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Composite adverse events compared early versus conventional cessation of hydrocortisone in patients with septic shock: Randomized-controlled trial (The CESSHYDRO study)

Kolanya Kangwanyotsak, Surat Tongyoo

Critical care division, Department of Internal Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700

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The data and code were available upon reasonable request (Surat Tongyoo, email address: surat.ton@mahidol.ac.th)

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Not required.

Corresponding author:
Surat Tongyoo
Critical care division, Department of Internal Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700
Tel: (+66) 2-419-7764
E-mail: surat.ton@mahidol.ac.th

ABSTRACT:

Background: Intravenous hydrocortisone has benefits in the treatment of septic shock patients, but there are adverse events mentioned in the secondary outcomes of several studies, such as hyperglycemia, hypernatremia, secondary infection, and muscle weakness. In addition, there are no recommendations regarding the precise duration and steps to discontinue hydrocortisone administration. The CESSHYDRO trial evaluates the adverse outcomes of intravenous hydrocortisone between early cessation versus conventional cessation of hydrocortisone in septic shock patients.

Methods: The CESSHYDRO trial is a single-center, double-blind, randomized controlled clinical trial conducted at Siriraj Hospital. One hundred and eighty septic shock patients receiving vasopressors and hydrocortisone at least 200 mg/day with hemodynamic stability will be included. The patients are randomized into 2 groups: intervention A (early cessation of hydrocortisone) and intervention B (conventional cessation). The primary outcomes were composite adverse events, including hyperglycemia, hypernatremia, muscle weakness, and new infections.

Hypothesis: We hypothesize that early cessation of hydrocortisone in patients with septic shock would reduce composite adverse events including hyperglycemia, hypernatremia, muscle weakness, and the new onset of infection.
Ethics and dissemination: The trial receives ethical approval from Siriraj Hospital, Mahidol University (COA No.SI012/2023).

Trial registration: ClinicalTrials.govNCT05818826. Registered on April 19, 2023.

Keywords: Hydrocortisone; Septic shock; Sepsis with hypotension; Hyperglycemia; Vasopressor

INTRODUCTION

Sepsis is a life-threatening clinical symptom indicating organ dysfunction due to an immune response to an infection[1]. According to the Surviving Sepsis Campaign 2021 guidelines [2], the treatment of septic shock includes administering broad-spectrum antimicrobial therapy to target the microorganism, providing adequate fluid resuscitation to restore intravascular volume, and using a vasopressor to support blood pressure. The guideline also suggests systemic corticosteroids, hydrocortisone, be administered at 50 mg every 6 hours or 200 mg continuous infusion daily if the first-line vasopressor, norepinephrine, reaches a dose of 0.25 micrograms/kg/minute for at least 4 hours and there is an ongoing requirement for a vasopressor.

The CORTICUS study [3], reported no significant difference in the 28-day mortality rate in 499 septic shock patients receiving intravenous hydrocortisone versus placebo. However, the hydrocortisone group achieved resolution of a shock earlier but had an increased rate of new infections, higher blood glucose levels, and higher serum sodium levels. The HYPRESS study[4], including septic patients receiving intravenous hydrocortisone versus placebo, shows no statistically significant increase in the incidence of high blood glucose levels, neuromuscular weakness, and new bacteremia in the hydrocortisone group. Moreover, three meta-analyses [5-7] reported similar adverse effects of systemic corticosteroids, including high blood glucose, high serum sodium, increased risk of secondary infections, and a higher incidence of muscular weakness (Muscular Disability Rating Scale; MDRS score >1).

Based on the aforementioned studies, it can be observed that the administration of hydrocortisone tends to reduce the duration of vasopressor use and hasten the resolution of shock. However, there are adverse events, including high blood glucose levels, high blood sodium levels, an increased rate of secondary infections, and an increased incidence of muscular weakness. These outcomes may be influenced by the duration of corticosteroid administration. Therefore, the rapid discontinuation of hydrocortisone in septic shock patients who have stable blood pressure may have favorable effects in reducing adverse events and not worsening the patient's condition.

Our hypothesis is that the short duration of using systemic corticosteroids can decrease adverse events such as hyperglycemia, hypernatremia, muscle weakness, and the new onset of infection in septic shock patients.

KEY MESSAGE:

• This study is a single-center, randomized, controlled trial that compares early cessation of hydrocortisone versus conventional cessation of hydrocortisone in septic shock patients. The primary endpoint is composite adverse events including hyperglycemia, hypernatremia, muscle weakness, and the incidence of a new infection within 14 days after randomization or until discharge from the hospital. The cessation of hydrocortisone starts with hemodynamic stability and tapering the vasopressor until a low dose.

OBJECTIVES

We designed the CESSHYDRO trial to evaluate the composite adverse events between early cessation versus conventional cessation of hydrocortisone in patients with septic shock patients.

MATERIALS AND METHODS

Trial design and setting

This is a single-center, randomized, double-blind, controlled clinical trial conducted at Siriraj Hospital, Mahidol University, Bangkok, Thailand. This study has been approved by the Siriraj Institutional Review Board, Mahidol University (approval number SI 012/2023) and has been registered in the US Clinical Trial Registry (Clin-

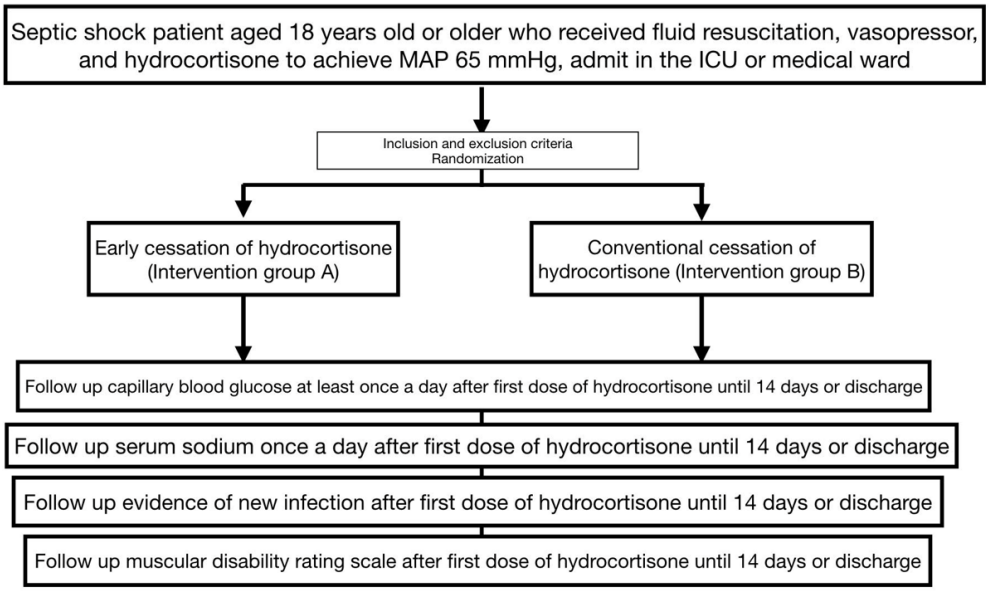

Figure 1. Flow diagram describing the enrollment and randomization.

icalTrials.govNCT05818826). Before being included in the study, each patient or their legal guardian provided informed consent. The co-investigators are responsible for conducting the screening and enrollment of all participants (Figure 1). The principal investigator and a statistician who is blinded to the patient enrollment and treatment process carried out the outcome evaluation, data management, and analysis.

Participant enrollment, blinding, and randomization

Septic shock patients aged 18 years old or older who receive fluid resuscitation, a vasopressor, and hydrocortisone to achieve a mean arterial pressure of 65 mmHg, are admitted to the intensive care unit or medical ward in Siriraj Hospital, and meet the eligibility criteria as described below are enrolled in the trial. If patients meet the exclusion criteria before randomization, they are excluded.

Eligibility criteria

1. Age ≥ 18-year-old
2. Septic shock is diagnosed according to SEPSIS-3 criteria and treated in the intensive care unit or medical ward in Siriraj Hospital.
3. The patient receives at least one vasopressor and hydrocortisone at least 200 mg/day achieving a mean arterial pressure of 65 mmHg.

Exclusion criteria

1. Patient receives steroid more than 7 days before randomization
2. Terminally ill patient and refuses treatment
3. Pregnancy
4. Do not accept informed consent.

After enrollment, patients are randomly assigned to one of two groups: early cessation of hydrocortisone (intervention group) or conventional cessation of hydrocortisone (control group) through a computer-generated randomized table obtained from a program called n4Studies[11]. This process is conducted by an investigator who is not involved in patient enrollment or management. Other investigators, patients, patient's family members, attending physicians, and nurses are all unaware of the study assignment, ensuring blindness throughout the research. (Figure 1)

Intervention and procedure

In this clinical trial, there are 2 interventions to taper off hydrocortisone, which are interventions A and B. The procedure of tapering hydrocortisone is initiated after all septic shock patients who meet the eligibility criteria receive fluid resuscitation, a vasopressor, and hydrocortisone according to the Surviving Sepsis Campaign 2021 guidelines[2] to achieve a mean arterial pressure of 65 mmHg and stabilize and titrate down the vasopressor until a dose 0.1 mcg/kg for at least 3 hours. After randomization, the hydrocortisone bag is replaced with either study drug A or B following the intervention.

- Intervention A is early cessation of hydrocortisone, which means there is no further hydrocortisone in this group. 100 ml of 5% dextrose in water is study drug A. The study drug A will be administered through either a peripheral line or central line and last for a continuous 24-hour drip. The duration of study drug A depends on the attending physician's decision to discontinue hydrocortisone.
- The intervention B is the conventional cessation of hydrocortisone. The study drug B is hydrocortisone combined with 100 ml of a solution consisting of 5% dextrose in water. The study drug B will be administered through either a peripheral line or central line and last for a continuous drip 24-hour period. The dose of hydrocortisone will be adjusted by the attending physician which means gradually tapering off hydrocortisone at least 50 mg daily from a total of 200 mg of hydrocortisone. For example, 150mg, 100 mg, and 50 mg of hydrocortisone for each day until off hydrocortisone. The duration of study drug B depends on the attending physician to discontinue hydrocortisone.

The study drugs A and B are prepared by a pharmacist who does not hold any other responsibilities in the trial and placed in containers of the same shape, marked with sequential numbers on sealed paper based on the order specified in the randomization table.

During the protocol of each intervention, blood for serum sodium and capillary blood glucose will be taken every day until discharge, or 14 days after the first dose of hydrocortisone. The attending physician will record the motor power of proximal and distal muscles in both extremities following the routine physical examination, then the investigator will determine the clinical muscle weakness to calculate the muscular disability rating scale** and observe evidence of new-onset infection* until 14 days after the first dose of hydrocortisone or until discharge. If the potential adverse event is detected, for example, hypotension after the intervention, the primary physician could stop the study drugs, report the event to the investigator, and go on with treatment as determined.

Outcomes

Outcomes will be collected by the investigator by hemodynamic, drug dose record review, case record form, or complication monitoring from the medical team and recorded.

Primary outcomes

The primary outcome is composite adverse events within 14 days after the first dose of hydrocortisone or until death or hospital discharge, whichever comes first, including

- Incidence of hyperglycemia (capillary blood glucose ≥ 180 mg/dL)
- Incidence of hypernatremia (serum sodium ≥ 150 mg/dL)
- New onset of infection* (evidence of infection requires antibiotics after 48 hours of randomization)
- Neuromuscular weakness (muscular disability rating scale** is 2 or more)

*new onset of infection, which means evidence of infection such as culture and adjusting or extending antibiotics to cover microorganisms.

**the muscular disability rating scale[8] is defined as 5

scores; 1 is no deficit, 2 is a minor deficit or motor power grade IV, 3 is a mild deficit or motor power grade III, 4 is a moderate motor deficit or motor power grade II, 5 is a severe motor deficit (almost no ambulation) or motor power grade I or 0. If the motor weakness is more than baseline, at least 1 grade is defined as a score of 2.

Secondary outcomes

The secondary outcome will be assessed for 14 and 28 days follow-up period, including

- 28-day mortality from any cause or until discharge from the hospital
- Time to re-initiate the vasopressor within 14 days
- Total insulin needed due to hyperglycemia
- Hypoglycemia; capillary blood glucose < 80 mg/dL
- Vasopressor free hour
- Ventilator free day
- Time to need a fluid bolus
- Recurrent shock***
- Time for the reversal of shock
- A new onset of infection within 28 days
- ICU length of stay

***Recurrent shock is defined as a patient with a mean arterial pressure lower than 65 mmHg after tapering or stopping hydrocortisone within 48 hours and receiving at least one modality, such as crystalloid or colloid, at least 200 ml drip in 15 or 30 minutes, restarting the vasopressor, increasing the dose of vasopressor ≥ 0.5 mcg/kg/min, or increasing the dose of hydrocortisone until reaching 200 mg/day

Timeline and follow-up period

The participant timeline is shown in Table 1.

DATA ANALYSIS PLAN

Sample size estimation

The sample size required is calculated based on the new incidence of adverse events after tapering hydrocortisone, which is mentioned in secondary outcomes in the CORTICUS study, which is approximately 35%. Due to a lack of previous data in RCT, there is no research comparing the early cessation of hydrocortisone with a conventional cessation in patients with septic shock who received vasopressor therapy, hydrocortisone, and achieved a mean arterial pressure of at least 65 mmHg. The investigator anticipates that the composite adverse events of early cessation of hydrocortisone are less than those in the placebo group, from 35% to 15%, which is approximately 20%. The output of the sample size calculation from n4Studies. Two dependent proportions formula with ratio =1. All analyses follow the intention-to-treat principle to achieve clinical significance at 80% power with a 5% alpha error.

$$n = \frac{[Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}]^2}{(p_1 - p_2)^2}$$

By $P = \frac{p1+p2}{2} = \frac{0.35+0.15}{2} = 0.25$

$$n = \frac{[1.96\sqrt{2(0.25)(1-0.25)} + 0.84\sqrt{0.35(1-0.35) + 0.15(1-0.15)}]^2}{(0.35 - 0.15)^2}$$

n = 72

A minimum of 72 subjects per group is required. After accounting for a 10% dropout rate, 80 subjects are required per group, and thus a total of 160 subjects will be recruited in two groups.

Table 1. Schedule of the study.

	Study period					
	Pre-enrollment	**Enrollment**	**Baseline**	**Allocation**	**Intervention**	**Closeout**
Time point	X					
Eligibility screen	X					
Consent to contact		X				
Informed consent		X				
Stratified randomization		X				
Intervention arm		←	—	—	—	→
Placebo arm		←	—	—	—	→
Hemodynamic data			X	X	X	
Complication monitoring		←	—	—	—	→
Adverse events						X
Mortality						X
Length of stay						X
Organ support						X

OUTCOME ANALYSIS PLAN

The qualitative variable, for example, sex is categorical data that will be expressed in frequencies and percentages. The quantitative variable, for example, age is continuous data. In normally distributed data, the mean and standard deviation will be expressed, but if a distribution is skewed, it will be expressed in the median and interquartile ranges. Outcomes' evaluation will be analyzed by both intention-to-treat and per-protocol analysis.

The primary analysis, composite adverse events within 14 days after randomization or until death or hospital discharge, will be analyzed by Chi-square when appropriate or Fisher's exact test with fewer than 5 observations.

The secondary analysis with categorical data will be compared by Chi-square or Fisher's exact test. All data analyses will be processed by the Statistical Package for Social Sciences (SPSS). A p-value < 0.05 with a two-tailed test and a mean difference with 95% confidence intervals will be considered statistically significant.

Missing data handling

All available data will be used in the analysis. The missing data will not be used for data analysis and summary.

DATA MANAGEMENT AND DATA MONITORING

Data management

The lead researcher will document participant details using authorized case record forms that have been approved by the Institutional Review Board (IRB). The study's data manager will then assess the data for completeness, remove identifying information, address any missing values, and transfer the data to an electronic database. The collected data will be shared with the study's statistician on an annual basis, either for interim evaluations or for the final comprehensive analysis.

Should any unforeseen incidents arise, the study administrator will document and relay this information to the safety board for review. Furthermore, any unexpected events or noteworthy data patterns that may necessitate corrective measures will be communicated to the principal investigator for further investigation.

Interim analyses will be conducted annually to assess the benefits and risks and to observe data trends. These analyses will aid in identifying potential patterns or deviations.

Confidentiality

The privacy of participants will be upheld by utilizing the initial two letters of both the first name and last name for patient identification purposes on all patients' data sheets throughout the study. To ensure security, patients' details will be stored in a database protected by a password.

Dissemination policy

The trial result will be disseminated through a presentation at a medical publication. Authorship will be considered and granted using the policy of Mahidol University. The funder will be acknowledged in the publication.

Table 2. Patient's baseline characteristic variable and data collection plan.

Baseline Characteristic	Collection method
Age - yr	Chart review
Sex - no. (%)	
Male	Chart review
Female	Chart review
BMI - kg/m^2	Chart review
APACHE II score	Chart review
SOFA score	Chart review
Murray score	Chart review
Comorbidities - no. (%)	Chart review
Diabetes mellitus	
Hypertension	
Chronic kidney disease	
Cirrhosis	
Stroke	
Coronary artery disease	
Atrial fibrillation	
Malignancy	
Post cardiac arrest	
Type of infection	Chart review
Community-acquired	
Hospital-acquired	

Baseline Characteristic	Collection method
Source of infection	Chart review
Pneumonia	
UTI	
IAI	
CNS infection	
SSTI	
Septicemia	
CRBSI	
Organism	Chart review
Gram negative	
Gram positive	
Virus	
Admission category - no. (%)	Chart review
Medical ICU	
Surgical ICU	

Table 3. Variable collected before intervention and data collection plan.

Variable before intervention	Collection method
Hemodynamic parameters	Collection from real time monitoring
Temperature - C	
Heart rate - bpm	
Systolic blood pressure - mmHg	
Diastolic blood pressure - mmHg	
Mean arterial pressure - mmHg	
Respiratory rate - bpm	
SpO_2 - %	
Central venous pressure - mmHg	
Ejection fraction - %	Echocardiographic report
Mechanical ventilation - no. (%)	Data collection from ventilator
Ventilator support at baseline	
Mode of ventilator	
PCV	
VCV	
Tidal volume - ml	
Inspiratory pressure	
PEEP - cm of water	
RR - bpm	
High flow nasal cannula - no.(%)	Chart review
Type of vasopressor	Chart review
Norepinephrine alone - no. (%)	
Combination of Norepinephrine and epinephrine - no. (%)	
Combination of Norepinephrine and Terlipressin - no. (%)	
Combination of Norepinephrine, epinephrine and Terlipressin - no. (%)	
Maximum dose of vasopressor - mcg/kg/min	
Maximum dose of Norepinephrine - mcg/kg/min	
Norepinephrine at randomization - no. (%)	
Epinephrine at randomization - no. (%)	
Dopamine at randomization - no. (%)	

Variable before intervention	Collection method
Dobutamine at randomization - no. (%)	
Milrinone at randomization - no. (%)	
Terlipressin at randomization - no. (%)	
Time to start antibiotics less than one hr - no.(%)	Chart review
Renal replacement therapy - no.(%)	Chart review
Intermittent hemodialysis	
SLED	
CRRT	
Peritoneal dialysis	
Indication of RRT	Chart review
Volume overload	
Metabolic acidosis	
Uremia	
Hemoperfusion	Chart review
Sedation use - no.(%)	Chart review
Fentanyl - no.(%)	
Midazolam - no.(%)	
Propofol - no.(%)	
Dexmedetomidine - no.(%)	
Neuromuscular blocking agent - no.(%)	Chart review
Glasgow coma score	Chart review
Receiving hydrocortisone	Chart review
Continuous drip - no. (%)	
Dose of hydrocortisone at baseline - mg/day	
300 mg/day - no.(%)	
200 mg/day - no.(%)	
Dose of vasopressor at starting hydrocortisone - mcg/kg/min	
Laboratory investigation at baseline	Chart review
Hb - g/dL	
Hct- %	
Leukocytes - thousands/mm^3	
Platelets - thousand/mm^3	
Serum Creatinine - mg/dL	
Serum Sodium - mmol/L	
Serum Potassium - mmol/L	
Cortisol - mcg/dL	
HbA1C - g/dL	
Blood lactate - mmol/L	

Table 4. Primary and secondary outcomes.

Primary outcome	**Early cessation of hydrocortisone (n=)**	**Conventional cessation of hydrocortisone (n=)**	**p-value**
Composite Adverse Events - no. (%)			
Secondary outcome			
Events of hyperglycemia need insulin - no. (%)			
Events of hypernatremia need treatment - no. (%)			

Secondary outcome	Early cessation of hydrocortisone (n=)	Conventional cessation of hydrocortisone (n=)	p-value
Death within 28 days - no. (%)			
Relative risk (95%CI)			
Absolute difference - % (95%CI)			
Death during hospitalisation - no. (%)			
Relative risk (95%CI)			
Absolute difference - % (95%CI)			
Cause of death - no. (%)			
Sepsis			
Hypoxia			
Bleeding			
Length of stay -days - no. (%)			
In ICU			
In hospital			
Recurrent shock -no. (%)			
Time to recurrent shock - hr			
Restart hydrocortisone - no. (%)			
Time to restart hydrocortisone - hr			
Duration of hydrocortisone - days			
Total dose of hydrocortisone - mg			

DISCUSSION

This double-blind randomized controlled trial hypothesizes that composite adverse events from the early cessation of hydrocortisone in septic shock patients are lower than the conventional cessation of hydrocortisone. According to the Surviving Sepsis Campaign Guidelines 2021, additional therapy for patients with septic shock is hydrocortisone. The dose of hydrocortisone is 200 mg/day, which is an intermittent bolus or continuous drip over a 24-hour period, but there is no mention of the duration of hydrocortisone. Various studies, such as the CORTICUS study[3], report 499 patients with septic shock who are administered intravenous hydrocortisone at a dose of 50 mg every 6 hours for 5 days, followed by a gradual tapering of the dose until discontinuation on day 11. Compared to placebo, there is a benefit to achieving resolution of shock, though there is no mortality benefit. However, the hydrocortisone group achieved resolution of a shock earlier but increased rates of new infection (OR 1.37; 95% CI 1.05-1.79), higher blood glucose levels (85% vs. 72%, OR 1.18; 95% CI 1.07-1.31), and higher blood sodium levels (29% vs. 18%, OR 1.59; 95% CI 1.13-2.22).

A study by Venkatesh et al. [7] involved 3,800 patients with septic shock who received 200 mg hydrocortisone daily for 7 days, compared to a placebo. The study found no difference in the 28-day or 90-day mortality rates. However, it found the incidence of hyperglycemia, hypernatremia, and neuromuscular weakness in the hydrocortisone group was higher than placebo. Various meta-analysis studies, Rygard et al. [5], Rochwerg et al. [6], and Fang et al. [9], concluded that the administration of systemic corticosteroids did not reduce short-term or long-term mortality rates but shortened the duration of shock. However, all three meta-analyses reported similar adverse effects, including hyperglycemia, hypernatremia, higher incidence rates of secondary infections, and muscular weakness in the corticosteroids group.

The research team was interested in investigating the impact of the duration of corticosteroid administration on adverse events. A retrospective cohort study conducted by Kristine et al. [10] mentioned no clinically significant statistics for recurrent shock within 72 hours in rapidly discontinued or gradually reduced doses of hydrocortisone in septic shock patients who received 200 mg daily of hydrocortisone and hemodynamic stability, but the secondary outcomes show the gradually reduced hydrocortisone had a higher incidence of hyperglycemia and required medication to lower blood sugar levels.

Based on the mentioned studies, it can be observed that the long duration of systemic corticosteroids in septic shock patients tends to have a higher incidence of adverse events. The research team designed the CESSHYDRO trial because, currently, there are no randomized controlled trials or prospective studies comparing the side effects of gradually reduced hydrocortisone dosage and rapid discontinuation. If this trial has a positive result, the routine practice of hydrocortisone cessation will tend to be shortened and more practical.

CONFIDENTIALITY
None

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AUTHORS' CONTRIBUTIONS
(I) Conceptualization: Kolanya Kangwanyotsak, Surat Tongyoo; (II) Data curation: Kolanya Kangwanyotsak, Surat Tongyoo; (III) Formal analysis: Kolanya Kangwanyotsak, Surat Tongyoo; (IV) Funding acquisition: Surat Tongyoo; (V) Methodology: Kolanya Kangwanyotsak, Surat Tongyoo; (VI) Project administration: Kolanya Kangwanyotsak, Surat Tongyoo; (VII) Visualization: Kolanya Kangwanyotsak, Surat Tongyoo; (VIII) Writing – original draft: Kolanya Kangwanyotsak, Surat Tongyoo; (IX) Writing – review & editing: Kolanya Kangwanyotsak, Surat Tongyoo.

ETHICS APPROVAL
The trial was approved by the Ethics Committee of Siriraj Hospital, Mahidol University (Approval number SI012/2023) and has been registered in the US Clinical Trial Registry (ClinicalTrials.govNCT05818826)

AUTHOR AFFILIATION
Critical care division, Department of Internal Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

SUPPLEMENTARY MATERIALS
None

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