12-7-2020

Evaluating the association between vasopressin use and in-hospital mortality in patients with septic shock

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Background

- Treatment of septic shock consists of immediate administration of intravenous fluids and empiric, broad-spectrum antibiotics. Vasoactive therapies are indicated if the patient remains hypotensive despite fluid resuscitation[1]
- The Surviving Sepsis Campaign recommends norepinephrine as the first-line vasopressor in patients with septic shock to maintain a mean arterial pressure (MAP) of at least 65 mmHg. A weak recommendation is made to use vasopressin as an adjuvant therapy to raise MAP to goal or reduce the norepinephrine rate required[1]
- The VASST trial showed no significant difference in 28-day or 90-day mortality with the addition of vasopressin to norepinephrine and open-label vasopressors in patients with septic shock[2]
- A sub-group analysis of the VASST trial evaluated vasopressin use in less-severe and severe septic shock[2]
  - Statistically significant difference in 28-day and 90-day mortality in favor of vasopressin for patients with less-severe septic shock
  - No statistically significant difference in 28-day and 90-day mortality for patients with severe septic shock
- The VANISH trial showed a lack of intensive care unit (ICU), in-hospital, and 28-day mortality benefit associated with vasopressin[3]
- Smaller-scale studies have failed to show mortality benefit associated with vasopressin use in patients with septic shock[4-7]
- Vasopressin was rebranded in 2015 resulting in a 1138% price increase[8]. As a result, optimization of vasopressin use has been prioritized

Objectives

- Determine the impact of vasopressin on the incidence of in-hospital mortality in patients on low-dose vasopressors
- Determine the impact of vasopressin on the incidence of in-hospital mortality in patients on high-dose vasopressors
- Establish the foundation for the development of a pharmacist-driven protocol to aid in the optimization of vasopressin use for patients in septic shock

Methods

- Study design: IRB-exempt, single-center, retrospective chart review of patients treated with vasopressors and diagnosed with septic shock between January 2018 and September 2018
- Study groups: Patients divided into two arms based on the maximum norepinephrine equivalent (NE) dose or the NE dose at the time of vasopressin initiation. Patients who received vasopressin were compared to those who did not receive vasopressin within each arm
  - Low-dose vasopressors (≤ 0.2 mcg/kg/minute NE)
  - High-dose vasopressors (> 0.2 mcg/kg/minute NE)
- Inclusion criteria: Individuals ≥ 18 years old with a diagnosis of septic shock documented in the medical record requiring vasoactive therapies
- Exclusion criteria: Pregnant patients, patients with documented cardiogenic shock in the medical record, patients with cardio-thoracic surgery during the specific admission, patients on vasopressors for less than 12 hours total
- Primary outcome: In-hospital mortality
- Secondary outcomes: Total time on vasopressors (hours); maximum number of catecholamine agents required; ICU length of stay (days); hospital length of stay (days)

Low-dose vasopressor arm (≤ 0.2 mcg/kg/minute)

Baseline characteristics

Characteristics	No vasopressin (n=35)	Vasopressin (n=20)	p-value
Age - years	70.7± 13.7	63.7 ± 18.7	0.12
Male sex – no (%)	23 (65.7)	11 (55)	0.43
APACHE II score	18.1 ± 5.8	18.1 ± 7.0	1.00
SOFA score	5.1 ± 2.2	5.6 ± 2.6	0.45
Lactic acid - mg/dL	3.0 ± 1.9	3.2 ± 2.6	0.74
MAP - mmHg	65.3 ± 12.0	63.7 ± 8.8	0.60
NE – mcg/kg/min	10.4 ± 5.4	10.6 ± 7.8	0.91
Steroids administered – no (%)	17 (49)	9 (45)	
Midodrine administered – no (%)	9 (26)	2 (10)	

All baseline characteristics at time of vasopressor initiation
All values displayed as mean ± standard deviation unless noted
NE dose equation from VASST
NE = Norepinephrine + epinephrine + (dopamine/2) + (phenylephrine/10)

Vasopressin administration

Mean time to vasopressin initiation – hours (range)	10.8 (0-45.3)
Mean duration of vasopressin – hours (range)	40.7 (12.3-90.8)

Outcomes

Outcomes	No vasopressin (n=35)	Vasopressin (n=20)	p-value
In-hospital mortality – no (%)	7 (20)	7 (35)	0.22
Mean time on vasopressors - hours	52.6 ± 56.3	75.5 ± 40.2	0.12
Mean time on vasopressors for patients surviving to discharge - hours	45.3 ± 38.4	66.9 ± 41.2	0.06
Mean ICU length of stay - days	3.6 ± 2.8	10.1 ± 9.0	0.0002
Mean hospital length of stay - days	12.8 ± 12.5	30.6 ± 27.4	0.001
Number of catecholamine agents at time of inclusion	One agent: 35 (100)	No other agents: 4 (20) One agent: 14 (70) Two agents: 2 (10)	
Maximum number of catecholamine agents following inclusion	One agent: 34 (97) Two agents: 1 (3)	One agent: 10 (50) Two agents: 9 (45) Three agents: 1 (5)	

Steroids and mortality

	Steroids (n=9)	No steroids (n=11)	p-value
In-hospital mortality – no (%)	2 (22.2)	5 (45.5)	0.28

High-dose vasopressor arm (> 0.2 mcg/kg/minute)

Baseline characteristics

Characteristics	No vasopressin (n=46)	Vasopressin (n=48)	p-value
Age - years	75.8 ± 10.8	73.2 ± 14.2	0.18
Male sex – no (%)	32 (69.6)	27 (56.3)	0.16
APACHE II score	21.2 ± 6.0	22.6 ± 6.5	0.28
SOFA score	6.0 ± 2.3	6.5 ± 3.1	0.38
Lactic acid - mg/dL	3.1 ± 1.9	4.7 ± 4.6	0.03
MAP - mmHg	67.1 ± 15.5	66.8 ± 15.3	0.93
NE – mcg/kg/min	42.4 ± 49.2	58.2 ± 53.3	0.14
Steroids administered – no (%)	21 (45.7)	25 (52.1)	
Midodrine administered – no (%)	20 (43.5)	19 (39.6)	

All baseline characteristics at time of vasopressor initiation
All values displayed as mean ± standard deviation unless noted
NE dose equation from VASST
NE = Norepinephrine + epinephrine + (dopamine/2) + (phenylephrine/10)

Vasopressin administration

Mean time to vasopressin initiation – hours (range)	24.7 (0-177.3)
Mean duration of vasopressin – hours (range)	62.4 (1.8-403)

Outcomes

Outcomes	No vasopressin (n=46)	Vasopressin (n=48)	p-value
In-hospital mortality – no (%)	20 (43.5)	34 (70.8)	0.007
Mean time on vasopressors - hours	95.4 ± 86.8 Median: 74.2	171.7 ± 211.2 Median: 76.5	
Mean time on vasopressors for patients surviving to discharge - hours	81.9 ± 71.8 Median: 70.6	141.6 ± 142.1 Median: 70.5	
Mean ICU length of stay - days	7.3 ± 6.8 Median: 5.0	9.4 ± 15.2 Median: 5.0	
Mean hospital length of stay - days	17.5 ± 12.0 Median: 14.0	16.1 ± 16.6 Median: 12.0	
Number of catecholamine agents at time of inclusion	One agent: 35 (76) Two agents: 11 (24)	One agent: 35 (73) Two agents: 13 (27)	
Maximum number of catecholamine agents following inclusion	One agent: 37 (72) Two agents: 13 (28)	One agent: 22 (46) Two agents: 21 (44) Three agents: 4 (8) Four agents: 1 (2)	

Steroids and mortality

	Steroids (n=25)	No steroids (n=23)	p-value
In-hospital mortality – no (%)	19 (76.0)	15 (65.2)	0.41

Limitations

- Vasopressin was administered at a higher dose than currently recommend by the Surviving Sepsis Guidelines (0.04 units/minute)
- Retrospective nature allows possibility for error due to inaccurate charting of vasopressor indication, time of initiation, time of rate change, and time of discontinuation
- Unable to collect data regarding fluid resuscitation prior to initiation of vasoactive therapy
- Extended outcomes outside of the hospital are unknown
- Small subset of patients receiving vasopressin on low-dose vasopressors (n=20) where potential benefit may exist

Conclusions

- Vasopressin was not associated with in-hospital mortality benefit for patients in septic shock requiring low-dose or high-dose vasopressors
- Vasopressin was not associated with a shorter duration of overall vasopressor therapy for patients in septic shock requiring low-dose or high-dose vasopressors
- Vasopressin was not associated with a shorter ICU or hospital length of stay for patients in septic shock on low-dose or high-dose vasopressors
- Vasopressin was not associated with a catecholamine sparing effect for patients in septic shock requiring low-dose or high-dose vasopressors

Future Implications

- Opportunity for optimization of vasopressin utilization for patients in septic shock, specifically those on high-dose vasopressors, based on poor associated outcomes
- Patients with less-severe septic shock should be investigated further for potential benefit of vasopressin especially when administered in addition to steroids
- Development and implementation of a protocol for automatic vasopressin discontinuation at certain NE threshold
- Limit use of vasopressin to refractory patients on low-dose vasopressors

Disclosures

- All authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have direct or indirect interest in the subject matter of this presentation

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Critical Care Med.* 2017; 45:486-552.
2. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008; 358:877-87.
3. Gordon AC, Mason AJ, Thirunavukkarasu N, et al; VANISH Investigators. Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. *JAMA.* 2016; 316:509-18.
4. Reardon DP, DeGrado JRm Anger KE, Szumita PM. Early vasopressin reduces incidence of new onset arrhythmias. *J Crit Care.* 2014; 29:482-485.
5. Hammond DA, Ficek OA, Painter JT, et al. Prospective open-label trial of early concomitant vasopressin and norepinephrine therapy versus initial norepinephrine monotherapy in septic shock. *Pharmacotherapy.* 2018;38:531-538.
6. Hammond DA, Cullen J, Painter JT, et al. Efficacy and safety of the early addition of vasopressin to norepinephrine in septic shock. *J Intensive Care Med.* 2019;34:910-916.
7. Wu JY, Stollings JL, Wheeler AP, Semler MW, Rice TW. Efficacy and outcomes after vasopressin guideline implementation in septic shock. *Ann Pharmacotherapy.* 2017; 51:13-20.
8. Der-nigoghossian C, Hammond DA, Ammar MA. Narrative review of controversies involving vasopressin use in septic shock and practical considerations. *Ann Pharmacotherapy.* 2020;0:1-9.