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*J. Biol. Regul. Homeost. Agents.* 2024; 38(6): 4987–4993
https://doi.org/10.23812/j.biol.regul.homeost.agents.20243806.398

# Efficacy and Prognosis of HA380 Perfusion Combined with Continuous Venovenous Hemofiltration in the Treatment of Sepsis

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Submitted: 25 August 2022 Revised: 2 November 2022 Accepted: 16 February 2023 Published: 1 June 2024

**Background: Effect of HA380 perfusion combined with continuous venovenous hemofiltration (CVVH) on sepsis and prognosis.**
**Methods: 60 patients with sepsis admitted to our hospital from November 2020 to March 2022 were selected as the research objects and divided into two groups by simple random method. The two groups were given medical treatment according to the sepsis diagnosis and treatment guidelines jointly issued by the American Society of Critical Care Medicine and the European Society of Critical Care Medicine. The control group was treated with CVVH, and the observation group was treated with HA380 perfusion combined with CVVH.**
**Results: Intestinal fatty acid binding protein, diamine oxidase, D-lactic acid, interleukin-6, tumor necrosis factor-$\alpha$, endotoxin, C-reaction protein, white blood cell, procalcitonin, blood lactic acid, serum creatinine, blood urea nitrogen, bilirubin, intra-abdominal pressure, one-day body temperature peak, sequential organ function score at 24 h, 48 h, and 72 h after treatment were lower than those at baseline, mean arterial pressure and oxygenation index were higher than those at baseline, with statistical significance ($p < 0.05$).**
**Conclusion: HA380 perfusion combined with CVVH in the treatment of sepsis can reduce intestinal barrier function damage and inflammation, and improve short-term prognosis.**
**Clinical Trial Registration: Chinese clinical trial registry. Number: ChiCTR2400082281.**

**Keywords:** HA380 perfusion; continuous venovenous hemofiltration; sepsis; intestinal barrier function; degree of inflammation

## Introduction

Sepsis is a life-threatening organ dysfunction caused by an imbalance in host responses to infection [1]. Continuous venovenous hemofiltration (CVVH) is a commonly used blood purification technology in clinical practice, which has therapeutic effect in patients with sepsis. CVVH can selectively remove water, electrolytes and inflammatory factors in the body, significantly improve coagulation function and immune function in patients with sepsis, and improve the homeostasis of the internal environment [2–4]. However, the effect of CVVH alone is limited, such as interleukin-1 (IL-1), interleukin-6 (IL-6), endotoxin clearance effect is not good. A recent study has shown that the effect of blood perfusion technology on the clearance of macromolecular inflammatory mediators is not good [5]. Therefore, combined blood perfusion based on CVVH is expected to improve the therapeutic effect of sepsis and further improve the prognosis of patients with sepsis.

At present, the effect of blood perfusion technology on intestinal mucosal barrier function in patients with sepsis is rarely reported. At present, the commonly used perfusator products are mainly oXiris (listed in China in 2017) from Bate and Jianfan HA380 (listed in 2019) from China [6]. The latter was applied in China in 2019. Compared with the general hemoperfusion apparatus, HA380 has advantages in removing endotoxin and inflammatory factors. It has been reported that HA380 hemoperfusion has a good effect on patients with acute type A aortic dissection receiving aortic arch surgery [7,8]. In addition, HA380 can assist in the clearance of drugs in blood purification treatment, which has certain clinical significance. At present, there is no study on the effect of HA380 perfusion combined with CVVH treatment on intestinal barrier function injury and inflammation in patients with sepsis. Based on the above, this study observed whether HA380 combined with CVVH treatment could effectively improve the intestinal mucosal barrier function and prognosis of patients with sepsis, providing new ideas for the gastrointestinal protection of sepsis.

Core tips: The key points are as follows prognosis of patients with sepsis is poor, and there is no specific treatment in clinic. CVVH is a blood purification method commonly used in patients with sepsis. Clinical experience has found that CVVH combined with blood perfusion is expected to improve the therapeutic effect of sepsis. The orig-

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inal Jianfan HA380 perfusion apparatus in China was applied in 2019. Compared with the general hemoperfusion apparatus, HA380 perfusion apparatus has advantages in removing endotoxin and inflammatory factors. This study is the first to study the effect of HA380 combined with CVVH on improving the intestinal mucosal barrier function and prognosis of patients with sepsis.

## Materials and Methods

### *General Information*

A total of 60 patients with sepsis admitted to our hospital from November 2020 to March 2022 were selected as the research objects and divided into two groups by simple random method. 30 cases in the control group, including 15 males and 15 females; age 18–75 (57.68 $\pm$ 9.58) years; acute physiology and chronic health evaluation II (APACHE II) score was (24.01 $\pm$ 4. 93) points. sequential organ function (SOFA) score (13.14 $\pm$ 2.76); etiology: 14 cases of severe pneumonia, 8 cases of blood-borne infection, 5 cases of abdominal infection, the other 3 cases. 30 cases in the observation group, including 17 males and 13 females; age 18–75 (56.91 $\pm$ 10.42) years; APACHE II score (23.95 $\pm$ 5.04); SOFA score (13.03 $\pm$ 2.83); etiology: 13 cases of severe pneumonia, 7 cases of blood-borne infection, 6 cases of abdominal infection, the other 4 cases. The general data was compared between the two groups, with the feasibility ($p > 0.05$).

Inclusion criteria: (1) Sepsis meets the diagnostic criteria of sepsis guidelines jointly issued by the American Society of Critical Care Medicine and the European Society of Critical Care Medicine [9]. (2) Age $\geq$18 years, $\leq$75 years. (3) APACHE II score $>$8. (4) This study was approved by the hospital ethics committee of the First Affiliated Hospital of Gannan Medical University (No. LLSC-2022040201), the informed consent of patients or their families. Exclusion criteria: (1) Blood purification contraindications. (2) Terminal state. (3) Pregnancy and lactation. (4) With autoimmune diseases, cerebrovascular diseases.

This study was performed according to the Declaration of Helsinki.

### *Methods*

Routine treatments such as fluid resuscitation, antishock, anti-infection, oxygen therapy or mechanical ventilation, nutritional support and correction of internal environment disorders were used. The control group was treated with CVVH, and the observation group was treated with HA380 perfusion combined with CVVH.

Control group: Fresenius Medical Care AG & Co., Bad Homburg, Germany, was used as the instrument, and the filter model was AV600S. CVVH mode was adopted with the femoral vein as the vascular pathway. Use citrate anticoagulation. Maintain blood flow in 120–200 mL/min range, replacement fluid flow 3000 mL/h, duration of 72 h.

Observation group: HA380 hemoperfusion was added based on the control group. That is, HA380 hemoperfusion apparatus (Zhuhai Jianfan Biotechnology Co., Ltd., Zhuhai, China) was connected in series at 0 h, 24 h and 48 h at the beginning of CVVH for hemoperfusion treatment, and the hemoperfusion time was 4 h each time.

### *Evaluation Indicators and Detection Methods*

The intestinal mucosal barrier-related factors, inflammatory related factors, renal function indexes, bilirubin, intra-abdominal pressure, one-day peak temperature, mean arterial pressure (MAP), oxygenation index (OI), SOFA score, mechanical ventilation time, intensive care unit (ICU) hospitalization time and 28-day mortality were compared between the two groups.

Laboratory examination of patients before and after treatment, collecting elbow venous blood 5 mL, 2500 r/min centrifugal 15 min after separation of upper serum to be measured, using enzyme-linked immunosorbent assay (20200919, Nanjing Xinfan Biotechnology Co., Ltd., Nanjing, China) to detect intestinal fatty acid binding protein (I-FABP), diamine oxidase (DAO), D-lactic acid, interleukin-6 (IL-6), tumor necrosis factor-$\alpha$ (TNF-$\alpha$) levels, the detection of FlexStation3 (American Molecular Devices, Los Angeles, CA, USA). The levels of Procalcitonin (PCT), C-reaction protein (CRP), blood urea nitrogen (BUN) and creatinine (Scr) were measured by immunoturbidimetry. Determination of endotoxin: The plasma was pretreated with anhydrous water dilution (1:10) and heating (75 °C, 10 min) for quantitative detection. Hemodynamic parameters were dynamically recorded at each time point: MAP, blood lactate (Lac), platelet and infection related organ failure score (SOFA), oxygenation index (OI).

Intra-abdominal pressure measurement method referred to WSACS standard [10], measured once every 5 minutes, repeated three times, take the average of three times as the final measured bladder pressure (intra-abdominal pressure) value.

The mechanical ventilation time, ICU hospitalization time and 28-day mortality of the two groups were recorded.

### *Statistical Methods*

The data were processed by SPSS (Version 23.0, IBM, Armonk, NY, USA). The K-S method was used to test the normality of the measurement data. The measurement indexes conforming to the normal distribution were described by ($\bar{x} \pm$ s). The *t*-test was used for comparison. The $\chi^2$ test was used to compare the enumeration data. $p < 0.05$ was statistically significant.

**Table 1. Comparison of intestinal mucosal barrier-related factors between the two groups ($\bar{x} \pm$ s, n = 30).**

| Factor | Control group | | | | Observation group | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours |
| I-FABP (ng/L) | 787.56 ± 141.36 | 654.22 ± 102.74* | 567.55 ± 94.21* | 451.36 ± 64.23* | 776.89 ± 138.57 | 570.13 ± 84.25*# | 457.52 ± 72.13*# | 398.25 ± 46.36*# |
| DAO (kU/L) | 4.12 ± 0.67 | 3.67 ± 0.58* | 3.12 ± 0.37* | 2.31 ± 0.27* | 4.35 ± 0.34 | 3.25 ± 0.29*# | 2.56 ± 0.24*# | 1.98 ± 0.26*# |
| D-lactic acid (mg/L) | 1.21 ± 0.23 | 1.02 ± 0.21* | 0.71 ± 0.15* | 0.59 ± 0.17* | 1.20 ± 0.26 | 0.91 ± 0.16*# | 0.53 ± 0.12*# | 0.42 ± 0.15*# |

*$p < 0.05$ means comparison with baseline; #$p < 0.05$ means comparison with control group.

Note: I-FABP, intestinal fatty acid binding protein; DAO, diamine oxidase.

**Table 2. Comparison of inflammation related factors between the two groups ($\bar{x} \pm$ s, n = 30).**

| Factor | Control group | | | | Observation group | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours |
| IL-6 (ng/L) | 178.25 ± 46.32 | 151.25 ± 33.25* | 132.52 ± 26.74* | 101.13 ± 24.58* | 180.14 ± 38.23 | 121.03 ± 26.14*# | 94.12 ± 21.05*# | 65.32 ± 16.42*# |
| TNF-$\alpha$ (ng/L) | 52.14 ± 10.36 | 45.12 ± 6.85* | 38.89 ± 5.12* | 35.63 ± 5.45* | 53.22 ± 8.95 | 40.05 ± 5.45*# | 31.52 ± 5.13*# | 18.96 ± 4.11*# |
| Endotoxin (EU/mL) | 23.68 ± 2.04 | 14.56 ± 1.63* | 8.69 ± 1.32* | 7.21 ± 1.03* | 23.49 ± 1.92 | 9.89 ± 1.41*# | 6.32 ± 1.21*# | 3.23 ± 0.74*# |
| CRP (mg/L) | 158.25 ± 34.25 | 101.14 ± 23.36* | 81.76 ± 21.43* | 69.36 ± 17.48* | 160.14 ± 29.863 | 85.69 ± 24.71*# | 60.13 ± 19.17*# | 49.36 ± 15.74*# |
| WBC count ($\times 10^9$/L) | 15.36 ± 2.14 | 14.12 ± 1.95* | 11.58 ± 1.45* | 8.23 ± 1.25* | 15.43 ± 2.08 | 13.08 ± 1.34*# | 9.55 ± 1.37*# | 7.04 ± 1.21*# |
| PCT (ng/mL) | 18.52 ± 3.69 | 16.58 ± 2.94* | 13.36 ± 2.54* | 14.02 ± 2.38* | 18.43 ± 4.01 | 9.63 ± 2.04*# | 6.36 ± 1.58*# | 4.02 ± 1.14*# |
| Blood lactic acid (mmol/L) | 6.58 ± 1.63 | 4.58 ± 1.41* | 4.02 ± 1.36* | 3.11 ± 1.04* | 6.61 ± 1.57 | 2.75 ± 0.52*# | 3.13 ± 1.01*# | 2.36 ± 0.67*# |

*$p < 0.05$ means comparison with baseline; #$p < 0.05$ means comparison with control group.

Note: IL-6, interleukin-6; TNF-$\alpha$, tumor necrosis factor-$\alpha$; CRP, C-reaction protein; PCT, Procalcitonin; WBC, white blood cell.

**Table 3. Comparison of renal function indexes and bilirubin between the two groups ($\bar{x} \pm s$, n = 30).**

| Factor | Control group | | | | Observation group | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours |
| Serum creatinine (μmol/L) | 471.25 ± 126.33 | 351.02 ± 105.23* | 275.36 ± 86.69* | 205.69 ± 67.36* | 464.25 ± 134.28 | 304.58 ± 91.52*# | 241.36 ± 64.37*# | 171.45 ± 58.33*# |
| Blood urea nitrogen (mmol/L) | 45.62 ± 7.23 | 27.85 ± 6.59* | 23.74 ± 5.12* | 17.55 ± 4.13* | 44.98 ± 7.85 | 22.36 ± 8.25*# | 18.89 ± 6.13*# | 15.63 ± 4.85*# |
| Bilirubin (μmol/L) | 46.85 ± 7.12 | 42.12 ± 6.53* | 41.55 ± 5.08* | 40.13 ± 5.99* | 47.23 ± 6.89 | 41.52 ± 6.05* | 41.05 ± 5.36* | 40.09 ± 6.13* |

*$p < 0.05$ means comparison with baseline; #$p < 0.05$ means comparison with control group.

**Table 4. Comparison of intra-abdominal pressure, single day peak temperature, map, OI and SOFA scores between the two groups ($\bar{x} \pm s$, n = 30).**

| Factor | Control group | | | | Observation group | | | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours | Baseline | Treatment 24 hours | Treatment 48 hours | Treatment 72 hours |
| Intra abdominal pressure (mmHg) | 20.12 ± 3.26 | 18.42 ± 2.78* | 16.23 ± 2.51* | 12.07 ± 2.36* | 20.05 ± 3.49 | 17.05 ± 2.36*# | 13.14 ± 2.58*# | 9.55 ± 2.14*# |
| Daily peak temperature (°C) | 38.95 ± 0.27 | 37.98 ± 0.26* | 37.51 ± 0.28* | 36.75 ± 0.27* | 39.01 ± 0.35 | 37.84 ± 0.25*# | 37.11 ± 0.28*# | 36.52 ± 0.31*# |
| MAP (mmHg) | 72.56 ± 4.96 | 80.57 ± 5.13* | 78.56 ± 4.78* | 78.66 ± 5.01* | 71.58 ± 5.31 | 78.55 ± 5.26* | 76.95 ± 5.04* | 80.11 ± 4.98* |
| OI | 137.58 ± 25.53 | 200.74 ± 28.32* | 207.36 ± 27.14* | 233.63 ± 29.01* | 140.01 ± 23.63 | 241.23 ± 30.89*# | 231.02 ± 26.34*# | 258.14 ± 30.13*# |
| SOFA score (branch) | 13.14 ± 2.76 | 11.84 ± 2.13* | 9.04 ± 1.78* | 8.55 ± 1.45* | 13.03 ± 2.83 | 10.63 ± 2.05*# | 8.15 ± 1.53*# | 6.74 ± 1.21*# |

*$p < 0.05$ means comparison with baseline; #$p < 0.05$ means comparison with control group.

Note: MAP, mean arterial pressure; OI, oxygenation index; SOFA, sequential organ function.

**Table 5. Comparison of mechanical ventilation time, ICU hospitalization time and 28 day mortality between the two groups.**

| Group | n | Mechanical ventilation time (d) | ICU Length of stay (d) | 28 day mortality (%) |
|---|---|---|---|---|
| Control group | 30 | 11.74 ± 2.58 | 19.58 ± 3.47 | 16 (53.33) |
| Observation group | 30 | 8.74 ± 1.86# | 12.78 ± 2.06# | 13 (43.33) |

#$p < 0.05$ means compared with the control group.

Note: ICU, intensive care unit.

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## Results

### *Comparison of Intestinal Mucosal Barrier-Related Factors between the Two Groups*

The baseline of intestinal mucosal barrier-related factors was compared between the two groups, with no statistical significance ($p > 0.05$). I-FABP, DAO and D-lactic acid at 24 h, 48 h and 72 h after treatment in the two groups were lower than those at baseline, with statistical significance ($p < 0.05$). And I-FABP, DAO, D-lactic acid in the observation group were lower than those in the control group at each time point after treatment, with statistical significance ($p < 0.05$). See Table 1.

### *Comparison of Inflammation-Related Factors between the Two Groups*

The baseline of inflammatory-related factors was compared between the two groups, with no statistical significance ($p > 0.05$). IL-6, TNF-$\alpha$, endotoxin, CRP, white blood cell (WBC) count, PCT and blood lactic acid at 24 h, 48 h and 72 h after treatment in the two groups were lower than those at baseline, with statistical significance ($p < 0.05$). The above inflammatory factors in the observation group at each time point after treatment were lower than those in the control group, with statistical significance ($p < 0.05$). See Table 2.

### *Comparison of Renal Function Indexes and Bilirubin between the Two Groups*

The renal function index and bilirubin baseline were compared between the two groups, with no statistical significance ($p > 0.05$). The levels of serum creatinine, blood urea nitrogen and bilirubin in the two groups at 24 h, 48 h and 72 h after treatment were lower than those at baseline, with statistical significance ($p < 0.05$). The serum creatinine and blood urea nitrogen of the observation group at each time point after treatment were lower than those of the control group, and the bilirubin was compared between the two groups, with no statistical significance ($p > 0.05$). See Table 3.

### *Comparison of Intra-Abdominal Pressure, One-Day Peak Body Temperature, MAP, OI, and SOFA Scores between the Two Groups*

The intra-abdominal pressure, one-day peak temperature, MAP, OI and SOFA score were compared between the two groups at baseline, with no statistical significance ($p > 0.05$). The intra-abdominal pressure, one-day body temperature peak and SOFA scores at 24 h, 48 h and 72 h after treatment in the two groups were lower than those at baseline, while MAP and OI were higher than those at baseline, with statistical significance ($p < 0.05$). The intra-abdominal pressure, one-day body temperature peak and SOFA score at each time point after treatment in the observation group were lower than those in the control group, and the OI was higher than that in the control group. The MAP was compared between the two groups, with no statistical significance ($p > 0.05$). See Table 4.

### *Comparison of Mechanical Ventilation Time, ICU Length of Stay, and 28-Day Mortality between the Two Groups*

The duration of mechanical ventilation and ICU stay in the observation group were shorter than those in the control group. The 28-day mortality was compared between the two groups, with no statistical significance ($p > 0.05$). See Table 5.

## Discussion

The pathogenesis of sepsis is complex, which can involve inflammation, immunity and other mechanisms. Its occurrence can be accompanied by the activation and response of the immune system [11]. Theoretically, CVVH can adsorb macromolecular solutes such as guanidines and organic acids, but it cannot remove inflammatory cytokines. Therefore, it is necessary to find a way to form complementary advantages in clinical practice. Blood perfusion can remove macromolecular inflammatory factors. Therefore, CVVH combined with blood perfusion can improve the therapeutic effect [12,13]. This study was the first to investigate the effect of HA380 perfusion combined with CVVH on intestinal mucosal barrier function and inflammatory factors in patients with sepsis.

Sepsis will not only aggravate the degree of inflammatory response, but also accompanied by damage to the body's organs. Clinically, organ damage needs to be evaluated. The inconsistency of clinical scoring systems will also cause different research results. The most commonly used clinical evaluation of organ damage is the SOFA scoring system [14]. The lower the SOFA score, the better the prognosis of patients with multiple organ dysfunction syndrome. In the course of sepsis, the function of heart, liver, kidney and gastrointestinal tract will be affected by the increase of intra-abdominal pressure. Blood purification can control intra-abdominal pressure [15,16]. Combined with the results of this study, the efficacy of HA380 perfusion combined with CVVH in the treatment of sepsis was reliable, which could improve the clinical indicators of patients, and the respiratory rate and heart rate of patients were improved. The body temperature gradually returned to normal, and the hemodynamics of patients was improved.

Assimakopoulos *et al*. [17] have shown that the damage of intestinal mucosal barrier function is closely related to inflammatory response. The incidence of gastrointestinal dysfunction in patients with sepsis is high. I-FABP, DAO and D-lactic acid are commonly used sensitive indicators to reflect the damage of intestinal mucosal barrier in clinic. The results of this study showed that the intestinal mucosal barrier-related factors, inflammation-related factors, renal

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function indexes, intra-abdominal pressure, one-day body temperature peak, SOFA scores at each time point after treatment in the observation group were lower than those in the control group, and the OI was higher than that in the control group. The lower the OI, the worse the pulmonary respiratory function. CVVH establishes a vein-vein vascular pathway and removes toxins and inflammatory factors by convection. CVVH has large blood flow and high removal efficiency of solutes. CVVH uses polymer filter membrane, which has small resistance to blood flow. The role of CVVH technology is close to the filtering effect of human normal kidney, improving hemodynamics, supplementing blood flow, maintaining the stability of the internal environment, and improving the ischemia and hypoxia of tissues and organs. Blood perfusion can remove some exogenous and endogenous toxins and metabolites *in vivo* through adsorption. This study found that the effect of HA380 perfusion combined with CVVH in patients with sepsis was better than that of CVVH alone.

HA380 hemoperfusion can make up for the deficiency of CVVH and reduce the levels of endotoxin and inflammatory factors in patients. Over time, the effect of inhibiting inflammatory waterfall reaction is more obvious. Blood lactate and ScvO2 can not only reflect the degree of hypoxia, but also reflect the severity of organ dysfunction [18]. Combined with the results of this study, HA380 perfusion can remove toxins that bind to proteins or high fat-soluble toxins. HA380 hemoperfusion device has good clinical application effect, not only can adsorb endotoxins, but also can rapidly improve blood lactate and ScvO2 levels.

CVVH combined with HA380 hemoperfusion treatment can improve the tissue perfusion of patients with sepsis, improve their oxygenation status, and reduce the SOFA score. It can be seen that after CVVH combined with HA380 hemoperfusion treatment of sepsis, organ function is improved. With the help of cardiopulmonary bypass device, HA380 perfusion introduces blood into the perfusion device equipped with solid adsorbent. Since CVVH and hemoperfusion have their unique clearance characteristics, this study combines the two and achieves good results.

Hellman *et al.* [19] have reported that patients with subarachnoid hemorrhage complicated with refractory shock were treated with HA380 hemoperfusion combined with CVVH. The dosage of vasoactive drugs was reduced, and the inflammatory indexes and lactic acid levels of patients were controlled. However, these are only case reports, and there is a lack of a large number of clinical studies to confirm. On the basis of previous studies, this study focuses on the effect of combined regimen on intestinal barrier function in patients with sepsis. The initiating factor of multiple organ failure is flora imbalance and translocation induced by intestinal mucosal dysfunction, and the increase of intestinal permeability, resulting in a large number of inflammatory factors entering the blood, aggravating sepsis [20]. HA380 perfusion combined with CVVH treatment can quickly stabilize the patient' s life indications, stabilize hemodynamics, reduce the degree of inflammatory response, improve intestinal barrier function, thereby shortening the duration of mechanical ventilation, ICU hospitalization time, and improve the symptoms of patients. Based on the advantages of blood perfusion and CVVH in the treatment of sepsis patients, this study is the first time to explore the effect of HA380 perfusion combined with CVVH on intestinal mucosal barrier function and inflammatory factors in patients with sepsis, which has certain clinical significance. This study only selects some commonly used detection items in clinical work, which can not well represent the pathophysiological process, and is insufficient. It is expected to better assist with relevant disciplines in future research and complete higher quality clinical research.

## Conclusion

HA380 perfusion combined with CVVH in the treatment of sepsis can reduce intestinal barrier function damage and inflammation, and improve short-term prognosis.

## Availability of Data and Materials

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

## Author Contributions

JW, XZ and HZ contributed to the concept and designed the research study. JW and XL performed the research. LY, KZ and JX contributed to the analysis and interpretation of the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

## Ethics Approval and Consent to Participate

This study has been approved by the Medical Ethics Committee of the First Affiliated Hospital of Gannan Medical University (No. LLSC-2022040201). The consent to participate has been obtained from every patient.

## Acknowledgment

The authors sincerely thank all the study participants.

## Funding

This work was supported by Guiding Science and Technology Plan of Ganzhou City (grant no. GZ2021ZSF010).

## Conflict of Interest

The authors declare no conflict of interest.

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