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RESEARCH PROTOCOL

Restrictive fluid management and early fluid de-escalation versus usual care in critically ill patients: A feasibility trial protocol for the REDUCE randomized clinical trial

Ukrit Prajantasen, Thummaporn Naorungroj

Division of Critical Care, Department of Medicine, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700

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Corresponding author:
Thummaporn Naorungroj
Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, 10700
Tel: (+66) 81-736-5788
E-mail: thummaporn.nao@mahidol.ac.th

ABSTRACT:

Background: Fluid therapy is an essential therapeutic intervention for critically ill patients. Both fluid overload and hypovolemia are associated with poor outcomes. However, the fluid strategy in intensive care units is still controversial, and there is no consensus on using the fluid strategy in patients with circulatory shock.

Objectives: To compare the efficacy of protocol-based fluid-restrictive management versus standard care in critically ill patients with circulatory shock.

Methods: This is a single-center, feasibility-based, randomized, controlled trial in critically ill patients with circulatory shock receiving either fluid resuscitation or vasopressors in two medical ICUs at Siriraj Hospital. Eligible patients will be randomly allocated in a 1:1 ratio and placed in the restrictive fluid strategy (intervention) group or standard care (control) group. The primary outcome is accumulative fluid balance 72 hours after enrollment.

Conclusions: This study will evaluate the efficacy and safety of a protocol-based fluid restrictive strategy in critically ill patients who have circulatory shock and are receiving fluid resuscitation or vasopressors.

Trial registration: TCTR20220719002

Keywords: Restrictive fluid management, Circulatory shock, Vasopressor, Fluid balance, Mortality

INTRODUCTION

Fluid therapy is a mainstay method to restore and achieve adequate tissue perfusion. It is widely used to maintain intravascular volume, correct electrolyte abnormalities, replace fluid loss, and dilute intravenous medications [1]. However, liberal fluid administration can induce fluid overload, leading to end-organ edema and multiorgan dysfunction [2].

Fluid overload is normally defined as an increase in body weight of over 10% relative to pre-admission hospital weight [3]. Several studies show that positive fluid accumulation is associated with higher mortality and adverse outcomes in critically ill patients [4-6]. On the other hand, conservative fluid therapy, which aims to achieve zero balance in the ICU, is able to restrict fluids in critically ill patients, particularly those with acute lung injuries (ALI) or acute kidney injuries

(AKI). Nonetheless, a recent randomized controlled trial in patients undergoing major abdominal surgery showed adverse outcomes with fluid restrictions [8]. Moreover, the current guidelines on volume of fluid resuscitation in circulatory shock are based on low-quality evidence.

Accordingly, we conducted a randomized, single-center, feasibility-controlled trial to compare a protocol-based restrictive fluid strategy against usual care in critically ill patients with circulatory shock after initial fluid resuscitation. We mostly focused on the feasibility and effects of protocol-based interventions on fluid balance in ICU patients.

KEY MESSAGES:

- Fluid overload is associated with adverse outcomes in critically ill patients.
- The restrictive fluid strategy is a protocol-based intervention to achieve zero balance in the ICU.
- This study is a single-center, randomized controlled trial that compares restrictive fluid management versus usual care in critically ill patients who have circulatory shock and receive fluid resuscitation or vasopressors. The primary outcome is accumulative fluid balance 72 hours after enrollment.

MATERIALS AND METHODS

Study design

This study was an investigator-initiated, randomized, single-center, unblended feasibility-controlled study at two medical Intensive Care Units (ICU) at Siriraj Hospital. We investigated all adult critically ill patients admitted to the study ICUs. The eligibility criteria are shown in Table 1.

Intervention

Eligible patients who fulfilled the randomization criteria were placed into sequentially numbered sealed envelopes using permuted blocks of variable size. Each envelope contained a study arm allocation. Randomization was carried out at a 1:1 ratio (blocks of four). This trial intervention is not blinded for investigators, attending staff, or patients. The trial period is the time spent in the ICU from randomization to a maximum of seven days. After randomization, patients will be allocated to either the restrictive fluid strategy (intervention) group or the standard care (control) group (Figure 1).

Intervention group

A protocol for daily fluid restriction aiming to achieve zero balance was applied. Fluid intake was restricted, including drugs, nutrition, parenteral fluid, and blood transfusions. A fluid bolus was given if clinically necessary. (Figure2)

Diuretics were used to promote diuresis or when fluid intake was greater than output, or about 500 ml per day. The initial dose of furosemide ranged from 20mg up to 1g per day, and the rate of infusion was not more than 4 mg/minute. (Figure3)

Control group

Standard fluid management in the ICU was adjusted by the attending physician.

Outcome

The primary outcome was a cumulative fluid balance during the first 72 hours after randomization.

The secondary outcomes were major adverse kidney event (MAKE) at day 30, mortality at days 30, incidence of AKI at days 3, 7, and 30, number of patients requiring RRT at days 3, 7, and 30, vasopressor-free status at day 30, mechanical ventilator-free status at day 30, incidence of fluid overload at days 3 and 7, length of ICU and hospital stay, and ICU and hospital mortality.

The safety outcomes were an incidence of hypotension during the first 3 days, a dose of vasopressor at day 3 after randomization, and an episode of electrolyte imbalance at day 3 after randomization.

Table 1. Eligibility criteria of the study.

Inclusion criteria	Exclusion criteria
1. Patients aged 18 or above 2. Patients with circulatory shock who need fluid resuscitation or vasopressors 3. Patient who have been in ICU for at least 12 hours, but not more than 72 hours	1. Patient with hypovolemic or hemorrhagic shock 2. Patient with active bleeding requiring blood transfusion 3. Patient who has severe AKI KDIGO stage 3 4. Patient expecting to initiate RRT within 24 hours 5. Patient who has received chronic RRT 6. Patient who requires maintenance fluid therapy (e.g.; diabetic ketoacidosis, and non-ketotic coma) 7. Patient who has a third space loss from severe ascites, severe burn, or bowel obstruction 8. Severe hyponatremia (Na <125 mmol/L) or hypernatremia (Na >155 mmol/L) 9. Congestive heart failure 10. Decompensated cirrhosis 11. Severe hypoalbuminemia (serum albumin <2.0 g/dL) 12. Patient with ongoing gastrointestinal loss (e.g. persistent diarrhea) 13. Patient with ongoing fluid loss from drainage (more than 500ml within 8 hours) 14. Patient with symptomatic fluid overload after fluid resuscitation 15. Pregnancy or lactation 16. DNR orders 17. Furosemide allergy

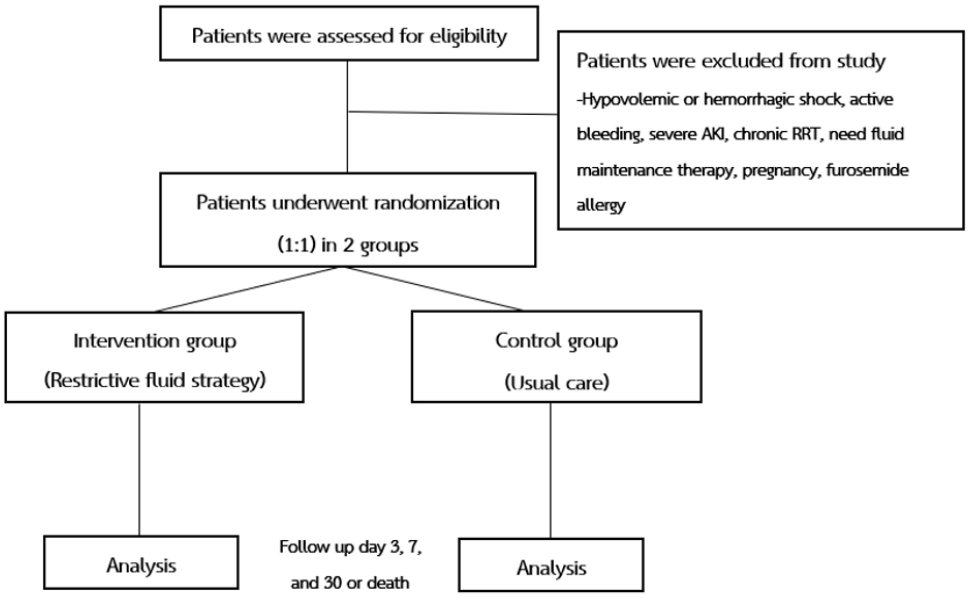


Figure 1. Flow of study. Abbreviations: AKI: Acute kidney injury; RRT: Renal replacement therapy.

Trial definitions

Definition of inclusion criteria

1. Age: the age of the participant in whole years at the time of randomization.
2. Circulatory shock: The patients who have circulatory shock are defined by
3. Hypotension: systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg or mean arterial pressure (MAP) < 65 and
4. Signs of tissue hypoperfusion include prolonged capillary refill times, poor skin perfusion, a decrease in urine output, a decreased level of consciousness, and serum lactate levels greater than 2 mmol/L.

Definition of exclusion criteria

1. Active bleeding: clinical bleeding needing transfusion of blood products as defined by the clinicians.
2. Severe acute kidney injury (AKI): AKI stage 3 according to KDIGO criteria.

Definition of AKI according to KDIGO criteria: increase in serum creatinine of ≥ 0.3 mg/dL or ≥50% within 48 hours or urine output of <0.5 mL/kg/hour for >6 hours.

Stage 1: Increase in serum creatinine ≥ 0.3 mg/dL in 48 hours, or 1.5 to 1.9 multiplied by baseline in 7 days.

Stage 2: 2.0 to 2.9 multiplied by baseline serum creatinine

Stage 3: 3.0 or more multiplied by baseline; increase in serum creatinine ≥ 4.0 mg/dL or beginning of renal replacement therapy regardless of a previous KDIGO stage.

3. Chronic renal replacement therapy (RRT): use of RRT at least once a week, e.g., chronic hemodialysis or hemofiltration, peritoneal dialysis, or kidney transplantation.
4. Diabetic ketoacidosis (DKA): presence of hyperglycemia (blood glucose greater than 250 mg/dl), arterial pH less than 7.3, serum bicarbonate less than 15 mEq/l, and the presence of ketonemia or ketonuria.
5. Non-ketotic coma: hyperosmolar hyperglycemic state; presence of coma with plasma glucose level >600 mg/dL and increased effective plasma osmolality >320 mOsm/kg in the absence of ketoacidosis.
6. Congestive heart failure (CHF): previous CHF with NYHA class 3 or 4 or measured LVEF < 40%.
7. Decompensated cirrhosis: presence or history of any one of ascites, variceal bleeding, hepatic encephalopathy, or jaundice in a cirrhotic patient.
8. Pregnancy: women with known a pregnancy based on clinical examination, the history, or human chorionic gonadotropin (hCG).

Definition of baseline variables

1. Sex: the genotypic sex of the participant
2. Age: defined in inclusion criteria
3. Date of admission to hospital: the date of admission to the hospital to which the patient was admitted during the current hospital admission.
4. Date and time of admission to the ICU: the date of admission to the ICU to which the patient was admitted during the current hospital admission.

Definition of corrected variables

Cumulative fluid balance: total fluid input minus total fluid output on a certain day of ICU admission.

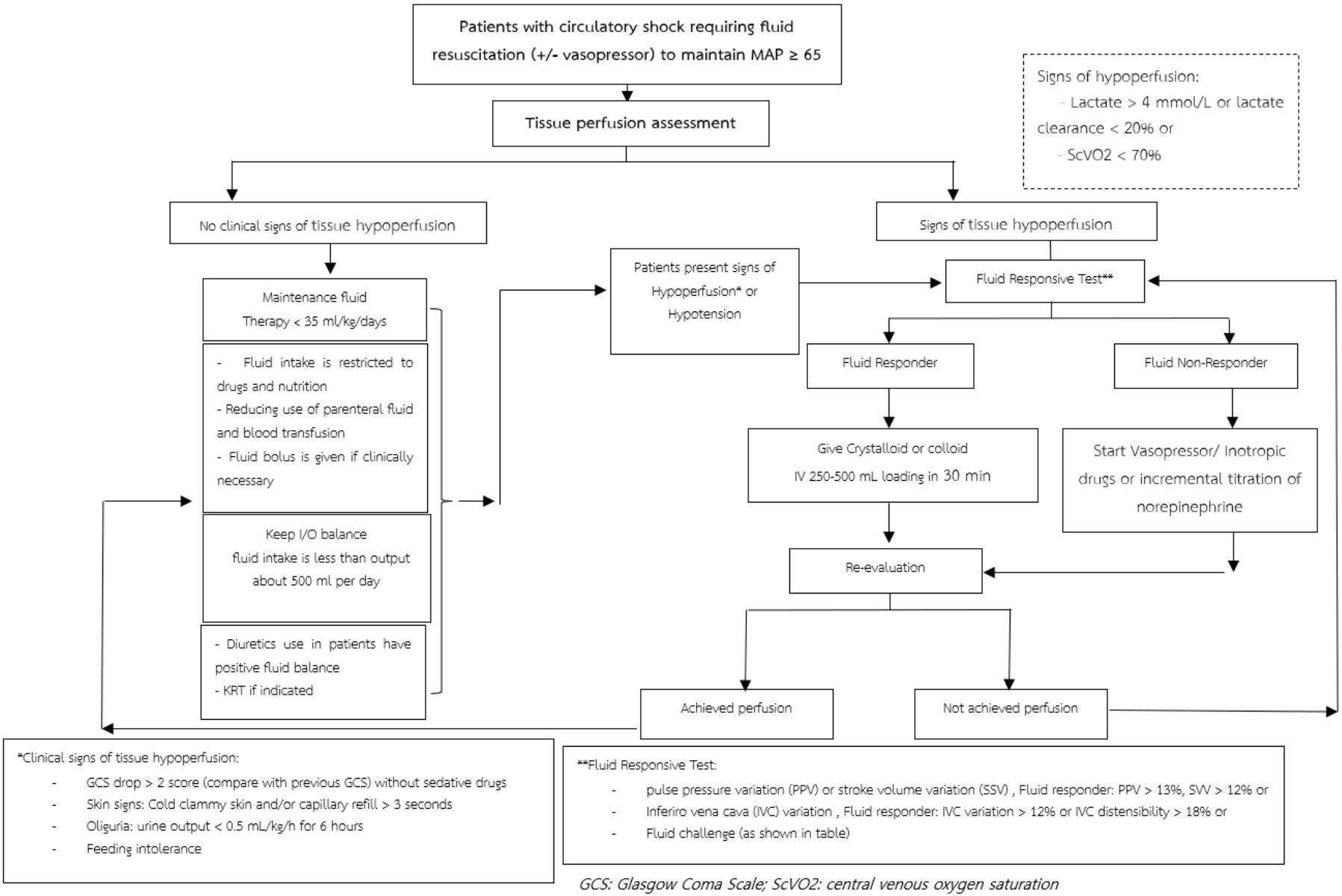
Definition of outcome measurement

Primary outcome

Cumulative fluid balance during the first 72 hours after randomization: total fluid input minus total fluid output within the first 72 hours after randomization.

Secondary outcome

Major adverse kidney event (MAKE) at day 30: The composite outcome of death, new renal replacement therapy, or persistent renal dysfunction within 30 days after randomization.



GCS: Glasgow Coma Scale; ScVO2: central venous oxygen saturation

Figure 2. Intervention protocol.

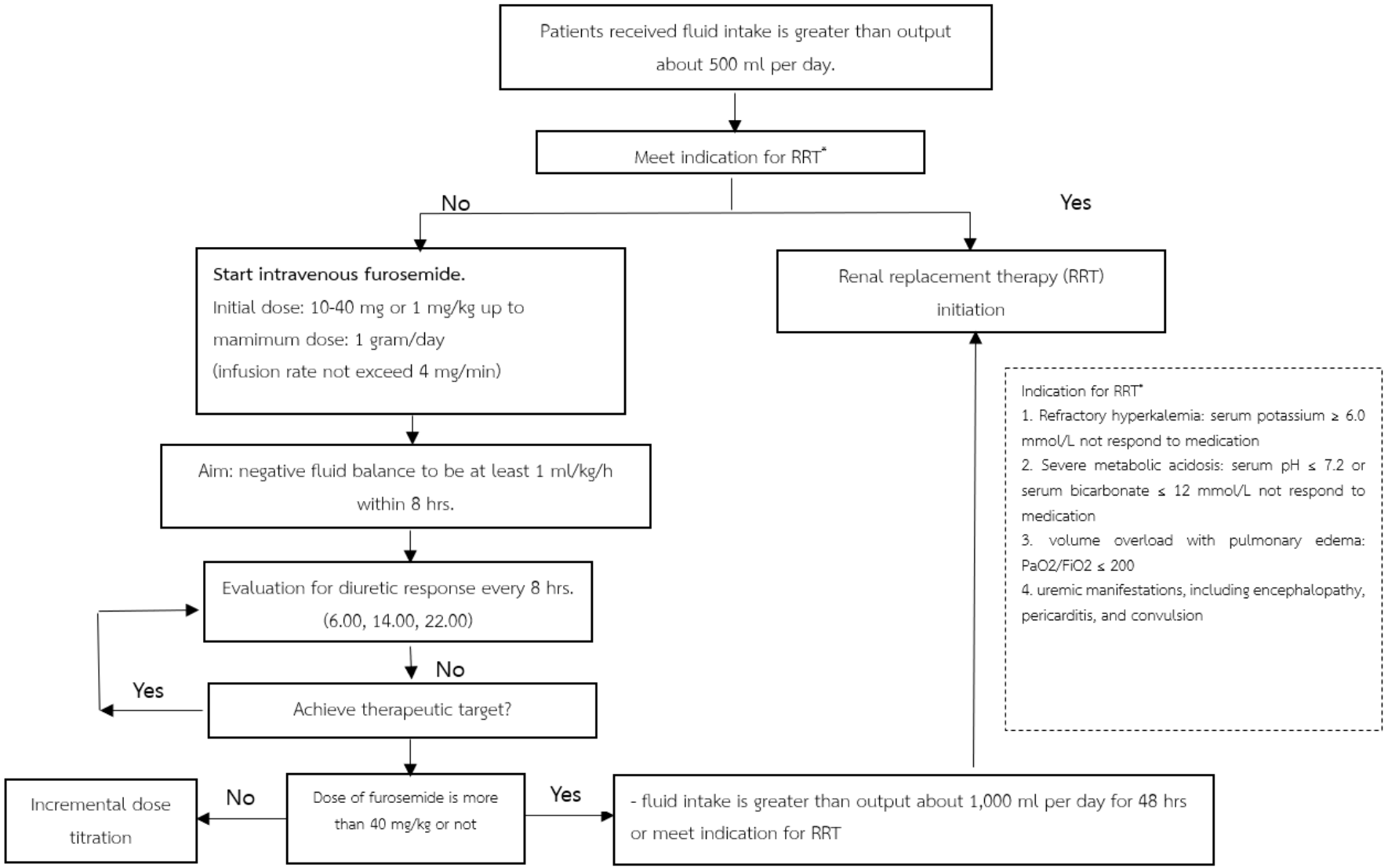


Figure 3. Fluid removal protocol.

30-day mortality: death from any cause within 30 days after randomization.

Incidence of AKI at days 3, 7, and 30: A new episode of AKI defined as KDIGO criteria at any stage on this day.

Definition of AKI according to KDIGO criteria: increase in serum creatinine of ≥ 0.3 mg/dL or ≥50% within 48 hours or urine output of <0.5 mL/kg/hour for >6 hours.

Number of patients requiring RRT at days 3, 7, and 30: Use of acute intermittent or continuous RRT (e.g., dialysis, hemofiltration, or hemodiafiltration) at any rate on this day.

Vasopressor-free status at day 30: total number of days alive without vasopressor use within 30 days after randomization

Mechanical ventilator-free status at day 30: Total number of days alive without mechanical ventilator support within 30 days after randomization

Incidence of fluid overload: presence of edema at more than one site (e.g., arms, legs, flanks, abdominal wall, pulmonary edema with PaO_2/FiO_2 < 300) and increase in body weight by more than 10% compared to preadmission body weight.

Length of intensive care unit (ICU) stay: the number of days from the day of ICU admission (counted as 1 day) to the day of ICU discharge within 30 days after randomization.

Length of hospital stay: the number of days from the day of hospital admission (counted as 1 day) to the day of hospital discharge within 30 days after randomization.

ICU mortality: death from any cause during ICU admission within 30 days after randomization.

Hospital mortality: death from any cause during hospital admission within 30 days after randomization.

Safety outcomes

Incidence of hypotension during the first 3 days: Systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg or mean arterial pressure (MAP) < 65.

Dose of vasopressor at day 3 after randomization: dose of vasopressor use (mcg/kg/min) at day 3 after randomization.

Episode of electrolyte imbalance at day 3 after randomization: The number of events involving electrolyte abnormalities includes.

- Hypokalemia: serum potassium < 3.0 mmol/L
- Hypophosphatemia: serum phosphate < 1 mg/dl
- Hypomagnesemia: serum magnesium < 1.2 mg/dl

Fluid responsiveness test

1. Invasive method: for central line or arterial line assessment

1.1 pulse pressure variation (PPV) or stroke volume variation (SSV)

Fluid responder: PPV > 13% or SVV > 12%

1.2 fluid challenge, as shown in Table 2 below.

2. Non-invasive method: ultrasound IVC parameters

2.1 Patients with mechanical ventilator

- IVC distensibility:

$$IVC\ distensibility = \frac{(D_{max} - D_{min})}{D_{min}} x100$$

Fluid responder: IVC distensibility > 18%

- IVC variation:

$$IVC\ variation = \frac{(D_{max} - D_{min})}{(D_{max} + D_{min})/2} x100$$

Fluid responder: IVC variation > 12%

2.2 Patients with spontaneous breathing

- IVC collapsibility:

$$IVC\ collapsibility = \frac{(D_{max} - D_{min})}{D_{max}} x100$$

Fluid responder: IVC collapsibility > 40%

*D max:maximum diameters (cm); D min:minimum diameters (cm)

DATA MANAGEMENT AND DATA MONITORING

Sample size estimation

The primary outcome of the study was cumulative fluid balance during the first 72 hours after randomization between a restrictive fluid strategy and standard care. We used data from the FINNAKI study cohort, which included 480 patients with AKI, and found that the median

Table 2. Fluid challenge protocol.

	CVP (cmH_2O)	PAOP (mmHg)	Fluid challenge
Before challenge			
	< 8	< 12	Give fluid 200 ml bolus over 10 minutes
	< 14	< 16	Give fluid 100 ml bolus over 10 minutes
	≥ 14	≥ 16	Give fluid 50 ml bolus over 10 minutes
During challenge			
At the end of bolus	Increase > 5	Increase > 7	Stop fluid challenge
	Increase ≤ 2	Increase ≤ 3	Continue fluid
	Increase 2-5	Increase 3-7	Wait for 10 minutes
After challenge			
Wait for 10 minutes	Increase > 2	Increase > 3	Stop fluid challenge
	Increase ≤ 2	Increase ≤ 3	Continue fluid

Central venous pressure, CVP; Pulmonary artery occlusion pressure, PAOP.

cumulative fluid balance at 72 hours was 2,653 mL (interquartile range from 427 mL to 5,918 mL). Cumulative fluid balance is associated with an increased risk of 90-day mortality, with an odds ratio of 1.09 (95% CI 1.04-1.13), p < 0.001. Thus, we assume that a decrease of 1.2 L in fluid balance may result in different patient outcomes.

Data analysis

Statistical analysis will be performed on the intention-to-treat (ITT) population, which was defined as all randomized subjects who consented to have their data used. The conclusions of the analysis will be based on the ITT analysis. A sensitivity analysis will be conducted in the protocol population, defined as the ITT population after exclusion of subjects who experienced one or several protocol violations or stayed less than 72 hours in the ICU after randomization. We will evaluate the primary outcome or amount of accumulative fluid balance using paired t-tests in normal distribution data or the Mann-Whitney U test in non-normal distribution data. The secondary outcomes are mortality and incidence of AKI after using the Chi-square or Fisher's exact test in discrete data and the independent t-test or Mann-Whitney U test in continuous data. A p-value of <0.05 will be considered statistically significant for all outcomes.

Data collection

We will collect information on demographics, principal diagnosis, vital signs, illness severity score, and ICU and hospital outcomes (e.g., admission and discharge, as well as ICU and hospital survival status). We will also collect information on fluid balance, intravenous fluid therapy, use of vasopressor drugs and dosage, use of mechanical ventilation and RRT, and all biochemical, hematological, and blood gas analysis variables. We will record mortality, the incidence of AKI, and the number of patients requiring RRT. All other variables collected will be routinely measured and recorded in electronic medical records or existing hospital databases and will not require any extra sampling or recording.

DISCUSSION

The restrictive fluid strategy is a protocol-based intervention to achieve zero balance in the ICU. This strategy includes restricting fluid intake, maintaining fluid cessation, reducing the use of parenteral nutrition and blood transfusion, and using diuretics to promote urine output.

From previous clinical trials, the benefit of a restrictive fluid strategy in critically ill patients is apparent in some populations, especially patients with ALI or AKI. A study by Wiedemann HP et al. [7] compared a conservative and a liberal strategy of fluid management in patients, with results showing that the conservative fluid management strategy improved lung function and shortened the duration of mechanical ventilation. Meanwhile, a study by Vaara ST et al. [9] compared restrictive fluid management to usual care among critically ill patients with AKI. The results showed that restrictive fluid management resulted in a lower cumulative fluid balance than usual care and a lower incidence of RRT. However, mortality outcomes in these studies were similar between the two groups.

However, a RELIEF study [8] compared a restrictive versus liberal fluid strategy in patients undergoing major abdominal surgery, with the results showing fluid restriction was associated with a higher rate of AKI (8.6% in the restrictive fluid group and 5.0% in the liberal fluid group, p<0.001).

The recently published randomized controlled trial, the Conservative versus Liberal Approach to Fluid Therapy of Septic Shock in Intensive Care (CLASSIC) trial [10], which compared two protocols of fluid restriction and standard care for resuscitation in patients with septic shock, showed that the mortality rate was similar between those two groups (adjusted absolute difference, 0.1 percentage points; 95% CI, −4.7 to 4.9; P=0.96). The protocol of the study was started during the initial phase of resuscitation, which was different from our study, where the protocol started after the initial phase of fluid resuscitation.

The strength of our study is that it is a randomized controlled trial that compares the efficacy of a protocol-based restrictive fluid strategy with standard care in high-risk critically ill patients for whom the protocol is feasible and reproducible in the ICU, especially the medical ICU. We also make use of basic bedside monitoring tools to identify and treat shock patients.

We acknowledge several limitations of this study, First, the study is an unblinded trial, so the outcome may be susceptible to bias. Second, our study is at a single center and has a small sample size compared to previous studies. Finally, the control group in our study is fluid management, depending on the personal preference of attending physicians, and this may introduce bias and interfere with the results of the control group outcomes.

CONCLUSION

This study will evaluate the efficacy and safety outcomes of protocol-based fluid restrictive strategies in critically ill patients with circulatory shock receiving fluid resuscitation or vasopressors.

ETHICS

The study protocol was developed by investigators and approved by the Siriraj Institutional Review Board (approval no. SI 277/2022). This study is already registered at www.thaiclinicaltrials.org (TCTR20220719002).

CONFIDENTIALITY

Data collection will begin after obtaining SIRB approval. The case record form does not indicate names, hospital numbers (HN), or any other factors that can identify individual subjects, and the investigator will use a code instead. The data will be kept for five years after the study is completed. Afterwards, the data will be disposed of.

DISSEMINATION POLICY

None

ACKNOWLEDGEMENT

None

SUPPLEMENTARY MATERIALS

None

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