be reconstructed. All patients will receive standard of care post imaging and the results of the CTP

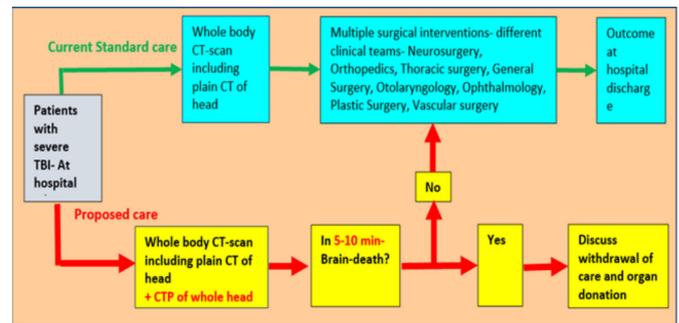


Figure 1 Illustration of the current hospital standard of care workflow (in blue) for severe TBI patients at admission and the intervention from our research protocol (in yellow). CTP, CT perfusion; TBI, traumatic brain injury.

will not be made available to the clinical team involved in patient care, since the prognostic value of CTP has not been established in this patient population.

Retention strategies

At our centre, one universal requisition is used for all diagnostic imaging tests. To improve study adherence and to remind the ED team of the study, a red stamp was placed on each requisition in the department (see figure 2). Furthermore, at the end of each month, the ED team and the Diagnostic Imaging team receive an email indicating the study's enrolment status, and a brief reminder of the study and its objectives. To facilitate the study's recruitment goal, the study team monitors the provincial diagnostic database system daily for CTP scans. A log of the screened patients is then kept by the study coordinator. The study design and intervention do not require significant changes to current standard clinical practice, as the addition of CTP images is the only change in practice. No issues are foreseen in data collection.

Timeline

We plan to complete the ACT-TBI study within 2 years. Study preparation including clinical research documentation, institutional ethics committee approvals, training of research staff involved in the study, and pilot validation took approximately 6 months. Ethics approval was obtained on 24 February, 2020. Actual patient enrolment began on 23 July, 2020. Most trauma centres receive a minimum of five patients with severe TBI per week. With a conservative enrolment rate of approximately 15–17 patients per month, the enrolment should be accomplished within 1 year. Data preparation including the CTP image analysis will commence in the final year of the study. A description of the study timeline can be found in table 1.

Data Collection and Management

Clinical data

Clinical data will be collected by a qualified data abstractor with knowledge of the study. A qualified data abstractor will collect data from the patient's chart using a chart abstraction tool. The case report form for our study can

Traumatic Brain Injury:

Head Injury	Yes	No
GCS ≤ 8	Yes	No

Figure 2 Study stamp for the diagnostic imaging requisition.

be found in online supplemental appendix A. Existing injuries will be documented using the new Injury Severity Scale.³³ Process metrics such as, the number of surgical interventions on each patient, the length of stay in ICU, and the hospital length of stay will be derived from the data collected. All clinical data will be entered into an Excel database. Clinical Data cleaning and validation will be completed by a master's student. The principal investigator will ensure quality assurance policies are being implemented to confirm study data are reported in compliance with the protocol, which include: reviewing the screening logs; monitoring of recruitment trends; reviewing the data collected on the case report forms; generating queries regarding outliers or missing data and implementing data tracking procedures.

Imaging data

CTP images will be acquired at the time of admission. An overview of the imaging data collected for our study can be found in online supplemental appendix A. The anonymized images will be transferred and stored in the secured imaging core lab in the department of Radiology at the University of Manitoba. The imaging centre (Department of Radiology, University of Manitoba, Winnipeg) is responsible for the postprocessing of the CTP raw data, image interpretation and image analysis. CTP will be processed using a semiautomatic deconvolution algorithm on a vendor neutral software package (Oleasphere). CTP will be assessed quantitatively such that brain death will be defined as CBF < 5 mL/100g/min and CBV < 2 mL/100g in the brainstem. CTP will also be assessed qualitatively with brain death being defined as

a matched decrease of CBF and CBV in the brainstem. During the first 48 hours of hospital admission and at the end of the patients hospital stay, the perfusion maps for CBF and CBV will be assessed for the binary outcome of 'dead' or 'not-dead', according to our previously published methods.^{4 31-34} The perfusion images will be reviewed by two-independent neuroradiologists, who will be blinded to the clinical status of the patient and also to each other's assessment. In case of disagreement, a consensus agreement will be employed for the final analysis.

Data analysis and power considerations

The gold standard for diagnosis of brain death is confirmation by clinical examination. Sensitivity is defined as the ability of CTP to correctly classify an individual as 'dead', while ability of CTP to correctly classify an individual as 'not-dead' is a specificity. Positive predictive value (PPV) is the percentage of patients showing features of brain death on CTP, who are clinically 'dead'. Negative predictive value (NPV) is the percentage of patients with no features of brain death on CTP, who were clinically 'not-dead'. An ideal triage test for confirmation of brain death should have no false positives, that is, calling someone 'dead' when they are not. Thus, an ideal triage test should have 100% specificity and PPV. In our pilot study, CTP showed 100% specificity and PPV as well as 75% sensitivity and 94% NPV for correctly classifying in-hospital mortality. Based on these preliminary results by employing the Buderer's formula,³⁵ we calculated a sample size for the ACT-TBI study. A total of 180 patients with severe TBI (with a conservative prevalence of in-hospital mortality of at least 40%) will be required to validate the features of brain death on admission CTP against in-hospital mortality. This will allow us to achieve a sensitivity of at least 75% and specificity of 95% with a CI $\pm 5\%$ around the point estimate. Since the study endpoint is at hospital discharge, we do not expect any loss to follow-up. With a plausible drop-out of 10% (including technical problems with CTP acquisition, protocol violation, consent withdrawal or possible contraindication for CTP), the sample size was increased by an absolute number of 20. Thus, a total of 200 patients with severe TBI will be targeted to enrol in the ACT-TBI study.

Baseline characteristics of patients will be described using frequency distribution statistics and measure of dispersion. The primary validity analysis will be performed using sensitivity, specificity, PPV and NPV for features of brain death on admission CTP compared with the in-hospital mortality along with 95% CI. Area under the receiver operating characteristics curve will be calculated to characterize the diagnostic ability of brain death features on CTP for in-hospital mortality. Interobserver agreement between two neuroradiologists will be assessed using the kappa statistic to assess the reliability of CTP. Logistic regression will be used to build predictive models for clinical outcome at discharge for admission CTP, IMPACT variables,³⁶ and other standard baseline variables such

Table 1 Description of Timeline for the ACT-TBI study

	Year 1	Year 2
Protocol and CRF finalisation	█	
REB submissions and approvals	█	
Start-up meeting and training		█
Site activation	█	█
Screening and enrolment	█	█
Data collection	█	█
Steering committee meetings	█	█
Adjudication		█
Data preparation and analyses	█	█
Dissemination		█

ACT-TBI, Early Diagnosis of Mortality using Admission CT Perfusion in Severe Traumatic Brain Injury Patients; CRF, clinical record form; REB, research ethics board.

as age, sex, baseline GCS score, nature of the baseline head injury. The predictive models will be used to calculate the area under the receiver operating characteristics curve to enable comparison of the models. Complications including renal failure or allergic reactions associated with CTP will be reported in percentage.

DISCUSSION

Outcomes of the ACT-TBI study will validate the admission CTP as a pioneer triage tool, thereby offering improved diagnosis and prognosis for brain death in patients with severe TBI, which can be further confirmed by the clinical examination gold standard. Adopting this triage tool in the routine practice to evaluate patients with severe TBI will help reduce the use of resource intensive and sometimes futile treatment to potentially dead patients in the emergency room. Furthermore, using CTP in this setting will improve trust and investment in organ transplantation in Canada and worldwide.

One study limitation is that our prospective study is a single centre study; this may affect its generalisability. Our prospective study, however, has rigour in that the study intervention is controlled and the outcome measures are preselected. ACT-TBI study is the first of its kind where admission CTP will be used to assess mortality in patients with severe TBI at the time of hospital admission. Besides this vital objective, we also planned two nested studies: (1) to examine the imaging biomarkers as predictors of functional outcome in patients with severe TBI and pathological correlation of the imaging biomarkers on autopsy, when possible and on receiving the separate consent and (2) health economic benefits of employing admission CTP.

ETHICS AND DISSEMINATION

We have received ethics approval from the University of Manitoba Health Research Ethics Board number-HS23683- (B2020:018) and the study is being conducted in compliance with Good Clinical Practices on Ethical Conduct for Research Involving Humans.

Deferral of consent has been approved by our institutional ethics board. Considering the altered level of the participant's consciousness, informed consent will be obtained from a substitute legal decision-maker by deferred consent within 1 week of enrolment. Informed consent will be obtained by the site research coordinator/research nurse.

All data collected for the study will remain strictly confidential. Anonymity of the study participants is addressed by using case numbers. A record of the patient's ID and case number is being kept in a separate secure password-protected file accessible only by the study coprincipal investigators and study coordinator. Data will be presented in an aggregate form only. Data collection forms will be stored for at least 10 years.

The dissemination plan includes the traditional dissemination vehicles (eg, presentations at local grand rounds, national and international conferences, publications of studies in open-access peer-reviewed journals). Once proven useful, admission CTP will be incorporated in the clinical guidelines for imaging in patients with severe TBI. This will bring the evidence-based clinical practice change at the national and international level. The knowledge translation plan will also employ other approaches that will aim to incorporate the findings into the design of future studies. A Café Scientifique session at the end of the study will be organized to inform the general public about the results of our study and how it will influence future clinical practice. In completing the study monitoring activities, we will be conducting a type of ongoing general quality improvement in the care of patients with severe TBI. This will function as a mechanism of integrative knowledge translation that will ultimately be transferable to implementation of this treatment in routine clinical practice.

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Contributors JJSS, FAZ, RG, ME, DM, AT, NS and SRA contributed to the conception and design of the study, provided input into the protocol, and gave critical feedback on the manuscript. JJSS, SA and DB obtain consents. SA and DB perform study coordinator duties and collect clinical data. DB collects the imaging data. ML provides ongoing study support within the ED. JJSS, FAZ, RG, ML, SA and DB attend quarterly ACT-TBI steering committee meetings. SA wrote the initial draft of the manuscript. All authors approved the final version of the manuscript.

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