e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(12); 220-226

Original Research Article

The Interaction of Vasopressin and Corticosteroids in Septic Shock: A Study in Southern Rajasthan

Akanksha Yadav[1], Abhyudaya Soni[2], Naresh Tyagi[3], Kamlesh Shekhawat[4]

[1,2]Resident, Department of Anaesthesia, Pacific Institute of Medical Sciences, Udaipur
[3,4]Associate Professor, Department of Anaesthesia, Pacific Institute of Medical Sciences, Udaipur

Received: 25-10-2022 / Revised: 25-11-2022 / Accepted: 13-12-2022
Corresponding author: Dr. Akanksha Yadav
Conflict of interest: Nil

Abstract

Overview: Vasopressin and corticosteroids are both commonly used adjunctive therapies in septic shock. Retrospective analyses have suggested that there may be an interaction between these drugs, with higher circulating vasopressin levels and improved outcomes in patients treated with both vasopressin and corticosteroids.

Material and methods: Prospective open-label randomized controlled pilot trial conducted at the intensive care units (ICU) within Pacific Institute of Medical Sciences, Udaipur, Rajasthan. Inclusion criteria were adult patients (≥16 years) who had sepsis and who required vasopressors despite adequate intravenous fluid resuscitation.

Result: Initial vasopressin intravenous infusion titrated up to 0.06units/minute and then intravenous hydrocortisone (50mg 6-hourly) or placebo. Plasma vasopressin levels were measured at 6-12 and 24-36 hours after hydrocortisone/placebo administration. Thirty-one patients were allocated to vasopressin + hydrocortisone and 30 patients to vasopressin + placebo. The hydrocortisone group required a shorter duration of vasopressin therapy (3.1 days, 95%CI 1.1-5.1, shorter in hydrocortisone group) and required a lower total dose of vasopressin (ratio 0.47, 95%CI 0.32-0.71) compared to the placebo group. There were no differences in mortality rates (23% 28-day mortality in both groups) or organ failure assessments between the two treatment groups.

Conclusions: Hydrocortisone spared vasopressin requirements, reduced duration and reduced dose, when used together in the treatment of septic shock but it did not alter plasma vasopressin levels. Further trials are needed to assess the clinical effectiveness of vasopressin as the initial vasopressor therapy with or without corticosteroids

Keywords: Vasopressin, Adrenal cortex hormones, Sepsis, Intensive care, Multiple organ failure, Drug interaction.

Introduction

Catecholamines remain the primary vasopressors used in treating hypotension during septic shock after intravenous fluid resuscitation [1]. Vasopressin has been proposed as an adjunctive therapy in septic shock and has shown to increase blood pressure and reduce catecholamine requirements [2, 3]. Firstly, in the a priori defined stratum of less severe shock (defined as patients requiring <15μg/min of

norepinephrine at baseline), there was a reduced mortality in the vasopressin group compared to the norepinephrine group (26.5% v 35.7% 28-day mortality difference -9.2%, 95%CI -18.5 to 0.1) [6]. In contrast, in the more severe shock stratum (≥15μg/min of norepinephrine at baseline), there was no difference in mortality (44.0% and 42.5%, respectively; difference 1.5%, 95%CI -8.2 to 11.2). Further post-hoc subgroup analysis suggested that vasopressin may be more effective at preventing deterioration in renal function, rather than reversing established acute kidney failure [7]. Another interesting finding in VASST was that there was evidence of interaction between vasopressin and corticosteroid treatment [8]. The combination of vasopressin and steroids led to a lower mortality compared to norepinephrine plus steroids (35.9% v 44.7% respectively, difference -8.8%, 95%CI -16.7 to -0.9). In contrast, patients who were treated with vasopressin and did not receive corticosteroids had increased mortality compared to patients who received norepinephrine and no corticosteroids (33.7% v 21.3%, difference 12.3%, 95%CI -0.2 to 24.9). However, patients who received corticosteroids as well as vasopressin had higher levels of circulating vasopressin as compared to patients treated with vasopressin alone. Similar findings were observed in other retrospective analyses where plasma vasopressin levels were elevated in patients on concomitant hydrocortisone [9] and also the survival rates were higher in patients treated with concomitant vasopressin and hydrocortisone [10]. The earlier use of vasopressin in septic shock and its interaction with corticosteroids needs further investigation in randomized controlled trials. Hereby we undertook a pilot trial to prospectively test our primary hypothesis that there was any interaction between vasopressin and corticosteroids and secondarily to test the feasibility of vasopressin use as initial vasopressor therapy in septic shock.

Materials and Methods

This open randomized placebo-controlled parallel-group trial was conducted between October 2021 and March 2022. Recruitment was initially from the intensive care units (ICU) within Pacific Institute of Medical Sciences, Udaipur, Rajasthan. Institutional Ethics Committee approval was obtained. Consent was obtained from the patient, or a personal or professional legal representative as soon as practically possible. In cases where a legal representative gave consent, retrospective consent was sought once the patient regained capacity. Inclusion criteria were adult patients (≥16 years) who had sepsis and who required vasopressors despite adequate intravenous fluid resuscitation. Exclusion criteria were patients who had received previous continuous infusion of vasopressors during this hospital admission, on-going requirement for systemic steroid, known mesenteric ischemia, Raynaud's phenomenon, end-stage renal failure, systemic sclerosis or other vasospastic disease, ongoing treatment for an acute coronary syndrome, death anticipated within 24 hours or if there was a treatment limitation within place, known pregnancy, enrolment in another interventional trial that might interact with the study drugs, or hypersensitivity to any of the study drugs.

Results

A total of 330 patients were screened for inclusion out of which 63 were randomized. The specific reasons for exclusion is patients met defined exclusion criteria, 155 patients were outside the 6 hours window of their first episode of shock and 8 patients were excluded for other reasons. 2 patients were excluded by the treating physician after randomization. Of the 31 patients allocated to vasopressin and hydrocortisone treatment, 23 patients required the maximum vasopressin infusion rate (0.06

units/min) and then received hydrocortisone. Among the 30 patients in the vasopressin with placebo group 27 patients required the maximum vasopressin infusion rate and received placebo. There were 6 patients in the hydrocortisone group who never received any norepinephrine and 2 patients in the placebo group. 5 patients in the placebo arm were given corticosteroids for the treatment of life-threatening hypotension and were considered as crossovers. No patients were lost to follow up. In 18 patients (30%) vasopressin was started as initial vasopressor infusion to treat hypotension. In the other 43 patients, norepinephrine was the most commonly used vasopressor to initially stabilize the patient in the emergency setting before being weaned off and the median time to starting the trial vasopressin infusion was less than 4 hours from the diagnosis of shock. The median time from vasopressin infusion starting and first sample collection (T0), once the maximum infusion rate was reached and before the second study drug was administered, was similar in both groups (145 minutes in the hydrocortisone group and 120 minutes in the placebo group). There was no convincing evidence of any difference in plasma vasopressin levels at any of the time points and similar results were obtained reanalysing the data as "intention-to-treat". As part of the sensitivity analysis, regression models were used to analyse these data with adjustment for baseline vasopressin levels and/or body weight. Adjusting the analyses for either or both of these variables did not change the result. The mean arterial pressure over time was similar in both treatment groups. However, the patients in the hydrocortisone group were weaned off the vasopressin infusion more quickly than those in the placebo group. This resulted in a 3 day (95%CI 1.1 - 5.1 days, p = 0.001) shorter duration of vasopressin infusion in the hydrocortisone group and a halving of the total dose (ratio 0.47, 95%CI 0.32 - 0.71, p = 0.001) of vasopressin required compared to the placebo group. The duration of additional norepinephrine infusion was 2 days (95%CI -7.0 to 0.0 days, p=0.015) in the hydrocortisone group compared to the placebo group. There was no difference in intravenous fluid administration, total fluid balance or lactate clearance between treatment groups. There was no difference in mortality rates, onset of new organ dysfunction or organ failure free days between the two treatment groups. In total there were 14 adverse events reported, out of which 4 were defined as serious adverse events. Only one serious adverse event was assessed by the treating physician as possibly related to the study drugs. Of the 5 minor adverse events, 3 were for cool / mottled peripheries, one rise in serum lactate and one rise in troponin.

Discussion

In this randomized controlled trial of vasopressin and corticosteroids compared to vasopressin and placebo, there was evidence of a clinical interaction between vasopressin and corticosteroids. The vasopressin requirements of patients randomized to receive corticosteroids were halved but there was no difference in plasma vasopressin levels. Vasopressin has consistently been shown to act as a vasoconstrictor in septic shock [3-5, 9, 12-15]. In the largest trial of vasopressin in septic shock to date [6], this was the hypothesis tested in the planned subgroup analysis, which stated that patients who had more severe shock would obtain the most benefit from vasopressin treatment. However, no benefit was seen in this group of patients which appeared to be confined to patients who had less severe shock (defined by norepinephrine requirements <15µg/min). Further exploratory work from the VASST study demonstrated improved outcomes in patients treated using vasopressin that only had mild forms of acute kidney injury at inclusion [7]. In contrast, there was no difference in outcomes in patients who had already sustained more severe kidney injury before

receiving vasopressin. However, it remains to be tested in prospective trials if vasopressin improves outcome compared to norepinephrine if used as initial vasopressor therapy. The 2012 Surviving Sepsis Campaign guidelines do not recommend vasopressin as the single initial vasopressor for treatment of sepsis-induced hypotension [16]. This study demonstrates that it is practicable to use vasopressin as first line therapy for treatment of septic shock. Although the logistics of a clinical trial in an emergency situation prevented all patients receiving vasopressin as the very initial vasopressor, 30% of patients did receive it as initial vasopressor infusion and half of all patients received vasopressin within 4 hours of the onset of shock. Furthermore, about 18% of patients did not require the maximum vasopressin infusion rate (0.06 units/min) to maintain blood pressure, and 8 patients (13%) received no catecholamines at any time, demonstrating that it is feasible to use vasopressin early and to avoid additional exogenous catecholamine infusions in some septic shock cases. In view of the concern about adverse effects of catecholamines, this is an important clinical finding [17]. The 23% mortality in this study compares favorably to local historical mortality rates (28% 28-day mortality in 2009-10) and is similar to the 24% 28-day mortality rate in the placebo group of a recent septic shock trial [18]. However, as all patients in this trial received early vasopressin infusions no comparison of effectiveness to catecholamines can be made. Vasopressin binds to V3 receptors located in the anterior pituitary and may increase adrenocorticotrophin hormone (ACTH) production and secretion [19] and may also directly stimulate adrenal glucocorticoid production [20]. Norepinephrine is known to inhibit the anti-diuretic effect of vasopressin in the kidney but requires cortisol [21]. Similarly corticosteroids have been reported to increase vasopressin messenger RNA [22] but other studies have found that corticosteroids do not change vasopressin levels [23] and others have suggested that corticosteroids may actually delay vasopressin release [24] and suppress vasopressin gene expression [25]. In two previous trials of vasopressin therapy, circulating levels of vasopressin have been found to be higher in patients given corticosteroids [8, 9]. Although these results both came from controlled trials, the use of corticosteroids was not controlled. Furthermore it should be noted that circulating vasopressin levels did not differ in patients who were not administered with exogenous vasopressin, suggesting there was little or no effect on vasopressin secretion [8]. Therefore, we undertook this study to randomize patients prospectively to receive exogenous vasopressin and either corticosteroids or placebo treatment, and then compare plasma vasopressin levels between the two groups. In this research we found no difference in plasma vasopressin levels at any time point and although the analysis was complicated by a few crossovers, the results were similar when the analyses were carried out as “intention to treat”, “as treated”, crossovers excluded or adjusting for baseline levels. As plasma vasopressin levels did not change, the mechanism behind this effect remains uncertain. Corticosteroid treatment may have improved vascular responsiveness. In animal models of sepsis, cytokine-mediated downregulation of vasopressin (V1a) receptors has been demonstrated [26] and this hypo responsiveness was reversed by high dose glucocorticoid treatment [27]. These findings are consistent with the effects seen in this study. The clinical implications of this corticosteroid effect remain uncertain. There was also a reduced requirement for additional norepinephrine in the hydrocortisone group in this study. Previous trials of corticosteroids in septic shock have demonstrated more rapid shock resolution [28] but this did not improve outcome 11. Furthermore recent studies have suggested that cortisol levels are elevated in septic shock and there is an impairment of cortisol metabolism [29]. It

should be noted that the dose of vasopressin infusion used in this trial (0.06 units / min) is higher than that recommended in the Surviving Sepsis Guidelines [16]. The optimum dose of vasopressin in septic shock remains unknown, although the dose of 0.067 units/min was more effective than 0.033 units/min at restoring cardiovascular function in a previous randomized controlled trial [9]. In that trial, as well as this current trial, circulating vasopressin levels were significantly higher than physiological levels seen in shock states. As vasopressin stimulates both V1a and V2 receptors it is possible that a selective V1a agonist might produce the same vasopressor effect and avoid the potential unwanted effect of V2 stimulation, such as release of von Willebrand factor [30] . Limitations of this trial should be considered. It was prospectively powered to detect any difference in plasma vasopressin levels at a single time point after reaching maximum rate of vasopressin infusion and corticosteroid administration. However, not all patients reached the maximum vasopressin infusion rate even though additional existing catecholamines were weaned off quickly, thus reducing the sample size and potential power in the analysis of plasma levels. [31]

Conclusions

In this randomized controlled trial of hydrocortisone versus placebo added to initial vasopressor therapy for the treatment of septic shock there was significant clinical interaction between vasopressin and corticosteroids. Hydrocortisone therapy reduced requirements of vasopressin but did not alter plasma vasopressin levels. It is feasible to use vasopressin as initial vasopressor therapy in septic shock.

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