

CASE REPORT

Use of Activated Recombinant Human Factor VII (rhFVIIa) for Colonic Polypectomies in Patients with Cirrhosis and Coagulopathy

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A coagulopathy is common in patients with advanced liver disease, particularly those with cirrhosis (1). Cirrhotics undergo endoscopic procedures for many different reasons (2, 3). In such cases, the endoscopist is often hesitant to perform a biopsy or even prophylactic varix banding not to mention a polypectomy or papillary sphincterotomy.

The prevalence of colonic polyps in patients with cirrhosis appears to be higher than that of the general population (4, 5). The current practice for a polypectomy in a coagulopathic cirrhotic patient involves the reversal of coagulopathy using fresh frozen plasma (FFP). The infusion of FFP requires additional nursing care, hospitalization, scheduling a second colonoscopy, and an overall increased utilization of resources. The infusion of FFP is associated with a risk of volume overload and transmission of bloodborne infectious agents. Alternatively, routine correction of the coagulopathy present in cirrhotics prior to an initial colonoscopy subjects the patient to all of the risks and cost of FFP infusion, even if no intervention is to occur.

In this report, four patients with advanced cirrhosis and a severe coagulopathy underwent one or more polypectomies after receiving an intravenous bolus infusion of recombinant human factor VIIa (rhFVIIa). The polypectomies were performed at the initial colonoscopy, thereby reducing patient and physician time, the number of clinical visits, endoscopy laboratory time, and without the added

risk of volume overload or acquisition of a bloodborne infection as a result of the administration of FFP.

Case 1. A 64-year-old white male with a history of diabetes, alcoholic cirrhosis, and hepatic encephalopathy was hospitalized for increasing lethargy and fatigue. He denied any recent history of nausea, hematemesis, melena, hematochezia, recent fever, abdominal pain, or increase in abdominal girth. The past medical history was remarkable for a history of prostate cancer that was treated with a radical prostatectomy.

His physical examination revealed scleral icterus, an enlarged liver without tenderness, no ascites, an enlarged spleen, and lower extremity edema. His mentation was slow. He manifested grade 3 asterixis. The results of his laboratory evaluation are shown in Table 1.

A work-up for anemia was initiated with an upper endoscopy that revealed nonbleeding grade IV esophageal varices. The varices were ligated with 10 bands. Antral biopsies showed goblet cell metaplasia without evidence of *H. pylori*. No complications were experienced.

On the third hospital day, a diagnostic colonoscopy was performed despite the patient's severe coagulopathy. Immediately prior to the procedure, his laboratory evaluation documented a hemoglobin (Hgb) of 8.7 g/dl, platelet count of 85,000/ μ l, a PT of 24.5 sec, INR 3.8, and a PTT of 41.4 sec. The colonoscopy revealed multiple colon polyps ranging from 2 mm to 2 cm in size. The coagulopathy was corrected in the endoscopy suite while the patient was being colonoscoped using an intravenous bolus administration of rhFVIIa at a dose of 120 μ g/kg. Serial PT, INR, and PTT measures were obtained (Figures 1 and 2). Thirty minutes after the infusion, the PT, INR, and PTT were 12.0 sec, 0.9, and 32.2 sec, respectively. All the visualized polyps were removed and retrieved successfully. Specifically, a 2-mm hepatic flexure polyp was removed using cold forceps. A 2-cm sigmoid polyp was removed using a snare cautery. Multiple rectal polyps with sizes ranging from 4 mm to 1 cm were removed using snare cautery. Histology of the hepatic flexure and sigmoid polyps revealed tubular adenomas. The five rectal polyps were found to be hyperplastic. At 10 hr after the procedure, the patient's PT was 16 sec with an INR of 1.6, and his PTT was 38.1 sec. The patient tolerated the procedure well without any clinical signs of post-polypectomy bleeding (Figure 3). Over a two-week follow-up

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TABLE 1. BASELINE CHARACTERISTICS

	Case			
	1	2	3	4*
Age (yr)	64	69	49	76
Gender (male/female)	M	F	M	M
Cause of cirrhosis	Alcohol	Hepatitis C	Alcohol	Cryptogenic
Hemoglobin (g/dl)	8.7	11.4	9.6	12.9
Mean corpuscular volume (fl)	105	82.6	88	92.9
White blood cell count (/ μ l)	4,000	11,400	8,800	3600
Platelets (/ μ l)	85,000	52,000	42,000	40,000
PT (sec)/ INR/PTT (sec)	24.5/3.8/41.4	17.2/1.9/34.3	20.1/2.6/49.5	24.3/3.8/43.4
Albumin (g/dl)	2.5	2.1	1.6	2.8
Total bilirubin (mg/dl)	16.1	10.9	24.7	1.9
Aspartate aminotransferase (Iu/liter)	45	31	60	26
Alamine aminotransferase (Iu/liter)	18	18	37	19
Alkaline phosphatase (Iu/liter)	69	53	69	102
Blood urea nitrogen (mg/dl)	9	16	17	12
Creatinine (mg/dl)	0.8	1.6	1.1	1.2
Venous blood ammonia (μ g/dl)	128	NA	63	NA
Iron (μ g/dl)/TIBC (μ g/dl)/Ferritin (ng/ml)	202/202/302	41/211/37	89/110/236	108/378/33
α -Fetoprotein (ng/ml)		2.6	2.9	

*On coumadin for DVT due to factor V Leiden mutation.

period his hemoglobin remained stable and no further gastrointestinal bleeding occurred.

Case 2. A 69-year-old white female with a history of treated hepatitis C and cirrhosis presented to hospital for a higher level of care after an episode of uncontrolled esophageal variceal bleeding at another hospital. One month prior to admission, the patient had an episode of hematemesis and an upper endoscopy was done. Esophageal variceal bleeding was found and ligated with six bands. She subsequently developed ascites for the first time. Two weeks later, another six bands were placed during a

second upper endoscopy performed due to hematemesis. Unexpectedly, the patient presented again with hematemesis, melena, and hematochezia; a third upper endoscopy revealed recurrent bleeding from esophageal varices and an additional four bands were deployed. Moreover, three units of packed red blood cells were transfused, and the patient was transferred to Loyola University Medical Center for a possible transjugular intrahepatic portosystemic shunt (TIPS) procedure.

Her past medical history was significant for colonic polyps, hypertension, hepatitis C, and cirrhosis documented by liver

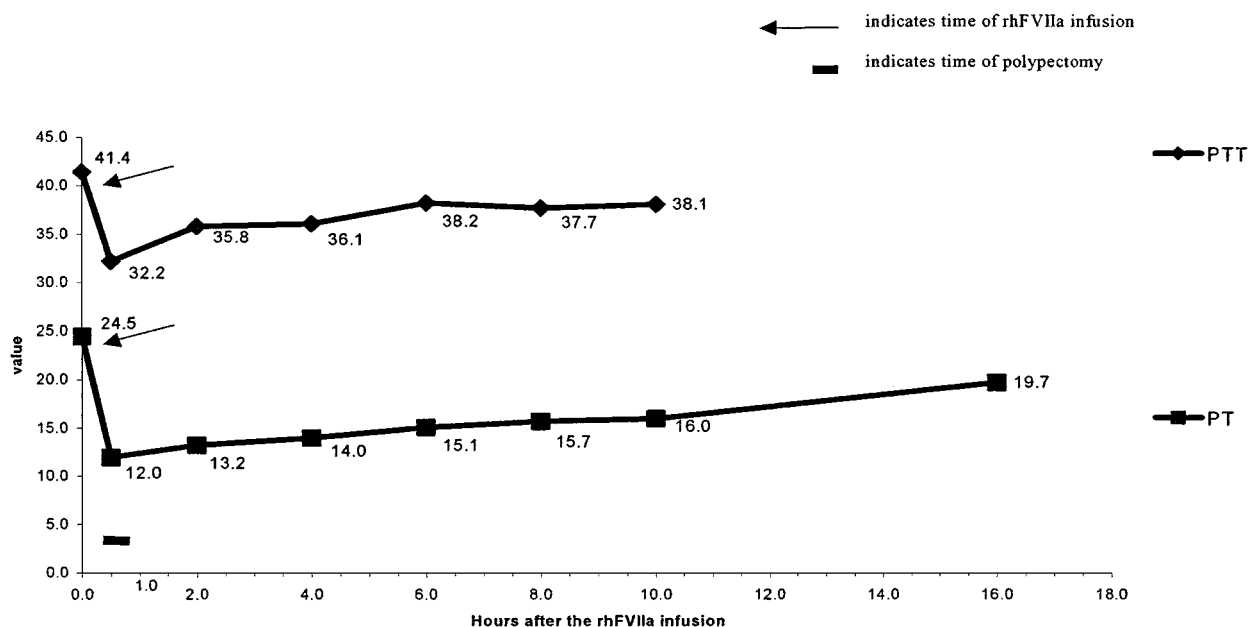


Fig 1. Sequential changes in PTT and PT with the intravenous bolus infusion of 120 μ g/kg of rhFVIIa in case 1. The arrow denotes the time of infusion.

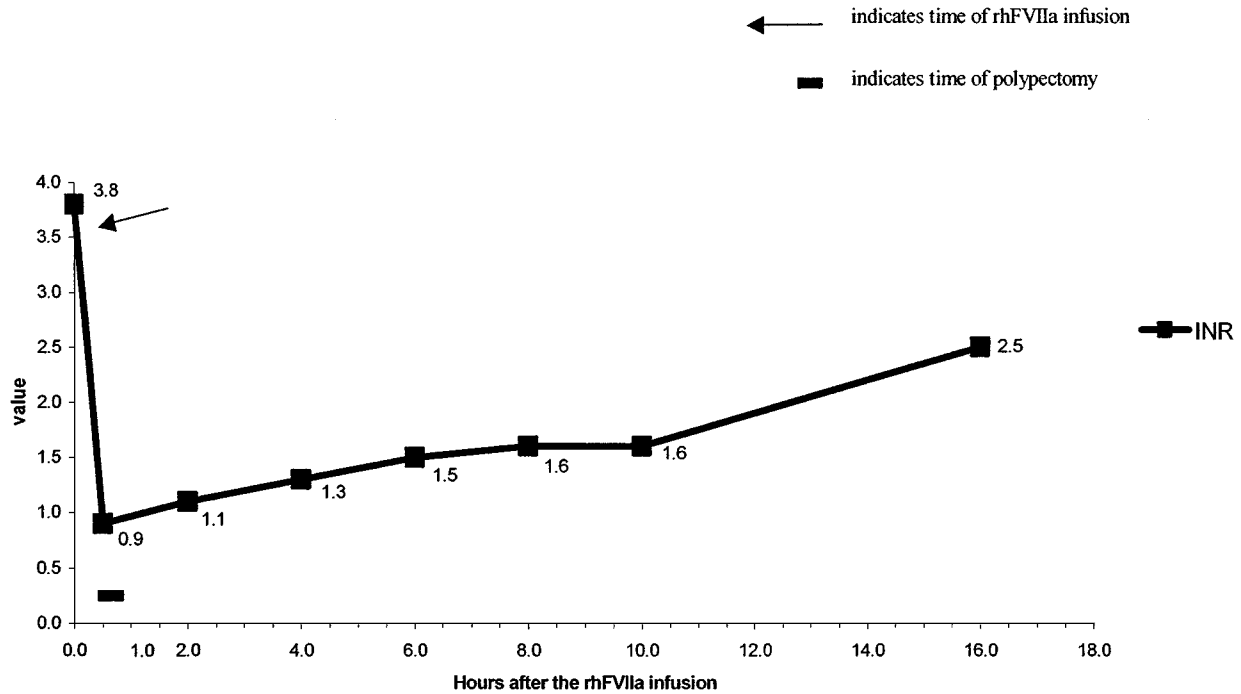


Fig 2. Sequential changes in INR with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 1. The arrow denotes the time of infusion.

biopsy five years previously. She admitted to receiving a blood transfusion in 1980. She was treated for hepatitis C with interferon and ribavirin for a six-month period three years ago with apparent resolution of her infection. Specifically, her HCV RNA qualitative assay (lower level of detection 200 copies/ml) was negative following the therapy and at the time of her current evaluation.

She arrived at Loyola intubated and receiving an intravenous infusion of octreotide. Her vital signs were stable. She was alert and followed simple commands. Her physical exam was positive for scleral icterus, an abdomen that was distended and nontender

with ascites, and a palpable spleen. She had pitting edema of the legs.

Her initial laboratory evaluation is shown in Table 1. The peritoneal fluid analysis was negative for bacterial peritonitis.

An upper gastrointestinal endoscopy was performed on the second hospital day. Grade III esophageal varices were noted and eight bands were placed. Additional findings included a mild portal hypertensive gastropathy but no gastric varices. She was extubated the following day.

A diagnostic colonoscopy was performed as part of her liver transplant evaluation. The preprocedure PT, INR and PTT were

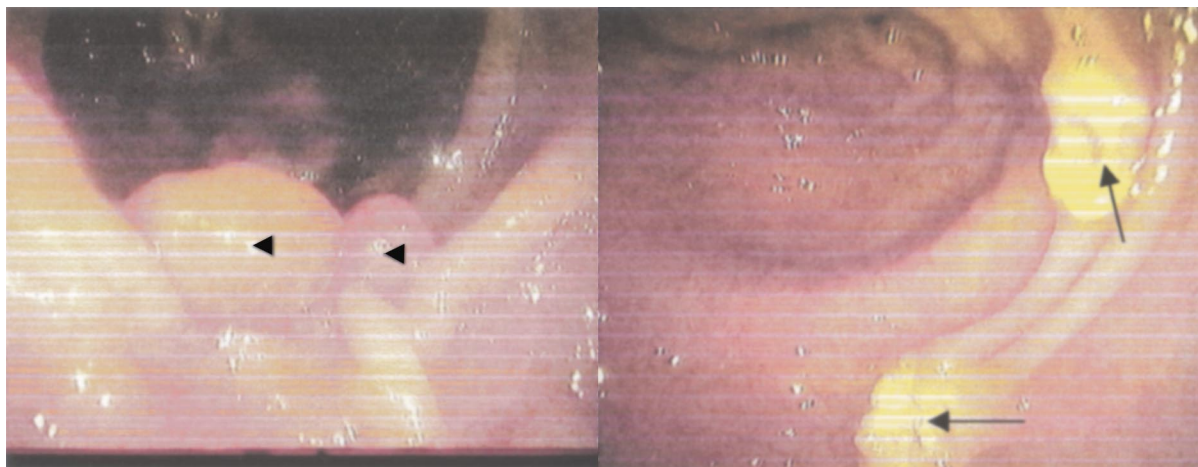


Fig 3. Sigmoid colonic polyps (arrowheads) and postpolypectomy sites (arrows).

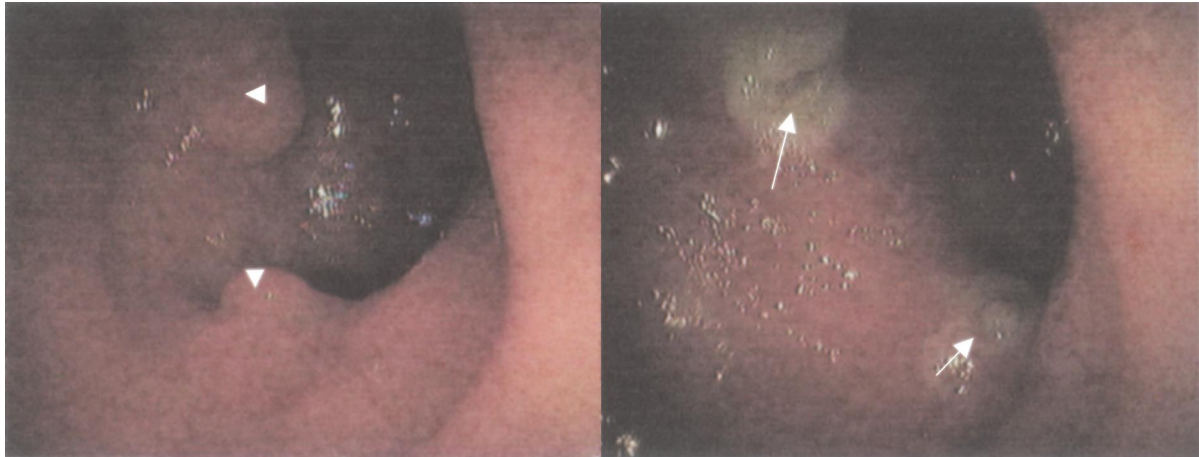


Fig 4. Rectosigmoid colonic polyps (arrowheads) and postpolypectomy sites (arrows).

17.2 sec, 1.9, and 34.3 sec, respectively. At colonoscopy, two rectosigmoid polyps of 4 and 8 mm and a diminutive rectal polyp, rectal varices, and internal hemorrhoids were identified. The patient's coagulopathy was immediately corrected with 120 $\mu\text{g}/\text{kg}$ intravenous bolus infusion of rhFVIIa. Both rectosigmoid polyps were removed using snare cautery, and the 3-mm rectal polyp was removed using cold forceps. The smaller 4-mm rectosigmoid polyp was not retrieved. The retrieved rectosigmoid polyp was a lipoma and the rectal polyp was hyperplastic. The patient tolerated the procedure well (see Figure 4). Serial follow-up of her coagulation parameters was accomplished to monitor the efficacy of the administered rhFVIIa (Figures 5 and 6). The patient

was discharged on hospital day 13 without requiring any further transfusions, as her hemoglobin remained stable (six days after polypectomy). She was subsequently seen in the outpatient clinic three weeks after discharge from hospital for follow-up without any evidence of rectal bleeding or a drop in her hemoglobin level.

Case 3. A 49-year-old white homosexual male with history of chronic alcoholism and cirrhosis was hospitalized for jaundice, increasing abdominal girth, weight gain, and confusion. He also reported associated exertional dyspnea, altered sleep pattern, and fatigue. There was no hematemesis, melena, or hematochezia. He denied fever, abdominal pain, or focal neurological deficits. His past medical history was unremarkable except for

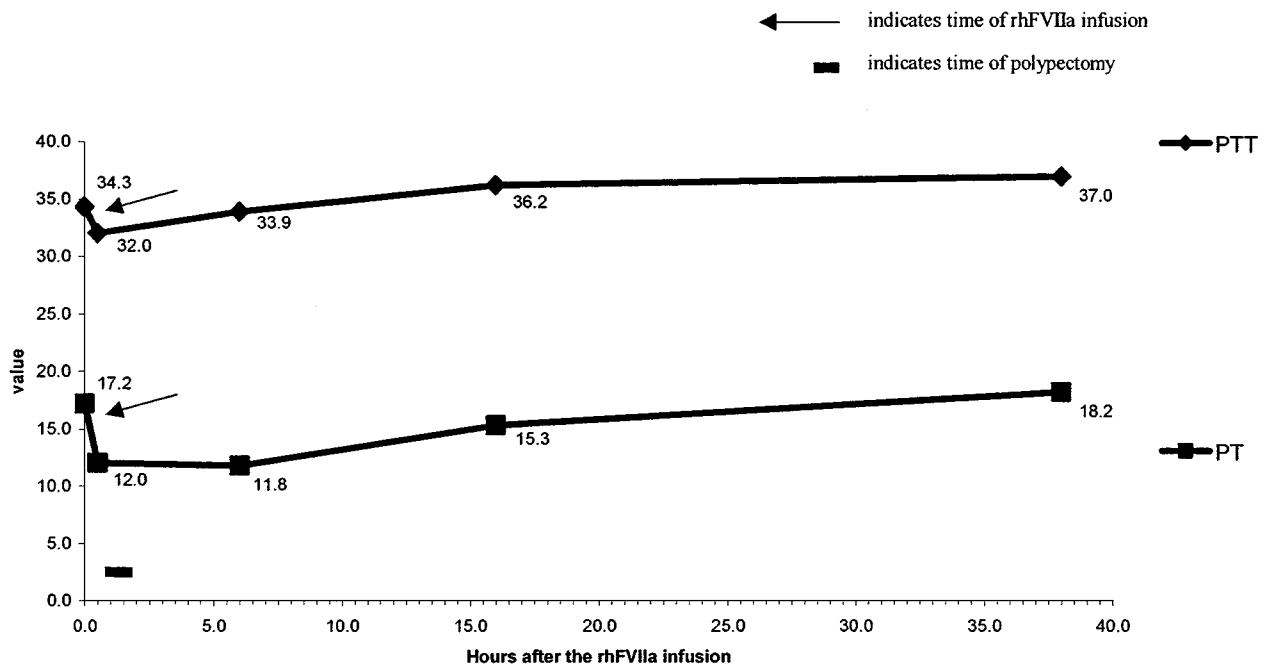


Fig 5. Sequential changes in PTT and PT with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 2. The arrow denotes the time of infusion.

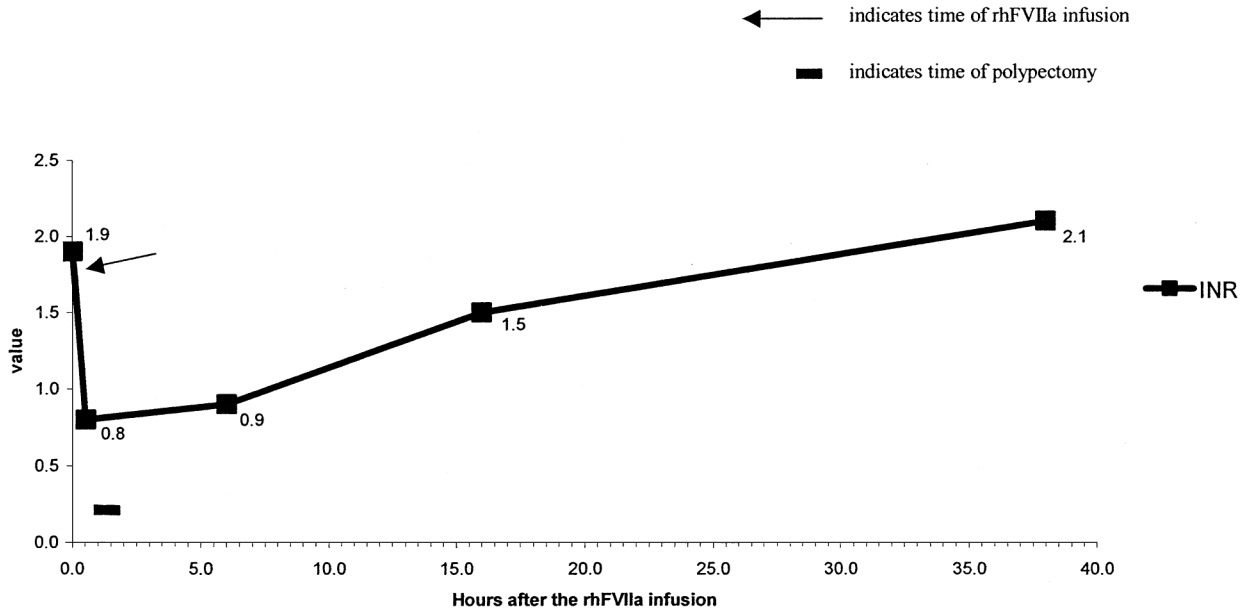


Fig 6. Sequential changes in INR with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 2. The arrow denotes the time of infusion.

hypertension. He had been drinking 5–6 cans of beer daily for more than 20 years. He claimed to have quit drinking only two months ago and did so because of the development of jaundice. He denied ever having received a blood transfusion or using intravenous drugs or having any tattoos.

His physical examination revealed scleral icterus, an enlarged liver without tenderness, massive ascites, a nonpalpable spleen, and lower extremity edema. He was lethargic and his mentation was slow. Asterixis was present.

An upper endoscopy was performed. It revealed nonbleeding grade IV esophageal varices that were ligated with seven bands. Gastric antral biopsies showed minimal chronic gastritis without evidence of *H. pylori*. No complications were experienced with the upper endoscopy.

A diagnostic colonoscopy was performed on the ninth hospital day. Immediately prior to the procedure, his laboratory evaluation showed a PT of 20.1 sec, INR 2.6, and a PTT of 49.5 sec. The colonoscopy revealed a 2.0-cm pedunculated polyp in the ascending colon and a 5.0-cm sessile polyp in the descending colon (Figure 7). The coagulopathy was corrected in the endoscopy suite while the patient was being colonoscoped with an intravenous administration of rhFVIIa at a dose of 120 $\mu\text{g}/\text{kg}$. Serial PT, PTT, and INR measures were obtained (Figure 8 and 9). Ten minutes after the infusion, the PT, INR and PTT were 11.4 sec, 0.8, and 43.4 sec, respectively. The polyps were removed and retrieved successfully using snare cautery. The histology of the ascending colon polyp revealed a tubular adenoma. The descending colon polyp revealed an intramucosal adenocarcinoma



Fig 7. Descending colon polyp (arrowhead) and postpolypectomy site (arrows).

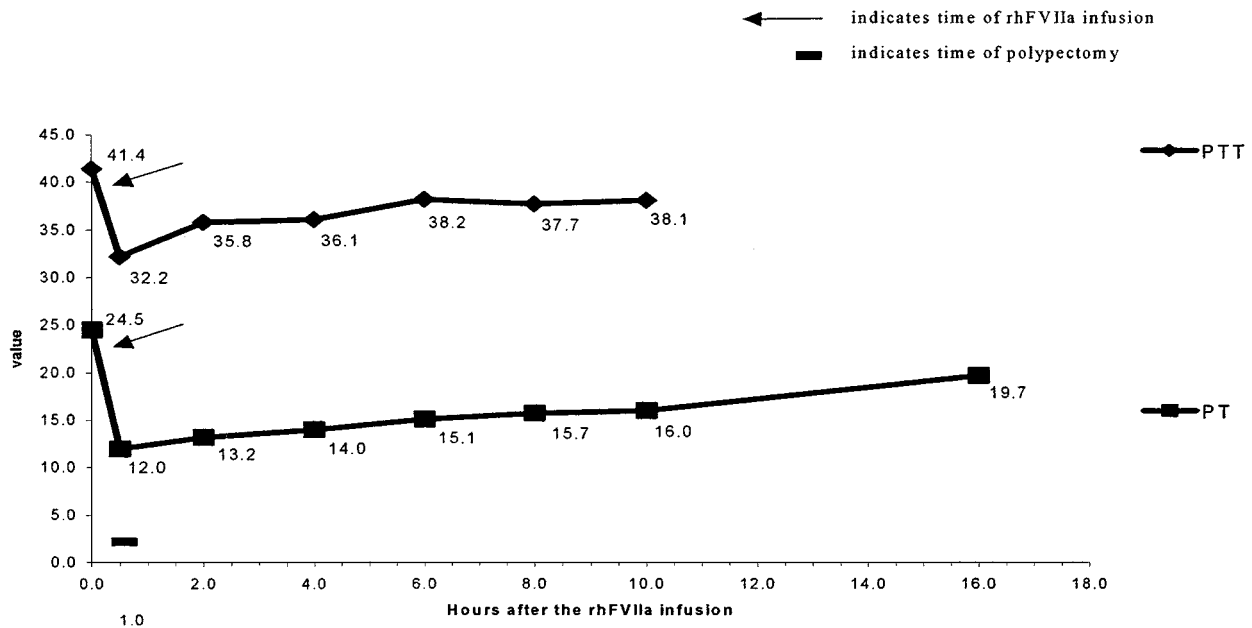


Fig 8. Sequential changes in PTT and PT with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 3 (first colonoscopy). The arrow denotes the time of infusion.

arising from a tubular adenoma with a definite tumor free margin. By 10 hr after the procedure, the patient's PT was 13.5 sec, INR was 1.2, and PTT was 42.7 sec. The patient tolerated the procedure well without any clinical signs of postpolypectomy bleeding. He was subsequently discharged home and at two weeks, his hemoglobin was noted to be stable and no further gastrointestinal bleeding had occurred.

He was readmitted two weeks later as a result of worsening liver disease. He continued to be lethargic and had developed massive ascites. There was no evidence of gastrointestinal bleeding.

To expedite the process of liver transplant, the patient underwent repeat colonoscopy to remove any residual polyps, especially from the previously resected site. Before the

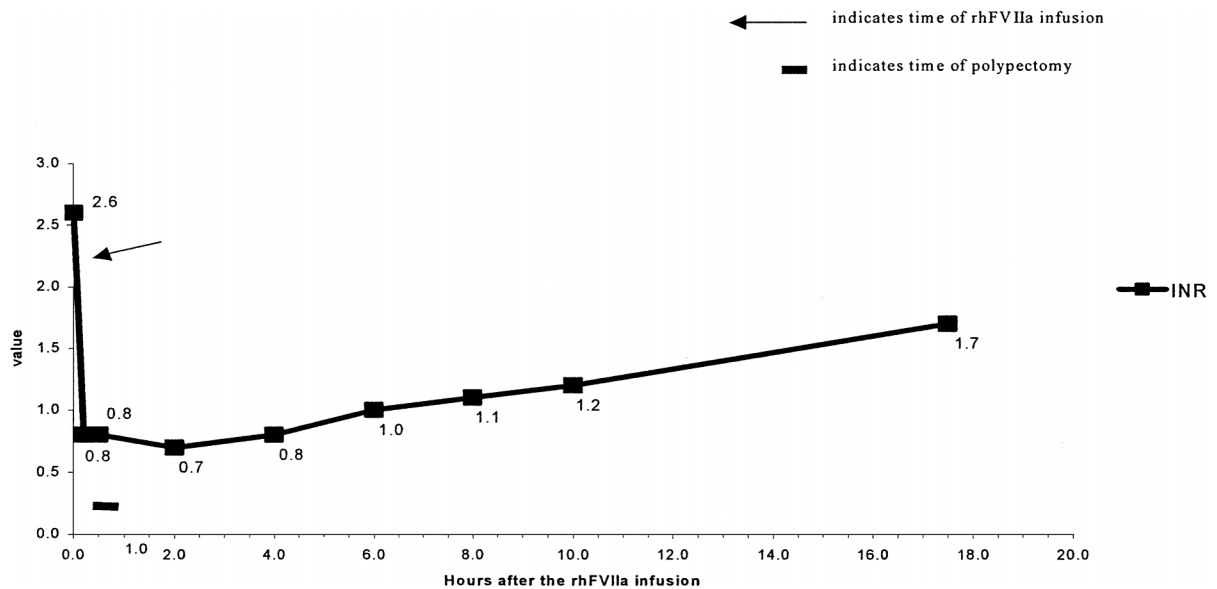


Fig 9. Sequential changes in INR with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 3 (first colonoscopy). The arrow denotes the time of infusion.

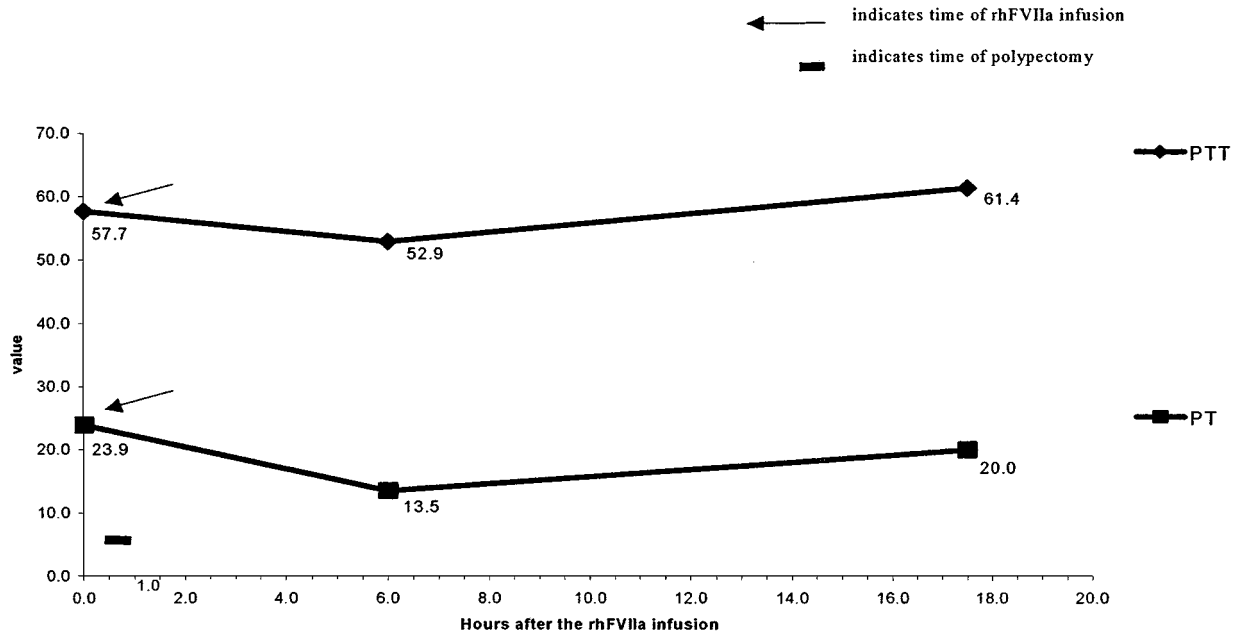


Fig 10. Sequential changes in PTT and PT with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 3 (second colonoscopy). The arrow denotes the time of infusion.

procedure, the PT was 23.9 sec, INR was 3.7, and PTT was 57.7 sec. The rhFVIIa was infused prior to the colonoscopy at a dose of 120 $\mu\text{g}/\text{kg}$. At colonoscopy, a 1.0-cm sessile cecal polyp and two 0.5-cm ascending colon polyps were removed using snare cautery. The previously resected polyp sites showed complete healing without any residual abnormal tissue. At 6 hr after the procedure, the PT was 13.5 sec, INR was 1.2, and PTT

was 52.9 sec (Figures 10 and 11). Again no postpolypectomy bleeding occurred.

Case 4. A 76-year-old male had a resection of his terminal ileum 10 years previously for idiopathic thrombosis of his visceral vessels. A subsequent work-up for a hypercoagulable state revealed homozygosity for the factor V Leiden mutation. He was placed on chronic anticoagulation using coumadin and was

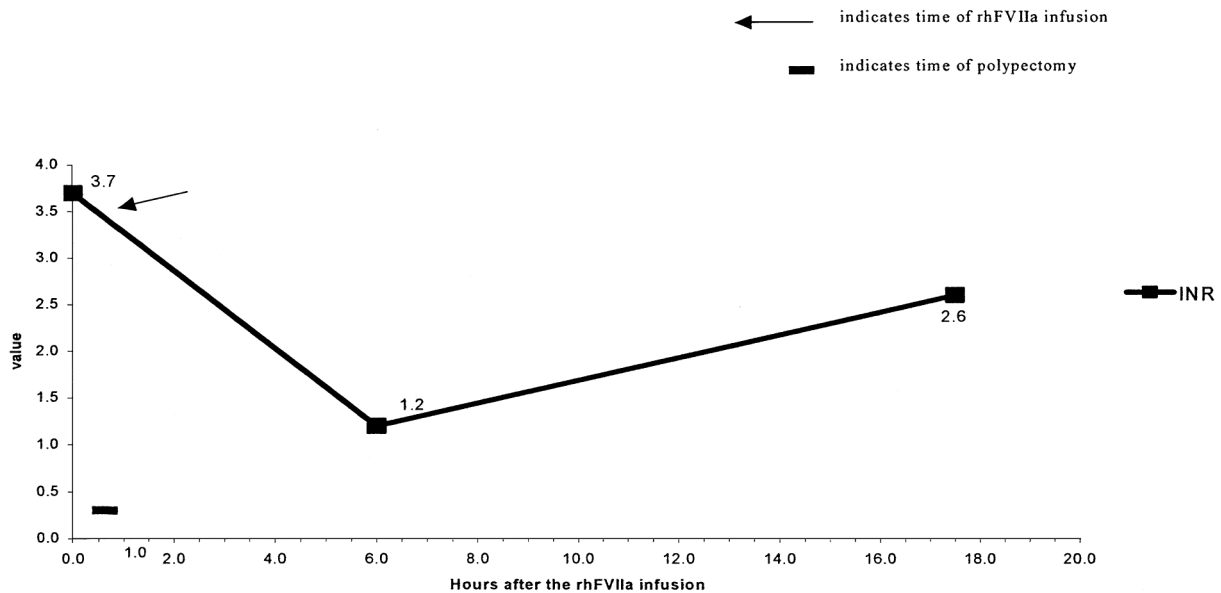


Fig 11. Sequential changes in INR with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 3 (second colonoscopy). The arrow denotes the time of infusion.

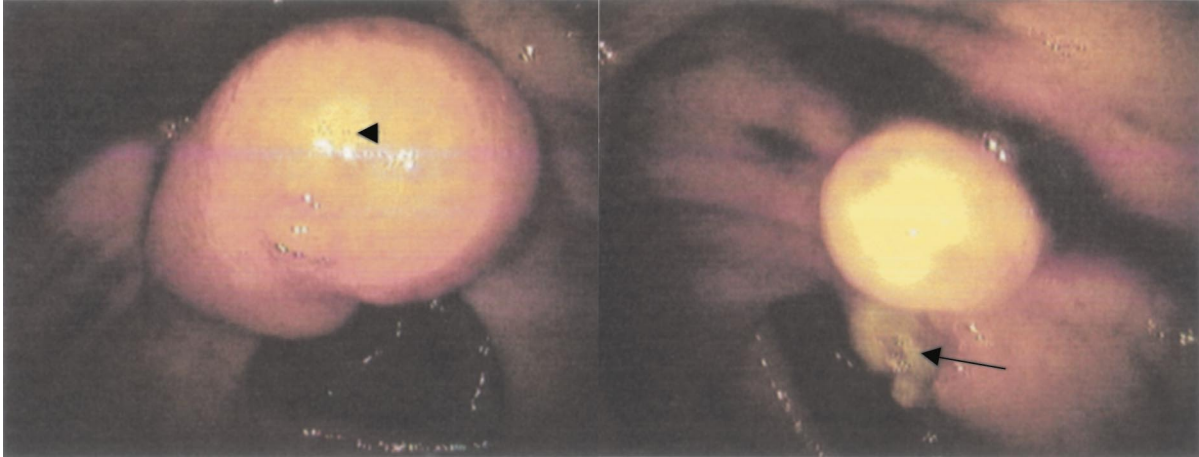


Fig 12. Ascending colon polyp (arrowhead) and postpolypectomy site (arrow).

maintained at an INR between 2.0 and 3.5. Recently, he was diagnosed with cryptogenic cirrhosis and was endoscoped and found to have grade IV esophageal varices. A liver transplant evaluation was initiated, with the idea that the new liver would correct his portal hypertension and his hypercoagulable state simultaneously. He underwent a screening colonoscopy as part of the liver transplant evaluation.

He was found to have a 5.0-cm sessile ascending colon polyp at colonoscopy (Figure 12). rhFVIIa at a dose of 120 $\mu\text{g}/\text{kg}$ was administered in the endoscopy suite as an intravenous bolus to correct the PT and INR, while the patient was being colonoscoped. Serial PT, PTT, and INR measures were obtained (Figures 13 and 14). At 10 minutes after the infusion, the PT, INR

and PTT were 13.6 sec, 1.2, and 37.7 sec, respectively. The polyp was removed and retrieved successfully using a snarecautery and a basket. Histopathology revealed the polyp to be a lipoma. At 6 hr after the procedure the patient's PT was 15.9 sec, INR was 1.6, and PTT was 39.2 sec. The patient tolerated the procedure well without any signs of postpolypectomy bleeding.

DISCUSSION

The prevalence of colonic polyps in patients with cirrhosis appears to be higher than that of general population (4, 5). This may be related to the use of alcohol and the

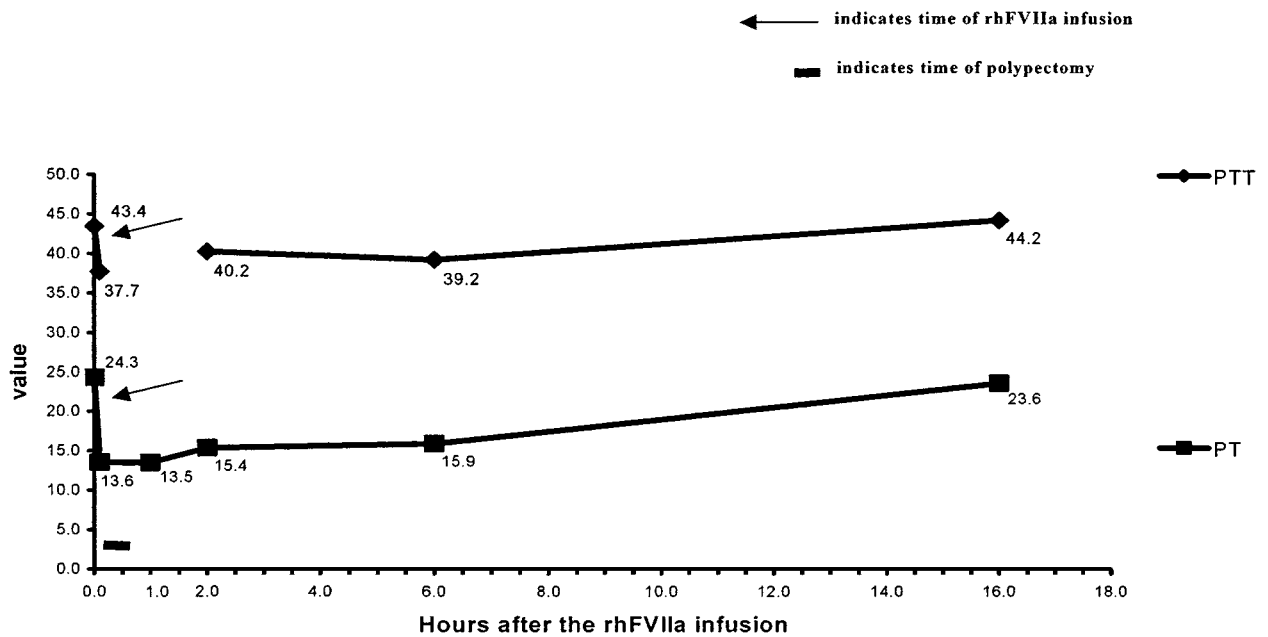


Fig 13. Sequential changes in PTT and PT with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 4. The arrow denotes the time of infusion.

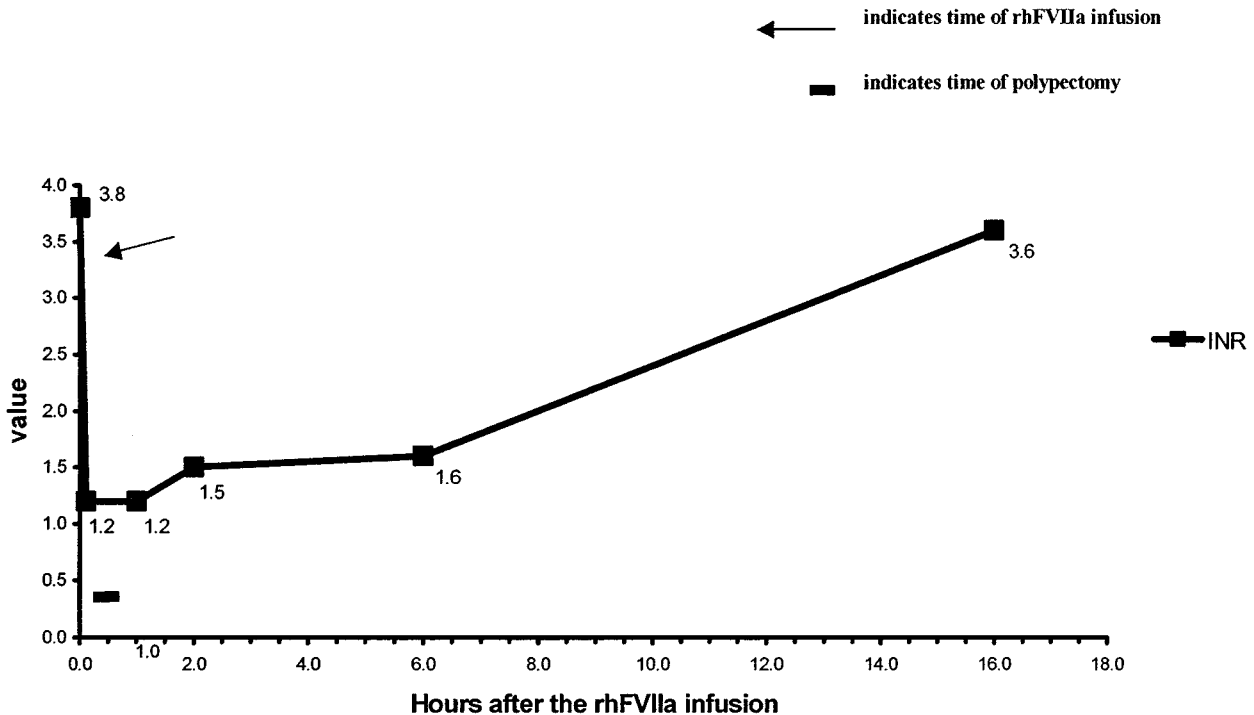


Fig 14. Sequential changes in INR with the intravenous bolus infusion of 120 $\mu\text{g}/\text{kg}$ of rhFVIIa in case 4. The arrow denotes the time of infusion.

presence of an abnormal or defective immune surveillance in cirrhotic patients.

In many liver transplant centers, colonoscopy is performed routinely as part of the pretransplant evaluation (2). The frequency of polyps detected by such screening colonoscopies in cirrhotic patients has been reported to be between 8.4 to 21% (6–9). Endoscopic resection of these polyps is often not accomplished because of the risk of postpolypectomy hemorrhagic complications due to the associated coagulopathy (2, 3). The risk of postpolypectomy bleeding in the general population is between 0.2 and 2.24% (10–14). The risk of postpolypectomy bleeding in patients with a coagulopathy due to cirrhosis is unknown, but it must clearly be higher than that of the general population. The risk of postpolypectomy bleeding in cirrhotic patients, as in the case of normals, appears to be related to both the size of the polyp and the severity of the coagulopathy.

The coagulopathy present in patients with liver disease is principally due to a decline in the levels of hepatically synthesized procoagulant factors. Other factors that contribute to the coagulopathy include thrombocytopenia (15) and the dysfibrinogenemia that occurs in some cirrhotics. Factor VII (FVII) is the most sensitive procoagulant to hepatocellular damage. FVII levels fall with progressive liver disease, followed by declines in factors II and X. Factor IX levels are much less affected by hepatocellular

lar disease. Other causes for bleeding in cirrhotics include a low-grade disseminated intravascular coagulation (DIC) that is present in a few and is manifested by reduced levels of fibrinogen and increased levels of fibrin split products and *d*-dimers (15). FVII appears to be the factor that is crucial for the initiation of the extrinsic coagulation cascade by forming a complex with the tissue factor (TF) (16).

A colonoscopic polypectomy is considered a high-risk procedure in a coagulopathic patient (17). The current practice for polypectomy in coagulopathic cirrhotic patients is to reverse the coagulopathy using fresh frozen plasma (FFP) prior to the polypectomy. The reversal of the coagulopathy in a cirrhotic patient is unpredictable and may require large volumes of FFP and frequent monitoring of the PT and PTT. The volume of FFP required to reverse the coagulopathy present in many cirrhotics often leads to fluid overload and occasionally pulmonary edema. In our experience, the volume of FFP required to reduce the INR to a value below 1.5 is about 1.5–2.0 liters of FFP. The administration of such a volume load can complicate the clinical management of the patient, particularly if there is associated renal or cardiac dysfunction. Additionally, large volume infusions can increase portal pressure and exacerbate variceal bleeding. FFP contains all the factors required for coagulation. However, the concentration of each factor in each

unit is highly variable. Importantly, FFP has no effect on platelet function. The use of FFP to correct a coagulopathy, prior to a polypectomy, would require repeat colonoscopy on another day, a prolonged hospital stay, and the use of additional nursing staff resources. The FFP infusion itself is associated with the potential risk of hypersensitivity reactions and transmission of bloodborne infectious agents. The routine preendoscopic correction with FFP infusion of a coagulopathy present in a cirrhotic patient who does not need an intervention is unjustifiable. In those with polyps, a second colonoscopy is performed after the infusion of FFP, usually several days later.

The use of rhFVIIa can overcome most of these problems associated with the use of FFP. In the four cases (five settings) presented, rhFVIIa was used in the endoscopy suite with successful reversal of the coagulopathy following a single intravenous bolus infusion over 2–4 min. The endoscopy nurse administered the infusion just before the polypectomy. The reversal of coagulopathy was immediate and predictable. This effect was similar to that seen in other studies wherein rhFVIIa has been used prior to cataract surgery, laparoscopic liver biopsies, and therapeutic alcohol injection of a hepatocellular carcinoma in a patient with cirrhosis (18–20). The successful use of rhFVIIa has been reported recently in noncirrhotic patients on coumadin who require invasive procedures (16, 26).

In patients with liver disease, the duration of the corrected coagulopathy following an infusion of rhFVIIa has been shown to be as long as 12 hr with a dose of 80 $\mu\text{g}/\text{kg}$ (16, 18–20). The total duration of the coagulation correction depends upon the dose of rhFVIIa used and the severity of underlying liver disease and associated coagulopathy (16, 18–21). The hemostatic effect can last for 10–16 hr with a 120 $\mu\text{g}/\text{kg}$ dose of rhFVIIa. This higher dose of rhFVIIa was used in the present study with the goal of achieving a hemostatic effect for 24 hr or more to prevent postpolypectomy bleeding. No early or delayed postpolypectomy bleeding was observed in any of the cases reported.

The use of rhFVIIa has been reported to control bleeding due to thrombocytopenia and thrombasthenia unlike FFP (16, 22–25). In the patients presented, the platelet counts remained unchanged and platelet function was not analyzed, as it was not considered to be a limiting factor. To our knowledge, this is the first report of the use of rhFVIIa for colonic polypectomies in patients with a coagulopathy and cirrhosis. These cases demonstrate that the use of rhFVIIa is safe in coagulopathic cirrhotic patients as well as in patients who are on coumadin. In patients, who are on coumadin, the requirement for hospitalization

and intravenous heparin infusion can be avoided by the use of rhFVIIa with reinstatement of coumadin therapy after the procedure, as occurred in the present case 4.

The reported adverse reactions to rhFVIIa infusion are minimal and have no definite relationship to rhFVIIa administration. The most frequently reported ones are mild fever, hypertension, skin reactions, and low-grade DIC (27). There were no adverse events related to rhFVIIa infusion in the patients included in this report.

The main deterrent to the wider use of rhFVIIa appears to be the cost of the material. Because the current Food and Drug Administration (FDA) approval has limited the indications for the use of rhFVIIa to bleeding episodes in hemophilia A or B patients with inhibitors to factor VIII or factor IX and the few individuals with a congenital deficiency of FVII, its usefulness in patients with coagulopathy due to liver disease has been recognized only recently. Its use in a coagulopathic cirrhotic patient currently costs 4 times the direct costs of the use of FFP. The indirect costs of the use of FFP in the cases reported can be estimated only by a controlled trial, but would include prolonged hospitalization, additional nursing and colonoscopy charges, as well as endoscopy suite charges. Part of the reason for the high cost of rhFVIIa appears to be its limited number of approved indications, which limits its market size. The cost of the agent may well be reduced if its use increases, as appears likely with its increased use in trauma, general surgery, and ICU settings.

SUMMARY

The prevalence of colonic polyps in patients with cirrhosis appears to be higher than that of the general population. The current practice for a polypectomy in a coagulopathic cirrhotic patient involves the reversal of the coagulopathy using fresh frozen plasma (FFP) prior to the polypectomy, usually at a second colonoscopy. The use of FFP is associated with many problems, particularly that of volume overload. Here we report four cases with advanced cirrhosis and severe coagulopathy that underwent polypectomies by snare cautery after an intravenous bolus infusion of recombinant human factor VIIa (rhFVIIa). The dose used was 120 $\mu\text{g}/\text{kg}$, which provided normalization of the coagulation parameters for 10–16 hr. The immediate use of rhFVIIa reduced the utilization of resources and enabled the performance of the polypectomies at the initial colonoscopy. No postpolypectomy bleeding was noted. The high cost of the drug is the only obstacle to a wider use of rhFVIIa for this purpose. The cost of the drug, however, is offset substantially by the cost of hospitalization for the administration of FFP,

the cost of a second colonoscopy, and the charges associated with a second utilization of the endoscopy suite.

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