The Use of Recombinant Coagulation Factor VIIa (NovoSeven®) in Severe Diverticular Bleeding

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Abstract: We report a 68-year-old man with sigmoid colon carcinoma who previously underwent an anterior resection. Five years later, he developed a severe diverticular bleeding which required multiple blood transfusions. He underwent an emergent low anterior colectomy with a right colostomy to protect the anastomosis. Nine days after the operation, he had another severe bleeding. Due to his elderly age and two previous colectomies, recombinant coagulation factor VIIa (rFVIIa) was given to avoid re-operation. The bleeding stopped after two doses of rFVIIa, 80 µg/kg followed by 40 µg/kg one hour later. There was no bleeding recurrence.

Keywords: Gastrointestinal hemorrhage, diverticulum, colon, rFVIIa, NovoSeven®.

INTRODUCTION

Diverticular bleeding is a common cause of major lower gastrointestinal tract bleeding in the elderly [1,2]. Bleeding occurs in 15% of patients with diverticulosis and it is estimated to be the source of 30% to 50% of massive colonic bleeding [3-5]. In most patients, the bleeding stops spontaneously; however, the risk of re-bleeding is approximately 30% after the first bleeding and increases to 50% after the second bleeding [5]. Continuous massive bleeding in a patient whose hemodynamic status is unstable is an indication for an emergent operation, which may be associated with high morbidity and mortality due to the elderly age of most patients [5].

Recombinant coagulation factor VIIa (rFVIIa; NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) is a hemostatic agent licensed for the treatment or prevention of bleeding in patients with haemophilia A or B with inhibitors to coagulation factor VIII or IX. Anecdotal data has shown that rFVIIa has successfully provided hemostasis in several other conditions associated with profuse bleeding, including surgery [6-10]. To the best of our knowledge, no literature on the use of rFVIIa in patients with diverticular bleeding has previously been published. We report an elderly patient with a severe diverticular bleeding who underwent a low anterior colectomy with a right colostomy. The bleeding recurred after the operation and was successfully treated with rFVIIa.

CASE

A 68-year-old man presented with severe rectal bleeding. Five years ago, the patient was diagnosed as having sigmoid colon carcinoma with TNM (tumor-node-metastasis) staging pT3 pN0 M0 and also a diverticular disease of all the colon, he underwent an anterior resection. He developed post-operative rectal bleeding possibly from diverticula, and required transfusion of six units of red blood cells and two units of fresh frozen plasmas. The bleeding stopped spontaneously. Due to the patient’s clinical condition, no investigation was carried out to confirm the diagnosis.

On the current admission, diverticula in descending colon were identified by colonoscopy as the source of bleeding. Despite receiving six units of red blood cells and two units of fresh frozen plasma in six hours, his hemoglobin level decreased from 12.5 g/dl at the time of admission to 9.3g/dl. Results on coagulation tests were within normal ranges (Quick, INR, PTT). As the bleeding continued and the patient’s hemodynamic status was unstable, an emergent laparotomy was carried out six hours after admission. A low anterior colectomy, with resection of the descending colon until the proximal rectum including the old anastomosis, was made. The low anastomosis was protected with a right colostomy. He was transfused with six units of red blood cells and four units of fresh frozen plasma during and immediately after the operation. Postoperatively, he also received low-molecular-weight heparin (certoparin) 3000 IU per day as a routine prophylaxis for thromboembolism.

The patient’s recovery was uneventful until day 9 post-operatively when he developed severe rectal bleeding, and was retransferred to the intensive care unit. Colonoscopy revealed a large amount of blood clots but the bleeding site could not be seen. An angiography of superior mesenteric artery showed a bleeding near to the transverse-colon-rectal anastomosis. We suspected another diverticulum as the source of bleeding. The patient was transfused with six units of red blood cells and four units of fresh frozen plasma in 16 hours, but the bleeding did not decrease. His hemoglobin level decreased from 10.1 to 7.9 g/dl; Factor VIII was minimally elevated, other coagulations tests (Quick, INR, PTT, Fibrinogen, Factor V, von Willenbrand Factor and Antiplasmin) were normal. As the patient was considered high-risk, elderly age with previous anterior and low anterior resections, a re-laparotomy with colo-anal anastomosis for reconstruction would have a very low chance of success and high morbidity. Furthermore, a definitive colostomy would also have a high morbidity and would affect the patient’s quality of life. Therefore, we decided to avoid surgical inter-
vention. We used rFVIIa as a last attempt to avoid re-operation. An intravenous bolus injection of 80 μg/kg rFVIIa (NovoSeven®, Novo Nordisk A/S, Bagsvaerd, Denmark) was given, followed by a second dose of 40μg/kg one hour later. At now no fresh blood was seen in the stool and the bleeding stopped completely without recurrence. No further blood transfusions were required. The next day Fibrinogen was light elevated and other coagulations tests (Quick, INR, PTT) were normal. There were no adverse events related to the use of rFVIIa. The patient was discharged from the hospital 17 days after the operation. Six months later, a follow-up barium enema and colonoscopy revealed a normal functioning anastomosis, and the protective colostomy was removed.

DISCUSSION

Severe diverticular bleeding in the elderly can be difficult to manage. Surgical intervention may be associated with high morbidity and mortality rates due to the underlying conditions of these patients. Therefore, hemostatic treatment that can avoid surgical intervention would be beneficial. Recombinant coagulation factor VIIa has been successfully used to control severe bleeding or reduce the need of blood transfusions in several surgical conditions, including liver transplantation, retropubic prostatectomy, and post-surgical intra-abdominal bleeding [6,8-10]. To the best of our knowledge, our patient is the first case of severe diverticular bleeding successfully treated with rFVIIa.

In the normal population, about 1% of circulating FVII is in the form of FVIIa; but, in the absence of tissue factor, activated FVIIa does not initiate coagulation. In pharmacological doses of FVIIa, the amount of FVIIa administered is very high. Even this amount of activated clotting factor does not result in clotting in the absence of functional tissue factor. The data suggest that the action of FVIIa is localized to the site of bleeding [11,12]. The hypothesis is that tissue factor is exposed at the site of bleeding, and this is sufficient to initiate coagulation. Factors V and X are activated, resulting in the formation of tiny amounts of thrombin sufficient to activate platelets. At the pharmacological doses of FVIIa given for bleeding episodes, all tissue factor sites are saturated, leaving excess FVIIa to bind loosely to activated platelets. FVIIa bound to activated platelets can then lead to direct activation of factor X [13-15]. Factor Xa in the presence of factor Va can then convert prothrombin to thrombin on the surface of these platelets.

Due to the elderly age of the patient and two previous colectomies, we used rFVIIa as a last resource to stop the bleeding, and to avoid re-operation and its potential complications. It might be possible that spontaneous cessation of bleeding would have been encountered without factor VII substitution, but exactly after injection of rFVII the bleeding stopped completely without recurrence, so we may postulate that rFVII successfully treated the bleeding. Currently, the acquisition cost of rFVIIa is relatively high. However, this may be offset by the costs of re-operation and its potential morbidity. Randomised, controlled clinical trials are needed to prove the safety and efficacy of rFVIIa in severe diverticular bleeding.

REFERENCES