Study Title: IMPROVEMENT OF SERUM FERRITIN LEVELS WITH INOTROPIC ADMINISTRATION IN EARLY PHASE COMPARED TO REFRACTORY PHASE IN PEDIATRIC PATIENTS WITH SEPTIC SHOCK: A PRELIMINARY RANDOMIZED CONTROLLED TRIAL STUDY

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Chief Investigator Signature:	

The authors declare that they have no competing interests

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

KEY CONTACTS

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1. BACKGROUND AND RATIONALE

Septic shock characterized by immune system dysregulation, systemic inflammatory response, circulatory system disturbances, and organ damage is still the primary cause of morbidity and mortality in the pediatric population, particularly in intensive care settings (Rusmawatiningtyas et al. 2017; Martin et al. 2015). In Indonesia, several studies have been carried out, including studies in the Pediatric Intensive Care Unit (PICU) of Cipto Mangunkusumo Hospital, in which 19.3% of 502 children were diagnosed with sepsis and the mortality rate was 54% due to septic shock (Latief et al. 2016). Meanwhile, a recent study conducted by Wati et al in 2019 reported that the incidence of sepsis in the pediatric population at PICU of Sanglah Hospital was 35.7% with incidence of septic shock reaching 60.7% and mortality rate of 39.3% (Wati et al. 2019).

The principles in the comprehensive management of septic shock include: clinical recognition, establishing intravenous access, initiating resuscitation, administration of antibiotics, and titration of inotropic agents if necessary (Rusmawatiningtyas et al. 2017; Lavis et al. 2017). Unfortunately, fluid resuscitation alone is often unable to restore organ perfusion pressure in septic shock resulting in refractory cases (Martin et al. 2015). In this case, therapy with inotropes or vasopressors should be started, ideally within the first 60 minutes resuscitation. In a study conducted by Ramaswamy in 2016 regarding the comparison of the effectiveness of dopamine versus epinephrine therapy in 61 children aged 3 months Until 12 years old, it was found that resolution of shock was more common in children given epinephrine versus dopamine (41% and 13%), and this pattern lasts up to 6 hours of administration. In addition, a decrease in Sequential Organ Failure Assessment (SOFA) score was significantly higher on epinephrine group compared to dopamine group (Ramaswamy et al. 2016). Therefore, epinephrine is an inotropic agent that can be used as first line therapy pediatric septic shock.

Studies regaring the administration of initial inotropic in septic shock is still controversial. To this date, there is no clear cut off duration of delayed fluid administration that causes rescucitation to be inadequate. Initial vasoactive administration in pediatric patients is also still in debate. Several markers have been studied to play role in evaluation the progressivity of septic shock, incluidng leukocyte count, troponin-I, C-reactive portein, ferritin levels, lactate and oxygen saturation. However, studies regarding the role ferritin levels, lactate and oxygen saturation have not been studied extensively. Studies regarding the comparison of initial inotropic administration and refractory phase inotropic administration are still limited. Thus, clinical trials that compare inotropic administration in the initial phase and refractory phase are needed to reduce the morbidity and mortaility rate of septic shock in pediatric patients.

2. OBJECTIVES AND OUTCOME MEASURES

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary Objective To compare the effect of initial inotropic administration and refractory phase inotropic administration on ferritin levels	Level of ferritin in blood samples from participants on each treatment arm.	Blood sampling at 1st, 6th and 24th hour
Secondary Objectives To compare the effect of initial inotropic administration and refractory phase inotropic administration on leukocyte, CRP, troponin-I, lactate and oxygen saturation levels	Level of leukocyte, CRP, troponin-I, lactate and oxygen saturation in blood samples from participants on each treatment arm.	Blood sampling at 1st, 6th and 24th hour

3. STUDY DESIGN

This study is a randomized trial without blinding (before and after with control design).

Experiment O1 --------- T1 --------- O2

Control O1 --------- T2 --------- O2

O1 = pre-test

T1 = treatment 1 (initial inotropic administration)

T2 = treatment 2 (refractory phase inotropic administration)

4. PARTICIPANT IDENTIFICATION

4.1. Study Participants

Study participants are pediatric septic shock patient who present to the pediatric emergency department of RS Prof Ngoerah in December 2019 – December 2020.

4.2. Inclusion Criteria

- Pediatric patients diagnosed with septic shock and present to to the pediatric emergency department of RS Prof Ngoerah in December 2019 – December 2020.
- Pediatric patient whose parents agree to sign the informed consent.

4.3. Exclusion Criteria

The participant may not enter the study if ANY of the following apply:

- Pediatric patients with congenital diseases, such as congenital heart disease
- Undergoing therapy for renal diseases
- History of prematurity
- Fluid rescucitation has been done in other healthcare facilities

5. PROTOCOL PROCEDURES

5.1. Recruitment

Participants of this study will be recruited through simple random sampling method (simple computer generated random numbers).

5.2. Informed Consent

The *participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing no less than: the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the study site.

5.3. Description of study intervention(s), comparators and study procedures (clinical)

5.3.1. Description of study intervention(s)

Early/initial phase group who received immediate epinephrine infusion (0.05–0.3 µg/kg/min via infusion pumps through peripheral catheters and were shifted to a central line as soon as the line was established.

5.3.2. Description of comparator(s)

Participants who received epinephrine infusion 1 hour after fluid resuscitation.

5.4. Early Discontinuation/Withdrawal of Participants

During the course of the study a participant may choose to withdraw early from the study treatment at any time. This may happen for several reasons, including but not limited to:

- The occurrence of what the participant perceives as an intolerable AE.
- Inability to comply with study procedures
- Participant decision

Participants may choose to stop treatment and/or study assessments but may remain on study follow-up.

5.5. Definition of End of Study

The end of study is the point at which all the study data has been entered and queries resolved.

6. SAFETY REPORTING

6.1. Definition of Serious Adverse Events

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

6.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was 'related' and 'unexpected' in relation to procedures done in thi study. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event.

7. STATISTICS AND ANALYSIS

7.1. Statistical Analysis Plan (SAP)

7.2. Description of the Statistical Methods

Before the data was analyzed, data entry, incomplete data completion, data cleaning, and data re-examination were carried out using the software. Univariate analysis was used to obtain the distribution of sample characteristics including age, gender, nutritional status, and PELOD score. Categorical-scale data is expressed in frequency and percentage, while continuous-scale data is expressed in mean and standard deviation if it is normally distributed, or median and interquartile

range (IQR) if it is not normally distributed. Bivariate analysis was used to determine the effectiveness of initial epinephrine infusion compared to epinephrine infusion after the refractory phase. Hypothetical testing is done using the mean difference test with the dependent and independent sample T-test if data is normally distributed, and Mann-Whitney, Wilxocon or Kruskal- Wallis if data is not normally distributed. The result of the analysis is considered significant if p value < 0.05 with a 95% confidence interval. Data analysis is done using data processing software (IBM SPSS Statistics 20).

8. ETHICAL AND REGULATORY CONSIDERATIONS

8.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

8.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

8.3. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. All the documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

9. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

10. REFERENCES

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