Case Report

Role of Recombinant activated factor VII in securing Haemostatic failure in gun Shot Trauma

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Abstract

Uncontrolled bleeding is the leading cause of mortality in the trauma victims. Massive bleeding after traumatic injury is a result of surgical and coagulopathic bleeding. We describe a case of gun shot injury brought to the hospital in a collapsed state because of massive blood loss in the abdominal cavity. Surgical intervention secured the surgical bleeding but coagulopathic bleeding continued which was controlled with Recombinant activated factor VII (rFVIIa). Guidelines of the use of factor VII in trauma are presented.

Introduction

Uncontrolled massive haemorrhage is the leading cause of early death in 5% of the victims of military and civilian trauma.1,2 Massive haemorrhage after traumatic injury is a combination of surgical and coagulopathic bleeding.3 Surgical bleeds originate from a recognizable source at the site of surgery, or trauma while coagulopathic bleeding results from impaired thrombin generation. Coagulopathy develops early after injury and is present in 25-36% of trauma victims upon admission to the emergency department.2,3

The mechanism of coagulopathy in trauma is complex and includes: dilutional coagulopathy, hypothermia, acidosis, hyperfibrinolysis, anaemia-induced and consumption coagulopathy, induced by exposure of tissue factor (TF) at the site of injury, leading to activation of the coagulation cascade at this site.4 This process results in laboratory findings resembling disseminated intravascular coagulation (DIC), such as prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), low levels of platelets and fibrinogen, and high levels of D-dimers and other markers of coagulation and fibrinolysis activation.4 Recently, role of red blood cells (RBC) has been identified in mechanical and biochemical functions in the coagulation process.5-7 It has been shown that reduction of the haematocrit (Hct) inhibits platelet adhesion and aggregation, e.g. Hct of 20% restricts aggregation to a degree similar to that observed with 2x10⁹/l. Therefore, anemia causes prolongation of the bleeding time, which can be corrected with a RBC transfusion.5,6

Conventional treatment of coagulopathic bleeding involves administration of blood components e.g. red cell concentrates, fresh frozen plasma (FFP), cryoprecipitate, and platelets. However, such replacement therapy is associated with increased risks of complications such as possibility of errors leading to ABO incompatible red cell transfusion, transfusion related acute lung injury, multi-organ dysfunction syndrome, and transmission of infectious agents (e.g. viruses, bacteria, prions).4 Few patients fail to show arrest of coagulopathic bleeding. This emphasizes the need for additional pro-haemostatic drugs like antifibrinolytic agents which reduce blood requirements in various types of
surgery (e.g. cardiac, hepatic, orthopaedic). Recombinant activated factor VII (rFVIIa) (Novo Seven; Novo Nordisk A/S, Bagsvaerd, Denmark) was approved by the U.S. Food and Drug Administration for the prevention and treatment of bleeding episodes in haemophilic patients with inhibitors to coagulation factor VIII or factor IX and in acquired haemophilia. Since the first report in 1999 of the use of rFVIIa in an exsanguinating trauma patient, an increasing number of case series and reports have described its efficacy in controlling massive haemorrhage.2,3,8

The recently developed cell base model of coagulation suggests rFVIIa enhances haemostasis at the site of injury without a systemic, hypercoagulable effect.10 Administration of pharmacological dose of rFVIIa results in a huge increase of VIIa level causing faster and higher thrombin generation. In addition, pharmacological concentrations of rFVIIa initiate the activation of a platelet dependent TF-independent mechanism that augments the coagulation process.11-13 Furthermore, in vitro analysis of the fibrin clots formed in the presence of a high thrombin concentration has shown that such clots have a different type of architecture that is stronger and far more resistant to degradation by fibrinolytic enzymes compared with normal clots. On this background, here we describe to our knowledge first case report from Pakistan using rFVIIa to control massive haemorrhage following gun shot injury.

Case Report

A 32 years old male with no known co-morbid factors was brought to the emergency room of a secondary care hospital with a gun shot injury. His blood pressure and pulses were not recordable and he was bleeding profusely from the site of the wound. The patient was awake and there was no focal deficit. Laboratory tests on presentation, Hb 7gm./dl, WBC count 8.9x10^9/l and platelet count 387x10^9/l. Renal functions and serum electrolytes were normal. After initial resuscitation in the emergency room, he was shifted to operation theatre where exploratory laparotomy was done. Per operatively, approximately 2 litres of blood was removed from peritoneal cavity, there was a perforation in descending colon and multiple small perforations were seen in small bowel. Mesenteric tear and retroperitoneal haematoma were also noted. Resection anastomosis was done, mesenteric tear repaired, peritoneal cavity was lavaged with saline and 2 drains were placed. Perioperatively, 9 units of whole blood and 4 units of FFP were given. Post operatively, he continued to bleed through the abdominal drains at a rate of 200-250 ml per hour. Dressing packs continued to soak and were changed 4-5 times during the next 48 hours. He maintained adequate urine output. The patient underwent second exploratory laparotomy 48 hours, later where generalized ooze was seen in the peritoneal cavity without any major bleeder. Post-operatively, the patient continued to bleed and the drain bags continued to accumulate blood at 200ml per hour. He was put on the ventilator. On 3rd day after gun shot injury, the patient was still bleeding profusely and had received 40 units of blood and FFP. At 7:00 pm, rFVIIa was given to the patient at a dose of 90 ug/kg over a period of 5 minutes. Table highlights the laboratory parameters and blood loss before and after the use of rFVIIa. The patient's vitals and

<table>
<thead>
<tr>
<th>Day post-op</th>
<th>Hb (gm/dl)</th>
<th>Plt x10^9/l</th>
<th>PT (in seconds)</th>
<th>APTT (in seconds)</th>
<th>Drains (mls)</th>
<th>Blood Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.7</td>
<td>150</td>
<td>18 / 13</td>
<td>42 / 30</td>
<td>2100 blood</td>
<td>25 units whole blood</td>
</tr>
<tr>
<td>2</td>
<td>5.5</td>
<td>120</td>
<td>16 / 13</td>
<td>38 / 30</td>
<td>1955 blood</td>
<td>15 units FFP</td>
</tr>
<tr>
<td>3</td>
<td>9.1</td>
<td>120</td>
<td>17 / 13</td>
<td>39 / 30</td>
<td>1140 blood</td>
<td></td>
</tr>
<tr>
<td>4 (7:00 pm)</td>
<td>7.5</td>
<td>115</td>
<td>13 / 13</td>
<td>34 / 30</td>
<td>emptied</td>
<td>rFVIIa 5.8 mg iv given</td>
</tr>
<tr>
<td>4</td>
<td>7.1</td>
<td>169</td>
<td>12 / 13</td>
<td>28 / 30</td>
<td>140 serous</td>
<td>No blood</td>
</tr>
<tr>
<td>5</td>
<td>6.7</td>
<td>182</td>
<td>13 / 13</td>
<td>29 / 30</td>
<td>245 serous</td>
<td>2 units top up packed red cells given</td>
</tr>
<tr>
<td>6</td>
<td>9.3</td>
<td>188</td>
<td>13 / 13</td>
<td>30 / 30</td>
<td>124 serous</td>
<td></td>
</tr>
</tbody>
</table>

Day post-op; day after first laparotomy, Hb; haemoglobin, Plt; platelet count, PT; prothrombin time, APTT; activated partial thromboplastin time, FFP; fresh frozen plasma
bleeding were developed. These advocate the use of rFVIIa in cases of uncontrolled thrombosis), appropriate replacement therapy (FFP: 10-15 ml/kg, cryoprecipitate 1-2 U/10 kg, platelets 1-2 U/10 kg), correction of acidosis (defined as pH >7.2) and warming of hypothermic patients. rFVIIa should be administered as early as possible (after conventional treatments have failed to arrest bleeding), and should be given in conjunction with transfusion of 8-10 U of packed RBC in order to avoid further loss of clotting factors, exacerbation of acidosis, and further lowering of body temperature.

The recommended initial dose of rFVIIa for treatment of massive bleeding is 100-140 ug/kg administered intravenously over 2-5 min. If haemorrhage persists beyond 15-20 min, following the first administration of rFVIIa, an additional dose of 100 ug/kg should be considered. If the response remains inadequate following a total dose of >200 ug/kg the preconditions for rFVIIa administration should be re-checked, if possible, and corrected as necessary before a third dose is considered. Currently, there is no laboratory method for monitoring the effect of rFVIIa. The best available indicator of rFVIIa efficacy is the arrest of haemorrhage judged by visual evidence, haemodynamic stabilization and a reduced demand for blood components. The PT is expected to shorten, frequently below the normal expected range (as there is TF in the test tube), but this does not reflect efficacy.

In this case rFVIIa maintained haemostasis effectively when all the medical and surgical means to control bleeding exhausted. This was life saving and the case was monitored for possible complications like thrombo-embolic episode which has been reported as a side effect of its use. The use of this novel haemostatic agent should be well controlled. Trauma guidelines and management of haemostatic failure in trauma guidelines should be strictly followed in order to use rFVIIa appropriately. Trauma injuries have a complex pathophysiology; irrational use of this haemostatic agent may harm the patient rather than doing any good. A haematologist’s advice should be sought before making any decision of its use.

References


