Informed Consent Form · Information Sheet

Dear Patient (or Family Member):

The doctor has diagnosed you (or your family member) with septic shock. We would like to invite you to participate in a research study. This study is a multi-center, randomized, placebo-controlled clinical trial to investigate the effectiveness and safety of methylene blue in the treatment of refractory septic shock. This research protocol has been approved by the Ethics Committee of the General Hospital of Southern Theater Command for conducting clinical research.

Before deciding whether to participate in this study, please read the following information carefully. This information will assist you in comprehending the study, its purpose, the study procedures and duration, as well as the potential benefits, risks, and discomforts associated with participation. If you wish, you can discuss it with your family members or friends, or ask the doctor to provide an explanation to assist you in making a decision.

1. Background and Objectives of the Study

1.1 Disease Burden and Current Treatment

Septic shock is a common disease in intensive care units and is defined as septicemia-induced shock, characterized by a host's dysregulated response to infection with underlying circulatory and cellular metabolic abnormalities that significantly increase the risk of organ dysfunction and mortality. Statistics show that in 2017, there were approximately 48.9 million cases of sepsis worldwide, with approximately 15% of sepsis cases progressing to septic shock, accounting for 10% of ICU death cases. Sepsis is mainly caused by infections in various systems of the body. When bacteria enter the bloodstream or certain toxins are released, patients with compromised immune systems, chronic diseases, or other high-risk factors may experience circulatory dysfunction, leading to septic shock. This can be manifested by persistent hypotension, increased heart rate, accelerated respiration, changes in consciousness, pale complexion, cold extremities with possible mottling, and reduced urine output, among other symptoms. The mortality rate of septic shock is high, with a 90-day mortality rate of 38.5% among septic shock patients according to a recent meta-analysis. The mortality rate in patients with refractory septic shock is usually as high as 60%.

Patients with refractory septic shock often experience vascular paralysis, resulting in poor response to vasopressor drugs. High doses of vasopressor drugs are required to maintain blood pressure, but in severe cases, high doses of vasopressor drugs may not raise blood pressure to a level sufficient to maintain systemic organ perfusion. After decades of research at home and abroad, it is currently believed that nitric oxide (NO) is one of the key intermediate steps in the development of septic shock.

Researchers have found that methylene blue can increase patients' blood pressure and improve hemodynamic performance by acting on the soluble guanylyl cyclase (sGC) binding site of the

NO pathway. Methylene blue is a drug that has been approved and marketed for many years and is mainly used in the treatment of methemoglobinemia caused by nitrate or nitrite poisoning and acute cyanide poisoning. It has demonstrated a high level of safety in clinical practice.

Some researchers have already conducted clinical trials of methylene blue in septic shock. The studies have found that methylene blue can significantly increase mean arterial pressure in septic shock patients and improve other hemodynamic parameters. If the efficacy of methylene blue in patients with refractory septic shock can be validated through clinical trials and subsequently applied in the treatment of septic shock, it may provide a new approach to the treatment of septic shock and potentially have beneficial effects on reducing mortality and hospitalization duration associated with septic shock.

1.2 Objectives of the Study

1.2.1 Primary Objective

To evaluate the effect of methylene blue on the total vasopressor dosage in refractory septic shock

1.2.2 Secondary Objectives

A. To evaluate the effect of methylene blue on other hemodynamic parameters (such as mean arterial pressure, central venous pressure, cardiac function, serum lactate level, etc.) in septic shock.

B. To investigate whether methylene blue can reduce the 24-hour, 48-hour, 72-hour and 7-day mortality and decrease the length of stay in ICU.

1.3 Participating Units and Expected Number of Participants

Participating Units: General Hospital of Southern Theater Command, Jiangmen Central Hospital, Zhanjiang Central People's Hospital, Zhujiang Rriver Hospital, Shenzhen Second People's Hospital.

Expected Number of Participants: 100 cases.

2. Who Should Not Participate in the Study

(1) Age <18 years old;

(2) Patients who are pregnant or breastfeeding;

(3) Known allergy to methylene blue;

(4) Patients with glucose-6-phosphate dehydrogenase deficiency;

(5) Patients with advanced-stage cancer;

(6) Patients who are simultaneously complicated by non-infectious factors causing death, such as uncontrolled major bleeding, cerebral herniation, etc.;

(7) Patients with irreversible conditions or in a terminal state;

(8) Patients who refuse active treatment or plan to leave the ICU within 48 hours;

(9) Patients who have participated in other trials.

3. What Will be Required if You Choose to Participate in the Study?

Before you (or your family member) are included in the study, the doctor will inquire about and document the patient's medical history and assess the patient's condition. If you meet the inclusion criteria and voluntarily agree to participate in the study, you will sign an informed consent form. If you choose not to participate in the study, it will not result in any bias or affect the medical care provided to you (or your family member).

If you voluntarily agree to participate in the study, the following steps will be followed:
The study team members will randomize the subjects into treatment groups according to a predetermined computer program sequence. There is a 50% chance for subjects to receive methylene blue treatment on top of standard treatment, and a 50% chance to receive standard treatment alone. Neither you nor the doctor can choose which treatment group the subjects will be assigned to. This ensures a fair evaluation of the study drug.

Intervention scheme for the methylene blue group: Intravenous injection of 50 ml of methylene blue injection solution at a dose of 2 mg/kg over 20 minutes using an infusion pump, followed by continuous intravenous infusion at a rate of 0.5 mg/kg/h for 48 hours.

Intervention scheme for the control group: Intravenous injection of 50 ml of 5% glucose injection solution over 20 minutes, followed by continuous intravenous infusion at a rate of 0.5 mg/kg/h for 48 hours.

During the trial, continuous hemodynamic monitoring, blood tests, and other examinations will be arranged for the subjects, and the results of these examinations will be collected. These tests are routine in the clinical diagnosis and treatment of septic shock and are beneficial for the doctor to evaluate the patient's condition and guide treatment.

Other matters that require your cooperation:
During the course of the study, new information regarding the study methods may emerge. If any new information arises, your research doctor will promptly inform you and discuss with you whether you still wish to continue participating in the study. If you decide to continue, you may be asked to sign a new informed consent form. During the follow-up phase, the doctor may assess the condition of the subjects through telephone calls, outpatient visits, or other means of follow-up.

Estimated Duration of Subject's Participation in the Study
The participation in the study is expected to last for 28 days from the start of enrollment.

4. Potential Benefits of Participation in the Study
Participating in this study may provide timely evaluation of the patient's condition and guide subsequent treatment, although no guarantees can be made. You will not receive any direct financial benefits from this study.

5. Possible Adverse Reactions, Risks, Discomfort, and Inconvenience of Participation in the Study
The dosage of methylene blue used in this study exceeds the routine dosage indicated in

instructions for the treatment of nitrite poisoning. Based on clinical research practices, the dosage used in this study has not increased the occurrence of adverse reactions. However, there may still be adverse reactions such as urine color changes, nausea, vomiting, abdominal pain, skin and mucosal swelling, difficulty breathing, altered consciousness, methemoglobin formation, and impaired organ perfusion.

If you experience any discomfort during the study, or if there are new changes in your condition or any unexpected situations, whether related to the study or not, you should promptly notify the doctor, who will make a judgment and provide appropriate medical treatment.

6. Expenses

The costs of routine tests, such as hemodynamic monitoring and blood tests, conducted during the study will be borne by the subjects according to the hospital's admission procedures. However, the expenses for data collection and analysis will be covered by the hospital.

During the study, the doctor will make every effort to prevent and treat any harm that may arise from the study. If adverse events occur during the clinical trial, the Medical Expert Committee will assess whether they are related to the study. The sponsor will provide appropriate treatment cost reimbursement for damages related to the study according to relevant regulations. If the study involves risks beyond the minimal risk limit, the sponsor will bear the treatment costs directly related to the study-related injury caused by the investigational drug and the study procedures, but will not provide compensation beyond the treatment costs.

7. Confidentiality of Personal Information

Any information and data obtained about the subject's personal information during the research process will be kept strictly confidential. The subject's blood samples will be labeled with a research number/digits instead of their names, and any identifiable information will not be disclosed to members outside the research team without your permission. Any public reports related to the study results will not disclose your personal identity. We will make every effort to protect the privacy of your personal medical information within the limits permitted by law.

8. Use, Storage, and Disposal of Biological Samples

The biological samples designed for this study are blood samples. After collecting the samples specified in the clinical trial protocol, each sample will be given a unique de-identification number. After collection, the samples will be stored in containers at 4°C within half an hour, transported to the laboratory for centrifugation and processing, and the plasma will be placed in a -80°C ultra-low temperature freezer. If sample shipment is required, it should be transported under conditions specified by relevant biosafety management regulations at 4°C. During the use of biological samples, the samples will be tested after blinding. All collected samples will only be used for the detection of cytokines and other chemical substances related to this research protocol and will not be used for other studies. After the completion of the clinical trial, the remaining samples and their derivatives will be disposed of in accordance with national biosafety regulations (high-pressure sterilization or incineration).

9. Explanation of Potential Conflict of Interest of the Investigator

The investigators of this study do not hold equity in companies related to the research project, nor have they received any compensation in any form from the companies producing the research drug. Among the companies involved in the research drug, they do not hold any management positions or serve as spokespersons, nor have they received significant amounts of compensation such as service fees, consulting fees, advisory fees, transportation allowances, or other financial remuneration from the companies related to the research drug within the past or future 2 years. No other financial conflicts of interest have arisen in this study.

10. How to Obtain More Information?

You can ask questions about this study at any time and receive corresponding answers. If any significant new information arises during the research process that may affect your willingness to continue participating in the study, your doctor will promptly notify you.

11. Voluntary Participation in the Study and Withdrawal from the Study

Whether or not to participate in the study is entirely up to you. You can refuse to participate in this study or withdraw from the study at any time, without experiencing discrimination or retaliation, and without affecting your medical treatment or other interests.

For the sake of your best interests, the doctor or researcher may suspend your participation in the study at any time if they deem it necessary.

12. What to Do Now?

Whether or not to participate in this study is your decision (and your family's decision). Before making a decision, please ask your doctor as many questions as possible.

Thank you for reading this information. If you decide to participate in this study, please inform your doctor, who will arrange everything related to the study for you. Please keep a copy of this document.

Informed Consent Form - Signature Page

Clinical Research Project Name: Multicenter, Randomized, Placebo-Controlled Clinical Trial to Evaluate the Effectiveness and Safety of Methylene Blue in the Treatment of Refractory Septic Shock

Responsible Unit: General Hospital of Southern Theater Command

Collaborating Units: Zhanjiang Central People's Hospital, Jiangmen Central Hospital, Zhujiang River Hospital, Shenzhen Second People's Hospital

Consent Statement:
I have read the information provided above about this study, and I have had the opportunity to discuss and ask questions about this study with the doctor. All the questions I asked have been satisfactorily answered.

I understand the risks and benefits associated with participating in this study. I understand that my participation is voluntary, and I confirm that I have had sufficient time to consider it. I understand the following:

I can consult the doctor for more information at any time.
I can withdraw from this study at any time without facing discrimination or retaliation, and it will not affect my medical treatment or rights.
I also understand that if I withdraw from the study, especially due to drug-related reasons, it would be beneficial for the study if I inform the doctor about changes in my condition, undergo the appropriate physical and laboratory examinations, and complete them.

If I need any other medication treatment due to changes in my condition, I will seek the doctor's advice in advance or truthfully inform the doctor afterward.

I agree that the Drug Supervision and Administration Department's Ethics Committee or the sponsor's representative may access my research data.

I will receive a signed and dated copy of the informed consent form.

Finally, I have decided to participate in this study, and I promise to follow medical advice to the best of my ability.

Patient's Signature:
Date:

Family Member's Signature (if applicable):
Relationship to Patient:
Date:

Contact Phone Number:

I confirm that I have explained the details of this trial to the patient, including their rights, potential benefits, and risks. I have provided the patient with a signed copy of the informed consent form.

Doctor's Signature:
Date:
Doctor's Work Phone Number: