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RESEARCH PROTOCOL

Early intravenous hydrocortisone in sepsis: A randomized control trial (Protocol)

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ABSTRACT:

Background: The evidence of the appropriate timing of hydrocortisone is still weak and controversial. Observational studies showed a trend towards greater benefits when hydrocortisone was given earlier in the course of septic shock resuscitation. This study evaluates the effects of early intravenous low-dose hydrocortisone administered at the beginning of the onset of sepsis-induced hypotension compared with standard care.

Methods: This study is a single-center, parallel-group, double-blinded, randomized control trial, conducted in a non-trauma emergency department. Adult patients with sepsis-induced hypotension will be included. Patients will be randomly assigned in a 1:1 ratio to receive early intravenous low-dose hydrocortisone or standard care. Blood inflammatory biomarkers at baseline will be collected. The primary outcome is 28-day mortality. Resuscitation-related secondary outcomes and safety outcomes will also be observed. Outcomes will be compared between groups. Subgroup analyses considering inflammatory biomarker levels will also be performed to evaluate the effect of early intravenous hydrocortisone, especially in patients with hyperinflammation.

Hypothesis: We hypothesize that early intravenous low-dose hydrocortisone administration in patients with sepsis-induced hypotension would result in less mortality and improve resuscitation outcomes, especially in subgroup of patients with hyperinflammation.

Ethics and dissemination: The study protocol was approved by the Siriraj Institutional Review Board with the certificate of approval number Si 917/2023.

Trial registration: Clinicaltrial.gov NCT06217939

Keywords: Corticosteroids; Sepsis; Hydrocortisone; Shock

INTRODUCTION

Sepsis accounts for 20% of annual deaths globally, with a mortality rate of up to 42% in intensive care patients.[1] Disruption of the immunological balance of inflammation and anti-inflammation, which resulted in generalized organ dysfunction, was described.[2] Attempts to mitigate these alterations were examined, including corticosteroids. Despite the fact that corticosteroids were associated with a higher rate of shock reversal and vasopressor-free days, systematic reviews and meta-analyses disclosed marginally reduced mortality without statistical significance.[3,4] As a result, Surviving Sepsis Campaign guidelines 2021 advocated the use of low-dose hydrocortisone (200-300 mg/day) after patients received norepinephrine or epinephrine ≥ 0.25 mcg/kg/min for at least 4 hours,

with weak recommendations and moderate-quality evidence.[5] The explanation for the unsatisfactory effect of corticosteroids in sepsis includes heterogeneity in sepsis pathophysiology, the timing of corticosteroid administration, and post-sepsis management.[6,7] Heterogeneity of sepsis phenotypes was reported in many studies.[8–10] Among these clinical phenotypes, the highest mortality was found in patients with highly elevated inflammatory biomarkers, especially interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor (TNF), procalcitonin (PCT), and C-reactive protein (CRP).[8,9] More importantly, patients with highly elevated inflammatory biomarkers represented up to 40-50% of all septic patients.[9]

The evidence of the appropriate timing of hydrocortisone is still weak and lacking. The timing of hydrocortisone infusion in septic shock patients still varied among institutions.[11] A small randomized trial comparing the effect of early hydrocortisone initiated at the same time with norepinephrine versus placebo failed to demonstrate a mortality benefit.[12] However, sicker patients were reported in the early hydrocortisone group, leading to an inconclusive result. The timing of hydrocortisone recommended in the latest Surviving Sepsis Campaign was based solely on the study protocols of the ADRENAL and APROCCHSS trials conducted in 2018.[2,13,14] However, observational studies showed a trend toward greater benefits when hydrocortisone was given earlier in the course of septic shock resuscitation.[15,16] Park and colleagues reported the lowest mortality in patients who received low-dose hydrocortisone within 3 hours after the onset of septic shock.[15] A trend with progressively higher mortality was also observed when the initiation of hydrocortisone was delayed. There was also a suggestion that the delay in the initiation of hydrocortisone might contribute to the futile effect on mortality of the previous trials.[7] Lastly, death and morbidities after sepsis reversal might dilute the effect of any interventions during sepsis resuscitation.

This study hypothesized that septic patients receiving early hydrocortisone would have a lower mortality rate compared with septic patients receiving hydrocortisone later in the course of shock, as recommended by the latest Surviving Sepsis Campaign guidelines. These effects would be more pronounced in the subgroup of patients with highly elevated inflammatory biomarkers. Therefore, we will conduct a randomized control trial to evaluate the effects of early intravenous low-dose hydrocortisone administered at the beginning of the onset of sepsis-induced hypotension compared with standard care. The effects of early hydrocortisone on patients with different levels of inflammation will also be explored. The study protocol was written according to Standard Protocol Items: Recommendations for Interventional Trials 2013 reporting guidance.[17]

OBJECTIVES

To evaluate the effects of early intravenous low-dose hydrocortisone administered at the beginning of the onset of sepsis-induced hypotension compared with standard care.

KEY MESSAGES:

- Hydrocortisone has demonstrated efficacy in septic shock resuscitation, but the optimal timing of administration remains unclear.
- Observational studies indicated a favorable trend when hydrocortisone was given earlier in the course of septic shock resuscitation.
- This randomized control trial aims to evaluate the effects of early intravenous hydrocortisone on mortality and resuscitation outcomes among hypotensive septic patients in comparison to standard care.

MATERIALS AND METHODS

Study design and setting

This study is a single-center, parallel-group, double-blinded, randomized control trial conducted in the non-trauma emergency department (ED) of Siriraj Hospital. Siriraj Hospital is a 2,000-bed academic tertiary hospital. The non-trauma ED has more than 20,000 visits per year, accepting only critical patients with emergency severity index levels 1 and 2, requiring immediate life-saving interventions, or having unstable vital signs.[18] After initial resuscitation in the ED, patients will be admitted according to the patient's conditions. For critically ill patients, intensive care units (ICUs) are preferred. The ICUs are capable of providing comprehensive multi-system life support, with intensivists available at all times. However, if ICUs are not available, the patients will be admitted to general wards in a designated area where intensive care could be provided and later transferred to the ICUs when available and indicated.

Participants

The study will include adults (≥18 years) in the ED with suspected or definite sepsis with hypotension. Sepsis is defined as an acute change in total Sequential Organ Failure Assessment (SOFA) score ≥ 2, according to the Third International Consensus Definitions for Sepsis and Septic Shock.[2] Sepsis is suspected when there is convincing evidence of infection with 2 of the following: altered mentation, a respiratory rate ≥ 22/min, and a systolic blood pressure (SBP) ≤ 100 mmHg.[2] Hypotension is defined as a mean arterial pressure (MAP) lower than 65 mmHg. Patients will be excluded from the study if one of the following criteria are met: randomization or administration of the study drug is not able to be executed within 3 hours after the onset of hypotension, causes of shock other than sepsis are identified, patients who are immunocompromised, hyperglycemic emergencies (diabetic ketoacidosis, hyperosmolar hyperglycemic state), pregnancy, post-cardiac arrest, systemic corticosteroids are indicated for conditions other than septic shock, patients receiving systemic corticosteroids within 4 weeks at any dose, cancer patients who are receiving palliative treatment, patients who refuse life-saving surgical intervention, and patients with do-not-resuscitate orders.

Immunocompromised status includes human immunodeficiency virus infection or acquired immunodeficiency syndrome, hematologic malignancy, active cancer receiving chemotherapy, and current use of immunosuppressive medication. Figure 1 summarizes the flow of the study.

Enrollment and randomization

Once patients meet the eligibility criteria, the treating physicians will notify one of the study investigators to invite the patients and their legal representatives to participate in the study. Written informed consent will be obtained before randomization. Each patient will be randomly assigned in a 1:1 ratio by the sequential enrollment numbers to receive early intravenous low-dose hydrocortisone (the EH group) or standard care. Randomization will be performed using a computer-generated sequence in the permuted block of 4 by the investigator, who is not involved in patient enrollment and assessment. The other investigators, the patients or their representatives, and the treating physicians are all blinded to the group assignment. Patients may withdraw from the study for any reason at any time. The investigators or the treating physician may also withdraw the patients from the study for safety reasons at any time.

Study protocol and interventions

Blood will be drawn from the patients in both groups at the time of randomization for baseline IL-6, IL-10, TNF, PCT, CRP, and cortisol levels. All patients will receive standard treatment and investigation for septic shock, including standard laboratory analysis, antibiotics, infection source control, intravenous crystalloids, vasopressors, and organ support, as directed by the treating physicians.

The study drug (low-dose hydrocortisone versus placebo) will be prepared by a pharmacist who has no role in the study, according to the sequential enrollment numbers. The study drugs will be packaged in identical containers labeled with sequential enrollment numbers. After randomization, the study drugs will be administered as soon as possible by the nurses who have no role in the study. For the EH group, 50 mg of hydrocortisone in 10 ml of normal saline will be given as an intravenous bolus, then 200 mg of hydrocortisone in 100 ml of normal saline will be given as a continuous intravenous infusion in 24 hours for 2 consecutive days (total 250 mg on day 1 and 200 mg on day 2). For the standard care group, a bolus of 10 ml of normal saline will be given, and then 100 ml of normal saline will be given as a continuous intravenous infusion in 24 hours for 2 consecutive days as a sham control. After completion of the study drugs for 2 days, the study drug will be discontinued without tapering.

An open-label 50 mg of hydrocortisone given as an intravenous bolus followed by intravenous hydrocortisone 200 mg/day given as a continuous infusion or divided bolus administration is suggested to be commenced in both study arms if the hemodynamic goal of the patient is not reached despite the dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 hours after the initiation of the vasopressors as recommended by the guideline.[5] The study drug in each arm will be discontinued once an open-label hydrocortisone is initiated. Capillary or venous blood glucose will be tested at least every 6 hours for 2 days, then at least once daily or more as appropriate for the first 7 days as a part of the study protocol.

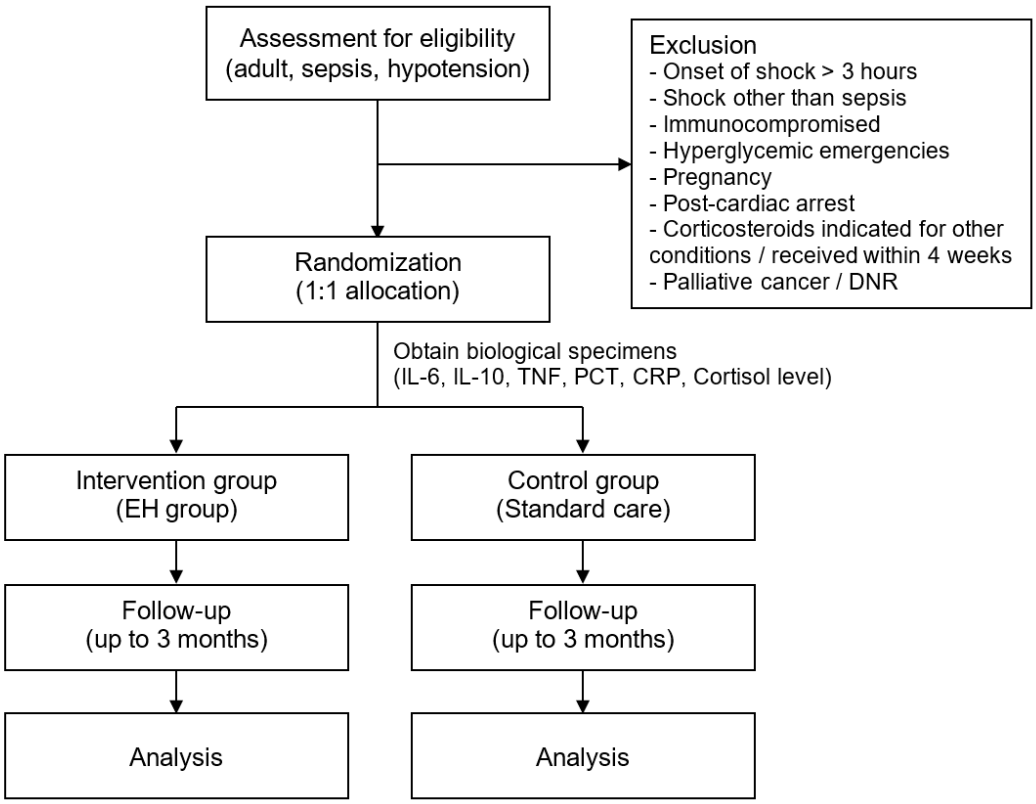

Figure 1. Study flow.

Abbreviations: CRP: C-reactive protein; DNR: do-not-resuscitate; EH: early intravenous hydrocortisone; IL: interleukin; PCT: procalcitonin; TNF: tumor necrosis factor.

The group allocation will be unblinded per request of the treating physicians or the principal investigators if the patient develops one of the following conditions: hyperglycemic emergencies (diabetic ketoacidosis and hyperosmolar hyperglycemic state), hypoglycemia, or active gastrointestinal hemorrhage within 7 days after randomization, undifferentiated hypotension or suspected adrenal insufficiency within 72 hours after the cessation of the study drug, and conditions related to hydrocortisone that the treating physicians concern to be harmful or potentially harmful to the patients.

The study protocol will be terminated if hyperglycemic emergencies or active gastrointestinal hemorrhages develop during the administration of the study drug. The investigators or the treating physician may also stop the study drug for safety reasons at any time.

Biological specimens

For inflammatory biomarkers (IL-6, IL-10, TNF, and PCT), 6 milliliters (ml) of whole blood in an ethylenediamine tetra-acetic acid (EDTA) tube will be collected from a patient and stored at 4 °C in a refrigerator in the ED for no longer than 12 hours. The blood sample will then be sent to the Department of Immunology and stored at -80 °C, waiting for analysis during working hours. Enzyme-Linked Immunosorbent Assay (ELISA) will be utilized to quantify the levels of IL-6, IL-10, TNF, and PCT.

For CRP and cortisol, 4-6 ml of whole blood in a lithium heparin tube will be collected and stored at 4 °C in a refrigerator in the ED for no longer than 12 hours. The blood sample will then be sent to the Department of Clinical Pathology for analysis. Particle-enhanced immunoturbidimetry will be utilized to quantify the level of CRP, while electrochemiluminescence immunoassay (ECLIA) will be utilized to quantify the level of cortisol.

Outcomes measures

The primary outcome is 28-day mortality, defined as death within 28 days after the onset of hypotension at randomization. Patients who are discharged alive before 28 days are considered to have no 28-day mortality.

The secondary outcomes and safety outcomes with related timeframes are depicted in Table 1. Shock control is defined as the achievement of sustained MAP ≥ 65 mm Hg or higher for at least 30 minutes together with evidence of adequate tissue perfusion (urine flow at more than 0.5 ml/kg/h for 2 consecutive hours or a decrease in serum lactate by more than 10% from the initial lactate level).[19] In-hospital mortality is defined as death before hospital discharge. Hospital length of stay (LOS) is defined as the time from randomization to hospital discharge or death. Ventilator-free day and vasopressor-free day are defined as the number of days that patients were alive and free of ventilators and vasopressors, respectively, up to day 28.[14] Patients who die before day 28 will be assigned a zero free day. Initiation of renal replacement therapy (RRT) includes the initiation of RRT in any mode in previously non-dialysis patients, or the initiation of sustained low-efficiency dialysis (SLED) or continuous RRT (CRRT) in previously hemodialysis patients. Routine hemodialysis in end-stage renal disease patients is not considered to meet a secondary outcome. Fluid received includes resuscitation fluid (crystalloids and colloids) and maintenance fluid. The fluid used for dilution of intravenous drugs will not be included. The highest vasopressor dose will be reported as a norepinephrine-equivalent dose.[20]

Safety outcomes will be observed for possible adverse effects of hydrocortisone. Superinfection is defined as a new infection occurring 48 hours or more after the initiation of a study drug.[21] Gastrointestinal hemorrhage includes both upper and lower gastrointestinal tract

Table 1. Secondary outcomes and related timeframe.

Outcomes	Timeframe	Maximum follow-up time
Secondary outcomes		
Time to shock control	From randomization to shock control	28 days
In-hospital mortality	From randomization to the end of hospitalization	90 days
Hospital length of stay	From randomization to hospital discharge or death	90 days
Ventilator-free day	From randomization to 28 days after randomization	28 days
Vasopressor-free day	From randomization to 28 days after randomization	28 days
Initiation of renal replacement therapy	From randomization to hospital discharge or death	90 days
Fluid received in 24 hours	From randomization to 24 hours after randomization	24 hours
Fluid received in 72 hours	From randomization to 72 hours after randomization	72 hours
Highest vasopressor dose	From randomization to shock control	28 days
Safety outcomes		
Gastrointestinal hemorrhage	From randomization to 28 days after randomization	28 days
Superinfection	From 48 hours after initiation of the study drug to 28 days after randomization	28 days
Hyperglycemia	From initiation of the study drug to 7 days after randomization	7 days

bleeding. Hyperglycemia is defined as an episode of plasma glucose or capillary blood glucose > 180 mg/dL. The occurrence of hyperglycemic emergencies will also be reported.

DATA ANALYSIS PLAN

Sample size

The sample size is calculated based on the expected 28-day mortality. Since there has been no study comparing early intravenous hydrocortisone versus the timing of hydrocortisone initiation suggested by the guideline, a comparable retrospective study is used to determine the sample size. Park and colleagues reported a 28-day mortality rate of 32% in septic shock patients receiving early hydrocortisone versus 51% in patients receiving late hydrocortisone.[15] Based on two-sided hypothesis testing [22], a total of 210 patients (105 patients in each arm) is required to achieve a statistical power of 80% at a 95% confidence interval. An additional 10% of patients will be included to compensate for unexpected drop-outs such as referral to other hospitals, consent withdrawal, and causes of shock other than sepsis later identified. Ultimately, a total of 230 patients will be required to complete the study.

OUTCOME ANALYSIS PLAN

Statistical analysis

Data will be analyzed according to an intention-to-treat principle for the primary analysis. Demographic data and baseline characteristics will be reported by treatment arms. Continuous variables will be tested for normality using the Shapiro-Wilk test and the Kolmogorov-Smirnov test. Continuous variables will be expressed as mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. For categorical variables, frequency and percentage will be reported. The EH group will be compared against the standard care group for the main analysis of the primary outcomes and secondary outcomes. Continuous outcomes will be compared using an independent t-test or the Mann-Whitney U test, as appropriate. The result will be reported as an absolute difference with a corresponding 95% confidence interval (CI). The Chi-square or Fisher exact test will be employed as appropriate for comparing binary outcomes. The result will be reported as an odds ratio (OR) with a 95% CI. Multivariate regression analyses will also be performed for the primary and secondary outcomes, adjusted for potential confounders. Potential factors will be tested and selected as confounders for the model when the p-value is less than 0.2 in the univariate analysis. The result will be reported as an adjusted OR (AOR) with a 95% CI. For all statistical analyses, a p-value of less than 0.05 is considered statistically significant unless defined otherwise.

Prespecified subgroup analyses will be conducted based on the hypothesis that patients with higher inflammatory biomarkers would benefit more from early hydrocortisone. The median value of each inflammatory biomarker and cortisol level will be used as cut-off values for the exposures (highly-elevated versus low inflammatory biomarker groups). Subgroup analyses will be performed using multivariable logistic regression models adjusted for confounders with interaction terms. The result will be reported as an AOR with a 95% CI for each inflammatory biomarker.

A single interim analysis for risk monitoring and safety will be performed after a total recruitment of 115 patients (50% of the total sample size). A significance level of 0.001 is selected as a stopping rule for harm, based on the Haybittle-Peto method.[25] The trial will be stopped early if there is a significantly higher rate of 28-day mortality at the significance level of ≤ 0.001.

DATA MANAGEMENT AND DATA MONITORING

Data collection and management

Demographic data include age, sex, and body weight. Baseline characteristics include admission type (medical, surgical), admission ward (ICUs, general wards), Simplified Acute Physiology 3 Score (SAPS 3) [23], Charlson comorbidity index [24], physiological variables at randomization such as temperature, heart rate, MAP, systolic blood pressure (SBP), and diastolic blood pressure (DBP), white cell count, platelet count, and baseline lactate and cortisol levels. Inflammatory biomarkers include IL-6, IL-10, TNF, PCT, and CRP. Primary sites of infection include pulmonary, abdominal, bloodstream, skin and soft tissue, urinary, others, and unknown sites of infection. Identified pathogens include gram-positive cocci, gram-negative bacilli, others, and unidentified pathogens. Time variables include time from sepsis diagnosis to receiving the first-dose antibiotics, time from the onset of hypotension to randomization, and time from randomization to receiving the study drug. The number of patients requiring open-label hydrocortisone will also be collected, together with the time from randomization to receiving an open-label hydrocortisone and the vasopressor dose when receiving an open-label hydrocortisone.

All data and outcomes will be collected prospectively by an investigator blinded to the group assignment. Another blinded investigator will be responsible for data quality control by reviewing the data entry for completeness and correctness.

Ethics and dissemination

This study protocol was approved by the Siriraj Institutional Review Board (certificate of approval number Si 917/2023) and registered at Clinicaltrial.gov (NCT06217939).

De-identified and anonymized patient data can be shared upon reasonable requests with the corresponding author.

DISCUSSION

Hydrocortisone has established effectiveness in shock control and reduction of vasopressor use, but the mortality benefits remain uncertain after decades of research.[3,4] The delayed timing of hydrocortisone administration in early studies was proposed to compromise the efficacy of hydrocortisone in reducing mortality.[7] In addition, diverse mortality rates have been observed across distinct clinical phenotypes of sepsis, suggesting varying respons-

es to different treatments.[9] Observational data supported the inflammatory regulation effect of hydrocortisone treatment in severe sepsis patients.[26,27] However, data on the clinical outcomes of hydrocortisone treatment in different clinical phenotypes remain insufficient, especially in patients with hyperinflammation.

This randomized trial will address the gap in evidence concerning the optimal time for hydrocortisone in sepsis resuscitation. It will also offer additional insights into the treatment effects of intravenous low-dose hydrocortisone based on the initial inflammatory status, moving towards a more personalized approach.

There are several limitations to this study. First, being a single-center study limits the generalizability of the study results. Second, due to limited funding, the levels of inflammatory biomarkers are not measured post-intervention. The anti-inflammatory effects of hydrocortisone will not be explicitly demonstrated. Last, the duration and tapering strategies of hydrocortisone treatment may vary across institutions. This study does not account for such variations.

CONCLUSION

This randomized control trial will evaluate the efficacy and clinical outcomes of early intravenous low-dose hydrocortisone in patients presenting with sepsis-induced hypotension. The results will provide supplementary insights to guide septic shock resuscitation and more personalized treatment based on the initial inflammatory status.

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AUTHORS' CONTRIBUTIONS

(I) Conceptualization: CP, WP; (II) Data curation: TC, PW, SS; (III) Formal analysis: CP, ST; (IV) Funding acquisition: CP; (V) Methodology: CP, WP, ST; (VI) Project administration: CP, WP, TC; (VII) Visualization: none; (VIII) Writing – original draft: WP; (IX) Writing – review & editing: CP, ST, TC, PW, SS.

SUPPLEMENTARY MATERIALS

None

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