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REGULAR ARTICLE

Recombinant activated factor VII in an unselected series of cases with upper gastrointestinal bleeding

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Abstract

Introduction: The mortality rate associated with UGI bleeding remains high at 7—14%. Pharmacologic and endoscopic interventions are the current standard treatment, but there are few alternative options should these fail. This study aimed to assess the efficacy and safety of recombinant activated factor VII (rFVIIa) in the rescue treatment of severe upper gastrointestinal (UGI) bleeding.
Method: Eleven patients (age: 8—64 years) were treated with rFVIIa at 15.0—90 μg/kg to control UGI bleeds. All three pediatric/adolescent cases and four of the eight adults had UGI hemorrhage associated with liver disease; the origins of the bleeds for remaining adults were trauma ($n=1$), peptic duodenal ulcer ($n=1$), hemorrhagic gastritis with sepsis ($n=1$) and pancreatitis ($n=1$).

Abbreviations: aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs; PRBC, packed red blood cells; PT, prothrombin time; rFVIIa, recombinant activated factor VII; TIPS, transjugular intrahepatic portosystemic shunt; UGI, upper gastrointestinal.

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Results: Bleeding stopped in seven patients and was markedly reduced in two patients, while there was no change in two patients. Coagulation parameters displayed a tendency to improve, and transfusion requirements were reduced in most patients. In total, five patients died within 2 weeks of rFVIIa treatment. In each case, fatality was judged unrelated to rFVIIa treatment. No thromboembolic events occurred.
Conclusions: These results suggest that, even if our data are optimistic, the use of rFVIIa in the treatment of severe UGI bleeding warrants further investigation in prospective, randomized trials.

Upper gastrointestinal (UGI) hemorrhage is a potentially life-threatening condition and an important cause of morbidity and mortality, with the incidence ranging from 36 to 150/100,000 population. In the US alone, 300,000—350,000 hospital admissions for UGI are reported to occur annually [1—3]. Although medical and surgical techniques have improved significantly over the last 40—50 years, the overall mortality rate for patients with acute UGI bleeding remains at 7—14% [3,4]. This may be a consequence of the increasing age of the general population with additional complications, such as augmented use of nonsteroidal anti-inflammatory drugs (NSAIDs) [2—4]. In those patients who develop bleeding complications during a hospital stay for other indications, reported mortality rates are even greater at ~33% [4]. Furthermore, risk factors for recurrent or persistent bleeding occur in up to one-third of UGI bleeds and may therefore increase mortality.

The most frequent cause of UGI hemorrhage is peptic ulcer, accounting for 35—50% of cases, and consumption of aspirin or NSAIDs occurs in approximately 20% of these patients [1,5]. The majority of remaining bleeds are caused by gastroduodenal erosions (8—15%), esophagitis (5—15%), varices (5—10%), and Mallory Weiss tears (15%). Due to the specific requirements for management, the presence of liver disease should be considered in any cases of acute UGI bleeding.

In patients with UGI bleeding that does not resolve spontaneously or who are at high risk of re-bleeding, the initial treatment aims to correct fluid loss and restore blood pressure, with immediate resuscitation in cases of severe bleeding [1,6,7]. Endoscopic therapy is indicated in a variety of UGI bleeds, including those caused by esophageal varices or ulcers with major stigmata of recent hemorrhage. The evidence for the effectiveness of pharmacotherapy in non-variceal hemorrhage is restricted to the treatment of peptic ulcer bleeds, where acid-blocking drugs alone demonstrate sufficient outcome improvement to warrant recommendation [1]. In contrast, pharmacologic agents (e.g. vasoactive drugs) are often used successfully to manage variceal bleeds, and have been shown to improve the efficacy of endoscopic treatment in this indication [8]. Transjugular intrahepatic portosystemic shunt (TIPS) may be used in the treatment of acute and recurrent variceal bleeds that cannot be adequately controlled with medical therapy. For ulcer bleeding, surgical techniques are reserved for cases in which endoscopic treatment has failed, while surgery for variceal bleeding is associated with high mortality rates and is rarely conducted.

Recombinant activated factor VII (rFVIIa, NovoSeven®, Novo Nordisk, Bagsvaerd, Denmark) is a hemostatic agent for patients with hemophilia and inhibitors to coagulation factors VIII or IX, as well as for patients with factor VII deficiency and Glanzmann's thrombasthenia [9]. It may also be of benefit in bleeding episodes of various etiologies, including coagulopathies other than hemophilia (e.g. thrombocytopenia), coagulation dysfunction resulting from liver disease, and bleeding associated with trauma, intracerebral hemorrhage and surgery in patients with normal coagulation functions [10—19]. The present case series describes the emergency use of rFVIIa in patients with severe UGI bleeding of various etiologies.

Patients and methods

We report the use of rFVIIa in the treatment of severe UGI bleeding in 11 patients from centers in Bulgaria ($n=2$), Denmark ($n=2$), Croatia ($n=1$), the Netherlands ($n=1$), Poland ($n=3$), Russia ($n=1$), and the United Kingdom ($n=1$). Details of all patients were reported on *Haemostasis.com*—an anonymous, web-based repository for information on the experimental use of rFVIIa [20]—between its launch in February 1999 and its closure in February 2004. The database was organized by Novo Nordisk A/S, the manufacturer of rFVIIa, but administered by an independent third party under the supervision of an academic steering committee. These activities received support from an unrestricted grant provided by Novo Nordisk A/S, Bagsvaerd, Denmark.