Impact of Low Fibrinogen Levels in the Puzzle of Trauma-induced Coagulopathy: Is This the Missing Link?

Juan C Duchesne, Chrissy Guidry, Timothy S Park, Eric Simms, Jordan RH Hoffman, Jiselle M Bock, Julie Wascom, James Barbeau, Peter Meade, Norman E McSwain Jr

**ABSTRACT**

**Background:** Patients with severe tissue injury and tissue hypoperfusion can present with low fibrinogen levels and signs of hyperfibrinolysis. The role of damage control resuscitation (DCR) in addressing the hyperfibrinolytic aspect of trauma induced coagulopathy (TIC) is unknown. We hypothesize a survival advantage when DCR is used in TIC patients with severe tissue injury and low fibrinogen levels.

**Materials and methods:** This is a 2 years prospective observational study of TIC patients who received DCR. TIC was defined as initial base deficit = –6 in combination with ISS = 12. Low fibrinogen was considered when serum level <200 mg/dl. Patients were stratified into those with an injury severity score (ISS) <20, and those with an ISS = 20. Variables analyzed between groups included: initial serum fibrinogen, INR, base deficit, intraoperative FFP: PRBC ratio and mortality.

**Results:** Of 67 patients with TIC, 29 (43.2%) had ISS < 20, and 38 (56.7%) an ISS ≥ 20. Mean ISS was 13.9 vs 32.8 (p = 0.0001) for the ISS < 20 group vs the ISS ≥ 20 group respectively. Mean initial fibrinogen levels for the ISS < 20 group vs the ISS ≥ 20 group was 357.4 mg/dl vs 148.5 mg/dl (p = 0.0007). Intraoperative DCR with FFP: PRBC for the ISS < 20 group vs the ISS ≥ 20 group showed no statistical difference: 1 to 1.12 vs 1 to 1.3 (p = 0.12). Overall mortality after controlling for DCR in the ISS < 20 group was 29 and 73% in the ISS ≥ 20 group (p = 0.0007). In a stepwise logistic regression, low fibrinogen levels was associated with mortality, p = 0.01; OR 1.01 (1.23-11.55) with area under the receiver operating characteristic curve of 0.701. The correlation coefficient for ISS vs initial fibrinogen level was −0.5635 (p = 0.0001).

**Conclusion:** Overall mortality was significantly increased in patients who had an ISS ≥ 20 with low fibrinogen level despite effective DCR. Given the correlated decrease in fibrinogen levels in patients with severe tissue injury, further investigation regarding potential benefits of antifibrinolytic agents in DCR needs further validation.

**Keywords:** Coagulopathy, Resuscitation, Fibrinogen, Fibrinolysis.


**Source of support:** Nil

**Conflict of interest:** None declared

**RESUMEN**

**Antecedentes:** Los pacientes con graves lesiones en los tejidos y con baja perfusión pueden presentar con bajos niveles de fibrinógeno y signos de hyperfibrinolysis. La función de control de daños reanimación (DCR) para hacer frente a los hiperfibrinolisis aspecto de Trauma inducido coagulopatía (TIC) es desconocida. Nuestra hipótesis es una ventaja en la supervivencia cuando DCR se utiliza en TIC pacientes con graves lesiones en los tejidos y los bajos niveles de fibrinógeno.

**Materiales y métodos:** Este es un estudio de 2 años observacional prospectivo de los pacientes que recibieron TIC DCR. TIC se definió como base inicial déficit = –6 en combinación con ISS = 12. Bajo fibrinógeno se consideró cuando nivel sérico <200 mg/dl. Los pacientes fueron estratificados en aquellos con un injury severity score (ISS) >20, y los que tienen un ISS = 20. Las variables analizadas entre grupos incluyen: fibrinógeno sérico inicial, INR, déficit base, intraoperatorio FFP: PRBC relación y mortalidad.

**Resultados:** De 67 pacientes con TIC, 29 (43.2 %) habia ISS < 20, y 38 (56.7 %) con ISS ≥ 20. ISS medio era de 13,9 frente a 32,8 (p < 0,0001) para ISS < 20 frente a la ISS ≥ 20 grupo, respectivamente. Niveles de fibrinógeno promedio inicial del grupo con ISS < 20 frente a ISS ≥ 20 grupo fue 357,4 mg/dl vs 148,5 mg/dl (p = 0,0007). Intra-operatoria DCR con FFP: PRBC para ISS < 20 grupo frente a la ISS ≥ 20 no mostró diferencia estadística: 1:1.12 vs 1:1.3 (p = 0,12). Mortalidad general después de controlar DCR en ISS < 20 fue de 29 y 73% en ISS ≥ 20 (p = 0,0007). De forma gradual regresión logística, bajo niveles de fibrinógeno fue asociado con mortalidad, p = 0,01 ; OR 1,01 (1,23-11,55) con área bajo la curva de características del receptor operatorio de 0,701. El coeficiente de correlación de ISS inicial vs fibrinógeno fue −0,5635 (p = 0,0001).

**Conclusiones:** La mortalidad fue significativamente mayor en los pacientes que habían tenido un ISS ≥ 20 con un bajo nivel de fibrinógeno a pesar de DCR. Habida cuenta de la correlación, disminución de niveles de fibrinógeno en pacientes con graves lesiones en los tejidos, más investigación acerca de los posibles beneficios de agentes antifibrinolíticos en DCR necesita validación adicional.

**Palabras claves:** Coagulopatía, Reanimación, Fibrinógeno, La fibrinólisis.

**INTRODUCTION**

Hemorrhage is one of the leading causes of preventable death in trauma. In patients with massive hemorrhage, damage control resuscitation (DCR) conveys a survival benefit with early intraoperative hemostatic resuscitation (IHR) when a close ratio of fresh frozen plasma (FFP) to pack red blood cells (PRBC) is achieved in combination with damage control surgery. A subset of this patients with severe hemorrhage will arrive to the emergency department with trauma induced coagulopathy (TIC). The etiology of this early coagulopathy associated with trauma is complex and directly associated with mortality.
TIC develops in approximately 24% of patients independent of acidosis and hypothermia but secondary to trauma itself.4 TIC develops in the presence of severe tissue injury and tissue hypoperfusion causing a cascade of events leading to systemic anticoagulation and in a subset of patients, hyperfibrinolysis.5-9 Recently, the CRASH-2 trial looked at the effects upon mortality by using an antifibrinolytic, tranexaminic acid (TXA), which works by modulating the activation of plasmin.10 TXA therefore inhibits clot breakdown, implying a favorable effect to patients with hemorrhage.10,11 Although, in their results TXA safely reduced mortality in bleeding trauma patients, the degree of injury severity and its correlation with DCR, degree of fibrinolysis and coagulopathy was not recorded. Our study investigates the impact of having low fibrinogen levels in TIC patients. We hypothesize a survival advantage when DCR is used in TIC patients with severe tissue injury and low fibrinogen levels.

MATERIALS AND METHODS

This was a 2-year IRB-approved prospective observational study from January 1 of 2009 until December 31 of 2010. All adult trauma patients with diagnosis of TIC upon presentation to our Level I Trauma Center requiring damage control surgery (DCS) along with DCR with ≥10 units of PRBC over 24 hours were included. TIC was defined as an abnormal base deficit with ISS of >12. Once identified, patients were stratified into 2 groups based on their ISS: those with presenting ISS < 20 were compared to those with ISS ≥ 20. This delineation was based on evidence that presenting with an ISS ≥ 16 is an independent risk factor for the development of acute traumatic coagulopathy11,12 and therefore a greater quantity of TIC patients. Once stratified, the means of serum fibrinogen concentration between groups were compared. Low fibrinogen concentration was considered when serum level <200 mg/dl.

DCR involved the utilization of a close-ratio FFP to PRBC with activation of massive transfusion protocol (MTP) that involved predetermined blood component transfusion ratios of 1:1 for FFP to PRBCs, and 1:2 for platelets (PLT) to PRBCs. Total transfused units of FFP, PRBC and PLT from initial presentation to the emergency department until 24 hours were recorded and a ratio for FFP to PRBC and PLT to PRBC calculated. DCR was accomplished in the context of DCS, which involved damage control laparotomy performed in the commonly described three-staged manner12 involving a truncated laparotomy, follow on physiologic optimization in the intensive care unit (ICU), and definitive organ management during a second operation.

Demographics compared between groups included: patient age (years), patient gender (male vs female), mechanism of injury (blunt vs penetrating), injury severity score (ISS) as defined by Baker et al15 and initial emergency department systolic blood pressure (mm Hg). Comparison of laboratory values included serum fibrinogen concentration (mg/dl), activated partial thromboplastin time (aPTT; herein referred to as PTT), INR, calculated base deficit, and hemoglobin (Hgb). This laboratory values were obtained at initial presentation to the emergency department, and approximately 6 hours afterward. Primary outcome of this study was to establish a correlation between ISS and serum fibrinogen concentration. Secondary endpoints included difference in mortality, ICU and hospital length of stay (LOS) between groups.

All statistical analyses were performed using MedCalc Version 10.2.0.0 (MedCalc Software, Mariakerke, Belgium). Logistic regression analysis utilized the stepwise method of independent variable input with a cut-off value of p = 0.5. Correlation coefficients were calculated as Pearson correlation coefficients.

RESULTS

During the 2-year study, a total of 67 trauma patients presented to the emergency department with diagnosis of TIC. There were 29 patients (43.2%) with ISS < 20 group and 38 (56.7%) with ISS ≥ 20 group. Mean age for each group ISS < 20 vs ISS ≥ 20 was 33.3 vs 35.8 (p = 0.78). Percent male gender for each group ISS < 20 vs ISS ≥ 20 was 89.6 vs 92.1% (p = 0.62). Mean ISS for each group was calculated to be 13.9 for the ISS < 20 group, and 32.8 for the ISS ≥ 20, (p < 0.0001). Mechanism of injury comparing a percentage of penetrating/blunt in ISS < 20 group vs ISS ≥ 20 was 72.4 vs 76.3% (p = 0.42) (Table 1).

<table>
<thead>
<tr>
<th>Table 1: Demographics</th>
<th>ISS &lt; 20</th>
<th>ISS ≥ 20</th>
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<tr>
<td>N (%)</td>
<td>29 (43.2)</td>
<td>38 (56.7)</td>
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</tr>
<tr>
<td>Age (SD)</td>
<td>33.3 (11.9)</td>
<td>35.8 (15.0)</td>
<td>0.78</td>
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<tr>
<td>Male gender</td>
<td>89.6%</td>
<td>92.1%</td>
<td>0.62</td>
</tr>
<tr>
<td>Mean ISS (SD)</td>
<td>13.9 (5.1)</td>
<td>32.8 (10.5)</td>
<td>0.0001*</td>
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<tr>
<td>Penetrating (%)</td>
<td>72.4%</td>
<td>76.3%</td>
<td>0.42</td>
</tr>
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</table>

Key: ISS— injury severity score; SD— standard deviation

Regarding intraoperative hemostatic DCR between groups, total transfused units of PRBC in the ISS < 20 group vs ISS ≥ 20 group was 26.0 ± 22.1 vs 20.5 ± 18.2; total transfused FFP units was 22.3 ± 19.6 vs 15.6 ± 16.2; and total transfused PLT was 10.1 ± 6.9 vs 6.7 ± 6.4. The mean PRBC-to-FFP ratio comparing ISS < 20 vs ISS ≥ 20 was 1:1.12 vs 1:1.3 (p = 0.12).
Initial laboratory analysis of the ISS < 20 group vs ISS ≥ 20 group, patients presented with a mean PTT of 32.9 ± 18.2 seconds vs 55.4 ± 43.2 seconds (p = 0.013), a hemoglobin of 10.8 ± 2.5 vs 9.8 ± 1.9 (p = 0.08), a mean INR of 1.2 ± 0.2 vs 1.8 ± 1.4 (p = 0.049), and a base excess of −3.0 ± 6.0 vs −3.6 ± 5.0 (p = 0.742). Patients with ISS < 20 vs ISS ≥ 20 presented with a mean initial fibrinogen of 357.4 ± 49.1 mg/dl vs 150.8 ± 47.1 mg/dl (p = 0.0001) (Table 2 and Fig. 1).

Table 2: Laboratory analysis, initial presentation

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<th>ISS &lt; 20</th>
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<td>PTT (SD)</td>
<td>32.9 (18.2)</td>
<td>55.4 (43.2)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Hgb (SD)</td>
<td>10.8 (2.5)</td>
<td>9.8 (1.9)</td>
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<tr>
<td>INR (SD)</td>
<td>1.2 (0.2)</td>
<td>1.8 (1.4)</td>
<td>0.049*</td>
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<tr>
<td>Base deficit (SD)</td>
<td>−3.0 (6.0)</td>
<td>−3.6 (5.0)</td>
<td>0.742</td>
</tr>
<tr>
<td>Fibrinogen (SD)</td>
<td>357.4 (49.1)</td>
<td>150.8 (47.1)</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

Key: PTT—partial thromboplastin; Hgb—hemoglobin; INR—international normalized ratio; SD—standard deviation

Additional laboratory values were again analyzed 6 hours after arrival. In an analysis of ISS < 20 group vs ISS ≥ 20 group, patients had PTT 30.7 ± 9.1 vs 45.0 ± 18.3 (p = 0.001), hemoglobin 11.4 ± 3.6 vs 9.5 ± 2.6 (p = 0.06), INR 1.3 ± 0.3 vs 1.6 ± 1.5 (p = 0.34), and base excess −0.5 ± 3.0 vs 0.6 ± 6.2 (p = 0.16). Serum fibrinogen 6 hours after presentation in ISS < 20 vs ISS ≥ 20 was 246.75 ± 112.5 vs 276.3 ± 135.8 (p = 0.07) (Table 3).

Table 3: Laboratory analysis, 6 hours postinjury

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<td>Fibrinogen (SD)</td>
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</tbody>
</table>

Key: PTT—partial thromboplastin; Hgb—hemoglobin; INR—international normalized ratio; SD—standard deviation

Calculation of Pearson product-moment coefficient for PTT, INR and base excess vs ISS showed no linear correlation between ISS and PTT (r = −0.027, p = 0.832), ISS and INR (r = −0.009, p = 0.946), or base excess and ISS (r = −0.093, p = 0.464). Calculation of the Pearson product-moment correlation coefficient for initial serum fibrinogen levels vs ISS yielded a value of −0.5635 with p = 0.0001.

A stepwise logistic regression evaluating the presenting initial variables of PT, INR, Hgb, calculated base excess and serum fibrinogen concentration found that of these, only initial fibrinogen levels were associated with mortality, having a significance level of p < 0.0001 (Graph 1). The resulting model yielded an odds ratio of 1.01 ± 0.087, an area under the receiver operating characteristic curve of 0.701. After DCR, patients with normal initial fibrinogen levels and ISS < 20 had an overall mortality of 29%, compared to those with low initial fibrinogen levels and ISS ≥ 20 with 73% overall mortality (p = 0.0007) (Graph 2).

**DISCUSSION**

Management of patients presenting with severe tissue injury and TIC remain clinically important. More severely injured trauma patients present with a greater degree of coagulopathy. This coagulopathy was demonstrated in our study with an abnormally high PTT/INR as well as a low initial serum fibrinogen concentration seen in patients with higher ISS. Initial serum fibrinogen was discovered to have a correlating inverse relationship with degree of injury and mortality. Better understanding and recognition of the significance of low fibrinogen levels could help improve future therapies toward the management of hyperfibrinolysis.
The mechanism for the development for hyperfibrinolysis involves the release of tissue plasminogen activator (tPA) and kallikrein-mediated plasmin activators following tissue injury. In part of a hemostatic balance, multiple inhibitors are also generated which include plasminogen activator inhibitor 1 (PAI-1), thrombin-activatable fibrinolysis inhibitor (TAFI), and α2-antiplasmin. Protein C is activated by thrombomodulin (TM) following injury and is also believed to promote release of tPA by consuming PAI-1, further activating plasminogen. Activation of plasminogen increases fibrinolysis, cleavage of fibrinogen to fibrin, resulting in a hyperfibrinolytic state (Flow Chart 1, columns 1 and 2).

Serum fibrinogen levels can also be affected by volume resuscitation strategies, acidemia, platelet interaction, and hypothermia. During volume replacement, the effect is primarily that of dilution, although hydroxyethyl starch solutions may directly cause impaired fibrin polymerization. Regarding production and breakdown of serum fibrinogen, acidemia increases fibrinogen breakdown with no effect on synthesis, while hypothermia to 32°C decreases synthesis of fibrinogen. As a multitude of cellular events occur after trauma, coagulopathy and bleeding worsen due to a dysregulated hemostatic balance postinjury.

Low fibrinogen serum levels were recorded at initial presentation in the ISS ≥ 20 group. Although these low fibrinogen levels normalized after DCR at 6 hours post-presentation, patients with ISS ≥ 20 had an overall higher mortality. Although the amount cryoprecipitate was not recorded in this study patients with ISS ≥ 20 received an average of 15.6 units of FFP during DCR yielding approximately 150 mg/dl of fibrinogen for a 70 kg individual. A normal, unstressed individual produces fibrinogen at an absolute synthesis rate of about 1.5 mg/dl/h, yielding approximately 9 mg/dl replenished over 6 hours. Therefore, the increase of serum fibrinogen levels 6 hours after presentation in the ISS ≥ 20 group is likely primarily due to effective DCR rather than patients’ own physiologic replenishment. Even though fibrinogen levels increased 6 hours after injury with DCR, the initial low fibrinogen level was a better predictor of mortality in patients with high ISS. Our study demonstrates that perhaps an adjunct to DCR is needed to decrease mortality in trauma patients with observed low fibrinogen levels seen with TIC.

The CRASH-2 trial prospectively addressed the effects of the hyperfibrinolysis through the pharmacologic inhibition of the activation of plasminogen to plasmin with tranexamic acid (TXA). Their results showed a decrease in all-cause
and bleeding-related mortality by 1.5%. Of notice in the CRASH-2 study, the degree of fibrinolysis was not quantified with laboratory findings and TXA was administered, if hemorrhage was clinically suspected, not necessarily proven. In a recent retrospective military study, MATTERS, patients requiring massive transfusion demonstrated a decrease in mortality when TXA was used in combination with component based therapy. They demonstrated an absolute reduction in in-hospital mortality of 13.7% and overall better 30-day survival. They also demonstrated an improvement in the coagulopathy profile when TXA was used. It is important to note that the patients that did not receive TXA and those that did receive TXA had an overall similar component-based resuscitation, indicating a pharmacological role in improving coagulopathy.

With findings from CRASH-2 and MATTERS, it could then be hypothesized that rapid correction of serum fibrinogen concentrations and its resultant role in clot stabilization, addressing TIC-related hyperfibrinolysis, plays a role in the survival benefit of DCR. Interestingly, an additional survival benefit was demonstrated in the MATTERS study after 48 hours, after surviving exsanguinating injuries. They conclude that TXA may have an additional protective role in the attenuation of inflammation, in addition to improving the coagulation profile (Flow Chart 1). Future prospective trials should focus in investigating the optimal resuscitation strategy consisting of component therapy in addition to antifibrinolytics pharmacotherapy in patients with severe tissue injury and low initial fibrinogen levels.

**CONCLUSION**

In our study, patients with severe tissue injury presented with below normal initial serum fibrinogen concentrations. Overall mortality was significantly increased in patients who had an ISS ≥ 20 with low initial fibrinogen level despite effective DCR. A decrease in this initial serum fibrinogen correlated with increased mortality even when other initial measures of coagulopathy, such as PTT and INR may not. Given the correlated decrease in fibrinogen levels in patients with severe tissue injury, further investigation regarding potential benefits of antifibrinolytic agents in DCR is warranted.

**REFERENCES**


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