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From the Institute for Clinical Evaluative Sciences (MMM, CVW, AB, JIW, CDN), Toronto, Ontario; the Department of Medicine (CVW), University of Ottawa and the Clinical Epidemiology Unit, Loeb Health Research Institute, Ottawa Hospital, Ottawa, Ontario; and Sunnybrook and Women's College Health Sciences Centre (CDN) and the University of Toronto (MMM, JIW, CDN), Toronto, Ontario, Canada.

Correspondence should be addressed to Muhammad Mamdani, PharmD, MA, MPH, Institute for Clinical Evaluative Sciences, 2075 Bayview Avenue-G215, Toronto, Ontario, Canada.

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Treatment of a Severely Bleeding Patient without Preexisting Coagulopathy with Activated Recombinant Factor VII

André J. Vlot, MD, PhD, Evelien Ton, MD,
Albert J. C. Mackaay, MD, PhD,
Mark H. H. Kramer, MD, PhD,
Carlo A.J.M. Gaillard, MD, PhD

Upper gastrointestinal hemorrhage is a life-threatening emergency with a mortality rate of approximately 7% (1). Inhibition of gastric acid secretion, endoscopic interventions, and surgery are the current mainstays of treatment. However, continued bleeding despite these treatments remains a problem in some patients. We describe the successful use of activated recombinant factor VII (NovoSeven, Novo Nordisk, Copenhagen, Denmark) in the management of a patient without a preexisting coagulopathy who developed refractory bleeding.

CASE REPORT

A 59-year-old man was admitted to our hospital because of hematemesis and melena. He had been well until 4 months earlier, when upper abdominal pain developed for which acetaminophen was prescribed. He had a history of hypertension for which he used an angiotensin-converting enzyme (ACE) inhibitor, a calcium channel antagonist, and a beta-blocker. He denied prior use of nonsteroidal anti-inflammatory drugs or anticoagulation therapy, and there was no family or personal history of hemorrhagic disorders. He smoked cigarettes and drank two glasses of alcohol daily. On physical examination, the patient appeared ill. The pulse was 81 beats per minute and the blood pressure was 115/60 mm Hg after volume replacement. An abdominal examination was normal. There were no stigmata of chronic liver disease. Laboratory investigations showed a low hemoglobin level (9.8 g/dL), with normal red blood cell morphologic features. The platelet count and serum electrolyte and aminotransferase levels were normal, as were the prothrombin and partial thromboplastin times. The patient was treated with intravenous histamine-2 (H₂)-receptor antagonists, colloidal solutions, and packed red blood cells. At endoscopy, a large ulcer in the duodenal bulb with an adherent clot was seen that could not be dislodged by washing. There were no signs of active bleeding.

However, bleeding occurred again on the second hospital day. This was initially managed conservatively, but because the patient's condition did not stabilize after the infusion of 5 units of packed red blood cells, surgery was performed. A bleeding ulcer located at the posterior wall of the duodenal bulb was managed by suture plication and pyloroplasty. Postoperatively, the plasma fibrinogen level was 0.8 g/L and the platelet count was $44 \times 10^9/L$. Fresh-frozen plasma and platelets were administered. The prothrombin and partial thromboplastin times were maintained within the normal range. Despite this, bleeding continued, and a second laparotomy was performed. Hemorrhage was observed posterior to the stomach; bleeding vessels were ligated. An external drain was left in the subhepatic space. Postoperatively, however, bleeding persisted, and the patient became hemodynamically unstable. At a third laparotomy, bleeding was observed, probably originating from the dorsal part of the duodenum. Additional vessels were ligated, and gauzes were left in situ. Tranexamic acid (0.25 g per hour), which inhibits fibrinolysis, was administered.

Despite treatment, massive bleeding continued, and the patient was in danger of exsanguination. A test for D-dimers was negative. Octreotide (50 µg per hour), a somatostatin analogue, was started. Shortly thereafter, since another operation was not considered an option and arterial embolization was not directly available, activated recombinant factor VII (factor VIIa) was adminis-

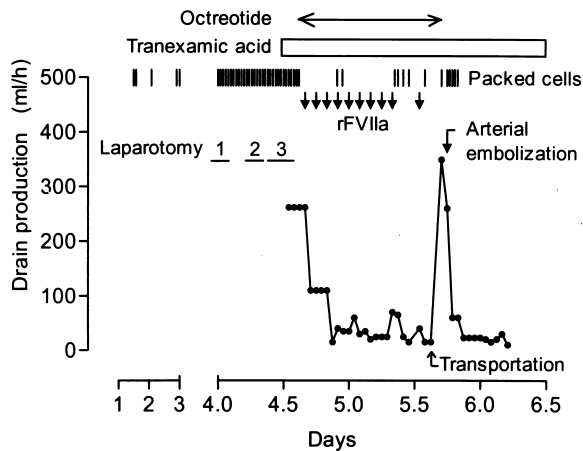


Figure. Drain production and transfusion requirements of a 59-year-old man with a bleeding peptic ulcer. The vertical arrows indicate when recombinant factor VIIa (rFVIIa) was infused.

tered at a dose of 90 $\mu\text{g}/\text{kg}$ every 2 hours for the next 21 hours. Drain production and transfusion requirements declined from a total of 65 units of packed red blood cells before the infusion of factor VIIa to only 2 units of packed red blood cells in the following 16 hours (Figure). The patient remained hemodynamically stable during the next 24 hours. Factor VIIa was discontinued when the patient was transferred to another hospital for angiographic intervention. Drain production increased during transportation until the gastroduodenal artery was embolized. The remainder of the patient's hospital course was uneventful, and no further bleeding occurred.

DISCUSSION

We describe a patient with a duodenal ulcer characterized by an adherent clot. Recurrent bleeding occurs in up to 36% of these patients, with most episodes occurring within 3 days of the initial episode, as in our patient (1) in whom bleeding continued despite extensive surgery and massive transfusion of packed red blood cells, platelets, and fresh frozen plasma. Angiographic intervention was not available. A marked decrease in transfusion requirements and drain production was observed after treatment with recombinant factor VIIa, and the patient became hemodynamically stable.

Because there was a substantial overlap in the treatment with factor VIIa, tranexamic acid, and octreotide, we cannot exclude the possibility that tranexamic acid and octreotide contributed to the cessation of bleeding. Bleeding recurred upon discontinuation of factor VIIa treatment during transportation of the patient; we cannot determine which, if either, of these two changes was responsible.

We treated our patient with factor VIIa even though he had an intact hemostatic system. The development of this coagulation factor is a recent addition to the available treatments for patients with hemophilia and inhibitors to factor VIII or IX (2,3). It has also been used in patients with thrombocytopenia (4), congenital defects in the platelet glycoproteins (5,6), and acquired thrombocytopenia (7).

The human coagulation system is traditionally divided into an intrinsic and extrinsic reaction pathway, which activate a common pathway through which thrombin and fibrin are formed. In vivo hemostasis is initiated by the extrinsic pathway in which factor VIIa binds to tissue factor, resulting in the activation of factors IX and X, which eventually leads to a burst of thrombin generation (8). Formation of sufficient amounts of thrombin, a central enzyme in hemostasis, is a prerequisite for effective hemostasis. Administration of recombinant factor VIIa leads to an acceleration in thrombin generation and thus to more effective hemostasis (9). We hypothesize that, in our patient, infused factor VIIa bound to tissue factor on the cell surface of the ulcer, and probably at other bleeding sites, initiating hemostasis in a wound that was otherwise too large for effective hemostasis.

In conclusion, recombinant factor VIIa, perhaps in combination with tranexamic acid and octreotide, may be effective in severely bleeding patients without a preexisting coagulopathy. If our findings can be confirmed, a controlled clinical trial should be undertaken.

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From the Departments of Internal Medicine (AJV, ET, MHHK, CAJMG), and Surgery (AJCM), Eemland Hospital, Amersfoort, The Netherlands.

Correspondence should be addressed to Carlo A.J.M. Gaillard, MD, PhD, Department of Internal Medicine, Eemland Hospital, 3818 ES Amersfoort, The Netherlands.

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A New Variant of Hermansky-Pudlak Syndrome due to Mutations in a Gene Responsible for Vesicle Formation

Vorasuk Shotelersuk, MD,
Esteban C. Dell'Angelica, PhD, Lisa Hartnell, BS,
Juan S. Bonifacino, PhD, William A. Gahl, MD, PhD

Hermansky-Pudlak syndrome is a recessive type of oculocutaneous albinism that is prevalent in northwest Puerto Rico due to a founder effect (1–3). In this syndrome, bleeding and bruising occur because of the absence of platelet dense bodies, which normally release serotonin, calcium, and adenosine diphosphate to trigger a secondary aggregation response (4). In addition, the accumulation of a lipid-protein complex called ceroid lipofuscin (5,6) is thought to cause the pulmonary fibrosis (7) and granulomatous colitis (8) seen in this disease.

One gene causing Hermansky-Pudlak syndrome, *HPS-1*, encodes a 700 amino acid protein of unknown function (9–11). Northwest Puerto Rican patients are homozygous for a 16 base pair (bp) duplication in *HPS-1*, but most non-Puerto Rican patients have no mutations in this gene (12,13). Consequently, it has become accepted that several different genes, when mutated, can cause Hermansky-Pudlak syndrome (12–14). This phenomenon, called locus heterogeneity, is also found in mice: 14 different mouse strains manifest a type of Hermansky-Pudlak syndrome (pigment dilution and platelet storage pool deficiency), each due to a different gene (15). To date, three of these genes have been cloned. *Pale ear* is the murine analogue of patients with *HPS-1* mutations (16,17), and *pearl* (18) and *mocha* (19) have defects in adaptor complex-3 (AP-3). One protein subunit of adaptor complex-3, called $\beta 3A$, is mutated in the *pearl* mouse, while another protein subunit, called δ , is mutated in the *mocha* mouse.

Adaptor complex-3 is an aggregate of four different

peptides and serves as a “coat” protein that concentrates in a donor membrane and recruits other membrane components to become part of a newly formed vesicle. These vesicles, such as lysosomes and peroxisomes, are functional compartments that provide an optimal environment for specialized biochemical processes. Adaptor complex-3 is thought to be responsible for the formation of pigment-forming vesicles (melanosomes) and platelet storage vesicles (dense bodies) (20,21).

We describe two brothers with Hermansky-Pudlak syndrome with mutations in the $\beta 3A$ subunit of adaptor complex-3 (22,23).

CASE REPORTS

We admitted 49 Hermansky-Pudlak syndrome patients to the NIH Clinical Center under an Institutional Review Board-approved protocol (24). Patient 40, aged 20 years, and patient 42, aged 25 years, were brothers who had normal gestations, deliveries, and birth weights. Bilateral congenital hip dislocations, due to dysplastic acetabulae, required closed reduction in patient 40 and splinting in patient 42. The family was of Dutch origin with no known consanguinity or miscarriages. The brothers' healthy parents had two normal, unaffected sons.

Nystagmus was observed in the newborn period. Skin color was light, and the brothers' white hair gradually turned blond. Bruising occurred in early childhood, with recurrent epistaxis decreasing in frequency by adolescence. In patient 42, extraction of several teeth was performed with minimal bleeding. Neither brother experienced hemoptysis, hematemesis, hematochezia, or melena. Hermansky-Pudlak syndrome was suspected when the patients were 8 and 13 years old, and absence of platelet dense bodies was documented by Dr. James White of the University of Minnesota.

From infancy to adolescence, the brothers had recurrent upper respiratory tract infections and episodes of otitis media that responded to antibiotic treatment. Neutropenia was consistently noted. The patients' unaffected siblings did not have recurrent upper respiratory tract infections.

Developmentally, the brothers achieved major milestones on time, but complained of poor balance causing stumbling and falling. They completed 11th grade and work on a family farm and nearby factory. Patient 42 smoked one half to 1 pack of cigarettes daily since age 13 years; patient 40 never smoked. Patient 40 had a physiologic cardiac murmur noted since age 3 years, with normal echocardiograms.

Patient 40 had a height of 172.3 cm, weight of 86.5 kg, and head circumference of 56.8 cm. Patient 42 had a height of 173.1 cm, weight of 67.9 kg, and head circumference of 56.5 cm. The brothers' hair was dark blond.