PRELIMINARY COMMUNICATION

Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis

A Randomized Trial

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Context Most patients with infected necrotizing pancreatitis require necrosectomy. Surgical necrosectomy induces a proinflammatory response and is associated with a high complication rate. Endoscopic transgastric necrosectomy, a form of natural orifice transluminal endoscopic surgery, may reduce the proinflammatory response and reduce complications.

Objective To compare the proinflammatory response and clinical outcome of endoscopic transgastric and surgical necrosectomy.

Design, Setting, and Patients Randomized controlled assessor-blinded clinical trial in 3 academic hospitals and 1 regional teaching hospital in the Netherlands between August 20, 2008, and March 3, 2010. Patients had signs of infected necrotizing pancreatitis and an indication for intervention.

Interventions Random allocation to endoscopic transgastric or surgical necrosectomy. Endoscopic necrosectomy consisted of transgastric puncture, balloon dilatation, retroperitoneal drainage, and necrosectomy. Surgical necrosectomy consisted of video-assisted retroperitoneal debridement or, if not feasible, laparotomy.

Main Outcome Measures The primary end point was the postprocedural proinflammatory response as measured by serum interleukin 6 (IL-6) levels. Secondary clinical end points included a predefined composite end point of major complications (new-onset multiple organ failure, intra-abdominal bleeding, enterocutaneous fistula, or pancreatic fistula) or death.

Results We randomized 22 patients, 2 of whom did not undergo necrosectomy following percutaneous catheter drainage and could not be analyzed for the primary end point. Endoscopic transgastric necrosectomy reduced the postprocedural IL-6 levels compared with surgical necrosectomy ($P=.004$). The composite clinical end point occurred less often after endoscopic necrosectomy (20% vs 80%; risk difference [RD], 0.60; 95% CI, 0.16-0.80; $P=.03$). Endoscopic necrosectomy did not cause new-onset multiple organ failure (0% vs 50%, RD, 0.50; 95% CI, 0.12-0.76; $P=.03$) and reduced the number of pancreatic fistulas (10% vs 70%; RD, 0.60; 95% CI, 0.17-0.81; $P=.02$).

Conclusion In patients with infected necrotizing pancreatitis, endoscopic necrosectomy reduced the proinflammatory response as well as the composite clinical end point compared with surgical necrosectomy.

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ACUTE PANCREATITIS IS A COMmon and potentially lethal disorder.[1] In the United States alone, more than 50 000 patients are admitted with acute pancreatitis each year.[2] One of the most dreaded complications in these patients is infected necrotizing pancreatitis that leads to sepsis and is often followed by multiple organ failure.[3] In these patients interventions are necessary to debride the infected necrosis, but the interventions themselves cause substantial morbidity.[4-6]

For editorial comment see p 1084.

The treatment of infected necrotizing pancreatitis has undergone fundamental changes in recent years. Whenever possible, intervention is postponed until the collections with necrosis are demarcated.[7,8] Demarcation facilitates necrosectomy and reduces complications related to the drainage and debridement procedures.[9] A recent randomized trial demonstrated that a step-up approach of percutaneous catheter

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drainage with subsequent minimally invasive surgical necrosectomy is superior to primary open necrosectomy.[10] The step-up approach reduced new-onset multiple organ failure and long-term complications such as diabetes and need for pancreatic enzyme supplementation. Approximately two-thirds of patients required necrosectomy after percutaneous catheter drainage. Current guidelines recommend surgical necrosectomy[4-6]; however, minimally invasive and open surgical necrosectomy for infected necrosis has a 55% to 81% complication rate.[10,11]

A less invasive approach to necrosectomy is natural orifice transluminal endoscopic surgery (NOTES),[12] which combines endoscopic and surgical techniques.[13] Endoscopic transgastric necrosectomy is a new technique that involves drainage and direct retroperitoneal endoscopic necrosectomy through the gastric wall using endoscopic ultrasound guidance.[14] Endoscopic necrosectomy is performed under conscious sedation without the need for general anesthesia and potentially reduces the proinflammatory response and risk of procedure-related complications such as multiple organ failure in these already ill patients.[15-17]

NOTES has not yet been compared with surgery in a randomized clinical trial for any disease. To our knowledge, the Pancreatitis, Endoscopic Transgastric vs Primary Necrosectomy in Patients With Infected Necrosis (PENGUIN) is the first randomized trial comparing the 2 procedures.

METHODS

Patients

Adult patients needing necrosectomy for suspected or confirmed infected necrotizing pancreatitis who could undergo both endoscopic or surgical necrosectomy, based on computed tomographic (CT) imaging, were eligible for randomization. *Infected necrosis* was defined as a positive culture of pancreatic or peripancreatic necrosis obtained from fine-needle aspiration or the first drainage procedure or operation or by the presence of gas in the collection on contrast-enhanced CT scan. *Suspected infected pancreatic necrosis* was defined as persisting sepsis or progressive clinical deterioration despite maximal support on the intensive care unit without documented infected necrosis. The trial was performed in 3 university medical centers and a large nonuniversity teaching hospital participating in the Dutch Pancreatitis Study Group. Exclusion criteria were previous surgical or endoscopic necrosectomy, previous exploratory laparotomy, pancreatitis as a consequence of abdominal surgery, a flare-up of chronic pancreatitis, abdominal compartment syndrome, perforation of a visceral organ, or bleeding as indication for intervention. All patients or their legal representatives gave written informed consent before randomization. This study was investigator initiated and was performed in accordance with the principles of the Declaration of Helsinki. The institutional review board of each participating hospital approved the protocol.

Quality Control

As previously described, an expert panel of 8 gastrointestinal surgeons, 3 gastroenterologists, and 3 radiologists evaluated all candidates prior to randomization.[10] The panel's advice on the decision to intervene and the possibility to randomize into either group was discussed with the treating physicians who made the final decision about whether to intervene. Whenever possible, intervention was postponed to at least a month after the onset of disease.[7,8] All interventions were performed by gastrointestinal surgeons experienced in pancreatic surgery and by experienced endoscopists.

Surgical Necrosectomy

Patients underwent video-assisted retroperitoneal debridement (FIGURE 1A).[10] This included debridement of all loosely adherent necrosis through a 5-cm flank incision, using a previously placed retroperitoneal percutaneous drain and videoscopic assistance for guidance. If video-assisted debridement was not possible because there was no safe retroperitoneal access route, open necrosectomy through laparotomy using a bilateral subcostal incision was performed.[18] Continuous postoperative lavage was performed using 2 large bore drains.

Endoscopic Transgastric Necrosectomy

All endoscopic transgastric necrosectomy procedures were carried out under conscious sedation using midazolam or propofol and fentanyl (Figure 1B). Linear-array endoscopic ultrasound was used to visualize the extent of the necrosis and to determine the optimal puncture site.[19,20] Under endoscopic ultrasound guidance, the collection was punctured using a 19-gauge needle (EUSN-19-T, Wilson-Cook). After withdrawal of the stylette, the content of the collection was aspirated to confirm the correction position. Through the 19-gauge needle, a 0.035-inch (0.89-mm) Jagwire guidewire (Boston Scientific) was advanced under fluoroscopic guidance. Using electrocautery, the outer sheath of a 10F (Wilson-Cook) or a 6F (Endotechnik) cystogastrostomy was advanced into the stomach wall followed by balloon dilatation of the tract up to 8 mm. Thereafter, 2 or more double-pigtail plastic stents (7F , 5 or 7 cm) and a 6F nasocystic catheter were placed and the necrotic collection was irrigated with 1 liter of normal saline per 24 hours. During the subsequent days, the site of access was dilated up to 15 or 18 mm using a dilatation balloon. A forward-viewing endoscope was advanced in the cavity and the necrotic tissue was evacuated with a basket, net, or polypectomy snare. At the end of each procedure, multiple 7F double-pigtail plastic stents were placed. This procedure was repeated until the majority of the necrotic material was removed (a video of an endoscopic transgastric necrosectomy procedure is available at http://www.jama.com).

Additional Interventions

Additional necrosectomies after surgical necrosectomy were only per-

formed if there was no clinical improvement. Acute complications such as bleeding were treated according to the treating physicians' preference. All patients received intravenous antibiotics (imipenem-cilastatin, meropenem, or piperacillin-tazobactam depending on center), which were adjusted according to culture results or stopped if there was clinical improvement.

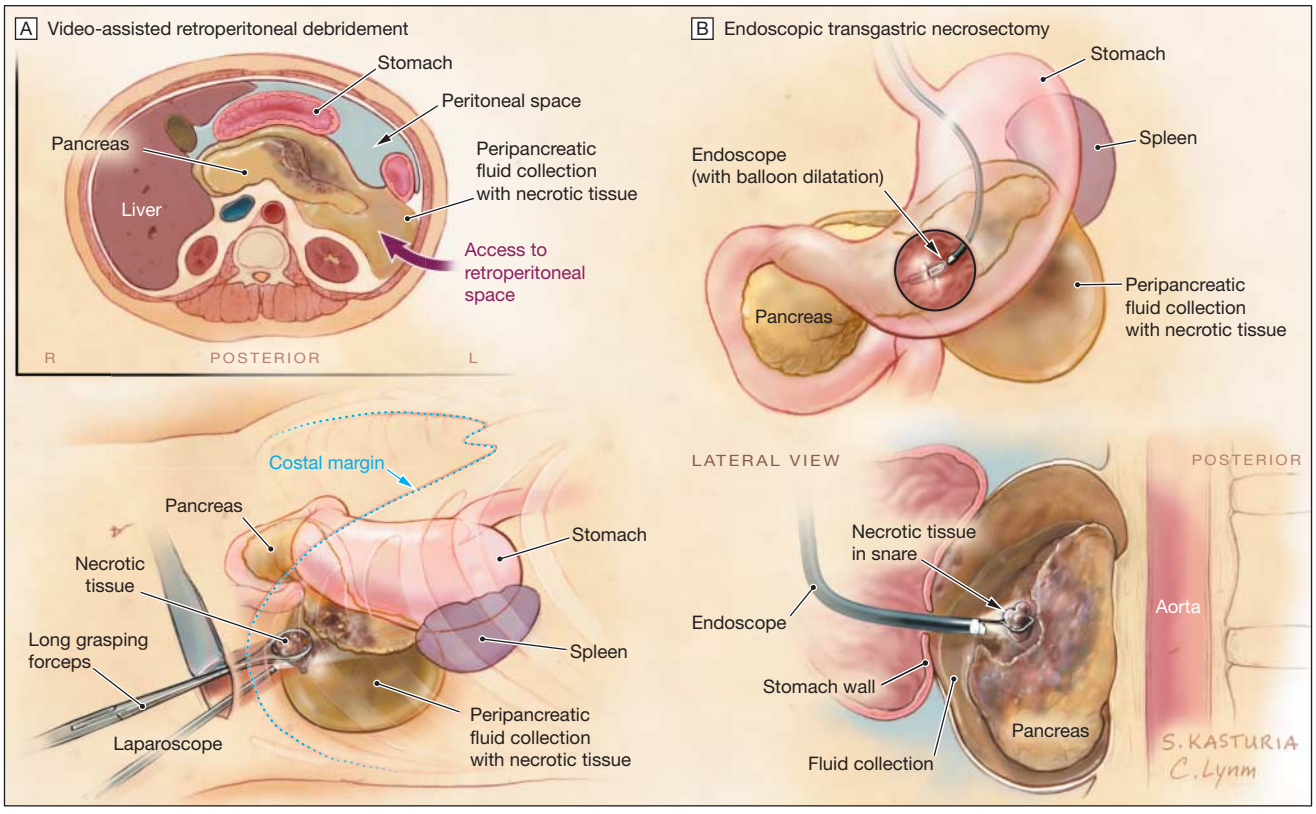
Outcome Measures

The primary end point was the proinflammatory response following surgical or endoscopic or surgical necrosectomy as measured by the serum level of the proinflammatory cytokine IL-6. Secondary end points included a composite clinical end point of death or major complications (BOX). Major complications comprised new-onset multiple organ failure, intra-abdominal bleeding requiring intervention, enterocutaneous fistula or perforation of a visceral organ requiring intervention, and pancreatic fistula. Other secondary end points included long-term complications such as new-onset diabetes, use of pancreatic enzymes, or persisting fluid collections measured at 6 months after discharge. Follow-up visits took place at 3 and 6 months after discharge. Data collection was performed by the study coordinator and the trial nurse at each study site. One experienced radiologist blinded for treatment allocation evaluated all CT scans for the presence and extent of necrosis prior to randomization and persisting fluid collections at 6 months after discharge. An adjudication committee consisting of 5 gastrointestinal surgeons and 2 gastroenterologists independently reviewed all clinical end points and performed a blinded outcome assessment.

Determination of IL-6 Levels

Interleukin 6 was used as a marker for the overall inflammatory state.[22,23] In both groups, blood samples were drawn just before the start of the first intervention; at 2, 5, and 24 hours; and 7 days thereafter. In the endoscopic group, the first procedure was the starting point of blood sampling; the first sample was drawn before gastric puncture, balloon dilatation, and drainage of the collection. This first step in treatment was anticipated to cause the great-

Figure 1. Video-Assisted Retroperitoneal Debridement and Endoscopic Transgastric Necrosectomy



A, Cross-sectional view depicting an enlarged, partially necrotic pancreas with a peripancreatic collection containing fluid and necrosis. The preferred access route for video-assisted debridement is within the left retroperitoneal space to reach the necrotic collection between the left kidney and descending colon. A laparoscope is inserted, and long grasping forceps are used to debride the necrosis. B, The access route for natural orifice transluminal endoscopic surgery is through the posterior wall of the stomach. The necrotic collection most often bulges into the stomach facilitating endoscopic transgastric necrosectomy. After balloon dilatation of the puncture site in the stomach wall, the endoscope is introduced into the retroperitoneal space and loose necrotic material is removed.

Box. Definitions of Clinical End Points

Organ Failure[a]

Pulmonary Failure

PaO_2 lower than 60 mm Hg despite fraction of inspired oxygen (FIO_2) of 30% or need for mechanical ventilation

Circulatory Failure

Circulatory systolic blood pressure below 90 mm Hg despite adequate fluid resuscitation or need for inotropic catecholamine support

Renal Failure

Creatinine level more than 2.0 mg/dL after rehydration or new need for hemofiltration or hemodialysis

Multiple Organ Failure

Failure of 2 or more organs at the same time

Major Complications

New-Onset Multiple Organ Failure

Multiple organ failure that had not been present in the 24 hours before randomization

Intra-abdominal Bleeding Requiring Intervention

Surgical, radiological, or endoscopic intervention

Enterocutaneous Fistula or Perforation of a Visceral Organ Requiring Intervention

Secretion of fecal material from a percutaneous drain or drainage canal after removal of drains or from a surgical wound; secretion comes from either the small or large bowel and is confirmed with imaging or during surgery and requires either surgical, radiological, or endoscopic intervention

Pancreatic Fistula

Output via a percutaneous or nasocystic drain or drainage canal after removal of percutaneous drains or from a surgical wound of any measurable volume of fluid with an amylase content greater than 3 times the serum amylase activity[b]

Long-term Complications

New-Onset Diabetes

The need for insulin or oral antidiabetic drugs to treat diabetes—which was not present before pancreatitis—6 months after discharge

Use of Pancreatic Enzymes

The use of oral pancreatic enzyme supplementation to treat clinical symptoms of steatorrhea—which was not present before onset of pancreatitis—6 months after discharge

Persisting Fluid Collections

The presence of pancreatic or peripancreatic fluid collections on computed tomographic scan 6 months after discharge.

SI converstion factor: To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

[a] Adapted from the 1992 Atlanta classification for acute pancreatitis.[21]

[b] Adapted from the International Study Group on Pancreatic Fistula Definition (ISGPF) criteria for postoperative pancreatic fistula.[41]

est proinflammatory response because manipulation of an infected collection under pressure could cause bacteremia and subsequent clinical deterioration. Blood samples were drawn, centrifuged at 4°C at 3000 rounds per minute for 10 minutes immediately, and plasma aliquots were stored at –80°C. Serum levels of IL-6 were determined in all blood samples using a multiplex suspension bead array system according to the manufacturer's protocol (Bio-Rad Laboratories). Data analysis was performed using the Bio-Plex 100 system and Bio-Plex Manager software version 4.1 (Bio-Rad). The lower limit of detection for IL-6 was 0.2 pg/mL. All analyses were done blinded to treatment allocation.

Statistical Analysis

When we designed the study, endoscopic necrosectomy was performed in only 4 specialized hospitals in the Netherlands and only a few small case series have been published on endoscopic necrosectomy. Furthermore, infected necrotizing pancreatitis is a relatively uncommon condition. For these reasons a primary end point was chosen with a relatively small sample size. Endoscopic necrosectomy was hypothesized to reduce the postprocedural proinflammatory response, as measured by serum IL-6, as compared with surgical necrosectomy. Calculation of the sample size was based on differences demonstrated in randomized trials of open vs laparoscopic abdominal surgery.[24,25] We calculated that 10 necrosectomies per group would be needed to detect a reduction of 45%, with 30% within-group standard deviation, with 80% power, and a 2-sided α level of .05.

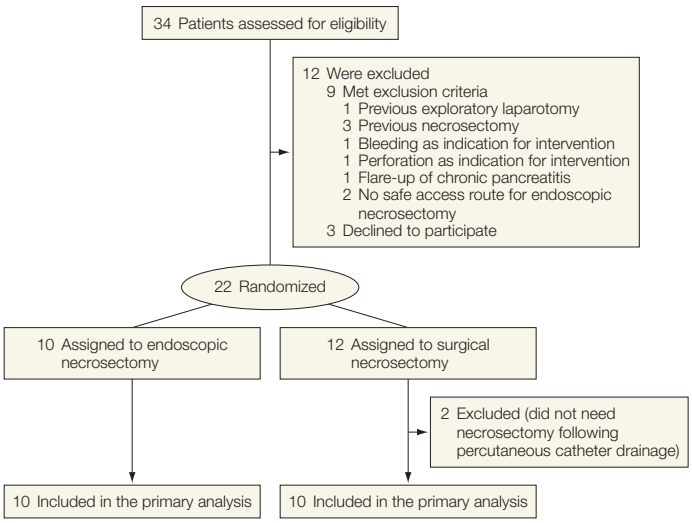
As predefined in the study protocol, patients excluded from the study for any reason (eg, withdrawal of consent) before the first endoscopic or surgical intervention was performed, were replaced by new patients because only after the intervention could the blood samples for the primary end point be drawn. Randomization was performed centrally by the study coordinator using a computer-generated permuted block sequence with a concealed block size of 4. Trends in serum IL-6 levels in both treatment groups were assessed using a linear random-affects model. We assumed a linear trend for the first 24 hours and a separate value after one week. Results are presented as fitted trend curves with 95% confidence intervals. Overall difference between both treatment groups was tested with the likelihood ratio test, whereas a Wald test was used for the differences at the different observation times.

Analyses were performed according to the intention-to-treat principle. A post hoc multivariable logistic regression was performed to investigate the confounding effect of the 2 variables showing strongest asymmetry at baseline. Continuous data are presented as

medians with interquartile ranges. Differences between the treatment groups were quantified via risk differences with 95% confidence intervals for dichotomous outcomes. The Mann-Whitney U test was used for all continuous data.

For the longitudinal analyses on IL-6, missing data were considered to be missing at random (6 out of 100 samples). For the other analyses, individuals with missing data were excluded; hence, data were considered to be missing completely at random. Data on long-term complications were not available from nonsurviving patients (5 out of 20 patients). No interim analysis was performed. All reported *P* values are 2-sided and have not been adjusted for multiple testing. *P* values lower than .05 were considered statistically significant. Analyses were performed using the R statistical program (version 2.13) and SPSS (version 15.0).

Figure 2. Study Flow Chart



RESULTS

Patients

Between August 20, 2008, and March 3, 2010, a total of 34 patients with signs of infected necrotizing pancreatitis were assessed for eligibility and 22 patients underwent randomization (FIGURE 2). Two patients underwent percutaneous catheter drainage after randomization. Subsequently, these patients clinically improved so that necrosectomy was no longer needed. As predefined in the study protocol, these patients were excluded and laboratory measurements for the primary end point were not performed. Baseline characteristics of the 2 groups of 10 patients were comparable (TABLE 1). Nineteen of 20 patients (95%) had infected necrosis as proven by cultures at the first intervention. The median time from onset of disease to randomization was approximately 48 and 59 days (*P*=.91). In the acute phase of the disease before randomization, 40% of all patients experienced organ failure and 30%, multiple organ failure.

Surgery

Of all 12 patients in the surgical necrosectomy group, 6 underwent video-assisted retroperitoneal debridement, 4 underwent laparotomy, and 2 were treated with percutaneous drainage only. All operations were performed under general anesthesia. The median number of necrosectomies was 1 (IQR, 1-2). In 1 patient with necrosis extending down the left and right retrocolic space, 4 necrosectomies were necessary. One patient underwent 3 relaparotomies following necrosectomy; 1 for a gastric perforation and 2 for irrigation of a contaminated abdomen. Another patient underwent an additional laparotomy for an enterocutaneous fistula caused by perforation of the large intestine following video-assisted retroperitoneal debridement.

Endoscopy

All 10 patients assigned to the NOTES group underwent endoscopic transgastric necrosectomy. Nine patients were sedated using midazolam and fentanyl, and for 1 patient, propofol was used. The median number of procedures was 3 (interquartile range [IQR], 2-6). For one patient, necrosectomy was performed during the first procedure. For 2 patients, an additional video-assisted retroperitoneal debridement was performed using a left-sided retroperitoneal percutaneous catheter as guidance following 7 endoscopic necrosectomies for 1 patient and 5 for the other. These 2 patients were kept in the endoscopic group for analyses.

Outcomes

With respect to the primary end point, IL-6 levels increased after surgical necrosectomy, whereas IL-6 levels decreased after endoscopy (FIGURE 3). Because IL-6 levels had a skewed distribution, a logarithmic transformation was used when fitting the model. Results are presented as fitted trend curves with 95% confidence intervals on the logarithmic scale. The corresponding original IL-6 values are shown on the axis. The overall test for difference between groups was significant (*P*=.004). The largest difference between the 2 groups was seen at 24 hours after intervention (*P*=.005).

The composite clinical end point of death and major complications was also reduced in the patients in the endoscopy group (20% vs 80%; risk difference [RD], 0.60; 95% CI, 0.16-0.80; *P*=.03; TABLE 2). New-onset multiple organ failure did not occur after endoscopic transgastric necrosectomy (0% vs 50%; RD, 0.50; 95% CI, 0.12-0.76; *P*=.03). Fewer patients in the endoscopic group developed pancreatic fistulas (10% vs 70%; RD, 0.60; 95% CI, 0.17-0.81; *P*=.02). At 6 months after discharge, patients assigned to endo-

scopic necrosectomy less often used pancreatic enzymes (0% vs 50%; RD, 0.50; 95% CI, 0.07-0.81; *P*=.04).

In total, 5 of 20 patients died (10% vs 40%, RD, 0.30; 95% CI, –0.08 to 0.60; *P*=.30). All deaths were attributable to persistent multiple organ failure. Following endoscopic necrosectomy, 1 patient died 8 days after randomization. Following surgical necrosectomy, 4 patients died at days 21, 29, 79, and 155 days after randomization.

Table 1. Baseline Characteristics of the Patients

Characteristic	Surgical Necrosectomy (n = 10)	Endoscopic Transgastric Necrosectomy (n = 10)	*P* Value
Serum IL-6 levels prior to intervention, pg/ml	42.4 (15.9-138.9)	49.7 (16.5-103.4)	.82
Age, median (IQR), y	64 (46-72)	62 (58-70)	.97
Male sex, No. (%)	8 (80)	6 (60)	.63
Cause of pancreatitis, No. (%)			
Biliary	7 (70)	6 (60)	.82
Alcohol abuse	2 (20)	2 (20)	
Other	1 (10)	2 (20)	
ASA class on admission, No. (%)			
I, healthy status	1 (10)	1 (10)	.59
II, mild systemic disease	8 (80)	9 (90)	
III, severe systemic disease	1 (10)	0 (0)	
BMI on admission, median (IQR)	27 (23-37)	29 (26-35)	.51
Disease severity at randomization[a]			
SIRS, No. (%)[b]	7 (70)	9 (90)	.58
APACHE II score, median (IQR)[c]	11 (7-14)	10 (6-14)	.76
C-reactive protein, median (IQR), mg/L	232 (140-275)	141 (11-196)	.29
White blood cell count, median (IQR), × 10^3/μL	17.9 (9.8-19.7)	11.8 (9.4-18.6)	.45
Organ failure, No. (%)	3 (30)	2 (20)	>.99
Multiple organ failure, No. (%)	1 (10)	2 (20)	>.99
Admitted to ICU, No. (%)	3 (30)	2 (20)	>.99
Disease severity anytime before randomization, No. (%)			
Organ failure	4 (40)	4 (40)	>.99
Multiple organ failure	4 (40)	2 (20)	0.63
Positive blood culture	2 (20)	3 (30)	>.99
Admitted on ICU	4 (40)	5 (50)	>.99
Computed tomography[d]			
Severity index, median (range)[e]	8 (4-10)	8 (4-10)	>.99
Extent of pancreatic parenchymal necrosis, No. (%)			
<30%	3 (30)	3 (30)	>.99
30%-50%	2 (20)	2 (20)	
>50%	4 (40)	4 (40)	
Peripancreatic necrosis only	1 (10)	1 (10)	>.99
Time since onset of symptoms, median (IQR), d	59 (29-69)	48 (36-74)	.91
Previous percutaneous catheter drainage	8 (80)	4 (40)	.17
Nutritional support anytime before randomization, No. (%)			
Enteral nutrition	5 (50)	6 (60)	.36
Parenteral nutrition	0 (0)	1 (10)	
Enteral and parenteral nutrition	4 (40)	1 (10)	
Oral diet	1 (10)	2 (20)	
Tertiary referrals, No. (%)	9 (90)	8 (80)	>.99
Infected necrosis, No. (%)	9 (90)	10 (100)	>.99

Abbreviations APACHE, Acute Physiology and Chronic Health Evaluation; ASA, American Society of Anesthesiologists; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; ICU, intensive care unit; IL, interleukin; IQR, interquartile range; SIRS, systemic inflammatory response syndrome.
SI conversion factor: to convert C-reactive protein from mg/L to nmol/L, multiply by 9.524
[a] Based on maximum values during 24 hours before randomization unless stated otherwise.
[b] Defined by the consensus-conference criteria of the American College of Chest Physicians-Society of Critical Care Medicine.
[c] APACHE II scores can range from 0 to 71, with higher scores indicating more severe disease.
[d] This information was derived from computed tomography performed just before randomization.
[e] Computed tomographic severity index can range from 0 to 10, with higher scores indicating more extensive pancreatic necrosis and peripancreatic fluid collections.

Sensitivity and Multivariable Analysis

All 22 randomized patients, including the 2 patients who were treated without necrosectomy, were included in a sensitivity analysis for clinical end points. One of the patients treated without necrosectomy used pancreatic enzymes at 6 months' follow-up. No other clinical end points were seen in these patients. When including all 22 randomized patients, the composite clinical end point occurred in 2 of 10 patients (20%) after endoscopic necrosectomy and in 8 of 12 patients (67%) after surgical necrosectomy (RD, 0.47; 95% CI, 0.05-0.71; *P*=.04). Furthermore, endoscopic necrosectomy still reduced new-onset multiple organ failure (0% vs 42%; *P*=.04) and pancreatic fistulas (10% vs 58%, *P*=.03).

Although not statistically significant, the number of patients with previous percutaneous drainage at baseline was higher in the surgery group than in the endoscopy group (80% vs 40%) and the median C-reactive protein was higher in the surgery group (232 vs 141 mg/L; to convert C-reactive protein from mg/L to nmol/L, multiply by 9.524). To investigate the effect on the clinical outcomes from asymmetries in patient and disease characteristics despite randomization, we performed multivariable logistic regression adjusting for percutaneous catheter drainage and C-reactive protein. After adjustment for these 2 asymmetric variables, endoscopic necrosectomy was still associated with a reduced risk of major complications or death (adjusted odds ratio, 0.06, 95% CI, 0.01-0.78; *P*=.03).

COMMENT

The transition from open to laparoscopic surgery over the past 25 years greatly reduced surgical morbidity.

Natural orifice transluminal endoscopic surgery has the potential for another quantum leap in improved surgical outcomes.[12] In this first randomized trial comparing endoscopic necrosectomy to current standard surgical therapy, NOTES was associated with reduced proinflammatory response as opposed to increases in the inflammatory marker IL-6 that was seen with surgical necrosectomy. Endoscopic necrosectomy was also associated with a significant reduction in the composite clinical end point of major complications or death. Within the composite end point, NOTES necrosectomy was associated with fewer episodes of multiple organ failure and pancreatic fistulas.

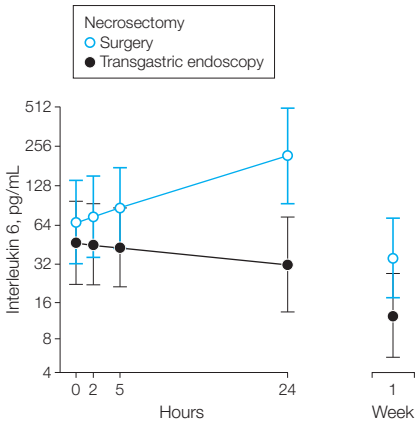
The lower rate of complications after endoscopic transgastric relative to surgical necrosectomy in this study (20% vs 80%) is consistent with prior reports for these procedures.[10,11,19,20,26-32] Previous, nonrandomized reports of outcomes for these interventions demonstrated encouraging results of endoscopic transgastric necrosectomy with complications rates of approximately 17%. Two recent European studies on minimally invasive and open surgical necrosectomy reported complications in 55% to 81% of patients.[10,11]

The very high complication rate following surgery in the current study is explainable by our preoperative protocol of percutaneous catheter drainage. In 80% of patients, surgery was performed in patients not responding to percutaneous catheter drainage; thus, patients were more ill than might have been observed in prior studies of pancreatic-infected necrosis.[7,10] Furthermore, 40% of patients in the surgical group required open necrosectomy, which accounted for the high complication rate. Open necrosectomy is typically associated with complication rates as high as 81%[11]

The reduction of organ failure with endoscopy is clinically relevant because organ failure is one of the major causes of long-term morbidity and death following acute pancreatitis.[33,34] Patients with acute pancreatitis and either organ failure or infected necrosis have a mortality rate of up to 30%.[35] When organ failure and infected necrosis coincide, outcome is even worse.[35] The current study was not powered to show a difference in death rate. A larger clinical trial would be necessary to determine whether NOTES can reduce mortality from infected pancreatic necrosis.

The reduced proinflammatory response and prevention of new-onset

Figure 3. Serum Interleukin 6 Levels After Endoscopic Transgastric or Surgical Necrosectomy



Error bars indicate 95% confidence intervals. Data were available from all 10 participants in the endoscopic transgastric group at all times except at 1 week (8 of 10). Similarly, all data were available among the 10 participants in the surgery group except at 2 hours (8 of 10) and at 24 hours and 1 week (9 of 10).

Table 2. Clinical End Points[a]

	Surgical Necrosectomy (n = 10)	Endoscopic Transgastric Necrosectomy (n = 10)	Risk Difference (95% CI)	*P* Value
Major complications or death, No. (%)[b]	8 (80)	2 (20)	0.60 (0.16 to 0.80)	.03
Death, No. (%)	4 (40)	1 (10)	0.30 (–0.08 to 0.60)	.30
Major complications, No. (%)				
New-onset multiple organ failure[c]	5 (50)	0 (0)	0.50 (0.12 to 0.76)	.03
Intra-abdominal bleeding requiring intervention	0 (0)	0 (0)		
Enterocutaneous fistula or perforation of a visceral organ requiring intervention	2 (20)	0 (0)	0.20 (–0.11 to 0.51)	.47
Pancreatic fistula	7 (70)	1 (10)	0.60 (0.17 to 0.81)	.02
Long-term complications, No. (%)[d]	(n = 6)	(n = 9)		
New-onset diabetes	3 (50)	2 (22)	0.28 (–0.17 to 0.63)	.33
Use of pancreatic enzymes	3 (50)	0 (0)	0.50 (0.07 to 0.81)	.04
Persisting fluid collections[e]	3 (50)	2 (22)	0.28 (–0.17 to 0.63)	.33
Health care utilization, No.	(n = 10)	(n = 10)		
No. of necrosectomies, endoscopic or surgical	1 (1 to 2)	3 (2 to 6)		.007
New ICU admission anytime after randomization, No. (%)	5 (50)	1 (10)	0.4 (–0.002 to 0.68)	.14
Days in hospital after randomization[f]	36 (17 to 74)	45 (12 to 69)		.91

[a] Continuous data are median and interquartile ranges.
[b] Multiple events in the same patient were considered as 1 end point.
[c] Only for patients without (multiple) organ failure at any time in the 24 hours before first intervention.
[d] Surviving patients were assessed 6 months after discharge from the index admission (readmission within 10 days was considered the same admission).
[e] Persisting fluid collections as seen on computed tomographic scans.
[f] Surviving patients only.

multiple organ failure after endoscopic necrosectomy might be explained by 2 factors. First, with the use of a natural orifice as access route to the retroperitoneal cavity, surgical dissection to reach the omental sac or retroperitoneum is no longer needed. Second, endoscopic necrosectomy is performed under conscious sedation and does not require general anesthesia. This is an important difference because general anesthesia is known to induce or prolong systemic inflammation in critically ill patients.[36]

Although, the results of our trial are consistent with earlier reports of endoscopic necrosectomy, there are important differences between the PENGUIN trial and other trials that preceded it. Nonrandomized studies are prone to selection bias, favoring the results of the intervention. Because our groups were randomly allocated, they were balanced, facilitating a more definitive comparison of the interventions than is possible by nonrandomized studies. Because patients only received our intervention after failing more conservative means of treatment, the proportion of them with infected necrosis (95%) is much higher than the 34% to 54% reported in the 2 largest series to date.[31,32] These other studies were of pancreatic necrosis that was not necessarily infected so that, on average, patients in those studies were less ill than those we treated. Another important difference between PENGUIN and prior studies was the use of measured inflammatory responses in addition to other outcomes. Most prior studies had radiological findings, such as resolution of the necrotic collection on CT scans, as the primary outcome measure.[26,28-32] Radiological findings do not necessarily correlate to the actual state of disease for pancreatitis.

This study has its limitations. The primary end point reflected the inflammatory response (ie, IL-6) and was not a clinical end point. Second, the requirement for necrosectomy is relatively rare resulting in a small number of patients enrolled in the PENGUIN trial. Nevertheless, despite the small numbers, the difference in clinical end points between groups was striking. A statistically significant difference in the composite clinical outcome was found even with the small number of patients we studied. The direction and magnitude of the clinical effect of endoscopic necrosectomy was similar to earlier reports of endoscopic necrosectomy.[37] Third, the first procedure in the endoscopic group was a drainage procedure. Transgastric necrosectomy was the second intervention. In the surgical group, necrosectomy was the first procedure. This might have influenced the IL-6 measurements following these procedures. However, new-onset multiple organ failure was measured up to 6 months after discharge, accounting for the cumulative effect of repeated necrosectomies. Although a median of 3 endoscopic necrosectomies were performed per patient in the endoscopy group, these repeated interventions did not result in new-onset multiple organ failure in these patients. Patients undergoing endoscopic necrosectomy required a relatively large number of procedures (median, 3; IQR, 3-6) that might limit the utility of this new approach. However, a reduction in serious complications, such as new-onset organ failure despite repeated endoscopic necrosectomies, may well justify NOTES.

Current literature suggests that endoscopic necrosectomy is increasingly used worldwide.[37] As occurred with the introduction of other new techniques such as laparoscopic cholecystectomy, widespread clinical implementation often preceded randomized trials.[38,39] The results of the present trial are preliminary; thus, larger, more definitive studies are needed before endoscopic necrosectomy can be recommended for routine clinical practice. A nationwide multicenter trial has been started in the Netherlands to confirm these first favorable results (current trial registration number is ISRCTN09186711). We would like to stress that responsible implementation of this new technique can only be achieved with the use of readily accessible training programs. This is recognized by various organizations involved in the clinical application of NOTES.[12,39,40]

In this first randomized clinical trial involving patients with infected necrotizing pancreatitis, endoscopic transgastric necrosectomy reduced the proinflammatory response as well as the composite clinical end point, including new-onset multiple organ failure, compared with surgical necrosectomy. However, these early, promising results require confirmation from a larger clinical trial.

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