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Original Article

Ulinastatin combined with glutamine improves liver function and inflammatory response in patients with severe acute pancreatitis

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Abstract: Objective: To explore whether ulinastatin combined with glutamine (Gln) can improve the liver function and inflammation in patients with severe acute pancreatitis (SAP). Methods: Altogether 78 patients with SAP treated in Tangshan Workers' Hospital were retrospectively enrolled and divided into the control group (CG, n=35, conventional treatment plus ulinastatin) and the research group (RG, n=43, additional Gln on the basis of treatment in the CG) according to the treatment regimen. The improvement of clinical symptoms after treatment was observed in both groups. The levels of IgM, IgA and IgG were tested by ELISA. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were utilized to evaluate the changes of the patients' condition before and after treatment, and the Balthazar CT score was used to assess the changes of the lesions. The changes of inflammatory cytokines were determined via Enzyme linked immunosorbent assay (ELISA). The liver function and amylase indexes of both groups were measured. Results: Patients in the RG experienced faster improvement in bloating and abdominal pain, first defecation, and bowel sound recovery than the CG (all $P<0.05$). After treatment, IgM, IgA and IgG in the RG were higher than those in the CG (all $P<0.05$). Besides, the RG exhibited markedly lower interleukin-6 (IL6), IL, tumor necrosis factor α (TNF-α), and high-sensitivity C-reactive protein (hs-CRP) levels than the CG after treatment (all $P<0.05$). After treatment, the indexes of liver function and amylase in both groups were decreased, and those in the RG were lower than those in the CG (all $P<0.05$). Conclusion: Ulinastatin in combination with glutamine is effective in treating severe pancreatitis, which efficiently reduces inflammation in patients and facilitates the recovery of immune, metabolic, and liver functions, and therefore it has a high clinical application value.

Keywords: Severe acute pancreatitis, ulinastatin, glutamine, liver function

Introduction

Acute pancreatitis is the leading cause of hospitalization due to gastrointestinal diseases [1] and its incidence has been increasing annually because of altered lifestyle habits and increased alcohol consumption [2]. According to statistics, the morbidity of acute pancreatitis ranges from 4.9 to 73.4 cases per 100,000 people, worldwide [3]. Although most patients have mild disease and good prognosis, 15% to 20% of acute pancreatitis patients develop a severe condition with high morbidity and mortality [4]. Severe acute pancreatitis (SAP) is one of the severe subtypes of acute pancreatitis with systemic and local complications [5], which are related to the systemic inflammatory response syndrome and multiple organ failure, and it has great harm to the body of patients and a higher risk of death [6]. Previously, scholars have pointed out that early death in patients with severe pancreatitis is usually due to multiple organ dysfunction syndrome (MODS) resulting from the systemic inflammatory response syndrome triggered by the release of various cytokines within the first two weeks [7], and approximately half of the patients die after two weeks because of infection, pancreatic necrosis and secondary MODS [8]. Research has shown that severe trauma can lead to stress response, resulting in a large number of endotoxins and inflammatory factors being released, along with blood coagulation dysfunction, immune imbalance, all leading to sepsis [9].

The liver is the most easily damaged organ due to inflammatory injury. Excessive production of free radicals, ischemia and hypoxia can cause damage to the function of membrane proteins, destruction of mitochondrial membrane and hepatocyte membranes, resulting in dysfunction of bilirubin secretion as well as uptake and transport of hepatocytes [10]. Therefore, knowing how to protect the liver from damage, improve the effect of treatment and reduce mortality are urgent problems to be solved.

Ulinastatin is a protease inhibitor [11], which can be obtained from the urine of healthy people. It is reported to have strong inhibitory activity against pancreatin and also has an anti-inflammatory effect on acute pancreatitis [12]. Pan Y et al. suggested that ulinastatin can increase the survival rate of rats with acute pancreatitis [13]. In addition, ulinastatin can affect the levels of inflammatory cytokines TNF-α and IL-1β [14]. Glutamine (Gln) is a free amino acid found in the human body [15], which can be converted from glucose *in vivo*, and it promotes muscle growth, improves brain function and enhances immunity [16]. However, the demand for Gln increases in disease conditions, and the body cannot synthesize enough of it to meet the body's needs [17]. Moreover, research has revealed that ulinastatin can improve microcirculation and scavenge oxygen free radicals, fundamentally controlling cell injury, as well as protecting patients' liver function [18]. We speculate that the combined treatment of the combined therapy may achieve greater effect. To verify our speculation, the clinical efficacy of ulinastatin plus Gln in treating SAP was analyzed and studied.

Materials and methods

Patient data

Of the clinical data of 78 patients with SAP treated in Tangshan Workers' Hospital from February 2018 to April 2020 were analyzed retrospectively. Among them, 35 patients received conventional treatment for acute pancreatitis combined with ulinastatin (control group, CG), and 43 additionally received Gln therapy (research group, RG). All patients enrolled and their family members signed an informed consent form. This research was approved by the Medical Ethics Committee of our hospital. Ethics code: HBTSLL (trial) 2018A082.

Inclusion and exclusion criteria

Inclusion criteria: patients who met the diagnostic criteria of SAP [1]; patients with complete data; patients who voluntarily agreed to participate in this experiment.

Exclusion criteria: patients who were pregnant or lactating; patients with drug allergy, other malignant diseases, liver, kidney or lung dysfunction, or tumor; patients with low compliance.

Methods

Patients in the CG received conventional treatment for acute pancreatitis combined with ulinastatin (Techpool, Guangdong, China, SFDA Approval No.: H19990134, 100,000 units). The scheme was as follows: reduce gastrointestinal pressure by fasting; control pancreatic secretion, anti-infection and other symptomatic treatment measures; support treatment such as intravenous nutrition; maintain electrolyte and water balance and supplement blood volume; give corresponding analgesic drugs. Besides, they received intravenous drip of ulinastatin (twice a day, dissolved in 500 ml 5% glucose injection) (Heilongjiang Bifu Jinbeiyao Pharmaceutical Co., Ltd., SFDA Approval No.: H20083521, 100 ml: 5 g). On this basis, patients in the RG received glutamine (Gln, Wuhan Docan Pharmaceutical Co., Ltd., SFDA Approval No.: H20064444, 100 ml: 20 g), and the intravenous drip was given 20 g a time, once a day.

Outcome measures

The improvement of clinical symptoms (improvement of bloating, improvement of abdominal pain, first defecation, and bowel sound recovery) after treatment was observed in both groups. The Acute Physiology and Chronic Health Evaluation (APACHE) II scores [19] were utilized to evaluate the changes of patients' condition before and after treatment, and Balthazar CT score [20] was used to assess the changes of lesions. The levels of inflammatory cytokines interleukin-6 (IL6), interleukin-8 (IL8), tumor necrosis factor-α (TNF-α), high sensitivity C-reactive protein (hs-CRP) and immunoglobulin (IgM, IgA, IgG, Abcam, USA,

Table 1. Comparison of baseline data

	Research group (n=43)	Control group (n=35)	x^2 or t/p
Age (Y)	52.6±2.9	51.5±3.4	1.542/0.127
BMI (KG/cm^2)	23.2±2.4	23.5±2.7	0.519/0.605
Gender			0.078/0.780
Male	32 (74.42%)	27 (77.14%)	
Female	11 (25.58%)	8 (22.86%)	
Cause of disease			0.107/0.948
Biliary	28 (65.12)	24 (68.57)	
Hyperlipidemic	8 (18.60)	6 (17.14)	
Alcoholic	7 (16.28)	5 (14.29)	
Smoking history			0.104/0.748
Present	28 (65.12%)	24 (68.57%)	
Absent	15 (34.88%)	11 (31.43%)	
Drinking history			0.042/0.838
Present	34 (79.07%)	27 (77.14%)	
Absent	9 (20.93%)	8 (22.86%)	
Living environment			1.794/0.180
Town	30 (69.77%)	29 (82.86%)	
Countryside	13 (30.23%)	6 (17.14%)	
Ethnicity			0.259/0.611
Han	35 (81.40%)	30 (85.71%)	
Minority	8 (18.60%)	5 (14.29%)	
Past medical history			
Hypertension	15 (34.88)	10 (28.57)	0.018/0.891
Hyperlipidemia	17 (39.54)	13 (50.00)	0.046/0.829
Diabetes	14 (32.56)	17 (48.57)	2.066/0.151
Cholelithiasis	10 (23.26)	6 (17.14)	0.442/0.506

Note: Chi-square test was used for counting data and t-test was used for measurement data.

ab214568, ab196263, ab100547) were measured by enzyme-linked immunosorbent assay (ELISA). The liver function indexes of both groups (alanine aminotransferase, ALT, aspartate aminotransferase, AST, γ-glutamyl transpeptidase, γ-GT, serum alkaline phosphatase and AKP) were evaluated by Beckman Coulter AU5800 biochemical analyzer, and the levels of blood amylase, urinary amylase and lipase were detected.

Statistical methods

The data were processed by SPSS 22.0, and figures were plotted by Graphpad7. Enumeration data were expressed by (%), and chi-square test was adopted for inter-group comparison. Measurement data were expressed by (mean ± standard deviation), and t test was adopted for inter-group comparison. P<0.05 denoted the difference was statistically significant.

Results

Comparison of baseline data

The comparison of age, body mass index (BMI), gender, cause of disease, smoking history, drinking history, living environment, and ethnicity between both groups exhibited no statistical differences (all P>0.05), as shown in **Table 1**.

Improvement of clinical symptoms after treatment

We compared the improvement of clinical symptoms, and found that patients in the RG experienced significantly faster improvement in bloating and abdominal pain as well as first defecation and recovery of bowel sounds than the CG (all P<0.05), as shown in **Figure 1**.

Changes in immunoglobulin before and after treatment

The changes of serum immunoglobulin in both groups before and after treatment were detected. The results showed that there was no remarkable change in the levels of IgM, IgA and IgG before treatment (all P>0.05). After treatment, these levels in the RG were higher than those in the CG (all P<0.05) (**Figure 2**).

APACHE II and Balthazar CT scores

We applied the APACHE II score and the Balthazar CT score to assess the changes of the patient's condition. The results revealed that there was no difference in the two scores before the treatment period (P>0.05). After treatment, the APACHE II score and the Balthazar CT score were reduced in both groups, and they were lower in the RG than the CG (P<0.05), as shown in **Figure 3**.

Changes of inflammatory cytokines

We detected the levels of inflammatory cytokines of IL-6, IL-8, TNF-α, and hs-CRP, and

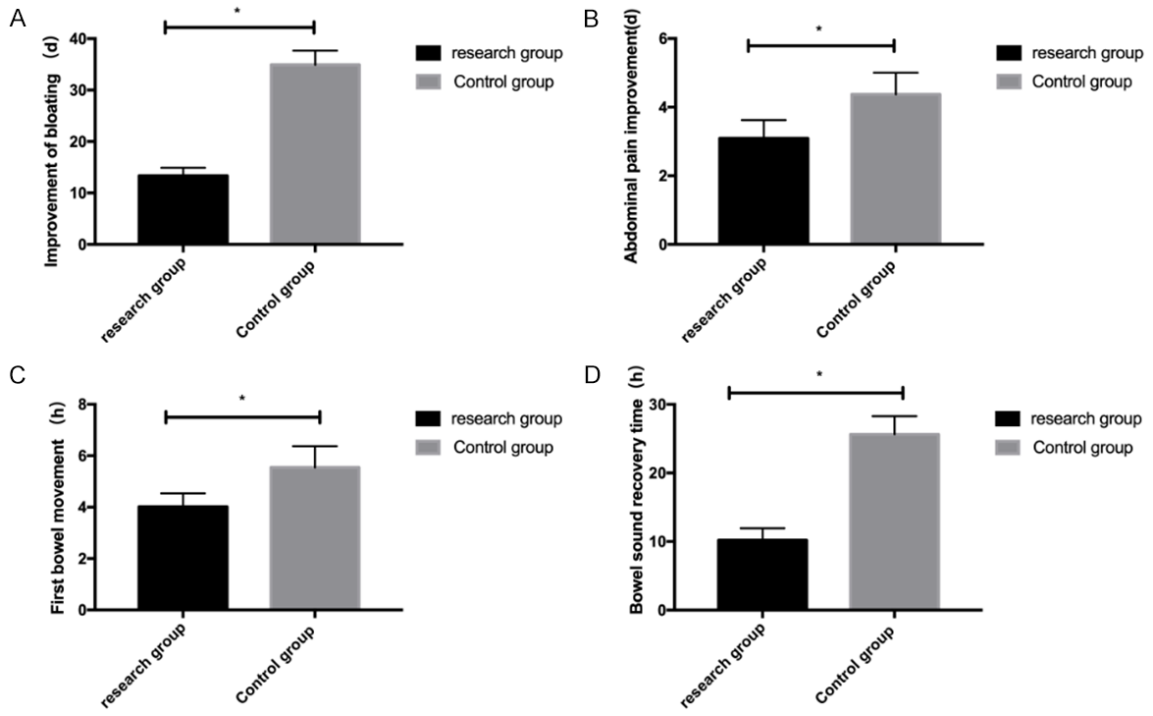

Figure 1. Improvement of clinical symptoms after treatment. A. Improvement of bloating after treatment in the two groups. B. Improvement of abdominal pain after treatment in the two groups. C. First defecation time of the two groups of patients. D. Bowel sound recovery time of the two groups of patients. *P<0.05, compared with the pre-treatment.

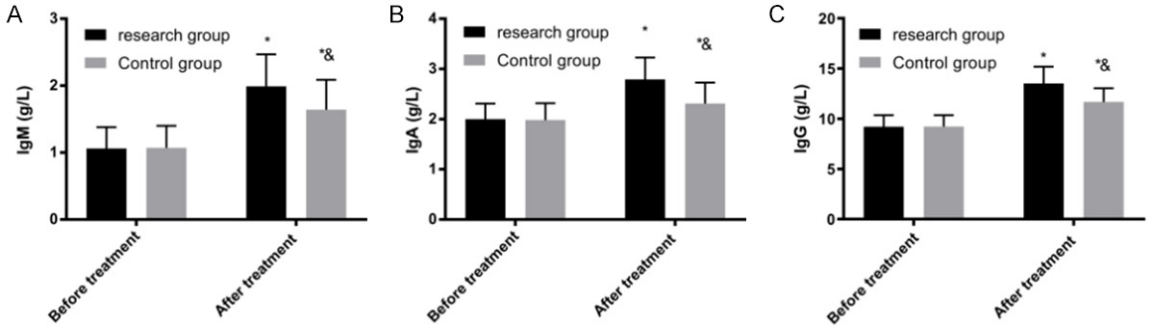

Figure 2. Changes in IgM, IgA and IgG in two groups of patients before and after treatment. A. Changes in IgM in both groups before and after treatment. B. Changes in IgA in both groups before and after treatment. C. Changes in IgG in both groups before and after treatment. *P<0.05, compared with the pre-treatment; &P<0.05, compared with the research group.

found no difference in their levels between both groups before treatment (all P>0.05). After treatment, all the cytokines above were reduced, and the RG was markedly lower than the CG (P<0.05), as shown in **Figure 4**.

Changes of liver function indexes in both groups

We detected liver function indexes of ALT, AST, γ-GT, and AKP, and found no significant difference in their levels before treatment between both groups (all P>0.05). After treatment, all the indexes above were reduced, and the RG was markedly lower than the CG (all P<0.05), as shown in **Figure 5**.

Changes of the amylase index in both groups of patients

We detected the levels of blood amylase, urinary amylase and lipase, and found that

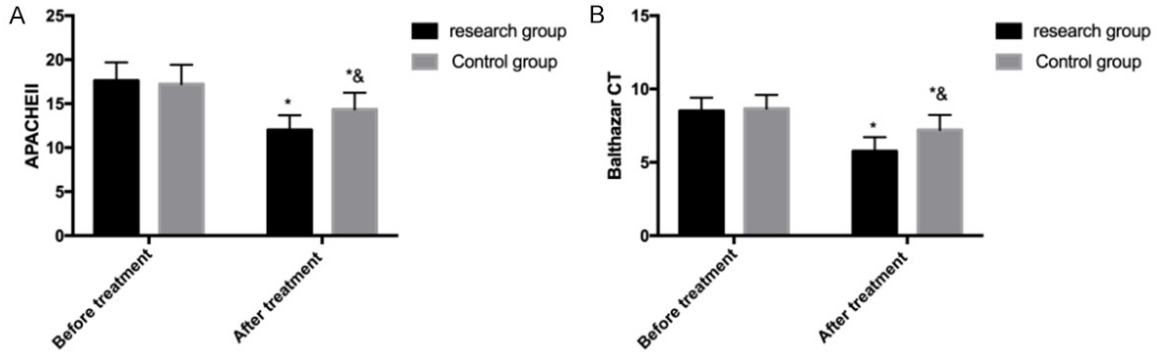

Figure 3. APACHE II and Balthazar CT scores before and after treatment in both groups. A. APACHE II score before and after treatment in the two groups. B. Balthazar CT score before and after treatment in the two groups. *P<0.05, compared with the pre-treatment; &P<0.05, compared with the research group.

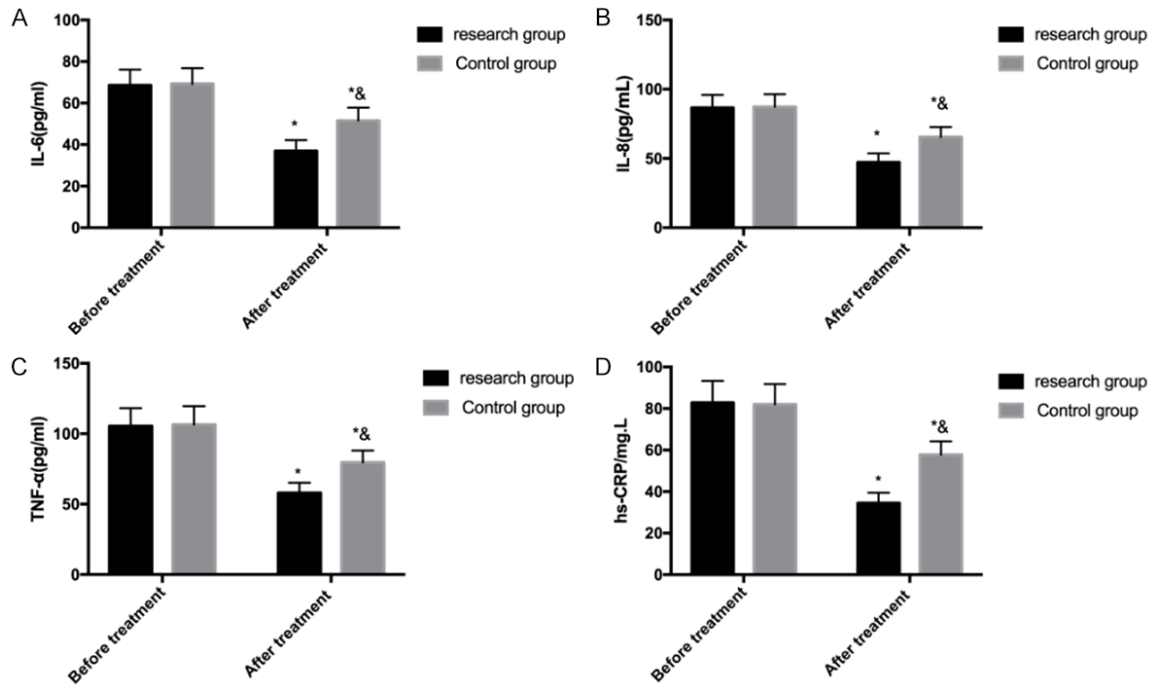

Figure 4. Changes of inflammatory cytokines before and after treatment in both groups. A. Changes in IL-6 before and after treatment in both groups. B. Changes in IL-8 before and after treatment in both groups. C. Changes in TNF-α before and after treatment in both groups. D. Changes in hs-CRP before and after treatment in both groups. *P<0.05, compared with the pre-treatment; &P<0.05, compared with the research group.

there was no difference between both groups before treatment (P>0.05). After treatment, the above-mentioned indexes decreased with significantly lower levels in the RG than the CG (P<0.05), as shown in **Figure 6**.

Discussion

SAP is a special type of pancreatitis with complex pathogenesis that results in pancreatic swelling, bleeding and necrosis, promoting the release of large amounts of inflammatory cytokines [21], triggering immune disorders and inducing multiple complications, which can eventually lead to multi-organ failure or even death if not treated effectively in a timely manner [22]. Therefore, it is crucial to reduce the inflammation, improve the immune system and lower the incidence of organ failure for the treatment of SAP [23]. Ulinastatin is a common-

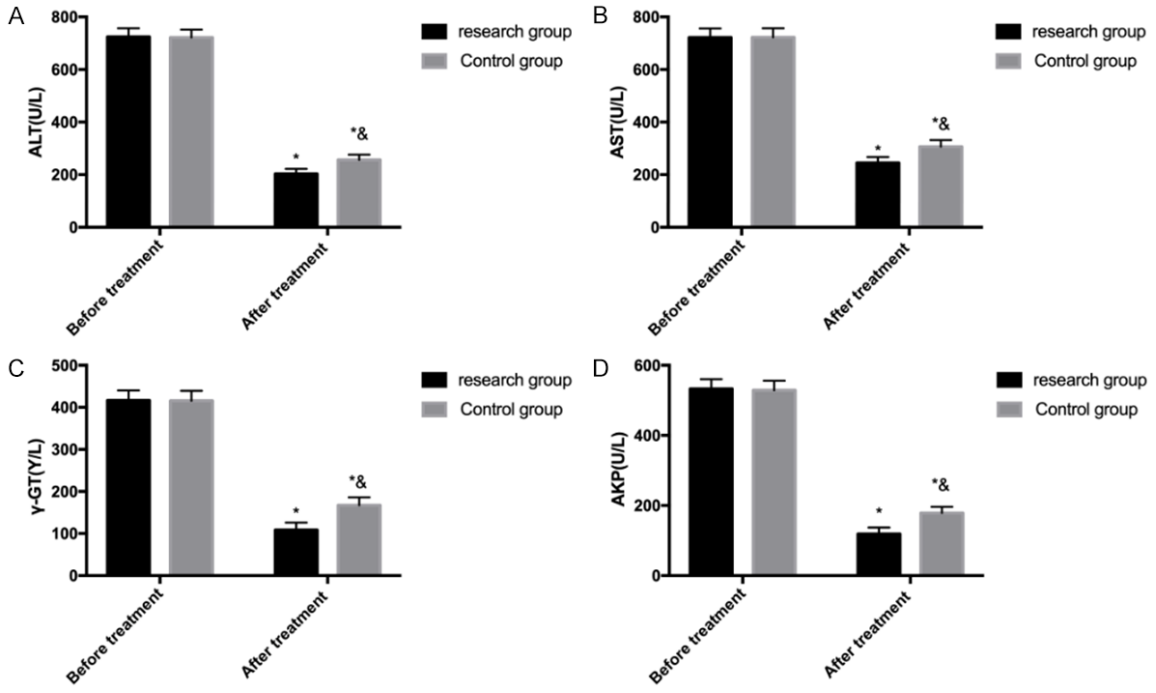

Figure 5. Changes in liver function indexes in both groups. A. Changes in liver function index ALT in both groups. B. Changes in liver function index AST in both groups. C. Changes in liver function index γ-GT in both groups. D. Changes in liver function index AKP in both groups $^{*}P<0.05$, compared with the pre-treatment; $^{\&}P<0.05$, compared with the research group.

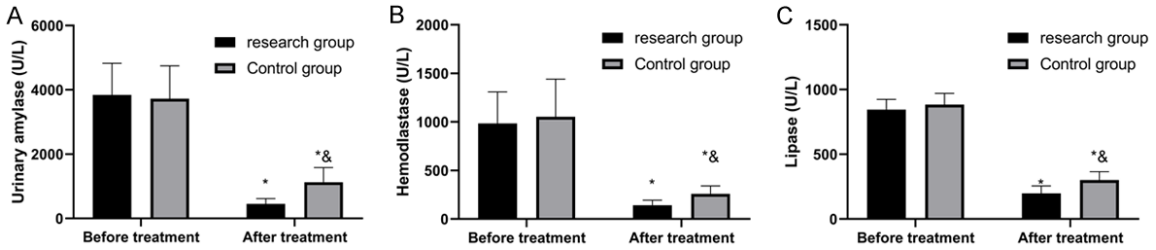

Figure 6. Changes in amylase indexes in two groups of patients. A. Changes in urinary amylase in two groups of patients. B. Changes in blood amylase in two groups of patients. C. Changes in lipase levels in two groups of patients. $^{*}P<0.05$, compared with the pre-treatment; $^{\&}P<0.05$, compared with the research group.

ly applied drug in treating acute pancreatitis [24], and Gln has been clinically proven to improve the immune function of the body and positively promote healthy body function [25]. Therefore, we conducted this study to explore the clinical effects of the combination of two drugs in the treatment of SAP, thus to provide a reliable theoretical basis for future clinical treatment.

First of all, we compared the improvement of clinical symptoms between the RG and CG and found that the RG experienced faster improvement in abdominal distension, abdominal pain, first defecation and bowel sound recovery than the CG. Moreover, we also found that the improvement of liver function and amylase in the RG was better than that in the CG. This suggests that the effects of ulinastatin combined with Gln on improving liver function is more significant than that of ulinastatin alone, and previous studies also revealed better therapeutic effects of ulinastatin plus Gln on pancreatitis, which supports our experimental results [26]. Ulinastatin, as a broad-spectrum protease inhibitor extracted from fresh urine, it has been proven to block the interaction between inflammatory cytokines and white blood cells in previous studies, and it can notably improve the inflammatory

response [27, 28]. The need for Gln increases in response to environmental damage, inflammatory processes, or oxidative stress [29]. During disease, the damaged tissues and cells cannot synthesize Gln normally, and this will aggravate the existing damage and cause a vicious circle [30]. Hence, appropriate Gln supplementation should be given to critically ill patients as one of the effective treatment options. According to our analysis, ulinastatin can inhibit the release of inflammatory factors and inhibit a variety of proteases. Glutamine can provide basic energy for the gastrointestinal tract and reduce the damage caused by inflammatory factors and oxygen free radicals in the organs of patients. They work together to reduce the level of inflammatory factors in patients and improve liver function, so as to imporve the clinical therapeutic effect. The theoretical effect of Gln supplementation would be highly valid in pancreatitis where gastrointestinal function is generally affected. This study fully confirmed this point. Similarly, APACHE II and Balthazar CT scores were adopted to assess the disease condition of both groups, and the results indicated a much better recovery in the RG, which verified our hypothesis.

Then, to further understand the effect of ulinastatin combined with Gln, we also detected T lymphocyte subsets and inflammatory cytokines in patients. As an excellent indicator of the immune and metabolic functions, the function of T lymphocyte subsets has been confirmed in many studies [31]. Compared with the CG, the RG showed higher levels of IgM, IgA and IgG, suggesting that patients in the RG have better immune and metabolic functions. Inflammation, as the key mechanism of pancreatitis, is related to the severity of the disease [32]. In this study, IL-6, IL-8, TNF-α and hs-CRP in the RG decreased considerably, which confirmed that ulinastatin plus Gln can effectively inhibit the process of inflammatory reaction. We believe that ulinastatin can reduce pancreatic tissue damage by simultaneously inhibiting the activity of trypsin and other enzymes through two active functional regions of the enzyme-inhibiting spectrum. In addition, ulinastatin is also found to block the TLR4/My D88/NF-κB signaling pathway in a dose-dependent manner [33], which is the key pathway in inflammation [34]. Besides, Gln can effectively block the overflow of intestinal toxins and prevent the secretion of inflammatory cytokines into surrounding tissues and cells through maintaining the normal function of intestinal barrier [35]. Hence, the combination of the two has a more significant inhibitory effect on inflammatory cytokines. At last, we also compared the liver function between the two groups, and witnessed notably better improvement of liver function in the RG, which proved that ulinastatin plus glutamine also has better protective effects on the liver function of pancreatitis patients. The reason for this may also be consistent with our above analysis that ulinastatin in combination with Gln has a more significant inhibitory impact on inflammation and oxidative stress, as well as a better impact on maintaining the immune and metabolic function of the body, thus enhancing the recovery of patients' liver function.

There are still many limitations in this study. For example, we did not follow up the patients for long term prognosis, and it is vague how ulinastatin combined with Gln affects the long-term outcome of pancreatitis patients. Further, more basic *in vitro* experiments are needed to confirm the action of ulinastatin combined with Gln in improving pancreatitis. We will conduct a more complete and comprehensive analysis of the application of ulinastatin in combination with Gln to obtain more effective experimental results.

To sum up, ulinastatin combined with glutamine is effective in treating severe pancreatitis, which can efficiently reduce the inflammation of patients and facilitate the recovery of immune metabolism and liver function, and therefore the combined treatment has a high clinical application value.

Disclosure of conflict of interest

None.

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References

[1] Leppaniemi A, Tolonen M, Tarasconi A, Segovia-Lohse H, Gamberini E, Kirkpatrick AW, Ball CG, Parry N, Sartelli M, Wolbrink D, van

Goor H, Baiocchi G, Ansaloni L, Biffl W, Coccolini F, Di Saverio S, Kluger Y, Moore E and Catena F. 2019 WSES guidelines for the management of severe acute pancreatitis. World J Emerg Surg 2019; 14: 27.
[2] Lee PJ and Papachristou GI. New insights into acute pancreatitis. Nat Rev Gastroenterol Hepatol 2019; 16: 479-496.
[3] Aloysius MM, Thatti A, Gupta A, Sharma N, Bansal P and Goyal H. COVID-19 presenting as acute pancreatitis. Pancreatology 2020; 20: 1026-1027.
[4] Shah AP, Mourad MM and Bramhall SR. Acute pancreatitis: current perspectives on diagnosis and management. J Inflamm Res 2018; 11: 77-85.
[5] van Dijk SM, Hallensleben NDL, van Santvoort HC, Fockens P, van Goor H, Bruno MJ and Besselink MG; Dutch Pancreatitis Study Group. Acute pancreatitis: recent advances through randomised trials. Gut 2017; 66: 2024-2032.
[6] Anand ER, Major C, Pickering O and Nelson M. Acute pancreatitis in a COVID-19 patient. Br J Surg 2020; 107: e182.
[7] Portelli M and Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management. Hepatobiliary Pancreat Dis Int 2017; 16: 155-159.
[8] Garg R and Rustagi T. Management of hypertriglyceridemia induced acute pancreatitis. Biomed Res Int 2018; 2018: 4721357.
[9] Li ST, Dai Q, Zhang SX, Liu YJ, Yu QQ, Tan F, Lu SH, Wang Q, Chen JW, Huang HQ, Liu PQ and Li M. Ulinastatin attenuates LPS-induced inflammation in mouse macrophage RAW264.7 cells by inhibiting the JNK/NF-kappaB signaling pathway and activating the PI3K/Akt/Nrf2 pathway. Acta Pharmacol Sin 2018; 39: 1294-1304.
[10] Lee B, Lee SY, Kim NY, Rha KH, Choi YD, Park S and Kim SY. Effect of ulinastatin on postoperative renal function in patients undergoing robot-assisted laparoscopic partial nephrectomy: a randomized trial. Surg Endosc 2017; 31: 3728-3736.
[11] Wang H, Liu B, Tang Y, Chang P, Yao L, Huang B, Lodato RF and Liu Z. Improvement of sepsis prognosis by ulinastatin: a systematic review and meta-analysis of randomized controlled trials. Front Pharmacol 2019; 10: 1370.
[12] Zhang X, Zhu Z, Jiao W, Liu W, Liu F and Zhu X. Ulinastatin treatment for acute respiratory distress syndrome in China: a meta-analysis of randomized controlled trials. BMC Pulm Med 2019; 19: 196.
[13] Pan Y, Fang H, Lu F, Pan M, Chen F, Xiong P, Yao Y and Huang H. Ulinastatin ameliorates tissue damage of severe acute pancreatitis through modulating regulatory T cells. J Inflamm (Lond) 2017; 14: 7.
[14] Li D, Ji H, Zhao B, Xu C, Xia W, Han L, Yu D, Ju Y and Jin C. Therapeutic effect of ulinastatin on pulmonary fibrosis via downregulation of TGFbeta1, TNFalpha and NFkappaB. Mol Med Rep 2018; 17: 1717-1723.
[15] Cruzat V, Macedo Rogero M, Noel Keane K, Curi R and Newsholme P. Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients 2018; 10: 1564.
[16] Leone RD, Zhao L, Englert JM, Sun IM, Oh MH, Sun IH, Arwood ML, Bettencourt IA, Patel CH, Wen J, Tam A, Blosser RL, Prchalova E, Alt J, Rais R, Slusher BS and Powell JD. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science 2019; 366: 1013-1021.
[17] Luengo A, Gui DY and Vander Heiden MG. Targeting metabolism for cancer therapy. Cell Chem Biol 2017; 24: 1161-1180.
[18] Wang J, Li Y and Qi Y. Effect of glutamine-enriched nutritional support on intestinal mucosal barrier function, MMP-2, MMP-9 and immune function in patients with advanced gastric cancer during perioperative chemotherapy. Oncol Lett 2017; 14: 3606-3610.
[19] Hui L, Liu J, Zhang H and Pan C. Study on correlation between mixed SvO2, P (va) CO2 and LAC with APACHE II score, SOFA score and disease condition. Chongqing Medicine 2017; 46: 1326-1329.
[20] Konur S, Ozkahraman A, Surmeli N, Gunduz I, Iliklerden UH, Dertli R and Kayar Y. The severity of acute pancreatitis according to modified balthazar classification in patients with pancreatic cancer. Tumori 2020; 106: 356-361.
[21] Garber A, Frakes C, Arora Z and Chahal P. Mechanisms and management of acute pancreatitis. Gastroenterol Res Pract 2018; 2018: 6218798.
[22] Trikudanathan G, Wolbrink DRJ, van Santvoort HC, Mallery S, Freeman M and Besselink MG. Current concepts in severe acute and necrotizing pancreatitis: an evidence-based approach. Gastroenterology 2019; 156: 1994-2007, e3.
[23] Manrai M, Kochhar R, Gupta V, Yadav TD, Dhaka N, Kalra N, Sinha SK and Khandelwal N. Outcome of acute pancreatic and peripancreatic collections occurring in patients with acute pancreatitis. Ann Surg 2018; 267: 357-363.
[24] Zhai Y, Gan L, Huang S, Xing Q, Zhou X, Wang L, Feng C, Chen L and Li T. Therapeutic effect of ultrasound interventional perirenal catheter-assisted early peripancreatic lavage of protease inhibitor on severe acute pancreatitis in

miniature pigs. Pancreatology 2019; 19: 158-162.
[25] Eelen G, Dubois C, Cantelmo AR, Goveia J, Bruning U, DeRan M, Jarugumilli G, van Rijssel J, Saladino G, Comitani F, Zecchin A, Rocha S, Chen R, Huang H, Vandekeere S, Kalucka J, Lange C, Morales-Rodriguez F, Cruys B, Treps L, Ramer L, Vinckier S, Brepoels K, Wyns S, Souffreau J, Schoonjans L, Lamers WH, Wu Y, Haustraete J, Hofkens J, Liekens S, Cubbon R, Ghesquiere B, Dewerchin M, Gervasio FL, Li X, van Buul JD, Wu X and Carmeliet P. Role of glutamine synthetase in angiogenesis beyond glutamine synthesis. Nature 2018; 561: 63-69.
[26] Yang C, Wen J and Xia M. Effect of glutamine nutrition support on the intestinal mucosal barrier function and inflammatory response in patients with severe acute pancreatitis. Journal of Hainan Medical University 2017; 23: 17-21.
[27] Xie X, Li T and Yuan H. Protective effects of Ulinastatin on oxidative stress and inflammation of rat-derived cardiomyocytes H9c2. Am J Transl Res 2019; 11: 7094-7103.
[28] Pavlova NN, Hui S, Ghergurovich JM, Fan J, Intlekofer AM, White RM, Rabinowitz JD, Thompson CB and Zhang J. As extracellular glutamine levels decline, asparagine becomes an essential amino acid. Cell Metab 2018; 27: 428-438, e5.
[29] Li T and Le A. Glutamine metabolism in cancer. Adv Exp Med Biol 2018; 1063: 13-32.
[30] Freitas AKL, Silva MTB, Silva CMS, Prata MMG, Rodrigues FAP, Siqueira RJB, Lima AAM, Santos AA and Havt A. Alanyl-glutamine protects the intestinal barrier function in trained rats against the impact of acute exhaustive exercise. Braz J Med Biol Res 2020; 53: e9211.
[31] Lechner A, Schlosser H, Rothschild SI, Thelen M, Reuter S, Zentis P, Shimabukuro-Vornhagen A, Theurich S, Wennhold K, Garcia-Marquez M, Tharun L, Quaas A, Schauss A, Isensee J, Hucho T, Huebbers C, von Bergwelt-Baildon M and Beutner D. Characterization of tumor-associated T-lymphocyte subsets and immune checkpoint molecules in head and neck squamous cell carcinoma. Oncotarget 2017; 8: 44418-44433.
[32] Gukovskaya AS, Gukovsky I, Algul H and Habtezion A. Autophagy, inflammation, and immune dysfunction in the pathogenesis of pancreatitis. Gastroenterology 2017; 153: 1212-1226.
[33] Cao C, Yin C, Shou S, Wang J, Yu L, Li X and Chai Y. Ulinastatin protects against LPS-induced acute lung injury by attenuating TLR4/NF-kappaB pathway activation and reducing inflammatory mediators. Shock 2018; 50: 595-605.
[34] Ju M, He H, Chen S, Liu Y, Liu Y, Pan S, Zheng Y, Xuan L, Zhu D and Luo Z. Ulinastatin ameliorates LPSinduced pulmonary inflammation and injury by blocking the MAPK/NFkappaB signaling pathways in rats. Mol Med Rep 2019; 20: 3347-3354.
[35] Biancur DE, Paulo JA, Malachowska B, Quiles Del Rey M, Sousa CM, Wang X, Sohn ASW, Chu GC, Gygi SP, Harper JW, Fendler W, Mancias JD and Kimmelman AC. Compensatory metabolic networks in pancreatic cancers upon perturbation of glutamine metabolism. Nat Commun 2017; 8: 15965.