Prospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
2019, Vol. 47(12) 6235–6243

DOI: 10.1177/0300060519880760
journals.sagepub.com/home/imr
SAGE

Effect of regional arterial infusion combined with early enteral nutrition on severe acute pancreatitis

Xiaojuan Wang[1], Jinbu Xu[1], Jiguang Li[2], Yajuan Cheng[1], Lu Liu[1] and Zhiqiang Du[1]

Abstract

Objective: To measure the therapeutic effects of regional arterial infusion (RAI) in combination with early enteral nutrition (EEN) in patients with severe acute pancreatitis (SAP).

Methods: A prospective randomized controlled study enrolled patients with SAP. They were randomly divided into a conventional treatment group that served as the control and a combination therapy group that received RAI combined with EEN. The Acute Physiology, Age, Chronic Health Evaluation II (APACHE II) scores, the levels of serum biochemical indices, functional recovery, the incidence of complications and total effectiveness rate were evaluated.

Results: A total of 100 patients were enrolled in the study. The APACHE II scores and the concentrations of blood glucose, serum amylase, white blood cell count, C-reactive protein, tumour necrosis factor-α, interleukin (IL)-6, IL-10 and IL-17 were significantly decreased, while albumin and serum calcium and total effectiveness rate in the combination therapy group were significantly higher than in the conventional treatment group. The combination therapy group had a significantly reduced time to abdominal pain relief, time of first defaecation, hospital stay and incidence of complications compared with the conventional treatment group.

Conclusion: The combination of RAI and EEN improved clinical biochemical indices, reduced the incidence of complications and promoted early recovery in patients with SAP.

Keywords

Early enteral nutrition, regional arterial infusion, severe acute pancreatitis

Date received: 4 July 2019; accepted: 16 September 2019

[1]Intensive Care Unit, the Second People's Hospital of Lianyungang, Lianyungang, Jiangsu Province, China
[2]Intensive Care Unit, the First People's Hospital of Lianyungang, Lianyungang, Jiangsu Province, China

Corresponding author:
Zhiqiang Du, Intensive Care Unit, the Second People's Hospital of Lianyungang, 41 East Hailian Road, Haizhou District, Lianyungang, 222002 Jiangsu Province, China.
Email: zhiqiangdu_12@163.com

Introduction

Acute pancreatitis (AP) is defined as a systemic inflammation of the pancreas that involves both peripancreatic tissues and distant organs. Approximately 20% of patients with AP develop severe AP (SAP), which is characterized by pancreatic necrosis and multiple organ dysfunction syndrome (MODS).[1,2] To the best of our knowledge, the mortality of SAP has two peaks.[3] The first peak is caused by a severe systemic inflammatory reaction in the early stage and subsequent organ function damage, which has been greatly relieved as a result of developments in organ support technology and intensive care in recent years.[4] The second peak is associated with complications caused by pancreatic and peripancreatic necrosis, which remains the leading cause of death for SAP patients.[5] The range and extent of early pancreatic necrosis directly determines the incidence and severity of peripancreatic infection.[6] Therefore, early intervention to alleviate pancreatic necrosis and avoid peripancreatic infection have become the focus of research in recent years.

Regional arterial infusion (RAI) is a drug delivery system,[7] which inhibits pancreatic necrosis by increasing the local concentration of therapeutic drugs in the pancreas; and minimizes side-effects by decreasing the peripheral drug concentration.[8,9] A previous study found that RAI with low-molecular-weight heparin stabilized haemodynamic profiles, improved systemic oxygenation and peripheral perfusion, alleviated histological injury of the pancreas and downregulated the inflammatory response in a porcine model of SAP.[10] RAI combined with lipoxin A4 relieved the severity of SAP in rats.[11] Related clinical reports have also been published. For example, a paediatric study reported that RAI with protease inhibitors and antibiotics was well tolerated and effective among children with SAP even under neutropenia.[12]

Severe acute pancreatitis is a typical septic syndrome caused by intestinal mucosal cell apoptosis, increased intestinal permeability and an intestinal flora imbalance.[13] Enteral nutrition support could improve the nutritional status of patients with SAP, protect intestinal barrier function, reduce intestinal bacterial translocation and regulate the inflammatory response. Early enteral nutrition (EEN) has been recommended for the nutritional management of patients with SAP due to its beneficial effects on improving the survival rate, maintaining the gut barrier, and reducing endotoxin and bacterial translocation and the inflammatory response.[14] Accordingly, this current study hypothesized that a combination of RAI and EEN might accelerate intestinal functional recovery and prevent overall complications in patients with SAP. The aim of the current study was to measure the therapeutic effects of RAI in combination with EEN in patients with SAP.

Patients and methods

Patients

This prospective randomized controlled study enrolled consecutive patients with SAP that were admitted to the Intensive Care Unit, the Second People's Hospital of Lianyungang, Lianyungang, Jiangsu Province, China between January 2016 and December 2018. SAP was defined as acute abdominal pain associated with elevated levels of serum amylase or serum lipase (>5 times upper limit of normal), ultrasound or computed tomography (CT) evidence of acute pancreatitis, an Acute Physiology, Age, Chronic Health Evaluation II (APACHE) II score >8 or

CT severity index (CTSI) score >7 or a C-reactive protein (CRP) level >150 mg/l. All CT examinations were performed on an SCT 4500 scanner (Shimadzu Medical Systems, Tokyo, Japan) and a Hispeed CT/Ispiral scanner (GE Medical Systems, Milwaukee, WI, USA) by two raters with 10 and 16 years of experience in interpreting abdominal CT images, who were blinded to the laboratory data and clinical outcome. The scan scope was set between the level of the roof of the diaphragm and the third lumbar region. Transaxial images of 5–7 mm thickness were obtained over the pancreas, and the rest of the abdomen was scanned in 10 mm sections, with a slice interval of 5–10 mm. Contrast-enhanced scanning was performed with intravenous bolus injection of 100 ml Ultravist 300® (Schering AG, Berlin, Germany) at a rate of 1.5–2.0 ml/s. For the CTSI score, the morphological severity of the pancreatitis was categorized as mild (0–3 points), moderate (4–6 points) or severe (7–10 points). Inclusion criteria were as follows: (i) conformed to diagnostic criteria of SAP; (ii) diagnosed with SAP on clinical CT examination and laboratory findings after admission; (iii) informed consent was obtained. Exclusion criteria were as follows: (i) patients with severe dysfunction of the heart, liver, kidney and other important organs; (ii) patients with diabetes mellitus, hypertension and autoimmune diseases; (iii) patients with a history of drug allergy; (iv) pregnant and lactating women. Patients were randomized using a random number table to either a conventional treatment group that received conventional management or a combination therapy group that received conventional management plus RAI and EEN.

All surgical and clinical procedures were approved by the Ethics Committee of the Second People's Hospital of Lianyungang. Written informed consent was obtained from all study participants.

Study design and methods

After admission, all patients received a comprehensive nursing intervention including oxygen inhalation, antibiotic therapy, pain relief, fluid infusion, blood volume supplementation and acid-base imbalance correction. Patients with SAP complicated with acute respiratory distress syndrome were treated with extracorporeal respiratory support, while patients with pleural effusion were treated with pleural drainage. In addition, decompression therapy was performed on patients with increased abdominal pressure.

Patients in the conventional treatment group just received a comprehensive nursing intervention and served as the control group. For patients in the combination therapy group, under X-ray monitoring, a 5-Fr Cobra catheter (C1; Cook Medical LLC, Bloomington, IN, USA) was inserted in a retrograde direction according to the lesion location as revealed by a CT scan and the tip of the catheter was placed at the celiac artery or splenic artery. After regular application of a heparin seal tube, patients were admitted to the intensive care unit and continuous arterial perfusion of heparin (100 IU/kg) was performed throughout 24 h for 1 week. When abdominal pain and distension had been alleviated, which was usually within 8 h of the RAI being initiated, patients then received continuous enteral nutrition for 12 h via a nasojejunal tube placed 30–40 cm distal to the ligament of Treitz under electronic gastroscopy. Subsequently, the patients were given 300–500 ml of 5% glucose saline. After no adverse reactions such as vomiting and abdominal pain, the enteral nutrition was gradually increased according to the patient's tolerance. The therapeutic effects

were evaluated and were classified as follows: (i) cure, the symptoms had been completely resolved; (ii) effective, symptoms had been partially relieved; and (iii) failure, no change in the symptoms.

Data collection

It is well documented that APACHE II scores are associated with the severity of SAP and its complications and mortality.[15] The APACHE II scores, measured using a Microsoft® APACHE II graded computer program, were recorded. Venous blood samples were taken after a 12-h fast to measure biochemical parameters. The levels of fasting blood glucose (BG), serum amylase (AMY), albumin (ALB), blood calcium, CRP, tumour necrosis factor (TNF)-α, interleukin (IL)-6, IL-10 and IL-17 were all measured using the following colorimetric and enzyme-linked immunosorbent assay (ELISA) kits from Abcam, Cambridge, UK: Glucose Assay Kit (ab65333), Amylase Assay Kit (ab102523), Human Albumin ELISA Kit (ab179887), Calcium Assay Kit (ab102505), Human C Reactive Protein ELISA Kit (ab99995), Human TNF Alpha ELISA Kit (ab181421), Human IL-6 ELISA Kit (ab178013), Human IL-10 ELISA Kit (ab46034) and Human IL-17 ELISA Kit (ab119535) according to the manufacturer's instructions. The total white blood cell (WBC) count was measured using an automatic haematology analyser (Sysmex XT-2000i; Sysmex Corporation, Kobe, Japan) according to the manufacturer's instructions. Observed indices also included the time it took to achieve relief of abdominalgia, time of first defaecation, hospitalization time, complications and the cure rate.

Statistical analyses

All the statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). Continuous data are presented as mean ± SD if normally distributed and median if not normally distributed; and compared using two-sided Student's *t*-test. Categorical data are presented as *n* of patients (%) and compared using χ^2-test. A *P*-value < 0.05 was considered statistically significant.

Results

This prospective randomized controlled study enrolled 100 patients with SAP that were randomly assigned to either a conventional treatment group (27 males and 23 females) with a mean ± SD age of 43.3 ± 7.1 years (range, 21–61 years) or a combination therapy group (28 males and 22 females) with a mean ± SD age of 44.0 ± 7.4 years (range, 22–60 years). At hospital admission, there was no significant difference in the APACHE II score between the two groups (Table 1). The APACHE II scores in both groups were significantly

Table 1. Comparison of APAHCE II scores before and after treatment in patients ($n = 100$) with severe acute pancreatitis enrolled in a prospective randomized study to evaluate the efficacy of regional arterial infusion in combination with early enteral nutrition compared with conventional treatment.

Time-point	Conventional treatment group $n = 50$	Combination therapy group $n = 50$
Before treatment	12.6 ± 1.9	12.5 ± 1.8
After treatment, 3 days	9.8 ± 1.1[a]	8.7 ± 1.0[a,c]
After treatment, 7 days	7.8 ± 0.9[a,b]	5.4 ± 0.8[a,b,c]

Data presented as mean ± SD.
[a]$P < 0.05$ versus before treatment; [b]$P < 0.05$ versus after treatment (day 3); [c]$P < 0.05$ versus conventional treatment group; two-sided Student's *t*-test.
APACHE II, Acute Physiology; Age, Chronic Health Evaluation II.

lower on days 3 and 7 after treatment compared with before treatment ($P < 0.05$ for all comparisons); and the scores were significantly lower on day 7 compared with day 3 in both groups ($P < 0.05$ for both comparisons). Patients in the combination therapy group had significantly lower APACHE II scores on both days 3 and 7 after treatment compared with patients in the conventional treatment group ($P < 0.05$ for both comparisons).

The effects of the two treatments on biochemical and prognostic indices are shown in Table 2. Patients in both groups had significantly lower levels of BG, AMY, WBC, CRP, TNF-α, IL-10, IL-6 and IL-17 after treatment compared with before treatment ($P < 0.05$ for all comparisons). The same factors were significantly lower in the combination therapy group compared with the conventional treatment group after treatment ($P < 0.05$ for all comparisons). Higher ALB and serum calcium levels were observed in both groups after treatment compared with before treatment ($P < 0.05$ for all comparisons except serum calcium in the conventional treatment group). Patients in the combination therapy group had significantly higher levels of ALB and serum calcium compared with the conventional treatment group after treatment ($P < 0.05$ for both comparisons).

As shown in Table 3, the time taken to achieve abdominal pain relief, the time of first defaecation and the duration of hospital stay experienced by patients in the combination therapy group were significantly shorter than those in the conventional treatment group ($P < 0.05$ for all comparisons).

Complications occurred in 14 patients (28.0%) in the conventional treatment group and five patients (10.0%) in the combination therapy group (Table 4).

In terms of therapeutic efficacy of the conventional treatment, nine patients (18.0%) were cured, 21 patients (42.0%) experienced effective treatment and 20 patients (40.0%) experienced treatment failure; giving a total effective rate of 60.0%. In the combination therapy group, 20 patients

Table 2. Comparison of biochemical and prognostic indices before and after treatment in patients ($n = 100$) with severe acute pancreatitis enrolled in a prospective randomized study to evaluate the efficacy of regional arterial infusion in combination with early enteral nutrition compared with conventional treatment.

	Conventional treatment group $n = 50$		Combination therapy group $n = 50$	
Variables	Before treatment	After treatment	Before treatment	After treatment
BG, mmol/l	15.6 ± 0.7	9.4 ± 0.5^{a}	15.6 ± 0.6	$6.1 \pm 0.6^{a,b}$
AMY, U/l	1251.4 ± 245.4	405.2 ± 50.1^{a}	1260.1 ± 237.1	$194.3 \pm 35.1^{a,b}$
ALB, g/l	23.7 ± 1.9	30.4 ± 2.5^{a}	23.5 ± 1.8	$35.5 \pm 2.95^{a,b}$
Serum calcium, mmol/l	1.7 ± 0.1	2.0 ± 0.2	1.6 ± 0.2	$2.3 \pm 0.2^{a,b}$
WBC, $\times 10^9$/l	23.1 ± 5.5	17.4 ± 3.5^{a}	23.7 ± 5.6	$11.1 \pm 2.1^{a,b}$
CRP, g/l	208.9 ± 25.6	143.2 ± 17.1^{a}	208.4 ± 23.2	$80.7 \pm 9.51^{a,b}$
IL-10, ng/l	160.1 ± 22.5	109.8 ± 33.1^{a}	165.4 ± 23.5	$88.2 \pm 28.4^{a,b}$
TNF-α, ng/l	602.2 ± 95.4	344.4 ± 24.1^{a}	610.3 ± 97.4	$284.1 \pm 22.4^{a,b}$
IL-6, pg/ml	18.6 ± 2.4	8.6 ± 1.8^{a}	19.1 ± 2.2	$6.8 \pm 1.5^{a,b}$
IL-17, ng/l	250.2 ± 15.4	140.2 ± 10.8^{a}	253.4 ± 15.1	$90.4 \pm 9.5^{a,b}$

Data presented as mean ± SD.

[a]$P < 0.05$ versus before treatment; [b]$P < 0.05$ versus conventional treatment group; two-sided Student's *t*-test.

BG, blood glucose; AMY, amylase; ALB, albumin; WBC, white blood cell count; CRP, C-reactive protein; IL, interleukin; TNF, tumour necrosis factor.

Table 3. Comparisons of functional recovery in patients ($n = 100$) with severe acute pancreatitis enrolled in a prospective randomized study to evaluate the efficacy of regional arterial infusion in combination with early enteral nutrition compared with conventional treatment.

Variable	Conventional treatment group $n = 50$	Combination therapy group $n = 50$
Abdominal pain relief time, days	4.2 ± 0.5	2.4 ± 0.4[a]
Time of first defaecation, days	5.5 ± 1.2	4.1 ± 1.0[a]
Duration of hospital stay, days	33.2 ± 3.8	18.4 ± 3.17[a]

Data presented as mean ± SD.
[a]$P < 0.05$ versus conventional treatment group; two-sided Student's *t*-test.

Table 4. Comparison of the overall complications in patients ($n = 100$) with severe acute pancreatitis enrolled in a prospective randomized study to evaluate the efficacy of regional arterial infusion in combination with early enteral nutrition compared with conventional treatment.

Group	*n*	Infection	UGIB	MODS	Total complications
Conventional treatment	50	6 (12.0)	5 (10.0)	3 (6.0)	14 (28.0)
Combination therapy	50	2 (4.0)	2 (4.0)	1 (2.0)	5 (10.0)

Data presented as *n* of patients (%).
UGIB, upper gastrointestinal haemorrhage; MODS, multiple organ dysfunction syndrome.

Table 5. Comparison of clinical therapeutic efficacy in patients ($n = 100$) with severe acute pancreatitis enrolled in a prospective randomized study to evaluate the efficacy of regional arterial infusion in combination with early enteral nutrition compared with conventional treatment.

Group	*n*	Cure	Effective	Failure	Total effective rate
Conventional treatment	50	9 (18.0)	21 (42.0)	20 (40.0)	30 (60.0)
Combination therapy	50	20 (40.0)[a]	26 (52.0)[a]	4 (8.0)[a]	46 (92.0)[a]

Data presented as *n* of patients (%).
[a]$P < 0.05$ versus conventional treatment group; χ^2-test.

(40.0%) were cured, 26 patients (52.0%) experienced effective treatment and four patients (8.0%) experienced treatment failure; giving a total effective rate of 92.0% (Table 5) ($P < 0.05$).

Discussion

Severe acute pancreatitis is an acute abdominal disease with a rapid onset and serious complications.[16] Diffuse necrosis and haemorrhage of the pancreas caused by excessive activation of trypsin can in turn release a variety of bioactive substances that can trigger the activation of mononuclear macrophages, which produce a variety of cytokines and inflammatory mediators, leading to shock, acute renal insufficiency, acute respiratory distress syndrome and other complications.[17] Systemic inflammatory response syndrome induced by an excessive inflammatory response is

the main cause of acute exacerbation of SAP.[18] Inflammatory mediators in the early stage can further trigger a proinflammatory cytokine cascade, thus resulting in MODS. Inflammatory factors also involve intestinal tissues, which cause damage to the intestinal mucosal barrier and intestinal bacterial translocation, which can produce a large amount of endotoxin, leading to the deterioration characteristic of SAP.[19] Thus, effective clearance of inflammatory mediators is the key to the early treatment of SAP.[20] The prognosis of SAP is dependent on the severity of the secondary infection.[21]

It is generally known that profound hypoperfusion of injured pancreatic tissues secondary to impaired microcirculation or vasospasm usually occurs in patients with SAP,[19] making it difficult to attain an effective concentration of intravenous medication. Facing these challenges when treating SAP, RAI might be an optimal method of drug administration.[10,22] The therapeutic efficacy of RAI has been previously reported.[23] A previous study demonstrated that RAI administration of fluorouracil and octreotide, alone or in combination, decreased the injury score in a canine model of SAP.[24] A meta-analysis involving 390 cases demonstrated that RAI using in patients with SAP alleviated abdominal pain, decreased the incidence of complications and mortality, shortened the duration of hospital stay and increased the curative rate compared with the intravenous infusion route.[25]

The advantages of EEN in SAP have been well documented. For example, a randomized controlled trial demonstrated that the combination of EEN and rhubarb significantly protected gastrointestinal function and mitigated disease-related damage of the liver and kidneys in patients with SAP.[26] In a meta-analysis, EEN within 48 h was superior to delayed enteral nutrition beyond 48 h for patients with SAP.[27] This current randomized controlled study demonstrated that a combination of RAI and EEN significantly reduced the APACHE II scores, BG, WBC, AMY, CRP, TNF-α, IL-10, IL-6 and IL-17, but increased the levels of ALB and serum calcium, compared with the conventional treatment group after treatment. Furthermore, patients receiving RAI and EEN had a significantly faster recovery in terms of abdominal pain and a shorter hospital stay compared with the conventional treatment group. Patients that received RAI and EEN has a significantly reduced overall complication rate and higher efficacy rate.

In conclusion, RAI combined with EEN during comprehensive community-based interventions for patients with SAP significantly improved gastrointestinal function and reduced the disease severity, systemic inflammation and overall complication rate.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Zhiqiang Du https://orcid.org/0000-0003-2380-3087

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