Journal of Clinical Neuroscience 29 (2016) 64–69

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Clinical Study

Normalization of coagulopathy is associated with improved outcome after isolated traumatic brain injury

Daniel S. Epstein [a,b], Biswadev Mitra [a,b,c,*], Peter A. Cameron [a,b,d], Mark Fitzgerald [c,e,f], Jeffrey V. Rosenfeld [f,g,h]

[a] Emergency and Trauma Centre, The Alfred Hospital, Commercial Road, Melbourne, VIC 3004, Australia
[b] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia
[c] National Trauma Research Institute, Melbourne, VIC, Australia
[d] Emergency Medicine, Hamad Medical Corporation, Doha, Qatar
[e] Trauma Service, The Alfred Hospital, Melbourne, VIC, Australia
[f] Department of Surgery, Monash University, Melbourne, VIC, Australia
[g] Department of Neurosurgery, The Alfred Hospital, Melbourne, VIC, Australia
[h] Department of Surgery, F. Edward Hébert School of Medicine, Uniformed Services University of The Health Sciences (USUHS), Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 8 August 2015
Accepted 8 November 2015

Keywords:
Blood coagulation
Coagulopathy
Craniocerebral trauma
Injuries
Isolated head trauma
Traumatic brain injury

ABSTRACT

Acute traumatic coagulopathy (ATC) has been reported in the setting of isolated traumatic brain injury (iTBI) and is associated with poor outcomes. We aimed to evaluate the effectiveness of procoagulant agents administered to patients with ATC and iTBI during resuscitation, hypothesizing that timely normalization of coagulopathy may be associated with a decrease in mortality. A retrospective review of the Alfred Hospital trauma registry, Australia, was conducted and patients with iTBI (head Abbreviated Injury Score [AIS] $\geqslant$3 and all other body AIS <3) and coagulopathy (international normalized ratio $\geqslant$1.3) were selected for analysis. Data on procoagulant agents used (fresh frozen plasma, platelets, cryoprecipitate, prothrombin complex concentrates, tranexamic acid, vitamin K) were extracted. Among patients who had achieved normalization of INR or survived beyond 24 hours and were not taking oral anticoagulants, the association of normalization of INR and death at hospital discharge was analyzed using multivariable logistic regression analysis. There were 157 patients with ATC of whom 68 (43.3%) received procoagulant products within 24 hours of presentation. The median time to delivery of first products was 182.5 (interquartile range [IQR] 115–375) minutes, and following administration of coagulants, time to normalization of INR was 605 (IQR 274–1146) minutes. Normalization of INR was independently associated with significantly lower mortality (adjusted odds ratio 0.10; 95% confidence interval 0.03–0.38). Normalization of INR was associated with improved mortality in patients with ATC in the setting of iTBI. As there was a substantial time lag between delivery of products and eventual normalization of coagulation, specific management of coagulopathy should be implemented as early as possible.

1. Introduction

Acquired disorders of coagulation, also termed acute traumatic coagulopathy (ATC), early trauma induced coagulopathy or acute coagulopathy of trauma, have been previously described in the setting of isolated traumatic brain injury (iTBI) [1–4]. The incidence of ATC in the setting of iTBI is estimated to be 8%, using an international normalized ratio (INR) $\geqslant$1.3 as a cut-off associated with higher mortality and adverse outcomes after iTBI [5,6]. However, the incidence of this condition has been variably reported depending on the study design and definition of coagulopathy used [1,7–9]. Regardless of definitions, in-hospital mortality in the setting of ATC and iTBI has been reported approaching 50% [2], and an abnormal initial INR, regardless of magnitude, in the setting of iTBI, was associated with poor outcomes [5,10–13].

It is hypothesized that early treatment of coagulopathy may improve outcomes. There are a number of blood products and synthetic agents that have been shown to be efficacious in treating coagulopathy. These include fresh frozen plasma (FFP), platelets, cryoprecipitate [14], factor concentrates [15,16], activated recombinant factor VIIa [17] and tranexamic acid [18]. At the time of

* Corresponding author. Tel.: +61 3 9076 2782; fax: +61 3 9076 2699.
E-mail address: biswadev.mitra@monash.edu (B. Mitra).

http://dx.doi.org/10.1016/j.jocn.2015.11.024
0967-5868/

writing there are no current guidelines towards management of ATC in patients with iTBI [4,19].

Among patients who presented to the emergency department with iTBI and ATC, we aimed to describe times to administration of procoagulant agents and normalization of coagulation status. The secondary aim was to determine the association between normalization of INR and in-hospital mortality. This information could form the basis of a prospective trial to determine the impact of early effective treatment of coagulopathy in trauma patients.

2. Methods

2.1. Setting

The Alfred Hospital is one of two tertiary adult trauma referral centers in Melbourne, Australia, receiving 57,000 patients a year to the Emergency and Trauma Centre, including 1300 major trauma patients per year. These centers serve a population of 5.5 million in the state of Victoria, Australia. Trauma teams are activated for patients meeting call-out criteria and trauma reception is standardized using algorithms prompted in real time using computer-aided support systems [20,21].

2.2. Patients and definitions

The Alfred Hospital Trauma Registry (ATR) is a trauma epidemiology, injury surveillance and performance-monitoring program that uses a fully integrated TraumaNet system allowing system monitoring for clinical care, education, audit and research in real time. Inclusion criteria to the ATR are all patients with injury severity score >15, intensive care unit (ICU) admission, transfers, death after injury and admission $\geqslant$72 hours after a traumatic mechanism.

Patients presenting to hospital with iTBI and ATC between January 2007 and December 2011 were the target population for this study. The accessible population were all adult (age $\geqslant$16 years old) cases in the ATR with Abbreviated Injury Score (AIS) head $\geqslant$3 and all other body AIS <3. Patients with missing data on INR or head injury details were excluded. ATC was defined as an initial INR of $\geqslant$1.3 on presentation to the emergency department, as this value has been shown to be a clinical horizon point in patients with iTBI, where mortality is around 42%. This mortality rate does not seem to increase with increasing INR value [5]. The International Sensitivity Index of thromboplastin used at our institution ranged from 1.03 to 1.09. This provides an indication for applying the results of this study to centers that use prothrombin time as their measure of coagulation. Patients presenting with previously prescribed anticoagulant medication were excluded from the analysis of association between normalization or INR and death.

2.3. Study design

A retrospective study using trauma data was conducted. The primary outcome measure was death recorded at hospital discharge. Secondary outcomes included ICU admission and neurosurgical intervention. Immediately on arrival to hospital blood was drawn and tested for a pre-determined panel of laboratory tests [20]. These results were used for the diagnosis of ATC. During the study period, pre-hospital blood, blood product or procoagulant drug administration were not parts of Ambulance Victoria protocol. Time from hospital admission to the administration of coagulants or blood products was calculated, as was the time from admission to INR normalization (INR <1.3). Prothrombinex-VF (CSL Behring, King of Prussia, PA, USA) is the most common coagulation factor concentrate used in our setting and contains factors II, IX and X and a small amount of factor VII.

2.4. Analysis

Normally distributed continuous data were reported as mean (with standard deviation), whereas skewed or ordinal data were reported as medians (with interquartile range). The t-test was used to test for a statistically significant difference between two mean values, while the chi-squared test was used to test for a statistically significant difference between two proportions. A p-value of <0.05 was considered statistically significant.

To determine the association between normalization of INR and in-hospital mortality, a multivariable logistic regression model was used. Patients who died in the first 24 hours prior to normalization of INR were excluded in order to adjust for survival bias. Variables that demonstrated any association with death ($p < 0.10$) were entered into a multivariable logistic regression model to determine independent associations. All data were stored and collated using Excel (Microsoft, Redmond, WA, USA) and analyzed using Stata version 12 (StataCorp, College Station, TX, USA). This study was approved by The Alfred Hospital Research and Ethics Committee.

3. Results

There were 1718 patients with iTBI identified in the study period. There were 157 patients who met the set criteria for ATC and were included in the study. There were 68 (43.3%) patients who received coagulant products in the first 24 hours (Fig. 1). The median time to delivery of the first product was 182.5 (115–375) minutes and the median time to normalization of INR among patients who received procoagulant agents was 604 (274–1146) minutes. Among patients who did not receive procoagulant agents but achieved normalization of INR, time to normalization of INR was significantly longer at 1517 (605–2613) minutes ($p < 0.01$).

FFP was the most common procoagulant agent used and was administered to 54 patients within 24 hours, with 40 patients receiving FFP in the first 4 hours. Other products administered in the first 24 hours were vitamin K (n = 7), Prothrombinex (n = 35), platelets (n = 14) and cryoprecipitate (n = 9). Table 1 illustrates the binary combination of products administered to patients.

There were 53 patients who required neurosurgical intervention, with 28 patients receiving a procoagulant agent: 27 received FFP, four received vitamin K, 15 received Prothrombinex, five received platelets and three received cryoprecipitate prior to surgery. There was no association between neurosurgical intervention and the volume of red blood cell usage (odds ratio [OR] 1.08; 95% confidence interval [CI] 0.94–1.24; p = 0.29). However, a higher proportion of patients undergoing a neurosurgical intervention were administered procoagulant agents (OR 3.25; 95% CI 1.54–6.88; $p < 0.01$). There were 26 patients with a history of oral anticoagulant use. Of these, 19 (73.1%) received procoagulant agents and patients on warfarin were at higher odds of receiving procoagulant agents (OR 4.54; 95% CI 1.78–11.58; p = 0.002).

Among the subgroup of patients undergoing a neurosurgical intervention (n = 53), 28 patients received a procoagulant and nine of these patients died, while 25 patients did not receive procoagulants and two of these patients died. Administration of a procoagulant agent was associated with higher odds of death (OR 5.45; 95% CI 1.05–28.31; p = 0.04). Among these 53 patients, 40 patients had normalized INR recorded with an outcome of death in four (10.0%) patients, whereas 13 patients did not achieve normalization of INR, with an outcome of death in seven (53.8%). Among patients undergoing neurosurgical intervention, there was a significant univariate association of normalization of INR with lower mortality (OR 0.09; 95% CI 0.02–0.43; p = 0.002).

There were 78 (49.7%) patients admitted to the ICU. Admission to the ICU was significantly associated with normalization of INR (OR 2.27; 95% CI 1.19–4.33). Patients admitted to ICU spent 63