Tropical Journal of Pharmaceutical Research December 2023; 22 (12): 2525-2530
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v22i12.15

Original Research Article

Application of a combination of lactated Ringer's solution and ulinastatin for early resuscitation in sepsis

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Sent for review: 1 December 2022 *Revised accepted: 27 November 2023*

Abstract

Purpose: *To investigate the effect of early resuscitation using a combination of lactated Ringer's solution and ulinastatin on the survival rate of patients with sepsis.*
Methods: *82 patients with septic shock admitted to Xi'an People's Hospital, China from June 2017 to December 2020 were enrolled and randomly divided into control and study groups (n = 41 each). Patients in control group were given conventional fluid resuscitation and anti-infective therapy, while patients in study group were additionally given ulinastatin. Acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score, and tissue perfusion were determined. Also, mechanical ventilation time, intensive care unit (ICU) stay time, and 28-day mortality rates were recorded.*
Results: *Both groups presented no significant difference in clinical characteristics before treatment. After treatment, APACHE II score, SOFA score, and lactic acid level of the study group significantly decreased ($p < 0.05$), and the patients' condition improved. Moreover, inflammation-related indices, viz, procalcitonin (PCT), white blood cells (WBC), and C reactive protein (CRP) were significantly reduced in the study group ($p < 0.05$). Renal function-related indices which include creatinine, and blood urea nitrogen (BUN) significantly decreased in study group ($p < 0.05$). Mechanical ventilation time, and ICU stay time were significantly shortened ($p < 0.0001$), while short-term survival rate significantly improved ($p < 0.05$).*
Conclusion: *Lactated Ringer's solution in combination with ulinastatin expedites tissue perfusion and recovery, suppresses inflammation, enhances renal function, and significantly enhances the survival rate of septic patients. These findings provide valuable information for exploring new therapeutic approaches to sepsis.*

Keywords: *Lactated ringer's solution, Ulinastatin, Sepsis*

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INTRODUCTION

Sepsis is a life-threatening syndrome of organ dysfunction that arises in response to an infection in the host [1]. Sepsis and septic shock are major healthcare problems that affect millions of people worldwide each year [2]. Despite the continuous improvement of clinical treatment strategies, pathogenesis of sepsis is extremely complex and incompletely understood, resulting in limited treatment methods. Therefore, it is important to develop new clinical treatment

strategies to improve the survival rate and life quality of patients. According to international guidelines for management of sepsis and septic shock, fluid therapy is a key part of resuscitation of sepsis and septic shock, and it is advised to administer at least 30 mL/kg of intravenous crystalloids within 3 h for patients with sepsis-induced hypoperfusion or septic shock [3]. At present, lactated ringer's solution is cost-effective, and widely used in clinical treatment. Its chemical composition is more similar to extracellular fluid, which can effectively replenish body electrolytes and tissue perfusion, and reduce organ injury. Therefore, lactated ringer's solution has been chosen as an early liquid resuscitation reagent. In addition, ulinastatin is a Kunitz-type human protease inhibitor found in urine, with physiological activities which involves suppression of neutrophil elastase and stimulation of multiple proinflammatory cytokines [4], and is commonly used in treatment of sepsis [5]. The goal of treating septic patients or septic shock is to improve survival. However, efficacy of lactated ringer's solution in combination with ulinastatin remains unclear.

This study investigates the effect of using the combination of lactated ringer's solution and ulinastatin on inflammatory responses and renal function of patients with sepsis by assessing tissue perfusion, changes in inflammation-related indices and renal function-related indices.

METHODS

General information

A total of 82 septic patients admitted to Xi'an People's Hospital from June 2017 to December 2020 were enrolled. The patients were randomly allocated to study and control groups comprised of 41 patients each.

Inclusion criteria

Patients who met to the 2017 international guidelines for management of sepsis and septic shock [6] and consented to participate in the study were enrolled.

Exclusion criteria

Patients with specific medical history, including malignancy, cognitive impairment, and heart failure, suspected or confirmed pregnancy or lactation, and known allergy to ulinastatin. Study protocol was approved by Institutional Ethics Committee of Xi'an People's Hospital (no. 2017051106XA), and met the criteria in the Declaration of Helsinki [7].

Treatments

In accordance with the 2016 international guidelines for sepsis and septic shock management, the patients received infection control, standard therapy, and anti-infection interventions, which encompassed fluid resuscitation, antibiotics, anti-inflammatory medications, vascular agents, and mechanical ventilation. Patient's vital signs, mean arterial pressure (MAP), central venous oxygen saturation ($ScvO_2$), central venous pressure (CVP), and urine output were measured. Patients were administered a cumulative amount of 500 to 1000 mL of 0.9 % lactated Ringer's solution. (Xuzhou No. 5 Pharmaceutical Factory, Sinophosphatid approval H32020445) within 1 h to maintain a MAP of 50 - 60 mmHg and urine excretion of 0.5 - 1.0 mL/kg/h. Subsequently, fluid volume was adjusted according to specific clinical situation. Patients in study and control groups were administered 200,000 IU per day ulinastatin (Techpool, Guangdong, China) and normal saline respectively during treatment. Ulinastatin was dissolved in normal saline and injected intravenously for 7 days.

Evaluation of parameters/indices

Clinical data

Clinical data collected were gender, age, infection site, inflammation and renal function-related indices.

Acute physiology and chronic health evaluation (APACHE II) score

Acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA) score were assessed within 24 h of admission, and the highest value was recorded.

Blood parameters

Blood samples were collected on first day after admission and 7 days after ulinastatin treatment to measure lactic acid level, white blood cell (WBC), procalcitonin (PCT), C-reactive protein (CRP), creatinine, and blood urea nitrogen (BUN).

Vital signs and changes in patients' condition

At the same time of blood sample collection, vital signs and changes in patients' condition were closely monitored, and the mechanical ventilation time, intensive care unit (ICU) stay time, and 28-day survival rate were recorded. The 28-day

survival rate is defined as life status 28 days after ICU admission. The ICU stay time is the duration of stay in ICU. Re-admission to ICU within 48 h was not considered a successful transfer out of the ICU, and then ICU stay time was calculated as sum of the two ICU stays. Mechanical ventilation was recorded in same way as ICU stay time.

Statistical analysis

Statistical package for social sciences (SPSS version 26.0 software) was employed for data analysis. Data were presented as mean ± standard deviation (SD), and evaluated using student *t*-test. Enumeration data were analyzed using chi-square test. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical characteristics

During the study period, a total of 96 septic patients were admitted to Xi'an People's Hospital, including 82 patients who met the inclusion criteria. Comparative analysis showed that the two patient groups had non-significant difference in age, gender distribution, underlying medical conditions, APACHE II scores, SOFA scores, lactic acid levels, infection locations, as well as biomarkers related to inflammation and renal function ($p > 0.05$). Thus, the overall health status and disease severity in both groups were essentially not different (Table 1).

Tissue perfusion

After one week of ulinastatin treatment, APACHE II and SOFA scores significantly reduced ($p < 0.05$), indicating that ulinastatin improved patients' condition (Table 2). Also, ulinastatin treatment further reduced lactic acid levels following lactated ringer's solution treatment ($p = 0.0398$, Table 2).

Inflammation

Three inflammatory indicators (PCT, WBC, and CRP) were evaluated to assess inflammatory responses and the results revealed that both control and study groups showed no difference in concentration of inflammatory markers before treatment.

Table 1: Comparison of baseline characteristics between study and control groups (N = 41)

Characteristic	Control group	Study group	*P*-value
Age (years)	60.2±8	59.4±6	0.2555
Gender			
Male	25	22	
Female	16	19	
APACHE II	23.19±3.23	24.21±4.82	0.4613
SOFA	8.23±2.65	9.42±3.81	0.5185
Infection site			
Abdominal infection	8	11	
Respiratory system infection	7	6	
Urinary system infection	11	9	
Blood infection	6	3	
Lung	4	7	
Others	5	5	
WBC (10^9/L)	12.58±2.69	13.15±3.1	0.6703
Lactic acid (mmol/L)	4.1±0.82	4.3±0.65	0.8823
PCT (µg/L)	0.48±0.21	0.53±0.18	0.3986
CRP (mg/L)	62.43±22.57	59.64±26.72	0.4872
Creatinine (µmol/L)	4.18±0.82	4.33±0.65	0.7866
BUN (mmol/L)	12.14±0.32	11.87±0.21	0.5289

Acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA), white blood cell (WBC), procalcitonin (PCT), C-reactive protein (CRP), and blood urea nitrogen (BUN)

Table 2: Comparison of disease improvement, and tissue perfusion after ulinastatin treatment (N = 41)

Indicator	Control group	Study group	*P*-value
APACHE II	20.7±5.41	16.29±3.73	0.0214
SOFA	7.84±2.03	5.12±1.96	0.0249
Lactic acid (mmol/L)	2.25±0.54	1.38±1.03	0.0398

Note: Acute physiology and chronic health evaluation (APACHE II) score, sequential organ failure assessment (SOFA)

However, combined use of lactated Ringer's solution and ulinastatin significantly reduced concentration of inflammation-related markers (Table 3).

Table 3: Comparison of inflammation-related markers (N = 41)

Indicator	Control group	Study group	*P*-value
PCT (μg/L)	0.41±0.35	0.33±0.24	<0.0001
WBC (10^9/L)	11.27±2.18	7.69±1.78	0.0073
CRP (mg/L)	55.39±23.86	21.94±19.62	<0.0001

Note: Procalcitonin (PCT), white blood cell (WBC), and C-reactive protein (CRP)

Renal function

Levels of Creatinine and BUN showed no significant differences before treatment in study and control groups (Table 4). Nevertheless, combination of lactated Ringer's solution and ulinastatin significantly downregulated their expression than lactated ringer's solution alone.

Table 4: Comparison of renal function-related indicators (N = 41)

Indicator	Control group	Study group	*P*-value
Creatinine (μmol/L)	2.25±0.54	1.38±1.03	0.0219
Blood urea nitrogen (mmol/L)	7.58±0.24	5.31±0.44	0.024

Survival rate

Mechanical ventilation time and duration of hospitalization in the ICU were significantly shorter in study group compared to control group ($p < 0.05$). Also, 28-day survival rate was higher in study group compared to control group ($p < 0.05$) (Table 5). Furthermore, 5 and 11 patients' death was recorded in study and control group respectively (Figure 1). Among the dead patients in study group, 3 died from multiple organ failure, and 2 died from acute respiratory distress syndrome and refractory shock. In control group, 6 died from multiple organ failure, 3 died from refractory shock, and 2 died from acute respiratory distress syndrome.

Table 5: Clinical observation indices (N = 41)

Indicator	Control group	Study group	*P*-value
Mechanical ventilation time (hours)	11.96±4.71	7.42±3.19	0.0011
ICU stay time (days)	23.53±3.46	12.41±5.28	< 0.0001
28-day survival rate	30(73.17%)	36(87.81%)	0.0376

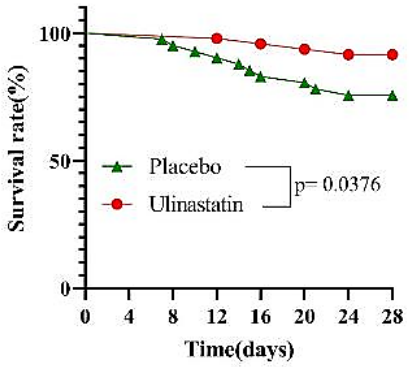

Figure 1: Survival at 28 days after combination of lactated Ringer's solution and ulinastatin

DISCUSSION

Patients with severe sepsis have a mortality rate of about 25 %, and the incidence of septic shock is close to 50 % [8]. Current treatment options are limited, and therefore survival rate and prognosis of patients are still poor. In this current study, patients were treated with lactated ringer solution and ulinastatin. The results indicated that combination therapy improved the condition of septic patients, tissue perfusion, inflammatory response, renal function, and early survival rate. Sepsis and septic shock cause tissue hypoperfusion and excessive inflammation [9]. Activation of inflammatory cells and release of pro-inflammatory factors seriously damage tissues and organs, resulting in low survival rate. According to sepsis guidelines, aggressive early fluid resuscitation is valuable for septic patients. Composition of lactated Ringer's solution is more similar to plasma, containing inorganic anions that rapidly convert to bicarbonates (namely lactate, lactate, acetate, and citrate), as well as cations to replenish lost electrolytes [10]. Studies have confirmed that an elevated lactic acid level carries significant importance in sepsis, being associated with a poorer prognosis and serving as an indicator of tissue perfusion [11-13].

Elevated lactate is defined as sepsis-3 septic shock, and serum lactate is a biomarker of tissue hypoxia and dysfunction [14]. Prompt and effective early fluid resuscitation can restore tissue perfusion and mitigate the risk of multiple organ failures due to reduced circulating blood volume. It has been demonstrated that ulinastatin effectively inhibits inflammatory factors, regulates cellular immunity, suppresses pro-inflammatory response, and enhances condition of septic patients [15]. Procalcitonin (PCT), C-reactive protein (CRP), and white blood cell count (WBC) are commonly used clinical markers for assessing inflammatory responses in septic

patients [16]. The study findings showed that combination therapy was more effective in improving tissue perfusion, and inflammatory response in septic patients. Furthermore, clinical data indicates that individuals with sepsis and septic shock frequently exhibit fever, excessive inflammation, shock, and organ dysfunction [9]. Pro-inflammatory factors such as PCT and CRP are excessively expressed in septic patients, and abnormal increase in WBC may cause tissue damage. Ulinastatin, a glycoprotein with broad-spectrum protease inhibitory properties, not only suppresses inflammatory responses but also regulates tissue circulation, removes oxygen free radicals, and reduce endothelial dysfunction [17]. In septic patients, creatinine and BUN decreased after combination therapy, which may be related to the inhibitory effect of ulinastatin on inflammatory response of renal tissue, and improvement of renal micro-circulation disorder [18]. In addition, clinical observations have shown that combination therapy reduced mechanical ventilation time and ICU stay time while improving the 28-day survival rate.

Limitations of this study

The sample size used was small, thus limiting validity of the results. In addition, the evaluated indicators are mainly related to biomarkers. Thus, tissue, organ damage and function of patients were not evaluated. As a result, more comprehensive inflammation- and tissue/organ function-related assessment is required or a larger sample.

CONCLUSION

Administration of lactated Ringer's solution in combination with ulinastatin effectively downregulates lactic acid level, improves tissue perfusion, inhibits inflammatory response, protects renal function, and effectively improves early survival of septic patients. These findings provide more valuable information for exploring new therapeutic approaches to sepsis.

DECLARATIONS

Acknowledgements

This study was supported by Scientific Research Starting Foundation of Xi'an People's Hospital (Xi'an Fourth Hospital), China (Grant no. CX-21).

Funding/Sponsorship

None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Hongyan Ma and Yuhui Zhou contributed equally to this study and should be regarded as co-first authors. YuYuan Min conceived and designed the study, and drafted the manuscript. YinBin He and Lei Tuo collected, analyzed and interpreted the experimental data. LiuMeiZi Fann and YaNing Xie revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethical Approval

This study was approved by by Institutional Ethics Committee of Xi'an People's Hospital (no. 2017051106XA).

Availability of Data and Materials

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

***Use of Artificial Intelligence*/Large Language Models**

None provided.

Use of Research Reporting Tools

None provided.

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