



Effects of Continuous Blood Purification without Heparin on Strem-1, NSE, and IL-10 Levels in Patients with Sepsis

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ABSTRACT

One of the most common causes of mortality and disability across the world is sepsis, a condition marked by an abnormal immunological reaction in the body. The prognosis of patients with sepsis is much improved when they are diagnosed early and provided with proper therapy. Soluble triggering receptors expressed on myeloid cells (STREM-1), Interleukin-10 (IL-10), neuronal serum enolase (NSE), and so on are possible biomarkers for the diagnosis of sepsis based on the pathophysiology. Blood purification treatment to control the cytokine storm induced by sepsis was regarded to be promising. Recently, the treatment of sepsis is likely to shift toward a multimodal approach. Hence in this paper, we investigated the effect of a continuous blood purification technique (hemofiltration without heparin followed by hemoadsorption) on STREM-1, NSE, and IL-10 levels in patients suffering from sepsis. A sample of hundred patients suffering from sepsis was randomly allocated to one of the two groups (study and control groups). The control group got standard sepsis care, whereas the research group got continuous blood purification treatment. To compare the differences between the two groups, we used t-statistical analysis. Blood STREM-1, IL-10, and NSE concentrations of the study group were significantly lesser than that of the control group after therapy. As a result, continuous blood purification can significantly minimize the dysregulated immune response in patients with sepsis, promote immune function and improve the survival rate.

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Introduction

Sepsis is one of the major causes of death and disability across the globe. More than five million people die each year from sepsis, affecting more than 30 million people yearly (1). The aging population and resistance to antibiotics are some of the contributing causes. The number of people who die each year from sepsis was estimated at 11 million, or 19.7 percent of all fatalities. Death rates may reach 19 to 31% when the condition develops into septic shock and circulatory collapse (2).

Sepsis is characterized by an immunological response that is out of control and may lead to organ failure and even death as a result of infection. For example, components of bacterial cell walls such as endotoxin or lipopolysaccharide, attach to pattern recognizing receptors namely toll-like receptors, to activate an immune function for pathogen clearance when an infection occurs. This may lead to cell malfunction and eventually organ failure if the

immune system is over-activated too much. Amplification of inflammatory cytokine levels is triggered by the discharge of damage-associated molecular patterns from the host cells that are injured (3).

The immunological and inflammatory systems get activated in sepsis, which may be lethal due to their imbalance and complexity. There is a range of pathogenic and non-infectious diseases that may contribute to hyperactive immune responses at the outset of sepsis, which are followed by immunoparalysis and reduced immune function during the later stages of sepsis. Figure 1 shows the difference in immune response occurring in normal and sepsis cases (4).

Markers used commonly in sepsis diagnostics like C-reactive protein (CRP) and procalcitonin (PCT) are not significantly sensitive. Therefore, novel indicators of acute inflammation, which would be a valuable predictive marker in patients having sepsis, are being

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explored. The inflammatory response caused by microorganisms is characterized by the production of proinflammatory mediators like IL-1 β , IL-6, and tumor necrosis factor and anti-inflammatory molecules like IL-10 that may impact clinical outcomes. STREM-1 is produced by the induced phagocytes and may be found in bodily fluids. Thus, STREM-1 may be used as a possible biomarker of sepsis diagnosis (5). The physiological serum concentration of immunological markers rises throughout the progression of pathogenic and noninfectious disorders, including injury, surgery, and so on, as well as autoimmune diseases (6). Even with extensive intensive care, sepsis remains a major illness to conquer. Recent studies are based on the application of blood purification in the treatment of sepsis (7).

In our study, we analyzed the effect of continuous hemofiltration without heparin followed by hemoadsorption on the treatment of patients with sepsis. The further organizations of the research paper are shown below. Section II shows the related works and problem statement. Section III provides the methods and materials for our study. Performance evaluation is given in Section IV. The paper's conclusion is given in section V.

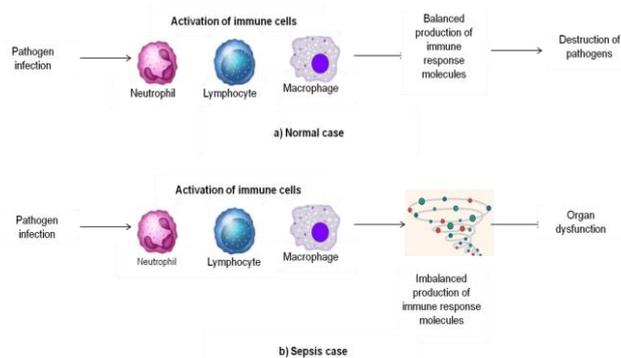


Figure 1. Immune response in normal and sepsis cases

Related works

Hinoue et al. 2021, (8) mention that recombinant human-soluble Thrombomodulin (rhsTM) may prevent clotting of circuits in patients suffering from sepsis receiving blood purification. They conducted the propensity-matched study at Nishichita General Hospital's critical care unit. Patients with severe sepsis may benefit from blood purification therapy because the removal of inflammatory mediators and/or

bacterial toxins from circulation may modify the inflammatory responses that lead to organ destruction. Although early excitement based on promising exploratory findings, further studies failed to establish a long-term survival advantage. To treat sepsis and septic acute kidney damage, (Shum et al. 2016) (9) will look at how blood purification procedures have evolved through time.

Arimura et al. 2017 (10) mention that using data from the Japan Society for Blood Purification in Critical Care's national registry, they performed cohort research to better understand the clinical state of blood purification treatment (BPT). Death was shown to be substantially linked with the APACHE II score and acute liver failure in multivariate regression analysis. In Japan, the results of this cohort research revealed the BPT's current clinical state. To evaluate whether BPT is safe and effective for critically sick patients, more research is needed. Chung et al. 2017 (11) determined if high volume hemofiltration (HVHF) improves the hemodynamic report of burn patients suffering from septic shock. A prospective, multicenter, controlled, and the randomized clinical study was done including seven US burn hospitals. A dosage of 70ml/kg/hour for 48 hours was provided to patients randomized to the HVHF, whilst controls were treated as usual in line with local practice. Karkar et al. 2020 (12) evaluated the continuous renal replacement therapy (CRRT) prescription in sick patients with sepsis, severe kidney injury, and multiorgan failure. In addition, it is important to consider the use of adsorptive methods in sepsis to remove endotoxins and other pathogens.

Kamijo et al. 2020 (13) reasoned that administering Nafamostat mesylate (NM) to sepsis patients while their blood was being purified would lower their fatality rate. They matched sepsis patients who received BPT in the critical care unit using a propensity score to investigate the impact of NM on death and bleeding complications. Davenport et al. 2021 (14) mentioned that in sepsis, CRRT can help remove too much fluid, even though it hasn't been proven yet. In these cases, CRRT can help with morbidity but not dead so far, but it can help. After a few decades, the timing of sepsis has become more important and is now more important than dosing. The idea of BPT has changed drastically in the last few years because of the discovery of several sorbents.

There is no doubt that COVID-19 has made people more interested in BPT in both sepsis and COVID-19. Even more so than sepsis, burns need the removal of excess fluid from the body. Ultrafiltration can help people with heart failure when diuretics stop working, but it can't help them live longer. CRTs have a lot of advantages over intermittent hemodialysis when it comes to brain injuries. It is unknown if single-pass albumin dialysis is superior to normal supportive treatment in patients with liver failure (15).

Tian et al. 2014 (16) mention that the goal of this research is to determine the best time to begin CRRT in patients having acute kidney injury (AKI). Nalesso et al. 2020 goal (17) is to give the best possible therapy for AKI in hazardous settings with limited human and technical resources by describing an innovative continuous venovenous hemodialysis (CVVHD) procedure. An anticoagulant method using a high cut-off (HCO) filter in the area of CVVHD was developed by them. When the HCO filter is used in diffusion, the smaller filtering fraction allows for better cytokine clearance while also decreasing filter clotting (18). They treated seven COVID-19 patients having AKI stages 2 and 3 at the start of the pandemic epidemic and monitored their circuit lifetime and the number of interventions. CVVHD in a biohazard setting having a lower blood flow rate and fewer bag changes seems safe, effective, and resource-saving while also reducing the biohazard. Despite the short sample size, our approach seems to have a low death rate. Cantaluppi et al. 2019 (19) explain that when it comes to blood purification, immunomodulation and organ support are key factors to consider. In the absence of concurrent acute renal impairment, conventional CVVHD has not been proven to be useful in sepsis. Combinations of plasma treatments, HVHF, hemadsorption, or any of these therapies look promising. But many unsolved questions remain. Middle-molecular-weight compounds are still unable to be removed by existing methods, and the present practice throughout the globe is quite diverse. Large-scale randomized clinical studies are also lacking. Current RRT techniques may benefit from new emerging technologies, such as high-porosity membranes, which boost intermediate molecule clearance. For these potential blood purifying technologies, multicenter randomized controlled studies are required.

Klein et al. 2018 (20) mentioned that polymyxin B hemoperfusion (PMX) was studied in patients with septic shock and endotoxemia (EAA 0.60). Mortality from all causes at 28 days did not vary. The effect of PMX usage in patients was investigated in a post hoc study. Ishizuka et al. 2014 (21) mentioned that is the most important factor in the death rate of patients getting PMX for septic treatment. The Cox proportional hazard model was utilized in univariate and multivariate analyses to assess which clinical trait was most closely linked to 28-day mortality.

Hara et al. 2015 (22) mention that Adacolumn and hemofiltration have been used to produce a novel BPT for managing overactive immunological reactivity in patients with severe sepsis. To assess the effect of adsorption of leukocytes, the activity of phagocytes and the adhesiveness of granulocytes were studied in five different experimental groups. Rimmelé et al. 2013 (23) explain that a hemoadsorption system capable of adsorbing cytokines and leukocytes was devised to assess the hypothesis that capturing leukocytes would change the profile of circulating cytokine and impact interactions between immunological cells in whole blood obtained from septic patients. Wu et al. 2021 (24) hoped that this study would shed light on the effects of CRRT in patients with sepsis-associated AKI. CRRT (group A) was given to 40 patients, while the others got standard treatment (group B). Between groups, they examined renal function indicators, namely BUN (blood urea nitrogen) and creatinine in serum, urine level, and curative indices. Both groups were also compared based on the incidence of cardiovascular events. They also looked at and compared the treatment's effectiveness (total effective rate).

Mariano et al. 2020 (25) illustrate that coupled plasma filtration adsorption (CPFA) is a sorbent-strategy that aims to remove soluble mediators of septic shock from the bloodstream. This study's purpose is to examine the CPFA's effectiveness and safety in this particular population of septic shock patients with AKI. They conducted a retrospective assessment of the medical records of all burn patients hospitalized at their adult Burn Center between January 2001 and December 2017 who received CPFA. CPFA patients were compared to other burn patients treated with treatments other than CPFA, who had acquired AKI over the same period and had the

same range of significant clinical features. Shan et al.2020 (26) mention that hemodiafiltration is a continuous BPT used to save patients with severe illnesses or organ failure, notably in critical care and emergency settings. Filters are designed with polymer materials as hollow fiber membranes. When the membrane comes into contact with blood, it's more likely to get obstructed. Heparin is a common anticoagulant used in therapeutic practice. Recently, heparin has been used to chemically or physically alter hollow fiber membranes to increase filtering performance. Their article outlines recent developments in hollow fiber membrane surface heparinization and filtration performance.

Problem Statement

Though standard antimicrobial therapy can favorably treat sepsis, it is not still accountable for efficient treatment. Patients' lives are at risk if sepsis is not diagnosed and treated correctly. The commonly used sepsis diagnostic markers, such as CRP and PCT, are neither sensitive nor specific enough. Recently immune markers like IL-10, STREM-1, and so on are gaining attention in the diagnosis of sepsis. Hemofiltration has been proposed for many years as a possible strategy to modulate the multiple inflammatory mediators. Systemic heparinization might expose the patient to the risk of bleeding due to over-anticoagulation. To avoid the disadvantages of systemic heparin during purification, saline flush has been described in hemofiltration. When different blood purification methods are combined, the treatment of sepsis can be enhanced. Hence, in this study, we analyzed the effect of heparin-free hemofiltration combined with adsorption.

Materials and methods

The goal of this research is to examine the effects of the suggested continuous blood purification therapy on serum immunological biomarker levels. This is a preliminary randomized trial. Patients with sepsis who are eligible for the trial will be assigned at random to one of two groups: control or study. Septic patients in the control group are given normal care, such as antimicrobials and nutrition assistance. The study group is provided with continuous hemofiltration treatment. ELISA (Enzyme-Linked Immunosorbent Assay) was utilized to find out the concentration of

STREM-1, IL-10, and NSE in blood before and after respective therapies. A t-test was carried out for statistical analysis of the difference between the two groups in terms of mean concentrations of immunological markers. The flow of our study work is presented in figure 2.

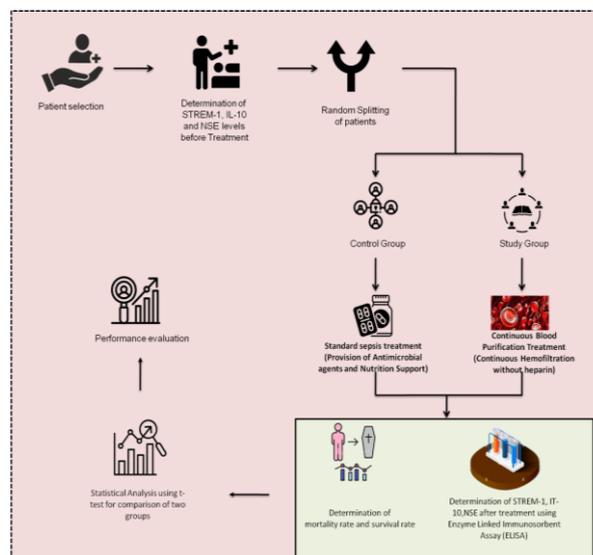


Figure 2. The flow of our research work

Patient Selection

Patients with sepsis admitted to the internal care unit (ICU) of Second People's Hospital of Shenzhen, China was selected for this study (27). This study is presently enrolling patients who fulfill the inclusion criteria of sepsis. An informed consent form must be signed by the patient or a representative approved by the patient before treatment may begin.

Inclusion Criteria

The following are the inclusion criteria for our study.

- Age limit: 18-60
- Suspected or documented infection
- Any two of the following stimulated by the infection
 - Body temperature: 36 °C-38 °C
 - The rate of heartbeat: >ninety beats per minute
 - Breathing rate: > twenty breaths per minute
 - The partial pressure of arterial carbon dioxide: < thirty-two mmHg
 - Count of white blood cells (WBC): Greater than $12 \times 10^9 \text{ L}^{-1}$, or immature structures of WBC greater than ten percent

- Any one of the following
 - Oxygenation index ≤ 300
 - Total bilirubin content of plasma: Greater than 2 mg/dL
 - pH: Lesser than 7.30
 - Arterial hypotension continuing for 1 hour or more despite sufficient resuscitation of fluid (systolic blood pressure: < 90 mmHg and mean arterial pressure: < 65 mmHg)
 - Number of platelets: Lesser than $10 \times 10^{12} \text{ L}^{-1}$
 - Activated partial thromboplastin time: Greater than sixty seconds
 - Acute oliguria (urine output $< 0.5 \text{ mg kg}^{-1} \text{ h}^{-1}$ for at least 2 hours), creatinine increase $> 2 \text{ mg dl}^{-1}$ within 48 h,

Exclusion Criteria

The following are the exclusionary criteria for our study.

- Women who are lactating or pregnant
- Patients who have got immune-suppressive or immune-enhancement therapy within the last three months
- Patients suffering from a suspected autoimmune disease
- Patients whose expected survival time is less than 28 days due to a terminal illness
- Patients with mental illness or poor compliance

A total of 100 patients who satisfy the above criteria are selected. They were randomly split into two groups namely the control group and the study group. The Control group consists of 48 patients and the study group consists of 52 patients. The serum level of STREM-1, IL-10, and NSE markers in each patient is determined using ELISA before the provision of treatment and recorded appropriately.

Standard Sepsis Treatment

Standard sepsis therapy was given to the control group. Sepsis therapy comprises the provision of antimicrobial drugs, as well as life support measures such as oxygenation and nutritional support, volume resuscitation and hemorrhage management, and approved ventilator support. The patients were not allowed to consume any liquids or food. Omeprazole sodium injection was used intravenously to preserve

the stomach mucosa and indirectly suppress pancreatic enzyme release in the early stages of controlled liquid resuscitation. Following parenteral feeding with a nasointestinal tube, patients received enteral nutrition, and the dosage was adjusted based on results from exams.

Continuous Blood Purification technique without heparin

The study group is provided with the suggested continuous blood purification technique (heparin-free continuous hemofiltration combined with hemoabsorption). It is carried out with an extracorporeal circuit. The hemofilter preceded the adsorption cartridge in the circuit. It consists of a synthetic polysulphone filter with an effective membrane area of 1.4 mm^2 . Patients received heparin-free continuous hemofiltration (CHF) treatment every day using an Ultraflux hemofilter. The blood is usually taken from a double-lumen CVC (central venous catheter) with the help of a blood pump and passed through a hemofilter. The ultrafiltration flow was maintained at 1,500-2,000 mL/h while the flow rate of the blood was 150-200 mL/min. Every half an hour to one hour, 200 to 300 ml of 0.9 percent saline was infused into the extracorporeal circuit for the saline flush. Cleaning the filter and keeping it from clotting are the goals of the continuous saline flushing approach. The filtered blood from the hemofilter was passed into the adsorption cartridge. The adsorption cartridge contains hydrophobic styrene resin constructed by several pores and channels that increase the surface area. It is effective in adsorbing inflammatory and non-inflammatory cytokines. The filtered blood from the adsorption cartridge was pumped into the body (Fig. 3).

Determination of serum immune factors using ELISA

After 7 days of treatment, three mL of fasting blood from peripheral venous limbs was extracted from patients in two groups and cryopreserved in a $-70 \text{ }^\circ\text{C}$ refrigerator for the test. ELISA test was carried out to determine the serum immune markers such as STREM-1, IL-10, and NSE. Two groups' mean concentrations of immunological markers may be compared using t-tests to discover whether there is a significant difference.

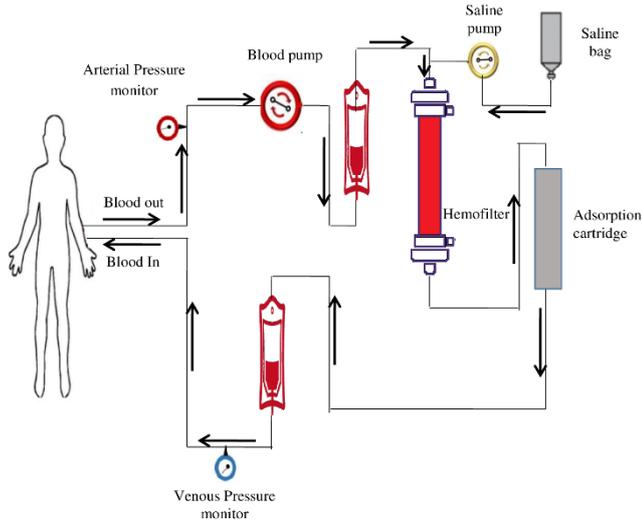


Figure 3. Continuous hemofiltration without heparin

Results and discussion

This section deals with the analysis of the impact of continuous blood purification treatment on serum immune biomarker levels. The Control group consisting of 48 patients received standard broad-spectrum antibiotic therapy and the study group consisting of 52 patients received heparin-free CHF combined with hemoadsorption (28). The statistical t-test was conducted to find the difference between the two groups. Before therapy, both groups had statistically greater mean concentrations of all investigated biomarkers in their blood. After seven days of therapy, the blood levels of several immunological markers such as IL-10, STREM-1, and NSE are shown in Table 1. The decrease in immunological factors was more significant in the study group than in the control group. A p-value of less than 0.05 is considered significant. Compared with the control group, the decrease of STREM-1, IL-10, and NSE in the study group was highly significant (p-value lesser than 0.05). There is a statistical difference between the effects of standard treatment and suggested CHF without heparin in reducing STREM-1, IL-10, and NSE.

Table 1. Comparison of serum immune factors between two groups after treatment

Group	Average Concentration of serum markers		
	IL-10 (pg/mL)	STREM-1 (pg/mL)	NSE (pg/mL)
Study Group	42.44±3.2	35.27±4.19	70.27±3.27
Control group	92.37±4.5	87.35±3.23	90.35±2.35
t-statistic	7.83	11.32	6.43
p-value	0.03	0.024	0.045

Figures 4, 5, and 6 show the mean concentration of IL-10, STREM-1, and NSE in blood before and after treatment in two groups. In the study, the serum levels of the immune markers were detected after the treatment using ELISA, and it was found that serum STREM-1, IL-10, and NSE content of the study group were lesser compared to the control group after the treatment, indicating that the continuous blood purification has actively filtered the immune factors, and helps to reduce the systemic inflammatory state in patients.

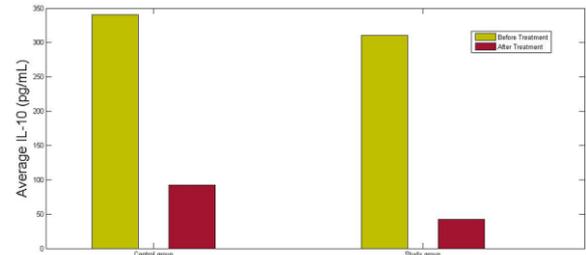


Figure 4. IL-10 levels before and after treatment in two groups

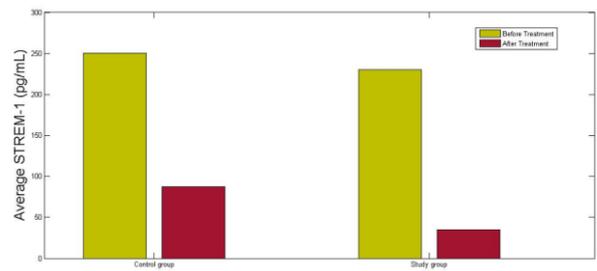


Figure 5. STREM-1 levels before and after treatment in two groups

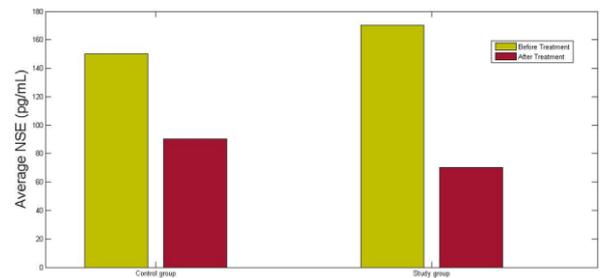


Figure 6. NSE levels before and after treatment in two groups

Figure 7 depicts the seven-day survival curve of control and study groups and patients receiving corticosteroid therapy. Patients in the study group had a far better prognosis than those in the control group and those who received corticosteroid medication. The survival rates on the 7th day were 85% in the study group, 55% in corticosteroid therapy, and 45% in the control group. This indicated that heparin-free

CHF combined with adsorption significantly improved the survival rate of sepsis patients compared to standard antimicrobial treatment.

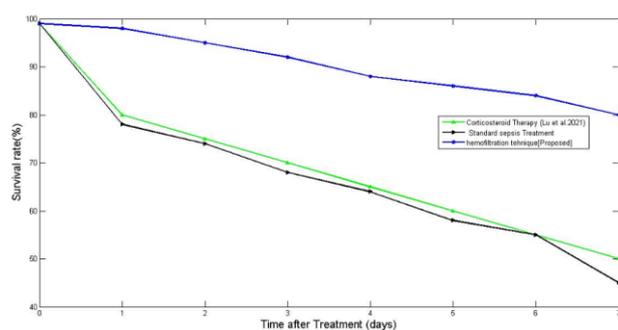


Figure 7. Survival rate versus time

Figure 8 depicts the seven-day mortality curve of patients receiving proposed hemofiltration treatment (heparin-free CHF with adsorption) and polymyxin B hemoperfusion (PMX). The mortality of the study group was lesser than that of patients receiving PMX therapy. This indicated that heparin-free CHF combined with adsorption significantly reduced the mortality of patients with sepsis compared to PMX therapy (29).

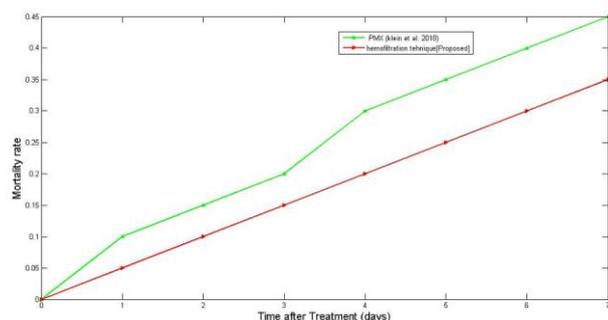


Figure 8. Mortality rate versus time

The feasibility of the proposed hemofiltration technique (heparin-free CHF followed by hemoabsorption) in patients with sepsis has received attention from many scholars, but the specific clinical curative effect of treatment is still not clear, and there is less clinical research in the field at present. To define the therapeutic effect of the proposed hemofiltration technique for patients with sepsis, we performed this research. The result analysis showed that there was a significant difference between the study and control groups. Standard sepsis therapy was less efficient for treating sepsis compared to CHF.

Through convection, and adsorption mechanisms of action, the proposed hemofiltration technique exchanges and removes not only the plentiful toxic and side metabolites in the patients but also the immune response sepsis markers, thus reducing the negative effect on the body's normal functions. CHF combined with hemoabsorption is well tolerated by patients with sepsis and has been shown to increase the survival rate. As a regular therapy strategy, this combination may be a safe and successful technique.

Septic shock in immunocompromised patients did not benefit from corticosteroids, as shown by (30, 31). Hemorrhagic instability, longer hospital stays, and an increased risk of hyperglycemia were all side effects of corticosteroid medication. The proposed CHF approach, on the other hand, is strongly linked to a safe and higher survival rate. Polymyxin-B hemoperfusion (PMX) therapy was researched by Klein et al. 2018 (20) to see how it affected patients with sepsis. An intravenous heparin infusion was administered in addition to the PMX cartridge and dialysis catheter as part of their trial treatment regimen. Despite the positive outcomes of PMX, patients with coagulopathy, persistent bleeding, or who have just had major surgery should avoid using anticoagulants. For individuals with a significant bleeding risk, our CHF without heparin is a better option.

Conclusions

Sepsis is a serious complication for patients and is one of the major causes of death in patients. As part of this research, we looked at how sepsis patients' STREM-1, NSE, and IL-10 levels were affected by a continuous blood purification procedure (hemofiltration without heparin followed by hemoabsorption) compared to standard antimicrobial treatment. STREM-1, IL-10, and NSE concentrations in the serum of the study group were considerably lower than those of the control group after therapy. Multiple mechanisms of blood purification, including convection and adsorption, seem to be present in this treatment, making it appear to be both safe and effective. Patients with sepsis may benefit from this medication because it may remove immune mediators non-selectively, reduce the inflammatory response, and restore the immune system's normal balance. There were just a restricted number of participants in

our research. It's also worth noting that we didn't assess the levels of immune factors for more than seven days after therapy. We must conduct 28-day research to see whether our proposed strategy has any impact on a large number of patients with sepsis.

Acknowledgments

Not applicable.

Interest conflict

The authors declare that they have no conflict of interest.

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