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ORIGINAL ARTICLE

Surgical Versus Nonsurgical Treatment of Infected Pancreatic Necrosis: More Arguments to Change the Paradigm

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Abstract
Objectives This study aimed to compare primary surgical versus nonsurgical treatment in a series of patients with infected pancreatic necrosis (IPN) and to investigate whether the success of nonsurgical approach is related to a less severe disease.
Methods Thirty-nine consecutive patients with IPN have been included and further subdivided into two groups: primary surgical (n=21) versus nonsurgical (n=18). Outcome measures were the differences in mortality, morbidity, and pancreatic function. Comorbidity, organ failure, and other severity indexes were compared between the two groups.
Results Mortality occurred in 16.7 % of cases in the nonsurgical group versus 42.9 % in the surgical group. In the primary nonsurgical group, seven were operated on due to failure of initial conservative treatment. In this latter group, mortality was 28.6 % and was performed significantly later than in the primary surgical group. The group of primary surgical treatment was associated with a significant higher rate of multiple organ failure (MOF) at IPN diagnosis, new onset or worsening of organ failure, and MOF and nosocomial infection after surgery.
Conclusions Initial nonsurgical approach in IPN is associated with better results both in cases which respond to this treatment as well as in those who, failing this conservative approach, have to be operated on after a delayed period. Primary surgically treated patients had a more severe disease at the time of IPN.

Keywords Acute pancreatitis · Necrotizing pancreatitis · Infected pancreatic necrosis · Necrosectomy · Percutaneous catheter drainage

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Introduction

Infected pancreatic necrosis (IPN) is a devastating complication in acute pancreatitis which in most cases leads to a dismal prognosis. Traditionally, the standard treatment for patients with IPN is surgical debridement,[1] as nonsurgical management has been associated with an extremely high rate of mortality. However, independently of the surgical technique used for removal of the necrotic tissue, intensive care, and management of postoperative complications, surgical treatment of infected pancreatic necrosis is still associated with an important index of morbidity, mortality, and pancreatic dysfunction even in specialized units.[2]

Clinically, IPN varies widely. While some patients are severely ill with multiple organ failure requiring intensive and demanding expertise therapy, others are much less symptomatic despite the infected necrosis demonstrated by

gas within the pancreatic or peripancreatic necrosis on CT scan or by fine needle aspiration, Gram, and culture.

The high rate of morbidity and mortality associated with the classical surgical treatment as well as the extreme variability in the clinical presentation of IPN led some authors to propose a more conservative management based on a combination of antibiotics with or without percutaneous drainage, with acceptable results.[3,4] In addition, recent advances in minimally invasive procedures have raised the possibility of treating IPN by the so-called step-up approach which has rapidly become an emerging alternative to the traditional open surgical necrosectomy.[5] Percutaneous drainage, endoscopic transgastric drainage, and laparoscopic or videoscopic retroperitoneal necrosectomy have been used to ameliorate sepsis and avoid the necessity of surgery or at least delay it as much as possible for the patient to be in better conditions.

Whether or not all cases with IPN may benefit from these much less invasive treatments or whether it should be reserved for only a selection of the less symptomatic or less severe cases is still unknown.

The aim of this paper is to compare the outcome of primary surgical versus nonsurgical treatment in a series of consecutive patients with IPN and also to investigate whether the success of the nonsurgical approach is related to a less severe disease.

Patients and Methods

Between 1998 and 2010, 1,377 patients with acute pancreatitis have been admitted at the Hospital Clinic University of Valencia, a tertiary and academic center. Data of all these patients have been collected prospectively in a database.

Among them, there were 39 cases of IPN, and this population is the object of our investigation.

The diagnosis of acute pancreatitis (AP) was based on the presence of suggestive clinical symptoms and increased blood amylase >3 times the upper normal level and/or radiological alterations. All cases were managed according to the following protocol: intensive fluid resuscitation during the first 48 h of admittance, no oral intake, analgesia, and low molecular weight heparin. Enteral feeding with nasojejunal tube was administered when necessary. CT scan was performed on all patients at 72–96 h after admittance.

Antibiotic prophylactic treatment was indicated when AP was predicted as severe. The severity of acute pancreatitis was assessed by Ranson score, Acute Physiology and Chronic Health Evaluation II (APACHE II) on admission, C-reactive protein (CRP) at 48 h, and CT severity index. Necrosis was defined as non-enhanced areas of the pancreas on a contrast-enhanced CT, and severity index was obtained according to Balthazar et al.,[6] as the result of morphologic CT score plus necrosis score.

Body mass index (BMI) was measured and comorbidity was calculated according to the Charlson index[7] which predicts mortality according to the presence of different clinical conditions. The total index is calculated by assigning a score of 1, 2, 3, or 6 to each disease depending on the severity and risk of mortality: myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, and chronic liver disease (1 point); hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, and lymphoma (2 points); moderate or severe liver disease (3 points); and malignant tumor, metastasis, and AIDS (6 points).

Organ failure was defined according to Atlanta classification,[8] (shock: systolic blood pressure less than 90- mmHg; pulmonary insufficiency: PaO_2 ≤60 mmHg; renal failure: creatinine of ≥2 mg/dL after rehydration) and quantified with the Marshall scoring system.[9] Duration of organ failure was measured and considered as persistent organ failure when longer than 48 h.[10] Multiple organ failure was defined as the presence of two or more organ failures. Organ failure was assessed within the first week and when the diagnosis of infected pancreatic necrosis was established. CRP was measured throughout hospital stay and the highest level of CRP previous to IPN was considered. The diagnosis of infected pancreatic necrosis was established when microbiological examination after CT-guided fine needle aspiration (FNA) was positive and/or gas was present within the pancreas or peripancreatic necrotic tissue on CT.

All cases with IPN were treated with intravenous antibiotics, organ and nutritional support, and ICU admission when persistent organ failure was observed.

At the beginning of this series, all cases with IPN were treated surgically. However, after observing good results in some cases with IPN and high morbidity with unacceptable surgical risk managed conservatively, we progressively changed our policy towards an initial conservative management. Surgical treatment was performed by open debridement, necrosectomy and drainage lavage according to Beger's technique or packing, and planned reexploration depending on the extension of the necrosis and adequacy of necrosectomy. All surgical procedures were carried out only by two surgeons during the 12-year period of the study. Conservative management was based on antibiotic therapy and/or placement of one or several percutaneous 8–14 F pigtail catheters by ultrasound or CT guidance as required when necrosis was organized. When conservative treatment did not achieve clinical improvement (persistence, progression, or new development of sepsis or organ failure) nor did radiologic resolution of infected necrosis throughout the following days, surgery was indicated.

Pancreatic exocrine and endocrine functions were evaluated 6 months after the episode of IPN. Fecal fat excretion

(van de Kamer method, normal value <7 g/24 h) and fecal elastase (normal value >200 μg/g) were used to measure the exocrine pancreatic function. Endocrine pancreatic function was evaluated according to the American Diabetes Association considering diabetes when one of the following was present: HbA1C ≥6.5 % or fasting plasma glucose levels ≥126 mg/dl (7.0 mmol/l) or 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test or a random plasma glucose ≥200 mg/dl (11.1 mmol/l) in the presence of classic symptoms of hyperglycemia.[11]

Primary outcome measures were the differences in mortality, morbidity (in-hospital infections, intraabdominal bleeding, pancreatic fistula, new onset organ failure defined as organ failure not present 24 h before treatment of IPN), and length of hospital stay, between the initially conservative and initially surgical groups, according to an intention to treat analysis.

Additionally, pancreatic exocrine and endocrine function was also analyzed in both groups. Finally, in order to investigate whether successful conservative therapy was related to better physiologic or general conditions of the patient or a less severe pancreatic disease, comorbidity, presence and intensity of organ failure, and other severity indexes were compared between the surgical and conservative groups at admission and when IPN was diagnosed.

Statistical Analysis

Results are presented as percentages or mean and standard deviation. Categorical data were analyzed by χ^2 test and two-tailed Fisher's exact probability test when cell numbers were too small for the χ^2 test. For continuous variables, the two-tailed Mann–Whitney *U* test was used. Differences were assumed to be significant at $p<0.05$.

Results

During the study period, 1,628 episodes of acute pancreatitis in 1,377 patients were admitted at our center, of which 364 (22.4 %) were classified as severe. The total number of patients receiving antibiotic prophylactic treatment was 385 (27.9 %). Necrotizing pancreatitis was diagnosed in 148 episodes (9.1 %) and 39 patients developed infected pancreatic necrosis (2.8 %), the latter becoming the population study for this investigation. These IPN cases were further subdivided into two groups, surgical ($n=21$) versus conservative ($n=18$), according to the primary treatment. Demographic and clinical data of both groups are presented in Table 1.

The diagnosis of IPN was established at a mean time after admission of 29.4±21.8 days ($r=5–85$) in the nonsurgical group versus 15.1±13.3 days ($r=1–57$) in the surgical group ($p=0.04$). In 21 cases, the diagnosis of IPN was carried out by FNA, in 7 by the presence of gas in CT scan, in 8 patients by both FNA and bubble gas in CT, and in 3 cases during surgical intervention.

The evaluation of persistent organ failure in surgical and conservative groups within the first week and when the diagnosis of infected pancreatic necrosis was established is shown in Table 2. While there are no significant differences in the presence of organ failure between the two groups during the first week of admittance, a significantly higher percentage of persistent renal insufficiency was observed in

Table 1 Demographic and clinical data

	Nonsurgical group ($n=18$)	Surgical group ($n=21$)	*p* value
Age (mean ± SD)	66.6±16.7	62.5±14.6	0.74
Sex (male/female)	9/9	10/11	0.57
Etiology			0.49
Biliary	11 (61.1 %)	14 (66.7 %)	
Alcohol	2 (11.1 %)	3 (14.3 %)	
Miscellaneous	4 (22.2 %)	4 (19 %)	
Idiopathic	1 (5.6 %)	0	
BMI >30	8/17 (47.1 %)	5/20 (25 %)	0.15
Comorbidity	10 (55.6 %)	11 (52.4 %)	0.55
Charlson index			0.78
1–2	8 (44.4 %)	8 (38.1 %)	
>2	2 (11.1 %)	4 (19 %)	
Ranson (mean ± SD)	4.8±1.9	4.4±2.1	0.87
APACHE II at admission (mean ± SD and range)	11.9±5.5 ($r=3–22$)	10.6±5.6 ($r=2–22$)	0.87
CRP 48 h (mean, mg/L)	221.9±114.3	235.4±147.3	0.17
CT severity index (median and range)	8 (5–10)	10 (6–10)	0.22

Table 2 Persistent organ failure during the first week and at diagnosis of IPN

	Nonsurgical group (n=18)	Surgical group (n=21)	p value
First week			
Renal failure	3 (16.7 %)	9 (42.9 %)	0.07
Respiratory insufficiency	11 (61.1 %)	13 (61.9 %)	0.61
Shock	2 (11.1 %)	5 (23.8 %)	0.27
Single organ failure	8 (44.4 %)	8 (38.1 %)	0.47
Multiple organ failure	3 (16.7 %)	8 (38.1 %)	0.14
Marshall score (median, range)	2 (0–9)	4 (0–7)	0.99
At diagnosis of IPN			
Renal failure	1 (5.6 %)	7 (33.3 %)	0.03
Respiratory insufficiency	6 (33.3 %)	8 (38.1 %)	0.51
Shock	1 (5.6 %)	4 (19.0 %)	0.22
Single organ failure	5 (27.8 %)	3 (14.3 %)	0.26
Multiple organ failure	1 (5.6 %)	5 (23.8 %)	0.13
Marshall score (median, range)	1 (0–4)	2 (0–7)	<0.01
Maximal CRP (mean ± SD)	336.3±75.1	309.2±111.6	0.10

the group of surgical treatment when infected pancreatic necrosis was diagnosed.

In the group of primary surgical treatment (n=21), surgery was performed at 18.6±16.9 days (r=1–76) after admission. In 18 cases, a Beger's necrosectomy was performed, while in three cases, open packing and planned reexplorations were carried out. A median of 1 open necrosectomy (range 1–8) was performed in the surgical group and seven patients required two or more laparotomies: in three cases due to intestinal bleeding, in three due to intraabdominal bleeding, and in one case because of ongoing sepsis. None of the patients of the primary surgical group had preoperative percutaneous drainage.

In the primary nonsurgical group, five cases were successfully treated with antibiotics only and 13 cases were treated by percutaneous drainage plus antibiotics. Catheter diameter varied between 8 and 14 Fr, mean time from admittance to drainage was 28±17 days (r=13–63), median number of catheters was 1 (r=1–3), mean duration of drainage was 18±17 days, and six patients required several drainage procedures (two patients two procedures, four patients three procedures). In 6 out of the 13 cases treated percutaneously, clinical and radiological improvement was achieved without the need of necrosectomy, while seven cases required definitive surgical treatment due to unsuccessful conservative treatment. In this latter group, surgery was indicated for the following reasons: persistence of sepsis (three cases), progression of organ failure (one case), new development of organ failure (one case), and no radiologic improvement (two cases). In those cases, surgery was carried out at 50.6±38.2 days (r=19–123), significantly later than in the primary surgical group (Fig. 1), and only one case required a re-laparotomy due to an ongoing sepsis.

Primary end point measures between surgical and nonsurgical groups are shown in Table 3. Despite not reaching statistical significance, mortality occurred in three cases (16.7 %) in the nonsurgical group versus nine cases (42.9 %) in the surgical group. Additionally, in this latter group, there was a significant increase in new onset or worsening of organ failure, persistent multiple organ failure, nosocomial infection, and pancreatic fistula.

Mortality in the primary nonsurgical group was due to multiple organ failure in two cases and in one case considered unfit for surgery due to non response. Both patients with multiple organ failure (MOF) had required eventual surgical debridement after failure of the conservative approach. In the surgical group, mortality was attributed to MOF in five cases (two of them secondary to nosocomial pneumonia), intraabdominal bleeding in one case, two cardiovascular cases, and one respiratory insufficiency.

In the 15 survival patients of the nonsurgical group, exocrine and endocrine pancreatic function was evaluated in 5 and 14 patients, respectively. Exocrine insufficiency was observed in one case and diabetes mellitus in four cases (28.5 %). In the surgical group, the functional evaluation of the 12 survival cases showed diabetes mellitus in four (33 %) and exocrine insufficiency in two cases.

Discussion

Nowadays, the standard treatment of infected pancreatic necrosis is still surgical necrosectomy. Nevertheless, this approach, even at experienced centers, is associated with a very high mortality with figures ranging from 20 to 45 % or higher.[12,13]

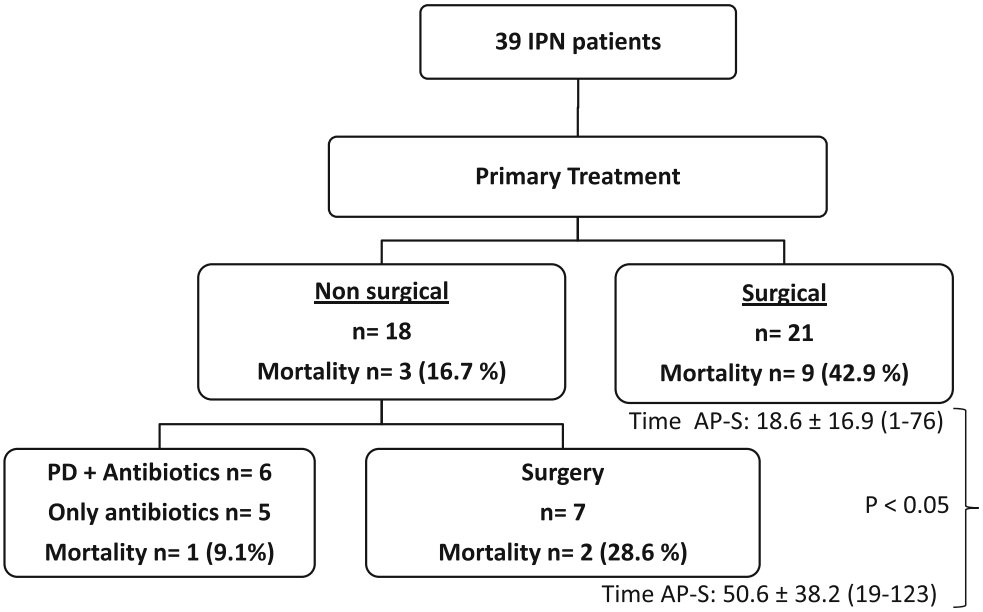

Fig. 1 Management and mortality of patients with IPN according to an intention to treat analysis. *PD* percutaneous drainage, *Time AP-S* time between acute pancreatitis and surgery

In latter years, several reports have shown a decrease in mortality when a less aggressive approach is adopted.[3] In this regard, several options have been developed including percutaneous drainage,[14] endoscopic transgastric drainage[15], or retroperitoneal necrosectomy by open or laparoscopic means[16] (combined or isolated), used on demand or by a step-up approach.[5]

In this report, we describe a series of patients with infected pancreatic necrosis treated surgically and nonsurgically. At our institution, the conservative treatment was begun in 2001 when we successfully treated a patient with IPN who showed an unacceptable surgical risk. Since then, we have progressively changed our policy towards a more conservative approach.

During the study period, from 1,628 episodes of AP admitted at our hospital, only 9.1 % presented pancreatic necrosis and 39 cases were diagnosed as having infected pancreatic necrosis. Therefore, the percentage of infection in pancreatic necrosis is 26.3 % and the percentage of IPN cases over the total number of patients is only 2.8 %. These figures are lower than the prevalence of necrotizing pancreatitis (13–42 %)[4,17,18] and the frequency of infected necrosis among necrotizing pancreatitis (20–39 %)[4,18,19] referred in other studies.

Table 3 Primary outcome measures in both groups after treatment of IPN

	Nonsurgical group (n=18)	Surgical group (n=21)	p value
Mortality	3 (16.7 %)	9 (42.9 %)	0.07
New onset or worsening organ failure	3 (16.7 %)	10 (47.7 %)	0.04
Single organ failure[a]	2 (11.1 %)	3 (14.3 %)	0.57
Multiple organ failure[a]	3 (16.7 %)	11 (52.4 %)	0.02
Renal failure[a]	2 (11.1 %)	6 (28.6 %)	0.17
Respiratory insufficiency[a]	5 (27.8 %)	13 (61.9 %)	0.03
Shock[a]	3 (16.7 %)	12 (57.1 %)	0.01
Nosocomial infection	4 (22.2 %)	12 (60 %)	0.02
Intraabdominal bleeding	2 (11.1 %)	4 (19 %)	0.41
Pancreatic fistula	0 (0 %)	6 (28.6 %)	<0.01
Hospital stay (mean ± SD, range days)	63.4±36.0 (18–129)	56.7±22.4 (4–90)	0.98
ICU admission after IPN	4 (22.2 %)	19 (90.5 %)	<0.01
ICU stay (mean ± SD, range days)	17.5±10.0 (9–32)	30.3±24.8 (1–80)	0.50

[a] Persistent organ failure (>48 h)

In our series, infected pancreatic necrosis is associated with a mortality of 30.7 %. In cases primary surgically treated, mortality was 42.9 %, and in the group of primary conservative therapy, mortality was 16.7 %, a clinically relevant result, but not reaching statistical significance. In addition, in cases that required surgery after failure of the initially conservative treatment, mortality was 28.6 %. Regarding morbidity, the new onset or worsening of organ failure was significantly higher in the primary surgical group (47.7 %) than in the primary conservative group (16.7 %). MOF, respiratory insufficiency, shock, and nosocomial infection were also significantly more frequent in the primary surgical group than in the conservative group. These results suggest that an initially conservative approach may improve the outcome in patients with IPN.

However, our study has several limitations: it is a retrospective investigation and not a randomized trial, and patients were selected for surgical or conservative treatment according to a policy of a less aggressive treatment throughout the years. An important concern for the authors of this study is whether these limitations could explain the better results of the conservative group. Also, could the better results with conservative treatment be explained by a less severe evolution of the patients included in that group? In this regard, despite there being no differences in several prognostic criteria on admission (Ranson, APACHE II, CRP at 48 h, CT severity index), organ failure during the first week, and maximal CRP at the time of diagnosis IPN between the groups, the primary surgical patients had significantly more renal insufficiency and higher Marshall score at the time of diagnosing IPN, than the nonsurgical patients. These facts confirm that in our series the primary surgically treated patients were sicker than the nonsurgically treated at the time of diagnosing IPN.

Another important factor which could be related to the worse results of cases treated initially with surgery versus those who required surgery after an initially conservative approach is the time when the procedure was performed. In this regard, in cases with primary surgical treatment, debridement was performed at a mean time of 18.6 days while in the other group it was significantly later, at a mean time of 50.6 days. The delay in surgical treatment of IPN has been demonstrated in several reports as having a pivotal role in the survival of such cases. It is associated with a better survival probably due to a better delimitation of the necrotic tissue thus facilitating necrosectomy.[20] Our investigation, with the aforementioned limitations, is in agreement with the authors who support an initial intent of treatment with a less aggressive approach.[5,21,22] The rationale of such approach may be argued with two aims: firstly, it may avoid a surgical necrosectomy, and secondly, at least in cases where conservative therapy fails, it allows a delay before surgery. As can be seen in our investigation, the earlier surgical intervention did not improve the worse physiologic status of such patients.

Summarizing, this paper adds a new series of cases of IPN treated with surgery or by an initial conservative treatment. This series confirms that in patients suffering from IPN, a nonsurgical approach may lead to better results both in those cases which respond to this treatment, hence requiring no surgery, as well as in those who, failing this conservative approach, were operated on after a delayed period.

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