

## **Early Versus Delayed Central Line Placement in Patients with Severe Sepsis and Septic Shock**

### **A. Study Purpose and Rationale**

In patients with severe sepsis and septic shock, Early Goal Directed Therapy (EGDT) has been the mainstay of management. Along with other treatment measures including broad spectrum antibiotics, EGDT attempts to stabilize the septic patient with 3 goals: resuscitating volume using fluids, improving tissue perfusion using vasopressors, and improving oxygen delivery with transfusions and dobutamine. Under current standard of care, the first step is volume resuscitation to a goal of central venous pressure (CVP) of 8-12 mmHg and the second is to administer vasopressors for a goal of mean arterial pressure (MAP) of over 65 mmHg [1]. While this approach has been shown to reduce sepsis mortality, many questions remain unanswered including the optimal CVP, the optimal timing for initiation of vasopressors, and optimal biomarkers for tissue perfusion. Furthermore, the measurement of CVP and administration of vasopressors requires the insertion of a central venous catheter, which carries the risks of bleeding/mechanical trauma (5-19%), infection (5-26%), and thrombus formation (2-26%) [2].

In the past decade, several technologies allow new modalities of assessing volume status, including ultrasound imaging of vena caval collapse and estimation of CVP using ultrasound compression tonography of a peripheral vein. Of these, the estimation of CVP using ultrasound compression tonography has been studied in healthy and ICU populations, and has shown strong correlation with CVP measured by central venous catheter [3, 4].

The purpose of this study is to investigate whether resuscitating fluid to a goal of CVP 8-12 mmHg measured non-invasively prior to the placement of a central venous catheter will decrease the number of central catheters placed and the number of complications of central venous catheters in septic shock patients.

### **Review of Literature**

Treatment of severe sepsis and septic shock is complex and involves multiple simultaneous interventions described as a bundle by the Surviving Sepsis Campaign, with the EGDT as a key component, and this has been shown to reduce mortality in patients with septic shock. However, EGDT is resource intensive, and the relative contributions of individual components of EGDT are poorly characterized [5, 6]. Thus far, no randomized control trial (RCT) or prospective study has investigated the optimal target for fluid resuscitation, though the current standard is a CVP of 8-12 mmHg and MAP of 65 mmHg. Prior to 2010, the standard goal of therapy for tissue oxygenation has been a target mixed venous oxygen saturation of 70% or higher, but recently, Jones et al has recently shown that measurement of "lactate clearance" of 10% or higher is a non-inferior biomarker for tissue perfusion and treatment target for packed red blood cell (pRBC) transfusion and dobutamine administration.

Thus far, all RCTs evaluating targets for treatment in the EGDT protocol immediately insert central venous catheters and measure CVP for patients who fulfill inclusion criteria, defined by systolic blood pressure of less than 90 mmHg and at least two systemic inflammatory response syndrome (SIRS) criteria after fluid challenge of 20-30 ml/kg or blood lactate of 4 mmol/L or more [1, 7]. No prospective trial has investigated whether delay of central venous catheter insertion or vasopressor administration affects mortality or outcomes. Over the past few years, new technologies have been developed for the purpose of estimating CVP non-invasively. Among the best described is measurement of CVP using compression ultrasonography, which

involves using an ultrasound probe and pressure manometer simultaneously to measure the pressure needed to compress a peripheral vein. In two studies, CVP estimated using these measurements have been shown to correlate strongly with CVP measured by central venous catheter in both healthy and ICU patients, though not specifically in patients with septic shock (about 25% of patients in both studies) [3, 4]. Using this technology, it is possible to estimate the CVP during volume resuscitation prior to placement of a central venous catheter, and therefore, in patients with adequate peripheral intravenous access with hypotension unresponsive to initial fluid resuscitation, physicians can gauge whether more fluid should be administered. Furthermore, it has been long known that individual measurements of CVP are not as useful in gauging volume resuscitation as the trend in serial measurements of CVP, and this technology facilitates these measurements in a non-invasive manner [8].

## **B. Study Design and Statistical Procedures**

The proposed trial will be based on the previous RCTs that investigated management of severe sepsis and septic shock {Jones, 2010 #12; Rivers, 2001 #1}. This will be a single center trial involving a tertiary care hospital in which patients who present to the emergency room with severe sepsis and septic shock will be recruited (definitions are based on those established by Rivers et al., see Study Design section below). After inclusion and exclusion, patients will be randomized to either immediate central venous catheter placement versus initial measurement of CVP using compression ultrasonography followed by fluid resuscitation, and delay of central venous catheter placement until a goal CVP of 8 mmHg is reached if the patient is still unresponsive to fluids.

### Hypothesis

For patients with severe sepsis and septic shock, using peripheral IV access for fluid resuscitation guided by non-invasive CVP measurements will decrease the number of central venous catheters placed and the number of complications of placing and maintaining central venous catheters by 10% at time of discharge from the hospital.

### Methods

#### 1. Conceptual and Operational Definitions:

The primary study outcome will be the number of central venous catheters placed. Secondary outcome will be the number of bleeding, infectious, and thrombotic complications attributed to central venous catheter placement (as agreed upon by two attending physicians), mortality at time of discharge, 28 days, and 3 months, and resuscitation end points, organ-dysfunction scores, coagulation-related variables, administered treatments, and the consumption of health care resources.

#### 2. Study Design

The study will be a longitudinal, prospective, un-blinded, parallel-arm, single-center, intention to treat, RCT, in a tertiary care center. Study subjects will include patients aged 18 and older with septic shock or severe sepsis defined by the criteria used in the EGDT and lactate clearance studies [1, 7]. That is, patients must fulfill of two of four criteria for SIRS and a systolic blood pressure no higher than 90 mm Hg after a fluid challenge of 20 to 30 ml per kg of body weight over a 30-minute period or a blood lactate concentration of 4 mmol/L or more). The criteria for exclusion are pregnancy, or presence of an acute cerebral vascular event, acute coronary

syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias as a primary diagnosis, contraindication to central venous catheterization, known upper extremity thrombosis, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate (DNR) status, or advanced directives restricting implementation of this protocol.

Afterwards, patients will have their CVP assessed by compression ultrasonography, but the results will be blinded from all participants in the study. Patients will be excluded from the study if they have no visible or no compressible peripheral veins.

After inclusion and exclusion, the patients will be randomized into two groups: those who will have a central venous catheter placed immediately in order to obtain CVP measurements invasively (the control group) and those who will have their CVP measured non-invasively using compression ultrasonography without insertion of central venous catheter (non-invasive group). In both groups, the patients' temperature, heart rate, urine output, and blood pressure, will be continuously monitored during the first 6 hours of treatment, and then every 8 hours for 72 hours. Arterial and venous blood gas values, lactate concentrations, PT/INR and PTT, and variables required for calculation of the Acute Physiology and Chronic Health Evaluation (APACHE II) score and the Multiple Organ Dysfunction Score will be obtained at baseline and at 3, 6, 12, 24, 36, 48, 60, and 72 hours.

In the control group, CVP will be measured continuously for the first 6 hours of treatment, and then every 8 hours for 72 hours, and management will be per EGDT with lactate clearance as a target for pRBC transfusion and dobutamine administration [7]. In the non-invasive group, the CVP will be re-assessed every 30 minutes for the first 6 hours, or after each 15 mg/kg of fluid administered and the patients will be volume resuscitated to a target CVP of 8 mmHg or greater. Upon achieving the target CVP, the blood pressure will be re-assessed. If the patient remains with MAP < 65 mmHg, then the patient will have a central venous catheter inserted and treatment will be per EGDT with lactate clearance as a marker for tissue oxygenation. After initial volume resuscitation, in patients in which a central venous catheter was not inserted, CVP will continue to be monitored every 8 hours and blood pressures check as previously described. At any point, if MAP < 65 mmHg, fluids will be administered to achieve a CVP of 8 mmHg or more, and if MAP remains < 65 mmHg, a central venous catheter will be inserted for administration of vasopressors, and the patient will be managed per with lactate clearance as a target for pRBC and dobutamine administration [7].

Estimating the number of central lines avoided is difficult, but we will set a smallest difference of clinical interest at a 10% decrease in number of central venous catheters needed. We will perform a sample size analysis using this assumption of 10% proportional decrease (100% versus 90%) and an alpha set at 0.05 and beta set at 0.2. Using chi square testing, this equates to an n=94 study participants in each study group.

### **C. Study procedures:**

#### Central Venous Catheter Placement

In the patients who qualify for central venous catheter placement (as described above), these devices will be placed in the internal jugular or subclavian veins using sterile technique and ultrasound guidance.

#### Compression Ultrasonography

Ultrasound imaging will be performed by experienced research investigators who will use an ultrasound device with an attached pressure manometer (see medical devices). After applying ultrasound transmission gel, the transducer with pressure meter will be placed on the skin with minimal pressure over a peripheral vein. After zero adjustment, slowly increasing pressure will be applied by the transducer until complete compression of the vein is achieved. The pressure at the collapse point corresponds to the venous pressure.

#### **D. Study Drugs:**

Please see the description for use of medications in the prior studies of severe sepsis and septic shock [1, 7]:

Dopamine

Norepinephrine

Dobutamine

#### **E. Medical Devices:**

##### Compression Ultrasound System

HDI 5000 duplex device (Philips, Best, the Netherlands) with a 5- to 12-MHz transducer (SonoCT, XRes, Philips). A pressure manometer (PPM0310, Baumann, Muensingen, Switzerland) is attached to the transducer. The manometer consists of a translucent silicon membrane (MVQ, Angst and Pfister AG, Zurich, Switzerland) connected to a pressure meter (Bourdon Haenni AG, Jegenstorf, Switzerland) with flexible pressure tubing.

#### **F. Study Questionnaires:**

N/A

#### **G. Study Subjects:**

As described above, the study subjects will include patients aged 18 and older who present to the emergency room with two of four criteria for SIRS and a systolic blood pressure no higher than 90 mm Hg after a fluid challenge of 20 to 30 ml per kg of body weight over a 30-minute period or a blood lactate concentration of 4 mmol/L or more.

The criteria for exclusion are presence of an acute cerebral vascular event, acute coronary syndrome, acute pulmonary edema, status asthmaticus, cardiac dysrhythmias as a primary diagnosis, contraindication to central venous catheterization, known upper extremity thrombosis, no visible or no compressible peripheral veins on ultrasonography, or extremely thin (less than 0.5 mm diameter) superficial veins, active gastrointestinal hemorrhage, seizure, drug overdose, burn injury, trauma, a requirement for immediate surgery, uncured cancer (during chemotherapy), immunosuppression (because of organ transplantation or systemic disease), do-not-resuscitate (DNR) status, or advanced directives restricting implementation of this protocol.

#### **H. Recruitment of Subjects:**

As mentioned above, study subjects who qualify will be recruited from those who present to the emergency department of a tertiary care hospital. The patient's physician in charge in the emergency department will then ask the consenting family member for their willingness to speak with a study representative.

**I. Confidentiality of Study Data:**

To ensure confidentiality, data will be associated with an individual participant only by an assigned identification number, the code for which will be kept in a single electronic file. This electronic file will be stored on a secure server and be password protected. Study staff are assigned a user ID and password to assess the server. Only the PI and study personnel listed on this protocol will have access to the file password. All hardcopy data will be stored in a separate locked, secure facility. Names will not be stored with data. The Principal Investigator will be responsible for ensuring that the confidentiality of the data is maintained at all times. These data will be obtained specifically for research purpose

**J. Potential Conflict of Interest:**

None

**K. Location of Study:**

Studies will be conducted entirely within the emergency department, hospital wards, and intensive care units of a tertiary care hospital.

**L. Potential Risks:**

All study subjects will be severely ill patients and thus the risk of death and complications will be extremely high. Furthermore, while there is no evidence that delayed insertion of central venous catheters and delayed administration of vasopressors affect mortality, other complications can occur. These include device failure of the compression ultrasound machine and a more emergent or dangerous insertion of the central venous catheter due to time constraints if the patient fails to respond to volume resuscitation.

**M. Potential Benefits:**

As described above, the study can reduce the number of central venous catheters placed and therefore the complications associated with placement and maintenance of these devices, including bleeding, infection, and thrombosis.

**N. Alternative Therapies:**

N/A

**O. Compensation to Subjects:**

none

**P. Costs to Subjects:**

none

**Q. Minors as Research Subjects:**

N/A

**R. Radiation or Radioactive Substances:**

N/A

## References

1. Rivers, E., et al., *Early goal-directed therapy in the treatment of severe sepsis and septic shock*. N Engl J Med, 2001. **345**(19): p. 1368-77.
2. McGee, D.C. and M.K. Gould, *Preventing complications of central venous catheterization*. N Engl J Med, 2003. **348**(12): p. 1123-33.
3. Thalhammer, C., et al., *Noninvasive central venous pressure measurement by controlled compression sonography at the forearm*. J Am Coll Cardiol, 2007. **50**(16): p. 1584-9.
4. Thalhammer, C., et al., *Non-invasive central venous pressure measurement by compression ultrasound--a step into real life*. Resuscitation, 2009. **80**(10): p. 1130-6.
5. Lewis, R.J., *Disassembling goal-directed therapy for sepsis: a first step*. JAMA, 2010. **303**(8): p. 777-9.
6. Delaney, A., et al., *Bench-to-bedside review: the evaluation of complex interventions in critical care*. Crit Care, 2008. **12**(2): p. 210.
7. Jones, A.E., et al., *Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial*. JAMA, 2010. **303**(8): p. 739-46.
8. Wilson, J.N., et al., *Central venous pressure in optimal blood volume maintenance*. Arch Surg, 1962. **85**: p. 563-78.