ACTA SCIENTIFIC MEDICAL SCIENCES

Volume 3 Issue 4 April 2019

Research Article

Surgical Treatment of Secondary Pancreatic Infection

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Received: February 25, 2019; **Published:** March 11, 2019

Abstract

Infected pancreatic necrosis, which occurs in about 40% of patients admitted for acute necrotizing pancreatitis, requires combined antibiotic therapy and local drainage. Few studies have evaluated minimally invasive drainage methods used under the conditions of everyday hospital practice. The aim of this study was to determine whether, compared with conventional open surgery, minimally invasive drainage was associated with improved outcomes of critically ill patients with infection complicating acute necrotizing pancreatitis. A two-centered observational study was conducted in patients admitted to the intensive care unit for severe acute necrotizing pancreatitis to compare the characteristics, drainage techniques, and outcomes of the 195 patients managed between January 2014 and December 2018. All patients were divided into two groups: a comparison group (92 patients with open surgery) and the main group (103 patients with SPI who used the tactic "step-up approach" of treatment). In the comparison group postoperative complications have arisen in 52 (56.2%) patients. After surgery died 26 patients (28.3%). In the main group postoperative complications have arisen in 33 (32%) patients. After surgery died 15 patients (14.6%). Our research showed that an individualized approach to patients with SPI using the step-up approach provides a reduction in the number of laparotomic pancreatic necrosectomy and allows postponing open surgical interventions for a period after the 4th week from the onset of the disease and reducing the number of postoperative complications and mortality (χ^2 = 6.976, P = 0.011).

Keywords: Acute Pancreatitis; Secondary Pancreatic Infection; Diagnostics, Tactic "step-up approach"; Surgery

Abbreviations

AP: Acute Pancreatitis; SPI: Secondary Pancreatic Infection; PCT: Procalcitonin; CECT: Contrast-Enhanced Computed Tomography; MODS: Multiple Organ Dysfunction Syndrome; ROC: Operational Characteristics Curves; FNA: Fine-Needle Aspiratione; ESR: Erythrocyte Sedimentation Rate; IPN: Infected Pancreatic Necrosis; AIPPFC: Acute Infected Pancreatic/Peripancreatic Fluid Collection; PS: Pancreatic Pseudocyst; WON: Walled-of Necrosis; VARD: Video Laparoscopic Retroperitoneal Necrosectomy.

Introduction

On a global scale, AP is the third most common gastrointestinal disorder. The epidemiological estimates presented in the study indicate that the incidence of the disease is increasing worldwide [1]. According to the WHO (2016), 33-74 cases per 100,000 people/year in different countries of the world and 1-60 deaths per 100,000 people/year with AP were detected. The region-based analysis showed that cases of AP and mortality were significantly higher in the American region than in the regions of Europe and the Western Pacific. It accounts for greater than 300,000 emergency room visits annually in the US, which is steadily increasing, with a mean length of hospital stay of 7 days, and stationary costs exceed $ 2.5 billion. Mortality with AP ranges from 1% to 2% in general, necrosis of AP develops in 10%-20% of patients is associated with local and systemic complications and higher mortality which reaches 30% [2].

Necrotizing AP, which is associated with an 8 to 39% rate of death, develops in approximately 20% of patients. The major cause of death, next to early organ failure, is secondary infection of pancreatic or peripancreatic necrotic tissue, leading to sepsis and multiple organ failure. SPI is a further factor that often leads to negative consequences is diagnosed in approximately 40% of patients and is associated with high mortality which exceeds 40% in the development of systemic complications [3]. Until recently, surgical necrosectomy was discovered by the standard treatment of SPI. This procedure caused a severe inflammatory reaction, often resulting in prolonged multi-organ failure (MODS) and secondary local complications associated with the operation, such as bleeding and gastro-intestinal fistulas [4]. The method of "step-up" in the treatment of SPI has recently been introduced which includes percutaneous drainage, endoscopic necrosectomy through the stomach or duo-

denum, laparoscopic necrosectomy and retroperitoneal surgical drainage [5,6].

The aim of this study was to evaluate the results using minimally invasive interventions compared with open necrosectomy in patients with SPI.

Materials and Methods

We conducted a retro- and prospective two-centered controlled study in 195 patients with AP who from January 2014 and December 2018 were treated at the Kharkiv Regional Clinical Hospital (Ukraine) and the "Zaitsev Institute of General and Emergency Surgery NAMS of Ukraine" (Table 1). The classification of the AP was used according to the recommendations of the International Consensus (2012) [7]. Patients included in the study were treated in accordance with international recommendations [8] adapted to our local resources and procedures. In the first phase of AP all patients were treated conservatively, in the second used a differentiated surgical approach. According to the goals and objectives of the study all patients were divided into two groups: the main group - 103 patients with SPI, which used tactics of treatment "step-up approach"; the comparison group - 92 patients with open surgical intervention. The exclusion criteria were postoperative AP and the patient's refusal to enroll in the study. The absence of clinical and laboratory data of SPI suspected of prolonged fever (> 38.5°C for > 5 days) with elevated WBC and PCT (BRAHMS Aktiengesellschaft, Germany), or the emergence of a new organ failure, or gas with CECT within pancreatic and/or peripancreatic reservoirs, or in the presence of a combination of these factors. The final diagnosis of SPI in a number of patients was determined after a positive microbiological analysis (FNA or after surgery). SPI was confirmed in all patients who were analyzed. In the study data were collected: patient, characteristic (gender, weight, height, body mass index), assessment of organ dysfunction (SOFA scale [9]), the characterization of the AP (etiology, the percentage of necrotizing parenchyma of pancreas), the nature of treatment (mechanical ventilation of the lungs, inotropic (catecholamines) support, artificial kidney, duration of stay in ICU), types of surgical interventions, the nature of complications, results (30-day mortality, local postoperative complications, 90-day mortality).

Characteristic	Comparison group (n = 92)	The main group (n=103)	P
Age, median (IQR)	58 [47–65]	57 [45–64]	0.663
Body mass index (kg/m^2), median (IQR)	24 [21–29]	25 [22–30]	0.948
Male/Female, n (%)	52/40 (56.5/43.5%)	56/47 (54.4/45.6%)	0.875
Cause of AP:	56 (60.9%)	58 (56.3%)	0.634
Alcohol, n (%)	32 (34.8%)	42 (40.8%)	
Cholelithiasis, n (%)	4 (4.3%)	3 (29%)	
Other, n (%)			
SOFA score, median (IQR)	12 [7-14]	12 [7-15]	0.965
Incidence of necrosis, n (%):	22 (23.9%)	24 (23.3%)	1.000
No data	27 (29.3%)	29 (28.2%)	
<30%	28 (30.4%)	34 (33%)	
30–50%	15 (16.4%)	16 (15.5%)	
>50%			
Fever > 38.5°C, n (%)	47 (51.1%)	52 (50.1%)	0.940
WBC, × 10^9/l, median (IQR)	15.7 [12.2-17.3]	16.1 [12.8-18.2]	0.916
Blood lactate level (mmol/l), median (IQR)	2.4 [1.5–4.1]	2.5 [1.4–3.9]	0.892
PCT (ng/ml), n (%):	16 (17.4%)	18 (17.5%)	0.992
2-10, n (%)	5 (31.3%	6 (33.3%)	
≥ 10, n (%):	11 (68.7%)	12 (66.7%)	
Mechanical ventilation of the lungs, n (%)	12 (13%)	13 (12.6%)	0.892
Catecholamines, n (%)	19 (20.7%)	21 (20.4)	0.891
Artificial kidney, n (%)	5 (5.4%)	3 (2.9%)	0.625
Postoperative complications, n (%)	52 (56.5%)	33 (32%)	0.043
30-day mortality, n (%)	21 (19.6%)	6 (5.8%)	0.021
90-day mortality, n (%)	5 (5.4%)	9 (8.7%)	

Table 1: The main characteristics of patients with SPI.

Statistical data processing was carried out using the statistical software package StatSoft Statistica 6.0. To determine the differences in the clinical picture distributed according to the classification of AP, including the development of their complications, the dispersion analysis of Kraskal-Wallis test and the median criterion, rank nonparametric criteria for comparing the distribution laws and their characteristics were used: Kolmogorov-Smirnov two-choice test, Wald-Wolfowitz and Mann-Whitney criteria, analysis of tables of bonding of nominal attributes. The significance of the connections between the crosstalk variables was estimated using the criterion χ^2. In all cases, the verification of statistical hypotheses was conducted with a confidence probability of more than 95%. To assess the adequacy of the comparisons and the accuracy of the quality of the forecast, the method of analysis of the operational characteristics curves (ROC) was used. The optimal correlation between the sensitivity and the specificity of the prediction method was chosen based on the Pareto criterion [10]. Prognostic effectiveness of the models was evaluated by discrimination on the basis of the AUC index. Model performance: limited - at AUC ≥ 0.70; good at AUC ≥ 0.80; great at AUC ≥ 0.90.

Results

Among the etiological reasons for the development of AP in 195 patients, the alcoholic's factor was the cause of the disease in 114 patients (58.5%), the biliary genesis prevailed in 74 patients (37.9%), in 7 cases (3.6%) the AP was idiopathic. In this case, the presence of IPN was noted in 38 observations (19.5%), AIPPPFC in 41 patients (21%), their combinations in 84 (43.1%), PS in 25 patients (12.8%), WON in 7 cases (3.6%). The type of defeat of retroperitoneum was dominated by patients with the upper left in 86 (44.1%) and right upper in 52 (26.7%) variants. Less commonly found the left lower in 17 (8.7%), the lower right in 18 (9.2%) and central in 22 types (11.3%).

In connection with the fact that when deciding on the choice of treatment program the presence of complications AP plays a fundamental role and their timely diagnosis is extremely important, the search was most sought for the confirmation of significant clinical signs. As the main symptoms of SPI the most commonly observed were pain, weakness, nausea and vomiting, body weight loss, infiltration in the abdominal cavity, fever (above 38°C), leukocytosis (above 12x109/l), jaundice; elevated ESR (above 10-15), the concentration of PCT serum. The statistical processing of the data obtained allowed to highlight the most important criteria: the presence of fever, leukocytosis and leukocyte left shift, increasing the concentration of PCT ≥2 ng/ml and ESR≥30 mm/hr. At the same time, the strongest link of signs with the presence of complications was observed for the concentration of PCT (G = 0.979487) and the presence of fever (G = 0.693156) in the presence of IPN. According to the results of paired comparisons for AIPPPFC only two significant clinical signs of the presence of complications were observed: presence of fever and increase in serum PCT concentration ≥2 ng/ml. In this case judging by the value of Gamma correlations, the level of prohormone has a greater diagnostic significance (G = 0.978022) than an increase in the body temperature of the patient (G = 0.777778). In patients with acute infected PS, PCT concentration ≥2 ng/ml (G = 0.961905), the presence of leukocytosis (G = 0.735849) with shift of the leukocyte formula to the left (G = 0.688623) was the most diagnostically significant. In patients with IPN the most important diagnostic value was PCT concentration ≥2 ng/ml (G= 0.99998), fever (G = 0.615385) and elevated ESR ≥ 40 mm/hr (male: G = 0.530201, female: G = 0.3474286).

Until recently, as the standard surgical treatment of suspected or confirmed IPN we used open method of execution laparotomy (upper-middle or subcostal transverse) necrosectomy, drainage (92 patients, 100%) and including programmed re-laparotomy (14 patients, 15.2%). Postoperative complications occurred in 52 (56.5%): erosive bleeding (4 patients, 7.7%), fistulas stomach and colon in 8 patients (15.4%), MODS in 40 patients (76.9%). After surgery 26 patients (28.3%) died: 14 (53.8%) who operated up to 2 weeks, 5 (19.2%) who operated up to 4 weeks, and 7 (26, 9%) who operated after 4 weeks after start of the disease. That is the 19 dead were 30-day mortality and at 7 were 90-day mortality. In regression analysis revealed a good postoperative mortality dependent on the availability of MODS for surgery (AUC = 0.864, 0.95% CI – 0.778-0.896), after surgery (AUC = 0.814, 0.95% CI – 0.783-0.877), and limited to the prevalence of necrosis of the software (AUC = 0.652, 0.95% CI - 0.583-0.745). In general, 63 (68.5%) patients in this group used necrosectomy and drainage ("closed" technique) and in 29 (31.5%) – "open" treatment methods, including 6 (20.7%) of them - using VAC-therapy. Most of them (94.6%) are operated for up to 4 weeks after start of the disease.

In analyzing the incidence of complications, it was found that they were significantly more likely to develop in patients with IPN than in infected AIPPPFC and PS (χ^2 = 14.571, P = 0.000), as well an infected WON (χ^2 = 10.428, P = 0.001). All three forms of the cavity formations of the pancreas statistically differed only in the localization of complications in the pancreas and in the omental. In this case complications in the pancreas were found to be significantly lower in the AIPPPFC than in the PS (Mann-Whitney U = 284.3, P = 0.011) and in the WON (U = 224.3, P = 0.002) of the same localization: differences between groups of patients with PS and WON weren't detected: U = 169.4, P = 0.475. When placement of infected PS in the omental, complications were observed much less frequently than at the AIPPPFC of the same localization (U = 219.3, P = 0.001).

The strategy of treating patients with suspects or confirmed IPN was significantly different in the main group. In this group, 62 (60.2%) patients were treated by percutaneous controlled ultrasound, 26 (25.2%) by VARDs and drainage, 5 (4.9%) by through the wall of the stomach or duodenum in the AIPPPFC and PS. In 10 (9.7%) open operations were performed (mini-lumbotomy, upper medial, left or right-winged mini-laparotomy with formation of mini-omentobursostomy) with pancreatic necrosectomy including 5 patients using decompressive VAC-laparostomy. In 44 of 62 patients (71%), puncture-drainage interventions allowed the interruption of the AP chain and patients recovered without the use of open surgical interventions. In 18 (29%) cases such procedures together with a conservative therapy allowed patients to stabilize and became the stage of preparation for further surgical treatment:

VARDs was performed in 4 (22.2%) patients, mini-laparotomy at 8 (44.4%), mini-lumbotomy in 6 (33.3%) patients. Postoperative complications arose in 33 (32%) patients: erosive bleeding (3 patients, 9.1%), fistula of the large intestine (6 patients, 18.2%), progressive MODS (24 patients, 72.5%). After surgery 15 patients (14.6%) died: 6 of them had a 30-day mortality (operated up to 4 weeks from the onset of the disease) and 9 to 90-day mortality.

Discussion

It is known that the principles of surgical interventions for pancreatic necrosis were sealed up by B. Moynihan in 1925 [11] and the main surgical methods for controlling SPI and sepsis included over the past 40 years: 1) an "open" method of treatment in the form of necrosectomy and open source treatment for the area of infection [12]; 2) necrosectomy with planned re-laparotomy [13]; 3) "closed" technique with necrosectomy, drainage and with continuous washing [14] or without it [15]. But today, the principles of treating necrotic pancreatitis and the role of surgery remain controversial. If before the 1990s more than 60% of patients in AP were treated using open interventions [16], but later the tactics of treatment of necrotic pancreatitis were changed. In 1991 E.L. Bradley and K. Allen recommended conservative treatment of sterile necrotic pancreatitis in selected cases [17]. M. Gagner was the first to perform and describe the minimally invasive video laparoscopic surgical treatment of SPI in 1996 including: laparoscopic retrocollar, retroperitoneoscopic and transgastric procedures [18].

Subsequently, a hypothesis was made that the transcutaneous drainage of the focus of pancreatic infection and the fluid reservoirs can have a positive therapeutic effect. This recommendation was based on clinical observations that showed no need for the maximum removal of all necrotic tissues for successful treatment of IPN patients. By drainage of infected fluid clusters, the authors have shown that the clinical state of patients may improve after these interventions, and necrotic tissues can be successfully treated in the subsequent immune system of the patient. That is, the purpose of drainage is the removal of infected fluid but not necrosis [3-5,19]. In the Netherlands in 2010 a group of researchers conducted a prospective, randomized, multicentre study "A Step-up Approach or Open Necrosectomy for Necrotizing Pancreatitis". In this study, the authors randomly assigned 88 patients with necrotizing pancreatitis and suspected or confirmed infected necrotic tissue to undergo primary open necrosectomy or a step-up approach to treatment. The step-up approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The primary end point was a composite of major complications (new-onset multiple-organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding) or death. The primary end point occurred in 31 of 45 patients (69%) assigned to open necrosectomy and in 17 of 43 patients (40%) assigned to the step-up approach (risk ratio with the step-up approach, 0.57; 95% confidence interval, 0.38 to 0.87; P = 0.006). Of the patients assigned to the step-up approach, 35% were treated with percutaneous drainage only. New-onset multiple-organ failure occurred less often in patients assigned to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, P = 0.002). The rate of death did not differ significantly between groups (19% vs.16%, P = 0.70). Patients assigned to the step-up approach had a lower rate of incisional hernias (7% vs. 24%, P = 0.03) and new-onset diabetes (16% vs. 38%, P = 0.02) [5]. This study showed that the minimally invasive step-up approach, as compared with primary open necrosectomy, reduced the rate of the composite end point of major complications or death, as well as long-term complications, health care resource utilization, and total costs, among patients who had necrotizing pancreatitis and confirmed or suspected secondary infection. With the step-up approach, more than one third of patients were successfully treated with percutaneous drainage and did not require major abdominal surgery. M.C. van Baal., *et al*. (2011) also reported meta-analysis data, which included 384 patients who used the technique of percutaneous drainage of fluid accumulation under IPN as the main treatment method [20]. Eleven studies, including 384 patients, fulfilled the inclusion criteria. Only one study was a randomized controlled trial; most others were retrospective case series. Four studies reported on the presence of organ failure before percutaneous catheter drainage; this occurred in 67.2% of 116 patients. Infected necrosis was proven in 271 (70.6%) of 384 patients. No additional surgical necrosectomy was required after percutaneous catheter drainage in 214 (55.7%) of 384 patients. Complications consisted mostly of internal and external pancreatic fistulas. The overall mortality rate was 17,4% (67 of 384 patients). Nine of 11 studies reported mortality separately for patients with infected necrosis undergoing percutaneous catheter drainage ; the mortality rate in this group was 15.4% (27 of 175).

Our study specifically compared two treatment strategies and it does provide a direct comparison of open necrosectomy with minimally invasive treatment of IPN including retroperitoneal necrosectomy. The analysis of the treatment results of the patients we examined showed that in both groups the surgical treatment of the IPN was selected in a different way, individually, in accordance with the phases and characteristics of the course of the disease. In patients of the comparison group, most of the operations (87 patients, 94.6%) were performed up to 4 weeks from the moment of the disease, which directly influenced the results of treatment in this category of patients. In the main group of patients, surgical treatment was performed sequentially, starting with the least invasive methods: puncture, puncture-draining transcutaneous and endoscopic. In 44 of 62 patients (71%), puncture-drainage interventions allowed the interruption of the AP chain, and patients recovered without the use of open surgical interventions. In 18

(29%) cases, such procedures, together with a cohesive conservative therapy, allowed patients to stabilize and became the stage of preparation for further surgical treatment using open necrosectomy with mini-access. Postoperative complications were noted in 85 patients (46.6%) in both groups. In all cases there are 2 or more complications (an average of 2.1 ± 0.7 per patient). When comparing the two strategies of treatment tactical approach we have established (Table 1) that in the main group of patients where the principles of "step-up approach" were used for the diagnosis and treatment of SPI, the number of postoperative complications and mortality were lower than in the group of patients which performed only open surgical intervention.

Conclusion

The research has shown that an individualized approach in patients with SPI with the use of tactics "step-up approach" provides a reduction in the number of laparotomic pancreatic necrosectomy and allows postponing open surgical interventions for the period after the 4th week from the onset of the disease and reduce the number of postoperative complications and mortality (χ^2 = 6.976, P = 0.011).

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