Intra-Abdominal Pressure Reduction After Percutaneous Catheter Drainage Is a Protective Factor for Severe Pancreatitis Patients With Sterile Fluid Collections

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Objectives: Severe acute pancreatitis (SAP) is a fatal disease with natural course of early SAP (ESAP) and late SAP (LSAP) phases. Peripancreatic percutaneous catheter drainage (PCD) is effective in management of LSAP. Although our previous study indicates that intra-abdominal PCD ahead of peripancreatic PCD benefits ESAP patients with sterile fluid collections, the mechanism is still uncovered.

Methods: According to therapeutic results, 452 SAP patients who underwent PCD were divided into sterile group (248 cases), secondary infection group (145 cases), and primary infection group (59 cases).

Results: The mortality was 4.1%, 10.9%, and 18.6%, respectively. Logistic-regression analysis indicated that multiorgan dysfunction syndrome (odds ratio [OR], 1.717; 95% confidence interval [95% CI], 1.098–2.685; $P = 0.018$), catheters located intra-abdominally (OR, 0.511; 95% CI, 0.296–0.884; $P = 0.016$), and intra-abdominal hypertension (OR, 1.534; 95% CI, 1.016–2.316; $P = 0.042$) were predictors for infection after PCD. Receiver operating characteristics curve delineated that decrease of intra-abdominal pressure (IAP) of more than 6.5 mm Hg after PCD had the ability to predict infection with sensitivity of 84.0% and specificity of 79.5%.

Conclusions: Intra-abdominal PCD for acute sterile fluid collections seems to be an effective option rather than peripancreatic PCD. Patients with a significant decrease of IAP had a lower incidence of infection and better alleviation of organ failure.

Key Words: early severe acute pancreatitis, intra-abdominal percutaneous catheter drainage, intra-abdominal pressure, acute sterile fluid collections

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Acute pancreatitis is one of the most common fatal diseases worldwide, with an incidence of 4.9 to 73.4 per 100000 individuals,[1] and an overall mortality of 5%.[2] Up to 15% to 20% of patients with acute pancreatitis present aggravating disease course.[3] Severe acute pancreatitis (SAP) can be divided into early SAP (ESAP) and late SAP (LSAP) according to its natural course, which are accompanied with a peak of mortality, respectively.[4,5] Early SAP is characterized by the systemic inflammatory response syndrome (SIRS) resulting from the release of inflammatory mediators in the first 2 weeks of disease history; LSAP is dominated by sepsis-related complications resulting from infection of pancreatic necrosis.[6–9] Infection is the most common and serious complication, and it might result in pneumonia and multiorgan dysfunction syndrome (MODS). Although LSAP with infection is critical, a notable step-up approach, which is based on peripancreatic percutaneous catheter drainage (PCD), may improve the prognosis dramatically.[3,10] Although our previous study indicated that intra-abdominal PCD (also called abdominal paracentesis drainage) ahead of peripancreatic PCD benefited ESAP patients with sterile fluid collections,[11] the mechanism of intra-abdominal PCD management for sterile fluid collections in ESAP is still uncovered. Meanwhile, using PCD intervention to manage ESAP patients with fluid collections is still controversial. On one hand, it is an effective method to control fluid collections just like in the management of liver cirrhosis. Reversely, because it may lead to infection and other complications, it is adopted only in cases of infected necrosis, and proven to be effective in alleviating organ failure and reversing sepsis.[10,12,13] However, the incidence of primary infection is up to 80% in the first few weeks, and the incidence of infection resulting from PCD has not been precisely calculated.[14–18] Moreover, it is still unclear whether infection after PCD is secondary or is just an eventuality of the natural course of the disease. Zerem et al[19] advocate that drainage of sterile fluid collections reduces the amount of inflammatory mediators and improves the prognosis. In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis is an indicator for drainage intervention.[20] Considering the benefits of PCD and the high incidence of infection in the natural course of pancreatitis, the aim of this study is to determine whether PCD is beneficial to patients with acute sterile fluid collections or whether infection secondary to PCD impairs the prognosis.

MATERIALS AND METHODS

Patients

We collected data for consecutive patients diagnosed with SAP from October 2010 to March 2013. The SAP patients who underwent simple PCD were included, whereas patients without acute sterile fluid collections, patients who had undergone surgery, and patients who did not get a safe puncture route for acute sterile fluid collections were excluded. The present study was conformed to the ethical standards of the World Medical Association Declaration of Helsinki and was approved by Chengdu Military General Hospital Medical Ethics Committee (Register Number: 2010073). All patients had signed written informed consent, and the information of all participants were anonymized and deidentified before analysis. The diagnosis of acute sterile fluid

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collections and SAP was based on the Revision of the Atlanta Classification 2012.[7]

Procedures

Intensive Care

All patients received standard intensive care treatment, consisting of supportive care including maintaining stable circulation, nutritional supplements, oxygen supplementation, mechanical ventilation, as well as monitoring for respiratory and renal insufficiency.

Percutaneous Catheter Drainage

The PCD decision depended on the sustained worsening of the patient's symptoms after normative controversial therapy. All the PCD procedures were performed under ultrasound guidance using an 8- to 16-Fr Pigtail Drainage Catheter Set (Bioteque, Taipei, China). The sterile group comprised the patients who did not develop an infection after PCD. The secondary infection group comprised the patients who were positive for infection over 72 hours after PCD. The primary infection group comprised the patients who were positive for infection within 72 hours after PCD. Acute sterile fluid collection was considered as an indicator for PCD; the decision to perform PCD was based on the opinions of the ultrasound doctor and clinician.

Choledochoscope-Guided Debridement

At our center, choledochoscope-guided debridement was adopted instead of open necrosectomy due to the high mortality rate and complications associated with the latter procedure.[21] The indications for choledochoscope-guided debridement were similar to those for open necrosectomy: ongoing fever, presence of necrotic tissue confirmed by CT or ultrasound, and less than 10 mL drainage liquid everyday, no response to treatment over a period of more than 72 hours.

Statistical Analysis

Statistical analysis was performed using SPSS Version 19.0 for Windows (SPSS, Chicago, IL). Continuous data were presented as the mean ± standard deviation (SD) and evaluated using Fisher exact *t* test or Mann-Whitney *U* test. Categorical data were described with frequency counts and assessed using the χ^2 test. Two-tailed *P* values less than 0.05 were considered to indicate statistical significance. Logistic regression was adopted to assess the factors that were significant in predicting infection after PCD.

RESULTS

Patients

A total of 863 SAP patients were retrospectively analyzed. We excluded 411 cases: 248 cases, no fluid collections or infection already confirmed before PCD; 31 cases, previous surgery; 132 cases, unsafe puncture route. Finally, a total of 452 SAP cases with fluid collections were included: the sterile group included 145 (32%) cases (37% of acute sterile fluid collection cases), the secondary infection group included 248 (55%) cases (63% of acute sterile fluid collection cases), and the primary infection group included 59 (13%) cases. The case recruitment was depicted in a consort diagram in Figure 1. The characteristics of the patients were shown in Table 1. In the sterile group, secondary infection group, and primary infection group, the incidence of intra-abdominal hypertension (IAH) was 46.2%, 56.9%, and 69.5%, respectively. The higher incidence of IAH in both infection groups (P^a = 0.041, P^c = 0.002, Table 1) indicated that intra-abdominal pressure (IAP) might be a predictor for infection and an indicator for early intervention with PCD.

Incidence of Infection and Mortality

Table 2 delineated the therapeutic outcomes of the 3 groups. The total mortality was 9.7% (44/452); it was 4.1%, 10.9%, and 18.6% in the sterile, secondary infection, and primary infection

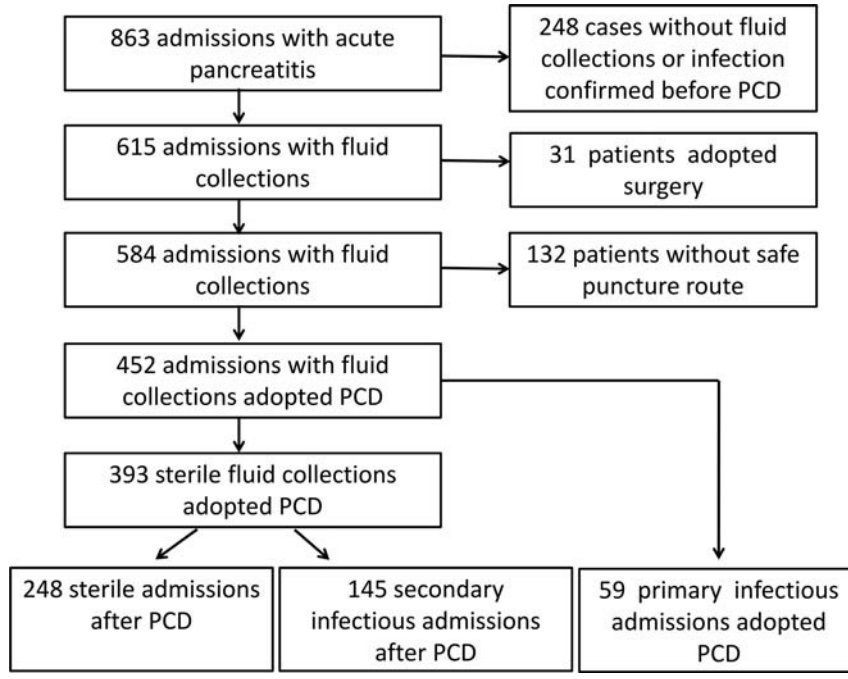

FIGURE 1. The consort diagram of case recruitment.

TABLE 1. Baseline Characteristics of All Patients in Each Group

Characteristics	Group A (n = 145)	Group B (n = 248)	Group C (n = 59)	P^*	$P^\dagger$	$P^\ddagger$
Sex						
Male	79	143	32	0.540	0.633	0.745
Female	66	105	27			
Age	42.2 ± 13.7	43.9 ± 15.7	39.8 ± 12.5	0.281	0.051	0.057
Etiology						
Alcohol	29	66	8	0.320	0.089	0.144
Biliogenic	47	77	24			
Hypertriglyceridmia	69	105	27			
Disease severity						
APACHE II score	8.2 ± 2.9	8.7 ± 3.6	9.0 ± 3.1	0.157	0.556	0.275
Ranson score	3.8 ± 1.7	3.6 ± 1.3	3.9 ± 2.1	0.179	0.197	0.414
CTSI score	6.9 ± 1.5	7.3 ± 1.6	7.8 ± 2.2	0.015	0.111	0.053
Organ failure						
None	25	39	13	0.055	0.385	0.208
Single	81	113	22			
Multi	39	96	24			
Onset to PCD, d	10.4 ± 5.1	12.9 ± 6.7	11.7 ± 8.1	0.092	0.237	0.294
IAH/ACS (%)	67 (46.2)	141 (56.9)	41 (69.5)	0.041	0.012	0.002
PCD duration time	41.8 ± 20.1	45.9 ± 18.6	50.2 ± 19.7	0.045	0.116	0.031
Total PCD procedures	3.7 ± 1.4	3.5 ± 0.9	3.8 ± 1.6	0.069	0.756	0.274
PCD catheters per patient	3.9 ± 1.9	4.1 ± 2.2	4.3 ± 1.8	0.364	0.498	0.298
<10 Fr	343	629	151	0.628	0.482	0.553
>10 Fr	223	388	103			
PCD locations						
Intra-abdominal	60	69	18	0.008	0.002	0.005
Peripancreatic	45	77	30			
Both	40	102	11			
Laboratory parameters						
Leukocyte (10^9/L)	15.3 ± 8.4	16.4 ± 9.1	17.8 ± 8.8	0.235	0.286	0.144
CRP	221.3 ± 109	212.4 ± 110	224.4 ± 102	0.438	0.703	0.565

Group A, sterile fluid collections after PCD; group B, infection secondary to PCD; group C: primary infection.

*P: comparison between group A and group B.

†P: comparison between group B and group C.

‡P: comparison between group (A + B) and group C.

group, respectively. Higher mortality and incidence of choledochoscope intervention were observed in the secondary infection group compared to the sterile group (P^a = 0.039, Table 2). However, the mortality of the primary infection group is higher than that of the secondary infection group, but the difference is not significant (P^b = 0.104, Table 2). Nevertheless, the mortality in the primary infection group was higher than the total mortality of the sterile group and secondary infection group (P^c = 0.017, Table 2). Similar results were found for the incidence of new-onset organ failure. The PCD intervention for acute sterile fluid collections might be beneficial, especially in patients who are uninfected after PCD; moreover, even in cases of infection secondary to PCD, the mortality was not elevated.

Next, we used univariable and multivariable logistic regression analyses to identify predictors of infection after PCD.

Logistic Regression Analysis

Table 3 showed the factors indicative of infection after PCD. There variables were significant differences between SAP patients with and without infection after PCD: numbers of organ failure (odds ratio [OR], 1.717; 95% confidence interval [95% CI], 1.098–2.685; P = 0.018, Table 3), catheters located intra-abdominally (OR, 0.511; 95% CI, 0.296–0.884; P = 0.016, Table 3), and IAH (OR, 1.534; 95% CI, 1.016–2.316; P = 0.042, Table 3). These factors were described as potential predictors for infection after PCD and were analyzed as variables in the multivariable logistic regression model.

In the multivariable logistic regression analysis, multiorgan failure (OR, 1.623; 95% CI, 1.021–2.579; P = 0.041, Table 4) and IAP (OR, 1.547; 95% CI, 1.019–2.347; P = 0.040, Table 4) were found to be significantly different between the sterile and infectious group, and were therefore identified as risk factors. It seemed that patients with IAH were more likely to be infected after PCD. However, PCD has been proven to be an efficient option for acute sterile fluid collections to alleviate organ failure and to prevent infection.[22–27] Therefore, despite our findings, it may be necessary to adopt PCD for patients with IAH.

For further assessment of the therapeutic effect of PCD, IAP before PCD and decrease in IAP after PCD (Δ-IAP) were accurately calculated. Although the IAP in patients with infection secondary to PCD (group B) was higher than that in the sterile

TABLE 2. Outcomes of All Patients in Each Group

Characteristics	Group A (n = 145)	Group B (n = 248)	Group C (n = 59)	P*	P†	P‡
Hospital stay, d	41.9 ± 23.9	50.1 ± 35.1	52.8 ± 27.9	0.013	0.562	0.173
ICU stay, d	11.8 ± 14.1	14.5 ± 19.3	21.1 ± 22.4	0.143	0.023	0.005
Complications				1.000	0.288	0.289
Bleeding	5	8	3			
Fistula	2	2	4			
Perforation	2	3	2			
New on-set organ failure	44	115	32	0.002	0.277	0.046
Catheter related complication				0.065	0.970	0.785
Clogging	13	31	7			
Kinking	17	13	3			
Displacement	7	11	3			
Necrosectomy under choledochoscope, (%)	4 (2.8)	21 (8.6)	9 (15.3)	0.043	0.052	0.111
Mortality, (%)	6 (4.1)	27 (10.9)	11 (18.6)	0.039	0.104	0.017

Group A, sterile fluid collections after PCD; group B, infection secondary to PCD; group C, primary infection.

*P: comparison between group A and group B.

†P: comparison between group B and group C.

‡P: comparison between group (A + B) and group C.

patients (group A) (23.1 mm Hg versus 20.4 mm Hg; $P < 0.05$; Fig. 2A), Δ-IAP presented a more dramatic reduction trend in sterile patients (group A) (8.8 mm Hg versus 5.3 mm Hg, $P < 0.01$, Fig. 2B). The area under the receiver operating characteristic curve of 0.838 ($P = 0.001$; 95% CI, 0.821–0.855; Fig. 2C), and it was found that a Δ-IAP of less than 6.5 mm Hg after PCD had the ability to predict infection with a sensitivity of 84.0% and a specificity of 79.5%.

DISCUSSION

Severe acute pancreatitis is one of the fatal diseases in critical medicine, and it is especially fatal when complicated with infection. Adopting PCD to manage the acute sterile fluid collections in ESAP is still controversial due to the risk of secondary infection. An interesting finding of this study is that the location of catheter seems to be a capital factor. Catheters located at the intra-abdominal places, such as right paracolic sulci, left paracolic sulci, or pelvic cavity present less infection risk and better prognosis. It coincides with what was found in our previous study.[11] Based on these results, we presumed that traditional PCD contained 2 different methods: intra-abdominal PCD also called abdominal paracentesis drainage and peripancreatic PCD. Van Santvoort[3] indicates that the "step-up approach," consisting of percutaneous drainage and/or minimally invasive retroperitoneal necrosectomy, dramatically improves the prognosis of LSAP with infected necrosis. Reading on these excellent articles with respect, we inferred that the PCD in the "step-up approach" actually indicates peripancreatic PCD. However, cases of early previous drainage for acute sterile fluid collections and PCD management in cases of abdominal compartment syndrome (ACS) in ESAP patients were excluded in these reported studies.[3,10] Thus, adopting intra-abdominal PCD to manage the acute sterile fluid collections in ESAP is not precisely known, especially in cases of SAP accompanied with IAH/ACS. Based on the natural course of the disease, intra-abdominal PCD is an effective method to control fluid collections in ESAP just like in the management of liver cirrhosis.

The ESAP is characterized as SIRS; organ failure in the SIRS phase usually results from severe systemic inflammation directly rather than infection.[2,28–33] Intra-abdominal PCD for acute sterile fluid collections may reduce inflammatory mediators and endotoxins, ameliorate early SIRS, reverse organ failure, and improve the prognosis eventually. In a prospective randomized control trail, Zerem et al[19] advocates that drainage of the sterile fluid collections reduces the inflammatory mediators and improves

TABLE 3. Univariable Logistic Regression Analysis of Infection After PCD

Variable	OR	95% CI OR Lower	95% CI OR Upper	P
APACHE II score	1.016	0.957	1.078	0.607
Ranson score	1.007	0.863	1.152	0.285
CTSI score	1.009	0.922	1.0103	0.852
MODS	1.717	1.098	2.685	0.018
Onset to PCD	1.014	0.987	1.042	0.305
IAP before PCD	1.534	1.016	2.316	0.042
PCD duration time	1.007	0.978	1.037	0.630
Toatal PCD procedures	1.019	0.870	1.193	0.818
PCD catheters per patient	1.010	0.867	1.176	0.901
Location of PCD				0.044
Both	1.000			
Intra-abdominal PCD	0.511	0.296	0.884	0.016
Peripancreatic PCD	1.185	0.782	1.303	0.408
Leukocyte (10^9/L)	1.021	0.951	1.097	0.560
CRP	1.002	0.996	1.007	0.383

TABLE 4. Multivariable Logistic Regression Analysis of Infection After PCD

Variable	OR	95% CI OR Lower	95% CI OR Upper	P
MODS	1.623	1.021	2.579	0.041
IAP before PCD	1.547	1.019	2.347	0.040

prognosis. LSAP is characterized by counteractive anti-inflammatory response syndrome; organ failure in this phase is related to infections, such as infected necrosis.[28] The step-up approach is probably a better option in such cases.[3] However, in the first phase, intra-abdominal PCD for acute sterile fluid collections is most likely to resolve the early organ failure resulting from SIRS.

Besides, IAH/ACS is closely interrelated with organ failure and high mortality in ESAP.[20,23,34–36] It is reported that the incidence of IAH and ACS is 40% and 10% in SAP patients, respectively.[37–39] Moreover, prospective cohort studies indicate that ACS in ESAP patients contributes to intestinal barrier failure and impairs intestinal barrier function, which could ultimately results in more bacterial translocation and consequent pancreatic infection.[20,23,26,40] Thus, ESAP concomitant with uncontrolled IAH/ACS may lead to primary infection, and intra-abdominal PCD is an alternative method to solve this problem just as it was used to manage ascites due to cirrhosis. The use of minimally invasive intra-abdominal PCD methods for managing ACS has been receiving more and more attention.[25,41,42] Dambrauskas et al[42] suggest that using intra-abdominal PCD management of acute intra-abdominal fluid collections before infection in acute pancreatitis is effective, safe, and associated with reduced morbidity. In this study, the incidence of organ failure was not significantly reduction between the primary and secondary infection group. Besselink et al[2] have proved that enteral bacteria crossing the mucosal barrier in the first 24 hours of the disease are responsible for the majority of infections in ESAP. Infection is an irreversible event in most LSAP patients who do not receive intervention. Some early studies on infected necrosis pancreatitis cases (within 14 days of onset) reported a high patient death rate of 89% from MODS secondary to infected pancreatic necrosis; nevertheless, the presence of MODS is ahead of infection.[2,29]

In this retrospective study, the overall mortality was 9.7%, and it was 4.1%, 10.9%, and 18.6% in the sterile, primary infection, and secondary infection group, respectively. The overall mortality was lower than that in some studies,[3,8,10,43–45] but higher than Zerem et al's report.[19] The inclusion of some moderate SAP cases with fluid collection but in absence of organ failure might be attributable to the differences. Nonetheless, the results indicated that ESAP patients with acute sterile fluid collections might benefit from intra-abdominal PCD. One of the reasons for this conclusion is that patients with acute sterile fluid collections who had persistent negative cultures after intra-abdominal PCD had lower mortality and showed better alleviation of organ failure. Second, even in cases of infection secondary to intra-abdominal PCD, the mortality was not elevated compared to the cases of primary infection. Finally, when the mortality of the sterile cases and the cases in which the patients were sterile before PCD and got infected after PCD (secondary infection group) was considered together, the mortality was lower than that in the group that received PCD after infection (primary infection group). Therefore, intra-abdominal PCD for the treatment of acute sterile fluid collections seems to be a potential and rational option, especially for those with persistent negative culture after PCD. Univariable and

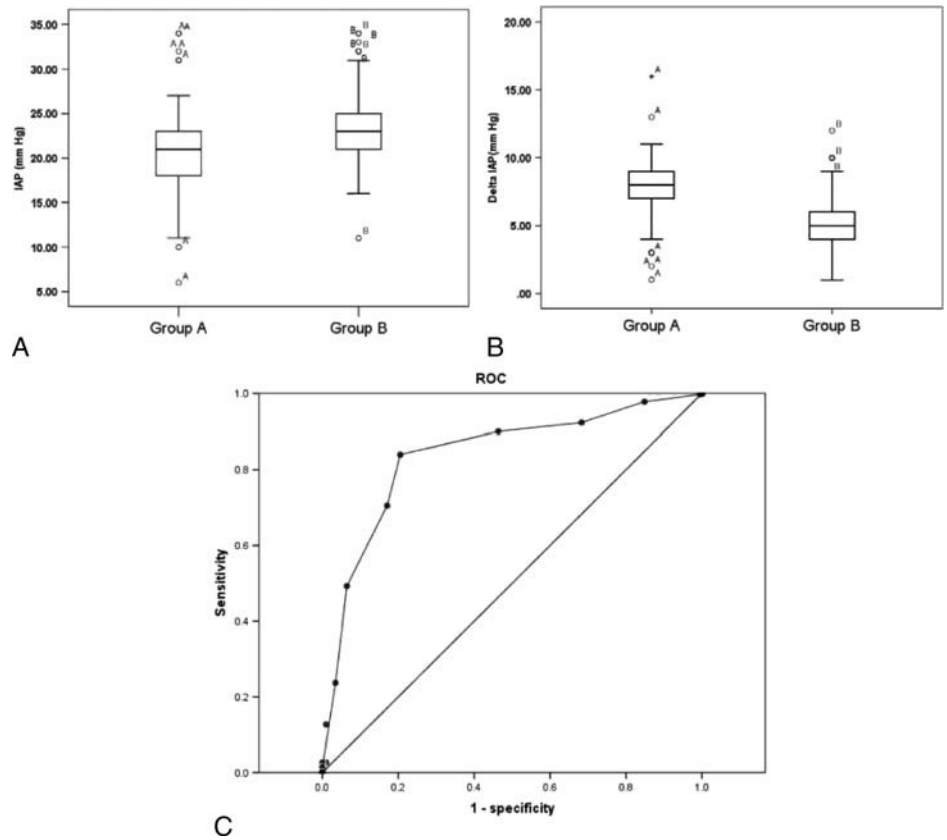

FIGURE 2. The IAP before PCD and the decrease of IAP after PCD (ΔIAP). A, The IAP before PCD in the sterile group (group A) and secondary infection group (group B) was 20.4 ± 5.4 and 23.1 ± 7.3 mm Hg, respectively. There was significant difference between the 2 groups ($P = 0.000$). B, The decrease of IAP after PCD in the sterile group (group A) and secondary infection group (group B) was 8.8 ± 2.2 and 5.3 ± 1.9 mm Hg, respectively. There was significant difference between 2 groups ($P = 0.008$). C, The ΔIAP presented a discrimination with area under the receiver operating characteristic curve of 0.838 ($P = 0.001$, 95% CI, 0.821– 0.855).

multivariable logistic regression analyses showed that multi organ failure and IAH/ACS before PCD were risk factors for infection after PCD. However, PCD proved to be an efficient option for managing IAH/ACS.[22–25] After the initial IAP were measured, and decrease of IAP after PCD was accurately calculated, more significant reduction of IAP as well as better prognosis was observed in the sterile group. These results indicated that dramatic reduction of IAP was a protective factor for PCD.

In conclusion, intra-abdominal PCD for acute sterile fluid collections seems to be an effective option rather than peripancreatic PCD. Patients with a dramatic decrease in IAP after PCD presented a lower incidence of infection and better alleviation of organ failure.

Because this was a retrospective study, some shortcomings need to be stated. First, it is difficult to avoid a data bias from the analysis because of derandomization. Second, the number of cases in the primary infection group is much less than that in the other 2 groups. Third, some cases of moderate SAP with fluid collection but in absence of organ failure are included in this study, and the severity in the primary infection group is higher than that in the other 2 groups. Finally, because patient discharge was set to the endpoint of this study, the follow-up time was not long enough. In the future, a randomized control trail with a long follow-up time is necessary to provide more evidence for the conclusions drawn from this study.

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