

## Original Research Article

# Effect of low molecular weight heparin and ulinastatin as a combined therapy on soluble myeloid cell expression and intestinal mucosal function in patients with severe pancreatitis

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### Abstract

**Purpose:** To investigate the effect of low molecular weight heparins (LMWHs) and ulinastatin on soluble myeloid cells and intestinal mucosal function (IMF) in patients with severe pancreatitis.

**Methods:** A total of 107 patients with severe pancreatitis were divided into two groups: control group (CG, n = 53) and study group (SG, n = 54). The CG was treated with LMWH while SG was similarly treated but in addition received ulinastatin simultaneously. The following parameters were evaluated in the two groups: treatment effects, IMF, time for various indicators to normalize, vascular endothelial function, complication symptoms, T lymphoid subgroup indicators, inflammatory factors, anti-inflammatory factors, soluble B7-H2, and soluble myeloid cell receptor-1 level changes.

**Results:** After treatment, SG showed lower levels of L/M value, DAO and D-lactic acid than in CG ( $p < 0.05$ ). Gastrointestinal function, leukocytes, amylase, and body temperature in SG had a shorter time to return to normal than in CG ( $p < 0.05$ ). The levels of IL-10 in SG were higher than in CG, while sB7-H2, TNF- $\alpha$ , sTREM-1 and IL-1 levels were lower than those in the CG ( $p < 0.05$ ). After treatment, NO levels in SG were higher, but TXB2, vWF and ET levels were lower than in CG ( $p < 0.05$ ). In addition, CD4+, CD4+/CD8+ indicators were higher and CD8+ lower in SG than in CG ( $p < 0.05$ ).

**Conclusion:** Ulinastatin + LMWHs improves IMF in patients suffering from severe pancreatitis, shortens the time for various indicators to normalize, and reduces incidence of complications. However, further clinical trials are required to ascertain this therapeutic strategy for the management of severe pancreatitis.

**Keywords:** Low molecular weight heparin, Ulinastatin, Severe pancreatitis, Soluble myeloid cell expression, Intestinal mucosal function, Treatment effect

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## INTRODUCTION

Severe pancreatitis is a common and frequently occurring critical illness. This disease develops

rapidly, has a critical condition as well as many complications. Therefore, it has a high mortality rate. If it is not treated in time, it will seriously threaten the life of patients [1]. The preferred

treatment option for such patients is conservative treatment, including acid-base and water-electrolyte balance, fasting, pain relief, and gastrointestinal decompression, etc. It was shown that about four out of five patients can be cured after conservative treatment [2]. The frequently used therapeutic drugs are ulinastatin and low-molecular heparin, of which low-molecular heparin is an anticoagulant that can effectively improve the microcirculation of pancreatic blood, and is now widely used in acute pancreatitis to avoid pancreatic necrosis or ischemia caused by microcirculatory disorders [3]. Ulinastatin is a protease inhibitor that inhibits the secretion of trypsin, lipase, inflammatory factors, and amylase [4]. It also has anti-shock, anti-inflammatory and anti-oxidative stress effects, and has a good therapeutic effect in multi-organ disorder syndrome [5]. In this study, the major purpose was to explore the effect of combined treatment of severe pancreatitis with ulinastatin + low molecular heparin on soluble myeloid cells and intestinal mucosal function in patients with severe pancreatitis.

## METHODS

### General data

One hundred and seven patients with severe pancreatitis from October 2020 to October 2021 were selected and randomly divided into two groups: the control group (CG) and the study group (SG). There were 53 cases in CG, with duration of 2 - 19 h (mean  $8.61 \pm 1.33$  h), age range of 29 - 64 years (mean,  $41.98 \pm 2.47$  years), and 24 female and 29 male cases. There were 54 cases in SG, duration of 2 - 18 h ( $7.99 \pm 1.27$  h), age range of 29 - 63 years (mean,  $42.07 \pm 2.39$  years), and 25 females and 29 males. The general profile was comparable between the two groups ( $p > 0.05$ ).

### Inclusion criteria

These include severe pancreatitis confirmed by enhanced CT, and disease duration < 48 h.

### Exclusion criteria

These include the presence of malignancy; contraindication to the study drugs; cardiac, renal and other insufficiency; indication for surgery; history of psychiatric disorders; presence of chronic diseases [6].

### Ethical approval

Signed informed consent was obtained from each participant before the study. The study

followed the guidelines of the Declaration of Helsinki [7], and was approved by the ethics committee of Nankai Hospital (approval no. 17ECA-no.20).

### Treatments

Both groups were given conventional treatments such as intravenous support, fasting, anti-infection, pain relief, gastrointestinal decompression and balance of water and electrolyte. The CG was treated with low molecular heparin, i.e., subcutaneous injection of low molecular heparin calcium injection (Tianjin Chase Sun -Pharmaceutical Co., Ltd., Tianjin, China; specification: 0.4 ml, 4000 IU), 5,000 IU, which was administered at an interval of 12 h, and the treatment effect was observed after 10 days of treatment. Apart from the low molecular heparin in the CG, the SG was additionally treated with ulinastatin (Gunagzhou Techpool Pharmaceutical Co., Ltd., Gunagzhou, China; specification: 2 mL, 100000 IU). Glucose solution (5 %; 250 mL) was prepared with 100,000 units of ulinastatin for intravenous infusion, and the drug was administered at an interval of eight hours. The effect was observed after 10 days of treatment.

### Evaluation of outcomes/parameters

#### Treatment effect/efficacy

This was defined as: *Markedly effective* - the patient's symptoms completely disappeared within three days of treatment, and the laboratory indicators were normal; *Effective* - the patient's symptoms improved within seven days of treatment, and the laboratory indicators were normal; *Ineffective* - failure to reach the standard of markedly effective and effective. Effectiveness was computed as the sum of markedly effective cases, divided by total no. of cases, expressed as a percentage.

#### Intestinal mucosal function

The indicators assessed include lactulose to mannitol ratio (L:M), DAO (serum diamine oxidase) and plasma D-lactate acid. D-lactate acid was measured by enzyme-linked immunosorbent assay; DAO by spectrophotometry; and L/M by high performance liquid chromatography [8].

#### Miscellaneous biochemical parameters

The gastrointestinal function recovery time, white blood cells, serum amylase and body temperature were observed in both groups, and

the level of the inflammatory factors, anti-inflammatory factors and soluble B7-H2 (sB7-H2) as well as sTREM-1 were determined as described in a previous report [9].

### Inflammatory factors

The levels of IL-10, TNF- $\alpha$ , IL-1, sTREM-1, and sB7-H2 levels were measured using Elisa kits according to the manufactures' protocols.

### Vascular endothelial function

This was evaluated according as reported in a previous study [10]. Five (5) mL of fasting morning venous blood was drawn from the patients before and after treatment, and the indexes included NO (nitric oxide), TXB2 (thromboxane B2), vWF (vascular hemophilia factor), and ET (endothelin) levels, with NO measured by nitrate reductase assay; ET and Txbox2 measured by immunoradiometric assay; and vWF measured by double-antibody sandwich ELISA.

### Complications

Complications such as the occurrence of sepsis, acute respiratory distress syndrome, acute renal failure, metabolic disorders and shock were also recorded in both groups. The incidence of complications was also calculated. Lymphatic subpopulation indices [11]: CD4+, CD8+, CD4+/CD8+, were determined using upper flow cytometry (USA, Beckman FC500 model) before and after treatment.

### Statistical analysis

The data were analyzed by SPSS statistical analysis software (version 26.0). If the data conformed to normal distribution, chi-square test

was used for the analysis of variability between groups. Count data were described by composition ratio and rate, measurement data were expressed as mean  $\pm$  standard deviation (SD), while t-test was performed for the analysis of variability between groups. The factors influencing the conditions of the cases were analyzed by logistic regression.  $P < 0.05$  indicated statistically significant difference.

## RESULTS

### Treatment effectiveness

The treatment efficiency was 92.59 % in SG and 71.70 % in CG ( $p < 0.05$ ), with a significant difference (Table 1).

### Intestinal mucosal function

There was no significant difference in L/M, DAO and D-lactate acid between the two groups *before* treatment ( $p > 0.05$ ), and the levels of L/M value, DAO and D-lactate acid decreased in both groups after treatment, and was lower in SG than in CG ( $p < 0.05$ ), (Table 2).

### Time to return to normal for each index

The time to return to normal for gastrointestinal function, white blood cells, blood and urine amylase, and body temperature in SG was shorter than that in CG ( $p < 0.05$ ), (Table 3).

### Inflammatory factors, anti-inflammatory factors, sB7-H2, and sTREM-1 levels

There was no significant difference in IL-10, TNF- $\alpha$ , IL-1, sTREM-1, and sB7-H2 levels before treatment between the two groups ( $p > 0.05$ ).

**Table 1:** Comparison of treatment effects (cases, %)

Group	Number of patients	Markedly effective	Effective	Ineffective	Total effectiveness
Control	53	14 (26.42)	24 (45.28)	15 (28.30)	71.70%
Study	54	24 (44.44)	26 (48.15)	4 (7.41)	92.59%
Chi-square					6.435
P-value					0.029

**Table 2:** Comparison of intestinal mucosal function (mean  $\pm$  SD)

Group	No. of patients	L/M (10-2)		DAO (U/ml)		D-Lactic acid (ug/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control	53	9.01 $\pm$ 0.87	7.47 $\pm$ 0.73	5.39 $\pm$ 1.47	3.98 $\pm$ 0.75	11.07 $\pm$ 1.27	7.75 $\pm$ 0.73
Study	54	9.49 $\pm$ 1.10	4.67 $\pm$ 0.45	5.61 $\pm$ 1.53	2.80 $\pm$ 0.63	11.13 $\pm$ 1.23	6.41 $\pm$ 0.62
T		1.309	16.217	1.298	16.106	1.274	16.008
P-value		0.089	0.041	0.077	0.039	0.081	0.040

**Table 3:** Comparison of the time to return to normal for each index (mean  $\pm$  SD, day)

Group	No. of cases	Gastrointestinal function	Leukocytes units	Serum amylase units	Body temperature
Control	53	5.94 $\pm$ 1.13	7.89 $\pm$ 1.47	6.87 $\pm$ 1.11	5.37 $\pm$ 1.14
Study	54	4.01 $\pm$ 1.07	6.06 $\pm$ 1.23	4.47 $\pm$ 0.65	3.73 $\pm$ 1.01
T		16.375	16.298	16.309	16.324
P-value		0.017	0.023	0.027	0.031

IL-10 levels in both groups were higher than before treatment after 3, 7, and 10 days of treatment. sB7-H2 levels, TNF- $\alpha$ , sTREM-1, and IL-1 were lower than prior to treatment. IL-10 levels in the SG were higher and sB7-H2, TNF- $\alpha$ , sTREM-1, and IL-1 levels were lower than those in the CG ( $p < 0.05$ ), (Figure 1).

### Vascular endothelial function

There was no significant difference in NO, TXB2, vWF, and ET levels between the two groups before treatment ( $p > 0.05$ ), and NO levels increased, while TXB2, vWF, and ET levels decreased in both groups after treatment. NO levels in the SG were higher and TXB2, vWF, and ET levels were lower than those in CG ( $p < 0.05$ , Figure 2).

### Complications

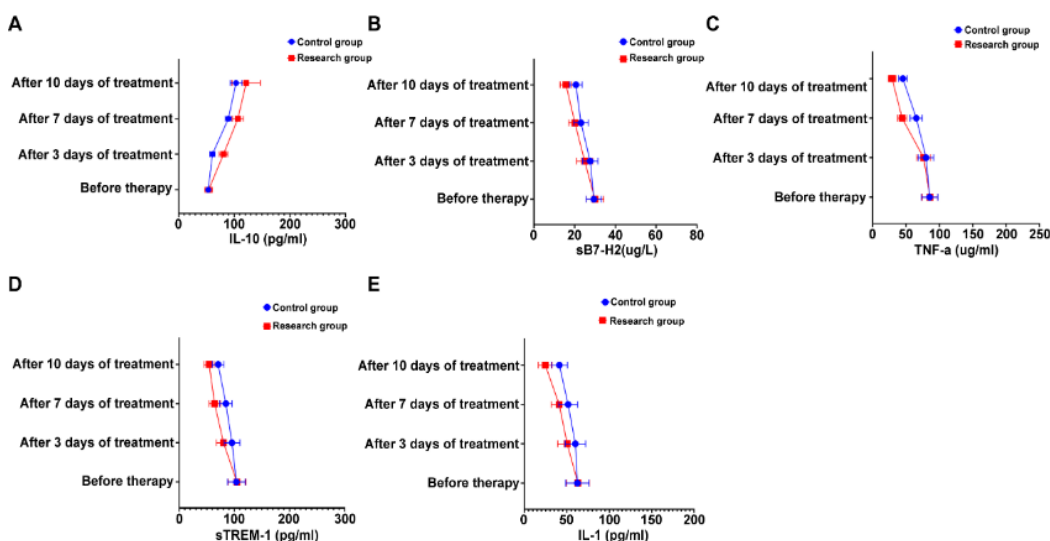
The total incidence of complications was 92.59 % in SG and 71.70 % in CG, and the difference was significant between two groups ( $p < 0.05$ ), (Figure 3).

### T-lymphatic subpopulation indices

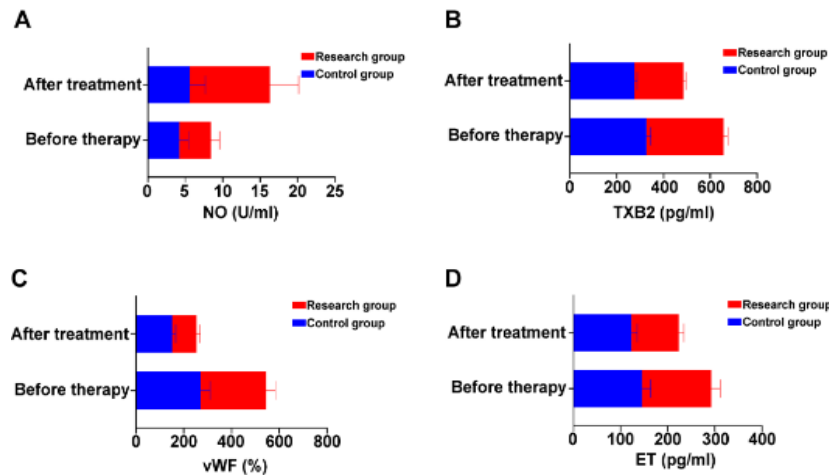
There is no significant difference in CD4+, CD8+, and CD4+/CD8+ indices between two groups before treatment ( $p > 0.05$ ), and after treatment, CD4+, CD4+/CD8+ indexes were higher and CD8+ indices were lower in both groups, and CD4+, CD4+/CD8+ indexes were higher and CD8+ was lower in SG than in CG ( $p < 0.05$ , Figure 4).

## DISCUSSION

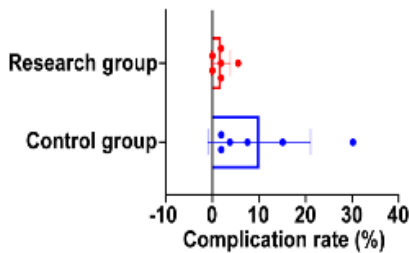
The mortality rate of severe pancreatitis is high, and conservative treatment usually fails to achieve satisfactory results; This disease tends to lead to multi-organ co-morbidities, so active, correct and effective treatment is of great significance [12]. Low-molecular heparin calcium is a commonly used anticoagulant that accelerates the microcirculation of the patient's pancreatic blood to avoid the occurrence of pancreatic necrosis and ischemia.



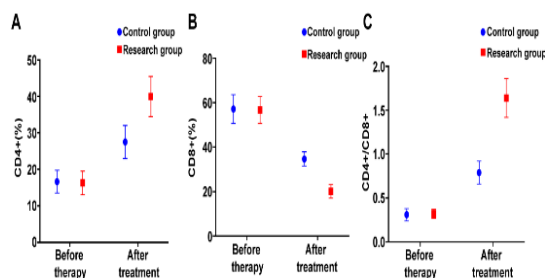
**Figure 1:** Comparison of inflammatory factors, anti-inflammatory factors, sB7-H2, and sTREM-1 levels. There is no significant difference ( $p > 0.05$ ) in levels of IL-10, TNF- $\alpha$ , IL-1, sTREM-1, and sB7-H2 levels between the two groups before treatment. IL-10 levels in both groups were higher than those before treatment. Levels of sB7-H2, TNF- $\alpha$ , sTREM-1 and IL-1 were lower than those before treatment. IL-10 levels in the study group were higher and sB7-H2, TNF- $\alpha$ , sTREM-1, and IL-1 levels were lower than those in the control group ( $p < 0.05$ )



**Figure 2:** Comparison of vascular endothelial function. The difference in NO, TXB2, vWF, and ET levels before treatment in the two groups were not significant ( $p > 0.05$ ). After treatment, all NO levels increased, and TXB2, vWF, and ET levels decreased. NO levels in the study group were higher, and TXB2, vWF, and ET levels were lower than those in the control group ( $p < 0.05$ )



**Figure 3:** Comparison of complications. The total incidence of complications in study group was 92.59% compared with 71.70% in the control group ( $p < 0.05$ )



**Figure 4:** Comparison of T-lymphatic subpopulation indexes. There was no significant difference in the comparison of CD4+, CD8+, and CD4+/CD8+ indexes between two groups before treatment ( $p > 0.05$ ). After treatment, CD4+, CD4+/CD8+ indexes were higher and CD8+ indexes were lower in both groups. CD4+, CD4+/CD8+ indexes were higher and CD8+ was lower in study group than in control group ( $p < 0.05$ )

It also regulates the expression of inflammatory mediators [13]. In contrast, ulinastatin is a commonly used trypsin secretion inhibitor, which can inhibit the secretion of inflammatory factors, and has good anti-oxidative stress, anti-inflammatory and anti-shock effects.

The intestinal mucosa is a tissue that produces D-lactate acid, and its level increases significantly when the intestinal mucosa is damaged. L/M is a landmark indicator to evaluate the damage to the intestinal mucosal barrier, and if the L/M is low, it means that the intestinal mucosal barrier is functionally damaged in the patient [14]. DAO can effectively assess the degree of intestinal damage as well as intestinal integrity, and is a marker enzyme of the small intestine. It has been shown that patients with severe pancreatitis have intestinal mucosal dysfunction, and the collective DAO level is significantly elevated [15]. The present results showed that the treatment efficiency in the SG was higher than that of the CG, and its L/M value, DAO and D-lactate acid values were lower after treatment than that of the CG. Thus, the combination of drugs can effectively improve the intestinal mucosal barrier function and enhance the therapeutic effect, which is beneficial to the early recovery of patients.

Since the pancreatic tissue in patients with severe pancreatitis is severely damaged, it easily triggers an inflammatory factor cascade reaction, leading to organ dysfunction as well as abnormal elevation of leukocyte and blood amylase levels [16]. The results showed that gastrointestinal function recovery time, leukocytes, blood and urine amylase, and body temperature in SG is shorter than in the CG, indicating that the combination of drugs can shorten the recovery time of all indicators in patients. The reason may be that the inflammatory response can be improved to the greatest extent when the drugs are combined, so the damage to the pancreatic

tissue is relatively small, and the patients can recover more easily.

Evidence has shown that inflammatory response, microcirculatory disorders and damage due to ischemia-reperfusion primarily contributes to the destruction of the intestinal mucosal barrier in patients with severe pancreatitis, and IL-1, which originates from macrophages of the pancreas and has an induction effect on shock, is a common inflammatory factor [17]. TNF- $\alpha$  has an activating effect on IL-6, and it induces an inflammatory response [18]. sB7-H2 is a novel inflammatory factor, and its specificity and sensitivity are critical in identifying the severity of the pancreatitis. IL-10 is an anti-inflammatory factor, and its elevated level indicates that the inflammatory response has been suppressed [19]. sTREM-1 is a member of the immunoglobulin superfamily, which is a factor that responds to systemic inflammation [20]. The results showed that the levels of IL-10 were higher in SG than in CG after 3, 7 and 10 days of treatment, while the levels of sB7-H2, TNF- $\alpha$ , sTREM-1, and IL-1 were lower than in CG), indicating that the combination of drugs effectively increased the level of the anti-inflammatory factors, and at the same time decreased the level of the inflammatory factors, which is beneficial to the recovery of patients. The underlying reasons may be that the anti-inflammatory effect of the combined drug is potent, and can cause an increase in the level of anti-inflammatory factors, while inhibiting the release of inflammatory factors, thus effectively antagonizing the increase in the levels of inflammatory factors [21].

TXB2 is a key factor in accelerating thrombosis, platelet coagulation, and vasoconstriction, while elevated ET leads to vasoconstriction and aggravates microcirculatory disorders of pancreatic blood [22]. The results showed that NO levels were higher and TXB2, vWF, and ET levels were lower in SG than in CG after treatment ( $p < 0.05$ ). The overall complication rate in the SG was 92.59 %, lower than 71.70 % in CG ( $p < 0.05$ ), indicating that the combination therapy can reduce complications and alleviate microcirculatory disorders with a protective effect on the intestinal mucosal barrier. Most patients with severe pancreatitis have suppressed immune function [23]. The results also showed that the CD4+ and CD4+/CD8+ indices were higher, and CD8+ was lower in the SG than in the CG after treatment, indicating that the combination was more effective in restoring the immune function of the patients. The reason may be that ulinastatin improves the immune function of the patients, and the combination of drugs has

a synergistic effect that enhances the efficacy of the drugs [24].

## CONCLUSION

The combination of ulinastatin and low molecular heparin is effective in patients with severe pancreatitis, and thus alleviates intestinal mucosal function, shortens the time to recovery of the indices, improves therapeutic effect and reduces the incidence of complications. Furthermore, the combination therapy increases the level of anti-inflammatory factors while reducing inflammatory factors, sTREM-1 and soluble BH2 levels, and thus improves vascular endothelial function as well as T-lymphatic subpopulation indices, which is conducive to the recovery of patients. However, further clinical trials are required prior to the use of this therapeutic combination in clinical practice.

## DECLARATIONS

### Acknowledgements

None provided.

### Funding

None provided.

### Ethical approval

None provided.

### Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Dong Qian and Xinyuan Luan contributed equally to this work and should be considered as equal first coauthors.

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