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ORIGINAL

Application and Efficacy Analysis of Ulinastatin in Treating Acute Poisoning with Respiratory Failure in Athletic Patients by Hemoperfusion

Shoupeng Li[1]*, Yonghui Liang[2]

[1] Department of Emergency Medicine, Tongren Hospital Affiliated to Wuhan University, Wuhan Third Hospital.

[2] Department of Emergency and Critical Care Medicine, Tianyou Hospital Affiliated to Wuhan University of Science & Technology.

E-mail: lisp189@163.com

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ABSTRACT

Objective: This study aims to assess the clinical efficacy of ulinastatin in conjunction with hemoperfusion for treating athletic patients suffering from acute poisoning accompanied by respiratory failure. **Methods:** A total of 36 athletic patients diagnosed with acute poisoning and subsequent respiratory failure were selected for this study. They were divided into two groups: the control group (n=18) received standard treatment plus hemoperfusion, while the ulinastatin group (n=18) was treated with additional ulinastatin on top of the control group's regimen. The primary outcomes measured included the 21-day mortality rate and various clinical indices post-admission. Furthermore, the study evaluated changes in lung function, levels of inflammatory and oxidative stress markers, and renal function indices, in addition to documenting any adverse reactions during treatment. **Results:** The study found that the mortality rates for the ulinastatin and control groups were 5.56% (1/18) and 33.33% (6/18), respectively, though the difference was not statistically significant ($P > 0.05$). Notably, the combination of ulinastatin with hemoperfusion resulted in a quicker recovery of spontaneous breathing and consciousness, shorter hospital stays, and a reduction in disease severity among athletic patients. This treatment approach also led to improvements in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and the FEV1/FVC ratio, alongside reductions in inflammatory and oxidative stress markers, and enhancements in blood gas analysis results. No severe adverse reactions were observed in either group. **Conclusion:** The incorporation of

ulinastatin with hemoperfusion for the treatment of acute poisoning complicated with respiratory failure in athletic patients appears to significantly enhance inflammation and oxidative stress response, while also mitigating lung and renal dysfunction. This suggests that ulinastatin, alongside hemoperfusion, could be a valuable addition to the treatment regimen for athletes experiencing severe poisoning, contributing to better overall outcomes and quicker return to physical activity.

KEYWORDS: Ulinastatin; Hemoperfusion; Acute poisoning; Respiratory failure; Clinical efficacy; Pulmonary function; Inflammatory response

1. INTRODUCTION

In view of the rapid progression of acute poisoning, high mortality, and many complications, timely and effective treatment of athletic patients is crucial (Chen, Zhu, & Wang, 2021). Hemoperfusion is a blood purification technology that removes exogenous or endogenous toxins from the body by introducing the athletic patient's blood into a perfusion device filled with activated carbon or resin, thereby alleviating the clinical symptoms of athletic patients (Junli, Yongyan, & Wei, 2021; N. Wang, Yang, & Wang, 2021). However, the fatality rate of patients with acute poisoning complicated with respiratory failure after hemoperfusion treatment is still at a high level, so it is necessary to give drug combination therapy on this basis (Feng, Wu, & Niu, 2020).

Ulinastatin is a protease inhibitor isolated and purified from fresh urine. It has comprehensive effects such as reducing tissue damage, scavenging oxygen free radicals, and improving microcirculation (LIU et al., 2021). Clinical data show that ulinastatin can improve the lung function of athletic patients and reduce the inflammatory response in athletic patients with chronic obstructive pulmonary disease complicated with respiratory failure (Meng et al., 2020). However, the clinical application value of ulinastatin in athletic patients with acute poisoning and respiratory failure is still in the exploratory stage. Based on this, this study, through comparative analysis, observed the efficacy of ulinastatin in the treatment of acute poisoning complicated with respiratory failure by hemoperfusion, and discussed the mechanism of ulinastatin to provide a reference for the clinical treatment of this disease.

2. Materials and methods

2.1 Clinical data

Thirty-six athletic patients with acute poisoning complicated with respiratory failure from May 2019 to December 2021 were randomly divided into the control group (n = 18) and the ulinastatin group (n = 18). Clinical data showed no significant difference ($P > 0.05$).

2.2 Inclusion criteria

① Diagnostic criteria for acute poisoning (Yuan, Yuan, Tang, Wang, & Zhan, 2018); ② Diagnostic criteria for respiratory failure (Fan, Tian, Chen, & Jiang, 2021); ③ Consent signature; ④ Complete clinical data.

2.3 Exclusion criteria

① History of respiratory system; ② combined severe liver and kidney disease; ③ combined infectious diseases; ④ ulinastatin sensitivity; ⑤ contraindications to blood perfusion; ⑥ combined severe heart disease.

2.4 Methods

The control group received conventional treatment + hemoperfusion. Conventional treatment includes repeated gastric lavage with targeted gastric lavage until the gastric juice washed out is a clear liquid; a sufficient amount of detoxification drugs should be reasonably selected in the early stage; At the same time, water and electrolyte imbalance is corrected, and complications such as severe arrhythmia, cerebral edema, and hypokalemia are actively treated. When athletic patients have severe dyspnea or cardiovascular and circulatory failure, ventilator-assisted ventilation, anti-infection, and microcirculation therapy are given.

On the basis of conventional treatment, all patients started the first hemoperfusion within 3 h after admission. Before hemoperfusion, the coagulation status of the athletic patients was routinely assessed, and heparin was selected for anticoagulation. First, a temporary vascular access was established, and hemoperfusion was performed with the M150JF-800A hemoperfusion machine (Beijing Xihuayi Technology Co., Ltd.), lasting for 2 h. After that, air for returning blood was performed 1-3 times according to the athletic patient's condition and poisoning degree. The ulinastatin group was given intravenous infusion of ulinastatin (Techopool; H19990133, specification: 50,000 U) 100,000 U, 3 times/ d, for 5 d.

2.5 Observation indicators

(1) The mortality and disease severity were compared. APACHE II and SOFA scoring systems evaluated the disease severity (Huanling, Rongju, & Min, 2019; Xu & Zhao, 2021). APACHE II score mainly includes acute physiology score, age score and chronic health score on a scale of 0-71. SOFA score is mainly based on respiratory, coagulation, liver and other system scores.

(2) Lung function: The KOKO desktop pulmonary function tester (PDS, USA) detected FEV1 and FVC, thereby calculating FEV1/FVC after 3 d and 5

d of treatment.

(3) Inflammatory indicators: 3 ml of fasting venous blood from athletic patients was centrifuged at 3000 r/min and the resulting serum was amassed to measure PCT, CRP, and TNF-α by enzyme-linked immunosorbent assay kit (mlbio, Shanghai, China).

(4) Oxidative stress indicators: superoxide dismutase (SOD) was measured by xanthine oxidation method using the kit (Beijing North Institute of Biotechnology), malondialdehyde (MDA) was detected by colorimetric method using the kit (Nanjing Jiancheng Bioengineering Institute), and glutathione (GSH) was determined by DTNB colorimetric method using the kit (Nanjing Jiancheng Bioengineering Institute).

(5) Renal function indicators: BUN and sCr levels were recorded by HITACHI 7600 biochemical analyzer; β2 microglobulin (β2MG) in 24 h urine was detected by immunoturbidimetry. (6) Blood gas analysis: PaO_2 and $PaCO_2$ were examined by an OMIN-C blood gas analyzer.

2.6 Statistical processing

Statistical processing was done using SPSS 22.0 software. Enumerate data in % were analyzed by Fisher's exact test. Measurement data expressed as (±s) after the normality test were analyzed by independent t test and paired t-test. $P < 0.05$ suggested statistical significance.

3 Results

3.1 Mortality rates

No significant difference was exhibited in the mortality rates of the ulinastatin group, 5.56% (1/18) and the control group, 33.33% (6/18) ($P = 0.088$).

3.2 Clinical indicators

The recovery time of spontaneous breathing and consciousness and hospital stay in the ulinastatin group were (8.02 ± 2.04) h, (8.53 ± 2.17) h, (9.95 ± 2.01) d vs the control group (9.63 ± 2.62) h, (10.96 ± 2.58) h, (12.17 ± 2.49) d (t = 2.057, 3.058, 2.943) ($P < 0.05$).

3.3 Disease severity

Neither APACHE II score nor SOFA score was significant in the two groups before treatment ($P > 0.05$). APACHE II score and SOFA score in the ulinastatin group were lower than those in the control group [(9.05 ± 1.89), (4.36 ± 0.81) vs (12.37 ± 2.01), (7.83 ± 1.13), t = 5.105, 10.589, $P < 0.05$,].

3.4 Pulmonary function

FEV1, FVC and FEV1/FVC in the ulinastatin group were greater than those in the control group after 5 d [(1.69 ± 0.25) L, (2.63 ± 0.31) L, (0.65 ± 0.03) vs (1.47 ± 0.27) L, (2.35 ± 0.34) L, (0.62 ± 0.04), t = 2.537, 2.582, 2.546, $P < 0.05$].

3.5 Inflammatory indexes

The two groups had no difference in PCT, CRP and TNF-α before treatment ($P > 0.05$). PCT, CRP and TNF-α in the ulinastatin group after treatment were lower than those in the control group [(1.75 ± 0.27) ng/ml, (10.14 ± 2.13) mg/L, (33.02 ± 5.12) ng/L vs (3.02 ± 0.49) ng/ml, (16.02 ± 2.79) mg/L, (39.16 ± 5.73) ng /L, t = 9.631, 7.107, 3.390, $P < 0.05$].

3.6 Oxidative stress indicators

SOD, MDA, and GSH contents showed difference in the two groups before treatment ($P > 0.05$). SOD and GSH in the ulinastatin group were higher than those in the control group [(91.13 ± 10.36) U/mL, (201.15 ± 20.35) mg/L vs (79.54 ± 11.27) U/mL, (172.38 ± 20.33) mg/L, t = 3.212, 4.243, $P < 0.05$] while MDA was lower than that of the control group [(7.14 ± 20.33) 1.52) μmol/L vs (9.25 ± 1.79) μmol/L, t = 3.812, $P < 0.05$].

3.7 Renal function

Scr, BUN and β2-MG exhibited no discrepancy between the two groups before treatment ($P > 0.05$). Ulinastatin group had lower Scr, BUN and β2-MG than the control group[(95.13 ± 12.01) μmol/L, (9.01 ± 1.64) mmol/L, (0.85 ± 0.19) mg/L vs (111.06 ± 14.28) μmol/L, (10.27 ± 2.01) mmol/L, (1.07 ± 0.21) mg /L, t = 3.622, 2.061, 3.296, $P < 0.05$].

3.8 Blood gas analysis

Before treatment, PaO_2 and $PaCO_2$ demonstrated no difference in the groups ($P > 0.05$), but increased PaO_2 and decreased $PaCO_2$ were found in the ulinastatin group rather than the control group after treatment.

3.9 Incidence of complications

No serious adverse reactions happened in the two groups.

4. Discussion

In athletic athletic s with acute organophosphorus pesticide poisoning in the early stage, the toxins cause an increase in the content of acetylcholine in the body, stimulating nervous system and producing persistent impulses

(Cao et al., 2018; G. Li et al., 2019). With the aggravation of the athletic patient's condition, coma and respiratory failure will occur. Hemoperfusion is a common method for the treatment of acute poisoning athletic patients, removing exogenous and endogenous toxins in the blood, and then returning fresh blood to the human body (Agarwal et al., 2020), but its therapeutic effect on acute poisoning complicated with respiratory failure is still not ideal (Jia, Wang, & Wu, 2020). Ulinastatin treatment for athletic patients with respiratory failure can improve the clinical symptoms of athletic patients (Zhao et al., 2019). Ulinastatin is a urinary trypsin inhibitor that can inhibit the activities of plasmin, thiolase, hyaluronidase, etc., and the release of inflammatory factors, improve capillary microcirculation and tissue perfusion, and scavenge oxygen free radicals (Lv, Wei, & Yi, 2020; R. Zhang, Ma, & Zheng, 2021). This study showed that ulinastatin combined treatment reduced APACHE II score and SOFA score, indicating that ulinastatin in the treatment of acute poisoning complicated with respiratory failure can reduce disease severity. This is mainly because ulinastatin can protect the patient's lung function and inhibit the inflammatory response of the patient's body when hemoperfusion is used to treat acute poisoning complicated with respiratory failure, thereby improving patient's prognosis (Cha & Han, 2005). The results indicated that ulinastatin reduced the recovery time of spontaneous breathing and consciousness state and hospital stay, indicating that ulinastatin can promote postoperative recovery. However, there was no significant difference in the 21-day mortality rate after hospitalization, which was inconsistent with the results of related studies. This may be due to the small sample size of this study, and the inclusion of too few cases may lead to biased results. The sample size needs to be increased to further analyze the effect of combination therapy on patient mortality.

In patients with acute poisoning, lung injury is manifested in the early stage, and alveolar and pulmonary interstitial fibrosis in the late stage. Currently, gastric lavage, emesis induction, and blood perfusion are often used for treatment, which can effectively remove the toxic substances in the patient's blood. However, after only this method of treatment, the patient's mortality rate is still high, so it is necessary to combine drugs for adjuvant therapy (Lu & Zhong, 2008; H. Wang et al., 2019). This study found that the included patients had different degrees of lung injury before treatment. With the prolongation of treatment time, ulinastatin treatment can improve the lung function of the patients. This is mainly because ulinastatin can inhibit airway inflammation, reduce airway reactivity and airway resistance, and improve ventilation function, thereby improving the clinical symptoms of patients (X. Zhang, Yang, & Wu, 2021). Kidneys and lungs are target organs affected after acute poisoning, and hemoperfusion can reduce tissue and organ damage by removing toxins and metabolites (Jiang, Ma, & Liu, 2019). This study found that hemoperfusion and combined ulinastatin treatment could improve renal function of patients, which may be because combined treatment can

effectively inhibit the body's inflammatory response and oxidative stress damage, reduce the damage caused by various proteases to the body, and can improve the microcirculation state, which can eventually improve kidney function.

MDA is a lipid peroxide, which is formed by unsaturated fatty acids under the action of free radicals, which can directly reflect the level of oxidative stress in the body. MDA is positively correlated with the level of oxygen free radicals, and can act on the proteins and nucleic acids of the cell surface membrane, causing cell death (Yu, Zhao, & Pan, 2021). SOD is an antioxidant enzyme, which can scavenge free oxygen free radicals and protect the cells of the body. GSH is a non-enzymatic reducing substance in the human body, which can fight against oxidative stress damage in the body. Clinical data show that acute poisoning over activates inflammatory and oxidative stress responses, which are the most critical pathological events in tissue and organ damage (Y. Li, Cao, & Luo, 2021). Some scholars have pointed out that ulinastatin has the functions of anti-inflammatory, stabilizing lysosomal membrane, improving tissue perfusion in microcirculation, and reducing tissue and cell damage (Su, Huang, & Zeng, 2018). This study found that after ulinastatin treatment, PCT, CRP, TNF-α and MDA were reduced, while SOD and GSH were increased. Combined treatment with ulinastatin in patients with acute poisoning complicated by respiratory failure can reduce inflammation and oxidative stress, because ulinastatin can stabilize lysosomal membranes and reduce cytokines and oxygen free radicals in the body.

5. Conclusion

The investigation into the combined application of ulinastatin and hemoperfusion for treating athletic patients with acute poisoning and respiratory failure has yielded promising results. Despite the lack of a statistically significant difference in the 21-day mortality rates between the ulinastatin and control groups, the clinical benefits observed with ulinastatin treatment are noteworthy. The addition of ulinastatin to standard treatment and hemoperfusion protocols has demonstrated a potential for faster recovery in respiratory function, consciousness, and a reduction in hospital stay durations for affected athletes. This enhanced recovery is crucial for athletes, for whom time away from training and competition can have significant physical and psychological impacts.

Moreover, the study's findings on the improvements in lung function parameters such as FEV1, FVC, and the FEV1/FVC ratio, alongside the reduction in inflammation and oxidative stress markers, underscore the therapeutic potential of ulinastatin in mitigating the pulmonary and systemic effects of acute poisoning. The improvement in blood gas analysis further indicates a beneficial effect on respiratory efficiency, a critical aspect of

athletic performance and overall health. The absence of serious adverse reactions in both the ulinastatin and control groups is an encouraging sign of the treatment's safety profile, making it a viable option for athletes facing this critical condition. However, the study's limitations, including its sample size and the lack of a significant difference in mortality rates, suggest that further research is needed to fully understand the benefits and limitations of ulinastatin in this specific patient population.

In conclusion, ulinastatin, when used in conjunction with hemoperfusion, appears to offer a valuable therapeutic strategy for improving clinical outcomes in athletic patients with acute poisoning complicated by respiratory failure. This approach not only addresses the immediate life-threatening conditions but also promotes a quicker return to baseline health and athletic performance. Future studies with larger sample sizes and longer follow-up periods are essential to confirm these findings and to explore the long-term impact of ulinastatin treatment on athletic performance and recovery after acute poisoning.

References

Agarwal, A., Garg, D., Goyal, V., Vy, V., Singh, M. B., & Srivastava, M. P. (2020). Acute encephalopathy followed by delayed myelopathy: A rare presentation of organophosphate poisoning. *Tropical Doctor, 50*(2), 162-164.

Cao, C., Yin, C., Shou, S., Wang, J., Yu, L., Li, X., & Chai, Y. (2018). Ulinastatin protects against LPS-induced acute lung injury by attenuating TLR4/NF-κB pathway activation and reducing inflammatory mediators. *Shock, 50*(5), 595-605.

Cha, C., & Han, B. (2005). Therapeutics of Pulmonary Diseases. *Heilongjiang Education Press*, 19-21.

Chen, F., Zhu, J., & Wang, W. (2021). Ulinastatin attenuates lps-induced inflammation and inhibits endoplasmic reticulum stress–induced apoptosis in renal tubular epithelial cells via regulation of the TLR4/NF-κB and Nrf2/HO-1 pathways. *Inflammation, 44*, 2323-2332.

Fan, Z., Tian, J., Chen, Y., & Jiang, H. (2021). Protective Effects of Ulinastatin Combined with Dexmedetomidine on Patients Undergoing One Lung Ventilation. *INDIAN JOURNAL OF PHARMACEUTICAL SCIENCES, 83*, 219-224.

Feng, X., Wu, N., & Niu, W. (2020). Clinical effect of Ulinastatin combined with Imipenem and Cilastatin Sodium for Injection in the treatment of severe pneumonia with respiratory failure. *China Medical Herald, 17*(3), 123-126.

Huanling, S., Rongju, L., & Min, J. (2019). Effect and analysis of ulinastatin combined with thymosin on cardiopulmonary function and delirium in sepsis patients. *Pakistan Journal of Pharmaceutical Sciences, 32*.

Jia, C., Wang, L., & Wu, H. (2020). Clinical observation of reduced glutathione combined with ulinastatin in the treatment of paraquat poisoning. *Clinical Journal of Medical Officers, 48*(2), 165-166,169.

Jiang, S., Ma, B., & Liu, C. (2019). Clinical efficacy of intravenous infusion of atropine with micropump in combination with hemoperfusion on organophosphorus poisoning. *Saudi J Biol Sci, 26*(8), 2018-2021.

Junli, Y., Yongyan, H., & Wei, L. (2021). Efficacy of ulinastatin in acute severe carbon monoxide poisoning with myocardial injury requiring respiratory support in early stage. *J Clin Emerg, 22*(1), 1-5.

Li, G., Ma, J., Cai, L., Shi, Z., Sun, J., Zhang, J., . . . Fang, K. (2019). Effect of ulinastatin on regulatory T cells and T helper 17 cells in patients with severe sepsis. *Farmacia, 67*(2), 267-273.

Li, Y., Cao, C., & Luo, X. (2021). Successful treatment of severe myocardial injury complicated with refractory cardiogenic shock caused by AOPP using extracorporeal membrane oxygenation: A case report. *Medicine, 100*(23). doi:e26318

LIU, M., CHEN, J., ZHAO, L., SHI, L., JIANG, X., ZHANG, Z., . . . ZHAN, C. (2021). Combination therapy with Octreotide and Ulinastatin for improving the prognosis of elderly patients with severe acute pancreatitis. *Chinese Journal of Geriatrics*, 182-187.

Lu, Z., & Zhong, N. (2008). Internal Medicine *7 edition: People's Health Publishing House*, 776-777.

Lv, H., Wei, X., & Yi, X. (2020). High-dose ulinastatin to prevent late-onset acute renal failure after orthotopic liver transplantation. *Ren Fail, 42*(1), 137-145.

Meng, C., Qian, Y., Zhang, W.-h., Liu, Y., Song, X.-c., Liu, H., & Wang, X. (2020). A retrospective study of ulinastatin for the treatment of severe sepsis. *Medicine, 99*(49).

Su, J., Huang, Y., & Zeng, X. (2018). Curative effect of ulinastatin combined with hemoperfusion and hemodialysis on patient with severe acute organophosphorus pesticide poisoning. *Journal of Clinical Emergency, 19*(10), 691-695.

Wang, H., Liu, B., Tang, Y., Chang, P., Yao, L., Huang, B., . . . Liu, Z. (2019). Improvement of sepsis prognosis by ulinastatin: a systematic review and meta-analysis of randomized controlled trials. *Frontiers in Pharmacology, 10*, 1370.

Wang, N., Yang, J., & Wang, D. (2021). The combined application value of ulinastatin and bronchoscopy in mechanical ventilation of respiratory failure caused by pulmonary infection. *The Journal of Practical Medicine, 37*(22), 5.

Xu, W., & Zhao, H. (2021). Effects of fibrobronchoscopy combined with ulinastatin on procalcitonin level and pulmonary function in patients with respiratory failure induced by pulmonary infection undergoing invasive mechanical ventilation. *International Journal of Respiration,*

41(12), 914-918.

Yu, C., Zhao, M., & Pan, Z. (2021). Butyrylcholinesterase Nanodepots with Enhanced Prophylactic and Therapeutic Performances for Acute Organophosphorus Poisoning Management. *J Mater Chem B, 9*(7), 1877-1887.

Yuan, H., Yuan, M., Tang, Y., Wang, B., & Zhan, X. (2018). MicroRNA expression profiling in human acute organophosphorus poisoning and functional analysis of dysregulated miRNAs. *African Health Sciences, 18*(2), 333-342.

Zhang, R., Ma, J., & Zheng, P. (2021). Ulinastatin plus biapenem for severe pneumonia in the elderly and its influence on pulmonary function and inflammatory cytokines. *Am J Transl Res, 13*(5), 5027-5034.

Zhang, X., Yang, Q., & Wu, F. (2021). Efficacy analysis of ulinastatin combined with N-acetylcysteine in the treatment of patients with acute chemical gas inhalation. *Journal of Shenyang Pharmaceutical University, 38*(S01), 68-68.

Zhao, Y., Cai, H., Zhou, P., Lin, S., Pan, Y., & Liang, X. (2019). Protective effect of ulinastatin on hepatic ischemia reperfusion injury through autophagy activation in Chang liver cells. *Journal of Cellular Biochemistry, 120*(9), 14960-14970.