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Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study

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ABSTRACT

Introduction: Fibrinogen may be reduced following traumatic injury due to loss from haemorrhage, increased consumption and reduced synthesis. In the absence of clinical trials, guidelines for fibrinogen replacement are based on expert opinion and vary internationally. We aimed to determine prevalence and predictors of low fibrinogen on admission in major trauma patients and investigate association of fibrinogen levels with patient outcomes.

Patients and methods: Data on all major trauma patients (January 2007–July 2011) identified through a prospective statewide trauma registry in Victoria, Australia were linked with laboratory and transfusion data. Major trauma included any of the following: death after injury, injury severity score (ISS) >15, admission to intensive care unit requiring mechanical ventilation, or urgent surgery for intrathoracic, intracranial, intra-abdominal procedures or fixation of pelvic or spinal fractures. Associations between initial fibrinogen level and in-hospital mortality were analysed using multiple logistic regression.

Results: Of 4773 patients identified, 114 (2.4%) had fibrinogen less than 1 g/L, 283 (5.9%) 1.0–1.5 g/L, 617 (12.9%) 1.6–1.9 g/L, 3024 (63.4%) 2–4 g/L and 735 (15%) >4 g/L. Median fibrinogen was 2.6 g/L (interquartile range 2.1–3.4). After adjusting for age, gender, ISS, injury type, pH, temperature, Glasgow Coma Score (GCS), initial international normalised ratio and platelet count, the lowest fibrinogen categories, compared with normal range, were associated with increased in-hospital mortality (adjusted odds ratio [OR] for less than 1 g/L 3.28 [95% CI 1.71–6.28, $p < 0.01$], 1–1.5 g/L adjusted OR 2.08 [95% CI 1.36–3.16, $p < 0.01$] and 1.6–1.9 g/L adjusted OR 1.39 [95% CI 0.97–2.00, $p = 0.08$]). Predictors of initial fibrinogen <1.5 g/L were younger age, lower GCS, systolic blood pressure <90 mmHg, chest decompression, penetrating injury, ISS >25 and lower pH and temperature.

Conclusions: Initial fibrinogen levels less than the normal range are independently associated with higher in-hospital mortality in major trauma patients. Future studies are warranted to investigate whether earlier and/or greater fibrinogen replacement improves clinical outcomes.

Introduction

Major bleeding is frequent in patients following major trauma. Massive transfusions are reported in approximately 4–20% [1–5] of major trauma patients, and this is associated with poor outcomes with reported mortality of 7–26% [1–6].

Acute traumatic coagulopathy (ATC) has been demonstrated in 8–50% of trauma patients at hospital admission [1–5], with reported rates varying according to the inclusion criteria and ATC definition. ATC may contribute to major bleeding and requirement for massive transfusion. Fibrinogen is an essential protein for coagulation, and consumption of fibrinogen and fibrinolysis by the action of plasmin are key components of ATC [7]. Fibrinogen is one of the earliest coagulation proteins to fall in major bleeding [8] and fibrin strands that form in a low fibrinogen environment are more susceptible to fibrinolysis [9].

Despite the importance of fibrinogen for clot formation and its role in ATC, there is little evidence to guide clinicians on fibrinogen

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replacement during initial resuscitation. Recent systematic reviews could not identify interventional studies to inform the use of fibrinogen replacement in trauma patients [10,11], and guidelines are based primarily on expert opinion [12–14]. In the presence of active bleeding, recommended thresholds for fibrinogen replacement vary, ranging from plasma fibrinogen of <1 g/L–<1.5–2.0 g/L [12–14]. Whilst there are few data on prevalence or predictors of hypofibrinogenemia in trauma patients, studies have reported association between lower fibrinogen levels and increased mortality [1,15,16]. Furthermore, one recent observational study reported an optimal fibrinogen concentration of 2.29 g/L, showing that levels below this value were associated with reduced odds of death of 0.08 for every unit increase in fibrinogen level [15].

In this study, we aimed to determine the prevalence and predictors of low fibrinogen on admission in a cohort of major trauma patients and to investigate the association of lower fibrinogen with patient outcomes.

Methods

Patients

The Australian state of Victoria (population approximately 5.4 million people [17]) has an inclusive trauma system, with two adult hospitals (the Alfred Hospital and The Royal Melbourne Hospital) designated the major trauma services (equivalent to level-1 trauma centres).

For this study, we used the Victorian State Trauma Registry (VSTR), which prospectively collects data on all major trauma patients in Victoria, to identify patients aged 18 or older who presented to the two major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. The VSTR uses on opt-out consent process, in which all eligible patients are recorded on the VSTR, provided with information regarding the registry, including data collected, and given the opportunity to be removed from the VSTR [18,19]. The VSTR has an opt-off rate of less than 0.1%, ensuring almost complete capture of all major trauma patients in the state [18,19].

Patients with major trauma were defined as those meeting any of the following criteria [19]:

- Death after injury;
- An Injury Severity Score (ISS) >15
- Admission to an intensive care unit (ICU) requiring mechanical ventilation for at least part of their ICU stay
- Urgent surgery for intrathoracic, intracranial, intra-abdominal procedures, or fixation of pelvic or spinal fractures.

Data sources

Data obtained from the VSTR were patient demographics, injury event details (time and mechanism of injury), ISS, Glasgow Coma Scale (GCS), systolic blood pressure (BP) and pulse rate recorded by ambulance and on hospital admission, pH and temperature on admission, in-hospital and 24-h mortality, intensive care unit (ICU) and hospital length of stay (LOS).

Data were obtained electronically from the hospital laboratory information system (LIS) at each of the two hospitals. This included all recorded haemoglobin (Hb) and platelet counts, coagulation studies (including international normalized ratio [INR], activated partial thromboplastin time [aPTT] and plasma fibrinogen levels), arterial blood gas results as well as information on all blood products issued, including type of component and time of issue.

The diagnostic laboratories at the participating hospitals performed the fibrinogen assays, with both using an automated Clauss assay (STA Fibrinogen, Diagnostica Stago Inc.). Both laboratories are accredited pathology providers and participate in external quality assurance programs.

Laboratory data were merged using a unique patient identifier and hospital site with the VSTR. The first laboratory results recorded after admission to hospital within the first 24 h of admission were identified for each patient.

Analysis

Descriptive statistics are reported as mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for non-normally distributed data. Hypothesis testing was performed using Chi Square for categorical data and either *t*-test or Wilcoxon rank sum for continuous data depending on data distribution. Fibrinogen was categorised as <1 g/L, 1.0–1.5 g/L, 1.6–1.9 g/L, 2.0–4.0 g/L (reference category) and >4 g/L to incorporate the normal reference range, as well as the commonly used thresholds for fibrinogen supplementation [12–14]. The GCS was categorised according to clinical convention with 3–8 representing severe, 9–12 moderate and 13–15 a mild head injury. Temperature and pH were categorised according to normal ranges, with categories for below, within and above the normal range. Platelet count was categorised according to normal range, with categories for below normal range, and INR was categorised according to normal range, with categories for above normal range. Patient age and ISS were categorised into quintiles. Patients were categorized as having received a massive transfusion if they had received 10 or more units of red blood cells (RBC) during the admission.

The association between first fibrinogen levels and in-hospital mortality was modelled using multiple logistic regression. Variables considered for the multivariable models were identified *a priori,* based on previous literature, and included age, gender, ISS, pH, temperature, GCS, injury type (blunt, penetrating, other), chest decompression, pulse and systolic BP on admission, time from injury to admission, Hb, platelet count, INR, aPTT and fibrinogen level. As there were a high proportion of patients with missing values, we including a missing category for those variables with high missing rates (>5% of patients). The relationship was modelled in two ways, with fibrinogen treated as a continuous variable, and categorised as outlined above. The models were constructed using both stepwise selection and backwards elimination techniques before undergoing a final assessment for clinical and biological plausibility. Predicted mortality across the range of fibrinogen values was estimated using multiple logistic regression. The association between hospital and ICU LOS in survivors was modelled using linear regression with ICU LOS log-transformed.

Sensitivity analysis for the association between mortality and fibrinogen levels was performed. As there were a high proportion of patients with missing values, we repeated our regression analysis using only patients with complete data to assess if the inclusion of missing category altered the findings of the regression analysis.

Predictors for low fibrinogen (defined as <1.5 g/L) on initial presentation were modelled using multiple logistic regression, including categories for missing values as in the mortality model.

To increase the robustness of the study, a two-sided p-value of <0.01 was used to indicate statistical significance.