Bratisl Lek Listy 2008; 109 (10)
438 – 440

CLINICAL STUDY

Recombinant activated factor VII in refractory gastrointestinal haemorrhage of unknown aetiology

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Abstract: We report a 27-year-old patient who suffered severe gastrointestinal (GI) bleeding of unknown aetiology after undergoing elective abdominal surgery to remove a colonic tumour. Although the immediate postoperative recovery period was uneventful, rectal bleeding and signs of haemorrhagic shock developed within 10 hours of surgery. Nasogastric aspiration and laparotomy failed to reveal the cause of the GI haemorrhage, and the patient remained unresponsive to conventional haemostatic therapy. Treatment with a single dose of recombinant activated factor VII (rFVIIa) 45 µg/kg led to reduced bleeding, improvements in haemodynamic status, and reduced transfusion requirements. Although further investigation is warranted, our findings suggest that rFVIIa may be useful in the rescue treatment of severe GI haemorrhage of unknown origin *(Tab. 1, Ref. 17).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: gastrointestinal haemorrhage, haemostatics, laparotomy, erythrocyte transfusion.

Bleeding from the upper gastrointestinal (GI) tract is a common and potentially life-threatening condition, with a reported annual incidence of up to 172 per 100,000 population and a case fatality rate as high as 14 % (1, 2). These figures may reflect the growing proportion of elderly individuals within the general population, as well as increasing use of non-steroidal anti-inflammatory agents (3). GI bleeding is most commonly caused by peptic ulcer (35–50 % of cases), gastroduodenal erosions (8–15 %), oesophagitis (5–15 %), varices (5–10 %), and Mallory Weiss tears (15 %). In approximately 20 % of cases, however, a specific diagnosis is never confirmed (4). Up to 40 % of such cases can be attributed to small bowel angiodysplasia, which represents the single most common source of haemorrhage in this subset of patients (5). The first priority in the management of GI haemorrhage is to restore blood pressure and replace lost fluids (4). When the patient becomes haemodynamically stable, endoscopy can be undertaken to find the cause of bleeding, determine the prognosis and, if necessary, administer haemostatic treatment. Surgical intervention is generally reserved for non-variceal bleeding that does not respond to endoscopic therapy (4), but is associated with high morbidity and mortality (6). Recombinant activated factor VII (rFVIIa; NovoSevenr, Novo Nordisk, Bagsvaerd, Denmark) is licensed for the treatment of patients with congenital haemophilia and inhibitors to factor VIII or IX. In Europe, it is also approved for use in patients with acquired hemophilia, factor VII deficiency, and Glanzmann's thrombasthenia refractory to platelet transfusion. Moreover, rFVIIa has also been successfully used to control bleeding in a wide variety of other indications, including non-haemophilic coagulopathies (7), surgery (8, 9), and trauma (10). A small number of anecdotal reports and clinical trials also indicate that rFVIIa can provide similar haemostatic efficacy in GI haemorrhage of varying aetiology (2, 11–14). Based on these favourable findings, we have successfully used rFVIIa in a young patient with uncontrollable GI bleeding of unknown aetiology following colonic surgery.

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Case report

The patient was a 27-year-old male who was admitted to the Intensive Care Unit (ICU) of our hospital in March 2005 after undergoing a left hemicolectomy with T-tube anastomosis to remove a tumour of the sigmoid colon. Post-surgical recovery was uneventful until 2200 hours on the day of surgery, 10 hours post-surgery, when the patient suddenly began to lose a large quantity of both old and fresh blood from the rectum. He also showed clinical signs of acute haemorrhage, including marked pallor, confusion, and an increased heart rate of around 160 bpm. Despite these observations, nasogastric aspiration did not reveal any signs of gastric bleeding.

Immediate resuscitation with fluids and red blood cells was started, and the attending surgeon made the decision to perform urgent laparotomy. The nature of the onset of bleeding and the patient's deteriorating clinical status suggested a surgical cause of bleeding and therefore endoscopy was not performed prior to surgery. Intestinal anastomoses were without signs of bleeding, and there was no blood in the abdomen, but large sections of the

Tab. 1. Patient coagulation parameters before and after treatment with rFVIIa.

Date	(Time)	Department	PT (%)	INR	APTT (sec)	TT (sec)	FG (g/L)	FBL (ks)	F XIII
14.02		INT	129	0.86	24	14	3.9	16.2	Present
02.03		INT	112	0.93	30	17	2.89	18.0	Present
04.03		ICU	85	1.11	31				
05.03	(08.00 h)	ICU	74	1.22	33				
05.03	(23.00 h)	ICU	77	1.21	39	17	3.0	21.6	
06.03	(05.00 h)	ICU	81	1.18	32				
06.03	(23.00 h)	ICU	54	1.50	32				
06.03	**(24.00 h)**		**rFVIIa administration – 45μg/kg**						
07.03	(05.00 h)	ICU	145	0.83	31				
07.03	(23.00 h)	ICU	138	0.86	30			AT III 71%	
08.03		ICU	118	0.94	32				
09.03		ICU	130	0.89	29				
10.03		ICU	107	0.96	32				
11.03		ICU	85	1.08	27				
12.03		ICU	89	1.06	25	17	5.2	5.2	
13.03		ICU	45	1.55	18				
14.03		ICU	93	1.05	24				
15.03		ICU	95	1.04	22				

INT – Department of Internal Medicine, ICU – Intensive Care Unit, PT – prothrombin time, INR – international normalization ratio, APTT – activated partial thromboplastin time, TT – thrombin time, FG – fibrinogen, FBL – fibrinolysis, FXIII – factor XIII, AT III – anti-thrombin III., rFVIIa – recombinant activated factor VII (NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark)

small intestine and colon were full of blood. Intraoperative gastroscopy showed several small gastric erosions and submucosal haematomas, but no signs of acute haemorrhage in the proximal part of the gastrointestinal tract. Because the cause of bleeding remained unclear, after the laparotomy, selective angiography (using a 4F catheter and iopromide [Ultravistr 300; Berlex, Montville, New Jersey, USA] as a contrast agent) was performed, but revealed no sites of haemorrhage, arteriovenous malformations or angiodysplasia within the celiac trunk, superior mesenteric artery, medial colic artery or jejunal arteries. Massive rectal bleeding continued, leading to haemodynamic instability and tachycardia of >120 bpm. Routine laboratory tests were performed (complete blood cell count and analyses of electrolytes, coagulation parameters and arterial blood gas) and the patient received conventional therapies over the next 48 hours (treatment with antibiotics, analgesics and a proton pump inhibitor, as well as intravenous administration of crystalloid and colloid fluids) without success, but the attending surgeon decided not to perform a repeat laparotomy. This decision was based on the findings of the relaparotomy and endoscopy performed two days earlier, which had shown no clinical signs of acute surgical illness.

During the treatment, coagulation tests were regularly performed (Tab. 1). After 48 hours of supplementation with red blood cells (10 units of red blood cells and 5 units of fresh frozen plasma) and continuous rectal bleeding, a single dose of rFVIIa 45 μg/kg was administered. Rectal bleeding ceased within 8 hours of rFVIIa administration and, within 24 hours, the patient's haemodynamic parameters had improved (Tab. 1). Melaena continued for approximately 72 hours after rFVIIa administration, requiring further transfusion of red blood cells (2 units). After cessation of melaena, the patient's recovery was uneventful and he was discharged from the ICU on the sixth postoperative day. No adverse events related to rFVIIa therapy were observed.

Discussion

In this young patient with a life-threatening GI haemorrhage of unknown cause, rFVIIa 45 μg/kg successfully controlled bleeding within 8 hours of administration after failure of conventional measures. Transfusion requirements also decreased after rFVIIa therapy, and coagulation parameters stabilised. Our data support those of other reports describing the use of rFVIIa in GI haemorrhage (2, 11–14). In a recent, unselected case series, 11 patients (aged 8–64 years) received rFVIIa 15–90 μg/kg for the rescue treatment of upper GI bleeding caused by liver disease, trauma, peptic ulcer, pancreatitis or haemorrhagic gastritis with sepsis. Therapy was effective in all but two of the patients, leading to reduced blood loss, decreased transfusion requirements, and improved coagulation status (2). Udvardy et al describe how massive coumarol-induced upper GI haemorrhage in an elderly patient was successfully managed using rFVIIa 50 μg/kg (11), and a recent randomised, double-blind trial found rFVIIa 100 μg/kg to be beneficial in reducing the proportion of patients who failed to control variceal bleeds (12). The dose used to treat our patient was not different from those previously reported in this indication (15–100 μg/kg) and, at 45 μg/kg, is markedly lower than the currently recommended dose for haemophilia patients (90 μg/kg). However, it is possible that a higher dose may have produced more rapid control of bleeding. We did not observe any adverse events following rFVIIa administration. This finding reflects previous clinical experience with the agent: despite increasingly widespread use in a growing number of indications, the number

of serious adverse events remains less than 1 % (15). Although isolated thrombotic complications have been reported (16), the vast majority of these have occurred in patients with comorbidities that predispose to thrombosis when thrombin generation is improved (15). According to current hypotheses, rFVIIa provides safe haemostasis by acting only at the site of vessel damage, where it forms complexes with exposed tissue factor (TF) to ‚drive' the TF pathway of coagulation and thus enhance thrombin generation (15). Further localisation of rFVIIa to the injury site is achieved through TF-independent binding to activated platelets. In this way, rFVIIa activates factor X to factor Xa on the activated platelet surface, initiating the assembly of the prothrombinase complex and resulting in a subsequent ‚burst' of thrombin generation (17). This mechanism of action not only ensures local haemostasis, but also avoids systemic activation of coagulation and thus reduces the risk of thrombosis. In conclusion, our findings suggest that rFVIIa may be of benefit to patients with refractory GI bleeding, even if a specific cause of haemorrhage cannot be found. Our data support those previously reported, and highlight the need for further investigation of the agent in this indication.

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Received March 25, 2008.
Accepted August 20, 2008.