Prevalence of secondary insults and outcomes of patients with traumatic brain injury intubated in the prehospital setting: a retrospective cohort study

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ABSTRACT
Background Prehospital neuroprotective strategies aim to prevent secondary insults (SIs) in traumatic brain injury (TBI). This includes haemodynamic optimisation in addition to oxygenation and ventilation targets achieved through rapid sequence intubation (RSI). The primary aim was to report the incidence and prevalence of SIs (prolonged hypotension, prolonged hypoxia and hyperventilation) and outcomes of patients with TBI who were intubated in the prehospital setting.

Methods A retrospective cohort study of adult patients with TBI who underwent RSI by a metropolitan road-based service in South-East Queensland, Australia between 1 January 2017 and 31 December 2020. Patients were divided into two cohorts based on the presence or absence of any SI sustained. Prolonged SIs were defined as occurring for ≥5 min. The association between SIs and mortality was examined in multivariable logistic regression and reported with adjusted ORs (aORs) and 95% CIs.

Results 277 patients were included for analysis. Median 'Head' Abbreviated Injury Scale and Injury Severity Score were 4 (IQR: 3–5) and 26 (IQR: 17–34), respectively. Most episodes of prolonged hypotension and prolonged hypoxia were detected with the first patient contact on scene. Overall, 28-day mortality was 26%. Patients who sustained any SI had a higher mortality than those sustaining no SI (34.9% vs 14.7%, p<0.001). Prolonged hypoxia was an independent predictor of mortality (aOR 4.86 (95% CI 1.65 to 15.61)) but not prolonged hypotension (aOR 1.45 (95% CI 0.5 to 4.25)) or an end-tidal carbon dioxide <30 mm Hg on hospital arrival (aOR 1.28 (95% CI 0.5 to 3.21)).

Conclusion SIs were common in the early phase of prehospital care. The association of prolonged hypoxia and mortality in TBI is potentially more significant than previously recognised, and if corrected early, may improve outcomes. There may be a greater role for bystander intervention in prevention of early hypoxic insult in TBI.

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Secondary insults (SIs) in traumatic brain injury (TBI) have a significant impact on patient outcomes.
⇒ The timing and duration of prehospital SIs may have additional prognostic value over the reporting of isolated events, although limited studies have investigated this.

WHAT THIS STUDY ADDS
⇒ In this retrospective cohort study of patients with TBI undergoing prehospital intubation, prolonged hypotensive and prolonged hypoxic episodes were common in the early phase of prehospital care with most corrected prior to hospital arrival.
⇒ Prolonged hypoxia was found to be a strong, independent predictor of mortality in our patient cohort but not prolonged hypotension or potential hyperventilation.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ This study emphasises the importance of rapid identification and prevention of hypoxia in TBI for emergency services and could be included in education for bystanders on scene.

INTRODUCTION
Traumatic brain injury (TBI) is one of the leading causes of trauma-related morbidity and mortality worldwide, with a global incidence of 939 per 100 000 people occurring each year.1 The deleterious effects of secondary insults (SIs) in TBI are well-known.2–13 Following the primary insult, a cascade of neuroinflammatory changes occurs resulting in impaired cerebral autoregulation and vasogenic oedema due to disruption of the blood–brain barrier, which in the presence of systemic hypoxia and hypotension, ultimately contributes to cerebral ischaemia.14 15

As it is paramount to reduce the incidence of SIs, early implementation of neuroprotective measures should occur at first patient contact in the prehospital environment. This may involve advanced interventions such as rapid sequence intubation (RSI) to achieve oxygenation and ventilation targets,1 2 10 16 in addition to targeted BP parameters9 12 and the use of hyperosmolar therapies.17 18

The aim of this study was to describe the incidence and prevalence of SIs including prolonged hypotension, prolonged hypoxia and hyperventilation in patients with TBI who were intubated in the prehospital phase of care. The secondary aim was to examine the association of SIs with patient outcomes.
METHODS
Setting
The Queensland Ambulance Service (QAS) High Acuity Response Unit (HARU) is an Australian prehospital road-based service. One HARU team is based in Brisbane and operates a single-response vehicle, providing care to a population of approximately 2.6 million people.18 A significant proportion of the HARU case-mix involves the management of critically unwell polytrauma patients, many of which have TBI. In the 2020 calendar year, the Brisbane HARU attended 736 trauma cases, of which 445 required HARU level interventions. Within Brisbane, these patients are transported to either of the two adult level one trauma centres: the Royal Brisbane and Women’s Hospital (RBWH) and the Princess Alexandra Hospital (PAH).

HARU is staffed by critical care paramedics and physicians with the ability to provide advanced interventions including RSI, administration of blood products and chest decompression with finger thoracotomy. In patients with severe TBI, HARU will administer 7.5% hypertonic saline (HTS) if the patient has a GCS <9 and one of either fixed, dilated pupil/s, unilateral neurological signs or a further drop in GCS of 2 points. Clinical oversight is maintained by a 24-hour on-call senior prehospital consultant, who is contacted to discuss all patients requiring advanced interventions.

HARU follows a standardised operating procedure for RSI, with indications including neuroprotection in TBI, airway or ventilatory compromise, global management of polytrauma and for humanitarian reasons (see online supplemental material— QAS Clinical Practice Procedures: RSI). The anaesthetic induction dosing used by HARU is tailored to the patient characteristics and physiological state as opposed to a per kilogram protocol. In patients with TBI, ketamine and fentanyl are commonly used as induction agents and neuromuscular relaxation is achieved with rocuronium. Patients are pre-oxygenated with a bag-valve-mask device, ventilated through the apnoeic period, and the use of nasal prong apnoeic oxygenation is encouraged.

Design
This was a retrospective, observational study of adult patients with TBI, who underwent prehospital RSI by the Brisbane HARU and were transported to the RBWH and PAH between 1 January 2017 and 31 December 2020. The study time frame was selected for pragmatic reasons as it corresponded with implementation of hospital electronic medical records and allowed sufficient time for patient outcome data to be collated prior to statistical analysis.

Inclusion criteria were any patient ≥16 years old involved in a traumatic event who required RSI and were documented by the HARU clinician to have a suspected TBI. As highest prehospital GCS was recorded, no cut-off was used for patient inclusion enabling capture of all patients with more severe TBI, including those whose GCS deteriorated prior to RSI. Patients were excluded if they were in cardiac arrest on first crew arrival or deceased upon arrival to hospital. Patients were enrolled before hospital outcome data were collated to reduce potential selection bias.

Prehospital data were sourced from the QAS electronic report forms, HARU audit database and the patient monitor trend page. Hospital data were sourced from electronic medical records and trauma service databases. Prolonged hypotension was defined as a systolic BP (SBP) <100 mm Hg ≥5 min and prolonged hypoxia was defined as oxygen saturation (SpO₂) <90% ≥5 min. A greater hypotensive threshold was used than the traditional SBP <90 mm Hg from past studies.4 5 7 11 13 This reflected recent evidence that higher SBP targets are needed in severe TBI1 2 9 and was considered an appropriate threshold in a predominantly younger polytrauma cohort.7 9 Prolonged SIs were recorded due to evidence suggesting they have a greater impact on patient outcomes over brief events.11 11 A minimum duration of 5 min was chosen as it corresponded with the default recording interval of the monitor trend page, allowing the capture of prolonged SIs if a patient had at least two consecutive readings of SBP <100 mm Hg or SpO₂ <90% ≥5 min.

The onset of prolonged hypotensive and hypoxic episodes was reported at sequential phases of prehospital care, including in patients who had two or more separate events. This included from the first reading on initial crew arrival, during initial on-scene management, pre-RSI and post-RSI (defined as the immediate reading of SBP and SpO₂ ≤5 min before and ≤5 min after intubation, respectively), up to 15 min after RSI, and en-route to hospital (defined as >15 min post-RSI until arrival at hospital if applicable). Additionally, the prevalence of hypotension and hypoxia was reported on first crew arrival and on arrival to hospital. Episodes of end-tidal carbon dioxide (ETCO₂) <30 mm Hg on hospital arrival were recorded as a surrogate for potential hyperventilation. Patients were divided into two cohorts based on those who sustained any SI (defined as either prolonged hypotension or prolonged hypoxia or an arrival ETCO₂ <30 mm Hg) compared with those who sustained no SI. Patient outcomes were additionally examined comparing those with isolated TBI (defined as a ‘Head’ Abbreviated Injury Scale (HAIS) ≥3 with all other AIS <3) with those with polytrauma TBI (defined as a HAIS ≥3 with at least one other AIS ≥3).

Primary outcome was 28-day all-cause mortality and secondary outcomes were post-traumatic amnesia (PTA) duration and 6-month extended Glasgow Outcome Scale (GOSE). PTA duration has been shown to predict functional outcomes20 and was documented in patient hospital records using the Westmead Post-traumatic Amnesia Scale (WPTAS). GOSE was assessed retrospectively and dichotomised into favourable (GOSE 5–8) and poor (GOSE 2–4) outcomes. To maintain validity, a single assessor used a standardised set of questions (see online supplemental material—GOSE Structured Questions) to determine GOSE based on detailed patient records outlining their functional abilities up to 6 months following injury. Study design followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.21

Statistical analysis
All data were collated in Microsoft Excel (IBM Corporation V2106). Statistical analysis was performed on R V.4.1.0 (R Foundation, Vienna, Austria). Descriptive statistics were used to report on patient data using numbers and percentages or medians and IQRs. Categorical variables were compared with the X² or Fisher’s exact test when frequencies were lower than 20. Continuous and categorical groups were analysed with the Mann-Whitney test.

Multivariable logistic regression was performed to test the association between SIs and 28-day all-cause mortality adjusted for important confounders. Due to the small study population, included variables were limited to SIs, polytrauma TBI and the most powerful clinical independent TBI prognostic factors from the impact study9 (age, GCS motor score and pupillary abnormalities). The seven variables met all statistical assumptions of logistic regression and were chosen based on their prehospital clinical relevance and not significance on univariate analysis.
Hypotension

Sixty-six (24.3%) patients were hypotensive upon first crew arrival. Prolonged hypotension occurred in 30.1% of patients, including three patients who had two separate episodes. The onset of most prolonged hypotensive events was detected with the first SBP recording on scene (figure 2), of which 48.8% had an unrecordable BP. Fifty per cent of the patients with an episode of prolonged hypotension and 82.8% of all patients went on to have an SBP >100 mm Hg upon hospital arrival.

Hypoxia

Eighty-seven (32.5%) patients were hypoxic upon first crew arrival. Prolonged hypoxia occurred in 25.4% of patients, 11 of which had two separate events. The majority of prolonged hypoxic episodes were identified during initial on-scene management and were corrected prior to RSI. In all, 89.7% of patients had SpO₂ >90% on hospital arrival, with 65.2% of the patients with an episode of prolonged hypoxia having SpO₂ >90% on arrival.

End-tidal carbon dioxide

Median ETCO₂ on arrival to hospital was 33 (IQR: 29–38) mm Hg. Eighty (30.4%) patients had an arrival ETCO₂ <30 mm Hg and had higher rates of prolonged hypoxia (37.5% vs 21.4%, p = 0.009) and finger thoracostomy (31.2% vs 14.8%, p = 0.004) than those with an arrival ETCO₂ ≥30 mm Hg. Patients with very low arrival ETCO₂ (<25 mm Hg) were more likely to have prolonged hypotension (50% vs 25.1%, p = 0.006). Patients who received HTS had a lower median arrival ETCO₂ (31 (IQR: 27–35) mm Hg vs 34 (IQR: 29–39) mm Hg, p < 0.001) compared with those not given HTS.

Hospital outcomes

On hospital arrival, 10 patients urgently went to theatre from the ED and 4 died before any imaging. Neurosurgical intervention was required in 132 (47.7%) patients. Seventy-two (26%) patients were deceased at 28 days (table 3). A further five patients died after 28 days. The SI cohort had a higher mortality than those with no SIs although no difference in mortality was found between isolated and polytrauma TBI.

Two hundred patients survived to discharge, of which 44 did not have radiological evidence of TBI with no intracranial injuries on CT and a normal cognitive assessment following extubation. Of the remaining 156 patients with TBI, 104 (66.7%) had a completed WPTAS with a median PTA duration of 21 min, together with age, motor score <4, pupillary abnormalities and prolonged hypoxia (table 4).

RESULTS

Over the 4-year period, Brisbane HARU performed 767 RSIs, of which 277 patients were eligible for study inclusion (figure 1). First pass intubation success rate of study participants was 92.4%. Median age was 33 (IQR: 23–51) and 79.1% were male (table 1). Median HAIS and Injury Severity Score (ISS) were 4 (IQR: 3–5) and 26 (IQR: 17–34), respectively. The proportion of head injury severity was similar between both the SI versus no SI cohort and the isolated versus polytrauma TBI cohort. Patients sustaining SIs were more severely injured and required a greater number of prehospital interventions (table 2).

DISCUSSION

In this retrospective cohort study, we describe the timing and the proportion of patients sustaining SIs and reported on factors associated with mortality. The described cohort was severely injured, with hypoxic and hypotensive insults being more prevalent in the early phase of care. In keeping with previous research, prolonged hypoxia (defined in the study as a duration of ≥5 min) together with age, motor score and pupal response were identified as independent prognostic factors in TBI.

The incidence of prolonged hypotensive (30.1%) and prolonged hypoxic (25.4%) episodes reflects the critical injuries sustained in the SI cohort, as evidenced by a median ISS of 29 and the majority (71.9%) requiring additional interventions. Another likely contributing factor is that by having RSI as an inclusion criterion, only the most critically unwell patients with a greater disposition for SIs were selected for study enrolment.
Our findings are similar to past TBI studies when looking at subgroup analyses of patients who underwent prehospital intubation, with rates of hypoxia from 28% to 32.9% and hypotension of 29.9%. Although congruent with our findings, we are hesitant to make strong comparisons with these intubated TBI cohorts due to differences in how they defined SIs (timing, duration and threshold) and the limited available data on demographics and injury characteristics. Indeed, this highlights one of the unique aspects of our study, in that we report in detail about an exclusively intubated TBI cohort and the onset of SIs according to sequential phases of prehospital care.

Our finding of SIs predominantly occurring early in the prehospital environment underscores the potential role of bystander first aid in TBI. Almost one-third of patients were hypoxic on first crew arrival and in all probability had already experienced a prolonged episode given the median time of 9 min from emergency call to paramedic arrival. Historically, despite bystander presence on scene in the majority of trauma cases, assistance is infrequent. This represents an opportunity for intervention during a critical period in TBI where first aid and appropriate patient positioning by bystanders may prevent hypoxia from airway obstruction and episodes of impact brain apnoea. These basic interventions may reduce morbidity and mortality in TBI with instructions provided by emergency medical service call centre staff and be a focus of future public awareness campaigns.

The benefits of prehospital intubation in TBI have long been debated. Although several systematic reviews have not shown any improvement in outcomes, they included studies with reduced data quality, unadjusted confounders, small sample sizes and where intubation was performed under suboptimal conditions without neuromuscular relaxation. Patients who were intubated by inexperienced personnel were found to have a higher mortality. In contrast, prospective studies including one randomised controlled trial have shown outcome benefits with prehospital RSI when performed in severely injured patients with TBI, which is congruent with the HARU case-mix. The Brain Trauma Foundation guidelines recommend intubation in isolated severe TBI. Although 36.4%...
of those in our study had at least one GCS > 8, trends were not recorded and it was clear that some patients deteriorated prior to RSI or had additional indications for intubation including respiratory failure and global management of polytrauma.

Predictably, patients with TBI who sustained SIs had a higher mortality. Although the SI cohort had a greater proportion of polytrauma and required more interventions, the presence of additional injuries independent of SIs does not appear to have impacted mortality in serious TBI. In logistic regression where polytrauma was not an independent predictor of mortality. What has been found in past studies and supported from a past prospective study using similar methodology.5 While there is unequivocal evidence demonstrating the harmful impact of both hypoxia and hypotension,2–13 very few published studies address prolonged prehospital hypoxia,5 13 which could have a greater association with mortality than previously recognised. This may in part relate to the depth and duration of hypoxia and how it is defined, which was beyond the scope of this study but could be explored in future studies commensurate with those published on hypotension.2 9 11 12

Almost one-third of the cohort had an arrival ETCO₂ < 30 mm Hg. While prolonged hypocapnia is associated with poorer outcomes due to cerebral vasocostriction and potential ischaemic injury,9 11 12 we did not find any independent mortality effect from an arrival ETCO₂ < 30 mm Hg. In our study, 43.8% of the hypocapnic patients also received HTS implying that hyperventilation may have been used as an additional temporising measure to reduce intracranial pressure. Another explanation is that most of these patients were not hypocapnic and instead had high ETCO₂ – arterial partial pressure of CO₂ (PaCO₂) gradients. This has been demonstrated in past studies

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Patient management</th>
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<tr>
<td></td>
<td>Total n=277</td>
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<tr>
<td>Prehospital care</td>
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<tr>
<td>Prehospital times, median min (IQR)</td>
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<tr>
<td>Call to first crew arrival</td>
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<tr>
<td>First crew arrival to RSI</td>
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<td>RSI to hospital arrival</td>
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<td>Prehospital interventions, N (%)</td>
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<td>Hypertonic saline</td>
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<td>Finger thoracostomy</td>
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<tr>
<td>Any intervention‡</td>
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<tr>
<td>Prehospital events, N (%)</td>
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<tr>
<td>Prolonged hypotension</td>
<td>82 (30.1)</td>
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<tr>
<td>Prolonged hypoxia</td>
<td>69 (25.4)</td>
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<td>Prolonged hypotension+hypoxia</td>
<td>45 (16.5)</td>
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<tr>
<td>Arrival ETCO₂ &lt;30 mm Hg</td>
<td>80 (30.4)</td>
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<tr>
<td>Hospital care</td>
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<tr>
<td>Hospital times, median min (IQR)</td>
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<tr>
<td>Triage to CT head (first image)§</td>
<td>23 (14–39)</td>
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<tr>
<td>Triage to craniectomy/craniotomy§</td>
<td>80 (61–129)</td>
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<tr>
<td>Neurosurgical intervention, N (%)</td>
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<tr>
<td>ICP monitor only</td>
<td>72 (26.0)</td>
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<tr>
<td>Craniectomy/craniotomy</td>
<td>52 (18.8)</td>
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<td>Other</td>
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<tr>
<td>Nil</td>
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<td>Length of stay/treatment, median days (IQR)</td>
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<td>Intubation</td>
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<td>Intensive care</td>
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<td>Hospital</td>
<td>15 (5–31)</td>
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<tr>
<td>Brain injury rehabilitation§</td>
<td>38 (20–73)</td>
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</table>

*Patients missing data on either prolonged hypotension OR prolonged hypoxia OR arrival ETCO₂ <30 mm Hg.
†Mann-Whitney test used for continuous variables; X² or Fisher’s exact test used for categorical variables.
‡Any intervention defined as administering hypertonic saline OR blood products OR performing finger thoracostomy.
§Triage to CT head: 14 patients did not have CT of the head in emergency; triage to craniectomy/craniotomy: 3 patients had a delayed operation during ICU admission; brain injury rehabilitation: 7 patients had ongoing admission at time of data collation.

ETCO₂, end-tidal carbon dioxide; ICP, intracranial pressure; ICU, intensive care unit; RSI, rapid sequence intubation; SI, secondary insult.
with gradients up to 15 mm Hg in polytrauma patients occurring secondary to alveolar dead space and hypovolaemia.\textsuperscript{10, 11} The ETCO\textsubscript{2}–PaCO\textsubscript{2} gradient is the possible explanation why arrival hypocapnic patients had a greater prevalence of prolonged hypotension, prolonged hypoxia and finger thoracostomy suggesting more severe chest injuries and hypovolaemia. Future prospective studies looking at simultaneous ETCO\textsubscript{2}–PaCO\textsubscript{2} gradients through prehospital ABG sampling may indeed confirm lower ETCO\textsubscript{2} targets are necessary to maintain normocapnia in a polytrauma TBI cohort.

This study has several limitations. The retrospective design is subject to selection bias and limits the evidencing of causation in outcomes. Additionally, the study focused on intubated patients from a single prehospital service so the results may not be broadly translatable. Furthermore, although over 200 patients were included in the analysis, the sample size may have been insufficient to identify prolonged hypotension and arrival hypocapnia as independent risk factors associated with mortality. The study size also restricted the number of logistic regression variables, potentially excluding other important prognostic predictors including interventions and SIs sustained in hospital, limiting reporting ability. In addition, as inclusion criteria were based on prehospital findings and not HAIS, 44 patients were later identified to not have a TBI. As logistic regression was performed on all patients to maintain study power, including those without TBI may have confounded the results. Finally, the recognised missing data, which although were minimal for most clinical variables (<6%), were more significant in functional outcome measures. Consequently, the use of retrospective GOSE as a prognostic indicator was variably documented, reinforcing the limitations when compared with a prospective structured patient interview. While PTA duration was also recorded, 52 patients did not have a completed WPTAS, including in patients who could not participate due to profound disability and those who discharged from hospital before their PTA resolved. This data loss resulted in an underpowered group analysis, which limited the ability to draw meaningful conclusions on functional outcomes.

**CONCLUSION**

This study identified that prolonged SIs in TBI were common in the prehospital setting with a significant proportion of these episodes corrected prior to hospital arrival through early Figure 2  Onset of prolonged secondary insults according to sequential phases of prehospital care. Prolonged episodes were defined as ≥5 min duration. Eighty-five separate episodes of prolonged hypotension were recorded in 82 patients. Eight separate episodes of prolonged hypoxia were recorded in 69 patients. RSI, rapid sequence intubation.

<table>
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<tr>
<th>Table 3  Patient outcomes</th>
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<tr>
<td><strong>Total</strong> n=277, Missing SI* n=15, No SI n=116, Any SI n=146</td>
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<tr>
<td>Primary Mortality (28 days), n (%)</td>
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<tr>
<td>Secondary PTA duration, median days (IQR)</td>
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<td>Favourable GOSE, n (%)</td>
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*Patients missing data on either prolonged hypotension OR prolonged hypoxia OR arrival end-tidal carbon dioxide <30 mm Hg.
†Mann-Whitney test used for continuous variables; X\textsuperscript{2} or Fisher’s exact test used for categorical variables.
‡Isolated TBI defined as an HAIS ≥3 with all other AIS <3; polytrauma TBI defined as an HAIS ≥3 with one other AIS ≥3.
§PTA duration: 52 patients did not have a completed PTA assessment; favourable GOSE: 58 patients had insufficient follow-up documentation preventing calculation of GOSE.
AIS, Abbreviated Injury Scale; GOSE, Glasgow Outcome Scale Extended; HAIS, ‘Head’ Abbreviated Injury Scale; PTA, post-traumatic amnesia; SI, secondary insult; TBI, traumatic brain injury.
neuroprotective interventions. The role that prolonged hypoxia has in the early stages of TBI is strongly associated with mortality and potentially surpasses the impact of other SIs during this critical period. There is scope for greater bystander intervention in preventing early hypoxic injury in TBI and is a focus for future studies and public education campaigns.

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Contributors The project was conceived by MB and DB. Data access was undertaken by MB and LP. MB analysed the data and wrote the first draft. All authors edited and approved the final manuscript. MB is the guarantor of the manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval Ethics approval for this study was granted by the RBWH Human Research Ethics Committee (LNR/2020/QRBW/70364), which waived requirements for individual patient consent.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. De-identified participant data available from corresponding author (michael.butterfield@health.qld.gov.au).

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Original research


