UAMS EM Journal Club
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Safety and Outcomes Associated with Vasopressin and Norepinephrine Compared to Norepinephrine Monotherapy

Clinical Bottom Line

In episodes of distributive shock requiring vasopressors, it appears that while the addition of vasopressin may be beneficial in instances of shock refractory to maximal catecholamine therapy; there is little evidence that favors early administration of vasopressin in regards to improving patient centered outcomes. Vasopressin should continue to be administered as an adjunct in refractory hypotension as outlined by the Surviving Sepsis Guidelines, however early administration should be done with caution until supported by further evidence.

P : Adult patients in distributive shock
I : Early administration of vasopressin
C : Norepinephrine monotherapy
O : Mortality, LOS, and adverse events

Background

Distributive shock, whether it be secondary to sepsis, cardiothoracic vasoplegia, spinal shock, or anaphylaxis, has a high rate of mortality and morbidity secondary to reduced end organ perfusion. Recent studies have shown that if left uncorrected, the mortality rate approaches 50%[1,2]. In treatment of these patients, when resuscitation with fluids does not improve mean arterial pressures (MAP), vasopressors should be administered per the Surviving Sepsis Guidelines. These guidelines recommend starting a catecholamine based vasopressor in distributive shock, most commonly norepinephrine. In the last decade, there has been more research to investigate if the administration of a secondary vasopressor reduces the amount of catecholamines used and their associated side effects.

Trial 1

Mcintyre, W. F., et al. (2018). Association of Vasopressin Plus Catecholamine Vasopressors vs Catecholamines Alone With Atrial Fibrillation in Patients With Distributive Shock. *Jama*,
319(18), 1889. doi: 10.1001/jama.2018.4528

https://www.ncbi.nlm.nih.gov/pubmed/29801010

Validity Rating

Moderate risk of bias, moderate quality of evidence

The Basics

Researchers conducted a systematic review and meta analysis of 23 randomized controlled trials that included 3088 patients. Various categories of distributive shock were included in the comparison of vasopressin and catecholamines compared to catecholamine monotherapy. An exhaustive search of multiple databases including unpublished data was performed. Rates of atrial fibrillation were the primary outcome investigated with secondary outcomes including; mortality, length of stay, need for renal replacement therapy, myocardial injury, ventricular arrhythmia and stroke.

Exclusion Criteria

- Participants under the age of 18
- Non RCT designs
- Interventions with additional pressors other than vasopressin

Primary Outcomes

- Rates of Atrial Fibrillation

Secondary Outcomes

- Mortality
- Myocardial Infarction
- Renal Replacement Therapy
- Ventricular Arrhythmias
- Stroke
- Length of Stay
- Digital Ischemia
- Acute Kidney Injury

Results

- Reduction in rates of atrial fibrillation with a RR of 0.77 (CI .67-.88), which prevented 68 cases in every 1000, with a NNT of 12.5.
- Mortality: there appeared to be a risk difference but if you break it down to studies with low risk of bias there was loss of statistical significance which indicated an element of fragility in the data.
- Digital ischemia: Statistically significant increased risk and even when high risk bias studies were excluded they still had an increased risk of ischemia. RR, 2.38 [95%CI, 1.37 to 4.12], I2 = 0; RD, 0.02 [95%CI, −0.01 to 0.04]; 24 additional cases per 1000 patients.
- No significant increased in pooled risks for other outcomes.

Limitations and Bias

A majority of studies had wide confidence intervals. The pooled data seen on the forest plot supports a reduction in the incidence of atrial fibrillation, however 40% of the patient population came from two studies which introduces the potential for bias into the data. As discussed above there was an element of fragility in the data when studies with high risks of bias were excluded. A large proportion of studies included were at high risk of bias, which further limits this study. While the methodology was of high quality, the results reiterate what previous studies have hinted at. While the co-administration of vasopressin may reduce some complication rates, there was no significant improvement in patient centered outcomes, and its addition does not go without consequences.

Trial 2

Hammond, Drayton A., et al. "Prospective Open-Label Trial of Early Concomitant Vasopressin and Norepinephrine Therapy versus Initial Norepinephrine Monotherapy in Septic Shock." *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, vol. 38, no. 5, 2018, pp. 531–538., doi:10.1002/phar.2105.

https://www.ncbi.nlm.nih.gov/pubmed/29600824

Validity Rating

High risk of bias; Moderate quality of evidence

The Basics

Researchers conducted a single-center prospective open-label trial on early addition of vasopressin to norepinephrine in patients who met criteria for septic shock. The primary outcome was targeting and maintaining a mean arterial pressure (MAP) of 65 mmHg for 4 hours. Delays in achieving MAP of 65 are thought to be associated with increased morbidity and mortality in septic shock patients.

Exclusion Criteria

- Participants under 18 of age
- Patients meeting < 2 SIRS criteria
- Source of shock not due to sepsis
- Patients with end stage renal disease or end stage hepatic disease
- Patients not expected to live greater than 48 hours in the opinion of the physician
- Patients who received a vasopressor not being studied prior to administration of study vasopressor
- Patients admitted from an outside hospital
- Patients enrolled in another clinical trial

Primary Outcomes

- Time to achieve and maintain a MAP of 65 mmHg for 4 hours

Secondary Outcomes

- Time to addition of secondary vasopressor
- Duration of vasopressor use
- Amount of vasopressor used
- Dose of norepinephrine (NE) at MAP 65 mmHg
- Maximum NE dose
- NE dose >15mcg/min
- Mortality during hospital stay
- Mortality at 28 days
- ICU length of stay
- Hospital length of stay
- New onset of arrhythmias
- Mechanical ventilation (Both requirement and duration)
- Renal replacement (Both requirement and type)

Results

- Time to MAP 65 mmHg was reduced in early concomitant vasopressor and norepinephrine group; though not statistically significant
- Secondary outcomes were not significantly significant between the two groups

Limitations and Bias

Although randomized, the treatment group was assigned by month and therefore was not concealed calling study validity into question. Assignment by month also has limitations given pattern of disease presentation in particular times of the year. Both time to achieve MAP of 65 mmHg and patients requiring mechanical ventilation approach a p value < 0.05 and therefore may show significance if repeated in a higher powered study. The initial rate of vasopressin in this study was 0.04 units/min contrary to the Surviving Sepsis Guidelines of 0.03 units/min and therefore conclusions from this study may have limited ability to be extrapolated to institutions who follow a starting dose of 0.03 units/min .

References

1. Machado FR, Cavalcanti AB, Bozza FA, et al; SPREAD Investigators; Latin American Sepsis Institute Network. The epidemiology of sepsis inBrazilian intensive care units (the Sepsis PrevalenceAssessment Database, SPREAD): an observational study.
2. SepNet Critical Care Trials Group. Incidence of severe sepsis and septic shock in German intensive care units: the prospective, multicentre INSEP study.