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Does high-dose vasopressor therapy in medical intensive care patients indicate what we already suspect?☆

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ABSTRACT

Purpose: This study was conducted to determine the association between vasopressor requirement and outcome in medical intensive care patients in an environment where treatment is not withdrawn.
Materials and Methods: This was an observational study of patients in the medical intensive care unit (ICU) over a period of 18 months to determine the correlation between vasopressor requirement and mortality. Outcome was determined for all medical ICU patients, for patients receiving "low dose" (<40 μg/min) vasopressors (noradrenaline and/or adrenaline) or "high dose" (≥40 μg/min) vasopressors. Receiver operator characteristic curves were constructed for ICU and hospital mortality and high-dose vasopressor use. High-dose vasopressor use as an independent predictor for ICU and hospital mortality was also determined by multiple logistic regression analysis.
Results: Patients receiving high-dose noradrenaline at any time during their ICU admission had an 84.3% mortality in ICU and 90% in hospital. The receiver operator characteristic curves for high-dose vasopressors had an area under the curve of 0.799 for ICU mortality and 0.779 for hospital mortality. High-dose vasopressor was an independent predictor of ICU mortality, with an odds ratio of 5.1 (confidence interval, 2.02-12.9; $P = .001$), and of hospital mortality, with an odds ratio of 3.82 (confidence interval 1.28-11.37; $P = .016$).
Conclusions: The requirement for high-dose vasopressor therapy at any time during ICU admission was associated with a very high mortality rate in the ICU and the hospital.

1. Introduction

As practicing intensivists, we intuitively appreciate when a patient's situation is becoming dire. We spend time at the bedside, examine the patient, order tests, and view the trend in the physiological parameters. In this setting, we may observe the inexorable escalation of vasopressor support in an attempt to maintain organ perfusion [1]. Vasopressor therapy is commonly used to defend organ perfusion when there is an inadequate response to intravascular volume repletion in patients in the intensive care unit (ICU). Indeed vasopressor therapy is recommended for septic shock, in particular [2,3], and it has also been shown to favorably influence outcome in patients with septic shock [4]. However, guidelines are lacking as to the maximal dose recommended for subgroups of critically ill patients.

Given the high incidence of shock and septic shock, in particular, presenting to ICUs [5], vasopressor therapy is very commonly used. However, at some point and in some patients, it becomes evident that there is poor or no response to vasopressor therapy, such as high-dose adrenaline, noradrenaline, and/or vasopressin. Most intensivists recognize this scenario as one in which the patient is unlikely to do well and indeed may make the decision to withdraw therapy on the grounds of medical futility. The literature is scant in terms of the prognostic predictive value of high-dose vasopressor therapy in this setting [6,7]. This issue is somewhat obscured by the concept of the *self-fulfilling prophesy* represented by withdrawal of treatment deemed to be futile (ie, "non-response to high-dose vasopressor therapy is a good indicator that the patient is not able to survive the current illness," so treatment is withdrawn and the patient dies).

We were interested in what actually happens to patients receiving high-dose vasopressor therapy in the clinical setting where treatment withdrawal is not practiced. The authors work in a cultural setting where withdrawal of treatment is not carried out, regardless of the perceived futility of ongoing intensive care treatment. The outcome of patients, in terms of mortality, is therefore not affected by the practice of withdrawal of therapy and represents a "true" outcome.

We undertook an observational study over the period April 27, 2008, to August 3, 2010, examining the outcome of patients admitted to our ICU who received no vasopressors, lower-dose vasopressors, or high-dose vasopressors.

☆ Conflict of interest: None of the authors have any conflict of interest in the conduct or reporting of the research described in this manuscript.

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Table 1
Demographic and clinical variables in the low-dose versus high-dose vasopressor groups

Parameter	Low dose <40, n = 115 (69%)	High dose ≥40, n = 51 (31%)	*P*
Age (y), mean ± SD	65.4 ± 17.8	57.9 ± 19.3	.017*
Sex, n (%)			.370
Male	59 (51)	30 (59)	
Female	56 (49)	21 (41)	
APACHE II, mean ± SD	29.3 ± 8.1	32.3 ± 8.3	.034*
Diagnoses, n (%)			
Pneumonia	30 (26)	16 (22)	.483
Respiratory (other)	25 (22)	11 (21)	.980
Neurologic	14 (12)	4 (7)	.408
Cardiac	26 (23)	8 (16)	.308
Infectious	59 (51)	31 (61)	.258
Renal	23 (20)	6 (12)	.197
GI + Hepatic	21 (18)	8 (16)	.687
Hematologic	10 (9)	8 (16)	.016*
Metabolic, n (%)	7 (6)	1 (2)	.252
Immunosuppressed, n (%)	22 (19)	14 (27)	.230
Preexisting cancer, n (%)	94 (82)	33 (51)	.017*
Dialysis, n (%)	32 (28)	13 (25)	.755
Steroid therapy, n (%)	51 (44)	31 (61)	.050*
Vasopressin therapy, n (%)	16 (14)	22 (43)	<.0001*
Outcome, n (%)			
ICU outcome			.0001*
Alive (65)	57 (49)	8 (16)	
Died (101)	58 (51)	43 (84)	
Hospital outcome			.0022*
Alive (42)	37 (32)	5 (10)	
Died (124)	78 (68)	46 (90)	
ICU LOS (d), mean ± SD	8.9 ± 7.94	8.9 ± 10.1	.4875
Hospital LOS (d), mean ± SD	25.3 ± 32.76	29.2 ± 36.77	.9550

Vasopressor group (n = 166). GI indicates gastrointestinal; APACHE II, Acute Physiology and Chronic Health Evaluation II.
* Indicates $P < 0.05$, i.e., significance.

2. Materials and methods

We applied to and received from the institutional ethics committee a waiver of the requirement for informed consent (review of records only and use of non-identified patient data). Data were then obtained from our unit database on all patients admitted over the period April 27, 2008, to August 3, 2010, representing 917 patients. Detailed data were then collected for patients receiving noradrenaline or adrenaline, being the vasopressors most commonly used in our unit. Of the 917 patients admitted during this period, 353 received a vasopressor or inotrope, and of these, 166 patients received noradrenaline and/or adrenaline at any time during the ICU admission.

2.1. Study groups

The 166 patients who received noradrenaline and/or adrenaline were then divided into 2 groups, those who received an infusion of vasopressor of less than 40 μg/min at any time during the ICU admission and those who received 40 μg/min or more for more than 1 hour at any time during the ICU admission, as an arbitrary cutoff point for "low"-dose versus "high"-dose vasopressor therapy, respectively. The dose of vasopressor was not indexed either for body mass or surface area because these data were not available. Demographic data for these 2 groups are listed in Table 1. The diagnostic category (as defined by unit practice) for patients who received vasopressors was noted, according to 10 diagnostic categories. The ICU admits almost exclusively adult medical patients, and this is reflected in the diagnostic categories. We excluded patients who received vasopressors other than noradrenaline or adrenaline and those who received vasopressors for less than 1 hour.

2.2. Outcome variables

The primary outcome of ICU and hospital mortality was determined for the entire study population and each subgroup. In addition, ICU length of stay (LOS), hospital LOS, and ICU and hospital mortality were determined for the low- and high-dose vasopressor groups. In addition, mortality after hospital discharge of our ICU patients was documented from the hospital medical records, which are updated regularly by the Ministry of the Interior. Our long-term mortality data are therefore updated up to April 1, 2012.

2.3. Data analysis

Sample size was determined based on previous data [6] showing a mortality difference of 20% between the low- and high-dose groups, requiring a total of 150 patients (50 for high-dose group and 100 for low-dose group) for a power of 80% and a significance of .05.

Demographic and diagnostic data between the low-dose and high-dose vasopressor groups were compared using χ^2 testing and paired *t* tests, as appropriate. Multivariate logistic regression analysis was performed to see if high-dose vasopressor use is an independent predictor of ICU and hospital mortality, when tested together with other variables that were found to be significant in univariate analysis. In addition, a continuous parameter of "maximal dose vasopressor" (determined as the maximal vasopressor dose used for each patient) was used in multivariate logistic regression analysis for the 2 outcomes. Other factors used in the multivariate analysis are listed in Appendix A.

Kaplan-Meier curves were constructed for the low- and high-dose vasopressor groups looking at long-term survival relative to ICU admission. Mortality data were censored at April 1, 2012. Receiver operator characteristic (ROC) curves, comparing vasopressor dose (maximal dose used in all patients), and outcome (mortality) in the ICU and in the hospital were constructed. The optimal vasopressor dose for determining ICU and hospital outcome with the highest sensitivity and specificity was determined.

The statistical package used was SPSS version 19.0 (IBM, Chicago, Ill).

3. Results

The results shown in Table 1 indicate a significant difference ($P < .05$) between the low- and high-dose vasopressor groups for age (younger patients received high dose) and APACHE II score (sicker patients in the high-dose group). The high-dose vasopressor group also had more patients with hematologic malignancies, but with less preexisting cancer. High-dose vasopressor therapy was also associated with more vasopressin use, not surprising given that vasopressin is used for refractory hypotension in our unit.

There was a highly significant difference in mortality, both in the ICU and in the hospital, between the low- and high-dose vasopressor groups (Table 1). The high-dose group had an 84.3% ICU mortality and 90% hospital mortality. The 2 groups were not different in terms of either ICU or hospital LOS.

The mortality outcomes for the study population are shown in Table 2.

Multivariate regression analysis to determine if high-dose vasopressor use was an independent predictor of ICU mortality showed that it was highly predictive of mortality in the ICU, with an odds ratio (OR) of 5.1 (confidence interval [CI], 2.02-12.9; $P = .001$), and of hospital mortality, with an OR of 3.82 (CI, 1.28-11.37; $P = .016$). (See Appendix A for all multiple regression analyses.)The maximal vasopressor dose, used as a continuous parameter with 1-μg/min increments, was also an independent predictor of ICU mortality, with an OR of 1.07 (CI, 1.03-1.0; $P < .0001$), and of hospital mortality, with an OR of 1.05 (CI, 1.02-1.08; $P = .002$), for each incremental dose.