The Incidence and Risk Factors for Hypofibrinogenemia in Patients with Traumatic Brain Injury Undergoing Surgery

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Abstract
Fibrinogen is the primary substrate of coagulation. Fibrinogen depletion occurs in acute traumatic coagulopathy and is associated with unfavorable outcomes. Fibrinogen levels also decrease following traumatic brain injury (TBI) due to hypothermia, acidosis, and hypoperfusion leading to hyperfibrinolysis. This study was conducted to identify risk factors and the incidence of hypofibrinogenemia following TBI and also its effect on perioperative complications and postoperative outcome. A total of 51 adult patients with TBI were included in the study, and 33.3% of them had hypofibrinogenemia. Patients with low fibrinogen levels had lower preoperative Glasgow Coma Score (GCS), had associated derangement of international normalized ratio (INR), received more blood transfusions, and had lower discharge GCS compared with those with normal fibrinogen levels. Patients with hypofibrinogenemia had higher incidence of repeat surgery. In conclusion, hypofibrinogenemia occurs commonly after TBI and is associated with poor outcomes.

Keywords
► traumatic brain injury
► hypofibrinogenemia
► coagulopathy

Background
Isolated traumatic brain injury (TBI) is frequently associated with coagulopathy with a high prevalence in the early and late phase of TBI, and it is a form of secondary insult. The incidence of coagulopathy varies in different studies based on the definition of coagulopathy used. According to a meta-analysis by Harhangi et al, the incidence is approximately 33%,¹ and increases up to 54% in the first 24 hours following trauma.² The presence of coagulopathy has been shown to be associated with increased risk of unfavorable outcomes. The etiology of coagulopathy is multifactorial and the possible mechanisms include release of tissue factor, hypoperfusion, hypothermia, and acidosis.

The levels of fibrinogen have been found to be reduced in experimental models of acute traumatic coagulopathy.³ Rourke et al have also shown that fibrinogen depletion occurs in acute traumatic coagulopathy and progresses during traumatic hemorrhage.⁴ Fibrinogen depletion was also associated with poor outcome and the outcomes improved with replacement therapy. There is paucity of literature on the occurrence of hypofibrinogenemia in TBI. In a study by Chhabra et al, the authors reported the incidence of hypofibrinogenemia to be 7% and was associated with poor outcome.⁵ The aim of this study was to determine the incidence and risk factors predicting hypofibrinogenemia, its effect on perioperative complications, and postoperative outcomes.

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Materials and Methods

Permission was obtained from institute's ethics committee prior to the conduct of this study. Patients with TBI presenting for surgery within 24 hours of trauma were prospectively included in the study. The following data were collected: patient demographics, time of injury, mode of injury, the intake of alcohol, computed tomographic (CT) diagnosis, preoperative Glasgow Coma Score (GCS), and pupillary reaction. The results of the following investigations performed were noted: pre- and postoperative hemoglobin, pre- and postoperative platelet count, blood urea, serum creatinine, serum bilirubin and hepatic enzyme levels, pre- and postoperative prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). After induction of anesthesia and before the start of surgery, 2 mL of blood was drawn for estimation of serum fibrinogen levels, and assessment of INR and PT was made using CoaguChek XS point-of-care monitor (Roche Diagnostics, Mannheim, Germany). The intraoperative estimated blood loss, crystalloids and colloids infused, and blood and blood products transfused were noted. Postoperatively, blood was collected for PT, INR, and aPTT. Patients were followed up for any repeat surgery, postoperative blood or blood product transfusion, length of hospital stay, and the discharge GCS.

Statistical Analysis

Serum fibrinogen level ≤ 200 mg/dL was considered as a cutoff to define hypofibrinogenemia. Patients with hypofibrinogenemia were compared with those who had normal fibrinogen levels and patients with poor outcome were compared with those with good outcome. Patients who died and those with motor score of GCS < 2 were taken as poor outcome. The continuous variables were compared using Mann-Whitney U test and categorical variables using chi-square or Fisher exact test between the two groups. A p value of < 0.05 was considered significant.

Results

A total of 51 patients were recruited for the study. Table 1 shows the patient characteristics and average values of the various parameters across the entire cohort.

Of the 51 patients, 17 patients (33.3%) had fibrinogen levels ≤ 200 mg/dL. On comparing patients with low fibrinogen levels and normal fibrinogen levels, patients with hypofibrinogenemia were younger, had lower preoperative GCS, received more number of blood transfusions, and had lower discharge GCS as shown in Table 2.

There was no difference between the two groups regarding sex, the influence of alcohol, the number of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypofibrinogenemia group (n = 17) Mean (SD)</th>
<th>Normal fibrinogen group (n = 34) Mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.18 (6.85)</td>
<td>40.26 (13.04)</td>
<td>0.009*</td>
</tr>
<tr>
<td>Preoperative GCS</td>
<td>8.06 (3.8)</td>
<td>10.76 (3.37)</td>
<td>0.016*</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>634 (276)</td>
<td>616 (305)</td>
<td>0.620</td>
</tr>
<tr>
<td>Crystalloids infused (mL)</td>
<td>2,470 (599)</td>
<td>2,415 (704)</td>
<td>0.748</td>
</tr>
<tr>
<td>Colloids infused (mL)</td>
<td>543 (113.4)</td>
<td>500 (0.00)</td>
<td>0.173</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>8.3 (10)</td>
<td>4.2 (3.2)</td>
<td>0.494</td>
</tr>
<tr>
<td>Discharge GCS</td>
<td>10.2 (4.2)</td>
<td>13.1 (2.1)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Blood transfusion (No. of units)</td>
<td>3.6 (1.9)</td>
<td>1.8 (1)</td>
<td>0.011*</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Scale; SD, standard deviation.

*p value < 0.05.
patients who underwent tracheostomy, those who did not survive, pre- or postoperative thrombocytopenia, liver dysfunction, and the number of patients who had deranged PT or aPTT. However, the number of patients who had deranged INR and those who underwent redo surgery were different between the groups (►Table 3).

There were nine patients with poor outcome and they were compared with those with good outcome (n = 42) on variables such as age, duration between trauma and surgery, preoperative GCS, estimated blood loss, amount of blood transfusion, fibrinogen levels, preoperative INR, and redo surgery as shown in –Table 4. We found that delay in surgery, low preoperative GCS, increased blood transfusion, low fibrinogen levels, any redo surgery, and deranged INR were predictors of poor outcome after TBI. However, owing to small numbers, the multivariate analysis did not yield meaningful results.

**Discussion**

The incidence of hypofibrinogenemia in our study was 33%. In a study by Chhabra et al, the incidence was 7% in patients with isolated TBI.5 In another study by Rourke et al, hypofibrinogenemia (< 200 mg/dL) was present in 40% of trauma patients.4 Fibrinogen is a 340-KD glycoprotein synthesized in the liver. It is converted by thrombin into fibrin monomers. It is the primary substrate for hemostasis and is the first factor to decrease critically following major blood loss. To maintain the integrity of coagulation function, it is recommended that fibrinogen be replaced when levels fall below 150 to 200 mg/dL.

Fibrinogen levels in patients with trauma could be affected by ongoing hemorrhage, hypothermia, or acidosis. Metabolic acidosis impairs thrombin generation and causes hyperfibrinolysis. Hypothermia causes decreased fibrinogen synthesis and impairs thrombin generation. Hypoperfusion activates protein C resulting in impaired clot generation and fibrinolysis. Hyperfibrinolysis decreases fibrin and fibrinogen levels.6 Trauma-mediated immune modulation may also contribute to coagulopathy.7

In a study to determine the admission variables to predict hypofibrinogenemia, the authors found that Triage-Revised Trauma Score (T-RTS) and prehospital fluid therapy were independent predictors of hypofibrinogenemia in blunt trauma victims. T-RTS along with serum fibrinogen levels predicted 7-day mortality.8 We found that the preoperative GCS was lower in patients with low fibrinogen levels. The severity of head injury is probably a good predictor for hypofibrinogenemia. Therefore, we postulate that in severe TBI, the low fibrinogen levels can worsen the coagulopathy, leading to increased hemorrhage and resulting in increased blood transfusion intraoperatively. The hemorrhage may further decrease the fibrinogen levels and a vicious cycle may ensue. This may have a significant effect on postoperative outcomes. In this study, we found an increased requirement for blood transfusion in patients with hypofibrinogenemia and low discharge GCS. There was no difference in estimated blood loss because it was a subjective assessment by the treating anesthesiologist. There was no increase in the length of stay, as several logistic factors such as financial constraints and bed availability could determine the decision to discharge a patient early.

**Table 3** Comparison of hypofibrinogenemia group with normal fibrinogen level group (categorical variables)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low fibrinogen level group (n)</th>
<th>Normal fibrinogen level group (n)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redo surgery (Yes:no)</td>
<td>4:13</td>
<td>0:34</td>
<td>0.01*</td>
</tr>
<tr>
<td>INR ≥1.3</td>
<td>3:8</td>
<td>0:23</td>
<td>0.028*</td>
</tr>
</tbody>
</table>

Abbreviation: INR, international normalized ratio.

*p value < 0.05.

**Table 4** Comparison of patients with good outcome versus those with poor outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD/% of patients</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good outcome</td>
<td>Poor outcome</td>
</tr>
<tr>
<td>Age (y)</td>
<td>37 ± 12.7</td>
<td>37 ± 9.6</td>
</tr>
<tr>
<td>Time between trauma and surgery (h)</td>
<td>14 ± 6.7</td>
<td>7 ± 5.2</td>
</tr>
<tr>
<td>Preoperative GCS</td>
<td>10.6 ± 3.4</td>
<td>6.3 ± 3</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>617 ± 298</td>
<td>650 ± 282</td>
</tr>
<tr>
<td>Total blood transfusion (units)</td>
<td>1.8 ± 0.857</td>
<td>3.8 ± 2.13</td>
</tr>
<tr>
<td>Fibrinogen level (low/high)</td>
<td>26/74</td>
<td>67/33</td>
</tr>
<tr>
<td>Redo surgery (no/yes)</td>
<td>98/2</td>
<td>67/33</td>
</tr>
<tr>
<td>Preoperative INR (normal/prolonged)</td>
<td>97/3</td>
<td>60/40</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Scale; INR, international normalized ratio; SD, standard deviation.

*p value < 0.05.
We also compared patients who had good outcome versus those with poor outcome and found that in addition to known factors such as preoperative GCS, increased blood transfusion, delay in surgery, and coagulopathy, low fibrinogen levels and redo surgery are associated with poor prognosis.

In a study involving 260 critically ill patients requiring massive transfusion, it was found that patients with fibrinogen level < 100 mg/dL had significantly increased in-hospital mortality (51.9 vs. 18.5%) compared with those with normal levels of fibrinogen. Critically low fibrinogen level was the most important predictor of mortality. In our study, we found that patients with low fibrinogen levels developed postoperative hematomas requiring reexploration. Based on this finding, we recommend close neurologic monitoring and repeat CT scan in patients with low fibrinogen levels. In our study, results of serum fibrinogen levels were not available for at least 3 days postoperatively as it was not a point-of-care test. Therefore, the management of patients could not be targeted to fibrinogen levels. However, we did not find increased mortality in this group of patients due to aggressive intraoperative management and postoperative care in the neurologic intensive care unit (ICU).

Rourke et al found that outcomes tend to improve with increasing total amounts of fibrinogen administered. Patients who received cryoprecipitate maintained their fibrinogen levels and had lower mortality rates than those who did not. Both cryoprecipitate and fibrinogen concentrate were effective at reversing traumatic coagulopathy.

The first limitation of our study is its small sample size due to financial issues pertaining to the test. Second, the results of serum fibrinogen levels were not available till at least 3 days postoperatively, as it was not a point-of-care test. The test was performed in the laboratory, based on immunoturbidimetry, by measuring antigen antibody reaction by end point method.

In conclusion, the early recognition and diagnosis of hypofibrinogenemia with replacement of fibrinogen has the potential to rapidly reverse trauma-induced coagulopathy and improve outcomes.

Note
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Contribution of Each Author
Sonia Bansal was responsible for data collection, compiling, and manuscript preparation. Rohini M. Surve and Nitin Manohar were responsible for data collection. Mariamma Philip was responsible for application of statistical methods; Bhadri V. Narayan for revision of the content and final approval of the version to be published; and B. Indira Devi for manuscript correction and editing. The article has been read and approved by all the authors, and requirements for authorship have been met.

References