The effect of dobutamine on mortality in septic patients with troponin elevations in the absence of EKG changes: A randomized, controlled prospective study.

Shanti Nulu, MD

A. Study Purpose and Rationale

Sepsis, defined as the presence of a systemic inflammatory response syndrome (SIRS) in response to culture-proven infection, is a critical illness that is responsible for over 200,000 deaths per year in the United States.[1] Severe sepsis is often accompanied by shock, characterized by a hypercirculatory hemodynamics with decreased systemic vascular resistance and an increased cardiac index. However, approximately 50% of patients with septic shock have some form of impairment of left ventricular systolic function.[2-4] This has clinical significance for the optimal management of these patients, for example with regard to the choice of vasoactive agent, as well as implications for prognosis.

Several studies have demonstrated a depressed left ventricular ejection fraction (LVEF) of <50% in approximately 50% of patients with severe sepsis.[2-4] Furthermore, one study using transesophageal echocardiography and invasive monitoring to assess systolic and diastolic function revealed that a depressed LVEF was associated with a worse prognosis.[4]

As the use of an invasive PA catheter for hemodynamic monitoring is without survival benefit and thus is often not performed, direct measurement of cardiac function is not always possible. Cardiac troponins, the regulatory proteins of the thin actin filaments of cardiac muscle, are biomarkers for myocardial injury that are elevated in patients with myocardial ischemia. Although it is most often used in diagnosis and risk stratification in patients with acute coronary, it is also found to be elevated in conditions causing myocardial ischemia other than coronary artery disease, including renal failure, pulmonary embolism, trauma, and sepsis.

Several studies have shown that a significant proportion of critically ill patients have troponin elevations, reporting the prevalence of troponin elevations among unspecified critically ill patients as 15-25%. [5-7]In addition, mortality among troponin-positive patients was higher compared to troponin-negative patients, regardless of the cause of troponin.[5] Patients with troponin elevations were more likely to be hypotensive, required more vasoactive agents, were more likely to receive mechanical ventilation, and had longer stays in the ICU. [5]

Several studies have reported a relationship between elevated cTnI and left ventricular dysfunction assessed by echocardiography or PA catheter . [8-10] For

example, Fernandes et al. showed that in a series of 10 patients with sepsis, all patients with LVEF <50% had elevations in cardiac troponin levels.[8] A larger study by Ver Else et al showed by 78% of patients with positive troponins had LV dysfunction as opposed to only 9% of troponin negative patients (p,0.0001).[10] In addition, the duration of hypotension and the maximal number of vasopressor doses administered were found to correlate to troponin levels. In addition, troponin elevations are associated with severity scores such as the APACHEII score.

While we understand that troponin elevations are associated with overall severity of illness as well as prognosis in sepsis, there is no evidence that any particular therapy that is targeted at improving or reversing cardiac depression is of benefit. It is often up to the discretion of the intensivist's clinical judgment to pursue therapeutic options for the potential cardiogenic etiologies of persistent hypotension in septic shock.

In early goal directed therapy, which is currently the standard of care, early central access is used in order to initiate aggressive therapy with goals of fluid rescuscitation until CVP>12, vasoactive agents to keep mean arterial pressure (MAP) >65 and blood transfusions and inotropic agents for mixed venous oxygen saturation (SvO2 <70%) and hematocrit < 30.[11]

In light of the evidence that troponin elevations among septic patients is associated with a poorer prognosis, further investigation is needed to evaluate the efficacy of additional interventions targeted at improving cardiac function in the hopes of also improving prognosis. Dobutamine is an inotropic agent that is used commonly in the critical care setting to improve cardiac contractility and function. This study proposes to investigate the therapeutic benefit of the addition of dobutamine for troponin-positive septic patients.

B. Study design and Statistical Analysis

This study will be conducted as a prospective, randomized controlled study of patients with a new diagnosis of sepsis who also have been found to have elevations in troponin I in the absence of EKG changes, comparing the use of an inotrope, dobutamine, versus standard early goal directed therapy for shock, with primary outcome measured of overall mortality. As the mortality from septic shock is related to severity of illness, patients will be stratified prior to randomization based on APACHE II scores. The Acute Physiologic and Chronic Health Evaluation scoring system is a scoring system used to predict severity of illness and prognosis, and is based on 12 routine physiologic measurements, including vital signs, electrolyte values, presence of chronic medical conditions, hematocrit, renal function, and others. There will be 4 different strata in which

patients can be randomized based on APACHE II scoring, which are to be determined.

Chi squared analysis revealed that 414 subjects must be enrolled in this study to detect a 10% difference in mortality.

The primary outcome to be measured is in-hospital mortality. Secondary outcomes measured include length of ICU stay, number and duration of vasopressor agents, requirement of mechanical ventilation, duration of hypotension, evidence of end-organ damage including low urine output, acute kidney disease, and liver function test abnormalities.

C. Study Procedure

Patients admitted the MICU service at CUMC with a new diagnosis of sepsis will be referred by the admitting physician for consideration for study participation. Consent for study participation will be obtained on initial evaluation. All potential study patients will be initiated on standard therapy for sepsis, i.e. with early goal directed therapy. All patients will have serial troponin levels checked every 8 hours within the first 24 hours as well as an admission electrocardiogram and admission APACHE II scores will be computed for all patients. Patients with a new diagnosis of sepsis who also have elevations in troponin I in the absence of EKG changes , and who, after initiation of early goal-directed therapy, have a CVP >8-12 with fluid resuscitation and a mean arterial pressure (MAP) <65 (thus requiring vasopressor support) will be referred for the study. Patients will be randomized in a stratified fashion based on their admission APACHE II score to the interventional versus control arms of the study. If a patient is randomized to a the control arm, the patient will continue to receive standard therapy with no further intervention, which entails early goal directed therapy, and vasopressor choice that will be determined by the intensivist based on clinical context. Dobutamine may or may not be utilized based on the mixed oxygen venous saturation of the patient (is started if mixed venous oxygen saturation remains <70% per protocol). If the patient is randomized to the interventional arm, they will receive inotropic therapy with dobutamine along with other vasopressor support. The initial dose of dobutamine used is 2.5 ug/kg/min, and uptitration of dobutamine at 2.5 ug/kg/min every 30 minutes will be performed if mixed venous oxygen saturation is <70%. As dobutamine is known to cause hypotension in some patients, a second vasopressor (typically norepinephrine, but left to the clinical judgment of the intensivist) is initiated for persistent MAP<65. Duration of inotropic therapy will vary dependent upon the clinical picture of the patient but is discontinued for heart rate >120 or persistent hypotension below set MAP goals despite the use of a second vasoactive agent.

D. Study Drugs

Dobutamine is a positive inotropic agent that is used for left ventricular dysfunction. It acts on beta-1 adrenergic cardiac receptors, improving contractility and heart rate.

E. Medical Devices
N/A

F. Study Questionnaires
N/A

G. Study Subjects

Inclusion criteria:

- new diagnosis of sepsis
- age >18
- troponin I elevation within the first 24 hours (at least 1 out of 3 q8H tests positive)
- patients being treated with early goal directed therapy
- CVP >12 and MAP<65 (thus requiring vasopressor support)

Exclusion criteria

- absence of new electrocardiographic changes as compared to a previous electrocardiogram (ECG), or if previous ECG is not available, the absence of any EKG findings suggestive of myocardial infarction (such as ST changes).
- recent MI within the past 30 days
- atrial fibrillation
- ventricular arrhythmias
- severe aortic stenosis

This study is not limited by age, gender, race, ethnicity, or socio-economic status. In addition, no restrictions are placed on the etiology or source of sepsis as well as the pre-existing or chronic conditions of study patients.

H. Recruitment of Subjects

Patients with an admission diagnosis of sepsis to the MICU service at CUMC hospital will be referred by the admitting physician to the study. On admission,

consent for the study will be obtained for all potential study patients (all septic patients without the above exclusionary criteria). If potential patients meet the above inclusion criteria (including the CVP And MAP numerical criteria), they will then be randomized based on admission APACHE II score and enrolled in the study.

I. Confidentiality of Subjects

Patients will be initially referred to the study by name, medical record number, and date of birth. Then, once enrolled, they will be de-identified with each patient received a unique study identifier number. All data will be stored in a secure location and password protected. All materials containing identifying information will be discarded after the study identifying number is issued.

J. Potential Conflict of Interest

The investigators have no proprietary interest in any drug under investigation in this study and they will not benefit financially in any way from the results of this investigation.

K. Location of the Study

The study will be performed within the MICU of the CUMC

L. Potential Risks

The major risks associated with this study are related to the possible adverse effects of dobutamine, which include cardiac arrythmias, hypotension, tachycardia.

M. Potential Benefits

The potential benefit to patients enrolled in the interventional arm is a potential improvement in mortality in the face of critical illness as well as improved end-organ perfusion and cardiac function.

N. Alternative Therapies

The alternative therapy available to patients is to not enroll in the study and receive routine standard of care of sepsis, which entails early goal directed therapy.

O. Compensation of Subjects

No compensation will be provided to study participants.

P. Costs to Subjects

The subjects will not incur any further hospital-related costs due to being enrolled in the study.

Q. Minors as Research Subjects

N/A

R. Radiation and Radioactive Substances
N/A

S. References

1. Angus DC et al. Edipdemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29: 1303-1310

2. Parker MM et al. Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 1984; 100: 483-490.

3. Ognibene FP et al. Depressed left ventricular performance. Response to volume infusion in patients with sepsis and septic shock. Chest 1988; 93:903-910.

4. Poelaert J et al. Left ventricular systolic and diastolic function in septic shock. Intensive Care Med 1997; 23:553-560.

5. Guest TM et al. Myocardial injury in ritically ill patients : a frequently unrecognized complication. JAMA 1995; 273: 1945-1949/

6. Kollef MH. Clinically reognize cardiac dysfunction: an independent determinant of mortality among critically ill patients. Chest 1997; 111: 1340-1347.

7. Wright RS et al. Elevations of cardiac troponin I are associated with increased short-term mortality in noncardiac critically ill emergency department patients. Am J Cardiol 2002; 90:634-636.

8. Fernandes et al, Cardiac troponin: a new serum marker of myocardial injury in sepsis. Intensive Care Med 1999; 25: 1165-1168.\

9. Spies et al Serum cardiac troponin T as a prognosti marker in early sepsis. Chest 1998; 113: 1055-1063.

10. Ver Elst KM et a. Cardiac troponin I and T are biologic markers of left ventricular dysfunction in septic shock. Clin Chem 2000; 46: 650-657.

11. Rivers et al. Early goal directed therapy in the treatment of severe sepsis and septic shock. N Eng J Med 2001; 345: 1368-77

12. Maeder et al. Sepsis-associated myocardial dysfuntion: Diagnostic and Prognostic Imapct of cardiac troponins and natriuretic peptides. Chest 2006; 129: 1349-1364.