Combined Therapy with Corticosteroids and Vasopressin in a Patient with Septic Shock

Doson Chua and Christopher Lo

INTRODUCTION

Septic shock is a critical physiological state of infection-related inadequacy of tissue perfusion and hypotension that is often refractory to fluid resuscitation.[1] It is associated with a high mortality rate, especially in the setting of multiorgan dysfunction and if the initial antimicrobial therapy administered is inappropriate.[2,3] Appropriate antimicrobial therapy is the cornerstone of treatment, but adjunctive approaches have also been explored in recent years. Impairment of endogenous adrenal function and vasopressin deficiency are common in patients with septic shock.[4,5] Exogenous supplementation with corticosteroids had a proven mortality benefit in a specific set of critically ill patients,[6] and the benefits of vasopressin are slowly emerging.[7] However, the net effect of combination treatment with exogenous corticosteroids and vasopressin in patients with septic shock is unknown. This report documents a case in which combination therapy was employed, and the literature on corticosteroid and vasopressin supplementation in septic shock is reviewed.

CASE REPORT

A 78-year-old man was admitted to the medical–surgical intensive care unit (ICU) with hypotension, decreased level of consciousness, and inability to protect his airway after a right total hip replacement 5 days previously. He was intubated on admission to the ICU for respiratory failure, and infusion of norepinephrine was started for his acute hypotension, which was refractory to fluid resuscitation. The patient's medical history included morbid obesity, chronic obstructive pulmonary disease, 20-year history of smoking, osteoarthritis of the hips, and myocardial infarction 10 years before. His medications on admission to the ICU were subcutaneous dalteparin 5000 U daily, morphine IV as needed, salbutamol inhaler as needed, and acetaminophen 1000 mg 4 times daily.

On physical examination, the patient's temperature was 38.7°C, heart rate 120 beats/min, respiratory rate 22 breaths/min, urine output 15 mL/h, and blood pressure 80/56 mm Hg with infusion of 0.8 $\mu g\ kg^{-1}\ min^{-1}$ of norepinephrine. Diffuse crackles were heard in both lungs on chest auscultation. Laboratory results revealed hyperkalemia (potassium 5.3 mmol/L, normal range 3.5 to 5.0 mmol/L), renal insufficiency (serum creatinine 255 µmol/L, normal range 60 to 120 µmol/L) with an estimated creatinine clearance of 0.27 mL/s (16 mL/min on the basis of Cockcroft-Gault calculations), leukocytosis with a left shift (white blood cells 18.8 x 10^9/L, normal range 4 x 10^9/L to 10 x 10^9/L, with greater than 10% band forms), and a slightly elevated neutrophil count (8 x 10^9/L, normal range 2 x 10^9/L to 7 x 10^9/L). The serum lactate was 2.2 mmol/L (normal range 0.5 to 2.2 mmol/L). The patient had mixed metabolic and respiratory acidosis, with arterial blood gas results of pH 7.20, P_{CO_2} 45 mm Hg, P_{O_2} 78 mm Hg, and bicarbonate 18 mmol/L. The patient's ventilator settings were pressure control 18 breaths/min, tidal volume 500 mL, fraction of inspired oxygen 0.60, and positive end-expiratory pressure 8 cm H_2O.

Investigations into the source of infection involved culture of blood, urine, sputum, and the hip wound exudate, none of which demonstrated any growth. Significant mucoid sputum production was noted. The peripheral IV lines and urinary catheters were replaced.

Ultrasonography of the replaced hip did not show any signs of abscess or fluid collection. Abdominal sources of infection were ruled out by the results of the physical examination, the clinical presentation, and the patient's medical history. Chest radiography revealed mid and lower left lobe infiltrates, and the results of electrocardiography were unremarkable. A pulmonary artery catheter was inserted, and the following results were obtained: pulmonary artery pressure 30/18 mm Hg (normal range 15/5 to 30/15 mm Hg), pulmonary capillary wedge pressure 20 mm Hg (normal range 4 to 12 mm Hg), cardiac index 4.4 L min^{-1} m^{-2} (normal range 2.5 to 4 L min^{-1} m^{-2}), and systemic vascular resistance 531 dynes/cm^5 (normal range 700 to 1500 dynes/cm^5).

The patient's clinical presentation and laboratory findings suggested systemic inflammatory response syndrome (SIRS). The findings of mid and lower left lobe infiltrates on chest radiography and the significant sputum production implied that the cause of the SIRS was a pulmonary infection. Combined with the requirement for vasopressor support despite fluid resuscitation, these findings indicated that the patient was experiencing septic shock. The pulmonary artery catheter results suggested a distributive pattern of shock that is commonly found in septic shock (high cardiac output and low systemic vascular resistance). Empiric imipenem 500 mg IV every 12 h and infusion of vasopressin at 0.04 U/min was started, in addition to the existing norepinephrine infusion (0.8 µg kg^{-1} min^{-1}).

An adrenocorticotropin hormone stimulation test (Cosyntropin, Organon, Scarborough, Ontario) yielded the following results; cortisol level 1048 nmol/L at baseline, 1131 nmol/L 30 min after administration, and 1223 nmol/L 60 min after administration. Relative adrenal insufficiency was diagnosed on the basis of the maximal response to the cortisol stimulation test, an increase of 175 nmol/L (any increase of less than 250 nmol/L is indicative of adrenal insufficiency). Hydrocortisone 50 mg IV every 6 h and oral fludrocortisone 50 µg daily for 7 days were started 48 h after the initiation of vasopressin.[8]

Twenty-four hours after initiation of vasopression (i.e., after 24 h of therapy with both hydrocortisone and vasopressin), the norepinephrine was decreased to 0.07 µg kg^{-1} min^{-1}; at 36 h, both norepinephrine and vasopressin were discontinued, and a systolic blood pressure of greater than 90 mm Hg was maintained. The patient became afebrile by 48 h after the start of combination therapy, and his hemodynamics remained stable for the rest of his ICU stay. The hydrocortisone and fludrocortisone were discontinued on day 7 of his ICU admission. Subsequent cultures did not reveal any growth, and empiric imipenem was continued for a total of 14 days. The patient was discharged from the ICU to the surgical ward 6 days after admission.

DISCUSSION

According to the most recent definitions published in *Chest*,[1] this patient was exhibiting SIRS (temperature above 38°C, tachycardia, tachypnea, and leukocytosis) from an infectious cause, which led to the diagnosis of presumed septic shock. Although there were no definitive culture results to direct antimicrobial therapy, an empiric broad-spectrum antibiotic was initiated because of the patient's clinical presentation, the high mortality rate associated with inappropriate antimicrobial treatment of sepsis, and inability to identify a specific pathogen. Pulmonary infections have been cited as the most common source of sepsis, followed by intra-abdominal and urinary tract infections.[9] Blood culture results are positive in only 30% to 50% of patients with sepsis, and 10% to 30% of such patients do not have an identifiable source of infection.[9-11] The site of infection in this patient was presumed to be pulmonary, because of infiltrates noted on chest radiography and significant sputum production. Hospital-acquired pneumonia might have been involved in the development of sepsis in this patient, given the presence of patient risk factors for hospital-acquired pneumonia and the clinical presentation.

This patient was also given a combination of hydrocortisone and vasopressin as adjunctive therapy. The role of adjunctive therapy has received attention recently, given the results of several studies highlighting the importance of endocrine dysfunction in the pathophysiology of sepsis.[12]

The pathophysiology of septic shock involves inflammatory, thrombotic, and antifibrinolytic responses to infection.[13,14] The use of corticosteroids in septic shock is not a new approach, but recent studies have demonstrated that low, physiological replacement dosing provides more benefit than pharmacological doses. Early studies of septic shock used high-dose corticosteroids in the hope of arresting the pathophysiological progress of inflammation but failed to demonstrate any reduction in mortality rate.[15,16]

Similarly, 2 meta-analyses did not reveal any mortality benefit of high-dose steroids in patients with sepsis.[17,18] Recently, the role of corticosteroids has shifted from pharmacological doses to physiological replacement doses, because a large proportion of patients with septic shock also have relative adrenal insufficiency.[4] The inci-

dence of relative adrenal insufficiency in sepsis ranges from 0 to 77%, depending on the underlying severity of illness; it may be due to circulating suppressive factors released during SIRS; alternatively, it may be due to cortisol resistance or adrenal exhaustion.[4] As well, a blunted adrenal response to exogenous administration of adrenocorticotropin hormone (ACTH) in patients with sepsis was associated with a higher 28-day mortality rate than among patients with a normal adrenal response.[8] These findings, which suggest the involvement of adrenal insufficiency in the pathophysiology of septic shock, have led to some key trials.

In 2 studies, physiological replacement dosing of corticosteroids led to hemodynamic benefits in patients with septic shock receiving catecholamine support. Bollaert and others[19] compared hydrocortisone 100 mg IV every 8 h for at least 5 days with placebo in 41 patients with septic shock. The primary end point of shock reversal at 7 days (defined as systolic blood pressure greater than 90 mm Hg, dopamine use less than 5 μg kg^{-1} min^{-1}, and lactate less than 2 mmol/L) was achieved in 68% of the patients in the hydrocortisone group but only 21% of those in the placebo group (p = 0.007). Briegel and others[20] compared infusion of hydrocortisone (100 mg IV bolus, then 0.18 mg kg^{-1} h^{-1} while on vasopressor support, then 0.08 mg kg^{-1} h^{-1} for 6 days, then tapering by 24 mg/day) with placebo in 40 patients with septic shock. The end point of time to cessation of vasopressor therapy was achieved within 2 days in the hydrocortisone group and 7 days in the placebo group (p = 0.005).

A recent trial by Annane and others[6] demonstrated a mortality benefit with corticosteroid replacement. Three hundred patients with septic shock who were receiving catecholamine support were randomly assigned to receive either hydrocortisone 50 mg IV every 6 hours plus oral fludrocortisone 50 μg daily or placebo. The 28-day mortality rate was 53% in the hydrocortisone group and 63% in the placebo group (p = 0.04). This mortality benefit was seen only in the subgroup of patients with relative adrenal insufficiency, as determined by an exogenous ACTH stimulation test administered on entry into the study (increase of less than 250 nmol/L from baseline). Thus, because no benefit is seen in patients with normal adrenal function, exogenous administration of corticosteroids in septic shock should be targeted to patients with impaired adrenal response. Other issues such as the optimal timing of initiation of corticosteroids, the role of fludrocortisone, and the duration of corticosteroid treatment require further study.

Vasopressin is also deficient in patients with septic shock, and it has been postulated that this hormone is involved in the hemodynamic instability seen in sepsis.[5,21] Two small vasopressin studies investigated the effect of exogenous administration of vasopressin on hemodynamic parameters in patients with septic shock refractory to conventional vasopressor support.[7,22] Infusion of vasopressin at 0.04 U/min resulted in hemodynamic improvement in both studies (increased systolic blood pressure, increased systemic vascular resistance, and decreased catecholamine requirements). However, there have been no mortality trials of vasopressin use to date, and past trials involved very limited numbers of patients, without controls.

The combined use of corticosteroids and vasopressin in septic shock has not been evaluated. Given that these agents improve hemodynamic parameters by different pharmacological actions and given that they have been independently identified as deficient in septic shock states, it would be reasonable to expect at least an additive hemodynamic effect.

Previous studies investigating the hemodynamic effects of hydrocortisone in septic shock did not determine if the patients were adrenally insufficient, and all patients with septic shock received empiric hydrocortisone.[19,20] Given the recent findings of an association between adrenal insufficiency and sepsis-related mortality, steroid therapy is now used in a specific subgroup of patients with septic shock, those with adrenal insufficiency.[6,8] In the study by Annane and others,[6] adrenally impaired patients with septic shock who received corticosteroid supplementation required a mean time of 7 days before withdrawal of vasopressor therapy could be achieved. However, all patients in that study (with and without adrenal insufficiency) had a similar time course to withdrawal of vasopressor support. The time course for vasopressor withdrawal in the vasopressin studies is less clear because of the small number of patients involved. Malay and others[7] studied 10 patients with septic shock refractory to catecholamines; only 1 of the 5 patients who received vasopressin was able to discontinue all vasopressor support 24 h after initiation of vasopressin. It is difficult to interpret this finding, because the mean duration of all vasopressor requirements was not reported and because of the small number of patients. Tsuneyoshi and others[22] found that the mean duration of vasopressin therapy was 93 h (standard deviation 75 h) among patients whose septic shock was refractory to pharmacological doses of catecholamines. Catecholamine support was continued after the discontinuation of vasopressin, i.e.,

beyond 93 h. Overall, the mean time for withdrawal of catecholamine support in septic shock was 7 days with addition of corticosteroids and greater than 93 h with addition of vasopressin.

In the case reported here, the use of both corticosteroids and vasopressin resulted in the discontinuation of all vasopressors 36 h after initiation of combination therapy. This time course of vasopressor support compares favourably to the times reported in the clinical trials. The initiation of antibiotics might have helped with the rapid catecholamine weaning; however, the use of antibiotics in this patient was similar to antibiotic usage in the clinical trials described above. Antibiotics were started 3 h after the diagnosis of sepsis, and hemodynamic improvement was seen after 72 h of antibiotic therapy. Given that this patient demonstrated more rapid hemodynamic recovery from sepsis than reported in previous clinical trials and given that the antibiotics employed for this patient were similar to those used in the trials, it is thought that the antibiotics were not the predominant determinant of the results seen. Individually, corticosteroids and vasopressin have been shown to improve sensitivity to catecholamines, potentially by different mechanisms. Corticosteroid therapy is postulated to improve catecholamine sensitivity by increasing catecholamine and catecholamine receptor synthesis, and vasopressin is thought to potentiate the contractile effects of norepinephrine, possibly through prostaglandin mediation.[4,5] Given their different pharmacological actions in improving catecholamine sensitivity and their demonstrated individual clinical benefits in reducing catecholamine requirements, it is plausible that the actions of these 2 agents could be complementary. However, the end point of vasopressor withdrawal may not necessarily translate to clinical outcomes.

One concern with the administration of corticosteroids is hyperglycemia from steroid-induced gluconeogenesis. Hyperglycemia has recently been shown to be detrimental to clinical outcomes in critically ill patients, and corticosteroids may adversely contribute to this problem.[23]

However, the effects of corticosteroids and hyperglycemia have not been well studied in the sepsis trials. Annane and others[6] reported that the placebo and steroid groups in their study of 300 patients did not differ significantly with regard to steroid-related adverse events; however, glycemic control was not specifically reported. In the study by Bollaert and others,[19] there was a trend toward higher glucose levels in the steroid-treated group than in the placebo-treated group (11.3 and 9.6 mmol/L, respectively, on day 3 of steroid therapy). However, these sepsis trials were conducted before the realization that tight glycemic control is important in critically ill patients. Thus, the elevated glucose levels reported in past trials may have been influenced by the lack of tight insulin control in ICU patients or the methods used to maintain euglycemia (sliding-scale insulin regimens). Additional studies are needed to determine if corticosteroid use in septic shock would predispose a patient to hyperglycemia and if it would affect efforts to maintain euglycemia in critically ill patients.

Recombinant activated protein C (also known as APC or drotrecogin alfa), a synthetic form of the endogenous protein C with antithrombotic, anti-inflammatory, and profibrinolytic properties, was considered for this patient, on the basis that the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial had demonstrated mortality benefits in the treatment of sepsis and this patient met all of the clinical criteria for its use.[24] However, APC had not yet been approved by federal regulatory bodies and thus was not readily available for use. Given the extensive inclusion and exclusion criteria in the PROWESS trial, the use of APC would be targeted to a select population of patients with septic shock. It would have a role complementary to those of corticosteroids and vasopressin. However, much debate continues on the optimal use of APC in patients with sepsis.

In conclusion, this case illustrates that combination replacement therapy with hydrocortisone and vasopressin in presumed septic shock may have complementary hemodynamic benefits, leading to reversal of shock sooner than with either therapy alone.

Outstanding questions include the optimal timing for initiation of vasopressin therapy, the impact of the adverse effects of corticosteroids and vasopressin in patients with septic shock, and identification of patients who would benefit from such adjunctive therapies. Whether combination hydrocortisone and vasopressin therapy should be routinely used in all patients with adrenal insufficiency and septic shock, whether the effects are additive or synergistic, and whether this drug combination confers a mortality benefit all require further study.

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Doson Chua, BSc(Pharm), PharmD, is a Critical Care Pharmacy Resident at St Michael's Hospital, Toronto, Ontario.

Christopher Lo, BSc(Pharm), PharmD, is a Pharmacist at Langley Memorial Hospital, Langley, British Columbia.

Address correspondence to:
Dr Doson Chua
St Michael's Hospital
30 Bond Street
Toronto ON
M5B 1W8

e-mail: dchua3@yahoo.com