https://doi.org/10.31925/farmacia.2025.2.15 **ORIGINAL ARTICLE**

THERAPEUTIC EFFECT OF COMBINED ULINASTATIN AND GLUTAMINE FOR EARLY ENTERAL NUTRITION IN PATIENTS WITH SEVERE PANCREATITIS

XIU YANG, YANJUN WEI, HUA LI, KE XU, GUANGRONG YE, YAN ZHANG, TAO LU, JUAN YAN, JIABING PENG, GE ZHANG *

Department of Critical Care Medicine, The First People's Hospital of Longquanyi District, Chengdu, 610100, China

**corresponding author: zhanggelqy@126.com*

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Abstract

This study investigated the therapeutic effect of combining ulinastatin and glutamine with early enteral nutrition in patients with severe pancreatitis. A retrospective analysis was conducted on 104 patients admitted between June 2020 and June 2022, divided equally into control and experimental groups. The control group received ulinastatin and early enteral nutrition, while the experimental group received an additional glutamine supplement over two weeks. Results showed that the experimental group had significantly better clinical outcomes, including faster symptom recovery and improved biochemical parameters. Inflammatory markers such as LPS, TNF-α and IFN-γ decreased, while IL-2 levels increased. Gut flora improved with a decrease in *Escherichia coli* and *Staphylococcus*, and an increase in *Bifidobacterium*. Additionally, markers of oxidative stress, gut permeability, and organ function improved more significantly in the experimental group. Immune function indicators, including $CD3^+$, $CD4^+/CD8^+$, neutrophil count, and CRP, also showed favourable changes. APACHE II scores and the incidence of complications were significantly lower in the experimental group. These findings suggest that the combined therapy of ulinastatin and glutamine enhances clinical efficacy, modulates inflammation, supports intestinal and immune function, and may offer a valuable approach to treating severe pancreatitis.

Rezumat

Acest studiu a investigat efectul terapeutic al administrării combinate de ulinastatin și glutamină, în asociere cu nutriția enterală precoce, la pacienții cu pancreatită severă. A fost realizată o analiză retrospectivă pe un număr de 104 pacienți internați în perioada iunie 2020 – iunie 2022, împărțiți în mod egal într-un grup de control și un grup experimental. Grupul de control a primit tratament cu ulinastatin și nutriție enterală precoce, în timp ce grupul experimental a beneficiat suplimentar de administrarea de glutamină timp de două săptămâni. Rezultatele au arătat că pacienții din grupul experimental au avut evoluții clinice semnificativ mai bune, cu o recuperare mai rapidă a simptomatologiei și îmbunătățirea parametrilor biochimici. Markerii inflamatori (LPS, TNF-α și IFN-γ) au scăzut semnificativ, în timp ce nivelurile de IL-2 au crescut. Flora intestinală s-a îmbunătățit, fiind observată o reducere a populațiilor de *Escherichia coli* și *Staphylococcus*, concomitent cu o creștere a numărului de *Bifidobacterium*. De asemenea, parametrii de stres oxidativ, permeabilitate intestinală și funcție organică au înregistrat ameliorări semnificative în grupul experimental. Markerii funcției imune, inclusiv $CD3^+$, raportul $CD4^+/CD8^+$, numărul de neutrofile și CRP, au prezentat îmbunătățiri. Scorurile APACHE II, precum și incidența complicațiilor, au fost semnificativ mai mici în grupul experimental. În concluzie, terapia combinată cu ulinastatin și glutamină îmbunătățește eficacitatea clinică, modulează răspunsul inflamator, susține funcțiile intestinală și imună și ar putea reprezenta o opțiune în tratamentul pancreatitei severe.

Keywords: severe pancreatitis, ulinastatin, glutamine, early enteral nutrition, immune barrier function

Introduction

Severe pancreatitis is a prevalent critical condition in the domain of gastroenterology, distinguished by its sudden onset, rapid progression, and high mortality rates [1, 2]. Clinical interventions frequently entail the administration of medication under nutritional support conditions [3, 4]. The pathogenesis of severe pancreatitis is multifactorial, with impaired intestinal mucosal barrier function and increased intestinal mucosal permeability being pivotal pathophysiological features [5]. Impairment of the intestinal mucosal barrier function is manifested by an increase in mucosal permeability, allowing harmful substances such as bacteria and endotoxins in the intestines to easily penetrate the mucosal barrier and enter the bloodstream [6, 7]. During the onset of severe pancreatitis, the body is in a state of high metabolic stress, accompanied by significant energy consumption, leading to systemic inflammatory response syndrome (SIRS) and subsequent multiple organ failure [8-10].

Ulinastatin, a glycoprotein isolated and purified from the urine of healthy adult males, is a pharmaceutical agent employed in the treatment of severe pancreatitis and acute circulatory failure [11, 12]. The mechanism of action of ulinastatin involves the inhibition of various proteases, including those found in the

pancreas, such as trypsin. By inhibiting the activity of these proteases, ulinastatin can intervene in the pathophysiological processes of pancreatitis, reducing inflammation and tissue damage, and thus helping to protect the pancreas and other affected tissues. Oxygen free radicals are highly reactive molecules that can cause oxidative damage to cells and tissues. By scavenging oxygen free radicals, ulinastatin helps alleviate oxidative stress produced during pancreatitis, protecting cells from oxidative damage. Furthermore, ulinastatin has been shown to inhibit the release of inflammatory cytokines and the occurrence of inflammatory reactions, thereby reducing tissue damage caused by inflammation. In contrast, glutamine, a non-essential amino acid, plays a crucial role in the human body. It is one of the most abundant amino acids in the body and also serves as an energy source, especially for tissues in a high metabolic state, such as intestinal mucosal cells and immune cells. Furthermore, glutamine plays a pivotal role in regulating various physiological processes, including cell growth, apoptosis and other vital functions within the gastrointestinal tract [13]. Since patients suffering from pancreatitis experience an increased demand for glutamine due to inflammatory reactions and tissue damage, the supplementation of glutamine has been shown to help maintain normal metabolism and immune response in tissues [14]. The inhibitory effect of ulinastatin contributes to the alleviation of inflammation caused by pancreatitis, thereby aiding in tissue protection. The supply of glutamine helps maintain normal tissue metabolism and immune response. The synergistic action of these two components may contribute to more effective management of symptoms and improvement in treatment outcomes for patients suffering from pancreatitis.

The present study was conducted with the objective of investigating the impact of ulinastatin combined with glutamine, based on early enteral nutrition therapy, on severe pancreatitis. Through an in-depth exploration of indicators such as intestinal microbiota and mucosal function, it was hypothesised that scientific evidence for the treatment of severe pancreatitis would be offered. Additionally, it was expected that the exploration of the synergistic effects of ulinastatin and glutamine would contribute to innovative therapeutic approaches for future clinical practices. The potential benefits of this research are twofold: firstly, it may offer more effective and personalised treatment strategies for patients with severe pancreatitis; and secondly, it may provide significant clinical and scientific value.

Materials and Methods

General data

A total of 104 patients diagnosed with severe pancreatitis and admitted to the hospital from June 2020 to June 2022 were selected as the subjects for this study. These patients were randomly assigned to either the control group or the experimental group, with a total of 52 patients allocated to each group. The control group comprised 24 male and 28 female patients, aged 28 to 67 years (mean age: 51.4 ± 7.4 years), with a body mass index (BMI) of (23.7 ± 2.9) kg/m² and a course of disease (COD) of (17.5 ± 3.5) hrs. The EG group comprised 25 male and 27 female patients, aged 26 to 64 years, with an average age of (50.3 ± 6.8) years, BMI of (24.1 ± 3.2) kg/m², and a COD of (18.3 ± 2.9) hrs. The experimental and control groups exhibited no statistically significant disparities in their general data ($P > 0.05$). The study was approved by the ethics committee of The First People's Hospital of Longquanyi District, Chengdu, China.

The specific diagnostic criteria for severe pancreatitis are set out in the Guidelines for Diagnosis and Treatment of Acute Pancreatitis in China (2017 edition) [15]. Patients present with respiratory, renal, and circulatory failure, along with evident tenderness and rebound pain in the upper abdomen. Additionally, patients may experience abdominal distension and reduced bowel sounds. An APACHE II score greater than 8 points [16] is indicative of severe pancreatitis. Pancreatic enhanced CT showed pancreatic oedema and peri-pancreatic effusion and serum amylase levels in patients were three times higher than the normal value or more.

Patients enrolled in the study had to satisfy all the following conditions: firstly, they had to meet the diagnostic criteria for severe pancreatitis outlined in the Guidelines for Diagnosis and Treatment of Acute Pancreatitis in China (2019 edition), with serum amylase levels exceeding three times the normal value and an APACHE II score > 8; (III) COD ≤ 48 hrs; (IV) early enteral nutrition catheter placement to be completed within 24 hrs of admission; (V) no history of psychiatric disorders; and (VI) informed consent forms signed by both the patient and their family members. Conversely, patients with any of the following conditions had to be excluded. Firstly, patients with abnormal cardiac, liver, or kidney function. Secondly, individuals allergic to ulinastatin or glutamine drugs. Thirdly, pregnant or lactating women.

Treatment schemes

Following the diagnosis of severe pancreatitis in both groups, standard comprehensive treatments were administered, including oxygen therapy, fasting for water, correction of electrolyte imbalances, gastro-intestinal decompression, and acid suppression. Patients in the control group received early enteral nutrition therapy and ulinastatin treatment. Within 24 hrs of admission, a nasoenteric tube was placed for early enteral nutrition. The patient was positioned semi-recumbent, and the nasoenteric tube was inserted into the jejunum. Gastric fluid was then aspirated to check for colour and pH, and successful placement

was confirmed when the fluid was golden yellow, and the pH was > 7.0. Initially, 0.9% sodium chloride injection was infused without any adverse reactions, and then gradually switched to a short-peptide enteral nutrition preparation (Peptisorb; H20170170, Milupa GmbH, Germany) at a dose of 450 mL/day, increasing to 4000 mL/day within 4 days. The patient was fed at a rate of 100 - 125 mL/h. On the day of tube placement, the jejunum was infused with 0.9% sodium chloride injection using a pump. Ulinastatin (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., China) was administered intravenously at a dose of 100,000 U, dissolved in 250 mL of normal saline, twice daily.

The patients in the experimental group received ulinastatin combined with glutamine on the basis of the control group treatment. Ulinastatin (Guangdong Tianpu Biochemical Pharmaceutical Co., Ltd., China) was administered intravenously at a dose of 100,000 U, dissolved in 250 mL of normal saline, twice daily. The intravenous administration of glutamine (Hainan Tongyong Kangli Pharmaceutical Co., Ltd., China) was conducted at a dose of 20 g *per* infusion, once daily, for a duration of 2 weeks.

Observation indicators

Clinical efficacy. Following two weeks of treatment, a comparison was made of the clinical efficacy of the two patient groups. The evaluation of clinical efficacy was based on the Guidelines for Diagnosis and Treatment of Acute Pancreatitis in China (2017 edition). The assessment of clinical efficacy was conducted by evaluating the normalisation of CT and laboratory examination results, the disappearance of clinical symptoms, and the presence or absence of improvement in CT and laboratory examination results, as well as the extent of improvement in clinical symptoms. The following classifications were employed: "cure" for normalisation of CT and laboratory examination results, disappearance of clinical symptoms; "marked effectiveness" for essentially normal CT and laboratory examination results, basic disappearance of clinical symptoms; "effective" for partial normalization of CT and laboratory examination results, partial disappearance of clinical symptoms; and "ineffective" for no improvement in CT and laboratory examination results, no improvement in clinical symptoms. The calculation method for overall efficacy is outlined in [17].

Improvement of symptoms. The temporal requirements for the alleviation of abdominal discomfort, abdominal distension, the restoration of bowel sounds, the recovery of bowel movements, flatulence, and the restoration of blood amylase were compared between the two patient groups.

Nutritional status. The nutritional status of the groups was assessed by comparing the levels of pre-albumin and albumin. On the day before the commencement of treatment and on the morning of the first day after treatment completion at 6:00, 4 mL of fasting venous blood was drawn from the elbow vein of the patient. The samples were then subjected to centrifugation at 3,000 rpm for 10 min using a centrifuge 5702 machine (Eppendorf, Germany), after which the upper layer (the "supernatant") was collected. The prealbumin and albumin levels were subsequently measured using a 7600 fully automatic biochemical analyser (Hitachi, Japan).

Levels of inflammatory factors. The inflammatory status of patients in different groups was assessed by comparing the levels of lipopolysaccharide (LPS), tumour necrosis factor-alpha (TNF-α), interleukin (IL)-2, IL-6 and IL-10. Venous blood (4 mL) was drawn from the elbow vein of patients on the day before the start of treatment and on the morning of the first day after treatment completion at 6:00. The samples were then subjected to centrifugation at 3,000 rpm for 10 min using a centrifuge 5702 machine, after which the superior layer was collected. The levels of the corresponding inflammatory factors were subsequently measured using a 7600 fully automatic biochemical analyser (Hitachi, Japan).

Intestinal function. Comparison of gut function in patients was made by assessing the number of gut bacteria and serum levels of DLA, DAO, amylase (AMS), endothelin (ET), nitric oxide (NO), thromboxane B2 (TXB2), malondialdehyde (MDA), 6-keto-prostaglandin F1a (6-keto-PGF1a) and superoxide dismutase (SOD) before and after treatment. Fresh faeces (0.5 g) were collected from patients before and after treatment, inoculated onto *Escherichia coli*, *Staphylococcus* and *Bifidobacterium* selective culture media (Sigma, USA), and the corresponding bacterial counts were analysed and compared statistically. On the day before the start of treatment and on the morning of the first day after the end of treatment at 6:00 am, 4 mL of fasting venous blood was collected from the patients' elbow vein. Samples were processed using a Centrifuge 5702 (Eppendorf, Germany) at 3,000 rpm for 10 min. Serum DLA and DAO were determined using a DR6000 spectrophotometer (HACH, USA). AMS was measured using an α-amylase test kit (SNM309, Beijing Bio-Raid Biotechnology Co., Ltd., China). The levels of ET, NO, TXB2 and 6-keto-PGF1a were determined by enzyme-linked immunosorbent assay (ELISA), and ELISA kits were purchased from Shanghai Enzyme-linked Biotechnology Co., Ltd. MDA was detected using 7% thiobarbituric acid (Abcam, UK). SOD was measured using a cell superoxide detection kit (Abcam, UK).

Immune barrier function. The immune barrier function of the patients was compared by assessing the levels of T-cell subsets ($CD3^+$ and $CD4^+/CD8^+$), neutrophil count and C-reactive protein (CRP) in patients from different groups. On day 1, day 4 and day 7, 4 mL of fasting venous blood was collected from the patients' elbows at 6:00 am. T-cell subset levels were measured

using an Attune flow cytometer (Thermo Fisher, USA). Neutrophil count and CRP levels were measured using a 7600 fully automated biochemistry analyser (Hitachi, Japan).

Prognosis and adverse reactions. APACHE II, liver and kidney function, and the incidence of complications before and after treatment were compared for all patients [18]. APACHE II consists of the Acute Physiology Score (APS), the Chronic Health Status (CHS) and age. Patients' physiological parameters must be assessed and recorded within 24 hrs of admission, with the worst values of these parameters selected for scoring. Each parameter is scored from 0 to 4 points (doubling the score for acute renal failure with the Cr score), and the total score ranges from 0 to 71 points. A higher score indicates a more severe condition, poorer prognosis and higher mortality [19]. Patients' liver and kidney function was assessed by measuring aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (TBIL) and serum creatinine (Scr). On the day before the start of treatment and on the morning of the first day after the end of treatment at 6:00 a.m., 4 mL of fasting venous blood was collected from the patients' elbows. The samples were processed using a 5702 centrifuge at 3000 rpm for 10 min and then analysed using a 7600 fully automated biochemical analyser (Hitachi, Japan).

Statistical analysis

Data were processed using SPSS 26.0. Measurement data were presented as mean ± standard deviation and compared using the t-test. Count data were presented as frequencies or rates and compared using the $\chi 2$ test. $P < 0.05$ was considered statistically significant.

Results and Discussion

Clinical efficacy

After two weeks of treatment, the statistical results of clinical efficacy for all patients are presented and compared in Figure 1. The efficacy of patients in the experimental group in terms of cure rate (32.7%), marked improvement rate (38.5%), resulted in a much higher total effective rate (TER) (90.4%) than patients in the control group ($p < 0.05$). This indicates that treatment with ulinastatin in combination with glutamine based on early enteral nutrition therapy can effectively treat severe pancreatitis, promote the normalisation of CT and laboratory examination results and the disappearance of clinical symptoms in patients.

Symptom improvement

After treatment, all patients in the control and experimental groups showed an improvement in symptoms. The statistical analysis of time to improvement is shown in Figure 2. It was evident that the time required for symptom relief, including abdominal pain, relief of abdominal distention, recovery of bowel sounds, restoration of bowel movements, recovery of gas discharge and normalisation of blood amylase, was much shorter in the experimental group patients, showing a clear difference from those in the control group patients ($p < 0.05$). This means that treatment with ulinastatin combined with glutamine based on early enteral nutrition therapy can effectively alleviate the symptoms of discomfort in patients.

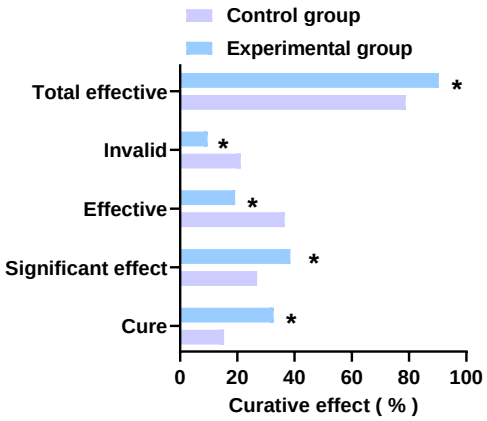

Figure 1.
Clinical efficacy of patients in different groups
* Compared with the control group, $p < 0.05$

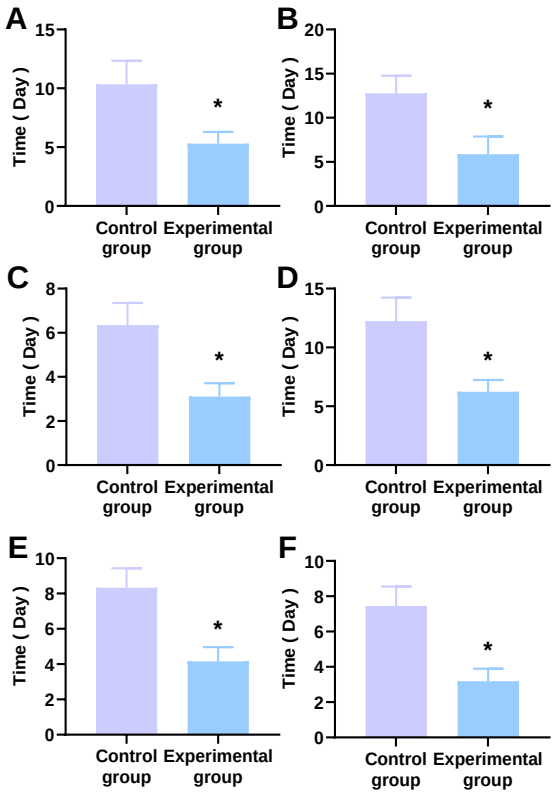

Figure 2.
Improvement of symptoms between patients in the control group and experimental group: A: relief of abdominal pain; B: relief of abdominal distension; C: recovery of bowel sounds; D: restoration of bowel movements; E: recovery of gas discharge; F: normalisation of blood amylase
* Compared with the control group, $p < 0.05$

Nutritional status of patients before and after treatment

After two weeks of treatment, the nutritional status of all patients improved compared to the pre-treatment status, as shown in Figure 3. On comparison, the pre-albumin and albumin levels in the experimental group were much higher and showed remarkable differences from those in the control group ($p < 0.05$).

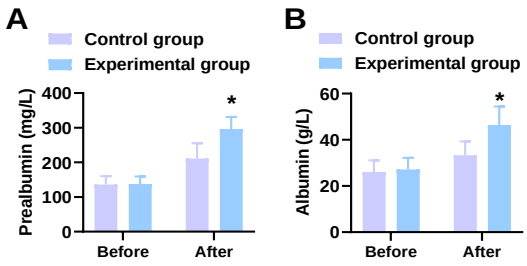

Figure 3.

Nutritional status of patients before and after treatment. A: prealbumin; B: Albumin

* Compared with the control group, $p < 0.05$

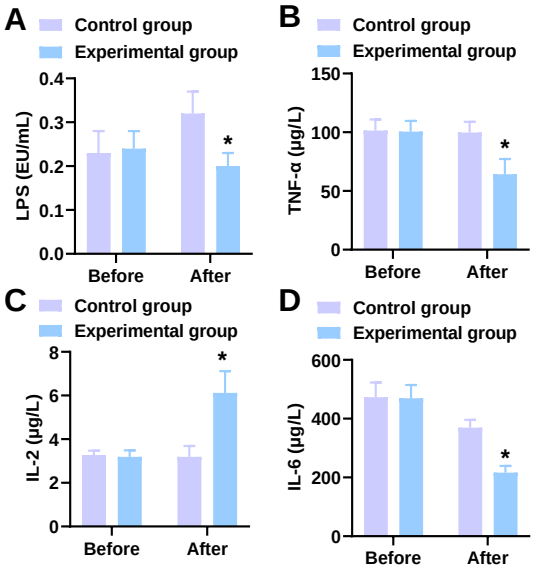

Figure 4.

Changes in inflammatory factor levels before and after treatment. A: LPS; B: TNF-α; C: IL-2; D: IL-6

* Compared with the control group, $p < 0.05$

Changes in inflammatory factor levels

The levels of inflammatory factors before and after treatment in the different groups were compared as shown in Figure 4. Before treatment, there was no significant difference in various inflammatory factors between patients in the experimental and control groups ($p > 0.05$). In contrast, the post-treatment LPS level in the control group patients increased sharply and was higher than the pre-treatment level ($p < 0.05$). The post-treatment LPS level in the experimental group patients decreased compared to the pre-treatment level and was significantly lower compared to the control group patients ($p < 0.05$). In addition, the differences in TNF-α, IL-2 and IL-6 levels within the control group before and after treatment were not great ($p > 0.05$). However, in the experimental group, TNF-α and IL-6 levels were significantly lower than in the control group after patients were treated with different regimens ($p < 0.05$). In addition, the post-treatment IL-2 level in the experimental group was significantly elevated compared to the control group ($p < 0.05$). This suggests that treatment based on early enteral nutrition therapy combined with ulinastatin and glutamine has a restorative effect on the abnormal levels of inflammatory factors caused by severe pancreatitis.

Intestinal function

Relevant indicators of gut function in patients before and after treatment were compared as shown in Figure 5. Figures 5A and 5B showed a remarkable decrease in the number of *Escherichia coli* and *Staphylococcus* in all patients after different treatments ($p < 0.05$). Meanwhile, the decrease in the number of *Escherichia coli* and *Staphylococcus* in the experimental group patients was significantly greater than that in the control group patients after treatment ($p < 0.05$). However, the number of *Bifidobacterium* increased in all patients, although they received different treatments, and the increase was more pronounced in the experimental group patients, while no significant difference was found when compared to the control group patients ($p > 0.05$). This suggests that treatment based on early enteral nutrition therapy combined with ulinastatin and glutamine can effectively improve gut health.

In addition, AMS, DAO and DLA levels in patients from the control and experimental groups were compared before and after treatment, as shown in Figure 6. The difference in AMS, DAO and DLA levels before treatment was found to be small ($p > 0.05$). However, after treatment, they were significantly down-regulated in all patients regardless of the treatment they received, showing a large difference compared to the pre-treatment levels ($p < 0.05$). In addition, the levels in patients in the experimental group were significantly lower than those in patients in the control group ($p < 0.05$).

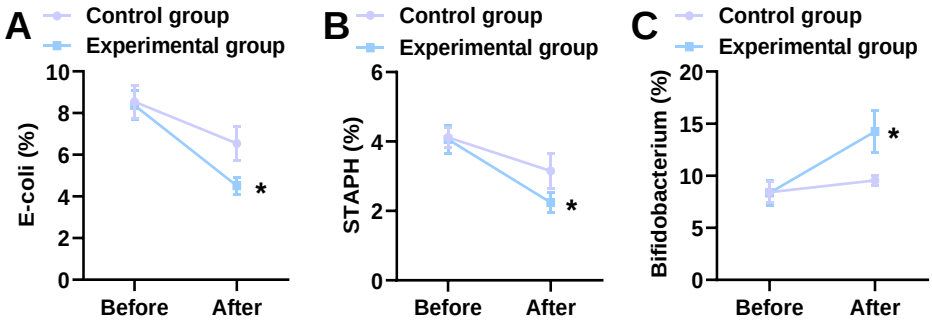

Figure 5.

The change in the number of intestinal flora before and after treatment. A: *Escherichia coli*; B: *Staphylococcus*; C: *Bifidobacterium*

* Compared with the control group, $p < 0.05$

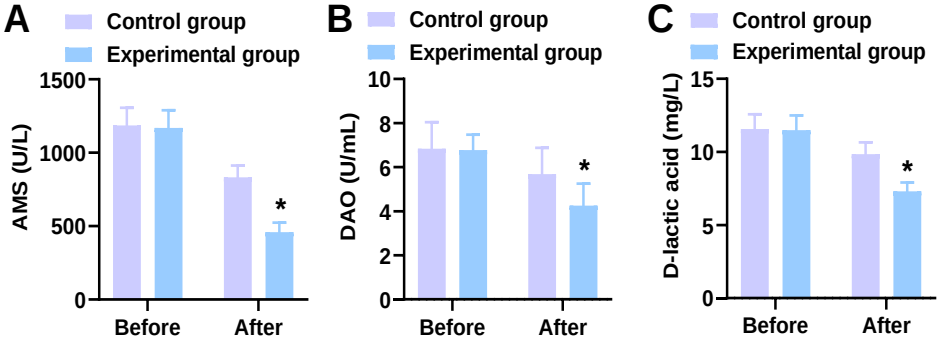

Figure 6.

Changes in AMS (A), DAO (B), and DLA (C) levels

* Compared with the control group, $p < 0.05$

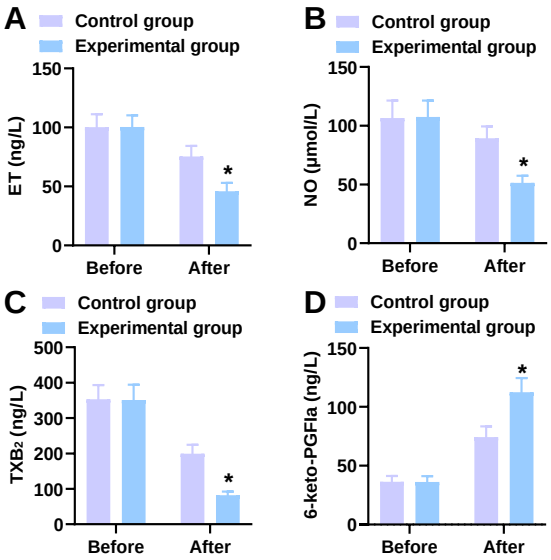

Figure 7.

Comparison between pre-treatment and post-treatment ET (A), NO (B), TXB_2 (C) and 6-keto-PGF1a (D) levels

* Compared with the control group, $p < 0.05$

Figure 7 below analyses and compares the changes in ET, NO, TXB2 and 6-keto-PGF1a levels before and after different treatments for patients in the control and experimental groups. Before treatment, no visible differences in ET, NO, TXB2 and 6-keto-PGF1a levels were observed between patients in different groups ($p > 0.05$). After treatment, ET, NO and TXB2 levels decreased significantly in the experimental and control groups ($p < 0.05$), and the comparison showed that the decrease was greater in the experimental group patients ($p < 0.05$). In addition, after treatment, 6-keto-PGF1a levels increased sharply in both the experimental and control groups ($p < 0.05$), and the comparison suggested a significant increase in the experimental group patients compared to the control group patients ($p < 0.05$).

The comparison of MDA and SOD levels before and after treatment in all patients is shown in Figure 8. There were no visible differences in MDA and SOD levels between patients in the experimental and control groups before treatment ($p > 0.05$). The post-treatment MDA level showed an obvious decrease in all patients, which was very different from the pre-treatment level ($p < 0.05$). Further comparison between groups showed that post-treatment MDA levels were lower in patients in the experimental group ($p < 0.05$). In addition, the post-treatment SOD levels showed an observable increase in all patients, also with a remarkable difference ($p < 0.05$). In addition, SOD levels in the experimental group patients were higher than in the control group patients, with a significant difference of $p < 0.05$.

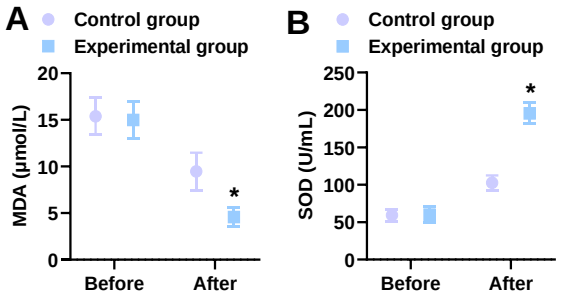

Figure 8.
Changes in MDA (A) and SOD (B) levels
* Compared with the control group, $p < 0.05$

Changes in immune barrier function

In addition, the immune barrier function of the patients was compared on days 1, 4 and 7 after treatment, and the results are shown in Figure 9. On the first day of treatment, there were no significant differences in $CD3^+$, $CD4^+/CD8^+$, neutrophil count and CRP levels between patients in different groups ($p > 0.05$). Over time, the $CD3^+$ level was highly elevated in all patients on days 4 and 7 ($p < 0.05$) and showed a significant difference between cases in the control and experimental groups ($p < 0.05$). On days 4 and 7 of treatment, the $CD4^+/CD8^+$ ratio, neutrophil count and CRP levels all decreased significantly in patients in different groups, with obvious differences compared to pre-treatment levels ($p < 0.05$). Similarly, patients in the experimental group had significantly lower levels of these indicators, as supported by the between-group comparison ($p < 0.05$).

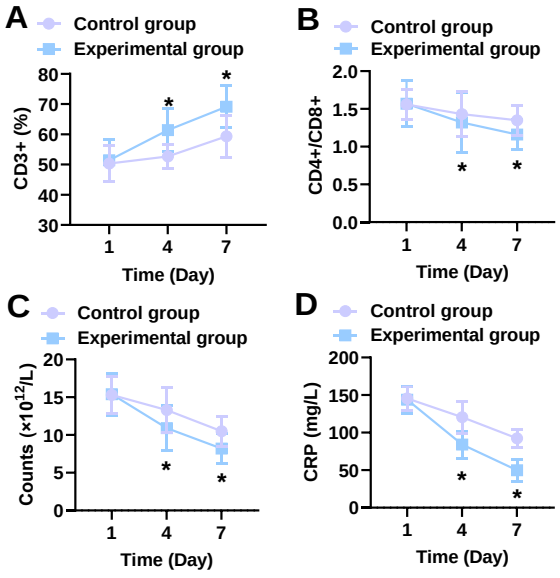

Figure 9.
Comparison of immune barrier function at different post-treatment time points. A: $CD3^+$; B: $CD4^+/CD8^+$; C: neutrophil count; D: CRP
* Compared with the control group, $p < 0.05$

Prognosis and ARs

The APACHE II scores of patients before and after treatment were compared to assess prognosis, as shown in Figure 10. The difference in APACHE II scores between patients in the control and experimental groups before treatment was negligible ($p > 0.05$). It was evident that APACHE II scores decreased significantly in all patients after treatment ($p < 0.05$), with a greater decrease in patients in the experimental group ($p < 0.05$). In general, a lower total APACHE II score indicated a relatively better physiological state and chronic disease burden, suggesting a better prognosis. This implied that treatment based on early enteral nutrition therapy combined with ulinastatin and glutamine led to better prognostic outcomes.

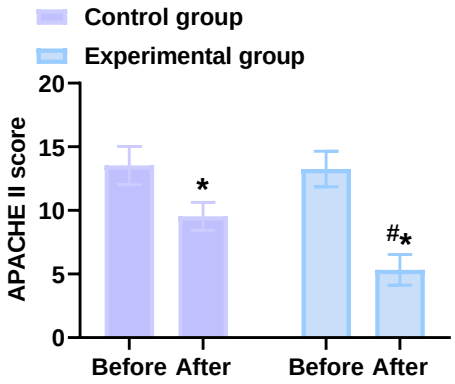

Figure 10.
Changes in and comparison of APACHE II scores
* Compared with the same group before treatment, $p < 0.05$;
# compared with control group, $p < 0.05$

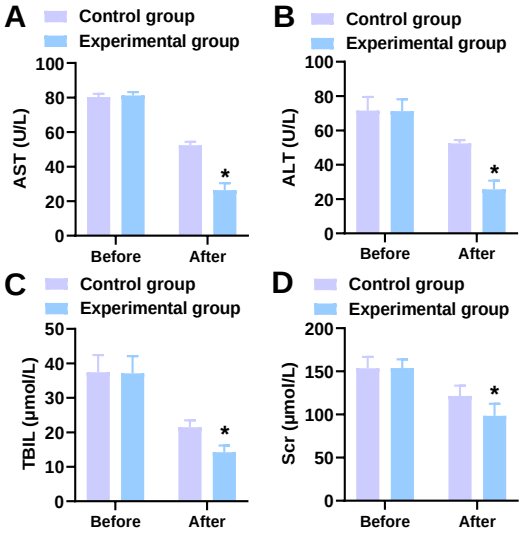

Figure 11.
Comparison of liver and kidney function of patients after medication. A: AST; B: ALT; C: TBIL; D: Scr
* Compared with the control group, $p < 0.05$

The liver and kidney function of the patients after medication was compared, as shown in Figure 11. After medication, the levels of AST, ALT, TBIL and

Scr in patients between the experimental and control groups showed a decreasing trend. However, when comparing patients in different groups after treatment, the levels of these indicators in patients in the experimental group were significantly lower than those in the control group ($p < 0.05$).

The occurrence of complications after treatment in all patients was analysed, and the results are shown in Figure 12. Patients in the experimental group were less likely to develop complications such as abdominal abscess, pancreatic necrosis, sepsis and bowel obstruction than patients in the control group. As a result, the overall incidence of complications in the experimental group patients (11.54%) was significantly lower than that in the control group patients (25.00%), showing a remarkable difference with $p < 0.05$.

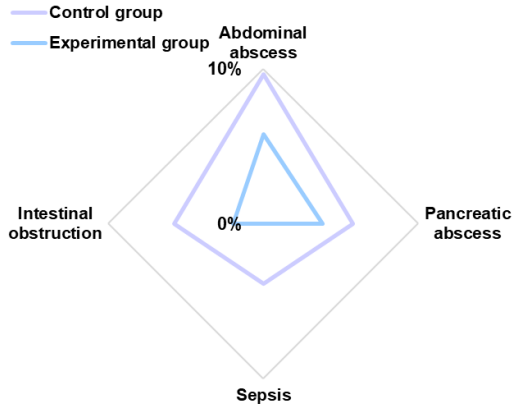

Figure 12.
The occurrence of posttreatment complications

Pancreatitis is a serious disease of the pancreas characterised by acute inflammation of the pancreatic tissue. The abnormal activation of pancreatic enzymes can lead to self-digestion, triggering an inflammatory response. In severe cases, patients may experience multiple organ failure due to the systemic effects of the inflammatory response. This study investigated the effect of ulinastatin combined with glutamine, based on early enteral nutrition therapy, on severe pancreatitis. By comprehensively monitoring various indicators, including clinical outcomes, levels of inflammatory factors, bowel function and immune barrier function, this work aimed to provide a scientific basis for the treatment strategy of severe pancreatitis.

Research has shown that the use of ulinastatin in the treatment of severe pancreatitis is significantly more effective than conventional treatment and can effectively improve the inflammatory response in patients [20]. Another study reported that glutamine can effectively promote the recovery of bowel functi on in patients [21]. In this paper, the combined use of ulinastatin and glutamine based on early enteral nutrition therapy was reported to significantly improve the clinical efficacy and symptoms of patients. The efficacy was superior to the use of ulinastatin alone, consistent with existing literature [22]. In addition, this work showed that the combined use led to an increase in pre-albumin and albumin levels in patients. Pre-albumin is mainly synthesised by the liver but is also directly influenced by nutritional status. Albumin is a major plasma protein synthesised by the liver and has several functions, including maintaining blood volume, transporting substances and regulating osmotic pressure. A decrease in pre-albumin and albumin levels reflects poor protein and nutritional status, while an increase indicates nutritional improvement [23]. This suggests that combined treatment with ulinastatin and glutamine, based on early enteral nutrition therapy, has a significant effect on improving the nutritional status of patients. A key step in inhibiting the development of severe pancreatitis is to suppress the body's inflammatory response. By measuring levels of LPS, TNF-α, IL-2 and IL-6 in patients, the combined treatment was found to be effective in reducing levels of inflammatory factors in the body, thereby preventing shock and infection caused by inflammatory responses. Ulinastatin and glutamine individually have certain effects in reducing inflammatory factor levels, and this work further investigated the comprehensive effects of their combined treatment, confirming their synergistic effect in reducing inflammatory factor levels.

By measuring the intestinal flora and related serum indicators, the combined treatment was found to be effective in protecting intestinal function. Ulinastatin combined with glutamine therapy effectively reduces the levels of *Escherichia coli* and *Staphylococcus* by regulating the intestinal flora, while significantly increasing the levels of *Bifidobacterium*. *Bifidobacteria* are generally considered to be a probiotic that helps maintain intestinal health and can effectively prevent the growth of harmful bacteria [24]. This change helps to maintain the balance of the intestinal micro-ecosystem, preventing the proliferation of harmful bacteria and creating favourable conditions for intestinal health. After treatment, the levels of AMS, DAO and DLA in EG patients decreased significantly, suggesting that the treatment contributes to the improvement of pancreatic and intestinal barrier function. An increase in DLA levels is usually associated with metabolic abnormalities or tissue ischaemia, while a decrease indicates improved tissue metabolism [25]. Elevated DLA levels indicate the presence of metabolic abnormalities or tissue ischaemia [26]. DAO is primarily found in the epithelial cells of the intestinal mucosa, and its function is to break down histamine produced in the tissues. Changes in DAO levels may be related to intestinal mucosal health and intestinal barrier function. Damage to the pancreas results in the release of AMS into the bloodstream, and a decrease in AMS indicates an improvement in pancreatic function [27, 28]. This suggests that ulinastatin combined with glutamine therapy based

on early enteral nutrition effectively improves gut health. In addition, this work has shown that the combined treatment has a positive effect on improving vascular function and inflammatory status in patients, including downregulation of ET, NO and TXB2 and upregulation of 6-keto-PGF1a. ET exerts a critical effect in regulating vascular tone, promoting vaso-constriction and facilitating NO release [29]. NO has vasodilatory and antiplatelet effects. TXB2 is involved in the regulation of platelet aggregation and coagulation, and elevated TXB2 levels may be associated with thrombosis and vascular pathology. 6-keto-PGF1a plays a role in regulating vascular tone and inhibiting platelet aggregation [30]. The reduction in ET, NO and TXB2 levels, together with the increase in 6-keto-PGF1a levels, suggests that ulinastatin combined with glutamine therapy based on early enteral nutrition has a beneficial effect on vascular function and inflammatory status in patients. In addition, this work showed that MDA levels in EG patients decreased significantly while SOD levels increased significantly after the patients were treated. The decrease in MDA suggests that the treatment helps to alleviate oxidative stress and reduce peroxidation damage to cell membrane lipids. The increase in SOD suggests that the treatment enhances the antioxidant defence system, reducing the generation of reactive oxygen species and aiding in cell protection and repair [31-33]. The decrease in MDA indicates that the treatment helps to alleviate oxidative stress and reduce peroxidative damage to cell membrane lipids. This can be seen as a sign of cell and tissue protection. It suggests that ulinastatin combined with glutamine therapy based on early enteral nutrition effectively ameliorates oxidative stress, alleviates tissue damage and promotes normal intestinal function.

Combined treatment with ulinastatin and glutamine may promote immune barrier function through multiple pathways, providing new theoretical support for the regulation of inflammation. Ulinastatin, as a protease inhibitor, may reduce inflammation by inhibiting the activity of inflammation-related proteins. Meanwhile, glutamine, as an amino acid supplement, may contribute to tissue repair and provide energy support [34]. In this work, a decrease in $CD3^+$, neutrophil count and CRP levels and an increase in $CD4^+/CD8^+$ levels were observed after combined treatment. $CD3^+$, $CD4^+/CD8^+$, neutrophil counts and CRP levels are associated with the degree of inflammation and immune response. Elevated $CD3^+$ levels, a marker for T lymphocytes, indicate that the treatment is helping to increase the activity of T lymphocytes, a sign of immune system recovery [35, 36]. This is crucial for fighting infections, regulating immune responses and promoting tissue repair. The reduction in $CD4^+/CD8^+$, neutrophil counts and CRP levels suggests that the treatment modulates the inflammatory response by reducing inflammation levels and consequently neutrophil activation, thereby controlling the overall inflammatory process [37]. This suggests that ulinastatin combined with glutamine therapy based on early enteral nutrition has a beneficial effect on the immune system and inflammatory status. The synergistic effects of both components may have a positive influence on regulating immune responses and improving intestinal barrier function. This provides a new theoretical basis for the treatment of inflammatory diseases and highlights the potential mechanisms of combined treatment in regulating the immune system. The main limitations of this work include a relatively small sample size and a single-centre design, which may affect the generalisability of the results. In addition, the analysis of treatment mechanisms is not explored in depth, and this work would benefit from long-term follow-up to comprehensively assess treatment outcomes. Future research should focus on investigating the long-term effects and potential side effects of treatment. Therefore, this work supports a more effective and personalised treatment option for patients with severe pancreatitis. By improving clinical efficacy and promoting recovery, this work promises to open new avenues in the treatment of pancreatic and systemic inflammatory diseases, with significant practical and clinical implications.

Conclusions

This work extensively investigated the clinical effects and impact on bowel function of the combined use of ulinastatin and glutamine based on early enteral nutrition therapy in patients with severe pancreatitis. The results showed that the combination therapy effectively improved clinical efficacy, accelerated symptom relief, reduced inflammatory markers, facilitated recovery of bowel function and improved immune barrier function. The comprehensive analysis of serum markers, gut microbiota and immune indicators highlighted the synergistic effects of ulinastatin and glutamine in achieving positive outcomes for patients with severe pancreatitis. This research provided a scientific basis for the individualised treatment of severe pancreatitis, emphasised the importance of early enteral nutrition therapy and offered new directions for future disease management and treatment strategies. Further validation and optimisation of this treatment approach through larger, multi-centre studies were expected to provide more precise and effective treatment options for patients.

Conflict of interest

The authors declare no conflict of interest.

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