Septic Shock Management Guided by Ultrasound: A Randomized Control Trial (SEPTICUS Trial)

RESEARCH PROTOCOL

dr. Saptadi Yuliarto, Sp.A(K), MKes

PEDIATRIC EMERGENCY AND INTENSIVE THERAPY

SAIFUL ANWAR GENERAL HOSPITAL, MALANG

MEDICAL FACULTY OF BRAWIJAYA UNIVERSITY

DECEMBER 30, 2020

SUMMARY

Research Title	*Septic Shock Management Guided by Ultrasound: A Randomized Control Trial (SEPTICUS Trial)*
Research Design	A multicentre experimental study in pediatric patients with a diagnosis of septic shock.
Research Objective	To examine the differences in fluid resuscitation outcomes for septic shock patients with the USSM and mACCM protocols • Patient mortality rate • Differences in clinical parameters • Differences in macrocirculation hemodynamic parameters • Differences in microcirculation laboratory parameters
Inclusion/Exclusion Criteria	Inclusion: Pediatric patients (1 month - 18 years old), diagnosed with septic shock Exclusion: patients with congenital heart defects, already receiving fluid resuscitation or inotropic-vasoactive drugs prior to study recruitment, patients after cardiac surgery
Research Setting	A multicenter study conducted in all pediatric intensive care units (HCU / PICU), emergency department (IGD), and pediatric wards in participating hospitals in Indonesia.
Sample Size	Calculating the minimum sample size using the clinical trial formula for the mortality rate, obtained a sample size of 340 samples.
Research Period	The study was carried out in the period January 2021 to December 2022
Data Collection Process	Pediatric patients who met the study inclusion criteria were randomly divided into 2 groups, namely the intervention group (USSM protocol) or the control group (mACCM protocol). Patients who respond well to resuscitation will have their outcome analyzed in the first hour (15-60 minutes). Patients with fluid refractory shock will have their output analyzed at 6 hours. Evaluation of the inotropic-vasoactive administration is carried out every 30-60 minutes. Follow-up intervention after 6 hours was not part of the study, but based on the assessment of the DPJP. All patient outcome data will be analyzed statistically.

TABLE OF CONTENT

INTRODUCTION

SEPTICUS Trial

The American College of Critical Care Medicine (ACCM) protocol for the treatment of septic shock has been widely used worldwide and is a guide to the 2012 Surviving Sepsis Campaign (SSC). Fluid resuscitation with a volume of 40-60 ml/kg in 5-10 times minutes is the first step in the management of septic shock.[1,2] If fluid refractory shock occurs, therapy is followed by administration of vasoactive drugs. Furthermore, if catecholamine-resistant shock occurs within the 60-minute treatment, hemodynamic monitoring based on cardiac output (CO) and superior vena cava saturation (ScvO2) is required to guide subsequent vasoactive therapy.[3,4] neonatal intensive care unit from 97% to 9%.[5–7] However, a large randomized controlled clinical trial had a higher mortality rate (relative risk 1.45; 95% CI, 1.13 to 1.86; P = 0.003) in these patients. severe infections that get fluid boluses.[8]

Clinical signs are a basic parameter in the selection and monitoring of fluid and vasoactive therapy. In general, cold and warm shocks, respectively, represent hypodynamic (cardiogenic) and hyperdynamic (vasoplegic) mechanisms. As a consequence, the ACCM protocol recommends low doses of epinephrine or dopamine in cold shock and high doses of norepinephrine or dopamine in warm shock. However, combined monitoring with ultrasonography and invasive blood pressure showed that in patients with clinical symptoms of refractory shock, 33% still had hypovolemia and 39.6% had cardiomyopathy. Likewise, some cold shock patients showed vasodilatory shock based on invasive blood pressure monitoring.[9] These data demonstrate the importance of combining several hemodynamic monitoring modalities to improve the accuracy of the test.

As the standard for monitoring cardiac output, pulmonary artery catheters show high validity and reliability; however, its use in the pediatric population is complicated by the difficulty and complication of insertion, as well as limited availability in tertiary hospitals.[10] Currently, ultrasonography is widely used in hemodynamic monitoring of pediatric patients.[11,12] Echocardiography and ultrasound cardiac output monitor (USCOM) provide bulk information. heart comparable to the gold standard for pulmonary artery catheter.[13,14] Ultrasound-based monitoring tools have the potential to be of great benefit, in terms of various examination parameters (cardiac output, myocardial function, structural abnormalities), as well as their non-invasive, rapid, and practical nature.

Currently, data on the effectiveness of using ultrasound in pediatric septic shock patients are still limited. The variety of hemodynamic parameters that can be measured by ultrasonography should make fluid and vasoactive management more targeted and precise. This is expected to reduce the morbidity and mortality rates for children with septic shock. Furthermore, if the patient outcome is better, ultrasonography can be recommended as the standard for hemodynamic monitoring of septic shock. This study aimed to compare the outcome of pediatric septic shock patients between the ultrasound-guided septic shock management (USSM) and modified-ACCM-guided sepsis management (mACCM) groups.

Sepsis

Sepsis is a life-threatening organ dysfunction caused by immune dysregulation against infection.[15] This definition has been used since 2016 in the adult population. In the pediatric population, they still use the 2005 criteria, namely systemic inflammatory response syndrome (SIRS) which is accompanied or caused by a suspect or proven infection.[16] Sepsis is triggered by the body's immune response to pathogenic infections, which causes the release of pro-inflammatory cytokines such as TNFα, IL-1, and IL-6. These cytokines play a role in the activation and proliferation of leukocytes, activation of the complement system, to increased thrombin production. In sepsis, the inflammatory activity has increased so that it has an effect on collateral damage and cell/tissue death.[15,17]

Sepsis induces increased activation of systemic coagulation, due to increased thrombin production and inhibition of tissue factor. Hypercoagulability results in the formation of microthrombi which can progress with impaired local perfusion to tissue hypoxia. Hypoxia in the cardiovascular system and the activity of inflammatory mediators will lead to cardiomyopathy and vasodilation of arteries and veins. This results in impaired heart function and increased vascular permeability, resulting in systemic tissue hypoperfusion. Impaired vascular permeability also results in leakage of plasma fluid in the interstitial space, causing edema conditions.[17,18]

RESEARCH OBJECTIVE

Objective

The aim of this study was to compare the use of the ultrasound examination-based fluid resuscitation protocol (USSM) with the currently approved fluid resuscitation protocol (mACCM).

Hypothesis

Fluid resuscitation using the USSM protocol provides a better outcome than mACCM via the following parameters:

- Lower mortality rate
- Better 1st and 6th-hour clinical parameters
- Better 1st and 6th-hour macrocirculation hemodynamic parameters
- Better 1st and 6th-hour microcirculation laboratory parameters
- The incidence of fluid overload is less

RESEARCH METHODS

Research design

This research was conducted in a multicentre with a Non-blinded experimental design, Randomized Controlled Trial (RCT).

Research Place and Time

The research was conducted in the High Care Unit (HCU) room, the Pediatric Intensive Care Unit (PICU), the Emergency Room (IGD), or the pediatric ward of the Hospital. Held in January 2021 - December 2022

Research Population

The study population was pediatric patients with septic shock who were admitted to the intensive care room, emergency room, or pediatric ward.

Research Approval

This research was conducted after obtaining approval by the Committee for Research Ethics at Saiful Anwar General Hospital, Faculty of Medicine, Brawijaya University, Malang.

Acceptance Criteria

- Inclusion criteria:
  a. Children diagnosed clinically and supported as septic shock
  b. Between 1 month old (corrected gestational age> 37 weeks) to 18 years
- Exclusion Criteria:
  a. Patients with uncorrected shunt congenital heart disease
  b. Patients who had already received fluid resuscitation prior to recruitment
  c. Patients who had received vasoactive-inotropes prior to recruitment
  d. Postoperative cardiac patients who find it difficult to distinguish between postoperative cardiogenic shock and septic shock

Sample Size Calculation

The sample size calculation used in this study uses the clinical trial formula for mortality rate:

$$n_1 = n_2 = \frac{(z\alpha+z\beta)^2\,(\Theta_1+\Theta_2)}{(\lambda_1-\lambda_2)^2}$$

$$\lambda = \frac{-\ln(0,5)}{M} \qquad \Theta = \frac{\lambda^2}{1-\exp(-\lambda T)}$$

N = sampel size

α = significance level with 0,05, thus z_α = 1,96

β = power of study with 0,2, thus zβ = 0,842

M = Median time survival (time when 50% of subjects survive)

- M intervention = 72 hours
- M control = 48 hours

Λ = insidence rate

T = monitoring time = 72 hours

So from this calculation, the sample size (n) is 170 samples per group. The total sample size is 340 samples

Randomization technique

Simple randomization was used to group the samples into treatment groups with randomization tables through a computer program. Each sample gets a serial number according to the order in which the patient was entered into the study sample.

Research variable

- Independent Variable

The independent variables in this study are:

1. USSM Protocol
2. mACCM protocol

- Dependent variable

The variables bound in this study are:

1. Mortality: amount and time

2. Clinical parameters
3. Macrocirculation hemodynamic parameters
4. Fluid overload parameter
5. Microcirculation laboratory parameters

- Basic Characteristics Variable

1. Age
2. Gender
3. Predicted mortality rate (PIM-2 score)
4. Organ dysfunction score (PELOD-2 score)
5. Diagnosis
6. Blood culture results
7. Volume of fluid resuscitation
8. Vasoactive-inotropic score
9. Duration of PICU care

Operational Definition

a. Sepsis: A sign of systemic inflammatory response syndrome (SIRS) that is accompanied or caused by a suspect or proven infection. The criteria for SIRS and infection were referred to the International pediatric sepsis consensus conference.

b. Septic Shock: Sepsis and cardiovascular organ dysfunction are characterized by: (i) drop in blood pressure (hypotension) <P5 for age or systolic <2SD below normal for age; (ii) requires vasoactive drugs to maintain blood pressure within normal ranges (dopamine> 5 μg / kg / min or dobutamine, epinephrine or norepinephrine); (iii) satisfies two of: unexplained metabolic acidosis (base deficit> 5 mEq / L; increase in arterial lactate> 2 times the normal value; oligouria: urine production <0.5 mL / kg / hr; increased capillary refill time (CRT))> 5 seconds; core temperature difference >3ºC.

c. USSM protocol (Ultrasound-guided septic shock management): An ultrasound cardiac output monitor (USCOM) guided shock management protocol. Algorithms are listed in the research flow section.

d. MACCM protocol (modified American College of Critical Care Medicine): A shock management protocol based on ACCM guidelines that is based on clinical assessment only, with modifications in the form of: (1) fluid bolus duration extended to 15-20 minutes, (2) no 60th minute evaluation. use advanced hemodynamic monitoring tools.1 Algorithms are listed in the subsection of the research flow.

e. Fluid resuscitation: Administration of crystalloid fluids (Ringer Lactate / Ringer Acetate) in the amount of 20 ml / kg per bolus within 15-20 minutes.10 Technique of fluid administration using a pressure bag or Push-Pull technique (PPT)

f. Vasoactive drugs: drugs for shock therapy; consists of groups:

1. Inotropes: dopamine 5-10 mcg / kg / minute, dobutamine 5-20 mcg / kg / minute, epinephrine 0.05-0.3 mcg / kg / minute, or milrinone 0.25-0.75 mcg / kg / minute
2. Vasodilators: milrinone 0.25-0.75 mcg / kg / min or sodium nitroprusside 0.5-4 mcg / kg / min
3. Vasopressors: norepinephrine 0.05-2 mcg / kg / minute, vasopressin 0.3-4 mU / kg / minute, epinephrine 0.3-1 mcg / kg / minute, or dopamine 10-20 mcg / kg / minute

g. Mortality: subject mortality measured at 2-time points, ie 72 hours and time of discharge from intensive care. What is measured is the number and time of death in the two periods of time. The time of death is expressed in minutes from recruitment.

h. Clinical parameters: clinical signs consisting of:

1. Heart rate: the number of heartbeats per minute, seen from a vital sign monitor. Expressed in beats per minute.
2. Capillary refill time (CRT): capillary filling time, checked on the sternum or glabella. Expressed in seconds.
3. Peripheral pulse strength: radial or brachial pulse strength compared to the central (carotid or femoral) pulse. Weak category, when the peripheral pulse is weaker than the central pulse or both are equally weak. Strong category when the peripheral pulse is as strong as the central pulse.

i. Cold shock: shock phenotype characterized by cold extremity temperature, CRT> 2 seconds, mottled skin, weak peripheral pulse strength, or narrowed pulse pressure

j. Warm shock: a shock phenotype characterized by warm extremity temperature, CRT <2 seconds, bounding pulse, or dilated pulse pressure.

k. Fluid overload parameter:

1. Pulmonary Edema: accumulation of fluid in the alveolar or interstitial spaces indicated by rhonchi sounds or increased LUS.
2. Lung Ultrasound Score (LUS): measurement of pulmonary parenchyma aeration using ultrasound on 12 scan areas (6 areas per hemithorax), by a doctor who is ultrasound-certified lung. Each hemithorax is divided by 3 vertical lines (parasternal, anterior axillary, and posterior axillary) so that it becomes 3 areas (anterior, lateral, and posterior); and 1 horizontal line dividing the hemithorax into 2 equal parts. In each area, a score is recorded. The final result is a total score of 12 areas. The scores are stated as follows:
    - 0 = no (or very few) B-lines
    - 1 = B-lines look many but separate (separated B-lines)
    - 2 = many B-lines and converge (coalescent B-lines)
    - 3 = lung consolidation
3. Liver Span: the width of the liver or the length between the upper and lower borders of the liver. Determined by light percussion of the abdomen in the right midclavicular line at the level of the umbilicus towards the cranial direction (starting from the tympanic region to the lower border of the liver) and light percussion of the chest wall in the right midclavicular line from cranial to caudal (starting from the sonor area to the Dim, Expressed in centimeters (cm).
4. ∆ Liver Span: difference in value between liver span before and after fluid resuscitation. Expressed in centimeters (cm).

l. Macrocirculation hemodynamic parameters:

1. Systolic blood pressure (TDS): systolic blood pressure that is measured non-invasively or invasively. Expressed numerically in mmHg and categorically (hypotensive if TDS <P5 appropriate for age and normotension if TDS ≥ P5). P5 according to age is determined by the provisions or formula: 2.26 • 1 month - 1 year: 70 mmHg • 1 year - 10 years: (70 + 2n) mmHg, n = years • 10 - 18 years: 90 mmHg
2. Mean blood pressure or mean arterial pressure (MAP): mean blood pressure as measured non-invasively or invasively. Expressed numerically in mmHg and categorically (hypotensive if MAP <P5 appropriate for age and normotensive if MAP ≥ P5). P5 according to age is determined by the formula: 1.5 n + 40 mmHg.

3. Inotropy: The power of the heart pump which on the USCOM examination is represented by the SMII (Smith-Madigan Inotropy Index) measurement and is expressed in Watts per meter squared (W / m²). Normal values range from 1.2-2.2 W / m².
4. Systemic Vascular Resistance Index (SVRI): Systemic vascular resistance is the burden facing the heart. Measured by USCOM and expressed in units d.s / cm5 / m². Normal value 800-1600. Classification: low SVRI <800, high CI> 1600.
5. Stroke volume index (SVI): ventricular ejection volume per beat divided by body surface area expressed in units of milliliters per meter squared (mL / m²). Normal value 30-60, Classification: low SVI <30, high SVI> 60.
6. Cardiac Index (CI): ventricular ejection volume in one minute divided by the body surface area expressed in units of liters per minute per meter squared (L / min / m²). Normal value 3,3-6,0. Classification: low CI <3.0, high CI> 6,0.

m. Microcirculation laboratory parameters:

1. Base deficit: base deficit value from blood gas analysis.
2. Blood lactate: lactate levels from arterial blood. Expressed in mmol / L.

n. Fluid refractory shock: persistent shock after fluid resuscitation, which is accompanied by:

1. Increased SVI or CI <10% post fluid bolus (in the USSM group), or
2. Addition of liver span or appearance of crackles/rales (in the mACCM group)

Research Flow

All patients who met the inclusion criteria were randomized and divided into intervention (USSM) or control (ACCM) groups. The research subjects will undergo 1 or 2 stages of research: (1) subjects who have achieved the target of therapy in stage 1 (fluid resuscitation), will stop their intervention and have all their outcomes analyzed in the first hour (15-60 minutes); (2) subjects with fluid refractory shock entered the second phase of the study (vasoactive-inotropic therapy), their intervention was discontinued and the outcome was analyzed at 6 hours. Evaluation of vasoactive-inotropic administration is carried out every 30-60 minutes. All interventions after the 6th hour were not part of the study but were based on the assessment and advice of the doctor in charge of services (DPJP). Advanced hemodynamic monitoring tools, measurement modalities, or management outside the study protocol can be used after 6 hours; or in the duration of the study period if the DPJP deems it necessary for patient safety. Observation of mortality was continued until the 72nd hour and on discharge of intensive care. All matters that deviate from the

protocol are recorded in the data collection sheet; the subjects will still be analyzed according to the randomization group.

Processing, Analysis, and Presentation of Data

This study uses an intention to treat analysis. All loss of follow up cases will still be analyzed as dead subjects. All cases with protocol violence or treatment outside the protocol were still analyzed in the same group, according to randomization results. An interim analysis will be performed after 30 and 70 percent of the subjects have achieved. If the mortality outcome was clinically and statistically significant, the study would be terminated. All basic characteristics were analyzed descriptively, presented in the form of mean ± SD or median ± IQR (interquartile range) in the frequency table. For all dependent variables, a Normality test was performed using the Shapiro-Wilk and a variant test (to determine whether the data variance was the same or not) using Levene's test. Independent T-test was used for comparison of numerical data with normal distribution. If the distribution of data is not normal and the variance of the data is not the same, the Mann Whitney test is used. Chi-Square and Fisher's Exact tests were used to determine differences in categorical variables between the two groups. The difference in mortality rates was tested using the Kaplan-Meier survival analysis. This research is significant if the p-value <0.05. All data processing techniques are performed using the 20 PS (SPSS 20PS) statistical product and service solution software.

REFERENCES

1. Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. 2017;45:1061–93.
2. Weiss SL, Peters MJ, Alhazzani W, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med 2020;21:e52–106.
3. De Oliveira CF, De Oliveira DSF, Gottschald AFC, et al. ACCM/PALS haemodynamic support guidelines for paediatric septic shock: An outcomes comparison with and without monitoring central venous oxygen saturation. Intensive Care Med 2008;34(6):1065–75.
4. Sankar J, Sankar MJ, Suresh CP, Dubey NK, Singh A. Early goal-directed therapy in pediatric septic shock: Comparison of outcomes “with” and “without” intermittent superior venacaval oxygen saturation monitoring: A prospective cohort study. Pediatr Crit Care Med 2014;15(4):157–67.
5. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC. The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003;167(5):695–701.
6. Hartman ME, Linde-zwirble WT, Angus DC, Watson RS. Trends in the Epidemiology of Pediatric Severe Sepsis. Pediatr Crit Care Med 2013;14(7):686–93.
7. Han YY, Carcillo JA, Dragotta MA, et al. Early Reversal of Pediatric-Neonatal Septic Shock by Community Physicians Is Associated With Improved Outcome. Pediatrics 2003;112(4):793–9.
8. Maitland K, Kiguli S, O.Opoka R, et al. Mortality after Fluid Bolus in African Children with Severe Infection. N Engl J Med 2011;364:2483–95.
9. Ranjit S, Aram G, Kissoon N, et al. Multimodal Monitoring for Hemodynamic Categorization and Management of Pediatric Septic Shock: A Pilot Observational Study. Pediatr Crit Care Med 2014;15:e17–26.
10. Ceneviva G, Paschall JA, Maffei F, Carcillo JA. Hemodynamic Support in Fluid-refractory Pediatric Septic Shock. Pediatrics 1998;102(2):e19–e19.
11. Levy J, Bachur R. Bedside ultrasound in the pediatric emergency department. Curr Opin Pediatr 2008;20(3):242–352.
12. Vermeiren GLJ, Malbrain MLNG, Walpot JMJB. Cardiac Ultrasonography in the critical care

setting: a practical approach to asses cardiac function and preload for the “non-cardiologist.” Anaesthesiol Intensive Ther 2015;47:s89–104.

13. van Lelyveld-Haas LEM, van Zanten ARH, Borm GF, Tjan DHT. Clinical validation of the non-invasive cardiac output monitor USCOM-1A in critically ill patients. Eur J Anaesthesiol 2008;25(11):917–24.
14. Horster S, Stemmler HJ, Strecker N, et al. Cardiac output measurements in septic patients: Comparing the accuracy of USCOM to PiCCO. Crit Care Res Pract 2012;2012.
15. Singer M, Deutschman CS, Seymour C, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA - J Am Med Assoc 2016;315(8):801–10.
16. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: Definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6(1).
17. Gyawali B, Ramakrishna K, Dhamoon AS. Sepsis: The evolution in definition, pathophysiology, and management. SAGE Open Med 2019;7:205031211983504.
18. Nguyen HB, Jaehne AK, Jayaprakash N, et al. Early goal-directed therapy in severe sepsis and septic shock: Insights and comparisons to ProCESS, ProMISe, and ARISE. Crit Care 2016;20(1).