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Effect of milrinone versus placebo on hemodynamic in patients with septic shock: A randomize control trial

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ABSTRACT:

Background: Sepsis is one of the most serious healthcare problems worldwide, which is associated with high mortality and financial burdens. The common causes of death are refractory shock and multi-organ failure. Myocardial dysfunction, a relatively common complication of septic shock, causes a significantly decrease in stroke volume and cardiac output. This results in insufficient blood supply to the organs, creates multi-organ failure and finally, leading to death. The Surviving Sepsis Campaign Guidelines 2016 also recommended using dobutamine in septic shock patients who had been resuscitated until achieving normal blood pressure target of mean arterial pressure 65 mmHg or more, but still had evidence of inadequate tissue perfusion. Milrinone action via an alternative pathway from the sympathetic inotropic agents, makes the milrinone to be used as an option for improve cardiac function among sepsis patients. However, there are few studies of milrinone in patients with
septic shock.

Methods: We plan to conduct a double blind randomized controlled trial, enrolling patients at Siriraj hospital and Hat-Yai hospital. The adults with the diagnosis of septic shock according to definition of SEPSIS III will be screened. Patients who receive fluid resuscitation at least 30 mL/kg, mean arterial pressure (MAP) ≥ 65 mmHg, with a clinical sign of poor tissue perfusion, or evidence of impaired left ventricular systolic function (left ventricular ejection fraction (LVEF) < 40%) will be enrolled. The patients were randomly assigned in a 1:1 ratio by their sequential number to receive either milrinone (intervention group) or placebo (control group). The physician performs an echocardiogram for assessing cardiac function, before the starting of the study drug and after the 6 and 24 hours. The monitoring of vital signs, urine output, and lactate at 6 and 24 hours after milrinone or placebo commencement is recorded.

Conclusion: This study will evaluate the efficacy of milrinone in improving cardiac output among adult patients with septic shock who is resuscitated to achieve target blood pressure but still have signs of poor tissue perfusion.

Keywords: Milrinone, Septic shock, Cardiac output, Poor tissue perfusion

INTRODUCTION

Sepsis is one of the most serious healthcare problems worldwide, which is associated with high mortality and financial burdens. According to the 2016 WHO database, there were approximately 30 million cases of sepsis per year, and up to 6 million deaths per year globally [1]. The mortality rate of septic patients in 16 Asian countries was reported at 44.2% [2]. A study from Thailand reported mortality up to 52.63% among those were diagnosed with septic shock [3]. The common causes of death are refractory shock [4] and multi-organ failure [5].

Myocardial dysfunction, a relatively common complication of septic shock [6], causes a significantly decrease in stroke volume and cardiac output. This results in insufficient blood supply to the organs, leading to multi-organ failure and finally death. Two previous studies support evidence about death in sepsis or septic shock patients with myocardial dysfunction. The first retrospective observational study in 2011 by Tongyoo S. et al. [7] was reported hospital mortality in right ventricular dysfunction (RVD) patients tended to be higher than the non-RVD patients (81.0% vs. 60.8%, p = 0.06). In addition, the RVD group had lower cardiac output and more frequently underwent renal replacement therapy. The second prospective cohort study in 2020 by Chayakul W. et al. [8] showed Sepsis-related cardiomyopathy was identified as a significant type of organ dysfunction in septic or septic shock patients, and the mortality rate was high (37.5% vs 11.8%, p = 0.009) while achieving tissue perfusion goals within six hours after resuscitation was a protective factor against in-hospital death. On the other hand, the retrospective observational study in 2020 by Myung Jin Song et al. [9] reported Sepsis-induced cardiomyopathy (SIC) was not associated with increased mortality compared to non-SIC (24.5% vs. 26.3%, P=0.936).

Inotropic agent was used as the treatment for improvement of myocardial contractility and cardiac output. The early goal-directed therapy study recommended to initiate dobutamine in patients with septic shock who had evidence of poor tissue perfusion despite receiving adequate fluid resuscitation and obtain optimal mean arterial pressure (MAP) [10].

The Sepsis Survival Campaign Guideline 2016 also recommended using dobutamine in septic shock patients who had been resuscitated until the mean arterial pressure (MAP) target of 65 mmHg or more was achieved, but still had evidence of inadequate tissue perfusion. The inadequate tissue perfusion was documented if there is any one of the following conditions: low cardiac output (CO), low urine output, high serum lactate level or low central venous oxygen saturation (ScvO2) [11]. In several studies, although dobutamine successfully increased cardiac output, it has also been reported to increase mortality rate [12], [13], [14].

Milrinone, a phosphodiesterase enzyme inhibitor, was an inotropic agent with pulmonary artery vasodilatation effect [14]. Its action via an alternative pathway from the sympathetic inotropic agents, make the milrinone to be used as an option for improving cardiac function among sepsis patients. However, there are few studies of milrinone in patients with septic shock [15], [16].

KEY MESSAGES:

- This study is a randomized controlled study to compare the hemodynamic effects of milrinone and placebo in septic shock patients with clinical hypoperfusion, including clinical outcomes and adverse events.
- We hypothesize that the change of cardiac index at 24 hours and lactate clearance may improve after milrinone administration.

The purpose of this study is to compare the efficacy of milrinone versus placebo in improving cardiac output among adult patients with septic shock who is resuscitated to achieve target blood pressure but still has sign of poor tissue perfusion.

The hypothesis of this study is the usage of milrinone in patients with septic shock and either clinical hypoperfusion or impaired left ventricular function would increase cardiac index more than placebo.

MATERIAL AND METHODS

Study design

We plan to conduct a double blind randomized controlled trial, enrolling patients at Siriraj hospital and Hat-Yai hospital. The adults who are 18 years old or over with the diagnosis of septic shock according to definition of SEPSIS III will be screened. Patients who receive fluid resuscitation at least 30 mL/kg(if not contraindication) and/or vasopressor drug until mean arterial pressure (MAP) ≥ 65 mmHg but still have clinical signs of poor tissue perfusion at least 1 of 3 of the following criteria, or evidence of impaired left ventricular systolic function (left ventricular ejection fraction, (LVEF) < 40%) will be enrolled. The signs of poor tissue perfusion include persistent serum lactate >2 mmol/L at 6 hours after resuscitation lactate clearance < 10% in 6 hr and/or urine output < 0.5 ml/kg at 6th hour after resuscitation. The patients with chronic kidney disease stage 5 and denied renal replacement therapy, life-threatening tachyarrhythmia (ventricular tachycardia, ventricular fibrillation) before enrollment and terminally ill patient who signs for do-not-resuscitation will be excluded from the study.

Ethical consideration and trial registration

The study protocol is developed by the investigator committee and approved by the Siriraj Institutional Review Board (approval no. Si 111/2021). The trial was funded by Siriraj research funding (No. R016431074). The funder has no role in the study design, analysis, or outcome assessment. The study is already registered in www.clinicaltrials.gov (NCT 05122884)

Recruitment

Investigators will directly contact the physicians who are in service at medical intensive care units and ask for notifying the investigators if they had a septic shock patient.

The investigator will check for inclusion and exclusion criteria. If the patient is eligible, the investigator will rap-

idly contact the patient or relatives to obtain informed consent.

The investigator will visit the patient or relatives (if the patient cannot give the informed consent) at the ward, before randomization, to inform and ask for the consent. If the relative is not present in the ward or not available at that time, the investigator will make a call to inform, ask for initial consent and make an appointment for obtainment of the formal informed consent later. The patients and their relatives received information, and pre-treatment consent will be given to investigators who are not involved in the treatment of patients. After the consent is signed, the patients were randomly assigned in a 1:1 ratio as simple randomization by their sequential number of enrollments to receive either milrinone (intervention group) or placebo (control group). The randomization will be performed using a computer-generated randomization table derived from www.randomization.com. This process will be provided by an investigator (S.T.) who had no other role in patient screening and enrollment. The other investigators, the patients, the patients' relatives, the attending physicians, and the nurses are all blinded to the study assignment.

Interventions

Intervention description

Patients who met the inclusion criteria for the diagnosis according to the above criteria in the medical intensive care unit will be treated according to the guidelines for the treatment of septic shock.

For the intervention group, the pharmacist prepares milrinone 20 mg in normal saline solution (NSS) 100 mL, then starts intravenous with the rate of 0.5 mg/kg/min for up to 12 hours. Other medications or interventions will depend on the patient's conditions and the attending physician's judgment.

For the placebo group the pharmacist prepares 100 mL of NSS, which is packed in the same format, rate, and administration route of the drug will be exactly the same as the milrinone group.

Drug administration during the study, if the MAP is less than 65 mmHg, the physician can adjust the vasopressor to keep MAP greater than or equal to 65 mmHg. If the MAP is greater than or equal to 75 mmHg for more than 30 minutes, the vasopressor dose will be reduced (epinephrine dose reduction first, followed by norepinephrine accordingly). Other treatments such as fluid infusion, vasopressors, antimicrobial drugs, nutrition support, mechanical ventilator, and renal replacement therapy were in the attending physicians' considerations.

The investigator performs an echocardiogram for assessing cardiac function, before the start of the study drug and after the 6 and 24 hours of drug administration. The vital signs, urine output, and lactate at 6 and 24 hours after milrinone or placebo commencement will be monitored and recorded.

Safety monitoring

While conducting research vital signs are monitored especially blood pressure, heart rate and electrocardiogram (ECG) during the intensive care unit admission. The basic laboratory tests include complete blood count (CBC), BUN, creatinine, electrolyte and liver function test will also be recorded.

The physician will observe early symptoms of cardiac arrhythmias and other complications from milrinone. If there is a suspected side effect of milrinone such as ventricular fibrillation, ventricular tachycardia and unstable atrial arrythmias, the physician considers stopping research and must notify the research team. If there are stable atrial arrhythmias or occasional PVC/PAC, the physician treats and observe follow arrhythmia treatment guideline. The research team will review the medications the patients received and collect the data, write a report to the Siriraj Institutional Review Board.

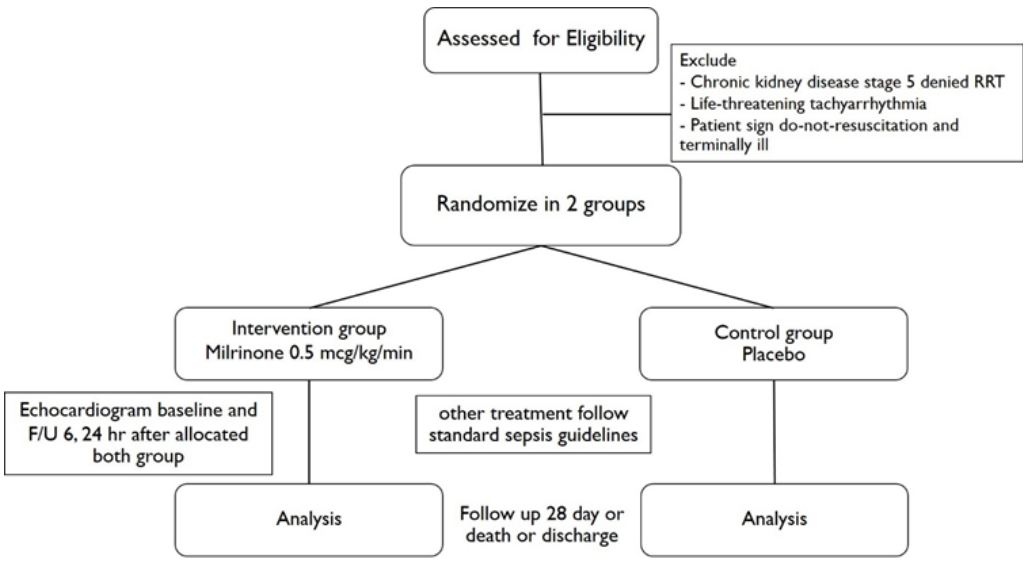

Figure 1. Flow chart of methodology

Outcome measurement

Primary outcome

- The change of cardiac output from baseline (before drug administration) to 24 hours (after study administration) by echocardiogram or Pulse contour analysis or Thermodilution technique using pulmonary artery catheter

Secondary outcome

- Mortality in Intensive care unit (ICU) between milrinone and placebo groups
- Mortality in hospital between milrinone and placebo groups
- 28-day mortality between milrinone and placebo groups
- Dose of vasopressor after intervention between milrinone and placebo groups
- Lactate clearance from baseline and hour 24^{th} after intervention between Milrinone and placebo groups
- Organ support free days (mechanical ventilator, RRT and ECMO) at day 28 after intervention between milrinone and placebo groups
- The incidence of tachyarrhythmia after intervention between milrinone and placebo groups

Sample size calculation

This study aimed to determine the increase in the change cardiac output in septic shock patients. We compared the effects ofmilrinone with placebo. Based on a 2015 study by Z. Wang et al. [16], sample sizes were calculated from www.ClinCalc.com. We hypothesize that the cardiac index in the control group was 3.0 ± 0.8 L/min/sqm and will be increased in the milrinone group to be 3.6 ± 0.8 L/min/sqm. With the type I error of 5% and the type II error of 20%, the sample size will be calculated to be 28 cases per group. To account for the data losts, the sample size will be increased by 10%. The total sample size of approximately 64 cases will be enrolled.

STATISICAL ANALYSIS PLAN

Gender presented as frequency and percentage. Quantitative variables, such as age, are continuous data, presented as mean and standard deviation if the data is normally distributed. If the data do not have a normal distribution, then the median and IQR are presented.

To compare the factors between the milrinone and placebo groups in patients with septic shock. Chi-square or Fisher's exact test will be used for comparison if the factors were categorical Data. If the factors are continuous data, Independent t-test or Mann-Whitney U test will be used. If any factor has p-value <0.05, it will be analyzed by Multiple logistic regression and presented as Adjusted Odds Ratio and 95% Confidence interval

DATA COLLECTION AND MANAGEMENT

Plans for assessment and collection of outcome

The case record form is used to collect baseline characteristics, interventions, and outcomes. All data will be imported into the study database by the investigators.

Data management

The study data are managed by the chief investigator to ensure the authenticity, integrity, and privacy of the data during the research process.

DISCUSSION

Milrinone in previous studies were improve cardiac index in septic shock patients, without increase in severe adverse events and mortality rate.

A study by Barton P. et al. [15], published in CHEST 1996, used milrinone in pediatric patients with septic shock and poor tissue perfusion. Approximate 12 cases of pediatric patient were showed an increase in the cardiac Index in the milrinone group from 3.7 ± 0.8 to 5.5 ± 1.6 L/min/m2 compared with the placebo group from 3.2 ± 0.6 to 3.2 ± 0.5 L/min/m^2 , which were a significant difference and without increase in severe adverse events

A study by Wang Z. et al. [16], published in Clinical drug investigation 2015, was performed to assess the effects of milrinone plus esmolol in patients with severe sepsis and divided patients into three groups; control group, milrinone monotherapy group and milrinone with esmolol group. Increases in the cardiac index were found in the milrinone monotherapy group and milrinone plus esmolol from 1.8 ± 0.4 to 3.6 ± 0.8 L/min/m^2 and 1.8 ± 0.5 to 3.5 ± 0.6 L/min/m^2, which were statistically different. The survival rate was increased both groups but not found in the control group.

A prospective cohort study in 2020 by Chayakul W. et al. [8] performed transthoracic echocardiography in patients with septic shock who were admitted to ICU. They found 11.8% in sepsis with preserved LVEF group while 37.5% in the sepsis-related cardiomyopathy group died in the hospital (p=0.009), while achieving tissue perfusion goals within six hours after resuscitation was a protective factor against in-hospital death.

According to previous studies, if we improve cardiac index in s patients with septic shock and either clinical hypoperfusion or impaired left ventricular function, It possibly reduces the mortality rate in septic shock patients.

CONCLUSION

This study will evaluate the efficacy of milrinone in improving cardiac output among adult patients with septic shock who is resuscitated to achieve target blood pressure but still have signs of poor tissue perfusion.

CONFIDENTIALITY

The subject's information is represented by a unique number, and the coded data is stored at the department of critical care medicine, faculty of medicine Siriraj hospital. The study data will be retained for 5 years after the study is finished. After that, the study data will all be disposed.

DISSEMINATION POLICY

We plan to disseminate the result of this study to national and international conferences and publish it in a peer-review journal.

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AUTHORS' CONTRIBUTIONS

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

SUPPLEMENTARY MATERIALS

None

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