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Efficacy and safety of fibrinogen concentrate in trauma patients—a systematic review☆,☆☆,★

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ABSTRACT

Purpose: Uncontrolled bleeding is the main preventable cause of death in severe trauma patients. Fibrinogen is the first coagulation factor to decrease during trauma-induced coagulopathy, suggesting that pharmacological replacement might assist early hemorrhage control. Several sources of fibrinogen are available; however, fibrinogen concentrate (FC) is not routinely used in trauma settings in most countries. The aim of this review is to summarize the available literature evaluating the use of FC in the management of severe trauma.

Methods: Studies reporting the administration of FC in trauma patients published between January 2000 and April 2013 were identified from MEDLINE and from the Cochrane Library.

Results: The systematic review identified 12 articles reporting FC usage in trauma patients: 4 case reports, 7 retrospective studies, and 1 prospective observational study. Three of these were not restricted to trauma patients.

Conclusions: Despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. Randomized trials are warranted to determine whether FC improves outcomes in prehospital management of trauma patients or whether FC is superior to another source of fibrinogen in early hospital management of trauma patients.

1. Introduction

Trauma is a major cause of mortality, with more than 5 million deaths annually worldwide. Young adults are particularly at risk, leading to many life-years lost or dependence on ongoing care. Hemorrhage is the most common cause of preventable death in trauma, with 55% of deaths due to prehospital bleeding [1]. Hemorrhage control is commonly thwarted by coagulopathy, which is present in more than 50% of trauma patients at emergency department (ED) admission [2]. Trauma patients who present to the hospital with coagulopathy already established, are 3 to 4 times more likely to die [3-6]. Prolonged hypotension and/or the adverse effects of massive blood product transfusion also lead to an increase in morbidity including acute kidney injury [4], multiple-organ failure [3], and an increased length of stay in the hospital and intensive care unit (ICU) [5,7]. Improving early hemorrhage control by optimizing treatment of coagulopathy might, therefore, lead to improved outcomes in severely injured trauma patients [1].

For many years, coagulopathy in trauma was thought to be attributable to 3 main mechanisms: (1) loss of coagulation factors due to bleeding and consumption, (2) dilution due to intravenous fluid and red blood cell (RBC) administration without sufficient clotting factors (in the form of fresh frozen plasma [FFP] and platelets), and (3) coagulation protease dysfunction due to hypothermia and acidemia. More recently, accumulating evidence has suggested that tissue hypoperfusion and direct tissue trauma initiate acute coagulopathy in trauma patients also called trauma-induced coagulopathy (TIC), in part through an increase of fibrinolysis [4,5,7,8].

Fibrinogen is the first coagulation factor to reach critically low levels during trauma, and hepatic synthesis is not sufficient to compensate for rapid massive consumption [9]. Although fibrinolysis secondary to activation of the coagulation cascade may be the primary reason for hypofibrinogenemia, other mechanisms play an important role in decreasing plasma fibrinogen. These include (i) increase in fibrinogen breakdown due to acidosis [10], (ii) dilution during fluid

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resuscitation [11], (iii) loss due to bleeding, and (iv) decrease in fibrinogen synthesis due to hypothermia [12] (Fig. 1). In addition, fibrinogen/fibrin polymerization is disturbed by colloid infusions [11]. Guidelines recommend replacement of fibrinogen if significant bleeding is associated with hypofibrinogenemia defined as plasma fibrinogen concentration less than 2 g/L or thromboelastometric signs of functional fibrinogen deficit, using the European guideline for management of bleeding and coagulopathy following major trauma [13,14]. Currently, there are 3 fibrinogen sources available to clinicians: fibrinogen concentrate (FC), FFP, and cryoprecipitate. Human fibrinogen concentrate is derived from human plasma and is currently manufactured as 4 different products: Haemocomplettan (CSL Behring, Marburg, Germany), Clottafact (LFB, Les Ulis, France), Fibrinogen HT (Benesis, Osaka, Japan), and FibroRAAS (Shanghai RAAS, Shanghai, China) [15]. Fibrinogen concentrate has several potential advantages over FFP or cryoprecipitate and is the only practical source of fibrinogen, which can be administered outside the hospital. Fibrinogen concentrate does not require ABO compatibility testing. Its lyophilized form allows FC to be stored in an ambulance for up to 5 years at 25°C and to be easily reconstituted and administered [16]. Fibrinogen concentrate avoids adverse effects associated with allogeneic blood products including transfusion-related acute lung injury and ABO incompatibility [14,17,18]. Although viral inactivation by heat treatment lessens the risk of pathogen transmission compared with other blood products, as a human plasma–derived product, transmission of infection cannot be completely excluded [16]. In addition, the high concentration of fibrinogen in FC (20 g/L) enables it to be replaced intravenously with a small volume (200 mL to administer 4 g of fibrinogen), whereas replacement of fibrinogen with cryoprecipitate where the concentration of fibrinogen is widely variable and lower (8-16 g/L) and FFP where the concentration of fibrinogen is much lower (2 g/L) requires a larger volume and thereby may lead to transfusion-associated circulatory overload [19]. Finally, there is growing evidence in nontrauma patients, for instance, in cardiac surgery, that the use of coagulation factor concentrates, including FC, guided by point-of-care coagulation analyses, reduces blood product requirements as well as overall treatment cost [20,21].

Although 1 systematic review compared clinical effectiveness of FFP with FC in surgical and/or massive trauma patients [22], only 1 review has summarized all the literature concerning FC in bleeding trauma patients. Published in 2011, the authors found 1 observational study and 3 case reports, with only 131 patients treated with FC [23]. Since then, interest in FC has been rising steadily because of perceived benefits of addressing TIC directly. As the prelude to a possible clinical trial in trauma patients, we aimed to review the entire current published experience of FC in early severe trauma with massive hemorrhage.

2. Methods

The review has been designed to maximize adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [24].

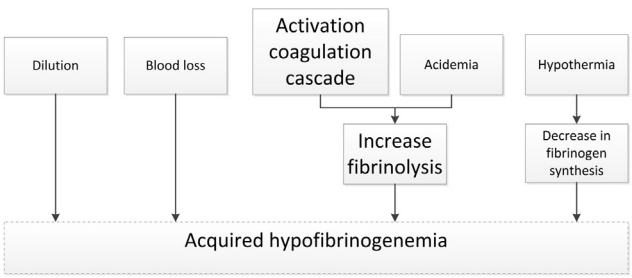

Fig. 1. Factors contributing to hypofibrinogenemia in trauma patients.

2.1. Eligibility criteria, information sources, and search strategy

We systematically searched in MEDLINE via OVID and in the Cochrane Library to identify published reports of clinical experiences of FC in adults with trauma, regardless of the study's outcome. We used the subject heading “fibrinogen” and the text words “fibrinogen concentrate.” Similarly, we searched for the subject heading “wound and injuries” and “multiple trauma” and the text words “trauma.” We confined our search to English language articles published between January 2000 and April 2013. Articles were eligible if they reported FC used in management of severe trauma patients. We excluded preclinical studies and pediatric studies. Additional articles were added if found in the references of the selected articles and if they fulfilled the eligibility criteria. Eligibility assessment was based on the title or abstract and on full text if required.

2.2. Data collection process and items

The following were extracted by 1 reviewer (CA): study design (for instance, case report, observational cohort, retrospective or prospective study), sample size, inclusion criteria, period, protocol (fibrinogen plasma level threshold, prehospital or hospital phase, comparative group), results (dose of FC administered, outcomes), and safety information.

3. Results

Three hundred four articles were identified. Most were excluded at the level of title or abstract based on relevance (Fig. 2). Twelve were considered eligible for this review: 4 case reports [25-28] and 8 observational case series [9,29-35]. Of these 8 case series, 7 were retrospective [9,29-31,33-35], including 3 with matched pairs analysis or propensity score matching [31,33,34] and 1 that used Trauma Injury Severity Score (TRISS) to control for patient severity [35]. One was a multicenter observational study. Of these studies, 3 were not restricted to trauma patients. There were no randomized controlled trials (RCTs).

3.1. Case reports

The 4 case reports illustrate successful resuscitation of trauma patients who had massive hemorrhage with FC in addition to other products (Table 1) [25-28]. In all cases, the administration of FC was in response to fibrinolysis as demonstrated by rotational thromboelastometry (ROTEM). Patients received between 5 and 16 g of FC in the ED or operating room (OR). Two patients also received prothrombin complex concentrate (PCC) and/or tranexamic acid [25,28]. One patient received 3 bags of FFP along with 5 g of FC [28]. These 4 cases suggest that aggressive management of coagulopathy with FC with and without antifibrinolytics and other coagulation factors is feasible and may be effective. Nonetheless, no clear conclusions, especially concerning savings in volume of blood products required, can be drawn.

3.2. Retrospective case series

Seven retrospective studies have reported the use of FC in trauma patients with serious bleeding (Table 2). Two reports from single centers were not restricted to trauma and included patients with other causes for massive hemorrhage receiving FC for low fibrinogen [9,29]. The administration of FC was based on plasma fibrinogen level with a threshold of 1 and 2 g/L, respectively. The study of Fenger-Eriksen et al [9] enrolled 43 patients including 6 with trauma and reported a significant decrease in transfusion requirements and a significant improvement in laboratory coagulation indices in individual patients after fibrinogen administration. The authors