Case Report
High Dose, Prolonged Epsilon Aminocaproic Acid Infusion, and Recombinant Factor VII for Massive Postoperative Retroperitoneal Hemorrhage following Splenectomy

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The antifibrinolytic agent ε-aminocaproic acid is used to decrease procedural blood loss in a variety of high risk surgeries. The utility of recombinant factor VII administration in massive hemorrhage has also been reported in a variety of settings, though the impact in a surgical context remains unclear. We describe the case of a patient who underwent massive open splenectomy and developed diffuse retroperitoneal bleeding on postoperative day one. Massive transfusion was initiated, but attempts to control hemorrhage with surgical and interventional radiology approaches were unsuccessful, as was recombinant factor VII administration. Commencement of a high dose aminocaproic acid infusion led to resolution of the hemorrhage, resulting in delivery of a large cumulative dose without evidence of adverse effects.

1. Introduction

ε-Aminocaproic acid is an antifibrinolytic agent used to decrease blood loss in surgeries with a high risk of severe hemorrhage. We present a case of massive bleeding occurring after open splenectomy. Multiple attempts to control the source surgically were unsuccessful, and bleeding continued despite massive transfusion of blood products and administration of recombinant factor VII. Initiation of a prolonged infusion of ε-aminocaproic acid led to resolution of the hemorrhage, resulting in delivery of a large cumulative dose without evidence of adverse effects.

2. Case Description

A 55-year-old man suffering from mixed myeloproliferative neoplasm (MPN) and myelodysplastic syndrome (MDS) who developed massive hepatosplenomegaly (Figure 1), anemia, and thrombocytopenia was scheduled to undergo palliative splenectomy. He had been treated with hydroxyurea for MPN/MDS overlap syndrome for years, before transforming to overt MDS with extramedullary hematopoiesis and excess blasts. His spleen had been enlarged to a cranio-caudal length of 32 cm (Figure 1), causing abdominal pain, decreased oral intake, and a repetitive requirement for platelet transfusion. Removal of the organ was planned to relieve these symptoms while evaluation for allogeneic bone marrow transplantation was underway.

Due to anticipated heavy intraoperative hemorrhage, interventional radiology consultation was sought and a splenic artery embolization was performed a day preoperatively. Hematology consultation was also obtained by the surgical service, to address whether the patient’s hematologic diagnosis might increase his risk of a consumptive coagulopathy to complicate the already high risk for surgical bleeding and if this could be addressed with any preoperative therapeutic intervention. Hematology consultants recommended commencement of a low dose ε-aminocaproic acid (E-ACA) infusion at a rate of 1 g every 6 hours to antagonize anticipated fibrinolysis. After transfusion of two units of platelets and two units of packed red blood cells (PRBCs) prior to surgery, his platelet count was 42,000/µL with a hematocrit (Hct) of 25.9.

Intraoperatively the patient sustained an estimated blood loss of three liters and he received platelets, PRBCs, and
plasma. Postoperatively he remained intubated due to concern for large fluid shifts resulting in airway and facial edema. He was transferred to the surgical intensive care unit (SICU). Three intraperitoneal Jackson-Pratt drains were placed during the procedure. His postoperative Hct was 24.4.

On the evening of postoperative day (POD) 1 the patient became hypotensive with systolic blood pressure in the 60–70 mmHg range. Several hundred milliliters per hour (mLs/hr) of frank bloody output came from the surgical drains and his hematocrit decreased to 19. Massive transfusion with PRBCs and FFP was initiated, and the patient was taken emergently to interventional radiology for attempt at further embolization of the mesenteric arterial circulation. However, no extravasation of blood was found from any arterial source and no embolization targets were identified. The patient returned to the SICU where he continued to have profuse bloody drainage averaging 200 mLs/hr. On the morning of POD 2 he received emergent exploratory laparotomy. Surgical exploration revealed diffuse retroperitoneal hemorrhage from extensive friable tissue and small vessel venous injury along the splenic bed, confirming lack of a major arterial source. Despite diffuse small vessel cautery and ligation throughout the retroperitoneal surface, he continued to produce 100–200 mLs/hr of bloody fluid into the JP drains. At this point his transfusion regimen included 14 units of PRBCs, 9 units of fresh frozen plasma (FFP), 4 units of platelets, 1 unit of cryoprecipitate and 5 mg of recombinant factor VII.

Following a recommendation from consulting hematologists, a second dose of recombinant factor VII was given. When bleeding persisted, a 5 g E-ACA loading dose was administered two hours later followed by a 1 g/hr continuous infusion. Within the next few hours, there was a decrease in the bloody surgical drain output to less than 50 mLs/hr. Plasma fibrinogen levels rose from 211 mg/dL to 475 mg/dL over the next day without any additional transfusion of FFP or cryoprecipitate (Table 1). The high dose E-ACA infusion was continued through all of POD 3, during which only one additional PRBC and two platelet units were transfused. Fibrinogen levels continued to be supranormal ranging between 504 and 541 mg/dL. By POD 4 the hemorrhage resolved as hematocrit stabilized at 27-28 and drain output was minimal. No further blood products were transfused. At this point, E-ACA was decreased to 1 g q3 h. On POD 5 E-ACA was discontinued and the patient was successfully extubated. Fibrinogen levels decreased to a normal value of 327 mg/dL within 4 hours after termination of the E-ACA

### Table 1: Postoperative transfusion requirements and degree of hemorrhage.

<table>
<thead>
<tr>
<th></th>
<th>Hematocrit (%)</th>
<th>Platelets (K/μL)</th>
<th>INR</th>
<th>Fibrinogen (mg/dL)</th>
<th>Postoperative blood products (cumulative)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline (2 hours preop)</strong></td>
<td>25.9</td>
<td>42</td>
<td>1.2</td>
<td>361</td>
<td></td>
</tr>
<tr>
<td><strong>Postoperative hour</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>12 hours</td>
<td>24.4</td>
<td>76</td>
<td>1</td>
<td>363</td>
<td>0</td>
</tr>
<tr>
<td>20 hours</td>
<td>23.3</td>
<td>62</td>
<td>1.1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>28 hours(^1)</td>
<td>19.1</td>
<td>39</td>
<td>1.3</td>
<td>259</td>
<td>6</td>
</tr>
<tr>
<td>36 hours</td>
<td>17</td>
<td>61</td>
<td>1.4</td>
<td>211</td>
<td>9</td>
</tr>
<tr>
<td>44 hours(^2)</td>
<td>25.9</td>
<td>70</td>
<td>1.3</td>
<td>282</td>
<td>14</td>
</tr>
<tr>
<td>52 hours(^3)</td>
<td>25.9</td>
<td>99</td>
<td>1.1</td>
<td>341</td>
<td>16</td>
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<tr>
<td>60 hours</td>
<td>24.7</td>
<td>73</td>
<td>1.3</td>
<td>388</td>
<td>18</td>
</tr>
<tr>
<td>68 hours</td>
<td>26.5</td>
<td>46</td>
<td>1.2</td>
<td>475</td>
<td>19</td>
</tr>
<tr>
<td>76 hours(^4)</td>
<td>28</td>
<td>117</td>
<td>1.2</td>
<td>541</td>
<td>19</td>
</tr>
<tr>
<td>100 hours(^5)</td>
<td>28.2</td>
<td>132</td>
<td>1.1</td>
<td>327</td>
<td>19</td>
</tr>
</tbody>
</table>

\(^1\) Massive hemorrhage identified. Factor VII given.
\(^2\) 2nd dose of factor VII and 5 g aminocaproic acid load.
\(^3\) Continuous aminocaproic acid infusion at 1 g/hr.
\(^4\) Aminocaproic acid infusion decreased to 1 g/3 hrs.
\(^5\) Four hours after aminocaproic acid infusion discontinued.
infusion. Renal function remained remarkably intact despite the hemodynamic instability and acute anemia that had occurred in the preceding days, as evidenced by a creatinine level of 0.37 mg/dL on POD 5. He was transferred out of the ICU on POD 7 and recovered uneventfully thereafter. No thromboembolic sequelae developed during hospitalization. He underwent allogeneic stem cell transplantation for MPN/MDS approximately a month after his discharge from intensive care.

3. Discussion

ε-Aminocaproic acid is a lysine analogue first described in the literature in 1957 for its antifibrinolytic properties [1]. It is one of the two lysine analogue fibrinolysis inhibitors used widely in current practice to decrease intraoperative blood loss for a variety of surgeries with elevated risk for significant hemorrhage, the other being tranexamic acid (TXA). A third antifibrinolytic agent, aprotinin, formerly enjoyed wide use particularly in cardiac surgery but was withdrawn by its manufacturer in 2008 after studies suggesting an association with increased incidence of myocardial infarction [2] and postoperative mortality [3].

E-ACA exerts its therapeutic action via inhibition of the serine protease plasmin, the principle agent in the native fibrinolytic process. Lysine analogues such as E-ACA and TXA are exogenous competitive inhibitors of plasmin’s proteolytic degradation of fibrin and also competitively inhibit the activity of plasminogen activators [4]. These analogues appear to bind to sites on plasminogen that would ordinarily attach to lysine residues on fibrin. The overall result is lower rates of fibrin dissolution and a more stable pace of thrombogenesis.

The 2015 American Society of Anesthesiologists’ (ASA) guidelines on perioperative blood loss management ascribes a Category A1 level of evidence (sufficient randomized controlled trials to support meta-analysis) favoring the use of intraoperative antifibrinolytic therapy in the perioperative setting to decrease blood loss and blood product transfusions in major cardiac, major orthopedic, and liver surgery [5]. A Cochrane meta-analysis suggests that the attributable loss for a variety of surgeries with elevated risk for significant hemorrhage that we observed clinically. While the exact mechanism for the elevation in fibrinogen level with E-ACA has never been clearly elucidated, we could hypothesize this to be a result of the lysine analogue’s effect in antagonizing the breakdown of polymerized fibrin by plasmin, which in turn decreases the exposure of the circulation to areas of tissue injury that would trigger the contact activation pathway for thrombin activity. This decreased activation of thrombin could in turn lead to decreased conversion of fibrinogen into fibrin polymer and elevation of plasma fibrinogen levels. We acknowledge that one of the limitations of our conclusion about the role of E-ACA in this case is the lack of a more detailed coagulation assay, such as thromboelastography (TEG), that might have more clearly exposed some of the changes brought on by antifibrinolytic therapy. We do note, however, that TEG analysis is not routinely used in most clinical situations to guide antifibrinolytic administration. In
this case, our decision to taper and ultimately discontinue the drug was guided clinically by a decrease of the bloody drainage output, lack of further need for blood product transfusion, and stability in the hematocrit level over several hours after the last PRBC transfusion.

Our case is notable for illustrating the crucial contribution that antagonizing the fibrinolytic pathway can have in treating severe hemorrhage from diffuse, surgically uncontrollable sources. Also interesting is that, in our patient, the cumulative dose of E-ACA over 5 days amounted to over 70 grams, substantially greater than the typical 10–25 g given in the cardiac surgery setting. While thromboembolic sequelae are a dreaded potential complication of antifibrinolytic therapy, our experience here is in accord with a general lack of findings in the wider clinical literature to suggest that E-ACA substantially increases pulmonary, coronary, cerebrovascular, or venous thromboembolism. In our case, a large dose of E-ACA was administered for a particularly precarious state of hemorrhage with poor prospects for interventional source control, with no resulting adverse hemotologic, neurologic, or renal outcomes.

In conclusion, we would urge providers to consider targeting the fibrinolytic pathway through an antifibrinolytic agent such as E-ACA in situations of massive hemorrhage from diffuse bleeding sources that are poorly amenable to procedural ligation. Augmentation of the coagulation cascade with recombinant factor VII, such as that we used in this case, while not strictly evidence based, may be of utility also in these difficult to salvage scenarios. The possibility of inadvertent overtreatment and precipitation of thrombotic disease is a rational concern; however, the literature supports the safety of E-ACA in high risk surgical bleeding. Our case illustrates that even large cumulative doses of the drug can be administered safely with good efficacy. Furthermore, while the preponderance of clinical data on E-ACA consists of studies on intraoperative administration to decrease procedural blood loss, we have here presented a case where it was successfully used to treat postoperative hemorrhage. We surmise that further studies may be warranted to evaluate the potential role of antifibrinolytic therapy in applications beyond the operating room setting.

Competing Interests

The authors attest that they have no conflict of interest or financial disclosures of relevance to the manuscript.

References


