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Research Article

The Effect of Using Vitamin C, Hydrocortisone and Thiamine Triple Therapy in the Treatment of Septic Shock - A Randomized Clinical Trial - Pilot Study

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Abstract

Introduction: Sepsis is a clinical syndrome with physiologic and biochemical derangements caused by a dysregulated inflammatory response to infection. A recent retrospective study demonstrated that vitamin C, hydrocortisone and thiamine in intensive care unit (ICU) patients with septic shock, when added to standard care, improved mortality and outcomes.

Methods: This prospective single-blinded study evaluated the effects of addition of triple therapy to standard ICU care on 28-day mortality in patients with septic shock defined as sepsis-induced hypotension requiring vasopressors with serum lactate level > 2 mmol/L. Patients were randomized to receive either standard ICU care (control) or standard care plus intravenous (IV) Vitamin C (1.5 gram every 6 hours) for 4 days or until ICU discharge, IV hydrocortisone (50 mg every 6 hours) for 7 days or until ICU discharge, and IV thiamine (200 mg every 12 hours) for 4 days or until ICU discharge.

Results: Analysis of 41 enrolled patients showed no significant difference at baseline between the two groups in terms of demographics or severity of septic shock. Triple therapy showed no effects on ICU length of stay, weaning from vasoactive drugs, clearance of lactic acid, preservation of renal function and weaning from ventilator support. The triple therapy group showed a trend towards increased mortality that did not reach statistical significance, but a low side-effect profile, indicating safety for use.

Interpretation: This prospective human study suggests triple therapy has limited use in the treatment of septic shock; larger studies should be pursued prior to widespread usage in septic shock.

Keywords: *Intensive Care Unit (ICU); Vitamin C; Intravenous (IV); Hydrocortisone*

Introduction

Sepsis is a clinical syndrome that has physiologic, biologic, and biochemical derangements caused by a dysregulated inflammatory response to infection. Sepsis and the ensuing inflammatory response can lead to multi-organ dysfunction resulting in death. In the 1970s, it was estimated that 164,000 cases of sepsis occurred in the United States annually. Since then the number of cases per year has significantly increased to over 1.5 million cases annually [1]. The reasons for this rise are multifactorial and include an older population

with more chronic diseases, increased use of immunosuppressive medications, and emergence of multidrug-resistant infections. Increased awareness and reporting also play a role [2,3].

Fortunately, mortality in sepsis has been decreasing in recent years [4,5]. A 12-year study of 101,064 patients with sepsis and septic shock from 171 intensive care units in Australia and New Zealand reported a 50% risk reduction (from 35 to 18%) in in-hospital mortality from 2000 to 2012 [2]. The primary reason for the improved mortality in sepsis can be attributed to improved understanding of the hemodynamic derangements in sepsis. Large clinical trials have led to improvements in the approach to fluid resuscitation and use of vasopressors [6]. However, advances have been more limited with regard to control of the overwhelming inflammatory response leading to endothelial damage and mitochondrial dysfunction. More than 100 phase 2 and phase 3 clinical trials have tested agents aimed at controlling the inflammatory response in sepsis, but all of these efforts have ultimately failed to produce a novel pharmacological agent that improves sepsis outcomes [7]. This may be because therapeutic agents aimed at a single molecular or cellular target may have unpredictable, unanticipated, or unwanted downstream effects and that a single agent is not responsible for the progression of the sepsis cascade.

The combination of vitamin C, hydrocortisone, and thiamine has been suggested to have promise as a combination adjuvant therapy for the treatment of sepsis based on *in vitro*, animal and clinical studies. *In vitro* studies have shown that vitamin C acts as a powerful antioxidant to scavenge free radicals, serves as a co-factor for catecholamine synthesis, and enhances T-cell function [9-12]. In animal studies, vitamin C prevents endothelial cell dysfunction. Phase I clinical studies in septic patients have shown decreasing vasopressor requirements and improved sequential organ failure assessment (SOFA) scores [13,14] with Vitamin C. Large randomized studies have not shown beneficial effects of hydrocortisone alone in the treatment of sepsis [15,16]. However, hydrocortisone has been shown to have a synergistic effect with vitamin C in preserving endothelial function in cultured lung tissue [17]. Thiamine has been shown to prevent renal oxalate crystallization when vitamin C is administered in high doses. Supplementation improves survival in septic shock patients with thiamine deficiency, possibly due to its role as a co-factor for enzymes in the KREBS cycle [18,19]. A recent study by Mark P., *et al.* showed that use of vitamin C, hydrocortisone and thiamine in septic patients hospitalized in the intensive care unit (ICU) in -- addition to standard care improved mortality and outcomes [8]. This was a before-and-after non-randomized retrospective study with 47 patients in both the experimental and control groups. Mortality was 8.5% in the treatment and 40.4% in the control group ($p < 0.001$). Given the high mortality and costs associated with sepsis and promising effects of vitamin C, hydrocortisone, and thiamine in *in vitro*, animal and clinical studies, we pursued the first randomized prospective study to evaluate the role of triple therapy in septic patients.

Materials and Methods

This randomized, prospective, non-blinded pilot study was designed to compare the efficacy of triple therapy in addition to standard ICU care to usual ICU care alone. Institutional review board was filed at University of Southern California and approved by the IRB committee on 09/2018, with IRB number: IRB00002880. All patients greater than 18 years old admitted to the Los Angeles County-University of Southern California (LAC-USC) Medical Center ICU from the emergency department or from the general medical floors with the primary diagnosis of septic shock were eligible for enrollment. Septic shock was defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation with a serum lactate level over 2 mmol/L as per the Third International Consensus Definitions for Sepsis and Septic Shock [20]. Exclusion criteria included patients unwilling or unable to consent, incarcerated patients, patients with terminal dementia or enrolled in hospice, patients with active malignancy, patients with other causes of shock including cardiogenic shock, cardiac tamponade, massive pulmonary embolism, tension pneumothorax, active hemorrhagic shock, abdominal compartment syndrome, active adrenal insufficiency, and active intracranial hemorrhage/ischemic cerebrovascular accident, pregnant or lactating patients, and patients with active kidney stones.

Randomization was performed via block randomization with blocks of 4 patients using RedCap software. After randomization, the study investigators informed the treating ICU teams about the results of the randomization. Those in the treatment arm were assigned to receive the treatment which included: IV vitamin C at 1.5g q6 hours for 4 days or until ICU discharge, IV hydrocortisone at 50 mg q6 hours for 7 days or until ICU discharge followed by a rapid 3-day taper to 50 mg q8 hours, 50 mg q12 hours, and 50 mg daily, and IV thiamine at 200 mg q12 hours for 4 days or until ICU discharge in addition to standard ICU care. Standard and usual ICU care (antibiotics, airway management, renal replacement therapy, laboratory assessment, vasopressor need) was provided at the discretion of the ICU team to all patients enrolled in the study. The control group received standard ICU treatment.

The primary endpoint of the study was 28-day ICU mortality. Secondary endpoints included: vasopressor or inotropic medication requirements, serum lactate, mechanical ventilation requirement, continuous renal replacement therapy (CRRT) or hemodialysis (HD) requirement, daily creatinine level and urinalysis, days in the medical ICU, days in the hospital. Data were collected via RedCap.

Data were analyzed using the statistical software R and GraphPad Prism v. 8.0. Baseline demographics and septic shock severity were compared between control and treatment groups: For normally-distributed continuous variables, group means and standard deviations were reported and student's *t*-tests were performed. Continuous variables that were not normally distributed were compared using Mann-Whitney *U* tests. Categorical variables were compared using chi-squared tests. For variables collected as repeated measures over time, a Restricted Maximum Likelihood (REML) mixed effects model was used to assess differences between treatment groups over time (interaction term). Predictors of mortality were assessed through a binomial multiple logistic regression model testing all baseline and demographic predictors. Significant predictors then were tested in a reduced model. For all analyses, a p-value<0.05 was considered statistically significant.

Results

A total of 41 patients were enrolled in this pilot study. Overall, the baseline characteristics were similar among both groups limiting confounders within the study; however, sex, BMI, and baseline lactate levels slightly, but significantly, differed between groups (p's <0.05) (Table 1). Groups had significantly different distributions of primary diagnosis ($p < 0.05$) as sources for septic shock; however pneumonia was the most common diagnosis in both groups. ICU length of stay was similar at 4.5 versus 3 days ($p > 0.35$). Mortality trended higher in the treatment group at 50% vs 25% but this did not reach statistical significance ($p < 0.20$). Heart rate significantly decreased over time ($p < 0.004$), and this pattern over time did not differ between groups (time x group interaction: $p < 0.12$) (Figure 1). Likewise, there was an overall decline in percentage of patients requiring vasopressors therapy over time ($p < 0.005$), which did not differ between the two groups (time x group interaction: $p > 0.72$) (Figure 2). Lactic acid resolution over time was significant for an increase in the treatment group at hour 72 prior to resolution at hour 84 in both groups (Figure 3). The percentage of patients requiring mechanical ventilation over time significantly differed between the two groups (time x group interaction: $p < 0.007$) (Figure 4). Finally, use of acute renal replacement therapy (CRRT) significantly differed over time (time x group interaction: $p < 0.02$) (Figure 5). No complications or adverse outcomes were reported in either group (Table 2). Additionally, a logistic regression model showed that a model including platelets and lactic acid at baseline were most predictive of mortality (Table 3). Calculated odds ratios estimate that a one unit increase in platelets leads to a 1.6% less odds of death at 28 days.

	Control (n = 21)	Treatment (n = 20)	p-value
Age	58.86	60.3	0.72
Sex - Male	10	15	0.07
BMI	23.8	28.1	.03
Time to antibiotics	99 minutes	41 minutes	.07
Primary Diagnosis (%)			.03
• Pneumonia	7 (33%)	6 (30%)	
• Urosepsis	4 (19%)	5 (25%)	
• Bacteremia	3 (14%)	2 (10%)	
• GI	3 (14%)	4 (20%)	
• Other	4 (19%)	3 (15%)	

Temperature	36.81	36.8	0.97
Hgb	11.8	9.55	.38
Platelet	149	117	.07
WBC	15.1	11.1	.45
Lactate	2.9	4.3	.01
Creatinine	1.21	1.31	.72
BUN	32	25.5	.71
MAP	77	70.5	.35
HR	105.7	105.6	.99
Procalcitonin	4.31	11.82	.14
SOFA	8.7	11.36	.10
APACHE II	18	24.45	.12
Mortality	25%	50%	0.19
ICU LOS	4.5 days	3 days	0.36

Table 1: *Demographics and baseline characteristics.*

	Control Group	Treatment Group
Adverse Events	0%	0%
Kidney Stones	0%	0%

Table 2: *Adverse outcomes were absent amongst the two groups.*

	Estimate	Std. Error	p-value	Odds Ratio (OR)	CI of OR: 2.50%	CI of OR: 97.50%	Z-value
Platelets	-0.017	.006	0.008	0.98	0.969	0.994	-2.635
Lactic acid	0.17	.08	.05	1.185	0.983	1.436	1.919

Table 3: *Platelet and lactic acid levels form a predictive model for 28-day mortality.*

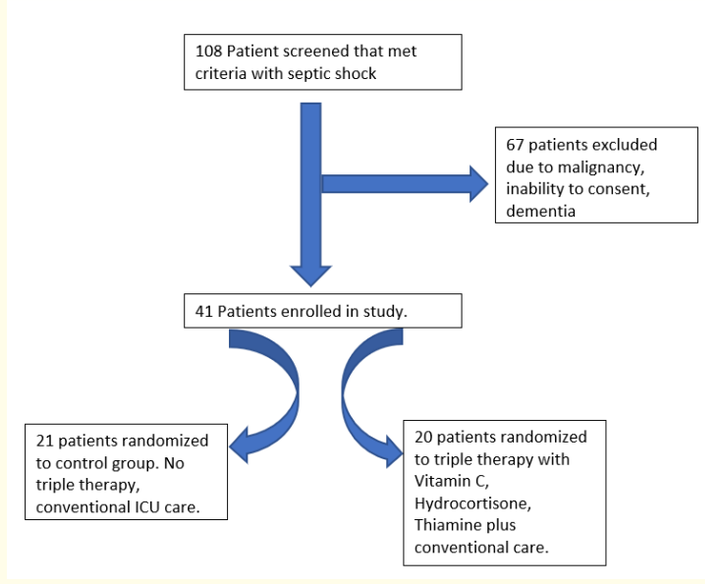

Figure 1: *Schematic of patient screening and selection.*

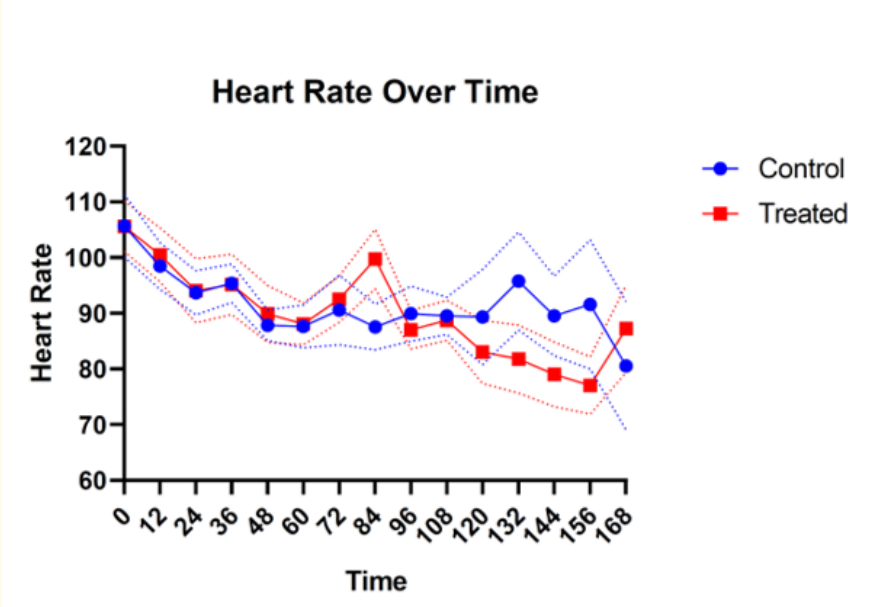

Figure 2: *Heart rate decreases over time similarly in each treatment group.*

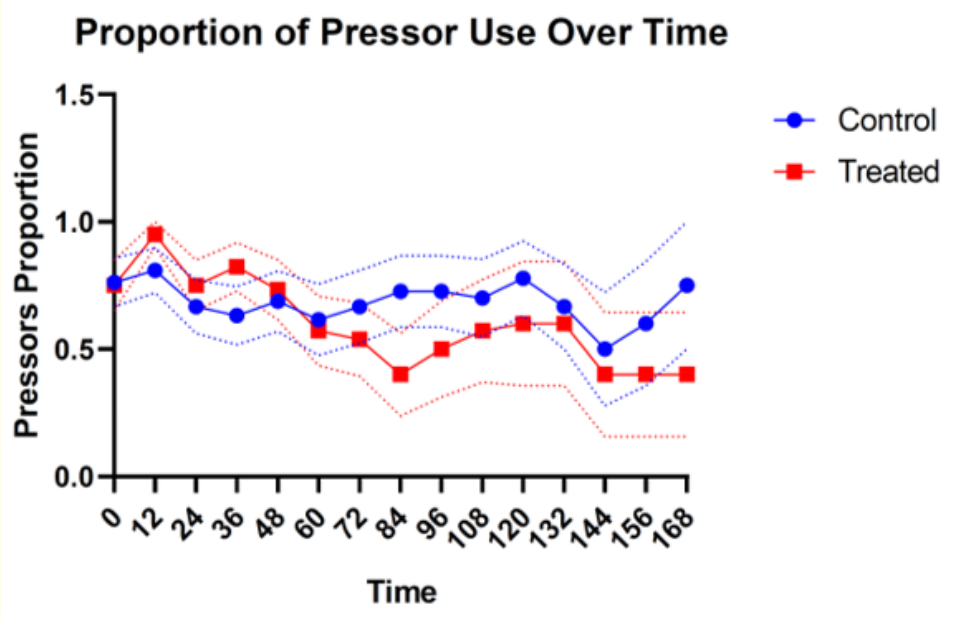

Figure 3: *Proportion of vasoactive use over time similarly decreases in both groups.*

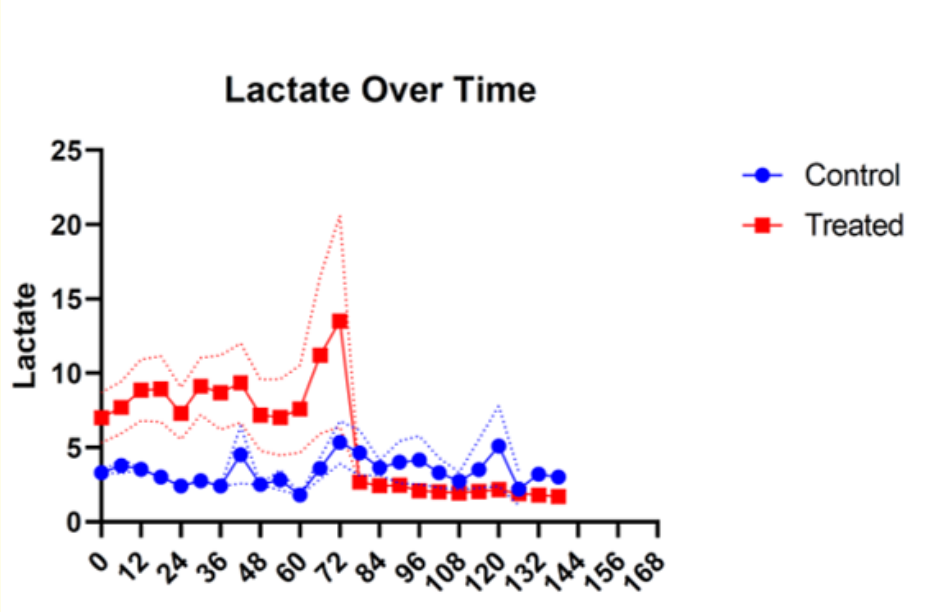

Figure 4: *Lactic acid levels do not significantly differ between groups over time.*

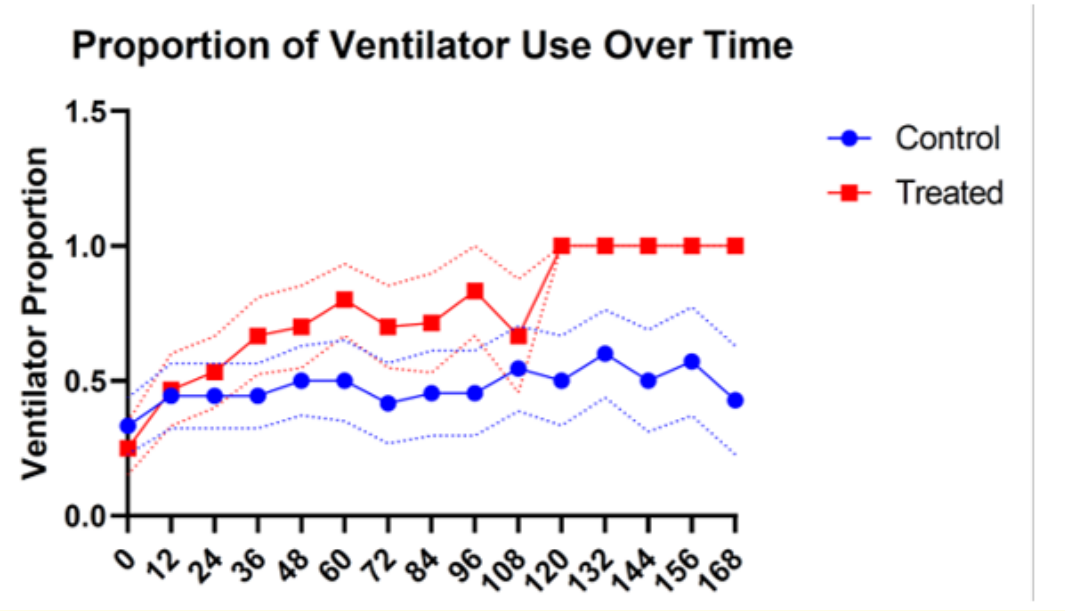

Figure 5: *Percentage ventilator use over time differs between treated and control groups.*

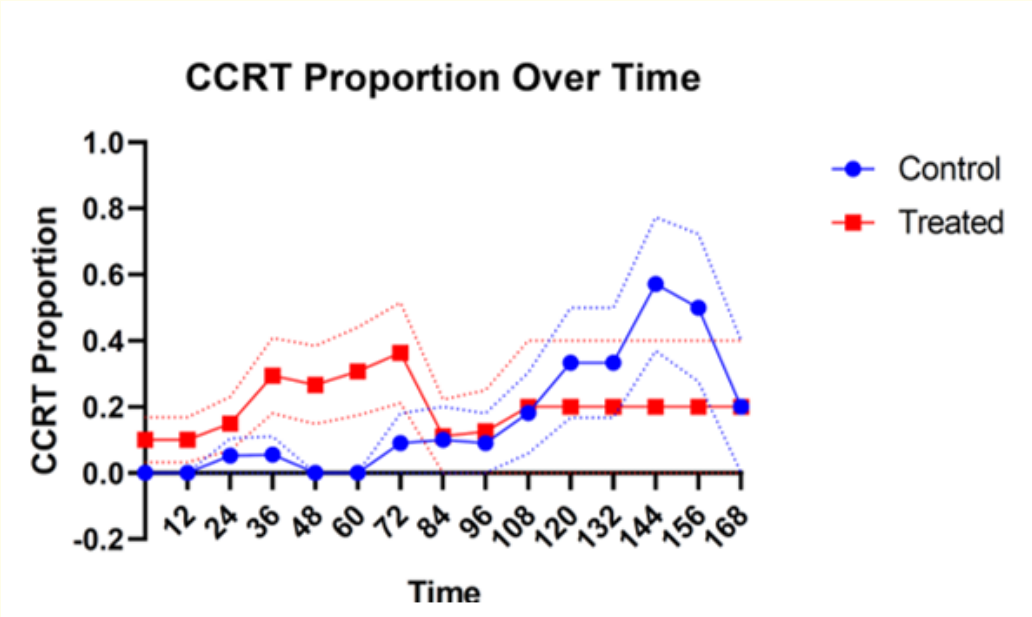

Figure 6: *CRRT use over time differs between treatment groups.*

Discussion and Conclusion

This pilot study is the first prospective evaluation of the effects of IV vitamin C, hydrocortisone and thiamine in the treatment of septic shock. Previous prospective studies have evaluated the effects of these medications individually in patients with septic shock; however, none have evaluated them synergistically [13-19]. In a retrospective study, Marik., *et al*. evaluated the effects of triple therapy in patients with septic shock, the protocol of which was the same as in the current study [8].

Our study suggests little benefit with the addition of triple therapy in the treatment of septic shock. Although our sample size was small, both triple therapy and control groups had similar baseline characteristics and severity of illness as defined by procalcitonin, SOFA scores and APACHE II scores. There was a slight difference in the lactic acid and BMI between the groups. This difference was likely due to the small sample size, however we do not think these affected the overall outcomes given that the rest of the baseline values were similar. There was a trend towards increased mortality in the triple therapy group that did not reach statistical significance perhaps due to the small number of patients. There were no significant differences in ICU length of stay, vasopressor use over time or lactic acid clearance. The treatment group showed a delayed in weaning from the ventilator that did reach statistical significance, as well as a higher requirement for acute renal replacement therapy. Even though the control group was able to be weaned from renal replacement therapy much faster, the number of patients requiring renal replacement therapy at the end of 7 days was similar. These results are in marked contrast to the published data of Marik., *et al.* study and smaller phase I studies investigating each medication individually in the treatment of septic shock Overall, this study showed no benefit to the addition of triple therapy in the treatment of septic shock, with an early propensity towards increased mortality, delayed weaning from ventilator support, and delayed improvement in renal function. This study suggests that triple therapy has no benefit in the treatment of septic shock, and may delay ventilator weaning and renal function, and may potentially increase mortality.

A binary logistic regression model of all the variables was calculated interpedently to determine whether any baseline characteristics had predictive value for 28 day in-hospital mortality. Our model found that baseline platelets and lactic acid were most predictive of the binary outcome hospital mortality. This preliminary finding warrants validation in an independent large sample to assess the predictive validity of these clinical measures.

This is the first prospective study looking at the effects of triple therapy, and all patients were randomized to treatment group and control group, therefore limiting confounders. Patient with history of malignancy were excluded to reduce con-founders. Our study had several limitations including a small sample size, which may affect the overall power and significance of the results. We did however elect to stop the study earlier than our planned enrollment of 40 patients in each group as there was a trend towards higher mortality in the triple therapy group. The study design had some intrinsic limitations unique to our hospital system. We were only able to enroll patients into the study after arrival into the ICU from the emergency department (ED) rather than on presentation to the ED. Informed consent was also difficult to obtain in our patient population as many patients were deemed unable to make decisions for themselves. The time it took to find appropriate surrogate decision makers delayed administration of triple therapy. However, all patients enrolled in the treatment arm of the study were able to receive triple therapy within 24 hours of sepsis diagnosis. A larger scale prospective trial is needed to confirm these results on the effects of triple therapy on septic shock.

Interpretation

This is the first prospective study evaluating the effects of triple therapy (IV vitamin C, hydrocortisone, and IV thiamine) in patients with septic shock. In this small sample size prospective pilot study, we show that triple therapy had no effect on ICU length of stay, weaning from vasoactive drugs or resolution of septic shock. However, there was a trend towards increased mortality in the triple therapy group, delayed weaning from ventilator support and delayed improvement in renal function. For these reasons, the study was terminated earlier than anticipated.

Take Home Point:

- **Study Question:** What is the effect of triple therapy (vitamin C, hydrocortisone, and thiamine) in septic shock in addition to standard ICU management?
- **Results:** No significant difference was identified in this prospective study with the addition of triple therapy. There was a slight increase trend towards increased mortality in the tripe therapy group which did not reach statistical significance.
- **Interpretation:** This prospective human study suggests triple therapy has limited use in the treatment of septic shock; larger studies should be pursued prior to widespread usage in septic shock.

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