Comparison of Norepinephrine and Vasopressin Versus Norepinephrine Alone for Achievement of Hemodynamic Stability in Patients with Septic Shock

Drayton A. Hammond, Pharm.D., MBA, BCPS[1]; Jacob T. Painter, Pharm.D., Ph.D., MBA[1];
Heather J. C. Flowers, Pharm.D. Candidate[1]; Krishna Kakkera, MD[2]; Nikhil Meena, MD, FCCP[2]
UAMS Faculty Advisor: Bill J. Gurley, Ph.D.[1] ACCP MeRIT Program Advisor: Kathleen Stringer, Pharm.D.[3]
[1]University of Arkansas for Medical Sciences College of Pharmacy, [2]University of Arkansas for Medical Sciences College of Medicine, [3]University of Michigan

Background

- Approximately 1.2 million people in the United States experience sepsis each year[1]
- Severe sepsis mortality exceeds 20% despite protocolized care[1-4]
- Current practice is to add vasopressors in a stepwise fashion, increasing the number of vasopressor agents until a mean arterial pressure (MAP) goal is met
- However, delay in or an inability to achieve the target MAP leads to end-organ failure and increased mortality
- Norepinephrine (NE) is the recommended first vasopressor in septic shock, but increased exposure is associated with mortality[1]
- Vasopressin (VP) is an ungraded recommendation as adjuvant therapy to improve systemic perfusion and reduce NE exposure[1]
- When VP has been added to NE within 6 hours of initiating vasopressor therapy, the dose and duration of vasopressors and the frequency of new-onset arrhythmias were reduced[5,6]

Purpose

To prospectively compare the ability of the combination of NE and VP to improve hemodynamic status in patients with septic shock compared with NE alone

Specific Aims

- **Specific Aim #1:** To determine the time to achievement of hemodynamic stability with early initiation of concomitant NE and VP compared with NE alone
- **Specific Aim #2:** To assess the relationship between the amount of fluid resuscitation and illness severity and the time to achievement of hemodynamic stability

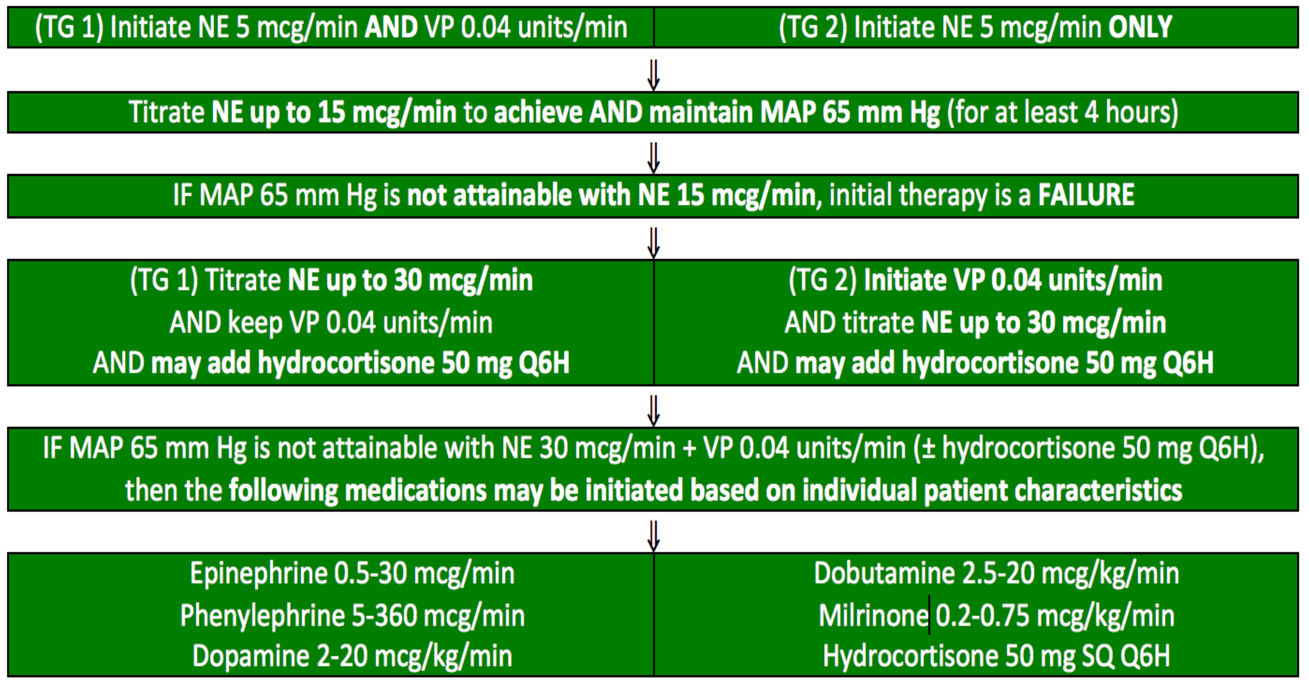
Objectives

- **Primary outcome:** Time to achievement of target MAP (65 mm Hg) for at least 4 hours between VP+NE group or NE alone group
- **Secondary outcome:** Is there a difference between treatment groups in the following:
  - Death from any cause at hospital discharge and 28 days
  - Intensive care unit (ICU) and hospital lengths of stay
  - Development of new-onset arrhythmias
  - Days free from advanced cardiovascular support up to 28 days
  - Days free from advanced respiratory support up to 28 days
  - Days free from advanced renal support up to 28 days
  - Receipt of advanced end-organ support (respiratory, renal)
  - Sequential organ function assessment score at 6 and 72 hours
  - Duration of NE continuous infusion

Clinical Trial Approach

- **Design:** IRB-approved, single-center, prospective, open label trial of patients admitted to University of Arkansas for Medical Sciences Medical Center beginning November 2015
- **Inclusion Criteria:**
  - Age ≥18 years (no maximum age)
  - At least 2 systemic inflammatory response syndrome criteria
  - Clinical suspicion for or confirmation of an infection
  - Admitted or being admitted to the medical ICU
  - MAP ≤50 mm Hg despite adequate intravenous fluid resuscitation (minimum 30 mL/kg within the previous 4 hours)
- **Exclusion Criteria:**
  - End-stage renal or liver disease
  - Not expected to be alive within 48 hours of enrollment
  - Current receipt of an intravenous vasoactive medication
  - Admission from an outside hospital
- **Assignment:** Pre-determined, alternating four-month blocks
  - November 2015 – February 2016: NE alone (group 2)
  - March 2016 – June 2016: NE + VP (group 1)
  - Alternating four-month blocks until enrollment achieved
- **Sample Size Calculation:**
  - Patients in Treatment Group 1 (NE+VP) will achieve goal blood pressure (BP) at 4 hours [standard deviation (SD) 1 hour][6]
  - Patients in Treatment Group 2 (NE alone) will achieve goal BP at 6 hours (SD 3.6 hour)[7]
  - Enrollment of 38 patients per group would detect a 33% reduction in time to goal MAP with 90% power, allowing for a loss to follow-up or withdrawal of 6%
- **Statistical Tests:**
  - Primary outcome: Fisher's exact test
  - Secondary analyses of the primary outcome will include odds ratio with adjustment for Acute Physiology and Chronic Health Evaluation (APACHE) IV score and fluid volume administered
  - Pre-specified subgroup analyses by testing interactions between APACHE IV score and fluid volume administered
  - Secondary outcomes will be analyzed using appropriate regression models to compare the treatment groups using Fisher's exact test for categorical data; Mann-Whitney U for continuous, nonparametric data; and student t-test for continuous, parametric data

Study Procedure



Significance & Innovation

- Recent trials suggest that usual care is as effective as EGDT, which necessitates new research be conducted into each component of EGDT to determine how and to what extent specific therapies are effective[2-4]
- A key aspect in caring for patients with septic shock is using vasopressor medications to achieve hemodynamic stability
  - An *a priori* subgroup analysis of patients in the VASST Trial receiving less than 15 mcg/min of NE in combination with VP showed decreased mortality (26.5% vs. 35.7%, p=0.05)[8]
  - No difference was found in the more severe septic shock subgroup, potentially because VP was initiated when NE rates reached 15 mcg/min (44.0% vs. 42.5%, p=0.76)[8]
- This would be the first randomized trial evaluating concomitant initiation of NE and VP in patients with septic shock

Limitations

- Intermediate outcome (time to achievement of target MAP) is associated with but still a surrogate endpoint for mortality
- Minimal data available to inform estimates for the expected times to target MAP in each treatment group
- Single-center design and month-based enrollment strategy
- No stratification based on pre-enrollment values

References

1. Dellinger RP. *Crit Care Med*. 2013;41(2):580-637.
2. ProCESS Investigators. *N Engl J Med*. 2014;370(18):1683-93.
3. ARISE Investigators. *N Engl J Med*. 2014;371(16):1496-506.
4. Mouncey PR. *N Engl J Med*. 2015;372(14):1301-11.
5. Gordon AC. *Crit Care Med*. 2014;42(6):1325-33.
6. Reardon DP. *J Crit Care*. 2014;29(4):482-5.
7. Trzeciak S. *Chest*. 2006;129(2):225-32.
8. Russell JA. *N Engl J Med*. 2008;358(9):877-87.

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