Low-Dose Vasopressin in Septic Shock: a randomized controlled clinical trial.

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A. Study Purpose and Rationale:

Despite major advances in therapy, mortality from septic shock remains alarmingly high—often 60-70%[12,3]. Standard of care remains the mainstays of antibiotics and supportive care and one newer modality, activated protein C, targets the presumed inflammatory cascade crucial to the body's response to overwhelming infection and has been shown to have significant survival benefit.[4] Nevertheless, directly treating the hypotension associated with septic shock is still imperative to avoid renal failure, myocardial injury and cerebral anoxia. To date, catecholamines have been the standard pressors of choice, but these can be associated with unwanted parenchymal vasoconstriction, worsening renal failure and distal limb ischemia. Moreover, resistance to catecholamine pressors is a common problem as sepsis progresses.[5]

The pathogenesis of septic shock is not yet fully understood, but the high plasma levels of endogenous vasoconstrictors such as norepinephrine[6] and angiotensin II [7]suggests that the peripheral vasodilation characteristic of septic shock is due to a defect in vascular smooth muscle function. This is due, in part, to activation of ATP-sensitive potassium (K_{ATP}) channels in the plasma membrane of smooth muscle[8] and to increased nitric oxide synthesis in many cell types, including vascular smooth muscle.[5] Recently, it has been observed that there are inappropriately low plasma levels of vasopressin in patients with advanced septic shock, and in a small series, administration of vasopressin markedly increased their arterial pressure.[9] The pressor action was seen at doses that that does not increase arterial pressure in normal subjects,[10]suggesting that the pressor sensitivity to this hormone may be enhanced.

To date there have been only a few small trials of vasopressin in various forms of vasodilatory shock[11] and of these, fewer were randomized or controlled. Endpoints in these trials have been hemodynamic variables (e.g. systemic vascular resistance, cardiac output, mean arterial pressure) as well as norepinephrine requirements. While the results of these studies have been extremely encouraging, no study so far has examined the effect on a large enough group of patients to show whether or not administration of vasopressin affects mortality.

HYPOTHESIS

Low-dose vasopressin is a potent pressor in patients with septic shock and its use in patients already requiring catecholamines improves survival.

B. Study Design:

Design

This is a prospective randomized double-blind controlled study, comparing low-dose vasopressin plus standard therapy with standard therapy alone in patients with septic shock. Patients, ICU nurses and physicians, nor study coordinators will be aware of the treatment groups. Hypotense patients will be initially started on intravenous norepinephrine. If they are still alive at 24 hours, with the norepinephrine still infusing, they will then be randomized to receive a blinded infusion of either vasopressin or an additional infusion of norepinephrine. It is necessary to have another pressor in the control arm to preserve blinding; otherwise, an observed rise in blood pressure after starting vasopressin could indicate the treatment group. The 2nd bag of norepinephrine will be mixed as 12mg in 250cc of 0.9% sodium

chloride solution and the bags of vasopressin will be mixed as 100 units/250cc 0.9% normal saline. They will each be started at 7.5 cc/hr and no increases of the 2nd bag will be permitted. The goal will be to titrate the first infusion (norepinephrine) down or up as needed to maintain an SBP>90 mmHg. If the first infusion is titrated off completely, then the second infusion will be titrated down slowly and, if possible, off completely.

Norepinephrine will be administered by a mechanical intravenous pump and readings will be taken every 15 minutes for 6 hours and then every 30 minutes until the end of the study. Pump readings will be recorded by the ICU nurses and the pressors will be titrated per the usual ICU nursing routine. All patients will have a central venous catheter (either IJ, subclavian, or femoral as the ICU team determines most appropriate), an arterial catheter (either radial or femoral as needed), a foley catheter, EKG monitoring and pulse oximetry monitoring. Vital signs and urine output will be recorded at least hourly. A pulmonary artery (PA) catheter will not be required for this study though the ICU team will be free to place one should they feel it is indicated. Although a PA catheter would be the most accurate way of ensuring inclusion of patients in vasodilatory shock and not those in cardiogenic shock, requiring one in all patients would create unnecessary morbidity and risk for those in whom the diagnosis was clear. In the event of PA catheter placement, cardiac output, systemic vascular resistance and pulmonary capillary wedge pressure will be recorded every hour. Moreover, to ensure adequate volume resuscitation the central venous pressure will be monitored from the central catheter and this will be maintained at 8-12 mmHg, in accordance with recent goal-directed protocols.[12]

Baseline laboratory values will be measured on arrival to the ICU, including complete blood count, serum chemistries, hepatic function panel, serum troponin, arterial blood gas and arterial lactate. Lab tests will then be drawn as frequently as needed according to ICU routine.

Outcomes

Our primary outcome will be 30-day mortality.

A secondary outcome will be percent decrease in norepinephrine requirements from the time of initiation of vasopressin to t = 30 minutes, 1 hour, 6 hours and 24 hours. Requirements will be defined as the rate of infusion (expressed as μg/min) needed to maintain the systolic blood pressure >90 mmHg (If patients are randomized to a second infusion of norepinephrine, these two infusion rates will be added.

Baseline APACHE II scores will also be calculated for each patient (with the worst values taken for the initial 24 hours).

Sample Size

Based on prior studies, the expected mortality from septic shock treated with standard care and norepinephrine as a pressor is approximately 60%.[13] Anticipating an improvement in survival of 20%, we will need approximately 108 patients in each group, totaling 216. Estimating roughly 20 patients with septic shock in the ICU per month, it would take less than one year to recruit enough patients to adequately power the study. However, as most of these patients will likely lack the capacity to consent for participation in the study, we will be limited to patients who already have a designated Health Care Proxy. As this is certainly the minority of patients in the ICU, we can anticipate a much longer recruitment period.

Statistical Analysis:

30-day mortality data will be reviewed using a chi-squared analysis. Mean norepinephrine requirements will be compared using an unpaired *t*-test. Differences will be deemed significant if the p value is <0.05 or if the *t* value exceeds the critical value of 5%.

C. Study Drug:

Vasopressin (synthetic 8-L-arginine vasopressin; PITRESSIN SYNTHETIC; Parke-Davis) is FDA-approved for the use in abdominal roentgenography, diabetes insipidus, and post-operative abdominal distention. For many years, however, it has been widely used for several other off-label indications, including the treatment of bleeding esophageal varices and as first line chemotherapy for ventricular fibrillation or pulseless ventricular tachycardia.[14]

Theoretical side effects of vasopressin infusion are related to its known activity in the coronary and mesenteric vasculature. However, the dose investigated in this study is much lower than known physiologic levels and neither coronary nor mesenteric ischemia has been observed in the few previous trials, and was well tolerated in normal individuals.[15]

D. Study Questionnaire

None.

E. Study Subjects

Patients are eligible if they are ≥18 years old, have septic shock, defined by the American College of Chest Physicians/Society for Critical Care Medicine Consensus Conference on sepsis and organ failure[16] as sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction (oliguria <30 mL/hr, lactic acidosis, and alteration in mental status evaluated without sedative drugs. Sepsis was defined by two or more of the following, temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 breaths/min or the need for mechanical ventilation; and white blood cell count >12,000cells/mm^2 or <4,000 cells/mm^2.

To avoid the inclusion of extremely moribund patients unlikely to survive regardless of treatment, we will require that patients survive at least 24 hours after arrival to the hospital before being included in the study.

Patients will be excluded if they are pregnant, have had a myocardial infarction within 24 hours or have evidence of ongoing myocardial ischemia (defined as new ST elevations in two contiguous leads or recent serum troponin I concentration >2 ng/mL), known decompensated congestive heart failure (high filling pressures, marked pulmonary edema on chest x-ray and cool extremities), suspected stroke within 48 hours or evidence of active mesenteric ischemia.

Each patient will be required to have a designated Health Care Proxy who can give written, informed consent for the patient's participation in the trial.

All patients who present to the Medical Intensive Care Unit at Columbia Presbyterian Medical Center and who meet the above criteria will be eligible for enrollment.

F. Confidentiality

All study data and identifying information will be coded and kept in a locked location, accessible only to study investigators.

G. Location of the Study

The study will take place entirely in the medical and cardiac intensive care units at Columbia Presbyterian Medical Center.

H. Potential Risks

As all patients in the study, regardless of their treatment group will be receiving standard therapy, the presumed risks of participation are only those associated with infusion of vasopressin (see study drug). Reported adverse effects include abdominal cramps, nausea, sweating, perioral pallor, tremor, headache, flatulence, vertigo, vomiting, diarrhea, uterine cramps, rash, fever and urticaria.

I. Potential Benefit

Patients may or may not benefit from participation in the study but we are hoping to show a survival benefit from the addition of vasopressin to standard therapy.

J. Alternative Therapies

The alternative to participating in the study is not participating. All patients will receive standard of care regardless of their treatment group.

K. Compensation

Subjects will not be compensated for their participation in the study.

L. Costs to Subjects

Subjects will not incur any additional costs as a result of participating in the study. The cost of vasopressin infusion and study administration will be covered by the research grant. All standard ICU costs, however, will be the responsibility of the subject.

M. Minors as Research Subjects

No minors will be used as subjects.

N. Radiation or Radioactive Substances

No radiation or radioactive substances other than routine ICU x-rays will be used.

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