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The association between admission systolic blood pressure and mortality in significant traumatic brain injury: A multi-centre cohort study

Gordon Fuller [a,1,*], Rebecca M. Hasler [b,1], Nicole Mealing [c], Thomas Lawrence [a], Maralyn Woodford [a], Peter Juni [c], Fiona Lecky [d]

[a] Trauma Audit and Research Network, Health Sciences Research Group, Manchester Academic Health Sciences Centre, Mayo Building, Salford Royal Hospital, Eccles Old Road, Salford M6 8HD, UK
[b] Department of Emergency Medicine, University Hospital Bern, Freiburgstr, 3010 Bern, Switzerland
[c] Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhubelweg 11, 3012 Bern, Switzerland
[d] School of Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street, Sheffield S1 4DA, UK

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ABSTRACT

Introduction: Low systolic blood pressure (SBP) is an important secondary insult following traumatic brain injury (TBI), but its exact relationship with outcome is not well characterised. Although a SBP of <90 mmHg represents the threshold for hypotension in consensus TBI treatment guidelines, recent studies suggest redefining hypotension at higher levels. This study therefore aimed to fully characterise the association between admission SBP and mortality to further inform resuscitation endpoints.
Methods: We conducted a multicentre cohort study using data from the largest European trauma registry. Consecutive adult patients with AIS head scores >2 admitted directly to specialist neuroscience centres between 2005 and July 2012 were studied. Multilevel logistic regression models were developed to examine the association between admission SBP and 30 day inpatient mortality. Models were adjusted for confounders including age, severity of injury, and to account for differential quality of hospital care.
Results: 5057 patients were included in complete case analyses. Admission SBP demonstrated a smooth u-shaped association with outcome in a bivariate analysis, with increasing mortality at both lower and higher values, and no evidence of any threshold effect. Adjusting for confounding slightly attenuated the association between mortality and SBP at levels <120 mmHg, and abolished the relationship for higher SBP values. Case-mix adjusted odds of death were 1.5 times greater at <120 mmHg, doubled at <100 mmHg, tripled at <90 mmHg, and six times greater at SBP < 70 mmHg, $p < 0.01$.
Conclusions: These findings indicate that TBI studies should model SBP as a continuous variable and may suggest that current TBI treatment guidelines, using a cut-off for hypotension at SBP < 90 mmHg, should be reconsidered.

Introduction

Traumatic brain injury (TBI) is a major determinant of global health, predicted to be the 4th largest burden of disease by 2020 [1]. Mortality has been reported to range from 25% to 50% in large cohorts of moderate and severe TBI patients [2–4], and even a small absolute benefit from improved treatment strategies could potentially avoid thousands of deaths each year.

Following injury, patient and injury factors interact to cause irreversible primary brain injury [5]. Subsequent physiological, infective, metabolic and structural insults may result in further secondary brain injury and worse outcomes. Low systolic blood pressure (SBP) has been identified as one of the most important secondary insults, and hypotension <90 mmHg has been consistently demonstrated to be associated with a doubling of mortality [6–8].

Despite its influence on outcome, the relationship between SBP and mortality following TBI has not been well characterised. TBI studies typically incorporate SBP as a binary variable with an

* Corresponding author. Tel.: +44 01484 684640/07968 280641.
E-mail addresses: gordonwfuller@doctors.net.uk, g.fuller@sheffield.ac.uk (G. Fuller).
[1] Equal contributions as first author.

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arbitrary cut-point of 90 mmHg. Such dichotomisation can result in loss of discriminatory power in prognostic scores, assuming that all values above and below the cut off have the same impact on patient outcome, and may compromise control of confounding in observational studies using regression modelling [9].

Moreover, consensus TBI treatment guidelines recommend that a threshold value of SBP < 90 mmHg should be avoided, but state that the 'defining level of hypotension' is unclear [10]. Recent work on trauma patients without TBI has also revealed a much higher SBP cut-off for hypotension of 110 mmHg, below which mortality rises [11]. Given the paucity of evidence in TBI examining the association with mortality across the full range of SBP, further studies are required to accurately identify resuscitation endpoints.

We therefore planned to investigate the relationship between admission SBP and mortality in patients with significant TBI, aiming to inform future TBI treatment recommendations and guide statistical modelling decisions in TBI studies. Specific objectives were to: characterise the shape of any relationship; identify threshold points associated with increased odds of death; and investigate the strength of association between admission SBP and mortality.

Methods

Study design and setting

We conducted a multicentre cohort study using prospectively collated data from the Trauma Audit and Research Network database (TARN), the largest European Trauma Registry [12]. TARN data collection and methodology has previously been reported in detail [13].

Briefly, the TARN database includes patients of any age who sustain injury resulting in any of: Hospital admission >72 h; intensive care or high dependency admission; transfer to a tertiary/specialist centre; in-hospital death within 30 days. Patients are excluded in the event of: femoral neck or single pubic ramus fracture in patients >65 years; simple isolated injuries *e.g.* uncomplicated ulnar fracture; or diagnosed as dead on hospital arrival, with no initiation of treatment.

TARN participating hospitals cover all regions of England and Wales, including a representative sample of specialist neuroscience centres (SNCs) and non-specialist acute hospitals. Over the study period approximately half of eligible trauma receiving hospitals submitted data.

Data collection

TARN data-collectors in member hospitals screen all trauma cases for database inclusion and abstract a dataset of demographic, physiological, investigation, and treatment variables from the clinical case notes of eligible patients. Details of all individual injuries are recorded and defined according to the abbreviated injury scale dictionary by trained injury-coders [14]. Information is submitted using a standard web-based data system. Records for patients undergoing inter-hospital transfer between participating hospitals are matched deterministically using unique patient identifiers. Outcome is assessed in terms of in-patient mortality at discharge or 30 days, whichever occurs first.

Study population

The study population consisted of patients with significant TBI, admitted directly to English SNCs, aged over 16 years, and entered into the TARN database. Significant TBI was defined as patients with head region AIS ≥3 scores, excluding scalp, cranial nerve or vascular injuries. This corresponds to abnormal CT brain scans and patients with clinical open or base of skull fractures. SNCs constituted an emergency department, intensive care unit, neurosurgical unit, and a range of supporting trauma specialties.

The study sample consisted of consecutive patients enrolled between 1st January 2005 and 31st July 2012. Patients transferred to non-TARN hospitals and patients with missing data were initially excluded from complete case analyses. The numbers of eligible cases in the TARN database during the study period determined the sample size, and given the fixed available sample *a priori* sample size calculations were not performed.

Previous studies have suggested differing responses to hypotension between TBI and non-TBI patients [15]. A major extracranial injury subgroup, defined as any non-head AIS score ≥3, was therefore specified *a priori* to investigate effect measure modification. Additionally, synergism has been previously reported between hypoxia and hypotension and statistical and biological interaction were also examined for patients with admission oxygen saturations <93% [16].

Primary analyses

The injury characteristics and demographics of included and excluded patients were initially compared using summary statistics and hypothesis testing. The distribution of confounding variables across exposure groups was also examined using one-way analyses of variance and Kruskal–Wallis tests for continuous data, and χ^2 tests for categorical data.

The first recorded emergency department SBP was defined as the exposure variable under investigation. Patients in cardiac arrest were considered to have a null value for SBP, regardless of the effects of resuscitative interventions. The relationship between exposure and mortality was then explored graphically in bivariate analyses with SBP as continuous variable. Relationships were examined using restricted cubic splines, a modelling technique allowing accurate characterisation of non-linear associations [17]. The presence of a threshold value for SBP was evaluated by inspection for the presence of inflection points in plots of SBP against the probability of death.

To further examine the association between admission SBP and mortality explanatory multilevel multivariable logistic regression models were developed according to principles recommended in consensus methodological guidelines [18–20]. In-patient mortality was the dependent variable and admission systolic blood pressure was entered as the exposure variable. SBP was categorised into 10 mmHg increments, allowing calculation of odds of death for differing levels of SBP compared to an unexposed reference range of 130–139 mmHg, recognised as the upper limit of normotension [21].

Patient-level case-mix variables were included as additional fixed effects, and individual SNCs modelled using a random intercept. The confounders considered as explanatory variables comprised: age, injury severity score (ISS), admission hypoxia (oxygen saturations <93%), admission Glasgow Coma Scale score (GCS), traumatic subarachnoid haemorrhage, and Marshall Score (derived from AIS scores using a previously published TARN algorithm) [22–24]. Model quality was assessed using Akaike's information criterion (AIC) and the area under the receiver operator characteristic curve.

Sensitivity analyses

To assess the robustness of results to selection bias and confounding a series of sensitivity analyses were undertaken. The effect of excluding patients from the analysis due to transfer to