Journal of Critical Care xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Early vasopressin reduces incidence of new onset arrhythmias

David P. Reardon, PharmD, BCPS *, Jeremy R. DeGrado, PharmD, BCPS, Kevin E. Anger, PharmD, BCPS, Paul M. Szumita, PharmD, BCPS

Department of Pharmacy Services, Brigham and Women's Hospital, Boston, MA

ARTICLE INFO

Keywords:
Vasopressin
Catecholamine
Sepsis
Septic shock

ABSTRACT

Purpose: The objective of this study was to determine the effect of early vs late vasopressin therapy on catecholamine dose and duration.
Materials and methods: We conducted a single-center, retrospective chart review of adult patients admitted to the medical intensive care unit between January 2010 and December 2011 with septic shock requiring catecholamine and vasopressin therapy. Patients were included in the early group if vasopressin was initiated within 6 hours and the late group if vasopressin was initiated between 6 and 48 hours of catecholamine(s).
Results: Duration of catecholamine and vasopressin therapy was similar between the 35 patients in the early group and the 36 in the late group. Vasopressin therapy was associated with a decrease in catecholamine requirements in both groups. Early vasopressin was associated with fewer new onset arrhythmias (37.1% vs 62.9%, $P < .001$). There was no difference in mortality, hospital, or intensive care unit length of stay between the early and late group vasopressin groups (88.6% vs 88.9%, $P = 1$; 14 vs 10 days, $P = .48$; 9 vs 7 days, $P = .71$, respectively).
Conclusions: Early initiation of vasopressin therapy in adult critically ill patients with septic shock was associated with no difference in total catecholamine requirements but decreased incidence of new onset arrhythmias.

1. Introduction

Sepsis requiring vasopressor support is a common reason for medical intensive care unit (ICU) admission [1-3]. Catecholamines, particularly norepinephrine, are an important part of hemodynamic support once patients have been adequately fluid resuscitated to maintain systemic perfusion and limit the negative outcomes linked with increasing fluid balance [4,5]. Arginine vasopressin (AVP) is frequently used as an adjunct to catecholamine therapy in patients in catecholamine-dependent septic shock [6-8]. During septic shock, persistent hypotension causes increased stimulation of the posterior pituitary and release of endogenous AVP [9]. Only 10% to 20% of stored vasopressin can be mobilized in the acute setting, and continued stimulation results in a decreased rate of release [10]. Continued release can lead to depletion of endogenous AVP store within 6 to 24 hours of septic shock onset [11].

Evidence suggests that adjunctive vasopressin may result in a decrease in total catecholamine requirements and mortality in certain patient populations, particularly those with less severe septic shock [12-14]. Catecholamine use has been linked to both an increased incidence of arrhythmias and increased cardiac ischemia [15]. New onset arrhythmias, specifically atrial fibrillation, have been shown to prolong ICU length of stay (LOS) and may be associated with a poorer prognosis. Patients experiencing atrial fibrillation without a return to a sinus rhythm had an increased mortality rate compared with those returning to a sinus rhythm [16].

Russell [17] reported that patients receiving early vasopressin had a trend toward improved outcomes compared with patients who received vasopressin later in their ICU stay. The purpose of this study was to determine the effect of early AVP on catecholamine dose and duration as well as catecholamine-related adverse events compared with late AVP as potential benefit has previously been described [18,19].

2. Materials and methods

This retrospective cohort analysis was approved by the Institutional Review Board at Brigham and Women's Hospital. An internal pharmacy database was used to identify all patients who received catecholamine therapy with concomitant AVP. Catecholamine therapy was defined as any continuous infusion of norepinephrine, epinephrine, phenylephrine, and/or dopamine lasting at least 6 hours. Patients were included in this study if they were admitted to the medical ICU, were at least age 18 years, and had a confirmed diagnosis or documented clinical suspicion of septic shock requiring catecholamine and AVP therapy between January 2010 and December 2011. Patients were included in the early group if AVP was initiated within 6 hours of catecholamine therapy and in the late group if AVP was initiated after 6 hours but before 48 hours of catecholamine therapy. Patients were excluded from this study if they were alive less than 24 hours after catecholamine initiation, AVP was initiated after 48 hours of

* Corresponding author. Brigham and Women's Hospital, L2 Department of Pharmacy Services, 75 Francis St, Boston, MA 02115.
E-mail address: dpreardon@partners.org (D.P. Reardon).

http://dx.doi.org/10.1016/j.jcrc.2014.03.005
0883-9441/

Table 1
Baseline characteristics

	Early vasopressin (n = 35)	Late vasopressin (n = 36)	*P*
Age (y)[a]	55 (49.5-66.5)	65 (58-71.5)	.007
Sex, male, n (%)	16 (45.7)	19 (52.7)	.6
APACHE II[a]	27 (20-32.5)	24 (17-28.5)	.1
Baseline hemodynamics			
MAP[b]	63.5 ± 11.2	57.1 ± 9.4	1
CVP[b]	12.2 ± 4.3	15.3 ± 6.8	.012
Time of CVP (hours after onset of septic shock)[a]	6 (2-9.75)	4 (2-10.25)	.4
Heart rate[b]	111.1 ± 31.4	111.3 ± 21.3	.5
pH[b]	7.24 ± 0.15	7.26 ± 0.12	.3
Lactic acid[b]	4.7 ± 4.1	4.1 ± 3.5	.7
MV, n (%)	27 (77.1)	26 (72.2)	.3
CA at baseline			
NE, n (%)	28 (80)	34 (94.4)	.002
DA, n (%)	1 (2.8)	1 (2.8)	.3
EPI, n (%)	0 (0)	0 (0)	1
PE, n (%)	15 (42.9)	12 (33.3)	.1
No. of CA[a]	1 (1-1.5)	1 (1-1.5)	.5
NE dose (μg/min)[b]	19.1 ± 27.2	16.7 ± 9.7	.7
DA dose (μg/kg per minute)[b]	1.8 ± 5.7	0.6 ± 3.4	.9
EPI dose (μg/min)[b]	0 ± 0	0 ± 0	1
PE dose (μg/min)[b]	71.1 ± 109.6	58 ± 99.2	.7
Vasopressin therapy			
Hours post-CA initiation	2 (1-4)	21 (14.5-30)	<.001

Abbreviations: *MV*, mechanical ventilation; *CA*, catecholamine(s); *NE*, norepinephrine; *DA*, dopamine; *EPI*, epinephrine; *PE*, phenylephrine.
[a] Median (IQR).
[b] Mean ± SD.

catecholamine therapy, AVP therapy lasted less than 6 hours, were pregnant, or had an incomplete medical record. All patients who met these criteria during this time frame were enrolled in this study.

The decision to initiate catecholamine therapy was clinician-dependent and was based on patient condition. Most clinicians at our institution initiate therapy with norepinephrine based on current practice guidelines and recommendations. The addition of AVP to catecholamine therapy is not standardized within our institution and therefore aided in the randomization of patients into the early and late groups.

Baseline demographic information was collected to describe the study population including the following: age, sex, weight, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, pH, serum lactic acid, baseline hemodynamic parameters (ie, heart rate, mean arterial pressure [MAP], and central venous pressure [CVP]), and need for mechanical ventilation. Baseline catecholamine requirements, defined as number of agents needed and maximum dose within the first 3 hours after initiation, were also collected. Catecholamine dose, expressed as norepinephrine equivalents based on previously published data, was recorded every 6 hours for 96 hours after initiation and every 1 hour after AVP initiation [14]. Catecholamine duration was defined as time from catecholamine initiation to cessation lasting at least 12 hours. Safety data included heart rate and MAP recorded hourly 12 hours before AVP initiation to 24 hours postinitiation as well as incidence of new onset arrhythmias (defined as any nonsinus rhythm in a patient with no known history of arrhythmias).

Outcomes evaluated in this study included the impact of AVP on catecholamine dose and duration between the early and late groups as well as ICU LOS, hospital LOS, mortality, duration of catecholamine and AVP therapy, and incidence of new onset arrhythmias. New onset arrhythmia was defined as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia in a patient without a documented history of that arrhythmia [15]. An analysis of systemic and cardiac perfusion, including serum lactic acid and creatinine levels as well as the cardiac biomarkers troponin T and creatine kinase–MB (CK-MB) was performed. Serum lactic acid and creatinine levels were recorded daily starting the day catecholamines were initiated. Serial troponin T and CK-MB were collected if patients had 3 levels drawn within the first 24 hours of catecholamine therapy. Continuous variables were reported as mean (SD) or median (interquartile range [IQR]) and compared via the Student *t* test or Mann-Whitney *U* test, where applicable. Comparison of categorical data was made via the χ^2 test. Statistical significance was defined as $P \leq .05$.

3. Results

Two hundred six patients who received vasopressin in addition to catecholamines for septic shock were evaluated for inclusion in this analysis. One hundred thirty-five were excluded: 59 were alive less than 24 hours after catecholamine initiation, 40 patients had AVP initiated after 48 hours, 22 patients had an incomplete medical record, and 14 patients received less than 6 hours of AVP. Seventy-one patients were included in this analysis: 35 patients in the early group and 36 patients in the late group.

Baseline characteristics are presented in Table 1. The 2 groups were similar at baseline in regards to sex, APACHE II scores, baseline hemodynamics, pH, serum lactic acid, and percentage of patients requiring mechanical ventilation. The patients in the early group were younger than those in the late group (55 [49.5-66.5] vs 65 [58-71.5] years; $P = .007$). The median time to AVP initiation after starting catecholamine therapy was 2 (1-4) hours in the early group vs 21 (14.5-30) hours in the late group ($P < .001$), and the AVP dose in both groups was 0.04 units/minute.

Overall, there was no difference in the dose and duration of catecholamine or AVP therapy between the 2 groups (Table 2). Initiation of AVP was associated with a decrease in total catecholamine requirements in both groups (Fig. 1). In patients alive at 96 hours, catecholamine requirements in the early group were statistically significantly lower than the late group (3.81 ± 5.76 vs 10.95 ± 8.06 μg/min; $P < .001$).

There was a statistically significant difference in the incidence of new onset arrhythmias between the early and late groups (37.1% vs 63.9%, $P < .001$) with the majority being rapid atrial fibrillation. The analysis examining serial markers of cardiac and systemic perfusion shows no difference between the 2 groups. Despite the lack of statistical significance, there was a trend toward worsening troponin T and CK-MB in the patients in the late AVP group (Fig. 2). Patients in the early group showed no difference in ICU LOS, hospital LOS, and mortality. Arginine vasopressin initiation was shown to decrease heart rate and increase MAP in both the early and late group.

Table 2
Outcomes evaluated

	Early vasopressin (n = 35)	Late vasopressin (n = 36)	*P*
ICU LOS (d)[a]	9 (5-14.5)	7 (4-14)	.5
Hospital LOS (d)[a]	14 (7-29)	10 (7-21)	.2
Mortality, n (%)	31 (88.6)	32 (88.9)	1
CA duration (hours)[a]	54 (42.5-78.5)	58 (36-101.5)	.4
AVP duration (hours)[a]	40 (32.5-66)	38 (27-56)	.2
New onset Arrhythmias, n (%)	13 (37.1)	23 (63.9)	<.001
Atrial fibrillation	10 (28.6)	12 (33.3)	
Ventricular tachycardia	3 (8.5)	10 (27.8)	
Ventricular fibrillation	0 (0)	1 (2.8)	

[a] Median (IQR).

Please cite this article as: Reardon DP, et al, Early vasopressin reduces incidence of new onset arrhythmias, J Crit Care (2014), http://dx.doi.org/10.1016/j.jcrc.2014.03.005