Surg Today (2016) 46:371–378
DOI 10.1007/s00595-015-1172-9

ORIGINAL ARTICLE

Early-phase peritoneal drainage and lavage in a rat model of severe acute pancreatitis

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Received: 9 October 2014 / Accepted: 24 February 2015 / Published online: 21 April 2015

Abstract
Purpose To evaluate the effects of early-phase drainage on the survival rates and pancreatic pathological changes associated with severe acute pancreatitis (SAP) in a rat model.
Methods Sprague–Dawley rats were divided into the following groups: SAP model (control), early drainage and delayed drainage. The 24-h survival rates were compared among the groups. In addition, the serum and ascites concentrations of interleukin (IL)-1β, IL-6, IL-8, IL-10 and tumor necrosis factor (TNF)-α were measured, and pancreatic pathological changes were observed.
Results The survival rate significantly improved in the early drainage group. Compared with that observed in the control group, the serum TNF-α and IL-8 concentrations in the early drainage group decreased, while the serum IL-10 levels increased, and the ascites concentrations of IL-1β, IL-6, IL-8 and TNF-α decreased, while that of IL-10 increased significantly. In the delayed drainage group, only the ascites concentrations of TNF-α decreased. Meanwhile, the pancreatic pathological changes at 3, 6 and 24 h worsened in the early drainage group; however, the pancreatic lesions in the early drainage group were less mild than those seen in the control group.
Conclusions Rebalancing the cytokine levels in ascites after early drainage may be a key factor for enhancing the survival rate in rats.

Keywords Severe acute pancreatitis · Pathological change · Peritoneal drainage · Survival rate · Cytokine

Introduction

Severe acute pancreatitis (SAP) is characterized by a sudden and severe onset followed by rapid deterioration. Complications, such as multisystem organ failure, shock and abdominal hypertension, can occur in the early stage of SAP [1, 2] and correlate with significantly poor scores in severity scoring systems, suggesting a poor prognosis with a high mortality rate [3]. Current management, including aggressive supportive intensive care, fluid resuscitation, enteral nutrition and antibiotic therapy, is aimed at reducing the systemic inflammatory response and multisystem organ dysfunction [4–7]. Surgical debridement performed in the early stage of SAP can be a "second-blow" to the systemic inflammatory response, which subsequently increases the burden on the body and causes further deterioration [8–10]. Non-operative strategies and delayed surgical intervention are thus recommended [11–14]. Image-guided percutaneous catheter drainage has recently been used to supplement intensive conservative treatment, and it has been reported that, under the guidance of ultrasound or computed topography (CT), intraperitoneal and retroperitoneal percutaneous catheter drainage and lavage can be used to reduce a high abdominal pressure and treat pancreatic necrotic infection and/or help to avoid or delay surgery in some patients with

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SAP [15–18]. However, according to current management guidelines for acute pancreatitis, the drainage procedure should be delayed, preferably for 4 weeks, in stable patients with infected necrosis, to allow for the development of a wall around the site of necrosis [19]. Nevertheless, whether it is beneficial to perform peritoneal drainage in the early stage of SAP and/or in patients without evidence of infection remains unclear. Fluid collection in the peripancreatic area and remote areas of the peritoneal cavity, as observed on CT, are common in early-stage SAP. Areas of fluid collection, mostly presenting as bloody ascites, are rich in activated lipolytic and proteolytic enzymes, vasoactive substances and inflammatory cytokines and are not necessarily infected [20]. Performing drainage of these potential toxic mediators from the peritoneal cavity is rational for alleviating the disease burden in critically ill patients. Based on the limited clinical data regarding the application of percutaneous drainage in patients with sterile necrotizing pancreatitis, the effectiveness of this procedure can be compared with that of drainage in patients with infected necrosis [17, 21, 22]. However, experimental research on this application is lacking. In the current study, we utilized the peritoneal catheter drainage (PCD) approach in the early stage of SAP in a rat model in order to observe the impact of these approaches on disease outcomes and pathological changes in the pancreas.

Materials and methods

Experimental materials

Male Sprague–Dawley (SD) rats (specific pathogen-free grade) weighing 200–230 g were purchased from B&K Universal Group Limited (Shanghai, China). Sodium taurocholate hydrate was purchased from Sigma-Aldrich China Inc. (Shanghai, China).

Experimental methods and groups

The present study was approved by the Ethical Research Committee of our institute. The SD rat SAP model was established via the antegrade puncture injection of sodium taurocholate, as follows. SD rats were housed for 1 week after receipt and fasted for 24 h prior to surgery. The rats were anesthetized using the intraperitoneal injection of sodium pentobarbital (45 mg/kg). An incision was made along the abdominal midline, and the biliopancreatic duct was identified with respect to the duodenum. An arterial clip was used to occlude the common bile duct near the hepatic hilus, and another arterial clip was used to occlude the distal pancreatic duct at its entry into the duodenum. A Becton–Dickinson needle (4.5 gauge) was used for antegrade puncture of the common bile duct and proximal pancreatic duct, and 5 % sodium taurocholate (0.1 mg/100 g) was injected at a slow rate of 0.2 mL/min. A sterile swab was pressed onto the puncture site for 1 min after the injection. Three minutes later, the distal and proximal segments of the pancreatic duct were re-opened. Pancreatic tissue congestion and edema with hemorrhagic foci were observed after the sodium taurocholate injection. The abdomen was subsequently closed with sutures, and, after the recovery from anesthesia, the rats were housed in individual cages, fasted and allowed free access to water.

Catheter drainage was performed as follows. After the model was established, a ventricular drainage tube (10 cm in length) was placed in the right lower abdomen of each rat. There were multiple side holes in the intra-abdominal segment of the tube, and the drainage could be turned on or off through the segment of the tube outside of the abdomen. Peritoneal lavage was performed with 5 ml of normal saline at an ambient temperature through the tube once per each 6 h.

The experimental animals were randomly divided into the following treatment groups: an SAP model group (no treatment after the model was established), an early drainage group (drainage and lavage were initiated immediately after the model was established) and a delayed drainage group (drainage and lavage were initiated 6 h after the model was established).

Serum and ascites samples were collected at 3, 6 and 24 h and centrifuged at 3500×*g* for 10 min. The supernatants were assayed for tumor necrosis factor (TNF)-α and interleukin (IL)-1β, IL-6, IL-8 and IL-10 according to an indirect sandwich enzyme-linked immunosorbent assay (ELISA) using the kit provided by Pusheng Biotech Inc. (Shanghai, China).

A pathological examination was performed as follows. After the rats were killed, the gross morphology of the pancreas and surrounding intestines was observed. The pancreatic specimens were fixed in formalin, routinely embedded in paraffin and stained with hematoxylin and eosin (HE) staining. The slides were reviewed, and the pancreatic sections were graded by a pathologist on a scale from 0 to 4 for the degree of edema, inflammation, hemorrhage and necrosis [23].

Statistical analysis

The Microcal Origin 6.0 statistical software program was used for the statistical analysis. Continuous variables are expressed as medians and ranges. The Chi-square test was utilized to compare the survival rates, and differences between groups were evaluated with the paired Student's *t* test. *P* values of <0.05 were considered to be statistically significant.

Results

Survival rates of the rats

The rats were alive 6 h after the model was established in each group. Compared to that observed in the control group, the 24-h survival rate in the early drainage group was significantly increased ($P < 0.01$). However, no significant differences were observed in the 24-h survival rates between the delayed drainage and control groups ($P > 0.05$) (Table 1).

Cytokine concentrations in the serum and ascites

In the pilot study of the model control group, the concentrations of almost all cytokines (except IL-8 in the ascites and serum and IL-10 in the ascites) reached the highest levels at 6 h in both the serum and ascites after the SAP model was established and maintained a plateau at a high level or with slight changes thereafter (Fig. 1). Early-stage peritoneal drainage and lavage were helpful for decreasing the serum concentrations of IL-8 and TNF-α, with elevated levels of IL-10; however, there were no obvious effects on the serum concentrations of IL-1β and IL-6 (Table 2).

Compared to that noted in the serum, the changes in the cytokine levels in the rat ascites were more dramatic. Compared with that observed in the control group, the ascites concentrations of IL-1β, IL-6, IL-8 and TNF-α were decreased and the IL-10 levels were significantly elevated in the early drainage group, while only the ascites concentrations of TNF-α were decreased significantly in the delayed drainage group ($P < 0.05$). Compared with that

Table 1 Twenty-four-hour survival rates of the rats in each group

Group	% Survival rate of the rats (no. of rats that survived/total no. of rats)	*P* value
Model control	12.5 % (2/16)	
Early drainage	75 % (12/16)	0.000957*
Delayed drainage	37.5 % (6/16)	0.054464

* $P < 0.01$ vs. the control group

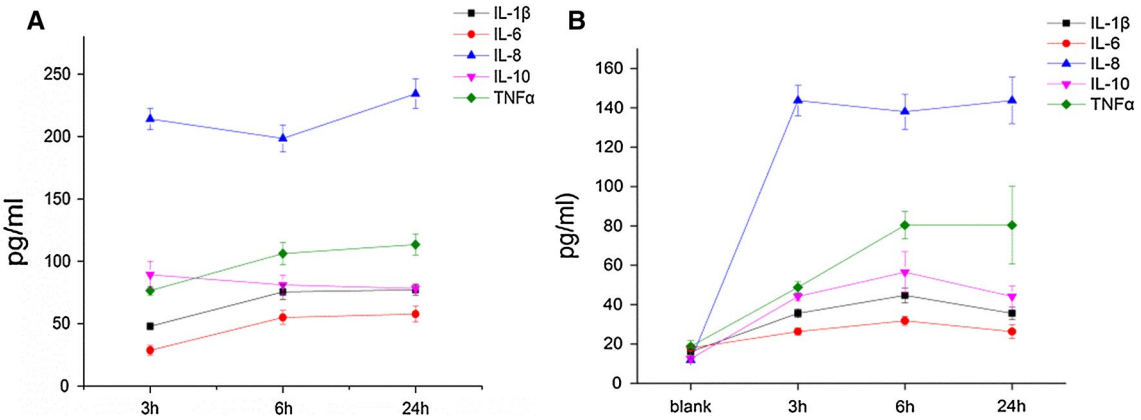

Fig. 1 Cytokine levels at different time points after SAP model established in model control group. The cytokine level after 6 h remained in a plateau or slightly changed. **a** Ascites cytokine levels in 3, 6 and 24 h after SAP model established. **b** Serum cytokine levels before (*blank*), and in 3, 6, 24 h after SAP model established

Table 2 Cytokine levels in the rat serum among the different groups ($\bar{x} \pm s$, pg/mL)

Group	IL-1β	IL-6	IL-8	IL-10	TNF-α
Model control	35.6 ± 3.15	26.29 ± 3.5	143.75 ± 11.85	44.11 ± 5.44	80.37 ± 19.70
Early drainage	46.20 ± 18.7	32.11 ± 7.97	75.86 ± 5.96*	86.3 ± 1.47*	55.39 ± 5.74*
Delayed drainage	26.94 ± 3.09	26.37 ± 5.59	106.97 ± 14.62	50.11 ± 20.15	74.13 ± 0.31

Data are expressed as the mean ± SEM

* $P < 0.05$ vs. the control group

Table 3 Cytokine levels in the rat ascites ($\bar{x} \pm s$, pg/mL)

Group	IL-1β	IL-6	IL-8	IL-10	TNF-α
Model control	77.05 ± 4.36	57.61 ± 6.33	234.29 ± 11.83	78.26 ± 3.86	113.4 ± 8.39
Early drainage	18.17 ± 1.00*	32.67 ± 3.49*	75.65 ± 12.23*	105.61 ± 16.45*	78.51 ± 10.87*
Delayed drainage	105.01 ± 5.78#	44.11 ± 12.87	246.51 ± 14.57#	47.09 ± 7.36#	58.55 ± 4.76*

Data expressed as the mean ± SEM

* $P < 0.05$ vs. the control group

# $P < 0.05$ vs. the early drainage group

seen in the early drainage group, the ascites concentrations of IL-1β and IL-8 increased in the delayed drainage group, whereas the IL-10 levels also decreased significantly ($P < 0.05$) (Table 3).

Pathological changes in the pancreas under light microscopy

SAP model group (control group)

The following pathological changes were observed under a microscope 3 h after the model was established: pancreatic edema and degeneration, dilation and stasis of the blood vessels, bleeding, infiltration of a small number of neutrophils and small plaques of saponification (adipose tissue necrosis with calcium deposition). At 6 h, pancreatic edema, degeneration and increased infiltration of neutrophils were observed under a microscope. At 24 h, large areas of coagulative necrosis, the absence of normal tissue and significant areas of plaques of saponification were observed.

Table 4 Histologic changes at varying time points in the early drainage group

Group (h)	Edema	Inflammation	Hemorrhage	Necrosis
3	0.77 ± 0.43	1.13 ± 0.35	1.73 ± 0.45	0.27 ± 0.15
6	1.27 ± 0.52*	1.27 ± 0.45	1.33 ± 0.48*	1.03 ± 0.41*
24	2.80 ± 0.41*	2.20 ± 0.48*	1.40 ± 0.49*	2.70 ± 0.47*

Data are expressed as the mean ± SEM

* $P < 0.05$ vs. the 3-h time point

Early drainage group

The following changes were observed under a microscope 3 h after drainage and lavage: pancreatic edema and degeneration, dilation and stasis of the blood vessels, bleeding, infiltration of sporadic inflammatory cells, a significant number of plaques of saponification and large areas of coagulation necrosis. At 6 h after drainage and lavage, an increased number of inflammatory cells, large plaques of saponification and areas of necrosis were observed under a microscope. At 24 h, partial coagulation necrosis was observed; however, a significant amount of normal pancreatic tissue remained.

Delayed drainage group

The following pathological changes were observed under a microscope at 24 h after drainage and lavage: pancreatic edema and degeneration, dilation and stasis of the blood vessels, bleeding, infiltration of a large number of inflammatory cells, large plaques of saponification and necrosis.

A worsening trend of disease progression was found in the comparison of the microscopic pathological changes at 3, 6 and 24 h in each group, even in the early drainage group (shown in Table 4).

Table 5 shows the histology scores for each group of rats. Early drainage and lavage decreased the grades of edema, inflammation, hemorrhage and necrosis to different degrees compared with that noted in the control group; however, the pancreatic lesions significantly worsened in the delayed drainage group (shown in Fig. 2).

Table 5 Comparison of the histologic grading of the rat pancreas between the groups at 24 h

Group	Edema	Inflammation	Hemorrhage	Necrosis
Model control	2.80 ± 0.41	1.93 ± 0.45	1.77 ± 0.43	3.73 ± 0.45
Early drainage	2.73 ± 0.75	1.97 ± 0.41	0.70 ± 0.47*	2.77 ± 0.57*
Delayed drainage	2.17 ± 0.38*	2.77 ± 0.43*	1.83 ± 0.46	2.90 ± 0.48*

Data are expressed as the mean ± SEM

* $P < 0.05$ vs. the control group

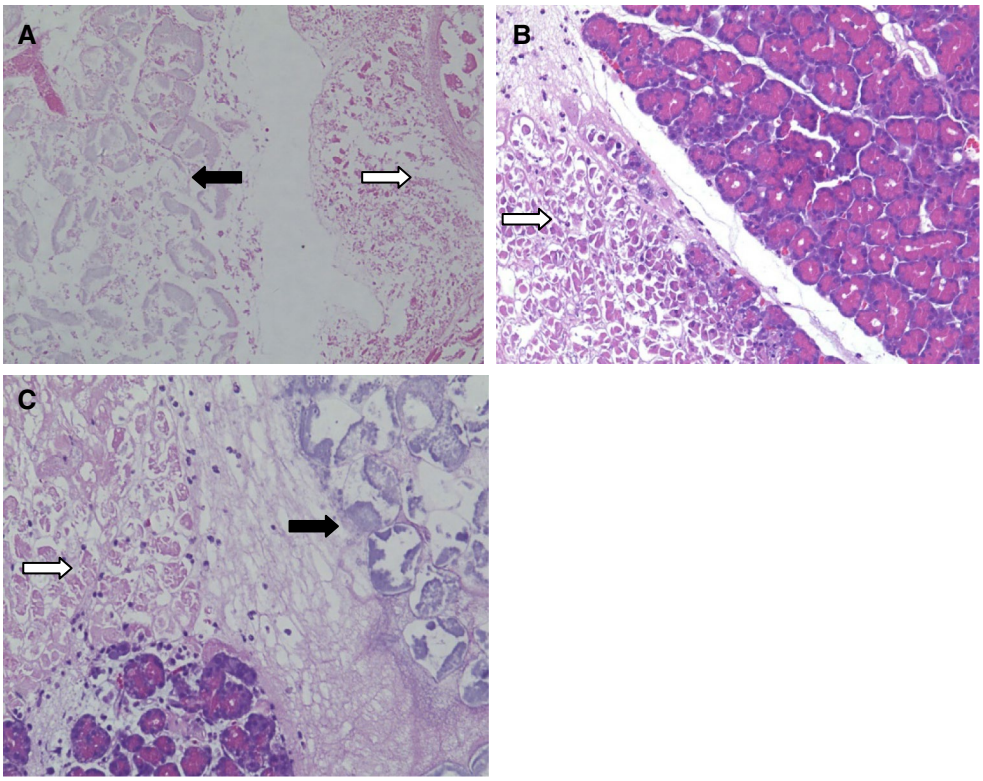

Fig. 2 Photographs of pancreas change under light microscope. **a** 24 h after the SAP model was established (×200), large areas of coagulative necrosis, no normal tissue, and large areas of saponification plaques. **b** 24 h after early drainage (×200), large areas of coagulation necrosis, residual normal tissue. **c** 18 h after delayed drainage (×200), large saponification plaques and large areas of coagulation necrosis. There was residual normal pancreatic tissue. *White arrows* indicate necrosis. *Black arrows* indicate saponification plaques

Discussion

Image-guided percutaneous drainage, as a component of minimally invasive therapy, has been reported to decrease the severity of illness and improve organ dysfunction in a subgroup of SAP patients, preventing the need for major debridement surgery or a prolonged interval to surgical debridement. As a result, patient tolerance to surgery has improved [24–26]. As an alternative to open necrosectomy, percutaneous drainage, endoscopic drainage and minimally invasive retroperitoneal necrosectomy can be performed in a 'step-up' approach. This step-up approach may reduce the rates of complications and death by minimizing surgical trauma in already critically ill patients [24, 27, 28]. A well-designed, nationwide multicenter study demonstrated that the step-up approach reduces the rates of new-onset multiple-organ failure and death among patients with necrotizing pancreatitis and infected necrotic tissue, compared with open necrosectomy. In that report, of the patients assigned to the step-up approach, 35 % were treated with percutaneous drainage alone [29]. Nevertheless, in the latest management guidelines for acute pancreatitis, the drainage procedure is recommended only for stable patients with infected necrosis, with a preferred delay of 4 weeks to allow for the development of a wall around the site of necrosis [19]. However, other current clinical data suggest that percutaneous drainage in early-stage SAP patients and those without clear signs of infection may be beneficial as well. In a report by Mortelé et al. [17] 11 of 22 SAP patients with sterile necrosis were successfully treated with CT-guided percutaneous catheter drainage, with effectiveness similar to that observed in patients with infected necrosis, indicating that the presence of multisystem organ failure, rather than infection, is a more important indicator of the outcome. In a recent report from Matsumoto et al. the administration of peritoneal lavage within 72 h after the initial onset of SAP reduced the mortality rate and incidence of infectious complications. However, for patients in whom a period longer than 72 h after the onset of SAP symptoms has passed, peritoneal lavage may be ineffective [30]. Nevertheless, experimental research on the impact of early-stage drainage and lavage on the progression of SAP, without signs or evidence of infection, remains limited.

This study investigated the effects of early-phase peritoneal drainage and lavage on the 24-h survival rates in a rat model of SAP. In the early stage of SAP, all specimens can be treated as theoretically sterile. In our study, a large amount of bloody ascites began to appear 3 h after the SAP model was established. Without any treatment, the survival rate at 24 h was as low as 12.5 %. When peritoneal drainage was initiated immediately and at 6 h after the model was established, the survival rates of the rats were 75 and 37.5 %, respectively. These improved survival rates represent statistically significant differences, which suggests a significant impact of early-phase drainage on the SAP prognosis.

Previous animal experiments have confirmed that hyperemia, edema, hemorrhage and necrosis are apparent in the rat pancreas 3 h after the establishment of the SAP model. In addition, swelling, hyperemia and edema in the liver and lungs have been reported, and varying degrees of pathological changes in the kidneys, intestinal mucosa, spleen, thymus and lymph nodes have been observed under a microscope [31], which implies that SAP is a disease with systemic involvement. The "cascade" effect caused by the excessive release and imbalance of inflammatory cytokines is considered to be the mechanism of action [32–34]. Shen et al. [35] reported that, in SAP patients, the time course of the serum pro-inflammatory cytokines levels and anti-inflammatory cytokines levels differs, resulting in immune dysregulation, which leads to multisystem organ failure, mortality and secondary infection. Norman et al. [36] demonstrated that the cytokine mRNA (IL-1 mRNA and TNF-α mRNA) concentrations reach the highest levels 6 h after the onset of acute pancreatitis. In the current study, we found that, after the establishment of the SAP model, all cytokine levels (except for that of IL-8 in the ascites and serum and IL-10 in ascites) in both the serum and ascites were elevated and reached the highest levels at 6 h after the model was constructed and were maintained at high levels, with a slight change thereafter. Therefore, we adopted 6 h after the establishment of the SAP model as the time point of full development of acute pancreatitis and the beginning of delayed drainage.

IL-1β, IL-6, IL-8 and TNF-α are thought to be the main pro-inflammatory factors that mediate systemic inflammatory response syndrome, and IL-10 is thought to be an anti-inflammatory factor [34, 37, 38]. Souza et al. found that 4 h of peritoneal lavage after the onset of SAP decreases the serum levels of IL-6 and TNF-α and increases the serum levels of IL-10 in a rat model. Moreover, early-phase peritoneal lavage demonstrates anti-inflammatory effects in an SAP rat model [39]. Compared with that observed in the blood, the concentrations of cytokines in ascites are much higher, and high concentrations of digestive enzymes and a lethal toxicity are detected in the ascites of patients with SAP [20, 40]. In the current study, we investigated the changes in the concentrations of IL-1β, IL-6, IL-8, TNF-α and IL-10 in both the serum and ascites. Consequently, we observed that early peritoneal drainage and lavage led to an increase in the serum levels of IL-10, similar to that reported by Souza et al., and a decrease in the serum levels of IL-8 and TNF-α, an observation that differs from the results of Souza et al. [39]. Furthermore, we observed a more prominent change in the cytokine levels in the ascites following drainage and lavage. Compared with that seen in the control group, the ascites concentrations of IL-1β, IL-6, IL-8 and TNF-α were decreased in the early drainage group, while the IL-10 levels were elevated significantly.

As the changes in the cytokine levels in the ascites were more dramatic than those in the serum, the possibility exists that the peritoneal cavity may be the main source of inflammatory factors. Although the cytokine production observed in cases of SAP has multiple sources [36], studies have demonstrated that peritoneal macrophages that produce cytokines under the stimulation of trypsin may play an important role in the pathology of SAP [41]. Achieving the early removal of these toxic ascites may improve the prognosis of SAP. In clinical practice, PCD is not effective for all patients, possibly due to the time lapse that occurs between disease onset and the time at which the patient receives a diagnosis and undergoes catheter drainage after hospital admission. The APACH II score and extent of intrapancreatic necrosis are principle factors determining the success of PCD [42], which may suggest that outcomes improve as PCD is applied sooner.

The mechanism underlying the elevation of the IL-10 level induced by peritoneal drainage and lavage is still not completely understood. Scholars have postulated that a special subset of macrophages with anti-inflammatory properties is activated during peritoneal drainage [43, 44]. As a consequence, early-phase drainage and lavage may help to restore the balance between pro-inflammatory and anti-inflammatory factors, which may lead to a better prognosis.

There are currently no reports regarding the impact of peritoneal drainage on pancreatic pathology. This study found that the microscopic pathological changes in the pancreas were less severe in the early drainage and lavage groups than in the control group, an observation that corresponded with the relatively higher survival rates of the rats in these experimental groups. When the results were analyzed based on the timing of drainage, the pathological lesions were found to be significantly more severe in the delayed drainage group. Notably, when the microscopic pathological changes at 3, 6 and 24 h after early drainage were compared, the worsening trend of the lesions remained, which suggests that, once SAP has been initiated, simple early-phase peritoneal drainage and lavage may not be sufficient to attenuate disease progression.

These interesting findings may explain the deaths of several rats in the early drainage group. However, compared with that seen in the control group, the lesions were significantly alleviated in the early drainage group at 24 h. These observations imply that, to some extent, the early-phase drainage approach may reduce the abdominal and systemic toxicity burden to a tolerable level, which may subsequently alleviate symptoms and delay disease progression.

Compared with peritoneal therapy using pancreatic enzyme inhibitors or high doses of anti-inflammatory cytokines, such as IL-10 [45, 46], the administration of single early drainage and lavage in the current study demonstrated a favorable result in terms of the prognosis of SAP in rats. Therefore, a link between reduced peritoneal toxicity, rebalancing cytokine production and pancreatic self-recovery may be anticipated. However, the current study observed only the influence of drainage and lavage 24 h after the onset of SAP. Hence, research over a prolonged time span is needed to further understand the effects of early-phase drainage and lavage.

Acknowledgments This study was funded by the Scientific Research Fund of the Shanghai Municipal Health Bureau (No. 2010144). All authors contributed to the intellectual content and approved the final version of the manuscript.

Conflict of interest No benefits in any form have been or will be received from any commercial parties related directly or indirectly to the subject of this article.

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