Injury, Int. J. Care Injured 45 (2014) 819–824

Contents lists available at ScienceDirect

Injury

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

Review

Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: A systematic review and meta-analysis

Daniel S. Epstein [a,b], Biswadev Mitra [a,b,*], Gerard O'Reilly [a,b], Jeffrey V. Rosenfeld [b,c,d], Peter A. Cameron [a,b,e]

[a] Emergency & Trauma Centre, The Alfred Hospital, Melbourne, Australia
[b] Department of Epidemiology & Preventive Medicine, Monash University, Melbourne, Australia
[c] Department of Surgery, Monash University, Melbourne, Australia
[d] Department of Neurosurgery, The Alfred Hospital, Melbourne, Australia
[e] Emergency Medicine, Hamad Medical Corporation, Doha, Qatar

ARTICLE INFO

Article history:
Accepted 13 January 2014

Keywords:
Wound and injuries
Coagulopathy
Blood coagulation
Traumatic brain injury
Craniocerebral trauma
Brain injuries
Isolated head trauma

ABSTRACT

Background and objectives: Acute traumatic coagulopathy (ATC) has been reported in the setting of isolated traumatic brain injury (iTBI) and associated with high mortality and poor outcomes. The aim of this systematic review was to examine the incidence and outcome of patients with ATC in the setting of iTBI.

Methods: We conducted a search of the MEDLINE database and Cochrane library, focused on subject headings and keywords involving coagulopathy and TBI. Design and results of each study were described. Studies were assessed for heterogeneity and the pooled incidence of ATC in the setting of iTBI determined. Reported outcomes were described.

Results: There were 22 studies selected for analysis. A statistically significant heterogeneity among the studies was observed ($p < 0.01$). Using the random effects model the pooled proportion of patients with ATC in the setting of iTBI was 35.2% (95% CI: 29.0–41.4). Mortality of patients with ATC and iTBI ranged between 17% and 86%. Higher blood transfusion rates, longer hospital stays, longer ICU stays, decreased ventilator free days, higher rates of single and multiple organ failure and higher incidence of delayed injury and disability at discharge were reported among patients with ATC.

Conclusions: ATC is commonly associated with iTBI and almost uniformly associated with worse outcomes. Any disorder of coagulation above the normal range appears to be associated with worse outcomes and therefore a clinically important target for management. Earlier identification of patients with ATC and iTBI, for recruitment into prospective trials, presents avenues for further research.

Contents

* Corresponding author at: Emergency & Trauma Centre, The Alfred Hospital, Commercial Rd., Melbourne 3004, Australia. Tel.: +61 3 9076 2782; fax: +61 3 9076 2699.
E-mail address: biswadev.mitra@monash.edu (B. Mitra).

0020–1383/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.injury.2014.01.011

Introduction

Acquired disorders of coagulation have been previously associated with traumatic brain injury [1–4]. The primary mechanisms of such disorders in the setting of trauma are acute traumatic coagulopathy (ATC, also termed early trauma induced coagulopathy, early coagulopathy of trauma and acute coagulopathy of trauma-shock) and delayed coagulopathy secondary to haemodilution [1–5]. Conventionally, the mechanism of ATC has been simplistically proposed as a result of depletion, dilution and dysfunction of procoagulant factors. It is now understood that the pathophysiology is much more complex than this.

A complex dynamic equilibrium exists between anti and procoagulant factors, platelets, endothelium function and fibrinolysis, with ATC a result of an imbalance in this complex system following tissue damage and hypoperfusion in trauma [6,7]. Hypothermia, continued blood loss and acidaemia are also known contributors to coagulopathy that lead to a global derangement in haemostasis and exacerbation of ATC [2,8,9]. The activation of protein C leading to inhibition of co-factors Va and VIIa appears to hold a key position in the development of ATC, and is triggered by hypoperfusion and endothelium damage. This leads to an overall disruption in coagulation via the decreased conversion of fibrinogen to fibrin. Over-activation of protein C occurs when hypoperfusion and endothelium damage releases thrombomodulin, a protein that combines with thrombin to form a complex which leads to the activation of protein C. The uptake of thrombin to form this complex also leaves less available to cleave fibrinogen [8].

The mechanism of platelet dysfunction in the setting of ATC is relatively unknown, but present in severely injured patients [10]. Platelet activation and fibrin generation are mutually dependent processes. Platelet thrombinase assembly creates a thrombin burst that propagates clot formation. Massive transfusion also can result in dilutional thrombocytopenia, this may be confused with true platelet dysfunction [8]. Other physiological factors contribute to global potentiating of coagulopathy in a non-causative relationship. In the context of shock and hypoperfusion, endothelium releases thrombomodulin which complexes with thrombin, which leaves less thrombin able to cleave fibrinogen whilst also helping activation of protein C, further inhibiting the extrinsic pathway and antifibrinolytic factors [5]. Shock is associated with a three-fold increase in the development of ATC [11]. Shock may also contribute to acidaemia caused by tissue hypoperfusion leading to anaerobic build-up of lactic acid. This change in pH alters protease function and increases risk of coagulopathy [11]. Hypothermia also plays a role in both generally impairing the coagulation pathways and hampering platelet function and adhesion [12]. This combination of hypoperfusion, hypothermia and acidaemia are common in the trauma patient and contribute to the exacerbation of ATC [2,6,8], leading to the 'triad of death' [13].

Coagulation disorders in the setting of traumatic brain injury have been associated with poor outcomes with in-hospital mortality up to 50% [14–18]. The true incidence of ATC in the setting of isolated traumatic brain injury (iTBI) is relatively unknown and has been estimated to be between 10% and 98% [14]. This very wide range has been attributed to inconsistent definitions of coagulopathy and criteria for iTBI [14]. Other factors included differences in times at which patients were tested for coagulopathy and sensitivity of tests. Defining the true incidence may help clarify the rationale for empiric management directed at ATC and subsequent development of appropriate guidelines.

The primary aim of this study was to determine the incidence of ATC in the setting of iTBI. Secondary aims were to investigate appropriate definitions of ATC and associated outcomes.

Methods

A systematic review and meta analysis were performed. The Prisma guidelines were followed in the development of this review. These guidelines [19] were developed to improve the quality and reporting of systematic reviews and meta-analysis. These guidelines were followed in the development of the methodology of this review.

Information sources

The authors searched for English language articles in MEDLINE (1990 – 20 February 2013), PubMed, Embase (1990 – 20 February 2013) and the Cochrane library (to Issue 1, 2013) using a combination of the following subject headings and keywords: "coagulopathy," "blood coagulation," "traumatic brain injury," "craniocerebral trauma," "brain injuries", "traumatic coagulopathy" and "isolated head trauma". Reference lists of relevant articles were scanned for further studies. Results were truncated to clinical trials, clinical studies, guidelines, and meta-analyses.

Study selection

Studies were included if they reported the incidence of acute isolated traumatic brain injury and coagulopathy as an outcome variable among adult patients (>16 years of age). Specific exclusion criteria were studies primarily involving patients with pre-existing coagulation disorders, patients on anticoagulants, studies primarily involving paediatric patients, non-traumatic brain injury, non-isolated traumatic brain injury, case reports and letters.

Eligibility was assessed by two reviewers scanning abstracts for suitability and reviewing the full text where necessary; disagreements were resolved by consensus.

Data collection

We extracted data about study size, number of patients, inclusion criteria, definitions of ATC, the proportion of patients that developed ATC and reported outcomes.

Analysis

The primary outcome was coagulopathy; the secondary outcome was mortality at a timeframe defined in the individual studies. Heterogeneity between studies was assessed using the Q test and I^2 statistic. In the case of significant heterogeneity, a random effects model was used to derive the pooled proportion with 95% confidence intervals. Statistical analyses were conducted using Stata v 12.0 (Statacorp, TX).