Vasopressin use in shock and effect on mortality

H. Hadid, MD, J. Jennings, MD, [*]

Division of Pulmonary and Critical Care Medicine

Henry Ford Hospital

Abstract

Background: Septic shock is a leading cause of mortality in the United States. Hemodynamic support with intravenous vasopressors such as norepinephrine have been associated with reduced mortality. While vasopressin has emerged as an adjunct vasoconstrictor in the treatment of these septic patients, its effect on mortality remains uncertain. In our institution, the routine use of vasopressin was restricted in 2014 due to cost. We hypothesized that decreased access to vasopressin would have no effect on mortality in patients with septic shock.

Methods: Our study included 1253 consecutive patients with septic shock requiring vasopressors who were admitted between 1/1/2014 and 6/29/2016. Of these, 554 were admitted after 1/1/2014 but prior to 9/1/2014, when vasopressin was still widely available (pre-restriction group). The remaining 699 patients were admitted between 9/1/2014 and 6/29/2016, when vasopressin use was restricted (post- restriction group). Patients >18 years of age with admission diagnosis of septic shock requiring at least 5 mcg/min of norepinephrine were included. Regression was used to control for confounders including severity of illness and doses of vasopressors.

Results: 1253 consecutive patients assessed for the study period (pre-group n=554, post-group n=699). Mean norepinephrine levels were lower in the pre-group (58 vs 65 mcg/min respectively, p-value= 0.015) while more patients in the post-group received a secondary agent, epinephrine; (5% vs. 11% respectively, p < 0.001). Unadjusted mortality was higher in the pre-group, compared to the post group, 51% vs 57%, p-value 0.026. However, when adjusting for secondary variables such as the use of phenylephrine and the severity of illness, that is, requiring higher doses of norepinephrine and having higher MPM scores, this mortality difference disappeared (adjusted OR 0.92 [0.70 1.22], p-value 0.574). In other words, our study showed that higher doses of norepinephrine (> 50 mcg/min) and higher admission MPM scores (>35%) predict mortality, despite the access to vasopressin. That is, sicker patients died because they are sicker, regardless of vasopressin restriction in our ICU.

Conclusion: When adjusting for severity of illness, the mortality of patients who were treated for septic shock when vasopressin was widely available in our intensive care unit was no different than those patients who had no easy access to vasopressin. Our study results are consistent with previous trials that did not find a mortality difference with the use of vasopressin

_____

1. Introduction

Septic shock is a leading cause of death in the intensive care unit in the United States 1 2. While norepinephrine is recommended as the initial vasopressor in septic shock3 severe or refractory shock states oftentimes warrant need for additional pressor therapy. Vasopressin, (also known as antidiuretic hormone) is a nonapeptide used as an adjunctive vasopressor in septic shock4. The Vasopressin and Septic Shock Trial (VASST) found no difference in mortality overall when vasopressin was added to norepinephrine in patients with septic shock. However, subgroup analysis suggested that in those patients with less severe shock, the mortality was significantly lower in those patients who received vasopressin.

Because of this discrepancy, our aim was to review outcomes in ICU patients who required vasopressor support. In 1/1/2014, we were faced with a steep increase in the cost of vasopressin at our institution. This, along with the results from VASST, led us to severely limit the access to vasopressin. This change in practice led to a "natural experiment" that allowed us to assess whether limiting the use of vasopressin would impact outcomes in septic shock patients admitted to our intensive care unit. We were interested in assessing whether the decrease in the use of vasopressin would lead to any changes in outcomes for all patients with septic shock of variable severity. .

2. Methods

This is a single center retrospective study conducted in a general teaching hospital with a large ICU-capacity. The data was collected from medical ICU patients admitted to the hospital between 1/1/2014 and 6/29/2016. The study protocol was submitted and approved by the internal review boards prior to data extraction (IRB #12575). An intention-to-treat analysis was used for the primary and secondary outcomes.

Study patients

Patients older than 18 years of age with a primary diagnosis of septic shock and requiring vasopressors were included. Septic shock was defined as refractory hypotension after adequate intravenous fluid resuscitation requiring vasopressor support with at least 5 mcg/min of norepinephrine to maintain a SBP > 90 mmHg. The patients included were either admitted to the medical ICU directly with a clinical diagnosis of septic shock, or transferred to the medical ICU from the general medical floor after developing septic shock. In order to avoid selection bias, all consecutive patients who met the above criteria were selected for data collection. All patients that did not meet the above criteria were excluded.

All patients admitted prior to the restriction of vasopressin use in our institution (9/1/2014) were assigned to the "pre-restriction group"; that is, prior to vasopressin restriction. All patients admitted between 9/1/2014 and 6/29/2016 were assigned to the "post-restriction group". The groups were referred to as Pre-group and Post-group, for short, respectively. Although this was an intention-to-treat study, data on whether the patients in the pre-restriction and post-restriction groups received vasopressin were also collected. We excluded patients who were not on high doses of the first vasopressor. We arbitrarily, and a priori, chose 50 mcg as a maximum dose. The primary outcome was 30 day hospital mortality.

Statistical analysis

Statistical analysis was conducted using STATA software, version 12.0 (Stata Corp, College Station, Texas). A univariate analysis using all recorded variables was performed to obtain unadjusted OR of mortality. A multivariate analysis was performed to adjust for variables and obtain an adjusted OR of mortality. A p-value of < 0.05 was considered clinically significant. The p-value is calculated by ANOVA for numerical covariates; and chi-square test or Fisher's exact for categorical covariates, where appropriate.

Table 1. Patient characteristics

Characteristic	Pre-Group (Vasopressin available) (n=554)	Post-Group (vasopressin restricted) (n=699)	P value
Age (years)	61.8	61.1	
Male, n (%)	299 (54)	394 (56.4)	0.397
African American, n (%)	236 (49.89)	282 (44.41)	0.061
Initial MPM 0 score, median (IQR)*	0.28 (0.13 – 0.63)	0.42 (0.17 – 0.75)	< 0.001
Any pressor, n (%)			
Norepinephrine	554 (100)	699 (100)	--
Vasopressin	162 (29.2)	29 (4.01)	<0.001
Epinephrine	26 (4.7)	74 (10.6)	<0.001
Dopamine	11 (2)	29 (4.2)	0.031
Phenylephrine	81 (14.6)	66 (9.4)	0.005
Glucocorticoids	189 (34.1)	271 (38.8)	0.090
Norepinephrine > 50	242 (41)	349 (59.1)	0.028
Total dose median (IQR)			
Norepinephrine	35 (15-100)	48 (2-15)	0.015
Epinephrine	100 (60-120)	120 (50-120)	0.693
Dopamine	7.5 (6-20)	10 (1-5)	0.854
Phenylephrine	287.5 (100-300)	210 (80-300)	0.537
Mortality, n (%)	282 (50.9)	400 (57.22)	0.026

*MPM 0 – Mortality Probability Model, first hour of ICU admission

In a sub-group analysis, a cut-off MPM of 35%, and norepinephrine dose of 50 mcg/min were used to distinguish the severity of illness. A multivariable analysis was performed to obtain an adjusted OR of mortality in this subset of sicker patients, in comparison to less sick patients.

3. Results

Data were collected on 1253 patients who met the inclusion criteria. Of the 1253 included patients, 554 were assigned to the pre-group group, and the remaining 699 patients were assigned to the post-group. The baseline characteristics of the two groups, demographics, and comorbidities are shown in Table 1. Both groups had similar age, gender, and race distribution. Both groups also had similar distribution of pre-existing conditions and comorbidities including chronic and acute renal failure, cirrhosis, and malignancy.

Severity of illness indices

The median Mortality prediction model (MPM) scores for the pre-group and the post-group were 0.38 and 0.46, respectively (p-value <0.001). The MPM score was statistically different reflecting a sicker patient population in the post-group. Additionally, the average maximum dose of norepinephrine was also higher in the post-group, 65 mcg/min, compared with 58 mcg/min in the pre-group, p-value 0.015, also reflecting the higher severity of illness observed in the post-group. Both of these factors have been adjusted for when analyzing the data to eliminate any factors that may confound the results.

Vasopressin use

In the pre- group, 162 (29 %) of patient received vasopressin, while 29 (4%) of patients in the post-restriction group received vasopressin (p-value <0.001). Severity of illness was higher in the post-restriction (median MPM 0.42 (95% CI 0.17 to 0.75] vs 0.28 [95% CI 0.13 to 0.63]); p <0.001).

Use of other secondary vasopressors

While the number of patients with at least 2 vasopressors was similar in both groups (20.3% and 21.6%, respectively), specific choice of secondary pressors differed significantly. Patients in the post group received more epinephrine (10.6% vs 4.7% respectively, p <0.001) and dopamine (2.2% vs 2%, p =0.031) as a second agent compared to the pre-group. .Conversely, patients in the pre group received more phenylephrine (14.6% vs 9.4%, p = 0.005).

Patients in the post group were more likely to receive norepinephrine doses > 50 mcg (59.1% vs 41%, p =0.28)). Inclusion in the pre-group was itself a significant predictor of epinephrine use (OR 0.46 [0.30 - 0.71], p < 0.001).

The use of stress dose steroids was similar in both groups (34% vs 39%; p-value of 0.09).

Mortality. Overall, 54.4% of patients died. In the post-group, unadjusted mortality was higher in

Table 2. Predictors of Mortality

Variable	Adjusted OR (95% CI)	p
Vasopressin available group	0.92 (0.7 – 1.22)	0.574
Norepinephrine > 50	13.18 (9.94 – 17.47)	<0.001
MPM	3.03 (1.90 – 4.82)	<0.001

comparison to the pre-group (57 vs 50.9%, p-value 0.026). However, OR adjusted for severity of illness

using MPM scores and doses of NE higher than 50 mcg/min, was not significant between groups (OR 0.92 [95% CI 0.70-1.22], p = 0.574). (Table 2)

To look for any predictors of mortality in our groups, a sub-group analysis of restricted cohorts was also performed. Patients who received less than total of 50 of norepinephrine, the crude OR was not a significant predictor of mortality (Crude OR 0.89 [0.64-1.26], p=0.518). Similarly, there was no significance with patients with an MPM < 35% (0.79 [0.58-1.08], p = 0.145. In other words, admission MPM scores of <35% and norepinephrine requirements <50 mcg/min did not have an effect on mortality.

Conversely, patients who required doses of norepinephrine in excess of 50 mcg/min and had an admission MPM score of > 35 %, had a significant increase in mortality, regardless of group assignment.

The median dose of maximal norepinephrine used was higher in patients who died (100 mcg [95% CI 40 – 140] vs 20.1 [95% CI 10 – 30] respectively, p <0.001)

Discussion

The main finding in this study was that in patients in shock, limiting access to vasopressin as an adjunct vasopressor led to higher utilization of other vasopressors, without an effect on mortality.

One explanation for differences in vasopressor selection could conceivably be due to selection bias of the sickest patients. We found that in patients with refractory shock (i.e. doses of norepinephrine > 50 mcg) there was no mortality difference between the groups. We chose 50 mcg to defined refractory shock based on the median dose being 40 . We noted

that those who died had a median of 100 and those that lived had a median of 20. SO we chose 50.

Our study is similar to other studies that looked at vasopressin use in septic shock patients. Most of the other studies, however, also looked at renal failure incidence and other end-organ failure, such as the VANISH5 and the VASST6 trials. Our study is limited in this perspective as we did not look at renal failure days, acute kidney injury incidence, or other end-organ damage. Moreover, our study did not look at length of mechanical ventilation or ICU stay. We chose not to include these potential secondary outcomes as our study was more focused on vasopressin use in relation to mortality in septic shock. Nonetheless, both of our groups had similar baseline demographics, characteristics, and similar rates of baseline organ failure such as CKD and cirrhosis. Our study did not report incidence of adverse events use in either group. Some variables such as baseline blood pressure, lactate values, and mechanical ventilation days were also not reported. We also did not report data on days to shock resolution as reported by many other studies on vasopressin use. For these reasons, a causal effect may not be as clearly defined in our study in comparison to similar studies.

A mortality prediction model (MPM-0) score was used to define the severity of illness in our study. This tool has been validated for assessing mortality in critically ill patients7. We used that as a measurement surrogate for severity of illness.

Norepnephrine dosing of 5 mcg/min was chosen based on prior studies that had designed their inclusion criteria using this value. "High" doses of

norepinephrine of 50 mcg/min were also chosen for similar reasons.

It is conceivable that if vasopressin was not an easily accessible vasopressor, clinicians would resort to other alternative vasopressors. It is not surprising that our study showed that patients in the post group had higher rates of epinephrine, dopamine, and phenylephrine usage as an adjunct to norepinephrine. The need to use multiple pressors indicates higher severity of illness, which was adjusted for in our study.

It was also noted that norepinephrine dosage was higher in patients in the post group. This could reflect a higher severity of illness in the post group, which is also reflected in the higher predicted MPM calculated for this group of patients. However, it is also possible that the dose of norepinephrine was higher in post-group given restriction to vasopressin in this population. This could be concordant with other studies that showed lesser use of norepinephrine and higher rates of shock resolution in patients on vasopressin. It is however, unclear to us why norepinephrine dosage was higher in this group of patients given the design of our study, and a causal relationship is difficult to establish. In any case, regardless of this observation, our study did not reveal a mortality difference between the groups.

Conclusion:

When access to vasopressin was restricted, patients received higher doses of NE, epinephrine

and dopamine. Despite this, there was no difference in mortality between the groups. In contrast to the post-hoc analysis in the VASST trial, mortality remained non-significant regardless of the severity of illness. Our study results are consistent with previous trials that did not find a mortality difference with the use of vasopressin.

References

1. Bauer M, Gerlach H, Vogelmann T, et al. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019- results from a systematic review and meta-analysis. Crit Care 2020;24(1):239. doi: 10.1186/s13054-020-02950-2 [published Online First: 2020/05/21]

2. Rhee C, Dantes R, Epstein L, et al. Incidence and Trends of Sepsis in US Hospitals Using Clinical vs Claims Data, 2009-2014. JAMA 2017;318(13):1241-49. doi: 10.1001/jama.2017.13836 [published Online First: 2017/09/14]

3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013;41(2):580-637. doi: 10.1097/CCM.0b013e31827e83af [published Online First: 2013/01/29]

4. Nagendran M, Russell JA, Walley KR, et al. Vasopressin in septic shock: an individual patient data meta-analysis of randomised controlled trials. Intensive Care Med 2019;45(6):844-55. doi: 10.1007/s00134-019-05620-2 [published Online First: 2019/05/08]

5. Castella X, Gilabert J, Torner F, et al. Mortality prediction models in intensive care: acute physiology and chronic health evaluation II and mortality prediction model compared. Crit Care Med 1991;19(2):191-7. doi: 10.1097/00003246-199102000-00014 [published Online First: 1991/02/01]