

## Perirenal space blocking restores gastrointestinal function in patients with severe acute pancreatitis

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### Abstract

**AIM:** To investigate effects of perirenal space blocking (PSB) on gastrointestinal function in patients with severe acute pancreatitis (SAP).

**METHODS:** Forty patients with SAP were randomly allocated to receive PSB or no PSB (NPSB). All the SAP patients received specialized medical therapy (SMT). Patients in the PSB group received PSB + SMT when hospitalized and after diagnosis, whereas patients in the NPSB group only received SMT. A modified gastrointestinal failure (GIF) scoring system was used to assess the gastrointestinal function in SAP patients after admission. Pain severity (visual analog scale, 0 to 100) was monitored every 24 h for 72 h.

**RESULTS:** Modified GIF score decreased in both groups during the 10-d study period. The median score decrease was initially significantly greater in the PSB group than in the NPSB group after PSB was per-

formed. During the 72-h study period, pain intensity decreased in both groups. The median pain decrease was significantly greater in the PSB group than in the NPSB group at single time points. Patients in the PSB group had significantly lower incidences of hospital mortality, multiple organ dysfunction syndrome, systemic inflammatory response syndrome, and pancreatic infection, and stayed in the intensive care unit for a shorter duration. However, no difference in terms of operation incidence was found between the two groups.

**CONCLUSION:** PSB could ameliorate gastrointestinal dysfunction or failure during the early stage of SAP. Moreover, PSB administration could improve prognosis and decrease the mortality of SAP patients.

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**Key words:** Perirenal space blocking; Therapeutics; Severe acute pancreatitis; Gastrointestinal function; Prognosis

**Core tip:** This work aims to investigate the effects of perirenal space blocking (PSB) on the gastrointestinal function and clinical outcome of patients with severe acute pancreatitis (SAP). Our results showed that PSB could commendably improve the gastrointestinal dysfunction or failure during the early stage of severe SAP. Moreover, PSB administration could improve prognosis and significantly decrease the hospital mortality of SAP patients.

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## INTRODUCTION

Severe acute pancreatitis (SAP) has two major clinical stages, early and late. The first (early) stage is characterized by systemic inflammatory response syndrome (SIRS) and lasts for 10 d, whereas the second (late) stage is characterized by infectious complications, which account for most deaths in late-stage SAP patients<sup>[1-3]</sup>. SAP patients present symptoms of flatulence, abdominal distention, nausea, and vomiting related to a disturbance in gastrointestinal motility. Bacterial overgrowth in the ileus plays a major role in the pathogenesis of pancreatic infection<sup>[4-7]</sup>. Therefore, amelioration of intestinal dysmotility and stasis during the early period of SAP is important in reducing the risks associated with serious complications. Recent studies show that early enteral nutrition led to significantly lower incidences of multiple organ dysfunction syndrome (MODS), SIRS and pancreatic infection, and relieved intestinal dysmotility<sup>[8]</sup>. Nevertheless, early enteral nutrition is not usually practiced in SAP patients presenting disturbed gastrointestinal motility<sup>[9]</sup>.

Gastrointestinal tract motor dysfunction in a pathological state is probably associated with muscular and neural dysfunction. For this reason, some researchers considered using epidural anesthesia therapy, which can shorten the duration of the postoperative intestinal paralysis, for patients with early-stage SAP<sup>[10,11]</sup>. Peridural anesthesia is also suggested by researchers but this therapy may not be applicable in all patients, and no rigorous, prospective controlled trials have been able to establish this therapy as a recommended treatment option<sup>[12]</sup>.

The perirenal space is filled with fat. In acute pancreatitis, the perirenal fat and the bridging septa can be involved in the direct spread of inflammation<sup>[13,14]</sup>. This conclusion shows the direct relationship between perirenal space and the peripancreatic area. During SAP, an inflammatory exudate containing pancreatic enzymes leaks out from the pancreas, and its action of dissolving tissue inevitably stimulates the rich splanchnic ganglia and plexuses around the pancreas, which causes adverse reactions and reflection in the visceral nervous system and a series of pathophysiological disorders in the viscera, including gastrointestinal tract motor dysfunction. Considering the physiological and anatomical characteristics of the splanchnic nerves and the pancreas, and the pathological characteristics of SAP, the effect of perirenal space blocking (PSB) of a visceral nerve in the pancreatic region using 1% lidocaine on SAP treatment is studied. A simple, low-cost technique that could lead to short-term hospitalization or clinical treatment will be obtained.

## MATERIALS AND METHODS

### Study design

This is a single-center, prospective, and randomized controlled clinical trial. Patients randomly received either PSB or no PSB (NPSB) upon admission.

**Table 1** The modified gastrointestinal failure score

Item	Points		
	0	1	2
Number of FI symptoms	None	1-2	≥ 3
IAP (mmHg)	12	12-20	> 20 or ACS
Endotoxin concentration (pg/mL)	< 10	10-50	> 50
Computed tomography findings	None	Bowel wall thickening or intestinal extension	Bowel wall thickening and intestinal extension

FI: Food intolerance; IAP: Intra-abdominal pressure; ACS: Abdominal compartment syndrome.

### Patients

All adult SAP patients ( $n = 40$ ) admitted within 3 d after the onset of symptoms to the Department of General Surgery, the First Affiliated Hospital of Henan University of Science and Technology, from January 2012 to March 2013 were included in this study. SAP was defined as the presence of one or more local complications (*e.g.*, pseudocyst, necrosis or abscess) and/or organ failure, and acute physiology and chronic health evaluation APACHE II score  $> 8$  according to the widely used Atlanta criteria formulated in 1992<sup>[15]</sup>. The following criteria were used to exclude patients from the treatments: age (18 years old and below, or older than 75 years), pregnancy, evidence of malignancy, known cardiac morbidity including arrhythmia, severe pre-existing liver or kidney disease, leukopenia, allergic asthma, and known allergies. All the SAP patients received specialized medical therapy (SMT) for SAP<sup>[16]</sup>, such as intensive monitoring, oxygen administration, fluid resuscitation, cessation of oral feeding, exocrine pancreatic suppression, and antibiotic prophylaxis. Patients in the PSB group received PSB + SMT upon hospitalization, whereas patients in the NPSB group only received SMT after a definite diagnosis. This study was conducted in accordance with the declaration of Helsinki, with approval from the Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology. Written informed consent was obtained from all participants or their first-degree relatives.

### Evaluation protocol for gastrointestinal function

A modified gastrointestinal failure (GIF) scoring system was used to assess the gastrointestinal function in SAP patients. The system combined food intolerance (FI) symptoms, intra-abdominal pressure (IAP), endotoxin concentration and computed tomography findings into a 3-grade score, which is the modified GIF score (Table 1)<sup>[17]</sup>.

### PSB

One Teflon epidural catheter was placed for intermittent perirenal space blockade under local anesthesia after a definite diagnosis. An epidural transfixion pin was used to puncture the right lumbar region of SAP patients and was positioned into the right capsule of the kidney by the vectoring of B-mode ultrasonic diagnostic equip-

ment. Subsequently, the catheter was placed within the perirenal space through the transfixion pin. The external end of the catheter was fixed to the skin of the lumbar region. The patients were allowed to recover by normal and calm breathing, and lidocaine (100 g/L, 0.08 L/8 h) was intermittently injected into the capsule through the catheter. This regimen was administered for 10 d for the PSB group immediately after the diagnosis, and before randomization.

### Data collection

Upon admission, we recorded the baseline data, including age, gender, etiology, diagnoses, and whether SIRS had been diagnosed. The APACHE II scores<sup>[18]</sup> were recorded daily for 1-3 d. C-reactive protein (CRP) level, and serum endotoxin concentration<sup>[19]</sup> were recorded 1, 3, 7 and 10 d after admission. According to the manufacturer's instructions, we measured serum endotoxin with Gram-negative endotoxin detection reagents (Beijing Gold Mountainriver Technology Development Corporation Limited, China). Contrast-enhancement computed tomography (CECT) was performed 1, 3, 7 and 10 d after admission and the computed tomography severity index<sup>[20]</sup> score was calculated thereafter. We also assessed the image of the gastrointestinal tract. IAP was measured using the bladder technique, according to the method recommended by the World Society of Abdominal Compartment Syndrome in 2006<sup>[21]</sup>. For the duration of hospital stay, we recorded the gastrointestinal functional rehabilitation time (including venting and defecation time), the number of patients that received operation, and the number of patients whose clinical course was complicated by systemic and local complications such as MODS or pancreatic infection. The hospital mortality and length of stay were also recorded. We evaluated the gastrointestinal function of the two groups of SAP patients using the modified GIF score upon admission and for the next 3, 7 and 10 d. Patient abdominal pain was recorded daily using a standard visual analog scale (VAS) ranging from 0 ("no pain") to 100 ("unbearable pain")<sup>[22]</sup>.

### Definitions

The following criteria were used to diagnose pancreatic infection: positive bacterial culture of peripancreatic fluid and repeated increases in body temperature<sup>[5,23]</sup>. IAH was defined by a sustained or repeated pathological elevation in IAP  $\geq 12$  mmHg<sup>[21]</sup>. Abdominal compartment syndrome was defined as a sustained IAP  $> 20$  mmHg associated with new organ dysfunction/failure<sup>[21]</sup>. MODS was defined as the dysfunction of two or more organs. Bowel wall thickening was defined as thickness of 3 mm or greater on CECT, and intestinal extension was defined as a dilatation of more than 2.5 cm on CECT<sup>[24,25]</sup>. Enteral feeding started as early as possible, if the patient had no obvious contraindications such as ileus or intestinal bleeding. FI was diagnosed when enteral feeding was unsuccessful and had to be discontinued because of repeated nausea, vomiting, high gastric residual volume,

**Table 2 Patient characteristics upon admission *n* (%)**

	PSB group ( <i>n</i> = 20)	NPSB group ( <i>n</i> = 20)	<i>P</i> value
Age (yr)	43 (34.5-55)	45 (35-60)	0.589
Sex (male: female)	11:9	12:8	0.749
Etiology			
Biliary origin	10 (50)	11 (55)	0.752
Hyperlipidemia	7 (35)	6 (30)	0.736
Alcohol abuse	2 (10)	1 (5)	0.548
Idiopathic	1 (5)	2 (10)	0.548
BMI	24.6 (23.5-26.8)	25.8 (23.9-28.8)	0.158
APACHEII score	9.5 (8.5-11)	10 (8-11.5)	0.994
CRP (mg/L)	203.5 (188-253)	195 (161-247.5)	0.214
Pain $> 77$ mm (VAS)	13	15	0.654

PSB: Perirenal space blocking; NPSB: No perirenal space blocking; BMI: Body mass index; VAS: Visual analogue scale; CRP: C-reactive protein.

abdominal pain or distension, and diarrhea<sup>[19,26,27]</sup>. We counted the frequency of signs for every patient as the number of symptoms of food intolerance.

### Statistical analysis

All the data are presented as median (interquartile range) if not stated otherwise. Categorical variables are expressed as absolute numbers or in percentages, and were analyzed using the  $\chi^2$  test. Continuous variables were compared by the Mann-Whitney *U* test or Wilcoxon signed-rank test, as appropriate. Statistical package for the social sciences (SPSS, version 17.0, Chicago, IL, United States) software was used for statistical analyses. *P*  $< 0.05$  was considered statistically significant.

## RESULTS

### Baseline data of patients

There were no significant differences between the 2 groups with regard to sex distribution, age, body weight, or cause of pancreatitis. The severity of pain, acute physiology and chronic health evaluation APACHE II, and serum CRP did not significantly differ between the two groups. The demographic data and clinical parameters of the patients upon admission are presented in Table 2.

### Effect on pain

During the 72-h study period, pain intensity decreased in both groups. VAS data were depicted as median values (ranges) for the evaluation of pain intensity at specific time points. The median pain decrease (VAS) was significantly greater in the PSB group (-53) than in the NPSB group (-23) at 24 h; -67 than -46 at 48 h; and -76 than -49 at 72 h. Thus, the magnitude of median pain relief was better in the PSB group compared with the NPSB group (Table 3).

### GIF score

During the 10-d study period, modified GIF score decreased in both groups, from 4.56 to 1.00 in the PSB

**Table 3 Pain intensity between two groups**

	Pain severity: Change from baseline ( $\Delta$ VAS)			
	Baseline (VAS)	At 24 h	At 48 h	At 72 h
PSB group ( <i>n</i> = 20)	78	-53	-67	-76
NPSB group ( <i>n</i> = 20)	77	-23	-46	-49
<i>P</i> value	1.000	0.005	0.018	0.025

PSB: Perirenal space blocking; NPSB: No perirenal space blocking; VAS: Visual analogue scale.

**Table 4 Modified gastrointestinal failure score variables between two groups**

	Before PSB performed	Hospital day			
		1 d	3 d	7 d	10 d
PSB group ( <i>n</i> = 20)	4.56	2.6	2.12	1.43	1.000
NPSB group ( <i>n</i> = 20)	4.34	3.98	3.56	2.58	2.13
<i>P</i> value	1.000	0.042	0.025	0.031	0.012

PSB: Perirenal space blocking; NPSB: No perirenal space blocking.

group and from 4.34 to 2.13 in the NPSB group. The median score decrease was initially significantly greater in the PSB group than in the NPSB group ( $P = 0.042$ ) after hospitalization for 24 h (PSB was performed as soon as PSB group patients were admitted). The variance tendency of the modified GIF score in the two groups is presented in Table 4.

### Comparison of outcome variables between the two groups

As presented in Table 5, patients in the PSB group had significantly lower incidences of hospital mortality, MODS, SIRS, pancreatic infection and shorter intensive care unit stay during hospital stay. However, no difference in terms of operation incidence was found between the two groups.

## DISCUSSION

The celiac plexus is a major interchange for autonomic fibers, receiving many of the thoracic splanchnic nerve fibers as they course toward the abdominal organs. Pain associated with pancreatic morbidity is intense and severe, and for many years, the celiac plexus has been a target for pain block treatments<sup>[28]</sup>. The celiac plexus lies in front of the aorta at the level of the celiac trunk<sup>[29]</sup>. It is composed of a dense network of sympathetic nerve fibers that travel in parallel to the anterior surface of the abdominal aorta and the origin of the celiac artery. The celiac plexus transmits neural signals originating from all abdominal viscera and the majority of pelvic viscera, including the pancreas, liver, gallbladder, stomach, renal pelvis, ureter, and intestine proximal to the transverse colon<sup>[30]</sup>.

Both the pancreas and kidney are retroperitoneal organs and are adjacent to each other. In the retroperitoneal

**Table 5 Clinical outcome variables *n* (%)**

	NPSB group	PSB group	<i>P</i> value
	( <i>n</i> = 20)	( <i>n</i> = 20)	
Hospital mortality	6 (30)	1 (5)	0.037
ICU stay (d)	12 (8-21)	9 (5-14)	0.033
Pancreatic infection	8 (40)	2 (10)	0.028
MODS	9 (45)	3 (15)	0.038
SIRS	14 (70)	7 (35)	0.027
Surgical operation	4 (20)	2 (10)	0.376

ICU: Intensive care unit; MODS: Multiple organ dysfunction syndrome; SIRS: Systemic inflammatory response syndrome; PSB: Perirenal space blocking; NPSB: No perirenal space blocking.

space, the left and right kidneys and their adipose capsules are next to the pancreas, celiac artery, and superior mesenteric artery root. Thorntons' findings show that the perirenal spaces communicate with each other across the midline, and with the pelvic extraperitoneal spaces. Clinical implications include the potential flow of perinephric collections into the pelvis or across the midline<sup>[31]</sup>. This means that the celiac ganglion and plexus, including the plexus pancreaticus, and the renal and superior mesenteric plexuses, are located in the gallery of bilateral perirenal spaces. During SAP, an inflammatory exudate containing pancreatic enzymes leaks out from the pancreas and its action of dissolving tissue inevitably stimulates the rich splanchnic ganglia and plexuses around the pancreas, which causes adverse reactions and reflection in the visceral nervous system and a series of pathophysiological disorders in the viscera, including gastrointestinal tract motor dysfunction.

Considering the physiological and anatomical characteristics of the splanchnic nerves and the pancreas, and the pathological characteristics of SAP, the effect of PSB of a visceral nerve in the pancreatic region using 1% lidocaine on SAP treatment was studied.

Nutrition support is important in the adjunctive management of SAP patients. Meta-analysis shows that in patients with acute pancreatitis, total parenteral nutrition significantly increases the risk of infective complications, the likelihood of a surgical intervention (to control pancreatic infection) and the length of hospital stay, compared with enteral nutrition<sup>[32]</sup>. Nevertheless, early enteral nutrition is not usually practiced in SAP patients presenting disturbed gastrointestinal motility<sup>[9]</sup>.

This clinical study investigated the effects of PSB on the gastrointestinal function and on the clinical outcome of SAP patients. We found that PSB could commendably ameliorate gastrointestinal dysfunction or failure during the early stage of SAP. Moreover, PSB administration could improve prognosis and significantly decrease the hospital mortality of SAP patients.

Recent studies have shown that early enteral nutrition led to significantly lower incidences of MODS, SIRS and pancreatic infection, and relieved intestinal dysmotility<sup>[8]</sup>. Gastrointestinal tract motor dysfunction in a pathological state is probably associated with muscular and neural dys-

function. For this reason, some researchers considered using epidural anesthesia therapy, which can shorten the duration of the postoperative intestinal paralysis<sup>[11]</sup>, for the patients with early-stage SAP<sup>[10]</sup>. In fact, the beneficial effect of epidural anesthesia has been attributed to blockade of a sympathetic nerve, which contributes to the recovery of gastrointestinal tract motor function<sup>[33]</sup>. Peridural anesthesia has also been suggested previously, but this may not be applicable in all patients and no rigorous, prospective controlled trials have been able to establish this therapy as a recommended treatment option<sup>[12]</sup>. Epidural anesthesia can selectively block sympathetic nerve fibers which supply the pancreas, but in clinical practice, this technique is difficult to implement because of the different effects of anesthesia in individuals and the different classes of nerve fibers. The risks include total spinal anesthesia, blood circulation disorders, respiratory inhibition, deep venous thrombosis, and bedsore. For the patients with SIRS, this method may lead to fatal complications such as intraspinal hematoma, and intraspinal infection. PSB can prevent these problems because of its common use for different treatments, including acute anuria, paralytic ileus, stomach cramps, bronchial asthma, postoperative abdominal distension, and burn shock. In clinical work, the technique of PSB is common, safe, simple, low-cost, exempt from B ultrasound guidance, and easy to implement in all hospitals. Furthermore, the manual operation is easy to replicate. There are several limitations in this study. Due to the small sample size and the single-center design, our results might be insufficient to reach a definite conclusion. Therefore, the accuracy should be tested further using a larger sample size. Moreover, since this study was not based on a pathophysiological model, the precise mechanisms of PSB in SAP patients should be verified by more basic experiments.

In conclusion, PSB could commendably ameliorate gastrointestinal dysfunction or failure during the early stage of SAP. Moreover, PSB administration could improve prognosis and significantly decrease the hospital mortality of SAP patients. However, the precise mechanisms of PSB for SAP are still not clear, and further studies are required to verify our conclusions.

## COMMENTS

### Background

Severe acute pancreatitis (SAP) has two major clinical stages, early and late. The first (early) stage is characterized by systemic inflammatory response syndrome (SIRS) and lasts for 10 d, whereas the second (late) stage is characterized by infectious complications, which account for most deaths in late-stage SAP patients

### Research frontiers

The paper is for the first time investigated the effects of perirenal space blocking (PSB) on gastrointestinal function in patients with SAP.

### Innovations and breakthroughs

PSB could ameliorate gastrointestinal dysfunction or failure during the early stage of SAP. Moreover, PSB administration could improve prognosis and decrease the mortality of SAP patients.

### Peer review

It is a good study, which showed that PSB was associated with a significant

decrement of pain, hospital mortality, multiple organ dysfunction syndrome, SIRS and pancreatic infection in patients with SAP.

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