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The Effect of Hybrid Blood Purification Combined with Ulinastatin for the Treatment of Severe Sepsis on APACHE II Score and Levels of miR-146a and miR-155

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Background: Severe sepsis is a systemic inflammatory response syndrome caused by infection, and the Acute Physiological Assessment and Chronic Health Evaluation II (APACHE II) scoring system is widely used to assess the severity of severe patients. Hybrid blood purification treatment (HBPT) and ulinastatin (UTI) have shown good efficacy in a variety of inflammatory diseases, and miR-146a and miR-155 were found to be closely related to inflammatory reaction. The purpose of this study was to investigate the effect of HBPT combined with UTI in the treatment of patients with severe sepsis, especially the effects on APACHE II score and miR-146a and miR-155 levels.

Methods: We carried out a retrospective analysis of clinical data with severe sepsis admitted to our hospital from January 2020 to June 2022. The patients were divided into an HBPT or HBPT+UTI group according to the treatment records. The APACHE II score, miR-146a level, miR-155 level, inflammatory factors, and rehabilitation status of both groups were analyzed and compared before and after treatment.

Results: A total of 150 were included in the analysis, there were 77 participants in HBPT+UTI and 73 in HBPT group. After treatment, the APACHE II score and levels of miR-146a, miR-155, and inflammatory factors were significantly lower than that before treatment. Furthermore, the HBPT+UTI group showed significantly lower values than the HBPT group (all $P < 0.05$). The recovery time of serum amylase, the disappearance time of abdominal pain, and the length of hospitalization in the HBPT+UTI group were significantly shorter than those in the HBPT group (all $P < 0.05$).

Conclusion: UTI treatment combined with the administration of HBPT could improve the APACHE II score, alleviate the inflammatory reaction, and significantly improve the short-term prognosis of the patients with severe sepsis.

Keywords: hybrid blood purification treatment, ulinastatin, APACHE II score, miR-146a, miR-155, severe sepsis

Background

Sepsis is the type of systemic inflammatory response syndrome caused by infection.[1] Severe sepsis is a clinically acute and critical disease and is characterized by acute onset and rapid progression.[2] If the patient does not receive timely and effective intervention, septic shock and multiple organ dysfunction may occur as the disease progresses, and death may occur in severe cases.[1–3] Therefore, timely implementation of safe and effective treatment for severe sepsis is of great significance.[3,4] The Acute Physiology and Chronic Health Evaluation II (APACHE II) scoring system, which takes into account the patient's physiological parameters, age and previous health status, and could provide a relatively accurate prognosis assessment, is a widely used tool to assess severity and predict in-hospital mortality.[5,6]

Most of the clinical interventions carried out for patients with severe sepsis include correcting electrolyte levels and administering anti-inflammatory and anti-infective drugs, but the overall treatment efficacy remains unsatisfactory.[7,8] Hybrid blood purification treatment (HBPT) is an important clinical treatment option for sepsis.[9,10] HBPT mainly uses

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continuous veno-venous hemofiltration and hemoperfusion.[9] It can effectively remove inflammatory factors and endotoxins to regulate the internal environment of the body and improve the health status.[10] Ulinastatin (UTI) is a broad-spectrum proteinase inhibitor, which is the first biological isolate from human urine.[11] It can inhibit the secretion of inflammatory factors and protect the organs and tissues of the body.[11,12] In clinical application, UTI has been used in the treatment of acute pancreatitis, acute circulatory failure and other inflammatory diseases, showing good efficacy. In recent years, the application of UTI in the treatment of severe sepsis has been explored. miR-146a is an important micro RNA (miRNA) that can affect the immune and inflammatory response of the body.[13] miR-155 can regulate the secretion and expression of inflammatory cytokines.[14] Therefore, monitoring the levels of miR-146a and miR-155 can determine the inflammatory reaction state of the body.[13,14] However, the literature on whether UTI-assisted HBPT for the treatment of severe sepsis affects the level of miR-146a and miR-155 is limited. Therefore, we retrospectively analyzed the clinical data of patients with severe sepsis in Peking University People's Hospital to clarify the effect of UTI-assisted HBPT on APACHE II scores and the levels of miR-146a and miR-155 levels.

Methods

General Data

All patients with a diagnosis of severe sepsis were enrolled, and the case records were performed from this hospital between January 2020 and June 2022. All of them were recruited through the department of Intensive Care Unit (ICU) of Peking University People's Hospital. We divided them into an HBPT and HBPT+UTI group according to the different treatments they received. Additionally, patients in both groups underwent standard treatment for a total of 7 days. All outcome data were collected before and after treatment. This retrospective study did not utilize approach of randomization and blinding to both patients and researchers. The protocol has been approved by the Ethical Committee of the Peking University People's Hospital (code 2024PHB066-001). All procedures involving human subjects adhered to the 1964 Declaration of Helsinki and its subsequent amendments or equivalent ethical standards. Given the retrospective nature of the study, informed consent was waived by the Ethical Committee of Peking University People's Hospital. All data were stored securely, and confidentiality was maintained throughout the study.

Inclusion Criteria

Patients diagnosed with severe sepsis according to the according to the Guidelines for the treatment of severe sepsis/septic shock in China;[2,15]
The age range is 18–80 years old;
Receiving HBPT or HBPT+UTI treatment;
Complete clinical records.

Exclusion Criteria

Incurable malignancies with documented metastases;
Patients with acute myocardial infarction;
Patients with chronic treatment with high-dose immunosuppressive drugs or high dose nonsteroid anti-inflammatory drugs within the previous 2 days;
Patients with chronic compensated organ dysfunction, such as chronic liver disease, dialysis-dependent renal failure, moderate-to-severe chronic heart failure;
Pregnant or lactating patients.

HBPT: Bedside blood purification machines (Fischer filter and Ultraflux AV600S filter) were selected to carry out continuous veno-venous hemofiltration. The displacement fluid flow was set to 2 L/h, and the blood flow was 50–200 mL/h. A single needle, double lumen catheter was inserted into the right femoral vein for vascular access. Disposable resin hemoperfusion device and bicarbonate replacement solution were used. Low molecular-weight heparin was used for anticoagulation treatment. The displacement fluid flow rate was set at 3000 mL/h, and the blood flow rate

was set at 200–500 mL/min. After 2 h of hemoperfusion, the hemoperfusion device was removed, and hemofiltration was performed.

UTI: (Guangdong Techpool Biochemical Pharmaceuticals Co., Ltd.; specification: 2 mL: 100,000 U) intravenous infusion of 50 mL normal saline + UTI 300,000 units.

The baseline data and related indicators before and 7 days after treatment were collected.

(1) The APACHE II score included the acute physiology score, chronic health score, and age, and ranged between 0 and 71. The higher the score, the greater the disease severity.
(2) miR-146a and miR-155 level: Briefly, 4 mL fasting venous blood was extracted and centrifuged. Trizol total RNA extraction reagent was used to extract total RNA from plasma, and a UV spectrophotometer was used to measure the absorbance of total RNA. Reverse transcription was performed using a reverse transcription kit to form cDNA, which was amplified by polymerase chain reaction (PCR). The amplification conditions were 95°C for 5 min, 95°C for 15s, 60°C for 60s, and 72°C for 30s. A fluorescent quantitative PCR kit (Roche, Switzerland) was used to detect the miR-146a and miR-155 levels. All experimental steps were carried out according to the kit manufacturers' instructions. The relative expression of miRNA was expressed by $2^{-\Delta\Delta CT}$.
(3) Serum inflammatory factor level: Briefly, 4 mL fasting venous blood was extracted and centrifuged at 3000 rpm for 15 minutes under a radius of 15cm, and the supernatant was collected. The serum levels of C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and procalcitonin (PCT) were measured by enzyme-linked immunosorbent assay. The kit was purchased from Wuhan Bodde Bioengineering Co., Ltd.
(4) Others included the time for blood amylase to return to normal, the time for abdominal pain to disappear, length of antimicrobial therapy and hospital stay, and adverse events were collected.

Statistical Analysis

The clinical data were input into Microsoft Excel, and SPSS version 26.0 (IBM Corp, Armonk, NY, USA) was used for statistical analysis. For continuous variables, the mean and standard deviation (SD) are calculated. For categorical variables, the frequency distribution is provided and expressed as a percentage. Chi-square test was used to compare the categorical variables such as sex distribution and primary disease type between two groups. $P< 0.05$ was considered to indicate a statistically significant association or difference.

Independent samples *t*-test was used to compare the average value of two independent samples, especially for continuous variables. The assumption of equal variance was checked and considered in the analysis. $P <0.05$ was considered to indicate statistically significant differences.

To evaluate the APACHE II score before and after treatment, repeated measurement analysis was carried out while considering the health status of the patient. Paired *t*-test was used to determine the difference before and after treatment in the group, while independent samples *t*-test was used for between-group comparisons before and after treatment.

Results

A total of 150 patients were included in this study, including 75 males and 75 females. The mean age was 52.28 ± 8.47 years (range: 36–74 years). There were 73 patients in the HBPT group and 77 in the HBPT+UTI group. There were no significant differences between the two groups with respect to sex, age, body mass index (BMI), APACHE II score, primary disease type, and other baseline data (all $P > 0.05$) (Table 1).

Before treatment, the APACHE II scores of HBPT+UTI and HBPT group were 22.49 and 23.19, respectively, and there was no significant difference ($P = 0.239$). After treatment, the scores in the two groups were 8.16 and 9.84, respectively, and the scores in HBPT+UTI were significantly lower than those in HBPT ($P < 0.001$). Moreover, there were significantly lower scores than those before treatment in the two groups (HBPT+UTI: $P < 0.001$, HBPT: $P < 0.001$) (Figure 1). Similarly, the same results were found in non-severe acute pancreatitis (Table 2).

Before treatment, the levels of miR-146a and miR-155 in HBPT+UTI and HBPT group were 6.54 and 6.63, 1.92 and 1.86, respectively, and analysis showed that there was no statistical difference (miR-146a: $P = 0.787$, miR-155: $P = 0.500$). After treatment, the levels in the two groups were 3.22 and 5.18, 1.09 and 1.36, respectively, and the scores in

Table 1 Comparison of Baseline Characteristics Between the Two Groups

Characteristic	HBPT+UTI Group (n=77)	HBPT Group (n=73)	t/χ^2	P
Sex			1.308	0.253
Male	42 (54.55)	33 (45.21)		
Female	35 (45.45)	40 (54.79)		
Age (year)	51.75±7.84	52.84±9.12	−0.781	0.436
BMI (kg/m^2)	23.40±2.66	23.12±2.93	0.491	0.624
Type of primary disease			3.658	0.301
Burn	26 (33.76)	18 (24.66)		
Septic shock	33 (42.86)	33 (45.20)		
Severe acute pancreatitis	15 (19.48)	14 (19.18)		
Other	3 (3.90)	8 (10.96)		
Co-morbid diseases				
Hypertension	19 (24.68)	19 (26.03)	0.036	0.849
Diabetes mellitus	19 (24.68)	16 (21.92)	0.159	0.690
Coronary heart disease	13 (16.88)	8 (10.96)	1.092	0.296
APACHE II score	22.49±3.55	23.19±3.69	−1.182	0.239

Note: Data are present as mean ± standard deviation or number (%).Other included peritonitis, adult respiratory distress syndrome, acute obstructive suppurative cholangitis, intestinal obstruction, and liver abscess.
Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment; APACHE, II Acute Physiology and Chronic Health Evaluation II.

HBPT+UTI were significantly lower than those in HBPT (miR-146a: $P < 0.001$, miR-155: $P < 0.001$). Moreover, there were significantly lower levels than those before treatment in the two groups (HBPT+UTI-miR-146a: $P < 0.001$, miR-155: $P < 0.001$; HBPT-miR-146a: $P < 0.001$, miR-155: $P < 0.001$) (Figure 2). Similarly, the same results were found in non-severe acute pancreatitis (Table 2).

Before treatment, the levels of serum CRP, TNF-α, and PCT in HBPT+UTI and HBPT group were 36.55 and 35.70 mg/L, 82.35 and 84.40 ng/mL, 24.31 and 23.84 ng/mL respectively, and analysis showed that there was no

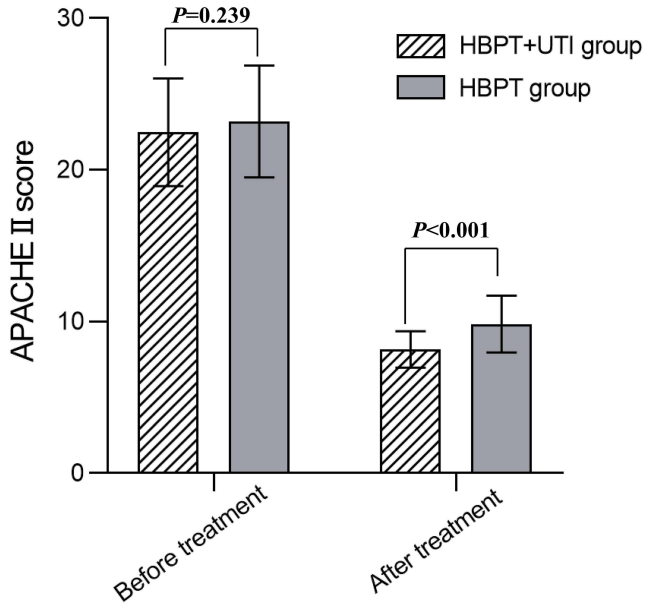

Figure 1 Comparison of APACHE II scores between the two groups.
Abbreviations: APACHE II, Acute physiological assessment and chronic health evaluation II; UTI, Ulinastatin; HBPT, hybrid blood purification treatment.

Table 2 Comparison of Two Groups Before and After Treatment in Overall and Non-Severe Acute Pancreatitis Patients

Variable	Overall			Non-Severe Acute Pancreatitis		
	HBPT+UTI Group (n=77)	HBPT Group (n=73)	*P*	HBPT+UTI Group (n=62)	HBPT Group (n=59)	*P*
Before treatment						
APACHEII, score	22.49±3.55	23.19±3.69	0.239	22.34±3.51	23.36±3.70	0.124
miR146a	6.54±2.17	6.63±2.03	0.787	6.52±2.16	6.63±2.13	0.766
miR155	1.92±0.50	1.86±0.45	0.500	1.92±0.53	1.82±0.42	0.254
CRP, mg/L	36.55±8.73	35.70±9.14	0.563	36.26±8.11	35.66±9.57	0.711
TNF-α, ng/mL	82.35±11.82	84.40±9.45	0.245	82.34±11.97	83.71±9.75	0.492
PCT, ng/mL	24.31±6.30	23.84±7.46	0.673	24.48±6.25	23.10±7.44	0.270
After treatment						
APACHEII, score	8.16±1.21	9.84±1.89	<0.001	8.15±1.20	9.81±1.82	<0.001
miR146a	3.22±1.35	5.18±1.55	<0.001	3.21±1.42	5.11±1.57	<0.001
miR155	1.09±0.28	1.36±0.31	<0.001	1.10±0.29	1.34±0.31	<0.001
CRP, mg/L	4.77±1.23	6.25±1.68	<0.001	4.78±1.19	6.11±1.62	<0.001
TNF-α, ng/mL	21.99±5.21	26.48±6.13	<0.001	21.82±5.25	26.42±6.30	<0.001
PCT, ng/mL	7.48±2.24	9.82±3.24	<0.001	7.69±2.23	9.42±3.16	0.001

Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment; APACHE II, Acute Physiology and Chronic Health Evaluation II; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; PCT, procalcitonin.

statistical difference (CRP: $P = 0.563$, TNF-α: $P = 0.245$, PCT: $P = 0.673$). After treatment, the levels in the two groups were 4.77 and 6.25, 21.99 and 26.48, 7.48 and 9.82 respectively, and the serum level in HBPT+UTI were significantly lower than those in HBPT (CRP: $P < 0.001$, TNF-α: $P < 0.001$, PCT: $P < 0.001$). Moreover, there were significantly lower levels than those before treatment in the two groups (HBPT+UTI-CRP: $P < 0.001$, TNF-α: $P < 0.001$, PCT: $P < 0.001$; HBPT - CRP: $P < 0.001$, TNF-α: $P < 0.001$, PCT: $P < 0.001$) (Figure 3). Similarly, the same results were found in non-severe acute pancreatitis (Table 2).

The recovery time of serum amylase, the disappearance time of abdominal pain, the length of hospital stays, and the length of antimicrobial therapy in HBPT+UTI and HBPT group were 5.30 and 6.92, 3.87 and 5.18, 12.45 and 15.07, 8.45

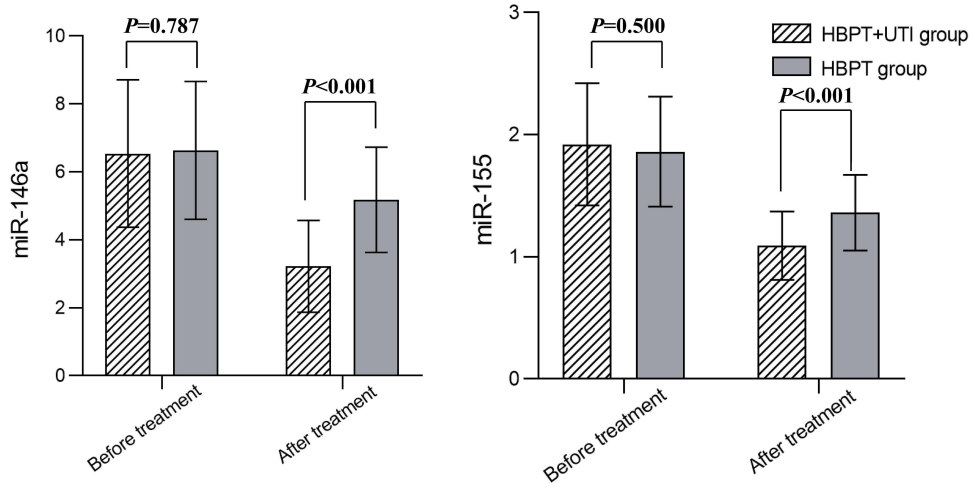

Figure 2 Comparison of miR-146a and miR-155 levels between the two groups before and after treatment.
Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment.

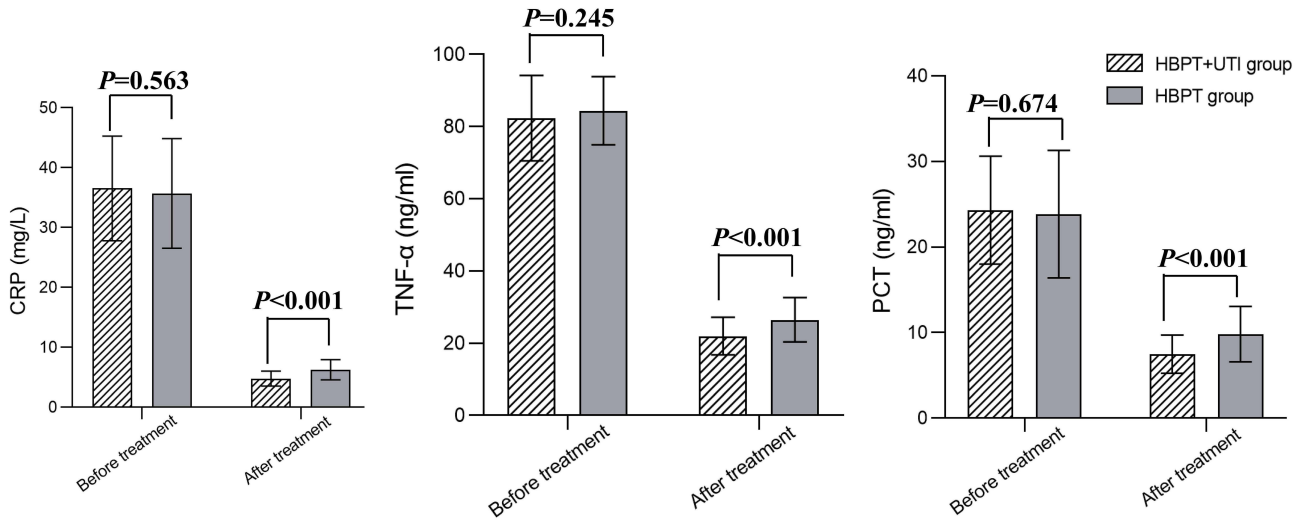

Figure 3 Comparison of serum inflammatory factor levels between the two groups before and after treatment.
Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; PCT, procalcitonin.

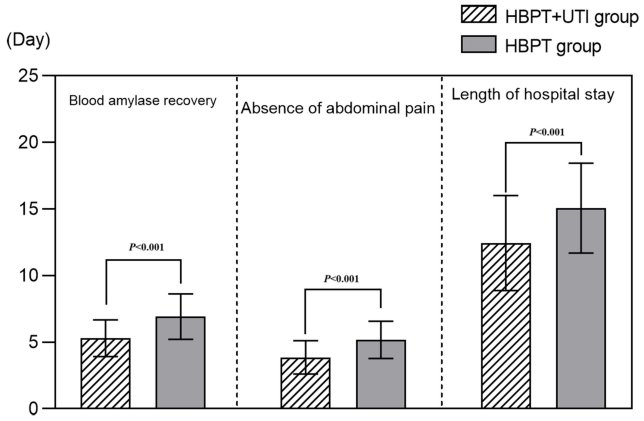

Figure 4 Comparison of rehabilitation between the two groups.
Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment.

and 10.28 days, respectively, and the duration of HBPT+UTI were significantly shorter than those in the HBPT group (all $P < 0.001$) (Figure 4). Similarly, the same results were found in non-severe acute pancreatitis (Table 3).

As for safety, several adverse events were recorded; however, no significant differences were detected between two groups (Table 4).

Table 3 Comparison of Two Groups in Overall and Non-Severe Acute Pancreatitis Patients

Variable	Overall			Non-Severe Acute Pancreatitis		
	HBPT+UTI group (n=77)	HBPT group (n=73)	*P*	HBPT+UTI group (n=62)	HBPT group (n=59)	*P*
The recovery time of serum amylase, days	5.30±1.37	6.92±1.71	<0.001	5.24±1.33	7.03±1.66	<0.001
The disappearance time of abdominal pain, days	3.87±1.25	5.18±1.40	<0.001	3.94±1.27	5.24±1.39	<0.001
The length of hospital stays, days	12.45±3.56	15.07±3.38	<0.001	12.34±3.59	15.25±3.23	<0.001
The length of antimicrobial therapy, days	8.45±2.25	10.28±3.15	<0.001	8.31±2.23	10.42±3.26	0.001

Abbreviations: UTI, Ulinastatin; HBPT, hybrid blood purification treatment.

Table 4 Comparison of Association Adverse Events Between Two Groups

Adverse events, and death	HBPT+UTI Group (n=77)	HBPT Group (n=73)	χ^2	*P*
Vomiting diarrhea	4(5.19)	3(4.11)	–	1.000
Hypotension	2(2.60)	2(2.74)	–	1.000
Hemorrhage	7(9.09)	6(8.22)	–	1.000

Note: - represents the Fisher's Exact Test method calculation.
Abbreviations: UTI, Ulinastatin; HBPTm, hybrid blood purification treatment.

Discussion

In our study, it demonstrated that UTI treatment combined with the administration of HBPT could improve the APACHE II score, alleviate the inflammatory reaction, and significantly improve the short-term prognosis of the patients with severe sepsis. Hakemi et al[16] analyzed the application value of blood purification in sepsis and found that the blood lactic acid level of patients decreased by 32.3% after treatment, and the mortality risk of patients also decreased significantly. In addition, studies have found that blood purification treatment can help improve the health status of critically ill patients and has positive significance in ensuring good prognosis.[17–19] HBPT has the advantages of continuous veno-venous hemofiltration and hemoperfusion, which can eliminate inflammatory factors in the body to the greatest extent.[19–23] Continuous veno-venous hemofiltration can remove small molecular substances and some medium-sized molecular inflammatory substances in the body through convection. The filtration membrane can also remove some large and medium molecular inflammatory factors through adsorption.[21,22] Hemoperfusion can drain the blood to extracorporeal circulation, adsorb inflammatory factors and toxins through the adsorbent in the perfusion device, and remove large and medium molecular substances. The combination of the two can achieve complementary advantages.[23] However, this study found that the related biochemical indicators and clinical symptoms of the HBPT group were improved after HBPT. Although this is consistent with other researchers' findings regarding blood purification in severe sepsis, there are still some clinical limitations; hence, it is essential to combine other measures to implement comprehensive intervention.[21–23] Study has shown that UTI reduces the expression of inflammatory factors by inhibiting JNK/NF-κB signaling pathway. At the same time, the activation of PI3K/Akt/Nrf2 pathway can enhance the antioxidant capacity of cells, thereby comprehensively exerting anti-inflammatory and cell protective effects.[24] Subsequently, HBPT combined UTI could more effectively alleviate the inflammatory reaction.

This study found that the levels of clinical observation indices in the HBPT+UTI group were better than those in the HBPT group. It is confirmed that UTI has high application value in severe sepsis. Meng et al[25] showed that the immune function of patients with severe sepsis was significantly improved after UTI treatment, which can effectively relieve the degree of coma and improve the health of the body. Su et al[26] showed that UTI can be used for comprehensive treatment for patients with sepsis. The results showed that the APACHE II score, inflammatory factor level, and immune function index level of patients were significantly improved compared with those before treatment, and the improvement effect was better than that of patients in the HBPT group who only received conventional treatment.[26,27] Relevant studies have also found that UTI can significantly reduce all-cause mortality and other related outcomes in patients with sepsis. UTI can not only improve the health of the body but also downregulate the expression of inflammatory factors, reduce the risk of multiple organ dysfunction syndrome, and lay a good foundation for disease prognosis.[27,28] Jiang et al[28] confirmed that UTI can reduce the 28-day mortality of sepsis and reduce the incidence of other related adverse events. The research results and conclusions of the above scholars are consistent with our study, which verifies the view of this study that UTI could improve the treatment effect of severe sepsis. As for safety, there were no significant differences of adverse events between the two groups. It suggested that HBPT combined with UTI might have an acceptable safety profile for severe sepsis. Therefore, it can provide practical reference for the clinical treatment of sepsis, guide the clinical implementation of targeted treatment, and ensure good disease prognosis.

This study has some limitations. First, this is a single center retrospective study. Incomplete medical records and the bias of recalling medical history increase the complexity of the study, and hence the results may be prone to selection bias. Later, we will further expand the sample and try to further verify the results with multi-center data. Second, the two

groups were not randomly assigned, and the baseline information may be unbalanced and biased, which is also one of the shortcomings of our retrospective study. Third, the treatment safety of the two groups was not compared and analyzed, and the prognosis of the patients was not followed-up. Finally, the safety of UTI-assisted HBPT in the treatment of severe sepsis and its impact on the prognosis of patients still need to be further explored and confirmed.

Conclusion

UTI treatment combined with the administration of HBPT could improve the APACHE II score, alleviate the inflammatory reaction, and significantly improve the short-term prognosis of the patients with severe sepsis.

Abbreviations

UTI, Ulinastatin; HBPT, hybrid blood purification treatment; APACHE II, Acute physiological assessment and chronic health evaluation II; CRP, C-reactive protein; TNF-α, tumor necrosis factor alpha; PCT, procalcitonin.

Data Sharing Statement

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

Ethics Approval and Consent to Participate

The ethics committee of Peking University People's Hospital approved this study with the number 2024PHB066-001, Date: June 10th 2024.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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