

## Clinical usefulness and current problems of pancreatic duct stenting for preventing post-ERCP pancreatitis

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### Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure with high frequency of accidental symptoms, and particularly some patients who develop and aggravate pancreatitis due to the procedure may need treatment of surgery or die. Various attempts were performed so far to prevent post-ERCP pancreatitis, however, it is impossible to completely prevent pancreatitis at this time because there are various factors for occurrence of post-ERCP pancreatitis. One of the most frequent causes of post-ERCP pancreatitis is considered to be congestion of pancreatic juice associated with duodenal papilledema after examination or treatment. Recently it is often reported that use of a pancreatic duct stent may prevent occurrence of pancreatitis which occurs because of an increased inner pressure of the pancreatic duct caused by congestion of pancreatic juice associated with duodenal papilledema. However, there are some patients who develop pancreatitis even if treated with the pancreatic duct stent, thus further clarification of the pathology and advancement of the prophylactic method will be needed.

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**Key words:** Endoscopic retrograde cholangiopancrea-

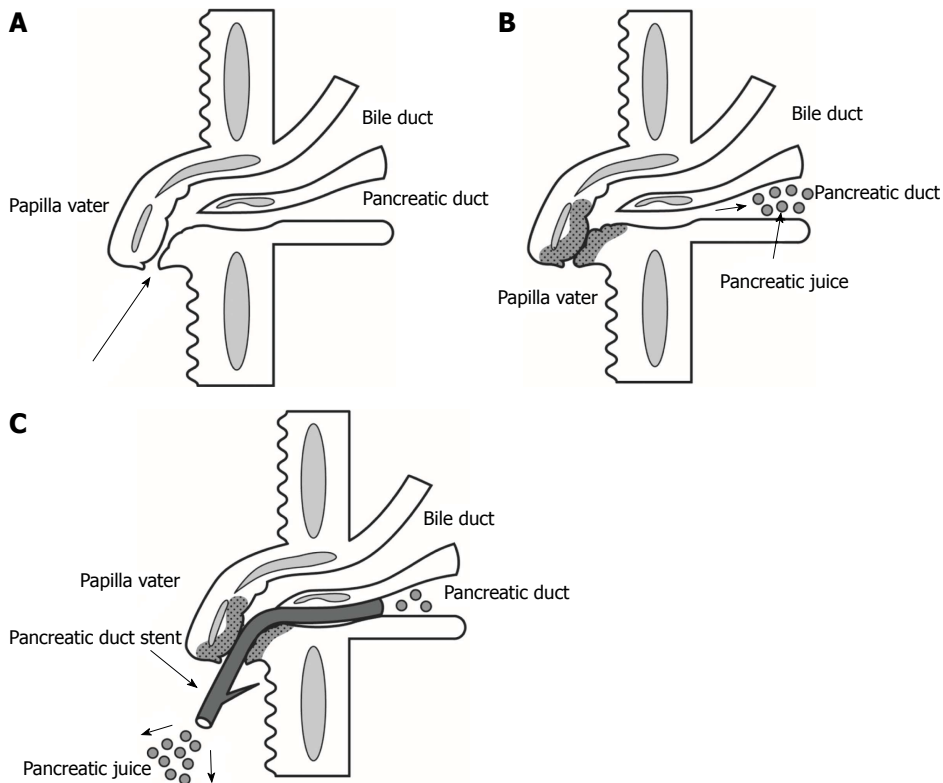
tography; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Pancreatic duct stent; Pancreatic stenting

**Core tip:** There are some patients who can avoid occurrence of post-endoscopic retrograde cholangiopancreatography pancreatitis (ERCP) pancreatitis by pancreatic duct stenting. However, it is impossible to prevent all post-ERCP pancreatitides by pancreatic duct stenting, and further examination will be needed.

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### INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) plays a very important role in diagnosis and treatment for pancreatic and biliary tract diseases. Post-ERCP pancreatitis is the early accidental symptom which occurs most frequently after ERCP. Although its frequency differs depending on the treated patients, procedure performed, definition of pancreatitis, or the investigation method, it is generally reported to occur in about 4.5% of treated patients based on the results of the large scale prospective studies<sup>[1-7]</sup> (Table 1). Although many cases of post-ERCP pancreatitis are alleviated by admission and treatment for a few days, some are aggravated, and about 0.04% need surgery and about 0.03% die<sup>[1,2,4,5]</sup>. Prophylaxis of post-ERCP pancreatitis is the great task which has not been resolved yet since introduction of ERCP, and various attempts have been performed. As one of such attempts, pancreatic duct stent is used to prevent occurrence of pancreatitis caused by duodenal papillede-



**Figure 1** Pancreatic duct stenting for preventing post-endoscopic retrograde cholangiopancreatography pancreatitis. A: Duodenal papilla before cannulation is performed; B: Duodenal papilledema occurs by frequent cannulation manipulation; C: Pancreatic duct stent is placed to regulate the passage of pancreatic juice.

ma due to the procedure, and its usefulness is frequently reported. In this article, we will describe the usefulness and problems of pancreatic duct stenting aiming at prophylaxis of post-ERCP pancreatitis.

## **PATHOGENIC MECHANISM OF POST-ERCP PANCREATITIS**

Post-ERCP pancreatitis is considered to occur due to various factors. The factors are broadly classified into five categories: (1) Increased inner pressure of the pancreatic duct by congestion of pancreatic juice caused by postoperative papilledema; (2) Mechanical irritation such as damaged pancreatic duct due to deep insertion of the catheter into the pancreatic duct or insertion of the device such as the guidewire; (3) Hydrostatic injury such as increased inner pressure of the pancreatic duct due to frequent pancreatography, manometry, or reflux water of pancreatoscopy; (4) Chemical injury due to infusion of the contrast medium or intestinal juice into the pancreatic duct; and (5) Thermal injury due to papilledema by radio-frequency radiation or thermal damages of the pancreas itself. Among them, one of the most frequent causes may be congestion of pancreatic juice associated with papilledema after examination or treatment<sup>[1,4,8]</sup>. There is a mechanism that congestion of pancreatic juice increases viscosity of pancreatic juice, aggravates obstruction of discharge of pancreatic juice, decreases the outflow of pancreatic juice into the small intestine, and promotes se-

cretion of pancreatic juice from the pancreatic acinar cell through increased cholecystokinin production. Through these processes, congestion of pancreatic juice is further aggravated, and eventually brings about activation of trypsinogen into trypsin within the acinar cell, and develops pancreatitis<sup>[8]</sup>.

## **REPORT ON PANCREATIC DUCT STENTING TO PREVENT POST-ERCP PANCREATITIS**

Although the pathogenic mechanism of post-ERCP pancreatitis has not been sufficiently clarified, various factors may be involved<sup>[1-6]</sup>. One of the pathogenic mechanisms of post-ERCP pancreatitis includes obstruction of discharge of pancreatic juice caused by papilledema or spasm of the sphincter of Oddi associated with the procedure. In order to regulate the passage of pancreatic juice for prophylaxis of post-ERCP pancreatitis, the pancreatic duct stent is used (Figure 1). Past articles comparing the pancreatic duct stenting group and non-pancreatic duct stenting group for prophylaxis of post-ERCP pancreatitis are shown<sup>[8-26]</sup> (Table 2). Review by RCT revealed that five of eight articles describe that post-ERCP pancreatitis occurred less in the stenting group with significant difference. Of other eleven articles, five articles describe that post-ERCP pancreatitis occurred less in the stenting group with significant differ-

**Table 1** Frequency of post-endoscopic retrograde cholangiopancreatography pancreatitis *n*(%)

Ref.	No. of patients	Post-ERCP pancreatitis	Surgery	Death
Freeman <i>et al</i> <sup>[1]</sup> , 1996	2347	127 (5.4)	3	1
Loperfido <i>et al</i> <sup>[2]</sup> , 1998	2769	36 (1.3)	2	1
Masci <i>et al</i> <sup>[3]</sup> , 2001	2444	44 (1.8)	-	0
Freeman <i>et al</i> <sup>[4]</sup> , 2001	1963	131 (6.7)	1	1
Cheng <i>et al</i> <sup>[5]</sup> , 2006	1115	168 (15.1)	-	1
Wang <i>et al</i> <sup>[6]</sup> , 2009	2691	116 (4.3)	0	0
Sakai <i>et al</i> <sup>[7]</sup> , 2013	720	14 (1.9)	0	0
Total	14049	636 (4.5)	6 (0.04)	4 (0.03)

ERCP: Endoscopic retrograde cholangiopancreatography pancreatitis.

ence. In seven articles of nine articles without significant difference, incidence of pancreatitis tends to be low in the pancreatic duct stenting group, thus pancreatic duct stenting is considered useful for prophylaxis of post-ERCP pancreatitis. Interestingly, as reported by Tsuchiya *et al*<sup>[18]</sup>, even if p-value of incidence of pancreatitis does not reach the value with significant difference, amylase value has become significantly low after ERCP in the stenting group. According to the review by Tsuchiya *et al*<sup>[18]</sup>, there were significantly less patients with abdominal pain in the stenting group, and there were no serious patients, which may be the effect of stenting. In addition, in the review of Sakai *et al*<sup>[23]</sup>, incidence of abdominal pain and post-operative amylase value are significantly low in the pancreatic duct stenting group, which is validly thought to be the effect of the pancreatic duct stent, taking into consideration that the background factors of both groups do not vary.

## INDICATION AND PROBLEMS OF PROPHYLACTIC PANCREATIC DUCT STENT

The risk factors of post-ERCP pancreatitis include young female, history of post-ERCP pancreatitis, recurrent pancreatitis, sphincter of Oddi dysfunction (SOD), and uncomplicated chronic pancreatitis as patient factors, and difficulty in insertion into the biliary duct, pancreatography, incision of the opening of the pancreatic duct, endoscopic papillary balloon dilation, and precut papillotomy as procedure factors<sup>[1-6]</sup>. However, it is hard to say it necessary to perform pancreatic duct stenting for all these patients, and it is necessary to select candidate patients for pancreatic duct stenting. Since pancreatic duct stenting regulates the passage of pancreatic juice, occurrence of occlusive pancreatitis is expected to be prevented. The procedure to indicate pancreatic duct stenting based on the past reports or theoretical thought includes: (1) Pancreatic duct guidewire-indwelling method or implementation of precut papillotomy from the opening of the pancreatic duct in patients with difficulty in insertion into the biliary duct, which may lead to papill-

edema<sup>[20,22,23,25]</sup>; (2) After endoscopic removal of duodenal papilla<sup>[17]</sup>; (3) Endoscopic sphincterotomy for SOD<sup>[13]</sup>; (4) Invasive procedure against pancreas such as the cytological diagnosis of pancreatic juice or biopsy of the pancreatic duct; and (5) Indwelling of the thick biliary duct stent instead of endoscopic sphincterotomy.

As for whether it is necessary to indwell the pancreatic duct stent in young females who are identified as the risk factor of post-ERCP pancreatitis or in patients with history of post-ERCP pancreatitis when there is no erroneous pancreatography or erroneous insertion of the guidewire, currently there is no clear evidence. Prophylaxis of pancreatitis by pancreatic duct stenting is frequently reported for patients with difficulty in insertion into the biliary duct. According to the past report, pancreatic duct stenting leads to less incidence of pancreatitis<sup>[20,22,23,25]</sup>, which is a good indication when considering to regulate the passage of pancreatic juice. However, discussion will be needed as to indication of pancreatic duct stenting in patients with difficulty in insertion into the biliary duct. It may be possible to perform pancreatic duct stenting in the comparatively stable situation in patients who underwent erroneous pancreatography or erroneous insertion of the guidewire into the pancreatic duct or in patients who underwent pancreatic duct guidewire-indwelling method which is the procedure performed by indwelling the guidewire in the pancreatic duct of patients with difficulty in inserting into the biliary duct. However, there remain patients with difficulty in pancreatic duct stenting. We give an example that in the case of patients who underwent pancreatography and had difficulty in advancing the guidewire caudally due to flexion or stenosis of the pancreatic duct or patients with difficulty in cannulation both into the biliary duct and pancreatic duct, although insertion into the biliary duct has become possible through precut papillotomy, it is still difficult to identify the opening of the pancreatic duct. If approach to the pancreatic duct in such patients for pancreatic duct stenting is attempted and failed, a possibility to induce or aggravate pancreatitis becomes high. Thus, discussion may be still needed as to timing or subjects or implementation judgment of pancreatic duct stenting in the patients with difficulty in insertion into the biliary duct.

What stent should be used is examined. Currently, there is no definite information regarding material quality, diameter, length, or shape of the stent. The stent is used only for drainage of the papillary edge, thus it is not always necessary to use a long stent, and those 3-4 cm in length are often used<sup>[18-26]</sup>. The stent with the flap in one duodenal side having no flap within the pancreatic duct (Figure 2) or one with the pig tail in the duodenal side having no flap within the pancreatic duct is expected to be spontaneously dislodged later after being indwelled. The stent with the flap in the pancreatic duct side is unlikely to deviate or be aberrant after stenting, however, it is necessary to perform endoscopy for removal several days later (Figure 3). Although currently it is difficult to set the strict term, if the pancreatic duct spontaneous dis-

**Table 2** Pathogenic frequency of post-endoscopic retrograde cholangiopancreatography pancreatitis in the pancreatic duct stenting group and the non-pancreatic duct stenting group

Ref.	No. of patients	Study design	No-stent (%)	Stent group (%)	P-value
Smithline <i>et al</i> <sup>[8]</sup> , 1993	93	RCT	18	14	0.299
Tarnasky <i>et al</i> <sup>[9]</sup> , 1998	80	RCT	26	7	0.03
Elton <i>et al</i> <sup>[10]</sup> , 1998	194	Retrospective c.c.	12.5	0.7	< 0.003
Vandervoot <i>et al</i> <sup>[11]</sup> , 1999	42	Prospective c.c.	28.1	0	0.08
Aizawa <i>et al</i> <sup>[12]</sup> , 2001	40	Retrospective c.c.	6	0	0.11
Fogel <i>et al</i> <sup>[13]</sup> , 2002	436	Retrospective c.c.	28.2	13.5	< 0.05
Norton <i>et al</i> <sup>[14]</sup> , 2002	28	Retrospective c.c.	11.1	20	> 0.05
Fazel <i>et al</i> <sup>[15]</sup> , 2002	76	RCT	28	5	< 0.05
Freeman <i>et al</i> <sup>[16]</sup> , 2004	225	Prospective c.c.	66.7	14.4	0.06
Catalano <i>et al</i> <sup>[17]</sup> , 2004	103	Retrospective c.c.	16.7	3.3	0.1
Tsuchiya <i>et al</i> <sup>[18]</sup> , 2007	64	RCT	12.5	3.1	> 0.05
Sofuni <i>et al</i> <sup>[19]</sup> , 2007	201	RCT	13.6	3.2	0.019
Ito <i>et al</i> <sup>[20]</sup> , 2008	113	Retrospective c.c.	22	4.7	0.01
Harada <i>et al</i> <sup>[21]</sup> , 2010	121	Retrospective c.c.	5.2	12.7	0.21
Ito <i>et al</i> <sup>[22]</sup> , 2010	70	RCT	23	2.9	0.0096
Sakai <i>et al</i> <sup>[23]</sup> , 2011	55	Retrospective c.c.	25	0	0.03
Sofuni <i>et al</i> <sup>[24]</sup> , 2011	425	RCT	14.6	9.4	0.076
Sakai <i>et al</i> <sup>[25]</sup> , 2011	198	Retrospective c.c.	11.1	3	0.049
Kawaguchi <i>et al</i> <sup>[26]</sup> , 2012	120	RCT	13.3	1.7	0.03

RCT: Randomized controlled trial; C.C.: Case controlled study; ERCP: Endoscopic retrograde cholangiopancreatography pancreatitis.



**Figure 2** Pancreatic duct stent with the flap in one duodenal side having no flap within the pancreatic duct (Pancreatic duct stent: Geenen®-COOK): Spontaneous dislodgement type.

lodgement stent indwelled is not spontaneously dislodged for a long time after stenting, there is a possibility that the stent is aberrant within the pancreatic duct, or pancreatitis occurs due to stent occlusion. Therefore, it should be endoscopically removed similarly to the pancreatic duct stent with the flap within in the pancreatic duct. It is important that the stent fits the shape of the pancreatic duct, and in the case of Z-shape pancreatic duct it is better to perform stenting beyond flexion depending on the case, and a long stent 7cm or greater is used in some cases. However, the longer stent tends to straddle the flexed portion of the pancreatic duct at the pancreas head, thus the stent made of the flexible material with high tracking ability is needed. The shorter spontaneous dislodgement stent less than 3cm may be dislodged after the procedure, thus attention should be paid. As for stent diameter, although the thicker stent gives impression of excellent drainage efficiency, to the contrary, such a stent



**Figure 3** Pancreatic duct stent with the flap in the pancreatic duct side (Pancreatic duct stent Zimmon®-COOK).

blocks the thinner branches of the pancreatic duct causing pancreatitis, or it is suggested that the stent itself may give mechanical irritation to the pancreatic duct<sup>[27]</sup>. For the thin stent with a diameter of 3Fr. or 4Fr., 0.018-0.025 inch guidewires are available<sup>[27]</sup>. Therefore, the guidewire has no resilience in inserting the pancreatic duct stent, and its insertion is difficult in some cases. Hereinafter multi-center RCTs on what pancreatic duct stent should be used is expected to be performed.

Furthermore, there is a problem that pancreatic duct stent should be inserted into what patients by doctors with what experience. Most of reports so far are performed in the expert centers, and even in such facilities, failure rate of insertion of the pancreatic duct stent is reported to be 5%-10%<sup>[9,13,28]</sup>. Freeman reported that failure of insertion of the pancreatic duct stent is very dangerous, and two thirds of patients develop moderate to severe pancreatitis<sup>[29]</sup>. Thus, Fazel *et al*<sup>[15]</sup> described that insertion of the pancreatic duct stent for prophylaxis

of post-ERCP pancreatitis should not be performed by doctors with less experience. Since pancreatitis, when being aggravated, may lead to fatal subsequence, pancreatic duct stenting should be performed by doctors with sufficient experience, and even the doctors with sufficient experience should perform with sufficient attention for stenting.

## CONCLUSION

In order to prevent post-ERCP pancreatitis, pancreatic duct stenting is considered useful. However, there are patients who fail to prevent post-ERCP pancreatitis. Development of complete prophylactic methods of post-ERCP pancreatitis is expected in the future.

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