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Concomitant vasopressin and hydrocortisone therapy on short-term hemodynamic effects and vasopressor requirements in refractory septic shock☆

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ABSTRACT

Purpose: The objective of this study was to evaluate the short-term hemodynamic effects as well as vasopressor requirements with concomitant vasopressin (AVP) and hydrocortisone (HCT) compared to either agent alone in refractory septic shock.

Materials and methods: This was a retrospective, cohort study conducted in adult septic shock patients. Patients received continuous infusion AVP at 0.04 units/min and/or HCT 200–300 mg intravenous daily in divided doses for refractory septic shock. Refractory septic shock was defined as systolic or mean blood pressure (MAP) of <90 mmHg or <70 mmHg, respectively, despite fluid resuscitation and requiring norepinephrine.

Results: A total of 300 patients were evaluated. The rate of achieving a "response" (norepinephrine dose reduction by ≥50% without any decrease in MAP) at 4 h from baseline was significantly higher in patients receiving concomitant AVP/HCT (88.5%) compared to HCT alone (62.3%) or AVP alone (72.9%) ($p = 0.0005$). The AVP/HCT group had higher "response" rates over the HCT and AVP monotherapy groups at 12 ($p = 0.052$) and 24 h ($p = 0.036$). Multivariate regression showed combination therapy to be independently associated with response at 4 h.

Conclusions: Concomitant AVP and HCT was associated with an immediate, additive catecholamine-sparing effect over either agent alone in patients with refractory septic shock.

1. Introduction

Severe sepsis and septic shock remains a significant problem in the critically ill patient population despite recent therapeutic advances. The incidence has been estimated at 751,000 cases annually with over 50% of these patients requiring admission to the intensive care unit (ICU) [1]. Sepsis has been identified as one of the leading causes of death in non-cardiovascular ICUs [2]. The mortality rate of severe sepsis and septic shock ranges from 30 to 60% [1-2]. The impact on healthcare resources and costs is also concerning. Total ICU costs associated with the management of severe sepsis have been estimated at $4651 (2014 U.S. dollars) per day [3].

Several therapeutic strategies are currently available in the management of septic shock [4]. Appropriate and timely antimicrobial therapy remains cornerstones in the initial management [4]. In addition, hemodynamic support with fluid resuscitation, inotropic therapy, and adrenergic vasopressor agents are often employed [4]. Although several novel therapies are either currently available or undergoing clinical trials for the treatment of septic shock (e.g. extracorporeal therapy, immunoglobulins, interferon-beta, etc.), no specific therapy has consistently demonstrated improved clinical outcomes [4-5]. However, a recent study has shown promise in possibly preventing progressive organ dysfunction in septic shock patients with the early administration of intravenous vitamin C, hydrocortisone, and thiamine [6].

The use of hydrocortisone (HCT) and arginine vasopressin (AVP) are viable options for patients with refractory septic shock [4]. Endogenous cortisol and vasopressin are necessary to maintain cardiovascular homeostasis [7-11]. However, relative deficiencies in endogenous serum concentrations of cortisol, vasopressin, or both have been found in septic shock patients, which may contribute to vasopressor-dependent, refractory septic shock [7-11]. Studies evaluating low-dose HCT in septic shock patients have demonstrated an improvement in hemodynamics, a decrease in vasopressor requirements, and a possible survival benefit although these findings are inconsistent [12-23]. Adjunctive AVP therapy in septic shock has also shown a beneficial impact on hemodynamics and vasopressor-sparing effects [24-33]. However, AVP has not been shown to impact mortality [30,33].

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Although HCT and AVP have separately shown beneficial effects in septic shock, the concomitant use of both agents remains controversial. Animal models have shown variable effects of AVP and corticosteroid therapy on the hypothalamic-pituitary-adrenal axis and serum vasopressin concentrations, respectively [34-43]. Corticosteroid administration may exhibit additive, inhibitory or equivocal effects on serum vasopressin concentrations, while AVP therapy has more consistently increased basal corticosterone concentrations [34-43]. Human clinical trials have not corroborated any significant changes in serum cortisol or vasopressin concentrations with HCT or AVP administration [44-46]. Despite frequent use in clinical practice, few studies have investigated the clinical effects of concomitant AVP/HCT in septic shock [46-49]. Lower mortality rates have been associated with adjunctive corticosteroid and AVP therapy although these findings were inconsistent [46-48]. Also, combination therapy may decrease the duration of vasopressor support [46-47]. Only one study evaluated the impact of concomitant AVP/HCT vs. AVP alone on mean arterial pressures (MAP), which found no significant difference in MAP between study groups [46]. Unfortunately, all of these studies compared patients receiving concomitant AVP/HCT and AVP monotherapy without any direct comparison to only HCT therapy. Therefore, the purpose of this study was to evaluate the short-term hemodynamic effects as well as vasopressor requirements between concomitant AVP and HCT compared to either agent alone in septic shock patients.

2. Materials and methods

2.1. Patients and study design

This was a retrospective, cohort study conducted at a major academic medical center. Banner University Medical Center Phoenix (Phoenix, AZ) is a Level I Trauma Center. With an average daily admission rate of about 94 patients and >34,000 adult inpatient admissions per year. Adult septic shock patients receiving AVP and/or HCT therapy were evaluated from January 1, 2012 to December, 31, 2015. Inclusion criteria consisted of the following: (1) ≥18 years of age; (2) known or suspected infection; (3) refractory shock [systolic blood pressure (SBP) <90 mmHg or MAP < 70 mmHg despite fluid resuscitation and requiring norepinephrine]; and (4) HCT 200–300 mg/day intravenous monotherapy, AVP continuous infusion at a rate of 0.04 units/min monotherapy, or concomitant AVP/HCT initiated <24 h after shock onset. Patients with concomitant therapy were only included if the second agent was administered <24 h after the first agent was started irrespective of whichever drug (HCT or AVP) was initiated first. Patients were excluded if AVP and/or HCT were used for purposes other than the management of septic shock; shock syndrome possibly attributed to other non-sepsis related causes (i.e. cardiogenic or neurogenic shock); or AVP infusion was administered for <2 h as there may have been questionable need or impending mortality.

Following Institutional Review Board approval, patients meeting criteria were identified through the electronic medical record database. Patients were categorized into one of three study cohorts: (1) HCT only; (2) AVP only; or (3) concomitant AVP/HCT groups. Patients were screened during the study period until 100 patients were identified into all three study groups. Groups were not matched or aligned according to underlying acuity of illness as all patients had refractory septic shock and were consecutively chosen for inclusion. Pertinent demographic and clinical data were collected including age, gender, weight, primary diagnoses, significant past medical history (e.g. diabetes mellitus, heart failure, cancer, or end-stage renal/liver disease), need for renal replacement therapy, volume of fluids administered over a 4-h period preceding baseline, Sequential Organ Failure Assessment (SOFA), and documented infection (organism and site of infection). Certain medications administered at baseline were also documented such as broad-spectrum antimicrobials as well as insulin and norepinephrine infusion rates. Hemodynamic data (MAP) and norepinephrine dosage (mcg/min) requirements were assessed at 8 h before baseline, baseline and at 1, 2, 4, 8, 12, 16, and 24 h following the initiation of HCT, AVP, or concomitant AVP/HCT therapy. Clinical outcomes including mortality rate, length of stay in the ICU and overall hospitalization as well as disposition status (discharged home or inter-facility transfer) for surviving patients were also collected.

2.2. Definitions

Baseline was defined as the time upon initiation for either HCT or AVP as documented in the medical chart for when the infusion was started or when the first dose was administered. In the concomitant AVP/HCT group, baseline was considered at the time when the second adjunctive agent was started, irrespective of which agent was first started. Patients in all study groups were categorized as "responders" or "non-responders" to HCT and/or AVP therapy. For the primary outcome, "responders" were defined as patients with ≥50% norepinephrine dose reduction at 4 h from baseline without any reduction from baseline MAP, while "non-responders" were all patients not achieving at least a 50% norepinephrine dose reduction or the MAP was reduced from baseline irrespective of the norepinephrine infusion rate. Despite the lack of a universally accepted definition for "response", the investigators determined this objective criteria based on previously published reports [29, 50–52]. To the best of our knowledge, only one study defined "treatment efficacy" (i.e. "response") a priori by the prevalence and extent of an increase in MAP within 30 min after starting AVP infusion and by the extent of norepinephrine dose decreases between 30 min and 24 h [29]. Unfortunately, this study did not report % change from baseline for MAP or norepinephrine dose reductions. Although other reports did not define "response" a priori, several studies evaluating the impact of AVP on norepinephrine dose requirements consistently observed decreases ≥50% at various time periods within 24 h of initiating AVP infusions [50–52]. However, these studies showed minimal changes in MAP (<10%) or no change at all from baseline [50–52]. Therefore, based on these study observations, we determined ≥50% norepinephrine dose decreases from baseline without any decrease in MAP as a "response". As secondary outcomes, "response" at 12 and 24 h after initiation of the study drugs was also assessed. Organ dysfunction was defined using objective criteria as previously published [53].

2.3. Statistical analysis

A sample size of 100 patients in each study group was determined to ensure at least 65 patients per group could be evaluated at 4 h. Assuming a desired response rate difference of ≥25% between any group, 65 patients per group would have 80% power assuming an alpha of 0.0167 as adjusted for multiple comparisons. The 4-h evaluation period was chosen by the investigators based on previously published reports of vasopressin's immediate effects on MAP and norepinephrine requirements [29,50]. The primary objective of the study was to evaluate the "response" rate in the AVP/HCT group compared to either agent alone at 4 h from baseline. Secondary analyses included "response" at 12 and 24 h after initiation of the study drugs and comparative assessments of MAP and norepinephrine requirements of "responders" and "non-responders" over 24 h from baseline. Mortality rates, length of ICU and hospital stay, and organ dysfunction observed in each study group were compared as well.

Univariate analyses of groups used Chi square test for categorical variables and Student *t*-test or analysis of variance for continuous variables. Parameters with p-values ≤ 0.1 were evaluated for effect on response using backward multivariate logistic regression analysis. These data are presented as odds ratio (OR) and 95% CI. Analysis of variance with Tukey's test for post-hoc analysis assessed multiple comparisons to the −8 h time point for hemodynamic data and rates of norepinephrine administration. A p-value of <0.05 was considered statistically