

[CASE REPORT]

Use of Nasopancreatic Drainage for Severe Post-endoscopic Retrograde Cholangiopancreatography Pancreatitis: A Case Series

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Abstract:

Five patients complaining of severe pain due to severe post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) underwent nasopancreatic drainage (NPD) placement. Pain relief was achieved on the second, fourth, and fifth day in three, one, and one patients, respectively. Four patients underwent pancreatic juice culture; all were positive. Our results suggest that NPD can relieve severe PEP with severe pain. Bacteria-induced protease-activated receptor-2 activation may be associated with PEP.

Key words: nasopancreatic drainage, severe post-endoscopic retrograde cholangiopancreatography pancreatitis, proteinase-activated receptor-2

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Introduction

Post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is an unexpected and serious event. Its mechanisms have not been completely analyzed; therefore, various mechanisms are presumed (1, 2). For PEP, fluid resuscitation is the only treatment (3), and severe cases have shown a poor prognosis (4, 5).

Duodenal papilla injury caused by cannulation during endoscopic retrograde cholangiopancreatography (ERCP) or biliary stent placement can induce papilla edema or hemorrhage, leading to its dysfunction, followed by the obstruction of the pancreatic juice flow, which is a major cause of PEP (6, 7). In another case, a positive pancreatic juice culture resulting in acute pancreatitis was reported (8), suggesting potential bacterial involvement in PEP. The relief of pancreatic juice obstruction and drainage of contaminated pancreatic juice are assumed to be effective for treating the disorder.

We performed nasopancreatic drainage (NPD) to treat severe PEP and cultured the pancreatic juice obtained through the placed tube. We herein report our results and discuss the

mechanisms of PEP.

Case Report

A total of 2,012 patients underwent ERCP between January 2012 and September 2016. One hundred and twelve patients (112/2,012; 5.6%) suffered from PEP; of them, 5 (0.25%) experienced severe PEP and agreed to undergo a second round of ERCP for NPD (Table 1). We decided to perform a second round of ERCP if 3 doses of analgesics were needed within 12 hours for severe pain. The age range was 51-75 years old (3 men and 2 women). The first round of ERCP was performed to diagnose and treat common bile duct stones (CBDs) with biliary stent (BS) (7 Fr, 7 cm, double-pigtail; Olympus, Tokyo, Japan) placement in 2 patients, bile duct cancer with nasobiliary drainage (NBD) (6 Fr, pigtail; Olympus) placement in 1, acute recurrent pancreatitis due to pancreas divisum with a pancreatic stent (PS; 5 Fr, 4 cm, tapered straight) placement in 1, and primary sclerosing cholangitis (PSC) with a bile duct biopsy with PS (5 Fr, 3 cm, tapered straight; Gadelius Medical, Tokyo, Japan) placement in 1. Three patients (two with CBDs and one with bile duct cancer) did not undergo pancreatic duct

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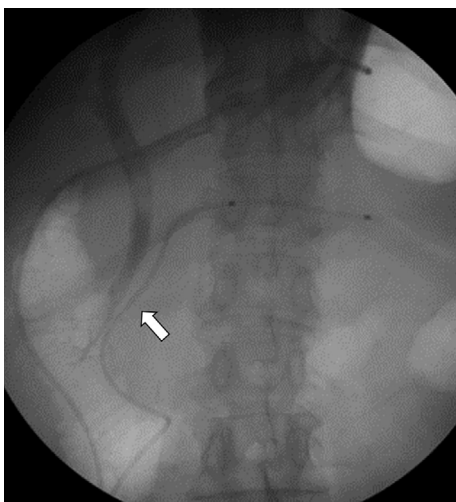
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Table 1. Patient Characteristics.

Case	Age	Sex	Diagnoses	Procedures during first ERCP	WBC (μL)	CRP (mg/dL)	APACHE II score (points)
1	73	M	Bile duct cancer	Bile duct biopsy and NBD	10,200	0.32	8
2	58	F	PD with ARP	PS	8,800	0.2	3
3	51	F	CBDS with cholangitis	BS	15,700	3.0	9
4	73	M	CBDS with cholangitis	BS	15,100	0.7	12
5	75	M	PSC	Bile duct biopsy and PS	16,400	12.38	8

ERCP: endoscopic retrograde cholangiopancreatography, CRP: C-reactive protein, APACHE: acute physiology and chronic health evaluation, M: male, F: female, NBD: naso-biliary drainage, PD: pancreas divisum, ARP: acute recurrent pancreatitis, PS: pancreatic stent, CBDS: common bile duct stone, BS: biliary stent, PSC: primary sclerosing cholangitis

**Figure 1. Nasopancreatic drainage tube placement (Case 3).**

injection of contrast medium. Sphincterotomy of the major or minor papilla was not performed in any cases.

According to our hospital's protocol, ERCP is performed during hospitalization, and the patient is discharged two days after the examination (on the third day) if PEP does not occur. Serum amylase and lipase concentrations are checked 2 hours after the examination and the next morning. If the patient suffers from abdominal pain after the examination, a blood examination, including serum amylase and lipase concentration analyses is performed using abdominal computed tomography (CT). If a PEP diagnosis is established, liquid resuscitation is started, and a non-opioid analgesic, such as a nonsteroidal anti-inflammatory drug, is given. The severity of the PEP diagnosis is determined using the Cotton criteria (1) and the Japanese severity criteria for acute pancreatitis (9), respectively.

If severe PEP occurred and a third administration of an analgesic was considered, a second round of ERCP for NPD (i.e., rescue ERCP) was performed. Written consent was acquired for ERCP. A new NPD tube (5 Fr, pigtail; Olympus) was placed by the removal of a previously placed stent or tube (Fig. 1). To place the NPD tube, pancreatography was conducted; however, some amount of contrast medium was used to reveal the main pancreatic duct. In four patients, pancreatic juice obtained through the NPD tube after place-

ment was cultured. NPD was maintained until no recurrence of pain after oral intake was observed. NPD was not changed to PS placement in any patients.

In this study, the clinical manifestations at PEP onset, ERCP findings for NPD tube placement, pain duration after tube placement, NPD duration, and pancreatic juice culture results were determined. In all patients, the CT grade during PEP onset was classified as 2, which was defined as extensive inflammation over the lower pole of the kidney or to the roots of the superior mesenteric artery (Fig. 2), and severe PEP was observed, according to the Japanese severity score for acute pancreatitis (9). The median time spent performing rescue ERCP was 12 hours after PEP onset (range, 8 hours to 8 days). The median white blood cell count, C-reactive protein level, and acute physiology and chronic health evaluation (APACHE) II score were 11,300 (range, 8,800-16,400/ μL), 3.0 (range, 0.2-12.8 mg/dL), and 8 (range, 3-12 points), respectively.

An NPD tube was successfully placed in all patients. On ERCP, all patients had edematous duodenal mucosae (Fig. 3c and d) and edematous and swollen duodenal major papillae (Fig. 3a and b). Three patients had impaired duodenal wall extensibility. In patients with CBDSs and bile duct cancer, the BS or NBD was removed, and an NPD tube was placed. The patient with pancreas divisum underwent PS removal during the first ERCP, and the patient's condition was observed. However, the pain was not relieved for 6 hours after PS removal, so an NPD tube was placed. The remaining patient with PSC underwent NPD placement without PS removal because the duodenal mucosa was severely edematous with impaired extensibility of the duodenal wall, and the major duodenal papilla could not be identified, probably due to the presence of pancreatic inflammation. The pancreatic duct was cannulated along the placed PS and another NPD tube was placed.

After NPD tube placement, pain relief was achieved in all patients (Table 2). The pain persisted for one, three, and four days in three, one, and one patient, respectively. The median NPD duration was 11 days (range, 10-21 days), while the median hospitalization period was 21 days (range, 16-47 days). All patients were discharged or underwent the planned surgery. The pancreatic juice cultures of four patients were positive with the following identified bacteria:

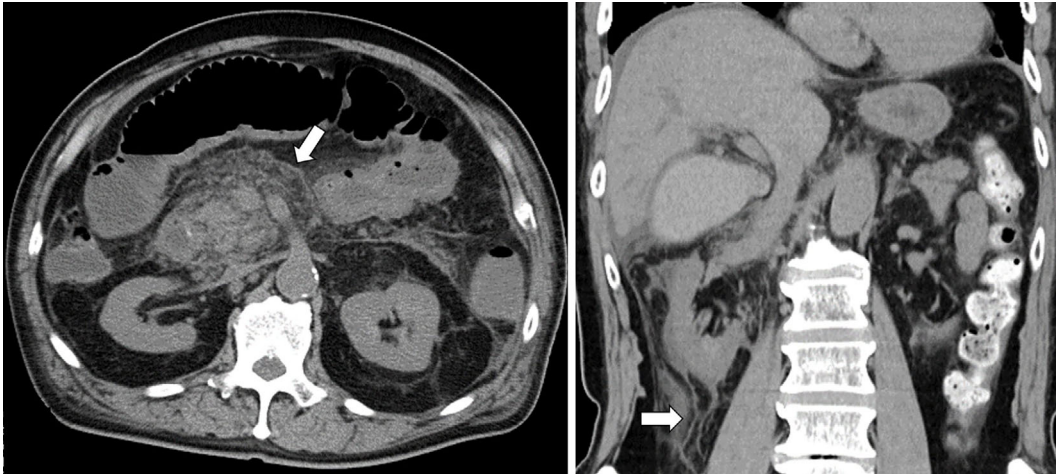


Figure 2. Computed tomography manifestations of grade 2 pancreatitis: wide extension of the inflammation over the lower pole of the kidney (Case 5) or to the roots of the superior mesenteric artery (Case 4).

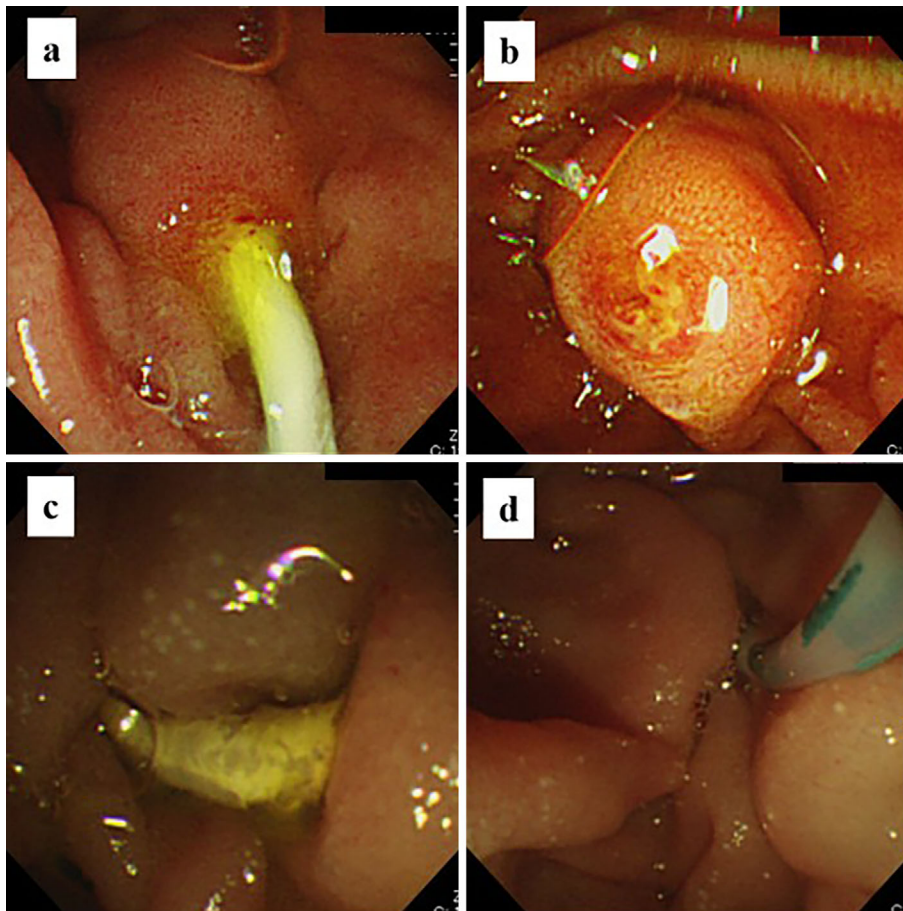


Figure 3. Endoscopic findings during endoscopic retrograde cholangiopancreatography: edematous and swollen duodenal major papillae (a, b: Case 3) and edematous duodenal mucosae (c, d: Case 4).

Table 2. Results of Nasopancreatic Drainage Placement.

Case	Time to rescue ERCP	Pain duration (D)	NPD placement (D)	Hospitalization (D)	Bacterial cultivation
1	11 h	1	21	21	<i>Streptococcus sanguinis</i> plus <i>Neisseria</i> species
2	12 h	4	10	17	N/A
3	8 h	1	11	39	<i>Enterococcus faecalis</i>
4	8 days	3	13	47	<i>Candida albicans</i>
5	2 days	1	11	16	<i>Fusobacterium varium</i> plus <i>Anaerococcus prevotii</i>

ERCP: endoscopic retrograde cholangiopancreatography, NPD: nasopancreatic drainage, D: day, N/A: not applicable

Enterococcus faecalis, *Candida*, *Streptococcus sanguinis* plus *Neisseria* species, and *Fusobacterium varium* plus *Anaerococcus prevotii*.

Discussion

Efficacy of pancreatic drainage

Fluid resuscitation is an accepted method of treating severe PEP (3), along with analgesics, but the prognosis remains poor (4, 5). Duodenal papilla injury through cannulation during ERCP or biliary stent placement can induce papilla edema or hemorrhaging, leading to its dysfunction followed by pancreatic juice flow obstruction, a major cause of PEP (6, 7). PS placement to relieve pancreatic juice flow disturbances has been widely accepted for preventing PEP (10), and placement has also been used for so-called salvage ERCP to treat PEP (11).

In the present study, an NPD tube was placed in 5 patients with intolerable pain due to severe PEP among 112 patients with PEP. As a result, all patients acquired pain relief after NPD placement and were discharged without additional interventional treatment. Our results show that pancreatic drainage is effective for PEP, suggesting that pancreatic juice stasis is responsible for PEP as well as PEP with severe pain. No patient suffered from exacerbation of severe PEP or required additional interventional treatment after NPD tube placement, indicating that the NPD prevented exacerbation. However, due to the restricted indications for such treatment, the number of cases was limited.

Pancreatic drainage method

For pancreatic drainage, PS placement has been widely accepted for preventing PEP (10); furthermore, it is reportedly effective as salvage ERCP for PEP (11). However, we must consider that the condition of the pancreatic duct epithelium after PEP onset may differ from that before PEP onset and that damage to the pancreatic duct epithelium by inflammation may be responsible for PEP onset. A PS can connect the pancreatic duct to the duodenum, facilitating the flow of pancreatic juice. It can also induce duodenal fluid reflux that includes bile and bacteria and result in PEP exacerbation due to infection of the damaged pancreatic duct epithelium or even pancreatic necrosis in cases of pancreatic duct disruption (12). Furthermore, a PS can easily become

occluded and cannot provide pancreatic drainage in some cases of pancreatic duct anomalies, such as complete or incomplete pancreas divisum. To avoid these risks, we selected NPD for pancreatic drainage. NPD allows us to check the condition of the pancreatic duct through pancreatography whenever needed (13, 14). We consider NPD preferable for PEP treatment, although confirmation of its superiority requires further studies, such as a comparative study between NPD and PS placement. The most serious problem associated with NPD is that it is placed through the nose, which can cause discomfort and other problems.

However, transpapillary pancreatic drainage may exacerbate PEP, since pancreatography itself carries a risk of PEP (7). Furthermore, poor conditions, including edema of the duodenal mucosa and impaired extensibility of the duodenal wall, may hinder the procedure's success. If pancreatic drainage fails despite pancreatography, the elevated intraductal pressure of the pancreatic duct due to the injection of contrast medium may exacerbate the PEP. When a patient has a pancreatic duct anomaly, such as branch-type pancreatic duct fusion or severe stricture of the main pancreatic duct, NPD placement may be challenging due to the difficulty in advancing the guidewire and tube to the upper stream of the main pancreatic duct. Therefore, NPD placement in patients with PEP should be performed by expert endoscopists only, and cannulating the pancreatic duct along the previously placed PS may be an alternative pancreatic drainage method.

Positive pancreatic culture in PEP: Presumed meaning

The positive pancreatic juice culture rate was significantly higher in patients with acute pancreatitis than in those with other pancreatic disorders involving pancreatic juice stasis (8). Indeed, the results of four patients with PEP who underwent pancreatic juice culture were all positive. This finding may suggest that bacteria are also involved with PEP onset, while NPD to drain the pancreatic juice may also remove bacteria from the pancreatic duct and contribute to PEP relief.

The relationship between protease-activated receptor (PAR)-2 and acute pancreatitis was recently verified (15). PAR is a unique family of seven transmembrane G protein coupled domain receptors (GPCRs), and the common major cell signals triggered by the activation of distinct PAR mem-

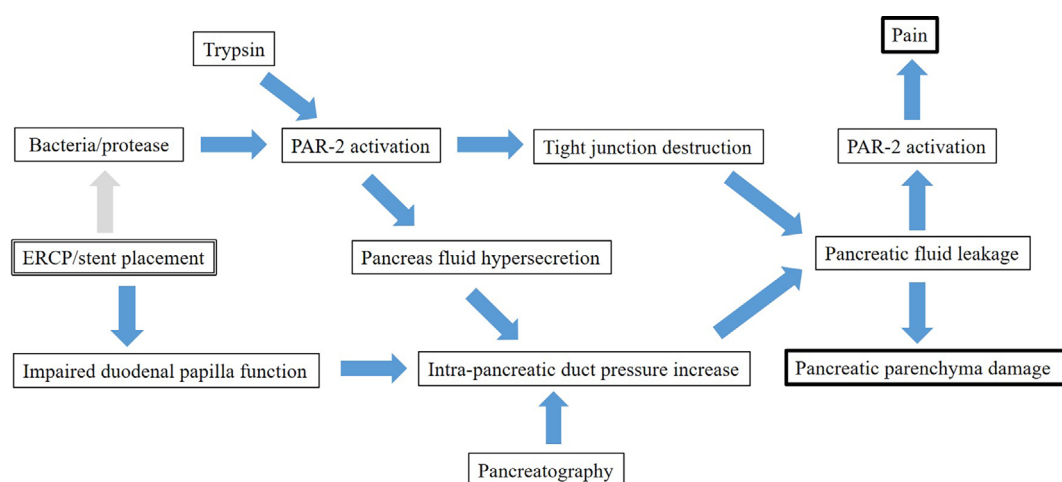


Figure 4. Mechanisms by which bacteria with protease stimulate protease-activated receptor-2 and initiate pancreatitis.

bers are phospholipase C_β activation, followed by Ca²⁺ mobilization and diacylglycerol-mediated activation of protein kinase C (16). PAR-2, the second member of the GPCR family, is highly expressed in the pancreas and intestine. It also plays a role in the development of skin allergies and some inflammatory disorders (17), such as colonic inflammatory diseases (18). Trypsin or serine protease secreted by bacteria promotes PAR-2 activation (15, 18). A recent study revealed that PAR-2 activation leads to leakage in the intestinal barrier, which increases the passage of fluids and even microorganisms across the gut mucosa (19). PAR-2 activation by serine protease produced by bacteria increases the barrier permeability and may initiate and exacerbate inflammation (20). Various types of bacteria, including Gram-negative and Gram-positive bacteria (e.g., *Staphylococcus* and *Streptococcus* species), and fungi have serine protease.

We hypothesize that, in acute pancreatitis, the same phenomenon with colonic inflammatory diseases may occur due to PAR-2 activation (Fig. 4). Bacteria may induce pancreatic inflammation by disrupting the tight junction of the pancreatic duct epithelium via PAR-2 activation (21) by secreting serine protease. Pancreatic juice leakage through the disrupted portion of the pancreatic duct epithelium leads to pancreatic parenchymal inflammation. The leakage might be exacerbated by increased intrapancreatic duct pressure with hyper-secretion of pancreatic juice due to PAR-2 activation (21), especially under conditions of a disturbed pancreatic juice flow caused by ERCP-induced papillary injury due to direct endoscopic trauma with hemorrhaging or edema (6, 7). This hypothesis is consistent with that of a previous report stating that increased intrapancreatic duct pressure is responsible for pancreatic parenchymal damage (22).

Acute pancreatitis is accompanied by sharp and severe pain. The PAR-2 expression in the sensory neurons is involved in pancreatic pain. In awake rats, the administration of PAR-2-activating peptides and trypsin into the pancreatic duct activates nociceptive neurons and induces a behavioral

pain response (23). During pancreatitis, endogenous or exogenous proteases such as trypsin or bacterial protease, which leak through the disrupted tight junction, may directly stimulate PAR-2 within the intrapancreatic sensory neurons (15). Pancreatic pain can indicate of PAR-2 activation, and continual pain may indicate persistent PAR-2 activation with destruction of the epithelial tight junction and leakage of the pancreatic juice; that is, persistent pancreatic pain may reveal persistent inflammatory activity of pancreatitis. Conversely, pain relief is a sign of pancreatitis inactivation. We believe that patients with PEP and severe pain may be candidates for NPD placement, the effectiveness of which can be determined based on pain relief.

Conclusion

Pancreatic drainage through NPD effectively relieved pain in patients with severe PEP, possibly by impeding PAR-2 activation. NPD can help drain contaminated pancreatic juice. Our results suggest that NPD may help prevent PEP exacerbation due to persistent PAR-2 activation by bacteria. To confirm its efficacy, further studies with more patients are required; however, NPD placement for the treatment of PEP should only be performed by expert endoscopists.

The authors state that they have no Conflict of Interest (COI).

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