

Case Series

Endoscopic Hemostatic Treatment with a Novel Self-Assembling Peptide Gel for Precut Fistulotomy-Related Bleeding

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Keywords

TDM-621 · Precut fistulotomy · Hemostasis

Abstract

Introduction: Precut fistulotomy is of interest as one of the salvage techniques for selective bile duct cannulation using endoscopic retrograde cholangiopancreatography. Of the various endoscopic treatments reported to date for bleeding associated with papillotomy incision, endoscopic hemostasis treatment with a novel self-assembling peptide (SAP) matrix-forming gel (TDM-621) (3-D Matrix Ltd., Tokyo, Japan) remains only insufficiently reported in the literature. **Case Presentation:** We herein report 6 cases of precut fistulotomy-related bleeding successfully treated with endoscopic hemostasis treatment with TDM-621, i.e., 5 and 1 cases during and after precut fistulotomy, respectively, in 2 males and 4 females aged 68–96 years (mean age, 85 years), 3 of whom had been on antithrombotic drugs. Types of bleeding treated included oozing bleeding ($n = 5$) and oozing bleeding from a visible vessel ($n = 1$). In all cases, complete hemostasis was achieved with TDM-621 without causing rebleeding. **Conclusion:** Endoscopic hemostasis with TDM-621 may prove effective for precut fistulotomy-related bleeding and represent a potential modality of first choice in hemostasis. In addition, endoscopic hemostasis with combined modality therapy using TDM-621 and endoscopic hemoclips may prove effective for bleeding from visible vessels.

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Introduction

Selective bile duct cannulation (SBDC) is among the most important and basic techniques in endoscopic retrograde cholangiopancreatography (ERCP), accounting for a success rate of 95–100% in the hands of expert endoscopists [1], while several alternative routine salvage techniques are being attempted after failed SBDC [2]. Of these, precut techniques are of interest, particularly precut fistulotomy (PF), which has been recommended by the European Society of Gastrointestinal Endoscopy (ESGE) as the preferred modality for precutting [3]. Bleeding has been reported as an adverse event associated with this procedure [4]. Recently, a novel self-assembling peptide matrix-forming gel (TDM-621) (3-D Matrix Ltd., Tokyo, Japan) has been reported to be useful for hemostasis in endoscopic sphincterotomy (EST)-related bleeding [5–7]. TDM-621 is reported to achieve hemostasis by rapidly forming nanofibers into a peptide gel as it comes into contact with blood or bodily fluids, coating the bleeding point and forming a mechanical barrier, thus triggering blood clotting [8]. Very recently, we reported a case of delayed bleeding following precut sphincterotomy successfully treated with TDM-621 [9]. While clinical reports to date have been limited, we herein report additional 6 cases of PF-related bleeding successfully treated with TDM-621, as a second report describing a case series, where EST was not attempted in all cases before proceeding to precut sphincterotomy. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see <https://doi.org/10.1159/000536620>).

Case Series

Case 1

A 78-year-old woman presented to our hospital for abdominal pain and was diagnosed with choledocholithiasis. She had a history of spinal stenosis and had been taking limaprost alfadex. ERCP was performed using the PF technique, and a biliary stent was inserted (Fig. 1a, b). Oozing bleeding was present and persisted from the site of precut papillotomy, and hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (Fig. 1c), and complete hemostasis was achieved (Fig. 1d). Limaprost alfadex was resumed from the day after hemostasis.

Case 2

A 94-year-old man was referred to our hospital for acute cholangitis with cholangiocarcinoma. He had been on antithrombotic therapy with the direct oral anticoagulant (DOAC) edoxaban. ERCP was performed using the PF technique, and a biliary stent was inserted. Following onset of melena 4 days later, he was found to be severely anemic (Hb, 6.7 g/dL). Emergency ERCP revealed oozing bleeding between the papilla and the stent (Fig. 1e). As the point of bleeding was difficult to identify, TDM-621 (3 mL) was applied to the bleeding site through a dedicated endoscopic catheter (Fig. 1f), which led to the bleeding volume being suppressed and to the bleeding point being identified (Fig. 1g). Hemostasis was subsequently achieved with an endoscopic hemoclip (Fig. 1h). Edoxaban was resumed the day after hemostasis.

Case 3

An 88-year-old woman was raced to our hospital for acute cholangitis with choledocholithiasis. ERCP was performed using the PF technique, and a biliary stent was inserted (Fig. 2a, b). Oozing bleeding was shown to be present and persist from the site of precut

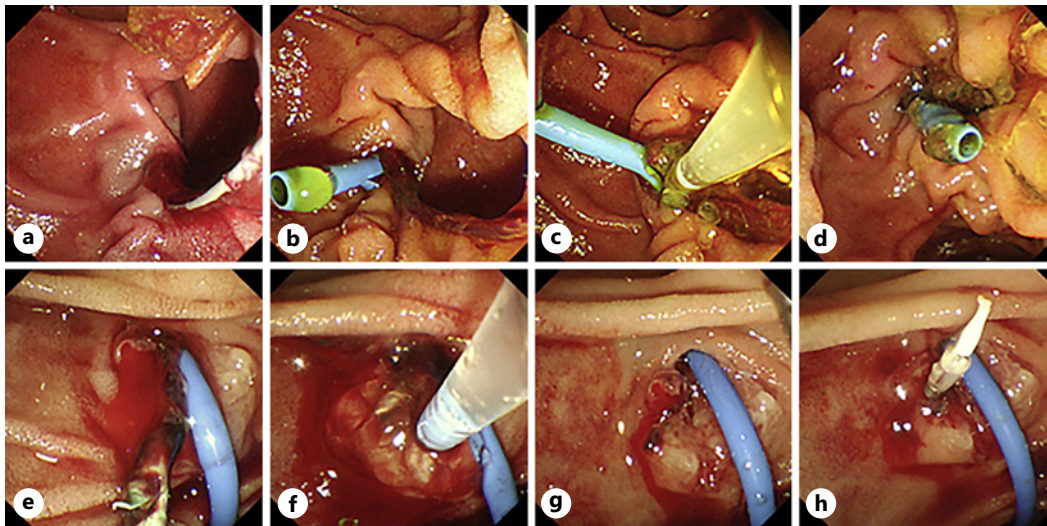


Fig. 1. Endoscopic retrograde cholangiopancreatography (ERCP). ERCP was performed using the PF technique, and a biliary stent was inserted (**a, b**). Oozing bleeding was present and persisted from the site of precut papillotomy, and hemostasis treatment was attempted. TDM-621 (3 mL) was applied to the bleeding site through a dedicated catheter (**c**), and complete hemostasis was achieved (**d**). Emergency ERCP revealed oozing bleeding between the papilla and the stent (**e**). As the point of bleeding was difficult to identify, TDM-621 (3 mL) was applied to the bleeding site through a dedicated endoscopic catheter (**f**), which led to the bleeding volume being suppressed and to the bleeding point being identified (**g**). Hemostasis was subsequently achieved using an endoscopic hemoclip (**h**).

papillotomy, and hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (Fig. 2c), and complete hemostasis was achieved (Fig. 2d).

Case 4

An 84-year-old woman was raced to our hospital for severe abdominal pain and diagnosed with acute biliary pancreatitis. ERCP was performed using the PF technique, and SBDC was achieved, but oozing bleeding was present and persisted from the site of precut papillotomy and hemostasis treatment was attempted (Fig. 2e, f) with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (Fig. 2g), and a biliary stent was inserted after complete hemostasis with TDM-621 (Fig. 2h).

Case 5

A 68-year-old man was referred to our hospital for obstructive jaundice with cholelithiasis. ERCP was performed using the PF technique, and SBDC was achieved (Fig. 3a). Although oozing bleeding was present, EST was performed followed by stone extraction using a balloon catheter (Fig. 3b). The oozing bleeding from the papilla was shown to persist; thus hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (Fig. 3c), and complete hemostasis was achieved (Fig. 3d).

Case 6

A 96-year-old woman was rushed to our hospital for heart failure with preserved ejection fraction. She had been on antithrombotic therapy with the DOAC apixaban. Since acute cholangitis developed during her clinical course, ERCP was performed using the PF technique,

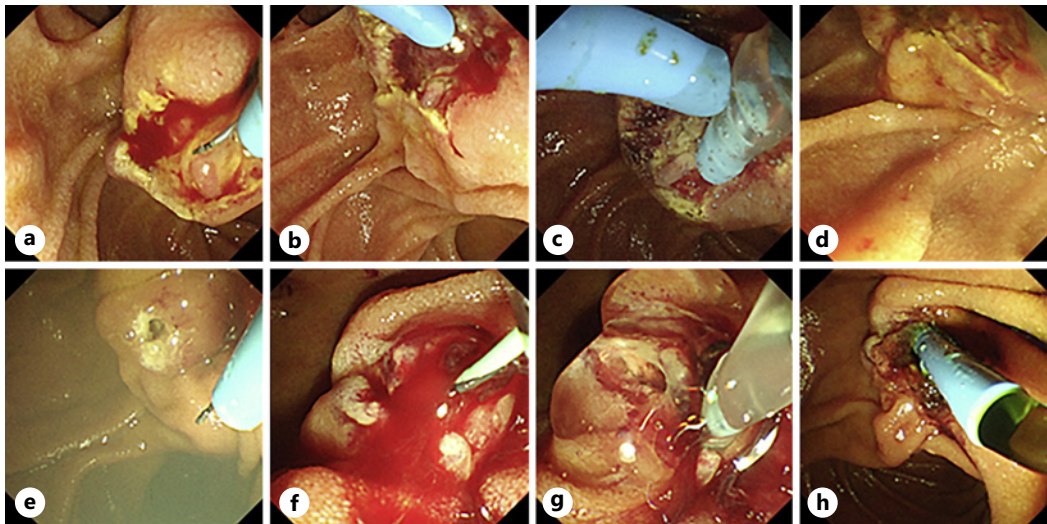


Fig. 2. Endoscopic retrograde cholangiopancreatography (ERCP). ERCP was performed using the PF technique, and a biliary stent was inserted (**a, b**). Oozing bleeding was present and persisted from the site of precut papillotomy, and hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (**c**), and complete hemostasis was achieved (**d**). ERCP was performed using the PF technique, and SBDC was achieved, but oozing bleeding was present and persisted from the site of precut papillotomy and hemostasis treatment was attempted (**e, f**) with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (**g**), and a biliary stent was inserted after complete hemostasis with TDM-621 (**h**).

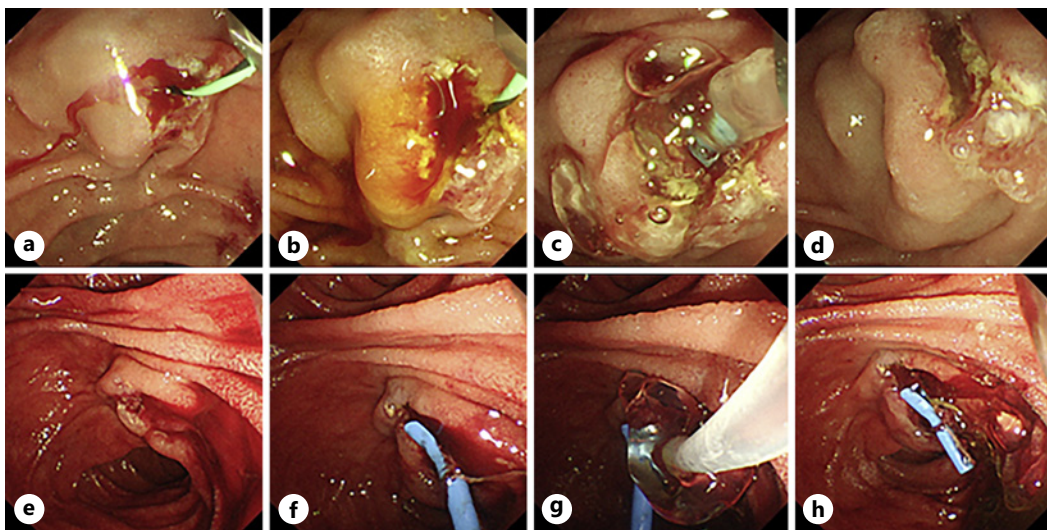


Fig. 3. Endoscopic retrograde cholangiopancreatography (ERCP). ERCP was performed using the PF technique, and SBDC was successful (**a**). Although oozing bleeding was present, EST was performed followed by stone extraction using balloon catheter (**b**). Oozing bleeding was present and persisted from the papilla, and hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (**c**), and complete hemostasis was achieved (**d**). ERCP was performed using the PF technique, and a biliary stent was inserted (**e, f**). The oozing bleeding from the papilla was shown to persist; thus hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (**g**), and complete hemostasis was achieved (**h**).

and a biliary stent was inserted (Fig. 3e, f). Oozing bleeding occurred at the site of precut papillotomy, and hemostasis treatment was attempted with TDM-621 (3 mL) applied to the bleeding site through a dedicated catheter (Fig. 3g), and complete hemostasis was achieved (Fig. 3h).

The patients thus treated were 2 males and 4 females aged 68–96 years (mean age, 85 years), 3 of whom had been on antithrombotic drugs. Those on antithrombotic drugs underwent ERCP based on the criteria for antithrombotic drug withdrawal set forth by the Japanese Gastroenterological Endoscopy Society (JGES) guidelines [10, 11]. SBDC was attempted initially with wire-guided cannulation and, if unsuccessful, was performed using the PF technique. All 6 patients had no rebleeding after hemostasis, and their clinical course was uneventful thereafter (Table 1).

Discussion

Two important implications emerged from our case series that could affect clinical practice. First, endoscopic hemostatic treatment with TDM-621 may prove useful for PF-related bleeding, while its supportive clinical data are very limited and its hemostasis technique remains only insufficiently described in the literature.

Bleeding associated with papillotomy incision using a needle-knife or papillotome is commonly observed, and balloon tamponade, endoscopic hemoclips, epinephrine injection, thermal therapy, and covered self-expandable metal stent have been reported to be effective as endoscopic hemostatic therapies for papillotomy-associated bleeding [12–14]. Of these, balloon tamponade and endoscopic hemoclips have the theoretical benefit of not causing tissue damage, unlike thermal treatments and sclerosants, while balloons are expensive and endoscopic hemoclips are technically difficult to perform under duodenoscopy [6, 14]. Again, while covered self-expandable metal stent is also useful, it is expensive and associated with the risk of acute pancreatitis [7]. In our experience, TDM-621 proved noninvasive, easy to use and did not interfere with the endoscopic view; also of note, as shown in the profile of our 6 patients summarized in Table 1, even in the event of PF-related bleeding (case 5), it allowed for additional treatment with EST thus achieving hemostasis after completion of the procedure.

All 6 patients had no rebleeding after hemostasis. TDM-621 has been reported in a rat model (1) to improve damage through downregulation of inflammatory cytokines and upregulation of wound healing-related factors [15] and (2) to lead to a reduction in delayed bleeding rate in a human study through promotion of mucosal regeneration and ulcer healing after large endoscopic resections [16]. It is thus suggested that TDM-621 may have contributed to the suppression of rebleeding after hemostasis for PF-related bleeding in this study.

The other implication of interest is that endoscopic hemostasis by combined modality therapy with TDM-621 and endoscopic hemoclips could prove effective for PF-related bleeding from visible vessels. Very recently, we reported that endoscopic hemostatic treatment with combined modality therapy involving TDM-621 and endoscopic hemoclips may prove useful for acute gastrointestinal bleeding from (1) visible vessels regardless of bleeding type and (2) ruptured gastric varices [17]. Of note, in case 2, delayed bleeding after PF, a procedure associated with a high risk of bleeding in patients receiving antithrombotic therapy with a DOAC, was treated with an endoscopic hemoclip applied to the bleeding from the visible vessel which had been revealed after control of its bleeding volume with TDM-621.

In conclusion, endoscopic hemostasis with TDM-621 may prove effective for PF-related bleeding and represent a potential modality of first choice in hemostasis. In addition, endoscopic hemostasis with combined modality therapy using TDM-621 and endoscopic hemoclips may prove effective for bleeding from visible vessels.

Table 1. Characteristics of patients undergoing precut fistulotomy (PF)

Case	Age	Sex	Diagnosis	Antithrombotic drugs given	Timing of onset of bleeding	EST	Type of bleeding present	Modality combined	Adverse events observed
1	78	F	Choledocholithiasis	Limaprost alfadex	During PF	No	Oozing	None	None
2	94	M	Acute cholangitis with cholangiocarcinoma	Edoxaban	After PF	No	Oozing	Endoscopic hemoclips	None
3	88	F	Acute cholangitis with choledocholithiasis	None	During PF	No	Oozing	None	None
4	84	F	Acute biliary pancreatitis	None	During PF	No	Oozing	None	None
5	68	M	Obstructive jaundice with choledocholithiasis	None	During PF	Yes	Oozing	None	None
6	96	F	Acute cholangitis	Apixaban	During PF	No	Oozing	None	None

EST, endoscopic sphincterotomy.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Review Board of National Hospital Organization Hakodate National Hospital (approval number: R5-0509001). Written informed consent was obtained from the patients for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose in association with this study.

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Author Contributions

Kimitoshi Kubo reported the case series and wrote the manuscript. Kimitoshi Kubo, Xinhan Zhang, and Ikko Tanaka treated the patients in this study. All authors declare that they contributed to all parts of the manuscript and that they have read and approved the final version of the manuscript for publication.

Data Availability Statement

All data generated and/or analyzed during the course of this study are included in the article. Any further query may be addressed to the corresponding author.

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