

# Comparative evaluation of structural and functional changes in pancreas after endoscopic and surgical management of pancreatic necrosis

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## Abstract

**Background** Patients with acute necrotizing pancreatitis may develop pancreatic insufficiency and this is commonly seen in patients who have undergone surgery for pancreatic necrosis. Owing to the paucity of relative data, we retrospectively evaluated the structural and functional changes in the pancreas after endoscopic and surgical management of pancreatic necrosis.

**Methods** The records of patients who underwent endoscopic transmural drainage of walled off pancreatic necrosis (WOPN) over the last 3 years and who completed at least 6 months of follow up were analyzed. Structural and functional changes in these patients were compared with 25 historical surgical controls (operated in 2005-2006).

**Results** Twenty six patients (21 M; mean age 35.4±8.1 years) who underwent endoscopic drainage for WOPN were followed up for 22.3±8.6 months. During the follow up, five (19.2%) patients developed diabetes with 3 patients requiring insulin and 1 patient with steatorrhea requiring pancreatic enzyme supplementation. The pancreatic fluid collection (PFC) recurred in 1 patient whose stents spontaneously migrated out. On follow up, in the surgery group, 2 (8%) patients developed steatorrhea and 11 (44%) developed diabetes. Five (20%) of these patients had recurrence of PFC. On comparison of follow up results of endoscopic drainage with surgery, recurrence rates as well as frequency of endocrine and exocrine insufficiency was lower in the endoscopic group but difference was not significant.

**Conclusion** Structural and functional impairment of pancreas is seen less frequently in patients with pancreatic necrosis treated endoscopically compared to patients undergoing surgery, although the difference was insignificant. Further studies with large sample size are needed to confirm these initial results.

**Keywords** Pancreatic necrosis, stent, diabetes, pseudocyst

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## Introduction

Initially it was believed that the pancreatic exocrine and endocrine functions return to normal even after an episode of acute severe pancreatitis [1,2]. This was because the majority

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of the patients who had recovered from an episode of acute necrotizing pancreatitis (ANP) and were asymptomatic were not subjected to investigations for diagnosing pancreatic endocrine or exocrine insufficiency. But many recent studies have reported that a large proportion of patients with acute pancreatitis have a variable degree of pancreatic insufficiency on follow up. The reported frequency of exocrine insufficiency varies from 2-86% whereas endocrine insufficiency has been reported in 7-90% for endocrine function after an episode of acute pancreatitis [3-8]. Moreover, it has been reported that the degree of functional impairment of the pancreas correlates with the severity of the attack of acute pancreatitis as evident by the extent of pancreatic necrosis [9,10]. One of the studies has also shown higher frequency of pancreatic functional impairment in patients with infected pancreatic necrosis as compared to patients with sterile necrosis [11].

The influence of surgical necrosectomy on the frequency of pancreatic insufficiency has also been studied with varying

results. Theoretically, surgical necrosectomy involves removal of pancreatic parenchyma and therefore these patients would be expected to be having a higher frequency of pancreatic insufficiency as compared to patients of ANP managed conservatively. Sabater *et al* found that necrosectomy led to significant impairment of pancreatic endocrine and exocrine function whereas the patients managed without surgical debridement had preserved pancreatic function [12]. Similar deleterious effects of pancreatic surgery on pancreatic endocrine and exocrine functions have been reported by other studies [13,14].

Endoscopic treatment of pancreatic necrosis is an upcoming, less invasive but technically demanding procedure associated with lower morbidity and mortality [15,16]. As the endoscopic techniques and instruments improved and since the endoscopic ultrasound (EUS) became available, the results of endoscopic management of pancreatic necrosis have been impressive [15-18]. Compared to surgery, endoscopic treatment of pancreatic necrosis has been shown to have a decreased proinflammatory response as well as decreased frequency of new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, pancreatic fistula or death [17]. However, the effects of endoscopic treatment of pancreatic necrosis on the pancreatic endocrine and exocrine functions have not been studied. In this study, we retrospectively evaluated the structural and functional changes in pancreas after endoscopic management of pancreatic necrosis and compared them with the results of historical controls that had been treated surgically in 2005-2006.

## Patients and methods

A retrospective analysis was done on the data of the patients who underwent EUS-guided transmural drainage of symptomatic walled off pancreatic necrosis (WOPN) between 2009-2012 and completed at least six months of follow up following recovery. Patients with recurrent acute pancreatitis, clinical or radiological features of chronic pancreatitis, previous pancreatic surgery, and a previous diagnosis of pancreatic exocrine or endocrine insufficiency were excluded. The recovery was defined as an asymptomatic patient who has resumed his daily activities along with resolution of all pancreatic fluid collections. All patients had been diagnosed with ANP based on the Atlanta classification before undergoing first endoscopic drainage procedure [11]. Indications for endoscopic drainage were computed tomography (CT) and EUS confirmed walled-off pancreatic necrosis located adjacent to the stomach or duodenum, with ongoing infection, defined by abdominal pain and fever despite administration of intravenous antibiotics, or gastric outlet or biliary obstruction by WOPN. Informed consent was obtained from all the patients prior to procedure and the procedure protocol had been approved by the institutional review board.

EUS-guided drainage was performed using the methodology described earlier [18]. The drainage was performed using

a linear scanning echoendoscope EG 3870 UTK (Pentax Inc, Tokyo, Japan). The optimal site for drainage was chosen under EUS and color Doppler guidance and the collection was punctured under EUS-guidance with a 19-gauge needle (Echotip; Cook Endoscopy, Winston-Salem, NC). After introducing a 0.035-inch guidewire into the cavity the access site was dilated using an endoscopic retrograde cholangiopancreatography (ERCP) cannula. If it was not possible to dilate the tract with the cannula because of thickened gastrointestinal tract wall, the tract was dilated using electrocautery with a wire-guided needle knife. The tract was further dilated using a wire guided hydrostatic balloon (CRE-balloon; Boston Scientific) up to 8-15 mm. One to three 7 F / 10 F double-pigtail stents, 5 cm in length, were inserted into the collection. Along with this a 7 F nasocystic catheter was positioned alongside the stents for short term irrigation of the necrotic debris. The transmural enteric fistula was kept patent by using double pigtail stents. In case, even after this aggressive transmural drainage, the WOPN persisted with symptoms, a decision for additional transmural drainage by stents, direct endoscopic necrosectomy (DEN) or surgery was taken after interdisciplinary consultation with pancreatic surgeons. Following the successful resolution of pancreatic necrosis, ERCP was performed to document pancreatic duct disruption. In patients with normal pancreatic duct, all the stents were removed whereas in patients with partial duct disruption, a transpapillary bridging stent was placed. A repeat ERCP was performed at 4 weeks to document healing of ductal disruption and thereafter all the stents were removed. In patients with disconnected pancreatic duct (DPDS), transmural stents were left indefinitely.

The patients who had completely recovered were advised 6-month follow up for pancreatic exocrine and endocrine functions. The patients who had recurrent symptoms were evaluated by magnetic resonance imaging (MRI) and/or CT and/or EUS for the morphological changes in the pancreas. The fasting and postprandial blood sugar and blood levels of glycosylated hemoglobin (HbA1c) were used to screen patients for endocrine insufficiency. The patients were questioned in detail about the history of steatorrhea. The 24-h fecal fat excretion test was performed in the patients willing to undergo this test. The fecal fat excretion of >7 g/24 h was considered as abnormal. The structural and functional changes in these patients were compared with 25 historical controls who had undergone surgery earlier for pancreatic necrosis and had completed at least 6 months of follow up (operated in 2005-2006).

## Statistical analysis

All results were expressed as mean  $\pm$  standard deviation, median or range as appropriate. The information thus collected was coded and transferred to a personal computer. For discrete variables comparison between different groups was done with Chi square test  $P < 0.05$  was considered as statistically significant.

## Results

The study included 26 patients (21 M; mean age 35.4±8.1 years) with WOPN who underwent endoscopic transmural drainage during the study period. These patients were followed up for a mean of 22.3±8.6 months (range: 6-34 months). The etiology of ANP was alcohol in 16, gallstones in 8 and idiopathic in 2 patients. The mean size of the WOPN drained was 10.8±3.4 cm. The mean CT severity index (CTSI) was 8 with it being 6 in 3 patients, 7 in 5 patients, 8 in 4 patients, 9 in 5 and 10 in 9 patients respectively. Twenty four patients could be successfully treated with aggressive transmural drainage using multiple stents whereas direct endoscopic necrosectomy was needed only in two patients.

The ERCP performed after resolution of WOPN revealed normal pancreatic duct in 4 patients whereas partial and complete disruption was observed in 5 and 17 patients respectively. The patients with partial disruption had successful healing of the pancreatic duct after placement of bridging transpapillary stent. In patients with disconnected pancreatic duct, the transmural stents were left in situ for an indefinite period. During the follow-up period, the patients with normal pancreatic duct and the patients with partial pancreatic duct disruption that healed after placement of bridging transpapillary stent remained asymptomatic. Six of 17 patients with DPDS had recurrence of abdominal pain and cross sectional imaging revealed recurrence of pancreatic fluid collection in one patient. In this patient, the transmural stents had migrated and he was treated with pain killers and subcutaneous octreotide. His pain was relieved and repeat cross sectional imaging 4 weeks later revealed marked reduction in the size of peri-pancreatic collection. He was subsequently discharged and is presently asymptomatic after five months of follow up.

In the remaining 5 patients, the transmural stents were observed to be in place and the pain responded to non narcotic pain killers and no other intervention was required for abdominal pain.

### Endocrine insufficiency

On follow up, five (19.2%) patients (4 males) developed diabetes with 3 patients requiring insulin and two patients

requiring oral hypoglycemic agents. All these 5 patients had diabetes detected during the first year after recovery. The etiology of acute pancreatitis was alcohol in 3 and gallstones in 2 patients.

### Exocrine insufficiency

During the follow up, only one patient (4%) had steatorrhea that required pancreatic enzyme supplementation and this patient had alcohol-related ANP. This patient developed steatorrhea in the tenth month of follow up and he also had endocrine insufficiency. Fecal fat excretion was done in 8 patients at 8-14 months post recovery and it was abnormal in 2 (25%) patients both of whom also had diabetes mellitus.

### Surgery group

The results of endoscopic drainage were compared with the results of 25 patients (20 males) who underwent surgery for pancreatic necrosis. The etiology of ANP was gallstones in 10, alcohol in 9, both in 2 and idiopathic in 4 patients respectively. The surgery done was necrosectomy and closed lesser sac lavage in 21 patients and drainage with closed lesser sac lavage in four patients. These patients were followed up for a mean of 31 months (range of 7-118 months). Two (8%) of these 25 operated patients developed steatorrhea that required pancreatic enzyme supplementation. Abnormal fecal fat excretion was observed in 9 (36%) patients. Eleven (44%) patients developed diabetes on follow up and six of them had insulin-dependent diabetes mellitus. Six (24%) patients had recurrent abdominal pain and 5 (20%) of these patients had recurrence of PFC.

### Comparison of endoscopic vs. surgical management of pancreatic necrosis

On comparison of follow up results of endoscopic drainage with surgical drainage, the recurrence rates as well as the frequency of endocrine and exocrine insufficiency was lower in the endoscopic group but the difference was not statistically significant, there was a trend towards lower frequency (Table 1).

**Table 1** Comparison of structural and functional changes in patients with pancreatic necrosis treated surgically or endoscopically

	Endoscopy (n=26)	Surgery (n=25)	P value
Recurrence of PFC	1 (4%)	5 (20%)	0.09
Diabetes Mellitus	5 (19%)	11 (44%)	0.07
Insulin dependent diabetes	3 (11%)	6 (24%)	0.29
Steatorrhea	1 (4%)	2 (8%)	1.00
Abnormal fecal fat excretion	2/8 (25%)	9/25 (36%)	0.68

PFC, pancreatic fluid collection

## Discussion

The initial belief of complete recovery of pancreatic endocrine and exocrine functions following ANP has been dispelled by many recent studies that have systematically studied these functions following recovery from an acute episode [3-11]. Also the severity of functional impairment of the pancreas correlates with the extent of pancreatic necrosis [9,10]. In the current study also ~20% of patients with ANP developed impairment of either endocrine or exocrine pancreatic function. Some of the studies have suggested that the pancreatic functions tend to normalize over a period of time following recovery from ANP [1,20]. The functional impairment of pancreas following ANP is still a topic of debate and one of the recent studies reported the results obtained from a very long follow-up period (mean 179.5 months) of non-operated patients with ANP and concluded that the pancreatic function recovers completely in the vast majority of patients [3]. The authors of this study during a long-term follow up hypothesized that operative management in many of the patients with ANP in previous studies on functional impairment would have led to bias in the results as during surgical necrosectomy because poor demarcation between necrotic areas and viable pancreatic parenchyma over removal of pancreatic tissue may occur. The hypothesized deleterious effects of pancreatic surgery on pancreatic endocrine and exocrine functions have been confirmed by a number of studies [12-14].

Endoscopic treatment of pancreatic necrosis is an upcoming, less invasive procedure associated with lower morbidity and mortality and excellent outcome but its effect on pancreatic functions have not been previously studied [15,16]. In the current study of 26 patients that have been followed for 6 to 34 months, we have shown that 19% of patients undergoing endoscopic treatment of pancreatic necrosis developed diabetes with 60% of these patients needing insulin for optimal sugar control. Symptomatic steatorrhea also developed in only one patient whereas asymptomatic increased fecal fat excretion was observed in 25% patients.

Compared to surgical controls, the frequency of both endocrine and exocrine insufficiency was lower in the endoscopic group although this difference was not statistically significant. In the current study, 19% of patients with ANP undergoing endoscopic necrosectomy developed endocrine insufficiency compared to 44% of patients who had under-

gone surgery. A similar trend of lower frequency of exocrine insufficiency was also observed in patients who were treated endoscopically (25% vs. 36% respectively;  $P=0.68$ ). This lower frequency of pancreatic insufficiency in endoscopically treated patients of pancreatic necrosis could be due to the minimally invasive nature of the procedure and probably less likelihood of over ablation of pancreatic tissue as a result of poor demarcation between viable and necrotic tissue as in surgical necrosectomy. In our study the majority of the patients were successfully treated with aggressive endoscopic transmural drainage and only two patients needed direct endoscopic necrosectomy. As DEN is a more aggressive procedure that involves endoscopic removal of necrotic tissue, theoretically it may lead to increased incidence of pancreatic insufficiency. It would be interesting to compare the long-term functional results of DEN with surgical necrosectomy.

ANP often results in main pancreatic duct disruption and persistent leakage of the pancreatic juice from this disruption complicates the course of the disease [21]. Complete pancreatic duct disruption with a considerable amount of viable pancreatic parenchyma upstream to the disruption lead on to DPDS [22,23]. Although the initial outcome of endoscopic transmural drainage in these patients is excellent, there is increased frequency of recurrence of PFC's because of the underlying uncorrected physiological abnormality [23]. This was also evident in the current study where 20% of patients who had undergone surgical necrosectomy without drainage of the pancreatic duct developed recurrence of PFC whereas none of the patients in the endoscopic group with non migrated transmural stents that were keeping the enteric communication patent had recurrence of PFC. This observation is in accordance with the results of our previously published study as well as the observations of other authors [24-26]. Our study has certain important limitations also. The small sample size and the fact that it is retrospective with historical surgical controls are important limitations of our study. The mean follow up was also 22 months and this may be inadequate to assess the impact on functional changes as longer follow up than this may be needed.

In conclusion, structural and functional impairment of pancreas is seen less frequently in patients with pancreatic necrosis who have been treated endoscopically compared to patients treated surgically, although the difference was insignificant. Further studies with large sample size are needed to confirm these initial results.

## Summary Box

### What is already known:

- A large proportion of patients with acute necrotizing pancreatitis have a variable degree of pancreatic insufficiency on follow up
- As surgical necrosectomy involves removal of pancreatic parenchyma and therefore these patients have higher frequency of pancreatic insufficiency
- Endoscopic treatment of pancreatic necrosis is an upcoming, less invasive but technically demanding procedure that is associated with lower morbidity and mortality but its long-term effect on pancreatic functions is not known

### What the new findings are:

- Compared to surgical controls, the endocrine and exocrine pancreatic insufficiency is seen less frequently in patients treated endoscopically although the difference was insignificant
- Recurrent pancreatic fluid collections are seen more frequently in patients treated surgically although the difference was insignificant. This could be due to the small sample size

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