Safety of Different Doses of Ulinastatin Combined with Remifentanil in the Treatment of Severe Sepsis in ICU and Their effect on Survival Rate and Organ Function of Patients

Luo Min
Li Li
Liu Yi-lin
Su Lei
Liu Zhi-feng

Abstract. Objective. The purpose was to explore the safety of different doses of ulinastatin combined with remifentanil in the treatment of severe sepsis in ICU and to analyze their effect on survival rate and organ function of patients. **Methods.** 57 patients with severe sepsis in ICU admitted to our hospital (2018.1.1-2021.6.30) were selected as the research subjects, and randomly divided into control group (28 cases) and experimental group (29 cases). The control group was treated with conventional dose of ulinastatin combined with remifentanil, while the experimental group was treated with high dose of ulinastatin combined with remifentanil to compare and analyze the treatment safety, organ function and survival rate in the two groups. **Results.** After treatment, the APACHE-II scores of both groups were lower than those before treatment, and the APACHE-II score in the experimental group was lower than that in the control group ($P < 0.05$). There were statistically significant differences in ventilator supporting time and ICU stay time between the two groups after treatment ($P < 0.05$). The expression levels of inflammatory factors in the experimental group were lower than those in the control group after treatment ($P < 0.05$). The lung function and PICCO indexes in the experimental group were better than those in the control group after treatment ($P < 0.05$). The peripheral blood $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and 28-day survival rate in the experimental group were higher than those in the control group ($P < 0.05$). No adverse drug reactions such as sudden vomiting, dyspnea and rash occurred in the two groups during the treatment. **Conclusion.** High-dose ulinastatin combined with remifentanil has good therapeutic effect on severe sepsis in ICU. Compared with conventional dose, high-dose ulinastatin can effectively protect the body's immune regulation, restore organ function and significantly improve the 28-day survival rate of patients, with medication safety, which has high value of clinical application and promotion.

Keywords: severe sepsis in ICU; organ function; remifentanil; ulinastatin
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LuoMin, 1.First CliniIcal Medical College of Southern Medical University,Guangzhou,510010,China. 2.Department of Critical Care Medicine,YueBei People's Hospital,The Affiliated Hospital of Shantou University, Shaoguan, 512026, China.Li Li, Department of Critical Care Medicine, YueBei People's Hospital,The Affiliated Hospital of Shantou University, Shaoguan, 512026, China.Liu Yi-lin, Department of Critical Care Medicine, YueBei People's Hospital,The Affiliated Hospital of Shantou University, Shaoguan, 512026, China. Su lei, 1.First CliniIcal Medical College of Southern Medical University,Guangzhou,510010,China. 2.Department of Critical Care Medicine, General Hospital of Southern Theatre Command of People's Liberation Army of China,Guangzhou ,510010,China.*Corresponding Author1: Su lei, Email: slei-icu@163.com.Liu zhi-feng*, 1.First CliniIcal Medical College of Southern Medical University,Guangzhou,510010,China.2.Department of Critical Care Medicine, General Hospital of Southern Theatre Command of People's Liberation Army of China,Guangzhou ,510010,China.* Corresponding Author2: Liu zhi-feng,Email: Lzhifeng-icu@163.com.*

Sepsis is a systemic inflammatory response syndrome caused by infection in the body, and patients often show symptoms such as fever, chills, palpation and shortness of breath. The disease can develop into severe sepsis and septic shock, resulting in systemic organ dysfunction and circulatory disturbance, with a high fatality

rate[1-4]. Sepsis is an extremely dangerous disease that kills about 14,000 people every day worldwide due to its complications. According to the epidemiological investigation abroad, the mortality rate of sepsis has exceeded that of myocardial infarction, and sepsis has become the main cause of death of patients with no heart disease in ICU. In recent years, although anti-infection treatment and organ function support technology have made important progress in China, the mortality of sepsis remains high. Combined with the high treatment cost, sepsis has posed a great threat to the life quality and health of human beings. Sepsis is mainly caused by infection of pathogenic bacteria in the body, mainly including gram-negative bacteria (meningococci, colibacillus and klebsiella) and gram-positive bacteria (staphylococcus aureus, pneumococcus and streptococcus). In addition, hemorrhagic fever with renal syndrome virus is also easy to cause sepsis[5-8]. At present, to explore the effective treatment of sepsis has become the focus and difficulty in the field of critical care medicine. In clinical practice, comprehensive treatment is often used to control the condition of sepsis, with the core of treatment still as the regulation of immune inflammatory response and antibiotic treatment. Uinastatin is a small molecular protein extracted from the fresh urine of healthy adult males, with good biological safety. As a common immunoregulatory drug in China at present, it is often used in the treatment of severe diseases such as paraquat poisoning, burns, scalds and acute hemorrhagic necrotizing pancreatitis[9-12]. According to relevant medical studies, high dose ulinastatin has not shown obvious adverse reactions in clinical studies. Based on this, this paper mainly explores the safety of different doses of ulinastatin combined with remifentanil in the treatment of severe sepsis in ICU, and analyzes their effect on the survival rate and organ function of patients, aiming to provide new medication ideas for the clinical treatment of sepsis, reported as follows.

MATERIALS AND METHODS

General Information

57 patients with severe sepsis in ICU admitted to our hospital (2018.1.1-2020.12.31) were selected as the research subjects, and randomly divided into control group (28 cases) and experimental group (29 cases). There were no significant differences in age, gender, primary disease and other general data between the two groups (P>0.05), which was suitable for comparative study, as shown in Table 1.

Table 1 Comparison of general data between the two groups

	Control group (n=28)	Experimental group (n=29)	X^2/t	P
Age (years old)	42.3±4.7	42.6±5.2	0.2282	0.8203
APACHEII score	23.7±6.5	23.6±6.4	0.0585	0.9535
Gender			0.1412	0.707
Male	17(60.71)	19(65.52)		
Female	11(39.29)	10(34.48)		
Primary diseases			0.1444	0.704
Lung infection	11(39.29)	11(37.93)		
Abdominal infection	8(28.57)	7(24.14)		
Multiple trauma	5(17.86)	6(20.69)		
Cerebrovascular accidents	3(10.71)	3(10.34)		
Severe acute pancreatitis	1(3.57)	2(6.90)		
Smoking			0.0081	0.928
Yes	19(67.86)	20(68.97)		
No	9(32.14)	9(31.03)		
Drinking			0.1713	0.707
Yes	19(67.86)	21(72.41)		
No	9(32.14)	8(27.59)		
Residence			0.2595	0.610
Urban area	25(89.29)	27(93.10)		
Rural area	3(10.71)	2(6.90)		

Inclusion Criteria

① It met the clinical diagnostic criteria of severe sepsis in *International Guidelines for Management of Sepsis and Septic Shock (2016)*; ② The patients were aged no less than 18 years

old; ③ The patients had complete clinical medical records; ④ This study was approved by the hospital ethics committee, and the patients and their families knew the purpose and process of the study, accepted the treatment plan and signed the informed consent.

Exclusion Criteria

① The patients had tumors or received organ transplantation; ② The patients had chronic organ failure; ③ The patients received immunomodulatory or immunosuppressive drug therapy during hospitalization; ④ The patients were allergic to drugs used in the study; ⑤ The patients were unable to or refused to cooperate due to personal reasons.

Methods

All patients received anti-infection, vasoactive drugs, fluid resuscitation, organ supporting and other routine treatment methods as prescribed by doctors.

The control group was treated with conventional dose of ulinastatin combined with remifentanil. On the basis of routine treatments, the patients were injected with 5000U.kg^{-1}·d^{-1} dose of ulinastatin (specification: 100,000U/vial; manufacturer: Techpool Bio-Pharma Co., Ltd.; SFDA approval number: H19990134) by intravenous drip, and 0.05μg/kg/min of remifentanil (specification: 1mg/vial; manufacturer: Jiangsu Nhwa Pharmaceutical Co., Ltd.; SFDA approval number: H20143314) for analgesia by continuous pumping with a micropump.

The experimental group was treated with high dose of ulinastatin combined with remifentanil. The dose of ulinastatin was adjusted to 25,000U.kg^{-1}·d^{-1}, and other operations were the same as those of the control group.

Observation Indexes

Perioperative basic condition. The APACHE-II scores, ventilator supporting time and ICU stay time of the two groups were recorded, statistically analyzed and compared.

Expression levels of inflammatory factors. The bronchial tubes involved in inflammation were sequentially flushed with sterile saline, and ELISA kits were used to detect the levels of TNF-α (tumor necrosis factor) and IL-6 interleukin-6) in plasma and lung tissue of patients. Enzyme-linked immunosorbent assay (ELISA) was used to detect CRP (serum C-reactive protein), and immunochromatography was used to detect the PCT (procalcitonin) expression level.

Lung function. The detection indicators included arterial partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), lactic acid (Lac) and alveolo-arterial oxygen partial pressure difference (A-aDO2).

Pulse indicate Contour Cardiac Output (PICCO). Cardiac output (CO), cardiac index (CI) and peripheral vascular resistance (SVR) of patients were mainly detected..

T lymphocyte subsets. Venous blood was extracted from patients and sent to the laboratory to detect $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ values.

Survival rate. The patients were followed up for 28 days, and the survival of the two groups after treatment was recorded.

Adverse reactions. Sudden adverse reactions occurred during medication in the two groups were counted.

Statistical Treatment

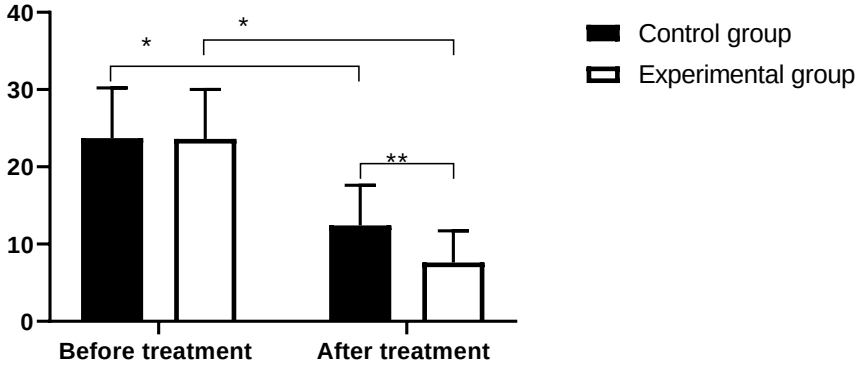
In this study, SPSS20.0 was selected as the data processing software, and GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used to draw pictures of the data. The data included in the study were count data and measurement data, tested by X^2 test, t test and normality test. The difference was statistically significant when $p < 0.05$.

RESULTS

Perioperative Basic Condition

After treatment, the APACHE-II scores of both groups were lower than those before treatment, and the APACHE-II score in the experimental group was lower than that in the control group, with statistically significant differences (Figure 1). There were statistically significant differences in ventilator supporting time and ICU stay time between the two groups after treatment (Figure 2).

Figure 1 Comparison of APACHE-II scores between the two groups ($\bar{x}$±s)



Note: The abscissa represents before treatment and after treatment, and the ordinate represents the score.

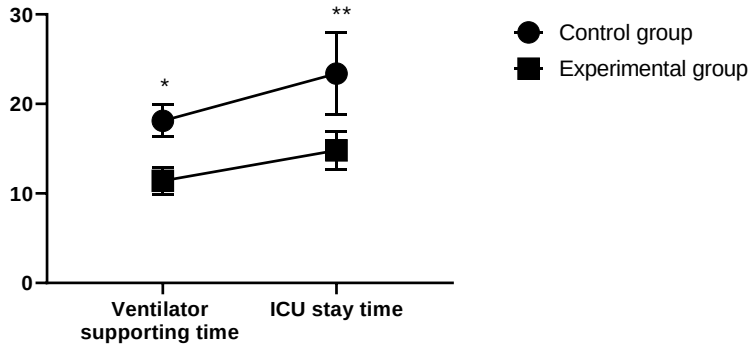
The APACHE-II scores of the control group before and after treatment were (23.7±6.5)and (12.4±5.2), respectively.

The APACHE-II scores of the experimental group before and after treatment were (23.6±6.4)and(7.6±4.1), respectively.

* from left to right indicated that the APACHE-II scores of the control group and experimental group before treatment were significantly different from those after treatment (t=7.2316, 11.2793; P=0.000).

** indicated a significant difference in the APACHE-II scores between the two groups after after treatment (t=3.8774; P=0.0003).

Figure 2 Comparison of ventilator supporting time and ICU stay time between the two groups ($\bar{x}$±s)



Note: The abscissa represents the evaluation dimensions (ventilator supporting time and ICU stay time), and the ordinate represents time (d).

The ventilator supporting time and ICU stay time in the control group were (18.1±1.8) and (23.4±4.6), respectively.

The ventilator supporting time and ICU stay time in the experimental group were (11.4±1.5) and (14.8±2.1), respectively.

* indicated a significant difference in the ventilator supporting time between the two groups (t=15.2882; P=0.000).

** indicated a significant difference in the ICU stay time between the two groups (t=9.1325; P=0.000).

Changes in the Expression Levels of Inflammatory Factors

The expression levels of inflammatory factors in the experimental group were lower than those in the control group after treatment (P < 0.05), with statistical significance, as shown in Table 2.

Table 2 Changes in the expression levels of inflammatory factors ($\bar{x}$±s)

Factors	Control group(n=28)	Experimental group (n=29)	t	P
TNF-α(ng/L)	100.5±39.6	75.6±25.7	2.8258	0.0066
IL-6(ng/L)	111.5±31.2	91.4±28.5	2.5410	0.0139
CRP(ng/L)	16.7±3.8	11.3±2.4	6.4384	0.000

PCT(mg/L)	1.06±0.23	0.85±0.16	4.0134	0.0002

Lung Function Changes

The lung function indexes in the experimental group were better than those in the control group after treatment (P < 0.05), with statistically significant differences, as shown in Table 3.

Table 3 Comparison of lung function indexes between the two groups($\bar{x}$±s)

	Control group(n=28)	Experimental group(n=29)	t	P
PO_2(mmHg)	85.3±5.4	104.2±7.3	11.0808	0.000
PCO_2(mmHg)	47.8±1.6	36.2±1.3	30.0905	0.000
Lac(mmol/L)	1.9±0.3	0.7±0.2	17.8274	0.000
A-aDO2(mmol/L)	14.8±3.3	9.1±3.2	6.6207	0.000

Picco Changes

The PICCO indexes in the experimental group were better than those in the control group after treatment (P < 0.05), with statistically significant differences, as shown in Table 4.

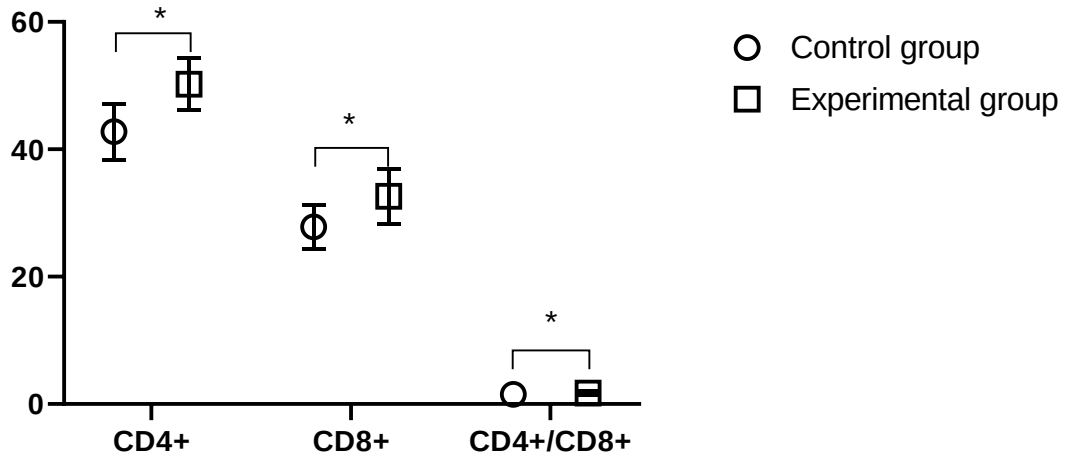
Table 4 Comparison of PICCO indexes between the two groups($\bar{x}$±s)

	Control group(n=28)	Experimental group(n=29)	t	P
CI(L/min)	6.2±0.3	5.7±0.4	5.3242	0.000
CO($L \cdot min^{-1} \cdot m^{-2}$)	3.9±0.1	3.1±0.2	18.9935	0.000
SVR(Dyn.s m^2/cm^5)	1084.9±85.6	1257.4±88.3	7.4849	0.000

Comparison of T Lymphocyte Subsets Between the Two Groups

The peripheral blood $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ in the experimental group were higher than those in the control group (P < 0.05), with statistically significant differences between the two groups, as shown in Figure 3.

Figure 3 Comparison of T lymphocyte subsets between the two groups ($\bar{x}$±s)



Note: The abscissa represents the detection indexes of T lymphocyte subsets, and the ordinate represents the percentage (%).

The $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ values of the control group after treatment were (42.8±4.4), (27.8±3.5) and (1.53±0.31), respectively.

The $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ values of the experimental group after treatment were (50.2±4.1), (32.6±4.3) and (1.72±0.36), respectively.

* from left to right indicated significant differences in the $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ values between the two groups (t=6.5719, 4.6126, 2.1319; P < 0.05).

Comparison of Survival Rates

The 28-day survival rate in the experimental group was higher than that in the control group ($P < 0.05$), with a statistically significant difference, as shown in Table 5.

Table 5 Comparison of survival rates between the two groups [n(%)]

Group	The first week	The second week	The third week	The fourth week
Control group(n=28)	25(89.29)	21(75)	19(67.86)	14(46.43)
Experimental group (n=29)	27(93.10)	25(86.21)	23(79.31)	18(62.07)
X^2				4.9278
P				0.026

Occurrence of Adverse Reactions

No adverse drug reactions such as sudden vomiting, dyspnea and rash occurred in the two groups during the treatment. The drugs had high safety.

DISCUSSION

Sepsis is the most serious complication of critically ill patients in the clinic at present, which is characterized by acute onset, prolonged illness, rapid development, high mortality and high cost. Therefore, the study of sepsis treatment options in clinic is even more urgent, and also becomes a medical focus and difficulty needing to be overcome in the ICU [13-16]. The reason why the treatment of sepsis is once an urgent medical problem is mainly due to its complex pathogenesis which involves a series of physiological changes such as inflammatory mediators, bacterial endotoxin, immune function inhibition, intestinal bacterial translocation and coagulation disorders. In particular, immunosuppression and imbalance of inflammatory response are considered as the key causes of multi-organ and mult-system damage in patients, and become the core event in the development of sepsis. Therefore, in clinical medical research, inhibition of inflammatory response and regulation of immune function are also taken as the main directions in the treatment of sepsis. Ulinastatin is a common drug in the treatment of sepsis in ICU, while remifentanil is a fentanyl μ-opioid receptor agonist that can reach the blood-brain balance in one minute after entering the body and can be rapidly dissolved by blood and tissues. Therefore, the drug has a rapid onset but a short duration. With the main purpose as analgesia, remifentanil is often used in combination with other drugs in general anesthesia induction and maintenance. It takes effect after intravenous injection for several minutes, and can cause dose-dependent sedative and analgesic effects, which can produce pleasure in patients, and lead to forgetting and loss of consciousness in patients with ultra-high dose. It can also produce dose-dependent respiratory inhibition. Because the drug directly excites the chemoreceptor of vomiting, it will produce nausea and vomiting. Sometimes remifentanil can also produce rigid abdominal wall, chest wall and upper respiratory muscles, so ventilation cannot be performed in the patients. Ulinastatin is essentially a glycoprotein with the effect of a broad-spectrum enzyme inhibitor, which can effectively scavenge free radicals, inhibit inflammatory mediators, reduce ischemia-reperfusion injury, and improve the circulatory state during shock [17-20]. Sepsis does not belong to a single organ or system disease, and usually requires comprehensive intervention treatment. The combination of ulinastatin and remifentanil can be used to treat sepsis, which still has great development potential. The analgesic effect and side effects of remifentanil will show a certain dependence with the dose change. In addition, remifentanil may also cause respiratory depression, rigid skeletal muscles, hypotension and other adverse events that will increase with the increase of dose. Therefore, the dosage of remifentanil is very limited, which needs to be adjusted in a certain dose range according to the patient's condition. In contrast, ulinastatin is an endogenous glycoprotein with high biological safety, so ulinastatin has a large dose range of medication safety[21-24].

This study showed that the APACHE-II scores of both groups after treatment were lower than those before treatment, and the APACHE-II score in the experimental group was lower than that in the control group. There were statistically significant differences in ventilator supporting time and ICU stay time between the two groups after treatment. These demonstrate that compared with the conventional dosage, high-dose ulinastatin combined with remifentanil can shorten the duration of mechanical ventilation and hospital stay of patients, and reduced the APACHE-II score. The expression levels of inflammatory factors in the experimental group were lower than those in the control group after

treatment, indicating that high-dose ulinastatin has a stronger inhibitory effect on inflammatory mediators. The lung function and PICCO indexes in the experimental group were better than those in the control group after treatment, suggesting that high-dose ulinastatin has a better effect on the on improving the organ function of patients. The peripheral blood $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ and 28-day survival rate in the experimental group were higher than those in the control group. No adverse drug reactions such as sudden vomiting, dyspnea and rash occurred in the two groups during the treatment, indicating high safety of the drugs. This results are consistent with those of Jianxun Ding et al.[25] who have stated that remifentanil combined with high-dose ulinastatin has a good clinical therapeutic effect on severe sepsis, and high-dose ulinastatin can exert a better effect on protecting the body of patients.[26]

In conclusion, high-dose ulinastatin combined with remifentanil has good therapeutic effect on severe sepsis in ICU. Compared with conventional dose, high-dose ulinastatin can effectively protect the body's immune regulation, restore organ function and significantly improve the 28-day survival rate of patients, with medication safety, which has high value of clinical application and promotion.

REFERENCES

1. Farhana,Mushtaq Ahmad,Basharat, et al.A PROSPECTIVE, RANDOMIZED STUDY USING ULINASTATIN FOR THE TREATMENT OF PATIENTS WITH SEVERE SEPSIS[J].,2014.
2. Yu, Zhaoxia,Rayile, Aisa,Zhang, Xiangyang, et al.Ulinastatin protects against lipopolysaccharide-induced cardiac microvascular endothelial cell dysfunction via downregulation of lncRNA MALAT1 and EZH2 in sepsis[J].International journal of molecular medicine,2017,39(5):1269-1276.
3. Heng Jin,Lijun Wang,Songtao Shou, et al.Ulinastatin mediates suppression of regulatory T cells through TLR4/NF-κB signaling pathway in murine sepsis[J].International immunopharmacology,2018,64:411-423.
4. Nakamura, Masaki,Takeuchi, Takashi,Kawahara, Tetsushi, et al.Simultaneous targeting of CD14 and factor XIa by a fusion protein consisting of an anti-CD14 antibody and the modified second domain of bikunin improves survival in rabbit sepsis models[J].European Journal of Pharmacology: An International Journal,2017,802:60-68.
5. Yang Jun,Wang Xin,Min Su, et al.Ulinastatin inhibited sepsis‐induced spinal inflammation to alleviate peripheral neuromuscular dysfunction in an experimental rat model of neuromyopathy[J].Journal of Neurochemistry: Offical Journal of the International Society for Neurochemistry,2017,143(2):225-235.
6. Si-tong LI,Qi DAI,Shu-xian ZHANG, et al.Ulinastatin attenuates LPS-induced inflammation in mouse macrophage RAW264.7 cells by inhibiting the JNK/NF-κB signaling pathway and activating the PI3K/Akt/Nrf2 pathway[J]. Chinese Journal of Pharmacology(English version),2018,39(8):1294-1304.
7. Karnad,D.R.,Bhadade,R.,Verma,P.K., et al.Intravenous administration of ulinastatin (human urinary trypsin inhibitor) in severe sepsis: A multicenter randomized controlled study[J].Intensive care medicine,2014,40(6):830-838.
8. Ma, Chi,Han, Dong-Feng,Jin, Hang, et al.A Combination of Ulinastatin and Xuebijing Amplifies Neuroprotection after Transient Cerebral Ischemia via Attenuating Apoptosis Signal Pathways in Hippocampus[J].Current pharmaceutical design,2018,24(44):5342-5347.
9. Wu, Jian,Yan, Xin,Jin, Guoqiang.Ulinastatin protects rats from sepsis-induced acute lung injury by suppressing the JAK-STAT3 pathway[J].Journal of cellular biochemistry.,2019,120(2):2554-2559.
10. Fan, Yingnan,Wang, Qianmei,Shi, Quanxing, et al.Ulinastatin and/or thymosin alpha 1 for severe sepsis: A systematic review and meta-analysis[J].The journal of trauma and acute care surgery,2016,80(2):335-340.
11. Shi, Heng,Hong, Yun,Qian, Jianfang, et al.Xuebijing in the treatment of patients with sepsis[J].The American journal of emergency medicine,2017,35(2):285-291.
12. Yu-Jun Wang,Li Yu.Effect of prostaglandin E1 combined with Xuebijing on the inflammatory response process and target organ function in patients with sepsis[J]. Journal of Hainan Medical University(English version),2018,24(4):112-115.
13. Chen, Shengguang,Dai, Guoxing,Hu, Jiawen, et al.Discovery of Xuebijing Injection Exhibiting Protective Efficacy on Sepsis by Inhibiting the Expression of HMGB1 in Septic Rat Model Designed by Cecal Ligation and Puncture[J].American journal of therapeutics,2016,23(6):E1819-E1825.
14. Guang-Ke Cao,Yu-Liang Zhao,Xiu-Mei Zhou, et al.Effects of blood purification combined with Xuebijing on coagulation, immunity, inflammation and vascular factors in sepsis patients[J]. Journal of Hainan Medical University(English version),2019,25(13):36-40.
15. Luo, Guoan,Dong, Linyin,Zhao, Hongzhi, et al.Identification of NF-kappa B Inhibitors in Xuebijing injection for sepsis treatment based on bioactivity-integrated UPLC-Q/TOF[J].Journal of Ethnopharmacology: An Interdisciplinary Journal Devoted to Bioscientific Research on Indigenous Drugs,2013,147(2):426-433.
16. Xu, Tanye,Zhou, Lin,Shi, Yingying, et al.Metabolomics approach in lung tissue of septic rats and the interventional effects of Xuebijing injection

using UHPLC-Q-Orbitrap-HRMS[J].The Journal of Biochemistry,2018,164(6):427-435.
17. Li, Ailin,Li, Jing,Bao, Yuhua, et al.Xuebijing injection alleviates cytokine-induced inflammatory liver injury in CLP-induced septic rats through induction of suppressor of cytokine signaling 1[J].Experimental and therapeutic medicine,2016,12(3 Pt.A):1531-1536.
18. Jin Li,Jiao Liu,Wei Liu, et al.A Green Antioxidant Activity-Integrated Dual-Standard Method for Rapid Evaluation of the Quality of Traditional Chinese Medicine Xuebijing Injection by On-Line DPPH-CE-DAD[J].,2016.
19. Qiuyue Zhong,Zhenhui Wang,Lihua Zuo, et al.Simultaneous determination and pharmacokinetic study of twelve bioactive compounds in rat plasma after intravenous administration of Xuebijing injection by UHPLC-Q-Orbitrap HRMS[J].Journal of Pharmaceutical and Biomedical Analysis: An International Journal on All Drug-Related Topics in Pharmaceutical, Biomedical and Clinical Analysis,2017,146:347-353.
20. Zuo, Lihua,Sun, Zhi,Hu, Yurong, et al.Rapid determination of 30 bioactive constituents in XueBiJing injection using ultra high performance liquid chromatography-high resolution hybrid quadrupole-orbitrap mass spectrometry coupled with principal component analysis[J].Journal of Pharmaceutical and Biomedical Analysis: An International Journal on All Drug-Related Topics in Pharmaceutical, Biomedical and Clinical Analysis,2017,137:220-228.
21. Tang, F. -B.,Dai, Y. -L.,Hu, S., et al.Xuebijing injection treatment inhibits vasopermeability and reduces fluid requirements in a canine burn model[J].European journal of trauma and emergency surgery: official publication of the European Trauma Society,2017,43(6):875-882.
22. Wei Chen.Effect of Xuebijing combined with ulinastatin on the homeostasis of sepsis patients[J]. Journal of Hainan Medical University(English version),2019,25(13):41-45.
23. Yu, Lechang,Chai, Yanfen,Cao, Chao, et al.ULINASTATIN PROTECTS AGAINST LPS-INDUCED ACUTE LUNG INJURY BY ATTENUATING TLR4/NF-KB PATHWAY ACTIVATION AND REDUCING INFLAMMATORY MEDIATORS[J].Shock: Molecular, cellular, and systemic pathobiological aspects and therapeutic approaches = The official journal of the Shock Society, the European Shock Society, the Brazilian Shock Society, the International Federation of Shock Societies,2018,50(5):595-605.
24. Xiao, Bing,Gong, Xun,Yuan, Ting, et al.Xuebijing combined with ulinastation benefits patients with sepsis: A meta-analysis[J].The American journal of emergency medicine,2018,36(3):480-487.
25. Jianxun Ding.,Shi-Hui Xiao,Liang Luo, et al.Curative efficacy and safety of traditional Chinese medicine xuebijing injections combined with ulinastatin for treating sepsis in the Chinese population[J].Medicine,2018,97(23).
26. Jiafeng Yao, Li Wang, Kai Liu, Hongtao Wu, Hao Wang, Jingshi Huang, Jianping Li. Evaluation of electrical characteristics of biological tissue with electrical impedance spectroscopy. Electrophoresis , 2020, 41(16-17): 1425-1432. doi: 10.1002/elps.201900420.