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RESEARCH PROTOCOL

Terlipressin for refractory septic shock: a study protocol of a single center, placebo-controlled double-blind phase III RCT (The TERESEP study)

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ABSTRACT:

Introduction: In septic shock, vasopressin is a standard treatment that increases blood pressure by vasopressin receptor activation. Vasopressin can reduce catecholamine dose requirement and reduce cardiac arrhythmia in septic shock. Terlipressin is specific vasopressin 1 receptor that may replace vasopressin for septic shock treatment.The TERESEP trial evaluates the benefit of terlipressin add-on catecholamine versus catecholamine only treatment for septic shock.

Methods and analysis: This single-center randomized controlled clinical trial is enrolling hospitalized intensive care patients with septic shock with norepinephrine doses of more than 0.2 microgram/kilogram/min or norepinephrine combine with epinephrine. Patient randomized for terlipressin combined with catecholamine or placebo combined with catecholamine. The primary endpoint is successful of shock treatment within 6 hours define as the rate of mean arterial blood pressure more than 65 mmHg achievement with catecholamine requirement dose less than 0.2 mcg/kg/min. The secondary outcomes include mean blood pressure, 28 days mortality, hospital mortality, intensive care unit range of stay, rate of urine output achievement, lactate clearance, accumulative catecholamine dose, cardiac arrhythmia, 28 days alive without any organ support. The main analysis will use intension to treat approach.

Ethic and dissemination: The Ethics Committee has approved this study of Siriraj hospital, Mahidol University (COA No. SI 049/2020). The trial result will be disseminated through the presentation at medical publication. Authorship will consider and grant using the policy of Mahidol University.

Trial registrations: ClinicalTrials.govNCT04339868. Registered on April 9,2020.

Keywords: Terlipressin, Septic shock, Catecholamine, Randomized controlled clinical trial.

BACKGROUND

Shock is inadequate cellular oxygen utilization stage[1]. The presentation of shock included low systolic blood pressure less than 90mmHg or mean blood pressure less than 65 mmHg with or without tachycardia. Clinical signs of tissue hypoperfusion that are detected from physical examination are cold cutaneous tissue, altered consciousness, and low urine output [2]. In clinical practice, the most common shock is septic shock [1,3]. The mortality of septic shock at Siriraj hospital in 2007 was 52.6%[4]. A recent study also showed high mortality among septic shock patients[5].

The main treatment of septic shock includes hemodynamic support and appropriate source control[6]. Hemodynamic support is a combination of treatments that aim to maintain tissue oxygen delivery. Fluid resuscitation is essential to restoring pre-load in patients suffering from septic shock. After adequate fluid resuscitation, if hypotension is severe or if it persists, the use of a vasoactive agent is indicated. The first-line vasoactive agents are adrenergic agonists because of their high potency, rapid onset, short half-life, and cost-effectiveness[1]. The stimulation of alpha-adrenergic receptors increases blood pressure and vascular tone. The stimulation of beta-adrenergic increases heart rate, cardiac contractility, and cardiac output; however, it also increases the risk of arrhythmic events and myocardial ischemia. On the other hand, overstimulate alpha-adrenergic receptor increases systemic vascular resistance which may result in decrease cardiac output and impair tissue blood flow. The effect of adrenergic stimulation is dependent on dose. However higher dose of the adrenergic stimulating agent can be associated with an increased complication. The surviving sepsis campaign recommended using norepinephrine as the first-line drug for septic shock[6]. Norepinephrine (NE) is highly potent alpha-adrenergic receptor and beta-adrenergic receptor that increase vasoconstriction and rise mean arterial blood pressure with minimal cardiac side effects.

The use of another vasopressor to synergies the effect and decrease the side effect from the high dose adrenergic agonist, has emerged. Vasopressin is a peptide hormone from the hypothalamus that is stored and released from the posterior pituitary gland. Vasopressin binds with 4 types of vasopressin receptors. V1 receptor activates the vascular smooth contract resulting in increased arterial blood pressure. V2 receptor activation enhances free water reabsorption at the distal convoluted tubule. V3 receptor stimulates ACTH hormone secretion. Vasopressin also binds with oxytocin receptors. In septic shock, relative vasopressin deficiency can occur because vasopressin concentration is elevated in the early stage but decrease to the normal range between 24-48 hours as septic shock continues[7,8]. The VASST trial is the randomized control trial that compared norepinephrine alone versus norepinephrine plus vasopressin in the treatment of septic shock. The result of the VASST did not show the benefit of adding vassopressin in the improvement of 28 days mortality (39.3% vs 35.4%, p = 0.026) in overall patients. However, in the less severe shock patient who received norepinephrine less than 0.25 mcg/min, the subgroup result showed that there was an improving survival outcome among vasopressin group (26.5% vs 35.7%, p = 0.05) [9]. In the pos-hoc analysis of the VASST trial, in the high RIFLE risk category patients, receiving vasopressin associated with a trend to lower rate of progression to renal failure or loss (20.8% vs 39.6% p= 0.03) and a lower rate of renal replacement therapy(17% vs 37.7% p=0.02)[10]. In the VANISH trial, the early vasopressin combination with norepinephrine trend to reduced renal replacement therapy and the adrenergic burden[11]. Furthermore, data from a meta-analysis of septic shock patients demonstrated vasopressin treatment associated with fewer arrhythmias. [Absolute risk different (ARD) - 2.8%, 95% CI - 0.2% to - 5.3%] but higher risk of digital ischemia [ARD 1.7%, 95% CI 0.3%-3.2%] [12].These side effects could be due to non-specificity of vasopressin to the V1 receptor binding.

KEY MESSAGES:

- This study is a single-center, randomized, controlled trial that compares Terlipressin versus placebo in septic shock. The primary endpoint is successful shock treatment within 6 hours, defined as the rate of mean arterial blood pressure more than 65 mmHg achievement with catecholamine requirement dose less than 0.2 mcg/kg/min.

In some countries, vasopressin is not available. Terlipressin, the more specific synthetic V1 receptor agonist, had been used for hepatorenal syndrome treatment and gastro-esophageal varices bleeding treatment. Due to the same mechanism of action, terlipressin may replace vasopressin in shock resuscitation. A randomized study (TERLIVAP trial) compared terlipressin continuous drip 1.3 mcg/kg/min to vasopressin continuous intravenous drip 0.03 unit/min and norepinephrine at a dose of 15 mcg/min in septic shock which unresponsive to fluid, showed no difference in mortality among the three groups, but in the patients who received terlipressin it associated with required lower catecholamine dose and had less recurrent hypotension[13]. In the multi-center, which recruited septic shock patients from China, and randomized the patient to receive either terlipressin (20-160 μg/h with a maximum infusion rate of 4 mg/day) or NE (4-30 mcg/min) before adding open-label vasopressors. There was no significant different in 28-day mortality between terlipressin (odds ratio 0.93 [95% CI 0.55-1.56]; p = 0.80)[14]. But in a meta-analysis of Yibing Zhu et al., terlipressin is associated with reduction of catecholamine dose, ICU length of stay, and reduction the ventilator days. However, the adverse events in the terlipressin group were not different from other groups[15]. This is consistent with the meta-analysis of Neto et al., which investigated the use of terlipressin and vasopressin in patients with vasodilatory shock, found that patients who received terlipressin or vasopressin had a lower mortality rate and lower dose of norepinephrine with no difference in side effects[16].

According to the previous studies of terlipressin, it may be able to treat septic shock, reduce catecholamine requirement dose and reduce the side effect of catecholamine. Today, only a few studies have compaired terlipressin in combination with catecholamine versus high dose catecholamines alone in septic shock.

OBJECTIVES

We designed the TERESEP trial to evaluate the efficacy of adding terlipressin to the treating of septic shock who required high dose catecholaminergic agent, compared with continuing catecholaminergic agent alone.

MATERIAL AND METHODS

Trial design and setting

This is a single-center, randomized, placebo-controlled, double-blind trial conducting at Siriraj hospital, Thailand. This study has been approved by the Ethics Committee of Siriraj hospital, Mahidol University (COA No.SI 049/2020) and has been registered in the US Clinical Trial Registry (ClinicalTrials.govNCT04339868)

Eligibility criteria

1. Age ≥ 18-year-old
2. Septic shock diagnoses according to SEPSIS-3 criteria [14,17] and treated in an intensive care unit (Patient suspected or document infection, SOFA score increase ≥ 2 when compared with baseline. Patient's blood pressure persisting hypotension requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation.)
3. Patient does not respond with fluid administration after 30 ml/kg of initial fluid resuscitation. The fluid responsiveness is estimated by invasive procedures or non-invasive procedures. (Central venous pressure 8-12 mmHg, Pulmonary artery occlusive pressure > 18 mmHg with CI > 2.2 L/min/m2, Passive leg raising test is negative by Cardiac Output after PLRT < 15%, IVC collapsibility index < 40% in spontaneous breathing patient, IVC distensibility index < 18% in invasive ventilation patient, Pulse pressure variation (PPV) < 15%)
4. Patient treated with norepinephrine > 0.2 mcg/kg/min or Norepinephrine combine with epinephrine for more than 6 hours, but cannot archive mean arterial blood pressure more than 65 mmHg or mean arterial blood pressure archive 65 mmHg with lactate persistence more than 2 mmol/L.

Exclusion criteria

1. Age < 18-year-old
2. Prolonged septic shock more than 48 hours before inclusion.
3. Fluid resuscitation less than 30 ml/hr within last 3 hours.
4. Do not resuscitate patient or terminal-ill patient.
5. Pregnancy.
6. Chronic kidney disease stage V without renal replacement therapy.
7. Chronic liver disease Child-Turcotte-Pugh score level C.
8. Contraindicate to fluid therapy. (Cardiogenic shock with cardiac index < 2.2 L/min/m2 and PAOP ≥ 18 mmHg, decompensated heart failure, left ventricular systolic function < 35%, acute coronary syndrome, severe valvular heart disease)
9. Life threatening arrhythmia before inclusion
10. Suspected or diagnosed mesenteric ischemia.
11. Systemic sclerosis with Raynaud's phenomenon.
12. Peripheral arterial disease
13. Do not accept informed consent

Intervention

Patients treated in the intensive care unit with septic shock with unresponsive to fluid therapy and catecholamine medication for more than 6 hours, will be screened. The patient who meets all of the inclusion criteria with no exclusion criteria will be invited for study enrollment. Informed and consented will obtain from the patient or caregiver. Participants will be randomized into two intervention arms 1:1 ratio according to a computer-generated randomization table derived from www.randomization.com. Predefined randomization lists with 1:1 are secured and stored in the sealed envelopes by the principal investigator who had no role in patient management. The envelopes will be opened after completion of the informed and consented.

In the intervention arm of the trial, the participant receives a blind label, terlipressin acetate I milligram, in normal saline (0.02 milligram/ml). The control arm of the trial receives a blind label, normal saline. The study drug started at 1 ml/hr. and titrated up 1 ml/hr every 30 minutes to achieve target mean arterial blood pressure of more than 65 mmHg. (Maximum of the study drug is 5 ml/hr.) The maximum terlipressin dose is 100 mcg/hr. If participant means arterial blood pressure achieves 75 mmHg more than 30 minutes, catecholamine drug (epinephrine and norepinephrine) taper down to 0.15 mcg/kg/hr. After the achievement of catecholamine drug to 0.15 mcg/kg/hr and mean arterial blood pressure more than 65 mmHg for 30 minutes, study drug is tapered 1 ml/hr every 30 min then discontinue. The attending physician can adjust the patient's catecholamine medication or add other medication to achieve blood pressure.

The investigator will collect the patient's demographic information, vital signs, laboratory, the result of fluid responsiveness parameters, and adverse reaction to both intervention and placebo groups. (Figure 1)

Hemodynamic data will be collected by patient's invasive or non-invasive monitoring according to the patient's hemodynamic monitoring equipment before and after terlipressin administration. The study drug and catecholamine associated complications such as digital ischemia, bowel ischemia, increase of hyperbilirubinemia, or poor lactate clearance will be collected after study drug administration. If a potential adverse event is detected, primary physician could stop the study drugs and report the event to the investigator. The serious associated complication will report to the ethics committee as soon as possible. The adverse event will declare the minor adverse event to the ethics committee annually.

Outcomes

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

Primary outcomes

The primary outcome is successful shock treatment within 6 hours. The successful shock treatment is defined by the achieving of mean arterial blood pressure more than 65 mmHg or over with catecholamine requirement dose less than 0.2 mcg/kg/min. The catecholamine requirement dose is calculated be summation of norepinephrine dose(mcg/kg/min), epinephrine dose (mcg/

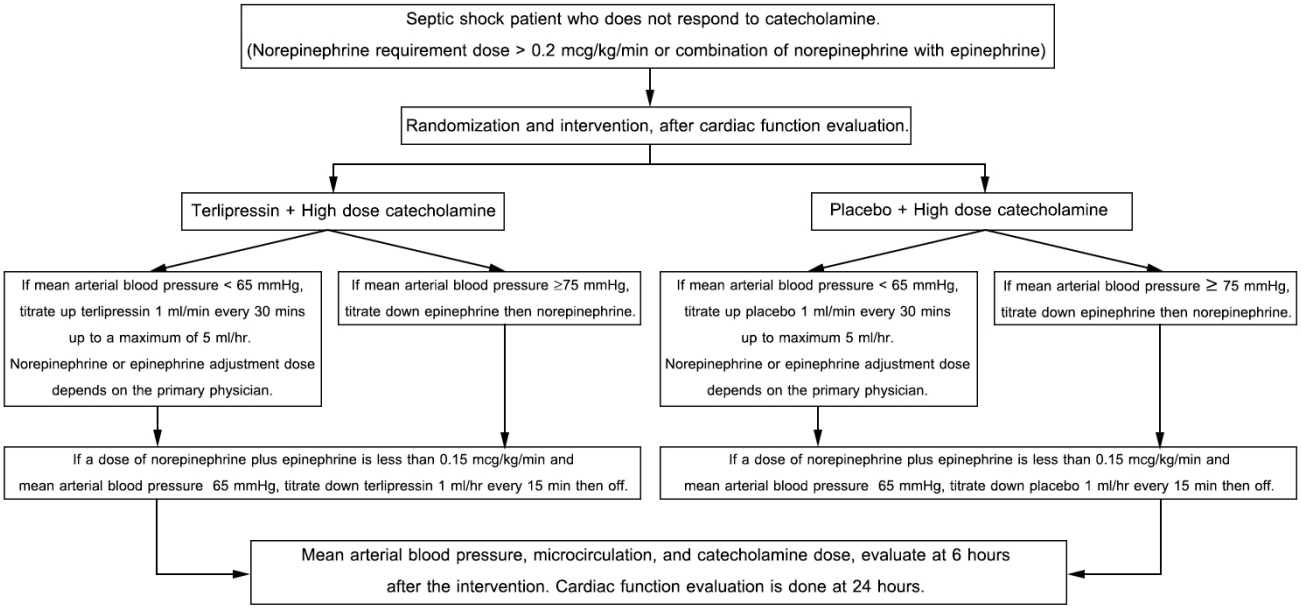

Figure 1. Patient flow, blood pressure, and study-drug.

kg/min), dopamine dose (mcg/kg/mi) and dobutamine dose(mcg/kg/min).

[Catecholamine dose = Norepinephirine dose + Epinephrine dose (Dopamine/100) + (Dobutamine/100)][18,19].

Secondary outcomes

The secondary outcome, all accessed for 28 days follow up period.

1. Mean blood pressure after study drug administration.
2. 28 days Mortality.
3. Hospital mortality.
4. Intensive care unit range of stay.
5. Rate of urine output achievement (More than 0.5 ml/kg/hr) and Lactate clearance achieve 10 percent within 6 hours.
6. Accumulative catecholamine dose.
7. Cardiac tachyarrhythmia.
8. 28 days alive without vasopressors.
9. 28 days alive without a ventilator.
10. 28 days alive without renal replacement therapy.
11. 28 days alive without any organ support.

Timeline and follow up period

Participant timeline showed in table 1

Table 1 Schedule of the study.

	Study period					
	Pre-enrolment	**Enrolment**	**Baseline**	**Allocation**	**Intervention**	**Close 0ut**
Time point	x					
Eligibility screen	x					
Consent to contract		x				
Informed consent		x				
Stratified randomization		x				
Intervention arm			←	—	—	→
Placebo arm			←	—	—	→
Hemodynamic data			x	x	x	
Complication monitoring			←	—	—	→
Mortality						x
Length of stay						x
Organ support						x

DATA ANALYSIS PLAN

Sample size estimation

The sample size required was calculated based on the increase of mean arterial blood pressure at 6 hours after study drug added with catecholamine dose less than 0.2 mcg/kg/min in ATHOS-3 study. The success rate from the ATHOS-3 study was 25%[18] . Due to lack of previous data about terlipressin versus placebo to achieve mean arterial blood pressure target. The investigator estimated the achievement rate of terlipressin therapy at 25%. To detect a between group different of mean arterial blood pressure achievement approximately 25%, at 80% power with a 5% alpha error.

$$n = \frac{\left[Z_{\alpha/2}\sqrt{P(1-P)} + \left(Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right)\right]^2}{(P_1-P_2)^2}$$

By $P = \frac{P1+P2}{2} = \frac{0.25+0.5}{2} = 0.375$

$$n = \frac{\left[1.64\sqrt{2(0.375)(1-0.375)} + 0.84\sqrt{0.25(1-0.25)+0.5(1-0.5)}\right]^2}{(0.25-0.5)^2}$$

A minimum of 57 subjects per group is required. After accounting for a 15 % dropout rate, 65 subjects are required per group and thus a total of 130 subjects will be recruited in two groups.

OUTCOME ANALYSIS PLAN

The categorical data will be expressed in frequencies and percentages. The quantitative data will be tested for normality of data. Normally distributed data will be expressed as mean and standard deviation. Skewed data will be expressed with median and interquartile ranges. Outcomes' evaluation will be analyzed by both intension-to-treat and per-protocol.

The primary analysis, successful of shock treatment within 6 hours, 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. The secondary analysis with continuous data, independent t-test or Mann-Whitney U test will be used. 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 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 investigator officer will record participant information on standardized case-recorded forms approved by IRB. The study's data manager will review, de-identified, check for missing values, and export data to the electronic database. The data will be passed to the study's statistician every year for interim analysis or final analysis.

Data of any unexpected event, received by the study administrator will be recorded and reported to the safety board reviews. In addition, information about the unexpected event or data trends requiring corrective action will be reported to a primary investigator for follow-up. The interim analysis will be analyzed for the initial benefit or risk identification and data trend every year.

Confidentiality

Confidentiality of participants will be maintained where a patient's two first letter of name and surname for patient identification will be used on patients' data sheets throughout the study. Patients' information will be kept on a password-protected database.

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.

DISCUSSION

Terlipressin is specific vasopressin 1 receptor which used to treat hepatorenal syndrome or variceal bleeding in cirrhosis patient. Terlipressin's side effect is increase blood pressure. Due to the same of mechanism of action, terlipressin may be replace vasopressin to treat septic shock. The TERESEP trial is randomized controlled trial that, will provide data on the effect of terlipressin add on catecholamine versus catecholamine only treatment in patient with septic shock. We hypothesize that terlipressin will be beneficial in septic shock in term of reducing catecholamine dosage and the complications from high dose catecholamine. This could be decreased overall mortality, reduced renal replacement therapy, reduced catecholamine dose requirement, reduced length of stay, and fewer complications of catecholamine. The previous studies sought the mortality benefit for terlipressin administration while the TERSEP trial focus on the catecholamine dose and renal replacement therapy.

ETHIC APPROVAL

This trial approved by the Ethics Committee of Siriraj hospital, Mahidol University (COA No.SI 049/2020) and has been registered in the US Clinical Trial Registry (ClinicalTrials.govNCT04339868)

AUTHOR AFFILIATION

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SUPPLEMENTARY MATERIALS

none

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