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RESEARCH PROTOCOL

Clinical efficacy of hemoperfusion with a cytokine adsorbent in norepinephrine-resistant septic shock: protocol for the CLEANSE randomized clinical trial

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ABSTRACT:

Background: Due to the pivotal role of inflammatory cytokines in sepsis, hemoperfusion with cytokine adsorbents may lead to better outcomes. Although previous studies showed inconclusive results, proper patient selection and timing of hemoperfusion may lead to improved survival.

Objectives: To examine whether patients with septic shock requiring high-dose vasopressors undergoing add-on hemoperfusion with a cytokine adsorbent have better clinical outcomes than those treated with standard treatment alone.

Methods: This is a multi-center, randomized controlled study in 2 tertiary care centers. 206 patients with septic shock receiving norepinephrine of 0.2 mcg/kg/min or higher are randomized to receive either standard treatment combined with 3-hour sessions of hemoperfusion with cytokine adsorbent for two consecutive days (HP group) or standard treatment alone (ST group). The primary outcome is 28-day mortality. Secondary outcomes include hospital and ICU mortality, shock reversal, vasoactive-inotropic score (VIS), organ support-free days, interleukin-6 levels, as well as safety data.

Conclusions: This study will provide information to guide the use of hemoperfusion with a cytokine adsorbent in patients with septic shock.

Keywords: Blood purification, Cytokine, HA-330, Hemoperfusion, Sepsis, Septic shock

INTRODUCTION

Sepsis and septic shock are major causes of ICU admission worldwide. Despite recent advances in treatment, including targeted resuscitation and timely use of antimicrobial agents, mortality of ICU patients with septic shock remains steadily high [1]. Especially in those requiring high dosage of vasopressors, whose 28-day mortality rate could reach 60% [2].

The pathophysiology of septic shock emphasizes on the role of dysregulated host immune response towards inciting microbes, producing excessive inflammatory cytokines which lead to tissue damage and subsequent organ failures [3]. Multiple therapies targeting the overwhelming inflammatory response in patients with septic shock have been studied [4]. While some showed promising results in modulating inflammation in observational studies, only systemic corticosteroids were associated with better clinical outcomes in the randomized controlled studies [5]. The reasons for the failures of these immune modulating therapies are the complexity of the inflammation cascades, where treatments specifically targeting parts of the process may not be able to achieve meaningful effects [4].

Hemoperfusion is an extracorporeal treatment option more extensively studied over the last decade [6]. By passing patients' blood or plasma through specifically developed absorbers, various inflammatory cytokines are absorbed to resins inside the devices and removed from the circulation. Decreasing levels of inflammatory cytokines may subsequently attenuate systemic inflammation leading to shock reversal and better survival.

HA-330 disposable hemoperfusion cartridge (Jafron®, China) is an absorber targeting hyper-inflammatory states including septic shock. It is designed to nonspecifically absorb molecules with molecular weight 10-60 kilo-Dalton, making it effective for removing various pro-inflammatory cytokines and potentially modulating the inflammatory cascade [6].

Previous randomized study in patients with sepsis compared between add-on 3 daily sessions of hemoperfusion with HA-330 adsorbent and standard therapy [7]. Circulating interleukin-6 and interleukin-8 levels in patients underwent hemoperfusion significantly reduced after two sessions when compared to baseline. Their values on day 3 were also significantly lower than those of the control group. Adjunctive hemoperfusion was associated with lower ICU mortality, but not significant difference in hospital and 28-day mortality. However, as 50% of enrolled patients had sepsis without shock, generalization of the findings to more severe cohorts of septic shock patients is therefore limited. Moreover, while the timing of hemoperfusion was not provided, most patients had already developed multiple organ failure at the time of treatment, potentially limiting clinical benefits.

Patients with septic shock have higher cytokines level than septic patients without shock [8]. Hence, they are theoretically more likely to benefit from therapies aiming to reduce cytokine levels. We hypothesize that adjunctive hemoperfusion with HA-330 adsorbent would be associated with better outcomes in a more severe group of patients with septic shock.

KEY MESSAGES:

- By removing inflammatory cytokines from circulation, hemoperfusion with cytokine absorbents may be associated with better outcomes in patients with septic shock.
- Prior study showed that in patients with sepsis, hemoperfusion with HA-330 adsorbent led to lower inflammatory cytokine levels and vasopressor use. A trend towards lower 28-day mortality was also demonstrated.
- This study is a randomized clinical study investigating whether adjunctive hemoperfusion with HA-330 would lead to better 28-day survival, compared to standard treatment alone, in a subgroup of patients with septic shock requiring high dose of vasopressors.

OBJECTIVES

Primary objective

• The primary objective of this study is to determine whether, in patients with septic shock requiring high dosage of vasopressors, standard treatment with adjunctive hemoperfusion with HA-330 results in better 28-day mortality when compared to standard treatment alone.

Secondary objectives

• The secondary objective is to examine the effect of hemoperfusion treatment with HA-330 on clinical efficacy and safety endpoints.

MATERIALS AND METHODS

Trial design and setting

This is a prospective multicentric randomized controlled clinical trial conducted at intensive care units (ICUs) in 2 tertiary referral centers in Thailand: The Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok and the Faculty of Medicine, Khon Kaen University, Khon Kaen. Enrollment started from September 2021.

The study protocol was approved by the Siriraj Institutional Review Board (approval number SI040/2021) and registered internationally (ClinicalTrials.gov NCT05 136183).

The trial is supported by the Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University.

Eligibility and exclusion criteria

The following inclusion criteria are used to identify eligible patients.

1. Adults age 18 years or older
2. Patients are diagnosed with septic shock according to the SEPSIS-3 criteria
3. Patients are receiving at least 0.2 mcg/kg/min intravenous norepinephrine or other equipotent vasopressors. Other vasopressors used are converted to norepineph-

rine-equivalent dose according to recent recommendations [9].

The following patients are excluded from the study:

1. Patients who met the vasopressor threshold for more than 24 hours
2. Patients who have acute coronary syndrome or life-threatening arrhythmias
3. Patients who have acute ischemic stroke
4. Patients who have uncontrolled bleeding
5. Patients with underlying comorbidities with no effective treatment and have expected life expectancy less than 6 months
6. Patients with moribund conditions with expected imminent death within 24 hours
7. Patients known to be pregnant at the time of screening

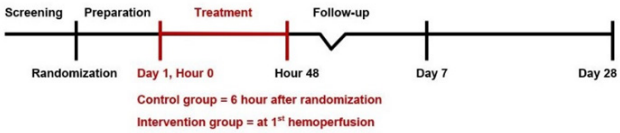
After screening, informed consent is obtained from the patients, or their legal guardian in case of patients' inability to provide consent.

Treatment allocation

After enrollment, participants are randomly assigned in a 1:1 ratio to either standard treatment group (ST group) – receiving standard treatment alone – or hemoperfusion group (HP group) – receiving standard treatment and adjunctive hemoperfusion with HA-330. The randomization is performed with blind envelops with variable block sizes of 4, 6 and 8 and is stratified by study sites.

Intervention

The intervention each participant received is divided into 3 periods, namely: preparation, treatment and follow-up period. (Figure 1)



The preparation period immediately starts after randomization for all participants. For those randomized to the ST group, a fixed 6-hour period is given. On the contrary, the preparation period for the HP group continues until the onset of the first hemoperfusion session, suggested to be within 12 hours from randomization. During this preparation period, for patients randomized to HP group, a vascular access is established. Double lumen dialysis catheter with 11.5-13.0 French gauge and 20 cm length is placed to femoral veins under ultrasonographic guidance. Other types and sites of vascular accesses are permitted according to physicians' discretion.

The start of the treatment period is denoted as Day 1 and Hour 0. Participants in the ST group would receive standard treatment for patients with septic shock deemed appropriate by treating physicians, without any mandated treatment protocol. Any use of life-support therapy, including renal replacement therapy, is also according to usual indications.

As for the treatment period for participants in the HP group, two hemoperfusion sessions are performed using HA-330 disposable hemoperfusion cartridges, starting at Hour 0 and Hour 24. The cartridge is primed with 5000 units of unfractionated heparin for 30 minutes and then flushed with 2 liters of 0.9% sodium chloride solution. Hemoperfusion is performed using available continuous renal replacement therapy systems. The initial blood flow rate is set at 100 mL/min and subsequently increased up to 200 mL/min according to hemodynamic status of the participant. No systemic anticoagulant is administered during a hemoperfusion session to prevent circuit clot. The use of systemic anticoagulants as prevention and treatment of other thromboembolic diseases are allowed according to treating physicians' discretion. A hemoperfusion session lasts 2 hours, after which the procedure is terminated and the vascular access is heparinized and dressed for the next session. After completion of the second session, the vascular access is removed unless it is required for other modes of renal replacement therapy.

After 48 hours of treatment period, participants are followed until Day 28 or hospital discharge. In the latter case, telephone appointments are arranged to determine clinical outcomes at Day 28 after randomization.

Outcome Measurement

The primary outcome of this study is 28-day mortality. And secondary outcomes include the following:

- ICU mortality up to 24 weeks
- Hospital mortality up to 24 weeks
- ICU-free days to Day 28
- Vasopressor-free days to Day 28
- Ventilator-free days to Day 28
- RRT-free days to Day 28
- Vasoactive-inotropic score at Hours 3, 6, 24 and 48 and Day 7 – which objectively quantify commonly used vasopressors and inotropes in clinical practice, previously validated in septic shock [9]
- Shock reversal at Hour 6 – defined as mean arterial pressure of 65 mmHg or more with either lactate reduction of more than 20% or average urine output more than 0.5 ml/kg/hour
- Arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) at Hour 24, Hour 48 and Day 7
- Acute Physiology and Chronic Health Evaluation II (APACHE II) score at Hour 24, Hour 48 and Day 7
- Sequential Organ Failure Assessment (SOFA) score at Hour 24, Hour 48 and Day 7
- Serum C-reactive protein (CRP) level at Hour 24 and Hour 48
- Plasma Interleukin-6 (IL-6) level at Hour 24 and Hour 48

For missing APACHE II and SOFA score values due to death, the worst possible score will be assigned. No other imputation will be done for other missing values, regardless of the cause.

Serious adverse events will be monitored until Day 28. Recorded serious adverse events will be reported to regulatory authorities and monitored until resolution. For safety outcome assessment, the following endpoints are specifically monitored until ICU discharge:

- Hypotension during RRT sessions – defined as reduction of either SBP > 20 mmHg or MAP > 10 mmHg or

increase in vasopressors equivalent to 0.1 mcg/kg/min of intravenous norepinephrine during any renal replacement therapy sessions

- Arrhythmias requiring medical treatment – including medications and electrical therapies
- Dialysis catheter-related bleeding requiring medical treatment – including transfusion, surgical procedures or any cessation of medications involving hemostasis
- Dialysis catheter-related infections
- New-onset leukopenia – defined as white blood cell count lower than 4,000/mm3
- New-onset thrombocytopenia – defined as platelet count lower than 20,000/mm3
- New episode of septic shock – indicated by the need to restart vasopressor, accompanied by either adjustment in antimicrobial regimen or procedure to control infection source

Sample size estimation

The 28-day mortality in the ST group is estimated to be 60% [10]. An absolute reduction of 20% (to 40% 28-day mortality) in the HP group is expected. A combined sample of 206 patients would have 80% power at a two-sided type I error rate of 5%, including adjustments for two interim analyses.

Data analysis plan

As this is, to our knowledge, the first randomized controlled study investigating the effects of hemoperfusion with HA-330 in this specific group of patients, two interim analyses are planned to investigate for early signals of benefits and harms of the treatment. The interim analyses are performed on the primary outcome when 30% and 60% of patients have been randomized and completed the 28-day follow-up. The analyzing statisticians will have unblinded access to all data. Asymmetric two-sided group sequential design is used. The bounds are derived using a Hwang-Shih-DeCani spending function with gamma = -2 for futility bound and gamma = -4 for efficacy bound. The futility bound is non-binding. On the other hand, discussion for potential stopping is warranted in case of crossing the efficacy bounds. The resulting one-sided p for efficacy at the first and second interim analyses are 0.011 and 0.0040, respectively. For the final analysis, the two-sided p is 0.0464.

All analyses will be done for the modified intention-to-treat population, where all participants who reach Hour 0 are included. That is, all participants in the ST group who survive for at least 6 hours after randomization and those in the HP group who undergo the first hemoperfusion session will be included.

Kaplan-Meier methods and Cox proportional hazards regression will be used to compare mortality endpoints. Time to death will be calculated from Day 1 to date of death. The analyses for differences between organ support-free days will be performed using both the Mann-Whitney U test and the Fine-Gray model for competing risk regression retaining analyses [11]. Differences of continuous data will be tested using the Mann-Whitney U test. Categorical data will be tested using the chi-square or Fisher's exact test, when appropriate.

All data analyses will be performed using R, version 4.1.2 (R Project for Statistical Computing).

DISCUSSION

Patients with septic shock, especially those requiring high dose vasopressors carry poor prognoses [1]. Hemoperfusion, a form of blood purification therapy, extracorporeally removes pro-inflammatory molecules from the circulation and potentially modulate shock. Multiple studies using the technique reported varied treatment results [6]. This heterogeneity could be partially explained by difference in adsorbents used, as well as patient selection.

HA-330, the cytokine adsorbent used in this study, was previously studied in a single center randomized trial in patients with sepsis [7]. The study showed reduction in pro-inflammatory cytokine levels as well as vasopressor dose used in patients treated with three daily hemoperfusion sessions. Their clinical outcomes, including 28-day mortality, were not significantly different from patients receiving only the standard cares [7]. The participants of this previous study were different from those enrolled in our study in that only 50% of theirs had shock. Moreover, in contrast to our study where participants were required to be enrolled within 24 hours after receiving high dose vasopressor, no timing was provided in the previous trial. The mean APACHE II score of the patients in this previous trial was reported at 29.1 [7], suggesting multi-organ failure had already present at the time of hemoperfusion treatment.

As patients with more severe shock tend to have higher cytokine levels than those with sepsis without shock [8], they potentially benefitted more from therapies aiming at removal of these excess cytokines. Similarly, this correlation between shock severity and cytokine levels suggests early hemoperfusion could lead to better hemodynamic outcome and potentially preclude further organ failures which are major cause of late mortality in patients with septic shock [12]. The design of our study is specifically targeting this subgroup of patients at high risk of death to maximize potential benefits of hemoperfusion with cytokine adsorbent treatment.

To our knowledge, this study is the first multicenter randomized clinical trial using this cytokine adsorbent in patients with septic shock requiring high dose vasopressor. The strength of our study firstly is targeting those with more severe shock, as judged by high dose of norepinephrine, as well as protocol for early hemoperfusion as an enrichment strategy. Secondly, the adsorbent used in our protocol non-specifically removes cytokines in septic patients, and therefore is more generalizable to various infectious organisms, as opposed to only gram-negative bacteria in the case of polymyxin B hemoperfusion. Major limitation of this study is the inability to blind treatments given to participants. However, the primary efficacy endpoint is 28-day mortality which should preclude potential biases.

CONCLUSION

This study investigates the use of adjunctive hemoperfusion with HA-330 in patients with septic shock receiving high dose of vasopressors. The results could determine its safety and efficacy, informing intensivists whether its ben-

efits outweigh the potential risks of such invasive procedures. The study could also provide additional information regarding a more generalized role of blood purification therapy in patients with sepsis.

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AUTHORS' CONTRIBUTIONS
(I) Conceptualization: R. Ratanarat; (II) Data curation: N. Wongtirawit, P. Deawtrakulchai; (III) Formal analysis: N. Wongtirawit, A. Panitchote; (IV) Funding acquisition: R. Ratanarat; (V) Methodology: N. Wongtirawit, R. Ratanarat; (VI) Project administration: N. Wongtirawit; (VII) Visualization: N. Wongtirawit; (VIII) Writing: N. Wongtirawit, R. Ratanarat.

SUPPLEMENTARY MATERIALS
None

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