Intensive Care Med (2010) 36:1484–1487
DOI 10.1007/s00134-010-1942-1

CLINICAL PERSPECTIVE

Marc O. Maybauer
Keith R. Walley

Best vasopressor for advanced vasodilatory shock: should vasopressin be part of the mix?

Received: 23 April 2010
Accepted: 23 May 2010
Published online: 1 July 2010

M. O. Maybauer (✉)
Division of Critical Care Medicine, Department of Anesthesiology, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0591, USA
e-mail: momaybau@utmb.edu
Tel.: +1-409-7721221
Fax: +1-409-7721224

M. O. Maybauer
Department of Anaesthesia and Intensive Care, Philipps University of Marburg, Marburg, Germany

K. R. Walley
Heart + Lung Institute, University of British Columbia, Vancouver, BC, Canada

Abstract Since the publication of the Surviving Sepsis Campaign guidelines, a number of additional and highly relevant studies have been published addressing the issue of vasopressor use during septic shock. While these new results are provocative, none of the studies are definitive. In sum, they suggest that maybe we should not be thinking of one vasopressor versus another in a winner-takes-all sense. Rather, we should be looking for the best balance of vasopressor agents and, further, the choice likely depends on clinical context. Clinical context may drive the choice of adrenergic agonist; for example, norepinephrine may be superior to dopamine when the potential for arrhythmias is of concern. Norepinephrine may be superior to epinephrine if elevated lactate associated with epinephrine use confounds the clinical picture. The Vasopressin and Septic Shock Trial (VASST) identified an effective dose of arginine vasopressin (AVP) when adrenergic agonist doses are low, but higher doses of AVP may be appropriate in the context of very high adrenergic agonist doses. The effect may be a direct beneficial AVP effect or indirect sparing of adrenergic agonist use. The choice to add AVP may also be influenced by the clinical context, including renal function or the concomitant use of corticosteroids. These interim conclusions, in truth, are hypotheses warranting randomized controlled trials adequately powered to test for survival differences in these severely ill patients.

Keywords Septic shock · Adrenergic agonist · Norepinephrine · Dopamine · Epinephrine · Arginine vasopressin

Introduction

Circulatory shock is a life-threatening condition that is associated with high mortality [1]. The administration of fluids is the first line therapeutic strategy to stabilize patients, but fluids alone often fail to restore hemodynamic stability [2]. The alpha and beta adrenergic agents norepinephrine and dopamine are frequently used to further stabilize the patient's condition. The latest consensus guidelines suggest that either agent may be used as first choice vasopressor in patients with septic shock, that low-dose (0.03 units/min) arginine vasopressin (AVP) may be added as a second line agent, and that epinephrine may be used when other agents are ineffective [3]. Not surprisingly, there has been much debate. Since the publication of these guidelines, new information has emerged that helps inform this debate. Here we review key results, particularly as they relate to the role of AVP (Table 1).

Table 1 Treatment options for advanced vasodilatory shock

Category/reference	Patients studied (*n*)	Indication	Conclusion
Guidelines			
Dellinger et al. [3]		Severe sepsis; septic shock	1st line vasopressors norepinephrine or dopamine; 2nd line (when 1st line ineffective) low dose AVP (0.03 U/min); stress dose steroids (200–300 mg/day) when unresponsive to fluids and vasopressors
Adrenergic agonists			
Annane et al. [4]	330	Vasodilatory shock; septic shock	No evidence for a difference in efficacy and safety between epinephrine alone and norepinephrine plus dobutamine for the management of septic shock
Myburgh et al. [5]	280	Vasodilatory shock	No difference in the achievement of an MAP goal between epinephrine and norepinephrine; potential drug-related side effects with epinephrine
De Backer et al. [6]	1,679	Vasodilatory shock	No significant difference in the rate of death between dopamine or norepinephrine; the use of dopamine was associated with a greater number of adverse events
Vasopressin			
Russell et al. [9]	778	Vasodilatory shock; septic shock	Overall no difference in mortality rates as compared with norepinephrine; in less severe septic shock (norepinephrine requirement $\geq$5 μg/min and $\leq$15 μg/min = 0.08–0.25 μg kg^{-1} min^{-1}), the mortality rate was lower in the AVP group than in the norepinephrine group at 28 days (26.5 vs. 35.7%)
Torgersen et al. [10]	50	Advanced vasodilatory shock	AVP infusion of 0.067 IU/min restores cardiovascular function in patients with advanced vasodilatory shock ($\geq$0.6 μg kg^{-1} min^{-1}) more effectively than AVP at 0.033 IU/min
Corticosteroids			
Bauer et al. [11]	42	Septic shock	Although corticosteroids did not improve the time to withdrawal of vasopressin-containing vasopressor therapy, they significantly increased the proportion of patients alive without vasopressors at day 7
Russell et al. [12]	779	Septic shock	Combination of low-dose AVP and corticosteroids was associated with decreased mortality and organ dysfunction compared with norepinephrine and corticosteroids
Torgersen et al. [10]	50	Advanced vasodilatory shock	AVP plasma levels increased in both (low and high dose AVP) groups (both $P < 0.001$), but were higher in the 0.067 IU/min group ($P < 0.001$) and in patients on concomitant hydrocortisone

Norepinephrine versus other catecholamines

Prior to the development of the current Surviving Sepsis Campaign guidelines, Annane et al. [4] had reported the results of a randomized controlled trial of norepinephrine plus dobutamine versus epinephrine alone in 330 septic shock patients. They found that the 28-day mortality rate was 34% in the norepinephrine plus dobutamine group compared to 40% in the epinephrine alone group. Following publication of the guidelines, Myburgh et al. [5] reported a comparison of norepinephrine versus epinephrine in 280 hypotensive critically ill patients. Twenty-eight-day mortality was 27% in the norepinephrine group compared to 23% in the epinephrine group. Both of these trials were underpowered to detect these small differences in mortality, and the reported differences go in opposite directions so that there appears to be no substantial difference in mortality between norepinephrine and epinephrine. Lactic acidosis was more prominent in the epinephrine-treated patients compared to norepinephrine-treated patients in both of these studies. There were no differences in serious adverse events between these two treatments in either study. Therefore, there is little clinical endpoint-driven evidence to choose one therapy over the other.

Most recently, because of a continuing controversy about whether one agent is superior to the other, De Backer et al. [6] directly compared norepinephrine with dopamine in a randomized, multicenter trial of 1,679 patients with shock. They found a 28-day mortality rate of 48.5% in the norepinephrine group compared to 52.5% in the dopamine group. While underpowered to detect this small mortality difference, they found that the use of dopamine was associated with a greater number of adverse

events. Specifically, arrhythmic events occurred in 12.4% of patients in the norepinephrine group and 24.1% of patients in the dopamine group ($P < 0.001$).

When should AVP be considered and at what dose?

Since Landry et al. [7] observed that vasopressin plasma concentrations had collapsed in patients with septic shock, AVP has been commonly used as an adjunct to catecholamines to support blood pressure in refractory septic shock. As a result, the effects of exogenous AVP in shock became a focus for numerous research projects, including AVP analogues and V1a receptor agonists [8], finally resulting in the Vasopressin and Septic Shock Trial (VASST) [9]. In this multicenter, randomized, double blind trial, the investigators compared low dose AVP (0.01–0.03 U/min) added to open label norepinephrine versus norepinephrine alone in 778 patients with septic shock. The authors showed no significant difference between the AVP and norepinephrine groups in 28- or 90-day mortality rates, and no difference in the overall rates of serious adverse events. However, in a prespecified analysis stratified according to dose, the VASST investigators found very divergent results.

This suggests that we do not know the correct dose of AVP to use in septic shock patients for at least two reasons. First, the VASST trial was conducted in the absence of a prior phase II dose-ranging study so that the dose tested in VASST was based on expert opinion—opinion that was necessarily limited since no one had much direct experience at the time that the VASST study protocol was designed. Second, effectiveness of the dose of AVP differs depending on the severity of shock as indicated above. When the VASST data were analyzed according to the prespecified strata of low severity of shock (baseline norepinephrine 5–15 μg/min) and high severity of shock (baseline norepinephrine >15 μg/min), very different results were observed. Low dose AVP (0.03 IU/min) reduced mortality in the low severity of shock group by almost 10% ($P < 0.05$) and this result persisted over 90 days. In contrast, survival in the high severity of shock group was essentially identical with completely overlapping Kaplan-Meier survival curves over the entire 90-day study period. Thus, while VASST may have identified an effective dose of AVP for patients with low severity of shock, we have not identified an effective dose of AVP for patients with high severity of shock—a vitally important issue in these patients because of the staggeringly high mortality rate.

In a recent issue of *Intensive Care Medicine*, Torgersen et al. [10] report that in patients with very severe septic shock a higher dose of AVP than used in the VASST trial results in more effective restoration of cardiovascular function. The authors test the null hypothesis that AVP 0.067 U/min is no different from AVP 0.033 U/min on hemodynamic function in 50 patients who had severe vasodilatory shock requiring norepinephrine >0.6 mg kg^{-1} min^{-1}. The number of patients randomized into this study (25 each in the lower dose and higher dose AVP groups) is sufficient to provide useful additional hemodynamic information, though not sufficient to test for differences in survival outcome. They find that 0.067 U/min infusion results in lower norepinephrine infusion rates. Importantly, the incidence of adverse events in the two groups was comparable. However, there are no other convincing differences that cannot be attributed to baseline imbalances in any hemodynamic measurement, in organ damage or function, or in mortality (ICU mortality 52% in both groups).

A number of encouraging supplementary observations further support the idea that the higher dose of AVP may be beneficial including less of an increase in troponin T over 48 h and a trend towards greater improvement in creatinine. These encouraging signs are muted by the further observations that the higher dose of AVP was associated with a greater decrease in mixed venous oxygen saturation and a slightly reduced improvement in base excess.

Whether this higher AVP dose will lead to improved survival outcome remains an open question, in part because the two study groups were different at baseline with more evidence of significant cardiac disease (CAD, CHF, troponin, hemodynamics) at baseline in the 0.033 U/min group compared to the 0.067 U/min group. These differences, while perhaps inevitable with a small sample size, make interpretation of the results more difficult. The authors appropriately adjust for baseline imbalances using statistical analysis, but these adjustments can never fully compensate.

What additional issues might be important?

An interesting interaction of AVP with corticosteroids is observed in the study of Torgersen et al. [10], as previously reported by Bauer et al. [11] and also by Russell et al. [12]. Torgersen et al. [10] find that concomitant use of steroids increases vasopressin concentrations in plasma in both the low dose and high dose AVP groups. Russell et al. [12] found the same effect on plasma vasopressin levels and Bauer et al. [11] and Russell et al. [12] found the AVP-corticosteroid interaction to be associated with improved survival outcome. Clearly this is an important emerging issue.

Vasopressin compared to catecholamine vasopressors was found to increase urine output and even creatinine clearance in several small preliminary studies [13]. When

this issue was addressed in a post-hoc analysis of the VASST data, Gordon et al. [14] found that for patients in the Risk category (according to the RIFLE scoring system), AVP resulted in reduced mortality compared to norepinephrine alone. Patients treated with AVP had a 50% reduction in progression to end-stage renal failure and had half the incidence of the use of dialysis. These observations suggest that the clinical judgement of whether to use AVP or not may depend on additional circumstances including renal function and the concomitant use of corticosteroids.

Conclusions

In the context of all of these recent studies, maybe we should not be thinking of one vasopressor versus another in a winner-takes-all sense. Rather, we should be looking for the best balance of vasopressor agents and, further, the choice likely depends on clinical context. Clinical context may drive the choice of adrenergic agonist; for example, norepinephrine may be superior to dopamine when the potential for arrhythmias is of concern [6]. Norepinephrine may be superior to epinephrine if elevated lactate associated with epinephrine use confounds the clinical picture [4, 5]. VASST identified an effective dose of AVP when adrenergic agonist doses are low, but Torgersen et al. [10] raise the possibility that AVP doses should be higher in the context of very high adrenergic agonist doses. The effect may be a direct beneficial AVP effect or indirect sparing of adrenergic agonist doses. The choice to add AVP may also be influenced by the clinical context, including renal function [14] or the concomitant use of corticosteroids [10–12]. While these new results are provocative, they are not definitive and these interim conclusions, in truth, are hypotheses warranting randomized controlled trials adequately powered to test for survival differences in these severely ill patients.

Acknowledgments This study was supported by Heart and Stroke Foundation of B.C. and Yukon.

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