

Refractory Bleeding after Endoscopic Sphincterotomy: A New Indication for Recombinant Factor VII Therapy?

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The therapeutic approach in post-ERCP bleeding depends on the severity of the episode. In most instances early bleeding is self-limited, but when it is severe enough endoscopic injection of epinephrine (EP) is the usual treatment. Nevertheless, in some cases bleeding relapses, whereas in between 5% and 10% of patients the refractoriness to endoscopic management may even be fatal and other therapeutic alternatives would be needed. Otherwise, in a small subgroup of cases the bleeding becomes massive, the vision is obscured, and the injection may be very difficult in a situation of hemodynamic instability. We here report a case of refractory post-endoscopic sphincterotomy (ES) bleeding in a patient without preexisting coagulopathy, successfully treated with a single injection of rFVII. This novel experience suggests that rFVIIa, besides its actual high costs, might be useful and safe as a second-line, noninvasive, therapeutic tool in selected cases of massive, or refractory, post-ES bleeding.

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INTRODUCTION

Papillary bleeding is one of the most frequent complications after endoscopic sphincterotomy (ES). Its prevalence varies according to the definition of bleeding episodes and to the presence or not of some risk factors, such as the use of precut, associated papillary stenosis, bleeding during the procedure, previous coagulopathy, early initiation of anticoagulant therapy after ES, and low case-volume on the part of the endoscopist (1, 2). In early series, which included cases of occult bleeding, the frequency ranged from 10% to 48%, but serious episodes of bleeding were much less common (5.3–12.1%) (3, 4). In more recent series, the rate of significant post-ES bleeding is even lower (0.8–2%) (2, 5), probably as a consequence of an improved technique.

Post-ES hemorrhage develops early during the procedure, though the complication may be delayed from 1 to as many as 10 days after sphincterotomy. Otherwise, the therapeutic approach mainly depends on the severity of the episode. In most instances early bleeding is self-limited, but when it is severe enough, prolonged, or in delayed episodes, endoscopic injection of epinephrine (EP) is the most commonly used, effective, and least expensive method. Nevertheless, in some cases bleeding relapses, whereas in between 5% and 10% of patients the refractoriness to endoscopic management may even be fatal (4, 6), so that other therapeutic alternatives would be sometimes needed. This report describes a case of refractory post-ES bleeding, in a patient without preexisting coagulopathy, successfully treated with a single injection of rFVII.

CASE REPORT

A 53-yr-old man was admitted to the hospital because of acute epigastric pain and jaundice. He had a two-month history of vague abdominal pain and mild jaundice. At admission, examination was unremarkable, except for jaundice and abdominal tenderness in the right upper quadrant. Laboratory data were the following: hemogram, prothrombin time, and activated partial thromboplastin time were normal. Serum AST was 621 U/L (0–37 U/L); ALT: 882 U/L (0–40 U/L); total bilirubin: 136 $\mu\text{g/dl}$ (<5 $\mu\text{g/dl}$); direct bilirubin: 119 $\mu\text{g/dl}$ (<5 $\mu\text{g/dl}$); gamma-glutamyl-transpeptidase: 426 U/L (11–49 U/L); and alkaline phosphatase: 390 U/L (90–258 U/L). Serology for hepatitis A, B, and C virus was negative. An abdominal ultrasonography revealed cholelithiasis and dilation of the intrahepatic and extrahepatic biliary tree. An endoscopic retrograde cholangiopancreatography confirmed the dilation of the main biliary duct, but after a standard sphincterotomy was performed no intraductal stones were found. No signs of bleeding were observed during the procedure (Fig. 1). Twenty hours later, the patient experienced a massive hematochezia and became hypotensive (80/50 mmHg) and tachycardic (125/min). An emergency duodenoscopy disclosed a spurting bleeding, flowing from the papillar area, which was injected with 5 ml of a solution of EP (1:10,000) and 6 ml of ethoxysclerol (1:100) (ET), with apparent cessation of the hemorrhage. During the next 12 h the patients had two episodes of melena, which were followed by a drop in hemoglobin levels (5 g/dl) and hematocrit (17 points). Two units of packed red blood cells were transfused.



Figure 1. No bleeding was observed after standard endoscopic sphincterotomy, but twenty hours later, the patient experienced a bleeding episode, which persisted after injection of epinephrine and ethoxysclerol.

A second endoscopy confirmed the persistence of the papillary bleeding. During the procedure, an intravenous bolus of 4.8 mg of recombinant factor VIIa (rFVIIa; NovoSeven; Novo Nordisk A/S, Bagsvaerd, Denmark) was injected. After 9 min a clot was observed at the bleeding point and 3 min later the hemorrhage had ceased (Fig. 2A and B); in the next 24 h a significant shortening of the prothrombin time was observed (13 vs 9.4 s). The patient remained hemodynamically stable, without the clinical signs of bleeding and recovered uneventfully. He was discharged after 6 days of follow-up and an elective cholecystectomy was performed three wk later.

DISCUSSION

Since 1974 ES is the preferred approach for the treatment of biliopancreatic diseases, but up to now there are limited data on the pathogenesis and the best management of post-ES bleeding, one of its main complication. In the experience of most endoscopists, three types of bleeding might be considered according to their severity and the time of appearance, and each should be handled differently (7): mild or moderate bleeding during the procedure, immediate massive hemorrhage, and delayed or recidivant hemorrhage of any degree of severity. Mucosal bleeding immediately after sphincterotomy is usually self-limited and does not warrant any treatment, unless it does not stop in 2–3 min. In this subgroup of patients, Leung *et al.* (4), in the only large retrospective series reported on this issue, recommend a sequential strategy, consisting of irrigation of EP on the bleeding point, followed by an injection of this vasoconstrictive agent if the hemorrhage continues. However, it has been hypothesized that those cases who responded to EP irrigation may have stopped spontaneously without any intervention. In fact, the usefulness of irrigation has not been demonstrated by other

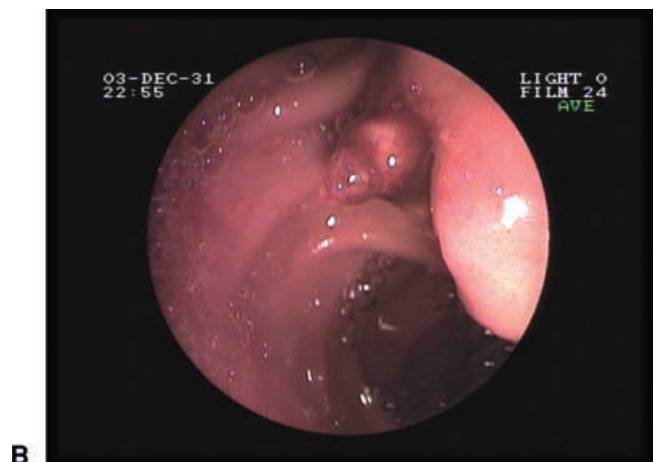


Figure 2. (A) A second endoscopy confirmed the persistence of papillary bleeding and an intravenous bolus of recombinant Factor VIIa was injected. (B) Twelve minutes later a hemostatic clot was observed at the bleeding point.

groups, whereas injection therapy with EP and/or sclerosants is successful in a high proportion of patients with immediate or delayed post-ES bleeding (4, 8, 9). However, in a small subgroup of cases the bleeding becomes massive, the vision is obscured, and the injection may be very difficult in a situation of hemodynamic instability. Otherwise, a variable proportion of patients relapses and a range of 1–3 treatment sessions may be necessary to obtain a stable hemostasis (8, 10). Fatalities have been reported only in these two problematic subgroups (11), in which other therapeutic resources would be needed.

Surgery is required in approximately 10–20% of patients with post-ES, but surgical therapy can be associated with a high mortality (10, 11). Therefore, in the previous years, some authors have successfully used other endoscopic modalities of treatment, such as electrocoagulation, fibrin glue injection, and argon plasma coagulation, in isolated cases (2, 12). However, there is scant experience and some concern regarding the risk of secondary pancreatitis and other potential side effects associated with the use of these methods to induce local hemostasis in the papillary area. More recently,

a growing amount of evidence is being reported on the usefulness and safety of rFVIIa in the treatment of severe bleeding of diverse etiology in patients without coagulation disorders. Their efficacy seems to be related to the ability of FVII of initiating local blood coagulation, on complexation with tissue factor, when a rupture in blood vessels occurs. A preliminary study (13) strongly suggests that rFVIIa is effective in patients with resistant variceal bleeding, allowing an early and durable hemostasis. Thus, we decided to employ this resource in our case, in order to prevent the injection of a larger volume of EP and/or ET in the bleeding point. The intravenous bolus of rFVIIa was followed by the early formation of a hemostatic clot, as seen in patients with variceal bleeding, and a permanent hemostasis. Thus, our novel experience with the patient here reported suggests that rFVIIa, besides its actual high costs, might be useful and safe as a second-line, noninvasive, therapeutic tool in selected cases of massive, or refractory, post-ES bleeding.

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