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Original Article

The clinical significance of early liquid resuscitation with hypertonic saline for regulation of the inflammatory response in patients with acute pancreatitis

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Abstract: Objective: To study the clinical significance of early liquid resuscitation with hypertonic saline (HS) for the regulation of the inflammatory response in patients with acute pancreatitis (AP). Methods: A total of 115 patients receiving treatment for AP in Peking University Shenzhen Hospital from March 2015 to August 2017 were selected and divided into groups according to the fluid resuscitation method: 56 patients in the control group were treated with early fluid resuscitation with Ringer's Solution. On the basis of Ringer's Solution, 59 patients in the observation group were treated with early fluid resuscitation with HS. Changes in the levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10), as well as the clinical therapeutic effect on both groups were analyzed. Results: After treatment, the levels of TNF-α, IL-6, and high-sensitivity C-reactive protein (hs-CRP) in the observation group were lower than those in the control group, while the level of IL-10 was significantly higher in the observation group compared to the control group (all $P<0.05$). Post-treatment procalcitonin and D-lactic acid levels in the observation group were 2.27±0.51 ng/mL and 5.59±1.43 mg/L, respectively, which were both significantly lower than that in the control group (both $P<0.05$). The total effective rate and the incidence of complications in the observation group were higher than those in the control group (both $P<0.05$). Conclusion: Early liquid resuscitation of HS can regulate the secretion of inflammatory cytokines in patients with AP and reduce complications, and therefore has good value for application.

Keywords: Hypertonic saline, fluid resuscitation, acute pancreatitis, Ringer's Solution

Introduction

Acute pancreatitis (AP) is a kind of the digestive system emergency characterized by pancreatic edema and systemic inflammation. Patients with severe AP may develop pancreatic cyst that lead to functional instability in other vital organs [1]. Although the exact mechanism of AP is still unknown, it is hypothesized that pancreatic cell lysis, brought about by various physical and chemical stimuli, leads to the abnormal activation of pancreatic enzymes which then destroys the pancreas and surrounding tissues. In addition, abnormal pancreatic function can also stimulate the release of inflammatory cytokines from immunocytes (such as lymphocytes, macrophages, etc.) and induce immune dysfunction [2, 3]. Elevation in the levels of serum inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6) in AP patients will lead to the occurrence of multiple organ dysfunction syndrome (MODS) in AP patients [4]. A clinical study has shown that fluid resuscitation with hypertonic saline (HS) can effectively improve the intravascular osmotic pressure, expand the patient's blood volume, improve intestinal mucosa barrier function, and reduce the extent of AP [5]. Early fluid resuscitation is an important measure during the acute reaction period therapy of AP patients. It can effectively stabilize the internal environment of patients and inhibit the formation of microthrombus in the pancreatic tissue. However, there are still some drawbacks in resuscitating with HS alone, such as tissue edema, decreased plasma colloid osmotic pressure, or increased liquid leakage [6]. The purpose of this study was to investigate the clinical effect of HS solu-

tion supplemented with liquid Ringer's Solution in the treatment of AP.

Materials and methods

General data

This study was approved by the Ethics Committee of Peking University Shenzhen Hospital. A total of 115 patients with AP were treated in Peking University Shenzhen Hospital from March 2015 to August 2017, of which 68 were male and 47 were female. The age of the patients ranged between 23-58 years, and the average age was 43.62±5.23 years. Of the 115 patients, 73 were had biliogenic AP, 18 had alcoholic AP, 17 had hyperlipidemic AP, and 7 had AP of unknown etiology. The patients were divided into the control group (n=56) that were resuscitated with Ringer's Solution, and the observation group (n=59) that were resuscitated early with HS supplemented with Ringer's solution.

Inclusion criteria: (1) First onset of AP without any prior treatment; (2) Patients confirmed clinical symptoms of AP including bellyache, elevated serum pancreatic enzymes, imaging changes in pancreas etc. [7]; (3) Patients without any mental illness; (4) Patients or their family members signed informed consent from.

Exclusion criteria: (1) Patients with infectious diseases associated with other causes; (2) Failure of vital organs (e.g. liver and kidney); (3) Patients with malignant tumors or other serious diseases.

Therapeutic methods

In case the AP patients had abdominal compartment syndrome, catheter induced gastrointestinal decompression was performed to reduce the intra-abdominal pressure below 10 cm H_2O, followed by the administration of analgesics and muscle relaxants. The resuscitation liquid containing bicarbonate was given to the patients by intravenous infusion to regulate the acid-base balance in the body and maintain the blood pH at 7.35-7.45. In patients with pancreatic fistula, somatostatin was given to inhibit pancreatic secretion so that the amylopsin concentration in the pancreatic duct drainage fluid was lower than 3 times the normal serum amylase level. Patients in the control group received intravenous infusion of Ringer's Solution 20 mL/(kg*h) at the beginning of resuscitation and their cardiac stroke volume was monitored. A 12-15% increase in cardiac stroke volume compared to pre-resuscitation values indicated relatively good (8 h/time) fluid reactivity, following which another infusion of Ringer's solution (3 mL/(kg*h)) was given. In the absence of liquid reactivity, Ringer's Solution of 20 mL/(kg*h) was given continuously. At the same time, the following indices were targeted during resuscitation to reach the resuscitation standard: (1) central venous pressure at 8-12 mmHg, (2) heart rate less than 120 beats/min, (3) specific volume of red blood cells between 30-35%, and (4) serum lactate level less than 2 mmol/L [8]. Liquid resuscitation ended after 24 hours or whenever the indices met the resuscitation standard (2 or more standards). In the observation group, the initial resuscitation was performed with 7.5% sodium chloride injection (4 mL/kg) within 30 minutes, followed by resuscitation with Ringer's Solution, steps and resuscitation indicators were followed by the control group.

Observation indices and evaluation of therapeutic effect

Venous blood samples (6 mL) were collected on the fourth and eighth day after treatment. After EDTA anticoagulation, the serum was collected by centrifugation at 320 g for 10min at 4°C and stored at 4°C. The 96-well plates were soaked and prepared according to the instructions provided in the ELISA kit (Shanghai Hengyuan Biotechnology Co., Ltd.). The serum samples were diluted to 1:100, 50 μL was loaded per well and the plates were incubated at 37°C for 30 minutes. After washing with PBS, 100 μL of substrate solution was added to each well and the reaction was carried out at 37°C for 30 minutes. The OD values were read with a Thermo microplate reader at 450 nm after adding 100 μL stop solution to each well. Each sample was tested in triplicate and standard curves were plotted to calculate the concentrations of tumor necrosis factor-α (TNF-α), high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), procalcitonin, and D-lactic acid. The first four are inflammatory cytokines and the latter two are markers for intestinal mucosal barrier function. Secondary observations included pulse, blood pressure,

Table 1. Comparison of two groups of general data

Variable	Control group (n=56)	Observation group (n=59)	t/χ^2	P
Age	41.23±7.34	45.16±6.54	3.246	0.084
Gender (male/female)	37/19	31/28	2.524	0.096
Type of AP			3.428	0.073
Biliary AP	35	38		
Alcoholic AP	10	8		
Hyperlipidemia AP	7	10		
Other AP	4	3		

Note: AP, acute pancreatitis.

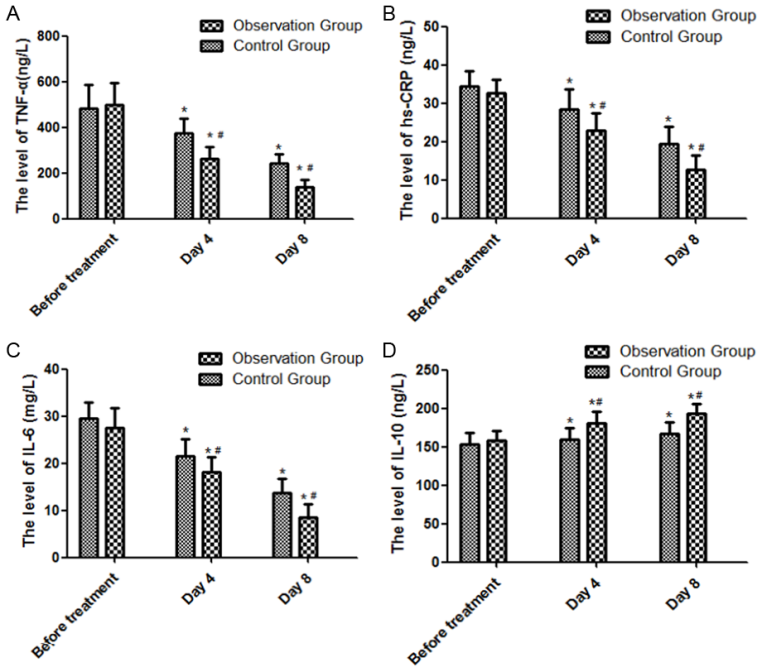

Figure 1. Analysis of post-treatment changes in the levels of TNF-α (A), hs-CRP (B), IL-6 (C), and IL-10 (D) in the two groups. Compared to pre-treatment data, *P<0.05; compared to day 4 data, #P<0.05. TNF-α, tumor necrosis factor-α; hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10.

and blood gas analysis during treatment. Criteria for remarkable effect included cessation in bellyache, vomiting, and other symptoms, and normalization of serum amylase levels. The criteria for effect were remission in bellyache, vomiting, and other symptoms, and improvement in serum amylase levels. The criteria for inefficacy were no improvement in bellyache, vomiting, and other symptoms, and abnormal serum amylase levels. The total effective rate was calculated as: (number of remarkable effect + number of effect)/total patient number * 100%. Finally, the incidence of complications like drop in lymphocyte counts, systemic inflammatory response syndrome (SIRS), pancreatic and peri-pancreatic infections, and MODS were also recorded in both groups [9].

Statistical methods

SPSS19.0 was used to analyze the data, and measurement data are expressed as mean ± standard deviation. The comparison between two groups of data was performed in accordance with normal distribution and analyzed by t test and expressed as t. The count data were analyzed by χ^2 test and Fisher exact probability method, and expressed by χ^2. A *P* value of 0.05 is set as the test standard.

Results

General data comparison

There were no significant differences between the two groups in terms of general demographic data (including age, gender and type of acute pancreatitis, all P>0.05) as shown in **Table 1**.

Changes in the levels of different inflammatory cytokines in the control and observation groups

No significant differences in TNF-α, IL-6, hs-CRP, and IL-10 levels were seen between the two groups prior to treatment (all P>0.05). Following treatment, the serum levels of TNF-α, IL-6, and hs-CRP decreased significantly in both groups (t=5.334, t=6.427, t=6.362, all P<0.05). The observation group had significantly lower levels of TNF-α, IL-6 and hs-CRP (t=6.273, t=5.841, t=7.348, all P<0.05) and significantly higher levels of IL-10 (t=5.638, P<0.05) compared to the control group on the fourth and eighth day after treatment (**Figure 1**).

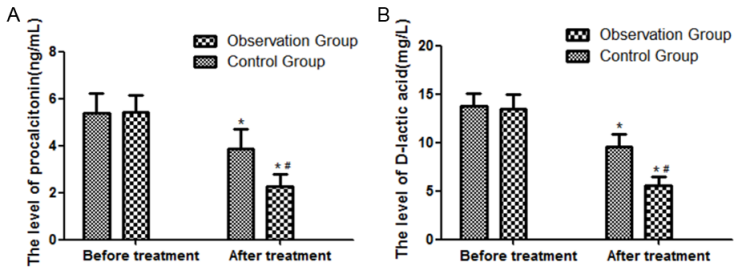

Figure 2. Changes in the levels of pro-calcitonin (A) and D-lactic acid (B) levels in the two groups after treatment. Compared to pre-treatment data, *P<0.05; after treatment compared to control group, #P<0.05.

Table 2. Comparison of the curative effect of the treatment on the two groups (n, %)

Variables	Control group (n=56)	Observation group (n=59)	χ^2	P
Remarkably effective	22 (39.28)	34 (57.63)	6.452	0.023
Effective	24 (42.86)	19 (32.20)	5.283	0.031
Ineffective	10 (17.86)	6 (10.17)	5.257	0.035
Total effectivity rate	46 (82.14)	53 (89.83)	6.248	0.028

Comparison of the intestinal mucosa barrier function between the two groups

There were no significant differences in the levels of pro-calcitonin and D-lactic acid between the two groups prior to treatment (both P>0.05). Both the procalcitonin (2.27±0.51 ng/mL) and D-lactic acid (5.59±1.43 mg/L) levels in the observation group were significantly lower compared to the control group (t=6.264, P<0.05; t=6.372, P<0.05, respectively) after treatment (**Figure 2**).

Comparison of the curative effect of the treatment on the two groups

After treatment, the number of patients who scored as "remarkably effective" and "effective" in the observation group were 34 and 19 respectively, and the total effectivity rate of 89.83% was significantly higher than that in the control group (P<0.05), as shown in **Table 2**.

Analysis of adverse reaction symptoms in the two treatment groups

The incidence of drop in lymphocyte counts, MODS, SIRS, and pancreatic and peri-pancreatic infections was significantly lower in the observation group compared to the control group (all P<0.05, **Table 3**).

Discussion

AP is the result of abnormal pancreatic enzymes activity induced by external stimulation of the pancreas, which leads to edema and necrosis of the pancreatic tissue. The main clinical symptoms are bellyache, vomiting, inflammatory infection, and shock. If the progression of AP is not controlled in time, it can be fatal for the patient [10]. At present, clinical treatment of AP involves improving blood vessel microcirculation, preventing shock, and administering anti-infective agents [11]. Hypertonic saline has been widely used in treating traumatic brain injury, hemorrhagic shock and sepsis with good results [12]. A study has shown that HS can increase peripheral tissue perfusion and reduce inflammatory response, inhibit toxic reactions of macrophages and neutrophils, and thus reduce the tissue injury caused by inflammation [13]. Since abnormal pancreatic function can lead to the release of proinflammatory cytokines such as TNF-α, IL-6, and IL-8, an imbalance of anti-inflammatory/pro-inflammatory responses is seen in AP which further aggravates its clinical symptoms [14]. IL-10 has been shown to antagonize these inflammatory cytokines in vivo and alleviate the degree of inflammatory response [15]. In this study, we found that the serum levels of TNF-α, IL-6, and hs-CRP in the observation group on the fourth and eighth day after treatment were lower than that in control group (all P<0.05). Meanwhile, the level of IL-10 was higher in the observation group compared to the control group (P<0.05), indicating that early liquid resuscitation with HS could effectively lower the degree of inflammation. Stimac et al. found that after HS increasing the osmotic pressure of the blood, it could significantly reduce the swelling of endothelial cells of blood vessels and alveoli, enhance capillary microcirculation, and decrease the levels of pro-inflammatory cytokines like IL-6 and IL-8, all of which were in agreement with the results of the present study [16].

At present, some clinical studies have found that AP can induce an intestinal microcircula-

Table 3. Comparison of adverse reaction symptoms between the two groups (n, %)

Variables	Drop in lymphocyte counts	MODS	SIRS	Pancreatic and peripancreatic infection
Control group (n=56)	24 (42.86)	18 (32.14)	29 (51.78)	37 (66.07)
Observation group (n=59)	16 (27.12)	13 (22.03)	17 (28.81)	21 (35.59)
χ^2	5.835	6.245	7.594	6.284
P	0.042	0.034	0.021	0.026

Note: MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammatory response syndrome.

tion disorder in addition to the inflammatory response, which can damage the intestinal mucosa barrier function, stimulate the release of procalcitonin, and D-lactic acid and lead to intestinal endotoxemia, all of which further aggravate the clinical symptoms of AP [17]. We found that the levels of procalcitonin and D-lactic acid in the observation group was lower than that in the control group, suggesting that the early liquid resuscitation with HS was also more beneficial to the intestinal mucosa shielding function of the patients. After early liquid resuscitation with HS, the total effectivity rate in the observation group was significantly higher than that in the control group, and adverse reactions such as lymphocytic decline, MODS, SIRS, pancreatic, and peri-pancreatic infections etc. were significantly reduced in the observation group. This might be the result of improvement in the balance of anti-inflammatory/pro-inflammatory responses by early liquid resuscitation with HS [18, 19]. Branquinho et al. showed that early liquid resuscitation with HS could significantly improve hemodynamics, alleviate the pancreatic ischemia caused by microcirculation, and improve the clinical symptoms of AP [20]. Since the relatively small sample size of this study can certainly influence the results, it is necessary to validate these results on a larger cohort in a multi-center study.

In conclusion, HS can effectively reduce the inflammatory response in AP patients, improve the intestinal mucosa barrier function, and reduce the incidence of complications, thereby proving its value in clinical applications.

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Disclosure of conflict of interest

None.

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