Review article

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Hydrocortisone, vitamin C, and thiamine as treatment of septic shock combined with cardiogenic shock: a case report and literature review

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Abstract

***Objective*: To determine whether the concomitant administration of vitamin C, hydrocortisone, and thiamine improves sepsis-related organ failure assessment (SOFA) score and mortality in a patient with septic and cardiogenic shock, multiple organ dysfunction syndrome (MODS), acute respiratory distress syndrome (ARDS), gram negative bacteremia, cardiomyopathy, disseminated intravascular coagulation (DIC), and 95% mortality on presentation.**

***Design*: A case report and literature review.**

***Setting*: Surgical Intensive Care Unit at NYU Winthrop Hospital.**

***Patient*: Patient with 95% mortality received appropriate treatment for septic and cardiogenic shock with no clinical improvement.**

***Intervention*: Hydrocortisone 50 mg intravenous push (IVP) every 6 hours for four days, vitamin C 1,500 mg IV every 6 hours for four days, and thiamine 200 mg intravenous piggyback (IVPB) every 12 hours for four days.**

***Measurements and results*: As seen in a retrospective study by Marik and associates analyzing patients with severe sepsis with elevated procalcitonin levels, administration of vitamin C, hydrocortisone, and thiamine significantly reduced the SOFA score and mortality rates. Patient was treated with combination regimen and within 72 hours of administration, he had significant improvement in his cardiac dysfunction, kidney failure, liver failure, and respiratory failure. His SOFA score greatly improved from 18 and 95% mortality to 8 and <33% mortality.**

***Conclusion*: Our patient had a remarkable survival of what was thought to be indefinite mortality with the intervention of vitamin C, hydrocortisone, and thiamine. The administration of the vitamin C protocol warrants a randomized controlled trial to change management of septic shock and mortality. We are very optimistic that it will show similar results yielding a significant decrease in mortality rates in patients with septic shock.**

Key words: Sepsis, septic shock, cardiogenic shock, vitamin C, hydrocortisone, thiamine.

Introduction

Overwhelming inflammatory response combined with signs of organ failure encompasses a clinical presentation known as septic shock. The time-sensitive nature of treatment in septic shock may lead to delays in therapy administration and increase mortality. (1) The 28-day mortality rates for sepsis in well developed countries are about 25%; however, when it comes to septic shock, mortality rates can range up to 50%. (2) Treatment for septic shock includes fluid replenishment, antibiotics, and vasopressor support. (3)

We report a case of a patient with septic and cardiogenic shock, cardiomyopathy, and multiple organ dysfunction syndrome (MODS) with a sepsis-related organ failure assessment (SOFA) score of 18, 95% mortality, and a procalcitonin that peaked at 1,960.5 ng/ml, who was treated with the novel combination of vitamin C, hydrocortisone, and thiamine, described in Marik and associates' study in Chest 2016, and had a remarkable outcome.

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Case report

A 53-year-old African-American male presented with acute low back pain associated with lower extremity tingling and burning pain with concur-

rent nausea, vomiting, weakness, and lethargy. Past social and medical history included tobacco use, peripheral artery disease, hypertensive cardiomyopathy, and abdominal aortic aneurysm (AAA) status post AAA repair. Subsequently, he had an aortic stent graft placed secondary to aortoenteric fistula and a left femoral popliteal bypass.

Patient presented without a palpable pulse, uncontrolled hypertension of 203/129 mmHg treated with labetalol, lower extremity coolness, and respiratory rate of 20. Critical laboratory parameters included a serum creatinine of 2.8, blood urea nitrogen (BUN) of 35 mg/dl, total bilirubin of 2.8 mg/dl, white blood cells (WBC) count of 16,600/µl, and platelet count of 21,000. Creatine phosphokinase (CPK) on presentation was 184 IU/l, troponin was <0.1 ng/ml, anion gap was 19 mEq/l, and patient had a left ventricular ejection fraction of 40%. Arterial blood gas portrayed a lactate of 11.5 mmol/l, pH of 7.21 with a pCO2 of 16 mmHg, and bicarbonate of 6.4 mmol/l.

Within 24 hours of admission, patient went into septic shock and cardiogenic shock with systolic blood pressure in the 70s, renal and liver dysfunction, acute respiratory distress syndrome (ARDS), and MODS, and patient was intubated. He was administered dobutamine, fluids, empiric antibiotics, and initiated on continuous veno-venous hemofiltration (CVVH). Patient's abdominal exam changed significantly and he underwent an exploratory laparotomy. He was found to have an aortoenteric fistula and had an open gut to the retroperitoneum and duodenum allowing air to fill the abdomen. However, he could not undergo surgical repair due to poor cardiac function. Swan Ganz was placed to monitor his cardiac output (CO) and mixed venous saturation consistent with an inappropriate cardiac index (CI). He had a CO of 3.46 l/min with a CI of 1.80 l/min/m^2. Central venous pressure (CVP) was 24 mmHg, mixed venous oxygen saturation (SvO2) was 57%, and his systemic vascular resistance (SVR) was 2,057. SOFA score was 18 with 95% mortality. Blood cultures were positive for gram negative rods after one day, including Escherichia coli extended spectrum β-lactamase (ESBL) and Klebsiella pneumoniae sensitive to meropenem and vancomycin. Significant rise in CPK posed a concern for ischemic muscle and rhabdomyolysis leading to a below the knee left leg amputation.

Day two, procalcitonin peaked at 1,960.50 ng/ml and total bilirubin increased indicating liver failure. Due to presence of septic and cardiogenic shock and MODS, hydrocortisone 50 mg intravenous push (IVP) every 6 hours for four days, vitamin C 1,500 mg IV every 6 hours for four days, and thiamine 200 mg intravenous piggyback (IVPB) every 12 hours for four days were initiated. Day three, total bilirubin peaked at 7.4 mg/dl and patient had severe thrombocytopenia. In addition to the patient's current prognosis and a mortality of 95%, he had a D-dimer of 31,349 ng/ml indicative of disseminated intravascular coagulation (DIC); together, this further increased the patient's mortality by about 60%. (4)

However, within 24 hours of administration of vitamin C, thiamine, and hydrocortisone, there was a 46% decrease in procalcitonin to 899.15 ng/ml, patient was stable and weaned off vasopressors; his blood pressure was elevated requiring a nicardipine drip. Enteral feeds were started via a nasogastric tube. Within 48 hours of treatment, patient's cardiac indices significantly improved with a CO of 6.37 l/min, CI of 3.33 l/min/m^2, SVR of 979, CVP of 12 mmHg, and SvO2 of 73%. Within 72 hours of treatment, procalcitonin decreased to 200 ng/ml, Swan Ganz was removed. He was extubated and titrated off intravenous continuous drips and transitioned to oral medications. By day 16, his chemistry panels normalized and liver and renal function returned to normal as patient was able to create urine and CVVH was discontinued.

After 15 days from initial sepsis diagnosis, patient was stabilized and tolerating tube feeds at goal. His repeat SOFA score was 8 with mortality <33%. Following therapy, he was transferred to another institution to continue medical care with his outpatient vascular physician who operated on his AAA, for indefinite repair of his aortoenteric fistula.

Discussion

As seen in a retrospective before-after clinical study by Marik and associates analyzing patients with severe sepsis or septic shock with elevated procalcitonin, administration of vitamin C, hydrocortisone, and thiamine significantly reduced the SOFA score and mortality rates. This study looked at 47 patients in each group comparing treatment with the vitamin C protocol to standard of care. During the treatment period, patients with a primary admitting diagnosis of severe sepsis or septic shock and a procalcitonin >2 ng/ml, were initiated on the vitamin C protocol. The protocol consisted of intravenous vitamin C 1.5 g every 6 hours for 4 days, hydrocortisone 50 mg every 6 hours for 7 days followed by a taper over 3 days, and intravenous thiamine 200 mg every 12 hours for 4 days, or all medications until ICU discharge. Hospital mortality in treated patients was 8.5% compared to 40.4% in the control group. Treated patients had a

72 hour change in SOFA score of 4.8±2.4 versus 0.9±2.7 in the control group. Procalcitonin clearance at 72 hours in the treatment group was 86.4% versus 33.9% in the control group.

It is believed that the combination of vitamin C, hydrocortisone, and thiamine synergistically reverses the pathophysiologic changes of sepsis. After administration of this combination, our patient demonstrated significant improvement. Within 72 hours, his SOFA score decreased from 18 and 95% mortality to 11 with 40-50% mortality. Additionally, the norepinephrine was discontinued within 10 hours and was slowly titrated off of the dobutamine at 72 hours indicating improvement in cardiac function. The procalcitonin level decreased by 90%, serving as a strong indicator of clinical improvement.

There are several studies that have shown synergistic effects of vitamin C and hydrocortisone. Vitamin C and hydrocortisone decrease the production of pro-inflammatory mediators by inhibiting nuclear factor-κB, maintain microcirculatory flow and endothelial function, increase the sensitivity to vasopressors and are necessary for the production of catecholamines. In sepsis, there is an increased presence of pro-inflammatory cytokines which leads to a reduction of sodium-vitamin C transporter-2 (SVCT2). SVCT2 transports vitamin C into the cells. The administration of hydrocortisone may increase sodium-vitamin C transporter-2 enabling vitamin C to penetrate the cells. (2,5)

Synergy is produced upon combination of vitamin C, hydrocortisone, and thiamine. Intravenous vitamin C is required instead of oral vitamin C as the oral formulation cannot adequately restore the severely low levels seen in critically ill patients due to the saturable SVCT1. However, upon administration of high dose vitamin C, there is an increase in conversion to oxalate. When vitamin C undergoes metabolism, it may leave an intermediate metabolite known as glyoxylate which is converted to oxalate or carbon dioxide. However, septic patients often have a deficiency in thiamine which causes an increased conversion of glyoxylate to oxalate and is associated with an increased risk of death. (2,5)

Thiamine is a cofactor for transketolase in the pentose cycle and for oxidative decarboxylation conducted by pyruvate dehydrogenase and α-ketoglutarate dehydrogenase within the mitochondria. (6) Decline in serum thiamine may cause an increase in lactate, associated with increased mortality, and may raise the potential for oxidative stress during sepsis causing transient injury to the mitochondria. Thiamine has a protective effect on the mitochondria and could reverse mitochondrial dysfunction seen in sepsis. (6) Therefore, the addition of thiamine to the combination of hydrocortisone and vitamin C is integral in maintaining the metabolic integrity of vitamin C as well as preserving mitochondrial activity within the cells.

Conclusion

We report a patient case with septic and cardiogenic shock and MODS with 95% mortality that had excellent outcomes with the combination of vitamin C, hydrocortisone, and thiamine. It remains to be seen that the use of four days of the vitamin C protocol not only improved vasodilatation, but resulted in improved severe cardiac dysfunction, kidney failure, liver failure, and respiratory failure. After administration of this protocol, the procalcitonin decreased by over 90%, and the cardiac indices, SOFA score, and mortality rate greatly improved. The administration of the vitamin C protocol warrants a randomized controlled trial to change management of septic shock and mortality. We are very optimistic that it will show similar results which will significantly reduce mortality in septic shock by about 30%. (2)

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