Impact of Direct Endoscopic Necrosectomy on Recurrence of Symptoms or Fluid Collections Following Successful Endoscopic Transmural Drainage of Walled-off Necrosis in Disconnected Pancreatic Duct

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Abstract

Background The impact of direct endoscopic necrosectomy (DEN) on risk of recurrence of symptoms or pancreatic fluid collections (PFCs) in patients with disconnected pancreatic duct (DPD) has not been previously evaluated.

Objective To compare the risk of recurrence of PFC in patients with walled-off necrosis (WON) and DPD undergoing DEN with that of not requiring DEN and not having permanent indwelling plastic stents.

Methods Retrospective analysis of database of patients with WON successfully treated with transmural metal stents over the past 5 years was done to identify patients with DPD and not having permanent indwelling transmural stents. These patients were divided into two groups: Group A: patients undergoing DEN and Group B: patients not requiring DEN.

Results Seventeen patients required DEN (Group A; mean age 37.8 years) and 21 patients were successfully treated without DEN (Group B; mean age: 37.7 years). In Group A, none of the patients developed either recurrence of symptoms or PFC over a mean follow-up period of 7 months. In Group B, 5 of 21 (23.8%) patients developed either recurrence of pain ($n = 2$) or PFC ($n = 3$) over a mean follow-up period of 22 months. New-onset diabetes mellitus developed in five (29%) patients in Group A and two (9%) patients in Group B. None of the patients in either group developed steatorrhea.

Conclusion Patients with WON and DPD treated with lumen apposing metal stent and requiring DEN seem to be having low risk of developing recurrence of pain or PFC.

Keywords
- endoscopic ultrasound
- pancreatitis
- lumen apposing metal stents
- walled-off necrosis

Introduction

Disconnected pancreatic duct (DPD) complicates the clinical course of patients with acute necrotizing pancreatitis (ANP) resulting in multiple interventions including surgery and prolonged hospital stay.[1–5] The complicated clinical course occurs due to the fact that the disconnected viable segment of pancreas continues to pour pancreatic secretions that do not drain into the lumen of gastrointestinal tract resulting in recurrent pancreatic fluid collections (PFCs), refractory

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external pancreatic fistula, and chronic abdominal pain/recurrent pancreatitis.[3,6] One of the strategies employed to decrease the risk of these clinical problems is to maintain the iatrogenic internal fistula created at the time of endoscopic transluminal drainage of PFCs by leaving transmural plastic stents in situ permanently.[7,8] This strategy of leaving plastic stents permanently has been shown to be safe as well as effective in preventing the recurrence of PFCs.[1,4,7–9]

The availability of lumen apposing metal stents (LAMSs) has improved the results of endoscopic drainage of pancreatic necrotic collections.[10,11] Few studies have also shown that risk of recurrence of PFC following successful endoscopic drainage of PFC with LAMS in patients with DPD is very low, and therefore, there is no need of permanent indwelling plastic stents in patients treated with LAMS.[2,12] Basha et al in a retrospective study did not replace LAMS with permanent indwelling plastic stents and reported recurrence of PFC in 17.4% patients and only 6.6% patients required intervention for PFC.[2] Dhir et al also did not replace LAMS with permanent indwelling plastic stents and also reported similar results with a recurrence rate of 13.2% with reintervention in only one patient.[12]

However, few studies have reported discordant results. Bang et al reported that PFC recurred in 1.4% patients with DPD in whom metal stent was replaced with plastic stent and in 25% patients without a plastic stent (25.0%) ($p = 0.001$).[1] Rana and Gupta also found similar results in a preliminary retrospective comparative analysis. The PFC recurred in 27% patients without plastic stent versus none in patients with a permanent indwelling plastic stent.[13] These discordant results suggest that factors other than the use of LAMS determine the risk of recurrence of PFC or symptoms in patients with DPD as patients with PFC and DPDs treated with large caliber metal stents still have uncorrected physiological abnormality of undrained upstream viable pancreatic parenchyma.

The clinical consequences of DPD, along with the uncorrected physiological abnormality of undrained pancreatic segment, also depend on various other factors including etiology of ANP, site of disruption (proximal/distal), and volume of pancreatic juice secreted from the disconnected segment, as well as the ability of body to contain this secretion.[5] Rana et al reported that patients with distal disconnection, post-ANP diabetes, as well as steatorrhea and pancreatic atrophy had low risk of recurrence of PFC in patients with DPD and without permanent indwelling plastic stents.[9] It appears that the amount of pancreatic parenchyma left viable after an episode of ANP is an important factor that determines the long-term clinical outcome of patients with DPD. Therefore, we hypothesized that direct endoscopic necrosectomy (DEN) could impact the long-term outcome of patients of walled-off necrosis (WON) with DPD treated with LAMS and thus, could be responsible for discordant results among studies on impact of LAMS on the long-term outcome of patients with ANP and DPD. In this retrospective study, we compared the frequency of recurrence of symptoms as well as PFC in patients with WON and DPD undergoing DEN with that of not requiring DEN and not having permanent indwelling plastic stents.

Patients and Methods

Retrospective analysis of prospectively maintained database of patients with WON (as defined by the revised Atlanta classification[14]) successfully treated with endoscopic transmural drainage using LAMS over the past 5 years was done to identify patients with DPD and not having permanent indwelling transmural plastic stents. We, at our center, follow a policy of leaving plastic stents in the transmural tract for an indefinite period in patients with DPD. In patients initially treated with LAMS, the metal stent is replaced with a permanent indwelling plastic stent following resolution of the PFC. However, it is not possible to replace LAMS with plastic stents in all the patients as the PFC cavity collapses completely in approximately one-third of patients following resolution of PFC. These patients in whom the LAMS could not be replaced with plastic stent following resolution of PFC were identified and retrospectively analyzed.

These patients were divided into two groups: Group A: patients who had undergone DEN after placement of LAMS and Group B: patients who did not require DEN and were successfully treated with LAMS drainage alone. The patient demographics, etiology of acute pancreatitis (AP), size of WON, type of stent used, outcome details, as well as long-term follow-up data including recurrence of symptoms or PFC or new-onset diabetes mellitus were retrieved from the database. All the endoscopic procedures were performed after obtaining informed consent from the patients.

Endoscopic Drainage

Endoscopic ultrasound (EUS)-guided drainage was performed using a linear scanning echoendoscope (EG-3870 UTK linear echoendoscope, Pentax Inc., Tokyo, Japan or UCT180 linear echoendoscope, Olympus Optical Co Ltd, Tokyo, Japan). The technical details of the EUS-guided drainage procedure have been published previously by us.[15] The patients included in this study underwent initial transmural drainage using LAMS (NAGI stent [14 or 16 mm], Taewoong Medical Co., Ltd., Seoul, South Korea or Plumber Stent [16 mm diameter], MI Tech Gyeonggi-Do, Korea or Hot Axios stent [15/20 mm diameter], Boston Scientific, Natick, Massachusetts, United States). Following drainage, patients underwent computed tomography (CT) of the abdomen 72 hours after the drainage procedure. Patients with new-onset fever or worsening of existing symptoms with persistent WON on CT (<50% reduction in size) underwent repeat endoscopic transmural drainage. If the LAMS was clogged with necrotic material, the stent was declogged and 7-Fr nasocystic catheter (NCC) was inserted through the LAMS into necrotic cavity. The NCC was flushed and aspirated with 200 mL normal saline or hydrogen peroxide (3%) every 4 to 6 hours. Following symptomatic improvement, the NCC catheter was removed. In nonresponders, DEN was performed through the LAMS using a combination of accessories such as

Fig. 1 Computed tomography: large walled-off necrosis with extensive pancreatic necrosis.

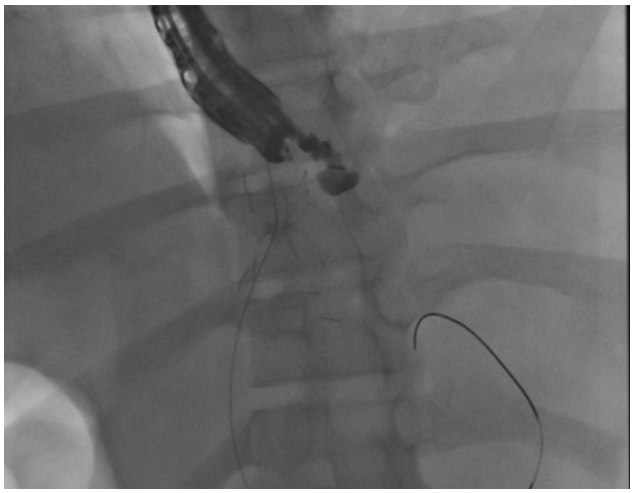

Fig. 2 Endoscopic ultrasound-guided drainage of walled-off necrosis with lumen apposing metal stent.

grasping forceps, snare, Dormia basket, and Roth basket (►**Figs. 1**–**4**).

Following clinical improvement, cross-sectional imaging to document resolution of WON was done at the discretion of the treating clinician. In patients with symptomatic improvement and resolved WON on CT, endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiography (MRCP) was done at the discretion of the treating clinician to document DPD. Thereafter, an attempt was made to replace LAMS with a 7- or 10-Fr double pigtail plastic stent and leave the plastic stents for an indefinite period. As mentioned earlier, patients included in this study had collapsed WON cavity at the time of removal of LAMS, and therefore, a permanent indwelling plastic stent could not be placed.

Follow-up and Outcome Measures

All these patients without a permanent indwelling transmural plastic stent were followed up in outpatient clinic once every 3 months for first year and thereafter every 6 monthly. The patients not reporting to the clinic were contacted telephonically. The patients underwent measurements of

Fig. 3 Computed tomography: postdrainage with lumen apposing metal stent (LAMS) shows a large residual necrotic collections with LAMS in situ.

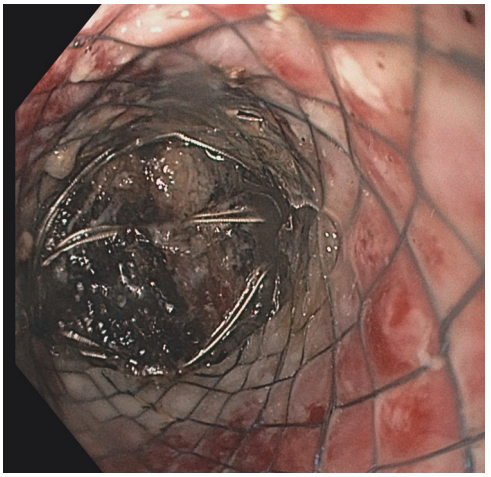

Fig. 4 Direct endoscopic necrosectomy being done through the lumen apposing metal stent.

fasting blood sugar as well as glycosylated hemoglobin (HbA1c) levels once in 6 months or when the patients reported symptoms of hyperglycemia. Patients having new symptoms such as abdominal pain, fever, or jaundice underwent CT for detecting recurrence of PFCs. The patients with recurrence of PFCs underwent further investigations such as MRCP, EUS, and ERCP at the discretion of treating clinician.

Statistical Analysis

The data were presented as percentages for categorical variables, and mean ± standard deviation for quantitative variables. The continuous variables were compared using Student's *t*-test, whereas the categorical variables were compared using the chi-square or Fisher's exact test. A *p*-value of <0.05 was considered as significant.

Results

Thirty-eight patients (mean age: 37.7 ± 6.8 years; male: $n = 31$) with WON and DPD successfully treated with LAMS and without permanent indwelling transmural plastic stents

Table 1 Demographics, etiology of acute pancreatitis, baseline imaging characteristics, and outcomes between the two groups

Parameter	Group A (requiring DEN) ($n = 17$)	Group B (DEN not done) ($n = 21$)	*p*-Value
Age (mean ± SD)	37.8 ± 7.9 y	37.7 ± 5.8 y	>0.05
Males (%)	15 (88)	16 (76)	>0.05
Etiology			
Alcohol	13 (76.4%)	13 (61.9%)	>0.05
Gall stones	2 (11.8%)	5 (23.8%)	
Idiopathic	2 (11.8%)	2 (9.5%)	
Others	0	1 (4.8%)	
>50% necrosis on CT done at days 3–7 of onset of illness	13 (76.4%)	5 (28%)	<0.05
Drainage for infected PFC	6 (28.5%)	13 (61.9%)	>0.05
Size of WON (mean ± SD)	12.6 ± 1.9 cm	11.7 ± 2.0 cm	>0.05
% Solid debris as documented on EUS	48.2 ± 9.2%	21.9 ± 9.3%	<0.05
Time taken for resolution of WON (d)	33.5 ± 5.8	26.3 ± 9.3	<0.05

Abbreviations: CT, computed tomography; DEN, direct endoscopic necrosectomy; EUS, endoscopic ultrasound; PFC, pancreatic fluid collection; SD, standard deviation; WON, walled-off necrosis.

were retrospectively identified and analyzed. Seventeen of these patients required DEN (Group A; mean age 37.8 ± 7.9 years), whereas 21 patients were successfully treated without the need of DEN (Group B; mean age: 37.7 ± 5.8 years). There was no significant difference in the demographics as well as the etiology of AP between the two groups (►**Table 1**). Contrast-enhanced CT of the abdomen done between 3 and 7 day of onset of ANP revealed >50% parenchymal necrosis in significantly more patients in Group A as compared with patients in Group B (76.4 vs. 23.8%; $p < 0.05$) (►**Fig. 1**). The size of WON was comparable between the two groups, but the amount of solid necrotic debris was significantly more in patients requiring DEN compared with patients who had successful outcome without DEN (48 vs. 22%, respectively; $p < 0.05$) (►**Table 1**). Also, patients needing DEN required longer time for resolution as compared with patients not requiring DEN (mean of 33.5 vs. 26.3 days; $p < 0.05$).

Recurrence of Symptoms/PFC after Resolution

In Group A, none of the patients developed either recurrence of any symptoms or PFC over a mean follow-up period of 7 months. In Group B, 5 of 21 (23.8%) patients developed abdominal pain over a mean follow-up period of 22 months (median time of recurrence from stent removal was 6 months; range: 3–13 months). On cross-sectional imaging, three of these patients had developed recurrent PFC and two patients needed repeat endoscopic transmural drainage using plastic stent. Following resolution of PFC, the plastic stent has been left in situ for an indefinite period and patients continue to be asymptomatic on last follow-up. The remaining one patient with PFC had a small collection (4 cm in size) and responded to pain killers. Thereafter, the patient continues to be asymptomatic and there has been no increase in the size of PFC on last follow-up. Two patients presented with upper abdominal pain not associated with either increase in serum pancreatic enzyme levels nor any imaging features of pancreatitis. The pain responded to nonsteroidal anti-inflammatory drugs and one of these patients developed one more episode of pain 4 months after the first episode of recurrent abdominal pain. Both these patients currently are on antioxidants and pancreatic enzymes supplement and continue to be asymptomatic on last follow-up. On comparing both groups at 7 months of follow-up, 3 of 21 (14.2%) patients in Group B had recurrence of symptoms, whereas none of the patients in Group A had recurrent symptoms. New-onset diabetes mellitus developed in five (29%) patients in Group A and two (9%) patients in Group B ($p > 0.05$). None of the patients in either group developed steatorrhea.

Discussion

Pancreatic duct disconnection is a frequent occurrence in ANP and this can complicate the clinical course of the illness.[5] Bang et al studied 361 patients with PFCs and found that DPD had a significant effect on endoscopic management of PFCs as patients with DPD required more hybrid treatment, reinterventions, and rescue surgery for achieving optimal clinical outcomes.[16] Another important issue is the risk of recurrence of PFC after successful endoscopic treatment of PFCs in patient with DPD. Recurrence rates varying from 13 to 40% have been reported previously in patients with DPD.[1,4–8,13,17,18] It has also been reported that maintaining the patency of iatrogenic transmural fistula by leaving plastic stents in situ for an indefinite period significantly decreases the risk of recurrence of PFCs.[1,3,4,7–9,18]

However, the issue of leaving transmural plastic stents for an indefinite period in patients with DPD is debated in

patients who have undergone initial drainage with LAMS. Few studies have reported very low frequency of recurrence of symptomatic PFCs in patients with DPD who had their initial PFC treated with LAMS and therefore, do not support the practice of leaving transmural stents for an indefinite period.[2,12] Discordant results have been reported by other studies of PFC being drained initially by LAMS where significantly high frequency of recurrence of PFC has been reported in patients with DPD without transmural stents compared with patients with permanent indwelling plastic stents.[1,5,13,17] These discordant results suggest that factors other than the use of LAMS determine the risk of recurrence of PFC in patients with DPD.

Rana et al reported that 37% patients of DPD without a permanent indwelling transmural plastic stent developed recurrent PFC.[9] All these patients with DPD had undergone successful transmural drainage of WON with multiple plastic stents. The authors reported that patients who had distal disconnection, post-ANP diabetes, as well as steatorrhea and pancreatic atrophy on imaging had low risk of recurrence of PFC in patients with DPD and without permanent indwelling plastic stents.[9] This observation suggests that patients with more extensive pancreatic necrosis are less likely to develop symptomatic DPD because of significant loss of viable pancreatic parenchyma upstream to the disconnection. Maatman et al also reported that patients with more extensive necrosis (>50% necrosis) are less likely to develop symptomatic DPD compared with patients with 30 to 50% parenchymal necrosis.[19] In the current study also, patients in the DEN group had significantly higher frequency of extensive pancreatic necrosis compared with patients in no DEN group. This observation suggests that patients with more extensive parenchymal necrosis are more likely to need DEN, and this observation is in accordance with our previous results as well as results from other studies.[20–22] The results of our current study also suggest that need for DEN is a surrogate marker for extensive pancreatic necrosis, and these patients despite having presence of duct disconnection are less likely to have symptomatic DPD because of lack of significant amount of viable pancreatic parenchyma. This observation also explains that the recurrence of PFC following successful endoscopic transmural drainage using LAMS in patients with DPD without permanent indwelling transmural stent is low.

There are, however, many limitations to the study. First and foremost, it is a retrospective study from a tertiary hospital and thus suffers from the inherent drawbacks of a retrospective study, including the selection bias. Also, there is unequal distribution of subjects in the comparing groups, and the sample size is also relatively small. This is however expected, considering the rarity of patients of PFC undergoing endoscopic transluminal drainage and not having long-term indwelling transmural stents. The study was conducted in the unit with extensive experience in pancreatic endotherapy, and therefore, the results may not be generalizable. Moreover, the follow-up was relatively shorter in patients in the DEN group compared with patients not requiring DEN. This is expected as DEN is a recent addition to the armamentarium and is being performed more frequently in recent times only.

In conclusion, patients with WON and DPD treated with LAMS and requiring DEN seem to be having low risk of developing recurrence of pain or PFC and therefore do not require permanent indwelling transmural plastic stents. However, further, large sample prospective studies are needed to confirm these results.

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Authors' Contribution
S.S.R. collected and interpreted the data, drafted the manuscript, as well as performed the critical evaluation of manuscript for intellectual content. N.B. collected and interpreted the data, and drafted manuscript. R.S. and R.G. collected the data.

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Conflict of Interest
None declared.

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