Usefulness of Early-phase Peritoneal Lavage for Treating Severe Acute Pancreatitis

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Abstract

Objective To improve the prognosis of severe acute pancreatitis, preventing infectious complications, particularly infected pancreatic necrosis, is important. The present study evaluated the efficacy of peritoneal lavage for improving the prognosis of patients with severe acute pancreatitis.

Patients We retrospectively reviewed the cases of 23 consecutive patients with severe acute pancreatitis who were treated with peritoneal lavage.

Results Peritoneal lavage was started within 72 hours after the initial onset of symptoms in 20 patients (87%). The duration of peritoneal lavage, which was significantly correlated with the number of prognostic factors according to the revised Japanese criteria, Ranson score and serum C-reactive protein level at the start of peritoneal lavage, was a median of seven (3-22) days. There were no adverse events associated with the peritoneal lavage. Eight patients (35%) concurrently underwent continuous regional arterial infusion. Five days after starting peritoneal lavage, the patients’ clinical conditions significantly improved. Overall, the survival rate was 96%. One patient (4%) died due to rupture of a pseudoaneurysm of the splenic artery. Complications occurred in seven patients (30%). Infectious complications were observed in three patients (13%) (one patient developed infected pancreatic necrosis and bacteremia, and two patients developed bacteremia). Pseudocysts and pancreatic fistulas developed in five and one patient, respectively. The incidence of complications was lower in the patients receiving peritoneal lavage within 72 hours from the initial onset of symptoms than in the remaining patients (20% vs. 100%; p=0.005).

Conclusion We speculate that peritoneal lavage reduces the mortality and incidence of complications in patients with severe acute pancreatitis.

Key words: acute pancreatitis, infection, peritoneal lavage, prognosis

(Intern Med 53: 1-6, 2014)
(DOI: 10.2169/internalmedicine.53.0745)

Introduction

Acute pancreatitis is an inflammatory disease of the pancreas characterized by acute abdominal pain in the epigastric area or the right upper quadrant and increased levels of serum pancreatic enzymes (1). Gallstones and excessive alcohol consumption are the two most common causes of acute pancreatitis. The mortality rate from acute pancreatitis is <5%; however, 20% of patients develop severe disease, with a mortality rate of approximately 20% (2). The primary causes of death among patients with severe acute pancreatitis are organ failure associated with circulatory failure in the early stage (within approximately two weeks after onset) and infectious complications, including infected pancreatic necrosis in the late stage (3).

The most important treatment for acute pancreatitis is fluid resuscitation (4). Insufficient fluid resuscitation may lead to organ failure in the early stage. If necessary, pain relievers, oxygen and antiemetics are administered. In addition, urgent (within 24 hours) endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy are per-
formed for gallstone-induced pancreatitis (5). Continuous regional arterial infusion (CRAI) of protease inhibitors and antibiotics prevents the development of pancreatic infection and decreases the mortality rate among patients with acute necrotizing pancreatitis (6, 7).

Trials performed in the 1980s and 1990s reported that peritoneal lavage does not reduce the rate of mortality or complications of this disease (8); however, a recent study demonstrated the anti-inflammatory effects of peritoneal lavage in patients with acute pancreatitis (9). Ascitic fluids in acute pancreatitis patients contain high levels of proinflammatory cytokines and pancreatic enzymes, such as phospholipase A2, which play a role in the development of distant organ dysfunction (10-12). Peritoneal lavage decreases not the ascitic, but rather the serum, levels of proinflammatory cytokines and pancreatic enzymes (9, 13). In addition, long-term (seven days), but not short-term (two or three days), peritoneal lavage has been reported to reduce the incidence of sepsis and the rate of death from sepsis among patients with severe acute pancreatitis (14, 15). Therefore, we speculate that peritoneal lavage for the period appropriate to the severity of the disease reduces the mortality rate of severe acute pancreatitis.

In this study, we retrospectively estimated the efficacy of peritoneal lavage for treating severe acute pancreatitis.

Materials and Methods

This study was approved by the Institutional Review Board at Mitoyo General Hospital.

Patients

We retrospectively reviewed 23 consecutive patients with severe acute pancreatitis who were treated with peritoneal lavage at Mitoyo General Hospital. The diagnosis of acute pancreatitis was made according to the presence of two of the following three manifestations: characteristic upper abdominal pain, elevated serum amylase levels and computed tomography (CT) findings suggesting acute pancreatitis (enlargement of the pancreas, an uneven density of the pancreatic parenchyma, an increased concentration of adipose tissue in the parapancreatic and retroperitoneal cavities and mesenterium and fluid collection) (16). The diagnosis of severe acute pancreatitis was made according to the revised Japanese criteria (2), which consist of nine prognostic factors and contrast-enhanced CT grades. Patients who met the criteria for three or more prognostic factors or CT findings of grade 2 or higher were diagnosed with severe acute pancreatitis.

Treatments

All patients were admitted to the intensive care unit to receive supportive care along with the monitoring of clinical, biochemical and hemodynamic parameters and treated with intravenous fluid resuscitation and the administration of pain relievers, oxygen and antiemetics (if necessary). In addition, broad-spectrum antibiotics (primarily 1,000 mg/day of imipenem) were administered intravenously.

All patients underwent contrast-enhanced CT at the start of peritoneal lavage. Patients showing inflammatory changes beyond the lower pole of the kidney or fluid collection on CT received peritoneal lavage. A catheter for peritoneal lavage was inserted into Douglas’ pouch or the rectovesical pouch using a formal, 4- to 5-cm incision created under local infiltration anesthesia. Peritoneal lavage was started within 48 hours from the patient’s admission to our hospital. The fluid used was peritoneal dialysis solution containing 1.5% dextrose (Dianeal®, Baxter, Tokyo, Japan), and 250 mg of cefazolin and 30 mg of nafamostat mesilate were added to each 2 L of fluid. In general, 2 L of the fluid was run into the peritoneal cavity under gravity over a 30- to 60-minute period. The fluid was left intraperitoneally for approximately two hours and then drained out by gravity. The peritoneal lavage was ended when relief of abdominal pain and an improvement in the number of systemic inflammatory response syndrome components (SIRS score) (17) to one or less were observed.

Evaluating the degree of pancreatic parenchyma necrosis on contrast-enhanced CT, we added CRAI to peritoneal lavage in the patients with a pancreatic hypoperfusion area of 30% or more. Following angiography of the pancreas, a 4-Fr catheter was placed in the celiac artery, and 100 mg/day of nafamostat mesilate and 1,000 mg/day of imipenem were administered.

Statistical analysis

All data were entered into an Access database (Microsoft Corp., Redmond, WA, USA). We used the SPSS statistical program (release 11.0.1 J, SPSS, Inc., Chicago, IL, USA) for the statistical analysis.

The Ranson score (18), Acute Physiology and Chronic Health Evaluation (APACHE)-II score (18), length of hospitalization, mortality rate and complications were evaluated. The SIRS score, white blood cell count, platelet count, base excess and serum levels of amylase, lactate dehydrogenase, blood urea nitrogen, creatinine, calcium and C-reactive protein were compared between the values obtained at the start of and five days after peritoneal lavage.

Continuous variables are expressed as medians and ranges. The Wilcoxon test was used to evaluate the significance of differences in the continuous variables between paired samples. Differences in continuous variables were evaluated using the Mann-Whitney U-test between two unpaired samples. Dichotomous variables were compared using the χ² test. The Spearman correlation coefficient was used to evaluate the consistency in the continuous variables between the two groups. p values of less than 0.05 were accepted as significant.
Table 1. Clinical Characteristics of the Study Population at the Start of Peritoneal Lavage

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, female (%)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Cause of pancreatitis, n (%):</td>
<td></td>
</tr>
<tr>
<td>Gallstones</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Excessive alcohol consumption</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (44)</td>
</tr>
<tr>
<td>Duration from initial symptoms to admission, n (%):</td>
<td></td>
</tr>
<tr>
<td>&lt;24 hours</td>
<td>18 (78)</td>
</tr>
<tr>
<td>24–72 hours</td>
<td>3 (13)</td>
</tr>
<tr>
<td>&gt;72 hours</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Duration from initial symptoms to peritoneal lavage, n (%):</td>
<td></td>
</tr>
<tr>
<td>≤72 hours</td>
<td>20 (87)</td>
</tr>
<tr>
<td>&gt;72 hours</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Revised Japanese severity scoring system:</td>
<td></td>
</tr>
<tr>
<td>Number of prognostic factors</td>
<td>2 (1–8)</td>
</tr>
<tr>
<td>Computed tomography point</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Number of prognostic factors ≥3 and CT grade ≥2, n (%)</td>
<td>10 (44)</td>
</tr>
<tr>
<td>Ranson criteria: Median (range)</td>
<td>3 (0–7)</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>14 (61)</td>
</tr>
<tr>
<td>≥6, n (%)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>APACHE-II score: Median (range)</td>
<td>7 (0–17)</td>
</tr>
<tr>
<td>≥8, n (%)</td>
<td>11 (48)</td>
</tr>
</tbody>
</table>

APACHE: Acute Physiology and Chronic Health Evaluation, CT: computed tomography

Clinical characteristics of the study population

The clinical characteristics of the 23 patients treated with peritoneal lavage are shown in Table 1. Eighteen patients (78%) were admitted within 24 hours of the initial onset of symptoms. Six patients (26%) with gallstone-induced pancreatitis underwent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy within 24 hours of admission. Ten patients (44%) satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage. Fourteen patients (61%) had a Ranson score of 3 or higher, and 11 patients (48%) had an APACHE-II score of 8 or higher.

Treatment

Peritoneal lavage was performed without any adverse events in all patients. Peritoneal lavage was started within 72 hours from the initial onset of symptoms in 20 patients (87%). The duration of peritoneal lavage was seven (3-22) days. The duration of peritoneal lavage was correlated with the SIRS score (r=0.52; p=0.036), number of prognostic factors according to the revised Japanese criteria (r=0.70; p=0.0054), Ranson score (r=0.49; p=0.049) and serum C-reactive protein level (r=0.65; p=0.0096) at the start of peritoneal lavage. Patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage required a longer duration of peritoneal lavage [8 (7-22) days vs. 5 (3-7) days; p=0.027]. Patients in whom peritoneal lavage was started within 72 hours from the initial onset of symptoms showed a tendency to have a shorter duration of peritoneal lavage [7 (3-14) days vs. 8 (7-22) days; p=0.088].

Eight patients (35%) concurrently underwent CRAI. Of note, CRAI was performed more frequently in the patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria than in the other patients (70% vs. 8%; p=0.0019). The patients who concurrently underwent CRAI exhibited lower platelet counts [9.3 (3.9-17) ×10^4/mm^3 vs. 16 (11-39) ×10^4/mm^3; p=0.0033] and higher serum levels of blood urea nitrogen [27 (17-51) mg/dL vs. 16 (7-38) mg/dL; p=0.011], creatinine [1.4 (0.8-2.2) mg/dL vs. 0.8 (0.6-1.6) mg/dL; p=0.0071] and C-reactive protein [23 (11-33) mg/dL vs. 10 (0.3-26) mg/dL; p=0.047] and tended to show higher Ranson scores (4.5 (2-7) vs. 3.0 (0-6); p=0.076) at the start of peritoneal lavage.

Changes in the SIRS scores and laboratory data

The SIRS score, white blood cell count, base excess and serum levels of amylase, lactate dehydrogenase, blood urea nitrogen, creatinine, calcium and C-reactive protein were significantly improved five days after the initiation of peritoneal lavage (Table 2). Among the patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage, the SIRS score [3.5 (1-4) to 1.5 (0-3); p=0.0097], white blood cell count [14,650 (8,100-17,300)/mm^3 to 9,100 (4,100-13,730)/mm^3; p=0.0093], base excess [0.4 (-9.9-5.7) mEq/L to 4.6 (2.5-8.1) mEq/L; p=0.0077] and serum levels of amylase [668 (159-1,093) mg/dL to 109 (21-534) mg/dL; p=0.0051], lactate dehydrogenase [495 (164-1,491) IU/L to 317 (101-612) IU/L; p=0.013], blood urea nitrogen [21 (10-51) mg/dL to 8 (5-17) mg/dL; p=0.0050], creatinine [1.1 (0.7-2.2) mg/dL to 0.7 (0.5-1.1) mg/dL; p=0.0074] and calcium [8.7 (5.7-9.1) mg/dL to 9.3 (7.9-10.3) mg/dL; p=0.012] were significantly improved five days after the initiation of peritoneal lavage.

Outcomes (Table 3)

The length of hospitalization was 50 (12-143) days. In the group of patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria, the length of hospitalization was significantly longer than that observed in the remaining patients [67 (45-143) days vs. 38 (12-61) days; p=0.0006].

Of the 23 patients, one who was admitted seven days after the initial onset of symptoms died due to rupture of a splenic artery pseudoaneurysm. The overall survival rate was 96%. All patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage...
of peritoneal lavage survived.

Overall, complications occurred in seven patients (30%). Infectious complications occurred in three patients (13%): One patient developed infected pancreatic necrosis and bacteremia and underwent CRAI and surgical drainage, while the other two patients developed bacteremia and underwent CRAI. Of the five patients (22%) who developed pseudocysts, one died due to the rupture of a pseudoaneurysm of the splenic artery, and another underwent surgical drainage. In the remaining three patients, the pseudocysts disappeared without treatment. One patient (4%) developed a pancreatic fistula and underwent surgery for its removal.

The incidence of complications was higher in the patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage (60% vs. 8%; p=0.0069) and lower in the 20 patients who received peritoneal lavage within 72 hours from the initial onset of symptoms (20% vs. 100%; p=0.005). Among the 10 patients who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria at the start of peritoneal lavage, two were treated with peritoneal lavage more than 72 hours after the initial onset of symptoms. In addition, four of the eight patients treated with peritoneal lavage within 72 hours from the initial onset of symptoms developed complications.

### Discussion

Severe acute pancreatitis frequently results in a fatal outcome. According to the revised Japanese criteria, the mortality rate of patients with severe acute pancreatitis who meet the criteria for over three prognostic factors and CT findings of grade 2 or higher has been reported to be 19%, while that of patients with CT findings of grade 2 and grade 3 is 14% and 15%, respectively (2). Furthermore, the mortality rate of patients with severe acute pancreatitis satisfying the criteria for both three or more prognostic factors and CT findings of grade 2 or higher has been reported to be 31% (2). However, in the present study, the mortality rate of patients treated with peritoneal lavage was better than that observed in previous reports. Of note is that all of the present study’s patients in whom peritoneal lavage was started within 72 hours from the initial onset of symptoms survived. In addition, the incidence of complications was lower in the patients receiving peritoneal lavage within 72 hours from the initial onset of symptoms. On the other hand, one patient in whom peritoneal lavage was started 10 days after the development of severe acute pancreatitis died due to rupture of a pseudoaneurysm of the splenic artery. Therefore, peritoneal lavage should be started within 72 hours from the initial onset of symptoms in patients with severe acute pancreatitis. In patients in whom a period longer than 72 hours from the initial onset of symptoms has passed, the efficacy of peritoneal lavage may be insufficient.

In order to improve the prognosis of severe acute pancreatitis, preventing infectious complications in the late stage is important. Infected pancreatic necrosis develops in approximately 20% of patients with severe acute pancreatitis.
with a mortality rate of approximately 30% (19). A few randomized controlled trials have reported that peritoneal lavage does not reduce the incidence of complications; however, in these reports, the duration of peritoneal lavage was only four days or less (13, 15). In contrast, in the present study, the median duration of peritoneal lavage was seven days, and the incidence of infected pancreatic necrosis was 4%. In addition, in the patients with severe disease, a longer duration of peritoneal lavage was used. Therefore, we speculate that the administration of peritoneal lavage for a period appropriate to the severity of the disease reduces the incidence of infected pancreatic necrosis in the late stage.

CRAI of protease inhibitors, such as nafamostat mesilate, and broad-spectrum antibiotics, such as imipenem, has been shown to reduce the incidence of infectious complications and the mortality rate of acute necrotizing pancreatitis. Yasuda et al. (7) reported that the incidence of infection (intra-abdominal necrosis or bacteremia) and mortality rate in patients with acute necrotizing pancreatitis treated with CRAI is 34% and 37%, respectively. In the present study, CRAI was performed more frequently in the patients with severe disease. Of the eight patients treated with peritoneal lavage combined with CRAI, three (38%) developed infectious complications; however, the mortality rate in these eight patients was as low as 13%. In addition, the three patients who developed infectious complications who satisfied the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria survived. Therefore, in patients with severe disease, such as those who satisfy the criteria for both three or more prognostic factors and CT findings of grade 2 or higher according to the revised Japanese criteria, peritoneal lavage combined with CRAI may be more effective in decreasing the mortality rate of infectious complications than peritoneal lavage monotherapy or CRAI monotherapy.

It remains uncertain whether peritoneal lavage prevents multiple organ failure in the early stage of severe acute pancreatitis. We observed that, in our patient series, peritoneal lavage decreased the SIRS score, white blood cell count and serum C-reactive protein level and improved the renal function. No patients died due to multiple organ failure in the early stage. These findings suggest that the use of peritoneal lavage promptly improves the general condition of patients with severe acute pancreatitis.

In this patient series, there were no adverse events related to the administration of peritoneal lavage. The insertion of a catheter into the abdominal cavity is necessary for peritoneal lavage, and the development of infectious complications may thus be feared. A meta-analysis showed that peritoneal lavage does not increase the incidence of intra-abdominal infectious complications (8). Peritoneal lavage can be carried out safely when it is appropriately managed; however, further studies are needed to evaluate adverse events related to peritoneal lavage.

Our study is associated with some important limitations. First, the study was retrospective. Second, the sample size was small. To confirm our findings, conducting a prospective randomized controlled trial or prospective cohort study with a large sample size in which peritoneal lavage is compared with the recent standard therapy is required.

In conclusion, we speculate that the administration of peritoneal lavage within 72 hours after the initial onset of symptoms reduces the mortality rate and incidence of infectious complications, such as infected pancreatic necrosis, in patients with severe acute pancreatitis. On the other hand, in patients in whom a period longer than 72 hours after the initial onset of symptoms has passed, the efficacy of peritoneal lavage may be insufficient. The efficacy of peritoneal lavage in patients with severe acute pancreatitis merits further investigation.

The authors state that they have no Conflict of Interest (COI).

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