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# Effects of nitroglycerin combined with continuous regional arterial infusion on severe acute pancreatitis, triglyceride, inflammatory factors and prognosis

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## Abstract

***Background**: To evaluate the effects of nitroglycerin combined with continuous regional arterial infusion (CRAI) on severe acute pancreatitis (SAP), triglyceride (TG), inflammatory factors and prognosis.* ***Methods**: SAP patients were randomly divided into control and observation groups (n=169). The control group was treated with intravenous infusion of nitroglycerin once daily for 2 d, while the observation group was treated with nitroglycerin combined with CRAI for 7 d. Their hospitalization time, abdominal pain relief time, abdominal distension relief time and intestinal function recovery time were recorded. The levels of inflammatory factors, and TG were measured. Their liver and kidney functions, hemorheological indices, prognosis, and adverse reactions were evaluated.* ***Results**: The observation group had significantly shorter hospitalization time, abdominal pain relief time, abdominal distension relief time, and intestinal function recovery time than those of the control group (P<0.05). After treatment, the levels of interleukin-6, tumor necrosis factor-alpha, endothelin, thromboxane A2 and TG significantly decreased in contrast with those before treatment in both groups, especially in the observation group (P<0.05). The hemorheological indices were significantly improved after treatment compared with those before treatment in both groups, and the observation group had better indices (P<0.05). The Acute Physiology and Chronic Health Evaluation-II score declined significantly in both groups after treatment, and the observation group had a more obvious decrease (P<0.05). During follow-up, similar incidence rates of adverse reactions were observed for both groups (P>0.05).* ***Conclusion**: Nitroglycerin combined with CRAI is prominently effective for treating SAP, which can facilitate the health recovery and reduce the incidence of microcirculation disturbance-induced adverse events such as organ failure.*

***Keywords**: nitroglycerin, continuous regional arterial infusion, severe acute pancreatitis, inflammatory factor*

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## Introduction

Severe acute pancreatitis (SAP), as a critical digestive system disease, accounts for 5-10% of acute pancreatitis cases, and its condition is severe. The fatality rate of SAP is up to 36-50%, and it leads to many complications. It can cause multiple organ dysfunction syndrome in the early stage, and has a higher fatality rate when combined with infection in the later stage (1). The major clinical symptoms of SAP include persistent severe pain in the upper abdomen, which is often accompanied by discomfort, such as radiating pain in the lower back, abdominal distension and nausea and vomiting. Its main clinical signs include peritoneal irritation sign, ascites, periumbilical subcutaneous ecchymosis (Cullen's sign) and lumbar costal subcutaneous ecchymosis (Grey-Turner's sign). The treatment of SAP has always been a difficult problem and a research hotspot for clinicians in recent years. Currently, it is commonly accepted that SAP treatment has changed from early surgical treatment to early non-surgical combined medical treatment (2). In recent years, the pathological changes and therapeutic significance of nitroglycerin in pancreatitis have attracted widespread attention. Nitroglycerin can directly relax vascular smooth muscles, especially the smooth muscle of small blood vessels, thus dilating blood vessels and improving the microcirculation. In addition, nitroglycerin interacts with intracellular sulfhydryl to release nitric oxide (NO). NO, as endothelial relaxing factor, activates guanylate cyclase to transform into cyclic guanosine monophosphate (cGMP), which increases cGMP in smooth muscles and other tissues, thereby causing dephosphorylation of myosin light chain, regulating the contractile state of smooth muscles, relaxing smooth muscles, and dilating blood vessels (3). Nitroglycerin dilates the arteriovenous bed mainly for dilating veins. Peripheral vein dilatation induces blood retention in the periphery, leading to decreases in returned blood volume and left ventricular preload. Dilation of the artery leads to reduced peripheral resistance (afterload). After arteriovenous dilatation, the microcirculation is ameliorated, which reduces myocardial oxygen consumption (4). Continuous regional arterial infusion (CRAI) is a non-surgical treatment approach recently developed with interventional radiology. As a synergistic non-surgical method for treating SAP, CRAI has been widely utilized due to advantages such as special administration route, abilities to relieve the clinical symptoms of SAP patients more quickly and to reduce the patients' pain, and low treatment cost (5). In this study, nitroglycerin was combined with CRAI in the treatment of SAP, aiming to render a new idea in clinical practice.

## Materials and methods

The prospective, randomized controlled clinical trial received approvals from the medical ethics committee of Zhuji People' Hospital. The study was implemented from January 2018 to May 2020. This study was accomplished as per the Declaration of Helsinki.

### *General data*

Two hundred and thirty-eight SAP patients undergoing treatment from January 2018 to May 2020 were prospectively enrolled as subjects and assigned into control and observation groups (n=169) using a random number table. The patients (120 males and 49 females) in the control group were 20-62 years old, with (44.7±5.8) years old on average. The causes of disease included overeating (n=89), biliary SAP (n=50) and alcoholic SAP (n=30), and their Acute Physiology and Chronic Health Evaluation (APACHE)-II score was (13.6±2.1) points. The patients (118 males and 51 females) in the observation group were 20-63 years old and had a mean age of (44.8±5.5) years old. The causes

of disease included overeating (n=86), biliary SAP (n=52) and alcoholic SAP (n=31), and their APACHE-II score was (13.7±2.2) points. The gender, age, causes of disease and APACHE-II score of the control group were not significantly different from those of the observation group (P>0.05).

***Therapeutic methods***

After admission, the patients were diagnosed as SAP based on corresponding examinations, and they were given combined treatments such as fasting and water deprivation, gastrointestinal decompression, acid suppression, anti-infection and correction of water-electrolyte and acid-base balances. The cases with respiratory failure were given mechanical ventilation, and a nasal oxygen tube was placed within 24-48 h after admission. The patients were treated with bowel cleansing and enteral nutrition according to the severity of their condition. The control group was treated with nitroglycerin (NMPN: H20058649, specification: 1 mL: 5 mg). Specifically, 5 mg of nitroglycerin was dissolved in 500 mL of saline, which was intravenously infused into patients at 24 h/d for 2 d. The observation group was treated with CRAI within 4 h after diagnosis. The specific procedures were as follows: The catheter was introduced through the femoral artery by using the Seldinger technique under X-ray or CT, and the proper catheter was selected according to the inflammation and necrosis of the pancreas. The catheter was introduced in the gastroduodenal artery in case that the head of the pancreas was affected, and introduced in the splenic artery in case that the tail of the pancreas was affected. In case of extensive lesions affecting the whole pancreas, the catheter was introduced in the abdominal trunk or in the superior mesenteric artery when necessary. After successful catheterization, the catheter was fixed at the puncture site, and an infusion pump was used for pressurized drug delivery at the micro-end of the catheter, which was generally retained for 5-7 d. The arterial pumping rate was controlled at 20-50 mL/h and 24 h/d, and the dose was the same as that for the control group. After treatment, a 3-month follow-up was carried out for all patients.

***Observation indices***

The hospitalization time, abdominal pain relief time, abdominal distension relief time, and intestinal function recovery time were recorded in both groups. The inflammatory factors and serum triglyceride (TG) were measured before, as well as after treatment. Specifically, the peripheral venous blood (3 mL) was centrifuged, and then the supernatant was collected for the determination of serum amylase (AMS) according to the kit's instructions (Beijing Zhongxi Huada Technology Co., Ltd., China) using AU2700 chemistry analyzer (Olympus, Japan). Serum interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α) and endothelin (ET) were tested by radioimmunoassay using corresponding kits (Shanghai YS Industrial Co., Ltd., China) with HBS-1096A microplate reader (Shanghai Tianshi Scientific Instrument Co., Ltd., China). Thromboxane A2 ($TXA_2$) was determined by ELISA according to the kit's instructions (Shanghai Hengyuan Biochemical Reagent Co., Ltd., China), and TG was measured with AU2700 chemistry analyzer (Olympus, Japan). As for hemorheological indices, the whole blood high-shear reduction viscosity, hematocrit, erythrocyte aggregation index (EAI) and erythrocyte sedimentation rate (ESR) were determined using a semi-automatic blood rheometer (SA-5000, Beijing Succeeder, China). The incidence rates of adverse reactions such as fever, headache, and gastrointestinal reaction were recorded during treatment and follow-up. The APACHE-II score was adopted for evaluating the prognosis (6), with a total score of 0-71 points. A higher score is predictive for a worse prognosis.

***Statistical analysis***

SPSS 23.0 software was utilized for data analysis. All measurement data were confirmed normally distributed with the Kolmogorov-Smirnov test. The measurement data expressed as mean ± standard deviation were compared between groups through the *t*-test, whereas the numerical data expressed as percentage were subjected to the $\chi^2$ test for comparisons between groups. P<0.05 bespoke a statistically significant difference.

## Results

***Treatment-related information***

The observation group had significantly shorter hospitalization time, abdominal pain relief time, abdominal distension relief time, and intestinal function recovery time than those of the control group (P<0.05) (**Table 1**).

***TG levels before and after treatment***

The level of TG had no significant difference between the two groups before treatment (P>0.05), while it significantly declined in both groups and was significantly lower in the observation group than that in the control group after treatment (P<0.05) (**Table 2**).

***Inflammatory factors before and after treatment***

Before treatment, the serum inflammatory factors IL-6, TNF-α, ET and $TXA_2$ had no statistically significant differences between the two groups (P>0.05). After treatment, the levels of IL-6, TNF-α, ET and $TXA_2$ dropped significantly in both groups, and the observation group had more obvious decreases (P<0.05) (**Table 3**).

***Hemorheological indices before and after treatment t***

Before treatment, no statistically significant differences were detected in the whole blood high-shear reduction viscosity, hematocrit, EAI and ESR between the two groups (P>0.05). After treatment, significantly inferior whole blood high-shear reduction viscosity, hematocrit, EAI and ESR were found in both groups, with the observation group having more inferior indices (P<0.05) (**Table 4**).

***Prognosis of patients***

The APACHE-II score exhibited a significant difference between the two groups before treatment (P>0.05), whereas it had a significant reduction in both groups after treatment, and a sig-

**Table 1. Treatment-related information (d).**

| Group | Hospitalization time | Abdominal pain relief time | Abdominal distension relief time | Intestinal function recovery time |
|---|---|---|---|---|
| Observation (n=169) | 22.7±5.4 | 2.9±0.4 | 3.3±0.5 | 3.4±0.3 |
| Control (n=169) | 43.2±5.7 | 4.1±0.5 | 4.6±0.7 | 4.7±0.4 |
| *t* | 33.941 | 24.363 | 19.646 | 33.800 |
| P | <0.001 | <0.001 | <0.001 | <0.001 |

**Table 2. TG levels before and after treatment (mmol/L).**

| Group | Before treatment | After treatment | t | P |
|---|---|---|---|---|
| Observation (n=169) | 58.79±11.23 | 10.31±1.46 | 55.653 | <0.001 |
| Control (n=169) | 58.82±10.78 | 23.28±2.67 | 41.602 | <0.001 |
| *t* | 0.025 | 55.407 | | |
| P | 0.980 | <0.001 | | |

**Table 3. Inflammatory factors before and after treatment (ng/L)**

| Group | Time | IL-6 | TNF-α | ET | TXA2 |
|---|---|---|---|---|---|
| Observation | Before treatment | 191.88±20.24 | 385.27±23.22 | 125.32±11.25 | 466.71±33.43 |
| | After treatment | 64.41±9.28 | 124.21±11.28 | 71.02±7.64 | 269.23±20.37 |
| | t | 74.423 | 131.466 | 51.908 | 65.579 |
| | P | <0.001 | <0.001 | <0.001 | <0.001 |
| Control | Before treatment | 192.38±21.23 | 384.28±24.37 | 124.89±13.28 | 471.29±24.39 |
| | After treatment | 89.28±13.22 | 147.23±14.21 | 82.35±11.28 | 316.71±21.32 |
| | t | 53.591 | 109.238 | 31.739 | 62.029 |
| | P | <0.001 | <0.001 | <0.001 | <0.001 |
| t (Before treatment) | | 0.222 | 0.382 | 0.321 | 1.439 |
| P (Before treatment) | | 0.845 | 0.702 | 0.748 | 0.151 |
| t (After treatment) | | 53.591 | 16.495 | 10.811 | 20.937 |
| P (After treatment) | | <0.001 | <0.001 | <0.001 | <0.001 |

**Table 4. Hemorheological indices before and after treatment.**

| Group | Time | Whole blood high-shear reduction viscosity | Hematocrit | EAI | ESR (mm/h) |
|---|---|---|---|---|---|
| Observation | Before treatment | 11.38±1.42 | 0.53±0.06 | 7.27±0.52 | 27.68±2.75 |
| | After treatment | 7.75±0.56 | 0.41±0.04 | 3.74±0.43 | 18.77±1.74 |
| | t | 30.915 | 21.633 | 68.009 | 35.594 |
| | P | <0.001 | <0.001 | <0.001 | <0.001 |
| Control | Before treatment | 11.45±1.29 | 0.54±0.05 | 7.29±0.49 | 27.75±2.78 |
| | After treatment | 9.28±1.34 | 0.47±0.02 | 5.88±0.53 | 21.89±2.14 |
| | t | 13.695 | 16.898 | 25.395 | 21.714 |
| | P | <0.001 | <0.001 | <0.001 | <0.001 |
| t (Before treatment) | | 0.474 | 1.664 | 0.364 | 0.233 |
| P (Before treatment) | | 0.636 | 0.097 | 0.716 | 0.816 |
| t (After treatment) | | 15.166 | 17.441 | 40.762 | 14.706 |
| P (After treatment) | | <0.001 | <0.001 | <0.001 | <0.001 |

nificantly lower APACHE-II score was observed in the observation group (P<0.05) (**Table 5**).

***Adverse reactions during follow-up***

There was no statistically significant difference with respect to the incidence rate of adverse reactions (P>0.05) (**Table 6**).

## Discussion

Compared with intravenous or micro-pump administration, CARI can greatly increase the concentration of trypsin inhibitors and antibiotics in pancreatic tissues, playing a powerful role in killing bacteria, controlling infection, suppress-

**Table 5. Prognosis (APACHE-II scores) of patients.**

| Group | Before treatment | After treatment | t | P |
|---|---|---|---|---|
| Observation (n=169) | 13.6±2.1 | 10.2±1.3 | 17.896 | <0.001 |
| Control (n=169) | 13.7±2.2 | 11.5±1.4 | 10.968 | <0.001 |
| t | 0.427 | 8.846 | | |
| P | 0.669 | <0.001 | | |

**Table 6. Adverse reactions during follow-up.**

| Group | Fever (n) | Headache (n) | Gastrointestinal reaction (n) | Adverse reaction [n (%)] |
|---|---|---|---|---|
| Observation (n=169) | 0 | 7 | 8 | 15 (8.88) |
| Control (n=169) | 0 | 8 | 9 | 17 (10.06) |
| $\chi^2$ | | | | 0.138 |
| P | | | | 0.710 |

ing trypsin secretion, reducing excessive inflammatory response and improving pancreatic microcirculation (7). Hence, CARI is helpful to reduce the infection and mortality rates in SAP patients. Likewise, in this study, the hospitalization time and abdominal symptom relief time of the patients treated with CARI were dramatically shorter, and the prognostic APACHE-II score was markedly lower than those of the patients receiving routine intravenous treatment.

During the progression of pancreatitis, pancreatic tissues and peripancreatic vessels are digested by a large amount of glandular fluid containing digestive enzymes, so tissues are injured and massive inflammatory factors are activated and released, thus triggering a cascade of cytokines and leading to systemic inflammatory response syndrome. In severe cases, multiple organ failure may occur (8,9).[9] The patients exhibit obvious abdominal pain, fever and local symptoms, and the levels of systemic indices such as AMS and inflammatory factors are significantly elevated. It is well-documented that the pancreatic microcirculation is suppressed in the early stage of the disease, subsequently leading to systemic microcirculation disturbance, which is associated with the release of inflammatory factors in the serum, including TNF-α, IL-6, ET, and so on (10,11). TNF-α is an inflammatory factor excreted by activated mononuclear macrophages. When TNF-α is elevated, it can drive the generation of oxygen free radicals as well as inflammatory factors like IL-6 and IL-1. ET can lead to persistent pancreatic vasospasm, aggravate the symptoms of ischemia and hypoxia, promote the production of oxygen free radicals and increase the content of lysozyme, thereby resulting in elevated $TXA_2$ level. The elevated $TXA_2$ level promotes the strong contraction of blood vessels and induces platelet aggregation that contributes to microthrombosis, thus facilitating pancreatitis progression and aggravating microcirculation disturbance. Hence, closely monitoring and improving the microcirculation level in patients is of great significance for the treatment of pancreatitis (12). In this study, the observation group showed significantly higher inflammatory factor levels and hemorheological indices than the control group, indicating that nitroglycerin combined with CRAI can remarkably improve the clinical therapeutic effect and prevent microcirculation disturbance, thus mitigating pancreatic necrosis.

Over 50% of SAP patients have various degrees of hyperlipidemia (HL), and the proportion of hyperlipidemic acute pancreatitis in SAP is also increasing annually. HL is both the cause of SAP and a common complication induced by metabolic disorder. Thus, HL and SAP interact, forming a vicious circle (13,14). A higher level of TG in SAP patients indicates a worse prognosis and higher mortality rate. The mechanism of HL leading to or aggravating pancreatitis may be as follows: (1) Increased free fatty acids induce acidosis and activate trypsinogen, which in turn gives rise to the self-digestion of acinar cells and aggravates the pathological damage of pancreatitis. (2) The lipoprotein lipase in plasma decomposes TG in chylomicrons and in very-low-density lipoprotein into glycerol and free fatty acids, the latter of which directly damage glandular cells and small blood vessels through cell mem-

brane lipid peroxidation, resulting in acute pancreatitis. (3) High concentration of free fatty acids and hypertriglyceridemia lead to viscous blood, which induces a hypercoagulable state of pancreatic blood. Meanwhile, microthrombus formation is induced easily, leading to pancreatic microcirculation disturbance, hemorrhage, and necrosis, and finally causing pancreatitis. (4) HL activates platelets, which promotes a massive release of $TXA_2$ with a strong vasoconstrictive effect. In the meantime, pancreatic vascular endothelial cells are damaged, which reduces the secretion of prostacyclin (PGI2) that has a strong vasodilating effect, resulting in $TXA_2$/PGI2 imbalance and aggravating pancreatic microcirculation disturbance. Therefore, eliminating the primary and secondary factors causing HL and lowering the level of serum TG may prevent the further progression of SAP. In this study, the level of TG displayed no significant difference between the two groups before treatment ($P>0.05$), while such level significantly decreased in the two groups, particularly in the observation group ($P<0.05$).

In summary, the operation of combining nitroglycerin with CRAI is simple. Although it cannot replace surgical treatment completely, it can be directly administered to pancreatic lesions to enhance the therapeutic effect and alleviate pancreatic inflammation, thus reducing complications caused by microcirculatory disturbance. However, this is a single-center study with a small sample size, and the efficacy of blood purification combined with CRAI has not been studied. In the future, further expansion of the sample size and comparison among different treatment schemes are essential to analyze their advantages and disadvantages, thus rendering references for treating SAP in clinical practice.

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**Authors' contribution**

BM: Study design; HZ: Data collection; KW: Writing

## Conflict of interests

The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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