Successful endoscopic sphincterotomy for choledocholithiasis in a patient with severe hemophilia A and inhibitors

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Abstract

Endoscopic sphincterotomy (ES) is a standard procedure for bile duct stone removal. However, the safety of ES in patients with hemophilia remains unknown. We treated a 46-year-old man who had choledocholithiasis and severe hemophilia A with high-responding inhibitors during immune tolerance induction therapy. Since coagulation factor VIII inhibitors neutralize and inactivate endogenous and exogenous factor VIII, bleeding risk is higher in hemophilia A patients with inhibitors than in those without inhibitors. With adequate pre- and post-procedure monitoring of the clotting factor and supplemented clotting factor, the patient could safely undergo ES without bleeding complications. ES can be also an effective and safe first-line therapy for choledocholithiasis in patients with hemophilia and inhibitors under the condition of appropriate management.

Keywords

Endoscopic sphincterotomy, Hemophilia, Choledocholithiasis

Introduction

Choledocholithiasis is a common disease that requires medical attention and intervention. Endoscopic sphincterotomy (ES) with endoscopic retrograde cholangiopancreatography (ERCP) is a procedure that is used worldwide for bile duct stone removal. Hemorrhage is one of the adverse events of ES, the incidence of which ranges from 2% to 5% [1, 2]. However, the safety of ES in patients with coagulopathy, such as hemophilia patients, is unclear. Hemophilia patients require blood clotting factor infusion before invasive procedures to prevent hemorrhage. A large volume of blood clotting factor is needed for hemophilia patients with inhibitors that neutralize infused factor VIII or IX. Immune tolerance induction (ITI) therapy is the only proven modality for achieving antigen-specific tolerance to factor VIII and for eliminating factor VIII antibodies in patients with hemophilia A.

Regarding the safety of ES in hemophilia patients, there has been only one report showing the safety of ES in hemophilia patients without an inhibitor [3]. We herein report successful ES in a patient with severe hemophilia A with inhibitors during immune tolerance induction therapy.

Case Report

A 46-year-old man with congenital severe hemophilia A and high-responding inhibitors (7 Bethesda units, BU) had been treated with recombinant human coagulation factor VIII (rFVIII) at 75 IU/kg three times per week as ITI for four months. In addition, he had been received regular ambulatory treatment of compensated hepatitis C virus cirrhosis waiting for liver transplantation. At the consultation to our department, laboratory tests showed elevated serum levels of aspartate aminotransferase (AST) (199 U/L), alanine aminotransferase (ALT) (116 U/L), alkaline phosphatase (ALP) (616 U/L), total bilirubin (T-BIL) (3.0 mg/dL) and direct bilirubin (D-BIL) (1.7 mg/dL). Prothrombin time activity (PT), 74.9 %; activated partial thromboplastin time (APTT), 133 sec; factor VIII activity was <1.0 %, respectively. Its inhibitor titer was gradually decreased by 1 BU due to ITI until the initial visit to our department. A diagnosis of choledocholithiasis with cholecystolithiasis was made on the basis of findings of small calculuses in the gallbladder in computed tomography (CT) and a defect in the distal common bile duct in magnetic resonance cholangiopancreatography (MRCP) (Fig. 1). Although he had no symptoms, we scheduled removal of the common bile duct stone due to fears of future acute cholangitis or gallstone pancreatitis. As endoscopic papillary

balloon dilatation (EPBD) had a higher risk of pancreatitis than ES [4-6], which might make liver transplantation difficult, we chose ES for removing a common bile duct stone.

Because of the effect of ITI, the patient with 1 BU of inhibitor could undergo high-dose FVIII therapy but not bypass therapy based on the Japanese guideline (Fig. 2) [7]. Although the theoretical dose of rFVIII for neutralization was 25 IU/kg for the patient [8], we considered that FVIII had a short half-life with an average of about 12 h in adults [9] and that bleeding could occur within a few days after ES as a late adverse event. Based on such a condition and an experienced hematologist's opinion, rFVIII was administered by bolus injection at 75 IU/kg as well as the high dose of ITI one day before the endoscopic procedure and 30 min before the procedure. Endoscopic cholangiography displayed a filling defect in the distal common bile duct. ES was performed (Fig. 3) and a stone was removed from the biliary tract by an extraction balloon catheter without major bleeding (Fig. 4). rFVIII was readministered to the patient by bolus injection at 50 IU/kg 3 hours after the procedure. Furthermore, rFVIII was administered at 75 IU/kg and 50 IU/kg alternately every 24 hours for 4 days after the stone removal with ES. After the treatment, factor VIII activity was over 50% and

APTT was almost within a normal limit (Fig. 5). No complication was observed and the patient was discharged 6 days after the procedure.

After discharge, he has continuously been treated with administration of rFVIII at 75 IU/kg three times per week as ITI, and neither gastrointestinal bleeding nor elevation of the inhibitor titer has been noted.

Discussion

The present case suggested that ES can be an effective and safe first-line therapeutic option as a treatment for choledocholithiasis with severe hemophilia with high-responding inhibitors.

Hemorrhage is one of the most common complications of ES, the incidence of which ranges from 2% to 5% [1, 2]. In some cases, hemorrhage can be severe and life-threatening with a mortality rate of approximately 0.3% [10]. The American Society for Gastrointestinal Endoscopy (ASGE) has provided general guidelines for endoscopic procedures [11] but has not addressed the performance of endoscopic procedures in patients with coagulopathy.

Van Os et al. [12] recommended that factor VIII or IX activity should be maintained at 30% to 50% or more for management of patients with inherited or acquired coagulopathy. Katsinelos et al. [3] reported that ES was a safe procedure for hemophilia patients and that activity of the deficient coagulation factor was maintained at 100% 24 hours before and after ES and at 50% or more 48 hours after ES by coagulation factor replacement. However, only two out of the six patients in their study had severe hemophilia and no patient had inhibitors.

Inhibitors occur in up to 30% of severe hemophilia A patients by replacement with exogenous recombinant or plasma-derived FVIII [13]. Inhibitors usually neutralize and inactivate residual endogenous and exogenous FVIII. ITI is the only proven modality for antigen-specific tolerance to FVIII and elimination of FVIII antibodies in patients with hemophilia A [14]. The patients can be categorized into low and high responders: high responders have had an antibody titer over 5 BU [15]. It is usually recommended that high responders with high titers of inhibitors should undergo bypass therapy, namely, administration of activated prothrombin complex concentrates (aPCCs) or recombinant FVII (rFVIIa) to prevent bleeding during invasive procedures [16]. However, bypass therapy is palliative and expensive. In addition, our patient was a high responder with low titers of inhibitors under ITI; therefore, we also could choose high-dose rFVIII therapy based on the Japanese guideline [7]. The gradually elevated and high level of the factor VIII activity was anticipated during the treatment. Thus, we finally chose high-dose FVIII therapy. After the treatment the plasma factor VIII activity level had been higher than 50% and APTT was normal as expected. Under such a condition, ES was safely performed.

Aside from ES, EPBD is another endoscopic procedure for bile duct stone

removal, especially in patients with coagulopathy [17-19]. However, it has been reported that there is a higher incidence of post-ERCP pancreatitis (10-16%) in patients who received EPBD than in patients who received ES [4-6], which can lead to a severe systemic condition. In addition, there has been no report about the safety of EPBD in hemophilia patients. Therefore, we finally chose ES for choledocholithiasis in our case.

In conclusion, ES can be effectively and safely performed in patients with hemophilia A and high-responding inhibitors after sufficient and appropriate preparation.

Disclosures

Conflict of interest: The authors declare that they have no conflict of interest.

Human Rights: All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent: Informed consent was obtained from the patient for being included in the study.

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Figure legends

Figure 1.

(a) Computed tomography showing the cholecystolithiasis. (b) Magnetic resonance cholangiopancreatography showing the bile duct stone.

Figure 2.

Hemostatic treatment algorithm for patients with congenital hemophilia with high-responding inhibitors regarding endoscopic therapies.

Figure 3.

(a) Endoscopic image showing the ampulla of Vater. (b) Endoscopic image of the ampulla of Vater during ES. (c) Endoscopic image of the ampulla of Vater after sphincterotomy.

Figure 4.

(a) Radiograph showing the biliary stones at hilar bile duct. (inset: endoscopic view) (b) Radiograph showing the biliary stones and the extraction balloon. (inset: endoscopic

view of the extracted biliary stones).

Figure 5.

Clinical course before and after the endoscopic procedure.

Fig. 1

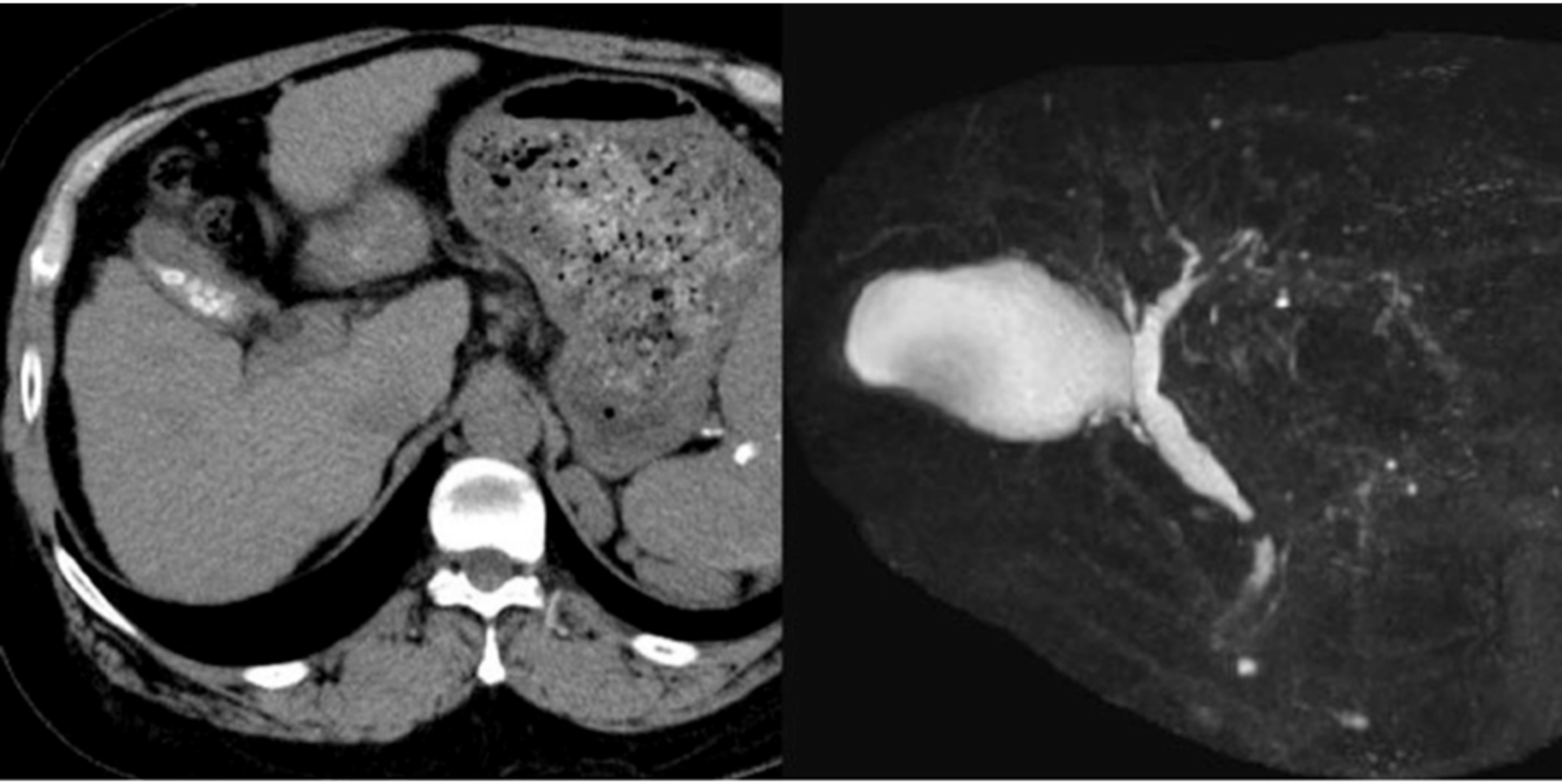


Fig. 2

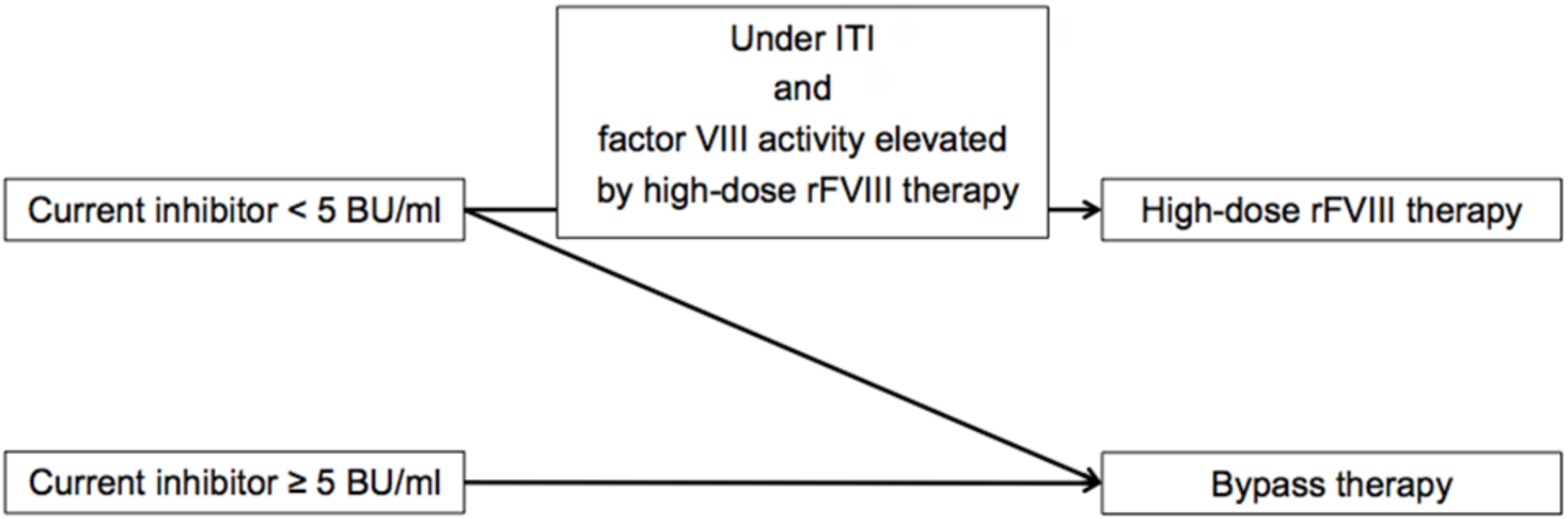

Under ITI
and
factor VIII activity elevated
by high-dose rFVIII therapy
Current inhibitor < 5 BU/ml
High-dose rFVIII therapy
Current inhibitor ≥ 5 BU/ml
Bypass therapy

Fig. 3

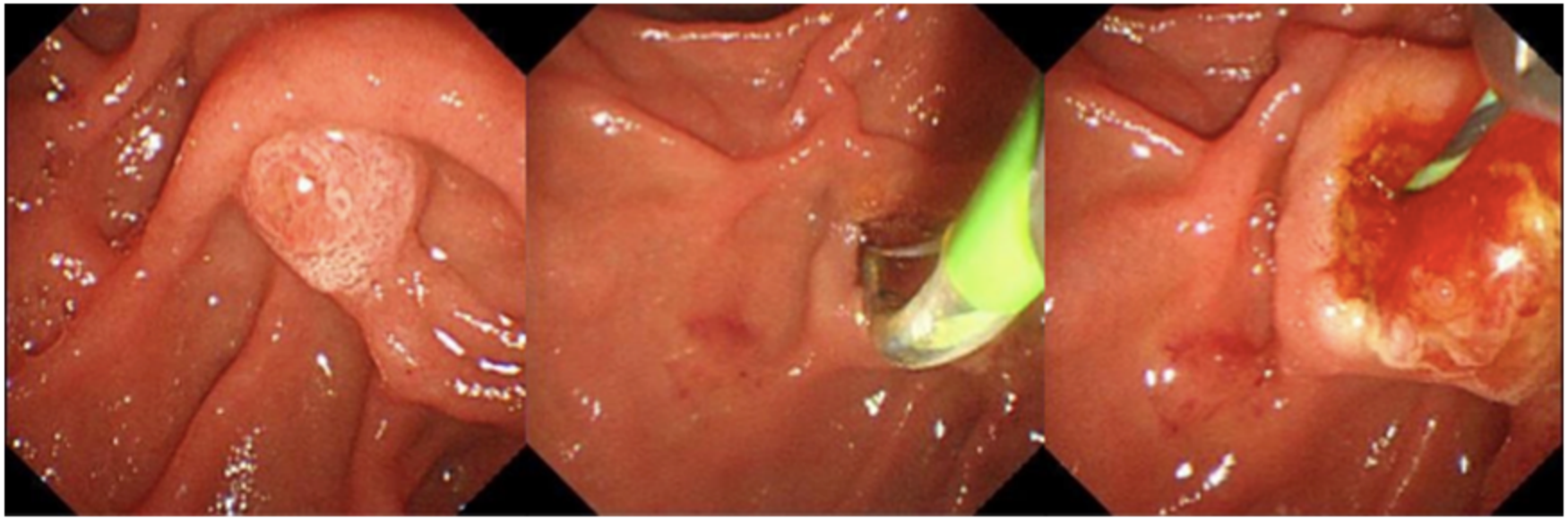


Fig. 4

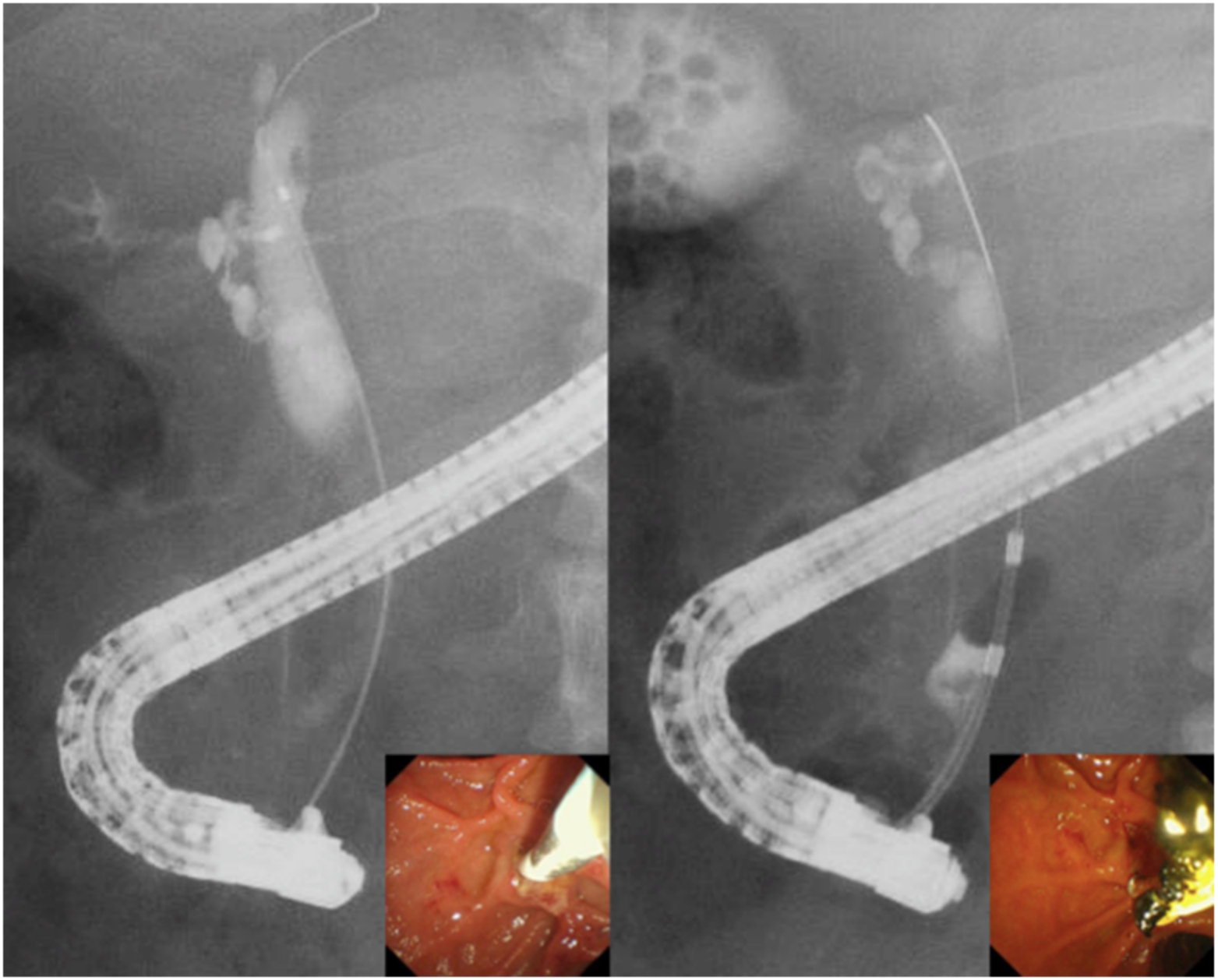
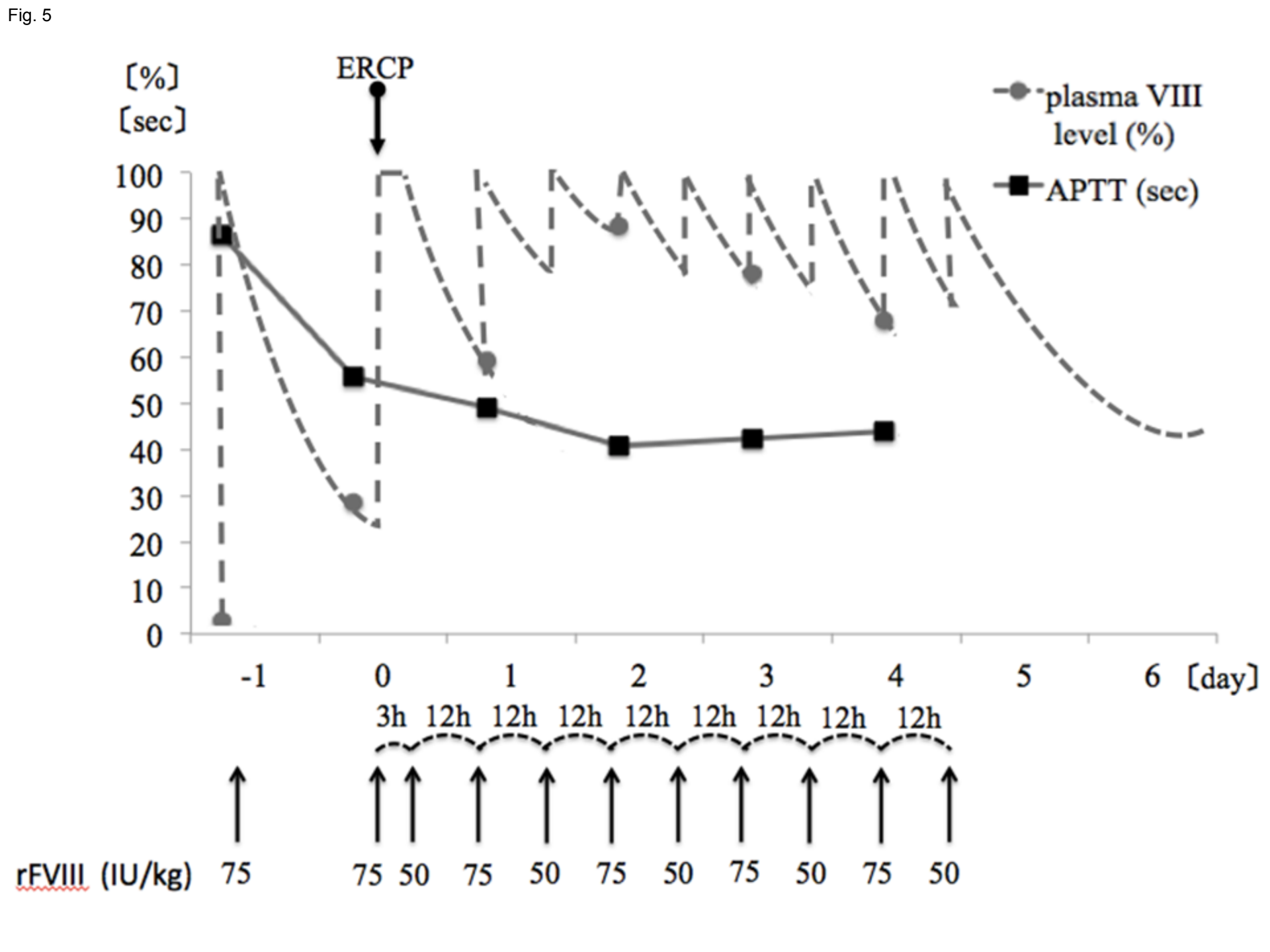


Fig. 5


〔%〕
〔sec〕
ERCP
plasma VIII level (%)
APTT (sec)
100
90
80
70
60
50
40
30
20
10
0
-1
0
1
2
3
4
5
6
〔day〕
3h
12h
12h
12h
12h
12h
12h
12h
12h
rFVIII (IU/kg)
75
75
50
75
50
75
50
75
50
75
50