Clinical research protocol

Project name: Application of severe ultrasound in fluid resuscitation of neonatal septic shock

leading unit: Guangdong Second Provincial General Hospital

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Research period: January 1,2022 to December 31,2023

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Abstract

object name	Lung ultrasound-guided fluid resuscitation in neonatal septic shock
goal of study	In this study, a prospective observational study was conducted to compare the effects of severe ultrasound-assisted fluid resuscitation and conventional fluid resuscitation on the prognosis of children with neonatal septic shock, so as to evaluate the application value of the two techniques in fluid resuscitation of neonatal septic shock.
research design	n this study, children with neonatal septic shock diagnosed in the neonatal intensive care unit of the Second People 's Hospital of Guangdong Province from January 1,2022 to December 31,2023 were included in the population. According to the different monitoring methods used in conventional / clinical shock treatment, 30 cases of fluid resuscitation assisted by severe ultrasound, 30 cases of fluid resuscitation assisted by NICOM and 30 cases of conventional fluid resuscitation were collected, a total of 90 cases. (1) The demographic data, blood examination and microbiological examination data of the two groups at admission were collected. (2) The fluid volume, blood lactic acid, blood pressure, vasoactive drugs (such as dopamine and epinephrine / norepinephrine), mechanical ventilation, renal replacement therapy and antibiotic use were collected before fluid resuscitation. (3) The cumulative fluid infusion volume during fluid resuscitation (6 hours), and the use of vasoactive drugs and mechanical ventilation for 6 hours were collected. (4) NICU hospitalization time, cumulative hospitalization time and mortality were collected.
Total number of cases studied	90 cases (30 cases in each group)
case selection	Inclusion criteria: 1 Born less than 28 days on admission; 2 Conform to the diagnostic criteria for neonatal septic shock in the ’ 2020 International Guidelines for Saving Sepsis Campaign: Management of Septic Shock and Sepsis-related Organ Dysfunction in Children; 3 For children

	diagnosed with septic shock, fluid resuscitation should be performed according to the routine diagnosis and treatment. 4 The legal guardian has signed the informed consent.
	excluded criteria: 1 combined with neurogenic shock, trauma and hemorrhagic shock; 2 symptomatic patent ductus arteriosus; 3 combined with congenital heart disease; 4 give up treatment or death within 24 hours of admission; 5 The legal guardian refused to participate in the study; 6 Key information and information missing.
Treatment plan	This study was an observational study. Clinicians developed a diagnosis and treatment plan based on the treatment plan for neonatal sepsis in the sixth edition of ″ Practical Neonatology ″ and the ″ International Guidelines for the 2020 Saving Sepsis Campaign: Management of Septic Shock and Sepsis-related Organ Dysfunction in Children. ″
efficacy evaluation	The main efficacy indicators: hospitalization time and cumulative hospitalization time, mortality. Secondary efficacy indicators: cumulative fluid volume during fluid resuscitation, use of vasoactive drugs and mechanical auxiliary gas.
	Safety evaluation index: Mortality.
statistical method	Measurement data and count data were expressed as mean ± standard deviation [or median (interquartile range)] and percentage (%), respectively. Normal and non-normal distribution data were analyzed by two independent sample t test and Mann-Whitney U test, respectively. The chi-square test was used to compare the count data rates between groups. Kaplan-Meier

	method was used to draw the survival curve, and Log-rank test was used to compare the difference of 28-day cumulative survival rate between the two groups. Baseline covariates were adjusted in the Cox proportional hazards model to calculate the hazard ratios (HRs) and their 95% confidence intervals. Logarithmic conversion was performed on hospital stay and organ support time and linear regression analysis was used to calculate a 95 % confidence interval for reporting. No data with missing information is interpolated. The above statistical analysis was performed using R software, and the test was bilateral, and $p < 0.05$ was considered statistically significant.
Research period	January 1, 2022 - December 31, 2023

一、Research background

Sepsis, especially the development of septic shock, is one of the most important causes of neonatal morbidity and mortality [1]. Although the understanding of the pathophysiology of septic shock continues to evolve, the treatment of neonatal septic shock remains challenging ; although considerable progress has been made in treatment, failure is still common [2]. In particular, the particularity of neonatal physiological development [3, 4] makes the tolerance of neonatal septic shock much lower than that of adults. However, the research progress in the field of neonatal septic shock is far behind that of adults [2, 5]. At present, non-invasive monitoring and clinical experience are mainly used to judge the organ function and volume status of patients and then treat them in clinical practice. However, empirical diagnosis and treatment can lead to insufficient volume or excessive fluid, which in turn leads to impaired function of important organs [6]. Ultrasound examination integrates structural and functional assessment, problem goal orientation, quantitative and qualitative combination, and dynamically evaluates volume status, volume responsiveness and organ function changes, so as to guide fluid resuscitation and positive inotropic drug use in a timely and accurate manner. It is an ideal medical tool for hemodynamic management in patients with septic shock [7, 8]. However, there is still a lack of relevant research in the field of fluid resuscitation in neonatal septic shock.

The incidence of neonatal sepsis varies with gestational age and onset time (35 % of live births) [10-13]. Sepsis neonates may develop or progress to septic shock, which is initially manifested as cardiovascular dysfunction requiring fluid resuscitation or muscle strength support [14]. If the development of infection cannot be prevented, the possibility of terminal organ damage and death will be greatly increased, especially in premature infants, sepsis has become an important source of morbidity and mortality. [2]. Although the exact incidence is not clear, a recent retrospective cohort study of 3800 newborns admitted to the Neonatal Intensive Care Unit (NICU) during the three-year period reported that the incidence of septic shock was 1.3 %, and the peak mortality rate associated with

very low birth weight (birth weight < 1000g) was 71 % [15].

Septic shock refers to life-threatening organ dysfunction caused by the body 's uncontrolled response to infection, accompanied by severe circulatory, cellular and metabolic abnormalities. The in-hospital mortality rate is as high as more than 40 % [16], and the proportion is higher in newborns [15]. In the early stage of septic shock, in order to maintain the stability of circulation, a large amount of fluid resuscitation treatment is usually needed. The effective circulating blood volume of the body is supplemented by intravenous infusion and other means, and the increase of stroke volume and cardiac output is promoted, so as to restore the perfusion of tissues and organs, improve their hypoxic state, and then correct septic shock [17]. Therefore, appropriate volume resuscitation is an important measure for clinical treatment of septic shock. How to effectively monitor the volume status of patients and reasonably guide clinical treatment has become the focus of clinical workers. The ' Save Sepsis Campaign ' emphasizes that sepsis and septic shock are clinical emergencies and require early comprehensive treatment. It is recommended to guide late fluid therapy through repeated hemodynamic monitoring after timely initial fluid resuscitation [18,19]. Hemodynamic monitoring in patients with septic shock is mainly used to evaluate whether continuous fluid infusion can improve organ perfusion and assist in deciding whether positive inotropic drugs are needed [17]. At present, non-invasive monitoring and clinical experience are mainly used to roughly judge the organ function, volume status and resuscitation effect of patients. ' Detachment after heavy irrigation ' has become a clinical norm, while empirical diagnosis and treatment can lead to insufficient volume or excessive fluid. Volume overload is often ignored until clinical signs or imaging signs of organ dysfunction occur, and continuous positive fluid balance will significantly increase the complications and mortality of patients [20,21]. Therefore, it is an important way to improve the therapeutic effect and prognosis quality of septic shock by establishing accurate and objective organ function monitoring methods in the process of diagnosis and treatment, carrying out appropriate fluid management optimization under the guidance of

scientific dynamic monitoring of disease, correctly evaluating the circulatory function of different stages of shock to adjust the treatment plan, and supporting organ tissue perfusion with the least amount of fluid and the least physiological cost.

In the past few decades, hemodynamic monitoring technology has developed from discontinuity to continuity, real-time, and less invasive, and the number and characteristics of indicators provided have also been continuously improved [22]. At present, the commonly used monitoring tools in clinical practice are divided into invasive and non-invasive. Among them, transpulmonary thermodilution method and pulmonary artery catheter are considered as invasive advanced hemodynamic monitoring methods, which can continuously and dynamically evaluate the cardiac volume and pressure status and systemic oxygenation status of critically ill patients, and are called the ' gold standard ' of hemodynamic monitoring [23]. However, it cannot be used as a routine monitoring tool due to its cumbersome operation, many complications, lack of evidence of benefits for patients, and inability to evaluate cardiac diastolic function. Early fluid resuscitation is the key to the treatment of septic shock, but so far, there is no unified guidance for fluid resuscitation. Blind fluid replacement can lead to insufficient fluid or excessive fluid, which can lead to acute heart failure, pulmonary edema and other complications [6]. Therefore, it is extremely important to establish an accurate and objective organ function monitoring method in the process of diagnosis and treatment, and correctly evaluate the circulatory function of different stages of shock to adjust the treatment plan. The traditional hemodynamic methods, including pulmonary artery floating catheter, pulse indicator continuous cardiac output and other monitoring techniques are invasive operations, and the clinical application process has high technical requirements, relatively many complications, and high prices [23]. In view of the characteristics of severe neonatal septic shock, poor consciousness and low cooperation, these invasive monitoring have certain difficulties, and the ideal non-invasive monitoring system should be accurate, economical and efficient, with few complications, easy to use and explain, with high specificity and sensitivity, and can be

widely used [24].

At present, non-invasive monitoring and inspection methods have broad application prospects in the field of fluid management of septic shock. Monitoring cardiac output in the ICU has become part of routine patient management, helping doctors assess patients ' clinical status and track their response to various interventions. Non-invasive cardiac output monitoring (NICOM) is a non-invasive cardiac output detection method that detects hemodynamic indicators by bioelectrical impedance method. NICOM can dynamically and conveniently detect the hemodynamic characteristics of patients on a non-invasive basis in real time. In recent years, NICOM has been gradually applied in pediatric NICU, especially in the treatment of neonatal septic shock patients, and has achieved certain results [24]. In addition, among various monitoring methods, ultrasound technology can provide cardiovascular system-related information from both functional and structural aspects, and is an important tool for hemodynamic monitoring in adult patients with septic shock [25]. More and more evidence shows that severe ultrasound-guided fluid resuscitation can improve the prognosis of critically ill patients, and was written into the 2015 ' Severe Hemodynamic Therapy-Beijing Consensus ' [26]. Ultrasound technology has the characteristics of non-invasive, real-time and repeatable, and integrates structural and functional assessment, problem goal orientation, quantitative and qualitative combination, dynamic assessment of volume status (cardiac function), volume responsiveness (inferior vena cava diameter) and organ function changes (lung ultrasound), so as to timely and accurately guide fluid resuscitation and positive inotropic drug use. It is an ideal medical tool for hemodynamic management in patients with septic shock and has been integrated into the diagnosis and treatment of adult septic shock [25, 27]. In particular, ultrasound diagnosis of pulmonary edema depends on the discovery of characteristic B lines, and has a high consistency with CT diagnosis. If the patient 's B line under lung ultrasound monitoring is significantly increased, suggesting increased lung water, increased lung permeability, such as reduced cardiac function and inferior vena cava dilatation, at this time, the presence of

excessive lung water volume load should be considered. Increases should begin to make adjustments in fluid therapy and respiratory therapy that are most suitable for patients [28]. However, previous studies are basically aimed at adults, and the number of studies in neonates is very limited. In clinical studies, due to the particularity of neonatal anatomy and physiology, there is a lack of research on the application of severe ultrasound technology in fluid resuscitation of neonatal septic shock. [29] There is an urgent need for an effective non-invasive monitoring method to assist fluid resuscitation in children with septic shock.

At present, the fluid resuscitation methods used in our department for neonates with septic shock mainly include : conventional fluid resuscitation, severe ultrasound-guided fluid resuscitation and NICOM-assisted fluid resuscitation. In this prospective observational study, children with neonatal septic shock diagnosed in the neonatal intensive care unit of Guangdong Second People 's Hospital from January 1,2022 to December 31,2023 were included in the study. According to the different monitoring methods used in shock treatment, 30 cases of severe ultrasound-assisted fluid resuscitation, 30 cases of NICOM-assisted fluid resuscitation and 30 cases of conventional fluid resuscitation were collected, a total of 90 cases. The hemodynamic differences, NICU hospitalization time, renal replacement therapy / mechanical ventilation, and 28-day mortality were compared among the three groups to comprehensively evaluate the application value of cardiopulmonary ultrasound and non-invasive cardiac output in fluid resuscitation of neonatal septic shock. Improve the therapeutic effect of neonatal septic shock, enrich the application field of clinical ultrasound, and promote the cross-fusion of ultrasound and pediatrics, and provide clinical basis for subsequent prospective studies.

二、research objective

1. Main Objective: To study the application value of severe ultrasound and non-invasive cardiac output technique in fluid resuscitation of neonatal septic shock.

2.Secondary purpose: To promote the therapeutic effect of neonatal septic shock and enrich the application field of clinical ultrasound technology.

三、Research Design Types, Principles, and Test Procedures

1. Research Design

In this study, children with neonatal septic shock diagnosed in the neonatal intensive care unit of the Second People 's Hospital of Guangdong Province from January 1,2022 to December 31,2023 were included. According to the different monitoring methods used in routine / clinical shock treatment, 30 cases of severe ultrasound-assisted fluid resuscitation, 30 cases of NICOM-assisted fluid resuscitation and 30 cases of routine fluid resuscitation were collected. The demographic data, blood examination and microbiological examination data of the three groups at admission were collected. The fluid volume, blood lactic acid, blood pressure, vasoactive drugs (such as dopamine and epinephrine / norepinephrine), mechanical ventilation, renal replacement therapy and antibiotic use before fluid resuscitation were collected. The cumulative fluid infusion volume during fluid resuscitation (6 hours), and the use of vasoactive drugs and mechanical ventilation for 6 hours were collected. NICU hospitalization time, cumulative hospitalization time and mortality were collected.

四、case selection

1. Inclusion criteria:

1 Born less than 28 days on admission; 2 Conform to the diagnostic criteria for neonatal septic shock in the ' 2020 International Guidelines for Saving Sepsis Campaign: Management of Septic Shock and Sepsis-related Organ Dysfunction in Children; 3 For children diagnosed with septic shock, fluid resuscitation should be performed according to the routine diagnosis and treatment. 4 The legal guardian has signed the informed consent.

2. excluded criteria:

1 combined with neurogenic shock, trauma and hemorrhagic shock; 2 symptomatic patent ductus arteriosus; 3 combined with congenital heart disease; 4 give up treatment or death within 24 hours of admission; 5 The legal guardian refused to participate in the study; 6 Key information and information missing.

3. Elimination criteria

Subjects who have been enrolled in the study but meet one of the following criteria should be excluded :

(1) After inclusion, those who did not meet the inclusion criteria or met the exclusion criteria were found.

(2) Those who have not used test drugs / interventions.

4. Standard for suspension of research

(1) If the following conditions occur during the experiment : cardiac arrest, intestinal perforation, intracranial and other serious complications ; (2) the need for rescue is not suitable for experimental related operators ; (3) The competent physician believes that the clinical condition is not suitable for continuing the experiment ; (4) If the clinical symptoms and other auxiliary examinations are inconsistent with the relevant non-invasive examination results ; (5) Parents did not agree to continue the experiment during the experiment.

4. Drop-out / exit criteria

Expulsion / withdrawal criteria : (1) the competent physician believes that the clinical condition is not suitable for the continuation of the experiment ; (2) If the clinical symptoms and other auxiliary examinations are inconsistent with the relevant non-invasive examination results ; (3) Parents did not agree to continue the experiment during the experiment.

五、research method

In this study, children with neonatal septic shock diagnosed in the neonatal intensive care unit of the Second People 's Hospital of Guangdong Province from January 1,2022 to December 31,2023 were included. According to the different monitoring methods used in routine / clinical shock treatment, 30 cases of severe ultrasound-assisted fluid resuscitation, 30 cases of NICOM-assisted fluid resuscitation and 30 cases of routine fluid resuscitation were collected. The demographic data, blood examination and microbiological examination data of the three groups at admission were collected. The fluid volume, blood lactic acid, blood pressure, vasoactive drugs (such as dopamine and epinephrine / norepinephrine),

mechanical ventilation, renal replacement therapy and antibiotic use before fluid resuscitation were collected. The cumulative fluid infusion volume during fluid resuscitation (6 hours), and the use of vasoactive drugs and mechanical ventilation for 6 hours were collected. NICU hospitalization time, cumulative hospitalization time and mortality were collected.

六、Observation items and detection time points

(1) The demographic data, blood examination and microbiological examination data of the three groups at admission were collected.

(2) The fluid volume, blood lactic acid, blood pressure, vasoactive drugs (such as dopamine and adrenaline / norepinephrine), mechanical ventilation, renal replacement therapy and antibiotic use before fluid resuscitation were collected.

(3) The cumulative fluid infusion volume during fluid resuscitation (6 hours), and the use of vasoactive drugs and mechanical ventilation for 6 hours were collected.

(4) NICU hospitalization time, cumulative hospitalization time and mortality were collected.

七、standards for efficacy appraisal

The main efficacy criteria : NICU hospitalization time and cumulative hospitalization time, mortality.

Secondary efficacy criteria : cumulative fluid volume during fluid resuscitation (6 hours), and use of vasoactive drugs and mechanical ventilation for 6 hours.

八、Observation of adverse events

Observation of adverse events : Clinicians should evaluate the fluid resuscitation of children at any time during the experiment. If the clinical symptoms and other auxiliary examinations (such as heart rate, liver size, mental state, X-ray, blood gas analysis, etc.) are

inconsistent with the relevant non-invasive examinations, the experiment should be terminated immediately and the superior physician should be found in time to assist.

九、Data security monitoring

Clinical research will develop a corresponding data security monitoring plan based on the size of the risk. All adverse events were recorded in detail, properly handled and tracked until they were properly resolved or stable. Serious adverse events and unexpected events were reported to the ethics committee, competent authorities, sponsors and drug supervision and management departments in a timely manner according to the regulations. The main researchers regularly conduct a cumulative review of all adverse events, and if necessary, convene a meeting of researchers to assess the risks and benefits of the study ; research that is greater than the minimum risk will arrange independent data monitors to monitor the research data, and high-risk research will establish an independent data security supervisory committee to monitor the accumulated security data and effectiveness data to make recommendations on whether the research will continue.

十、Statistical processing

Measurement data and count data were expressed as mean ± standard deviation [or median (interquartile range)] and percentage (%), respectively. Normal and non-normal distribution data were analyzed by two independent sample t test and Mann-Whitney U test, respectively. The chi-square test was used to compare the count data rates between groups. Kaplan-Meier method was used to draw the survival curve, and Log-rank test was used to compare the difference of 28-day cumulative survival rate between the two groups. Baseline covariates were adjusted in the Cox proportional hazards model to calculate the hazard ratios (HRs) and their 95 % confidence intervals. Logarithmic conversion was performed on hospital stay and organ support time and linear regression analysis was used to calculate a 95 % confidence interval for reporting. No data with missing information is interpolated. The above statistical analysis was performed using R software, and the test was bilateral, and $p < 0.05$ was considered statistically significant.

十一、Ethics in clinical research

Clinical research will follow the World Medical Congress ' Helsinki Declaration ' and other relevant provisions. Before the study began, the clinical study was carried out after the ethics committee approved the test plan. Before each subject is selected for this study, the researcher has the responsibility to fully and comprehensively introduce the purpose, procedure and possible risks of this study to the subjects or their agents, and to sign a written informed consent form. The subjects should be informed that they have the right to withdraw from the study at any time. Informed consent should be retained as a clinical research document for review. The personal privacy and data confidentiality of the subjects will be protected during the study.

十二、Research progress

January 1, 2022 - March 31, 2022 : Pre-project preparation, harmonization of data collection standards, training of personnel

From April 1,2022 to May 31,2023 : the specific implementation stage of the experiment, case data were collected.

From June 1,2023 to December 31,2023 : Write scientific research papers and project summary reports 1 Organize research data and conduct statistical analysis ; 2 writing and submission of scientific research papers ; 3 Summarize the research results and write the project summary report.

十四、reference

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