International Journal of Advanced Research in Medicine

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The effect of intravenous Vitamin C, thiamine and hydrocortisone on the outcome of septic patients

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Abstract
Background: Sepsis is a critical medical illness with potentially fatal consequences, prompting the exploration of novel therapeutic interventions aimed at improving patient outcomes. The objective of this study was to assess the influence of administering thiamine and intravenous vitamin C together with hydrocortisone on the prognosis of septic patients in the intensive care unit (ICU).
Methods: The current research encompassed 60 patients with sepsis or septic shock into two equal group: the treatment group received intravenous (IV) hydrocortisone, vitamin C and thiamine plus the ordinary medical treatment for sepsis however, the control group received only the ordinary medical.
Results: The sepsis related organ failure assessment (SOFA) score was lower in the treatment group compared to the control group, but it didn't reach a significant difference. The mortality rate was lower in the treatment group compared to the control group (46.7% and 63.3%); however, it didn't reach a statistically significant value. With multivariate regression analysis, presence of lower diastolic blood pressure (DBP) and hypertension (HTN) were shown as independent risk factors for mortality.
Conclusion: The use of mentioned drugs before did not provide a hastened recovery of septic shock as compared to traditional therapeutic approaches.

Keywords: Sepsis, septic shock, vitamin C, thiamine, hydrocortisone

Introduction

Septic shock and sepsis and have a worldwide impact, affecting a population exceeding 30 million individuals, with an associated fatality rate of around 25% [1, 2].

The prevailing protocols for patient care include ensuring sufficient fluid resuscitation, delivering wide spectrum antibiotics within a one-hour duration, selecting for norepinephrine as the preferred vasopressor, and contemplating the use of hydrocortisone in cases of septic shock that do not respond to initial treatment [2].

In recent years, there has been an increased focus on the utilization of thiamine, IV vitamin C and hydrocortisone as a therapeutic approach referred to as "the vitamin C protocol" [3] for septic shock and sepsis.

Vitamin C has been demonstrated to enhance glucocorticoid receptor sensitivity by exerting antioxidant properties and acting as a free radical scavenger. This property facilitates the increased cellular absorption of glucocorticoids, including hydrocortisone. Subsequently, Hydrocortisone enhances the activity of the sodium vitamin C transporter 2 receptor, leading to an increase in the absorption of vitamin C [4].

On the contrary, the degradation product of high-dose vitamin C is oxalate, which has the potential to accumulate in the kidneys and cause acute kidney injury (AKI). Thiamine is required for the transformation of this insoluble metabolite into a water-soluble byproduct [5-7] in order to facilitate its elimination.

Our research was to assess the impact of providing intravenous vitamin C and thiamine, together with hydrocortisone, on the prognosis of septic patients in the intensive care unit (ICU).

Patients and Methods

Prospective randomized comparative research was undertaken on a cohort of sixty patients, including individuals of both genders, who satisfied the clinical criteria for sepsis or septic shock and were within the age range of 50 years or younger.

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The study was done over a period of six months, spanning from 2021 to 2022, after the necessary consent from the Ethical Committee of Tanta University and the ICU departments of internal medicine and anaesthesia at Mabaret El Asafra Hospital in Egypt. The researchers received written informed consent from either the unconscious patient or their legal guardians.

The study's exclusion criteria were the lack of informed consent and a documented medical history indicating adverse responses to any of the drugs supplied.

The patients were then separated into equal groups by a random process

Group I: (Treatment group) consisted of 30 patients who were given hydrocortisone, intravenous vitamin C, and thiamine, in addition to the standard medical therapy including antibiotics, fluids, and vasopressors.

Group II: (Control group) consisted of 30 septic patients who had standard medical treatment, which included the administration of fluids, vasopressors, and antibiotics, without any further interventions such as tibial tuberosity transfer (TTT).

A full battery of diagnostic tests was administered to all patients, including taking their medical history, running blood tests (including a complete blood count, arterial blood gas analysis, serum sodium and potassium levels, liver and kidney function tests, and serum lactate levels), imaging studies (including CT scans of the brain or chest), and microbiological sample culture and sensitivity (including samples from sputum, urine, pleural fluid, or infected IV lines based on suspected site, type of infection, infection site, and pathogenic organisms). Finally, neurological evaluations were performed, using tools like the Glasgow Coma Scale and a quick sepsis-related organ failure assessment score recorded in the emergency department. The Respiratory Intermediate Care Unit (RICU) recorded the SOFA score upon admission and again on days 3 and 7. Furthermore, The Acute Physiology and Chronic Health Evaluation (APACHE II) score was recorded within 24 hours after the patient was admitted to the Respiratory Intensive Care Unit (RICU). The management protocol indicated in the most recent iteration of the Surviving Sepsis Campaign bundle was given to all patients [8].

1. Performing a serial measurement of lactate if it exceeded 2 mmol/L.
2. Blood culture performed before administering antibiotics.
3. Immediate administration of broad-spectrum antibiotics is recommended after blood culture aspiration. The preferred first drugs are mono-broad-spectrum antibiotics, carbapenems, or penicillin/β-lactamase inhibitors. Patients with septic shock, who were at a high risk of death, were treated with combination therapy using at least two different types of antibiotics. The treatment took into account factors such as the source of the infection, the kind of organism involved, and the most common organisms seen in septic patients.
4. Fluid resuscitation was initiated as soon as possible with 30 mL/Kg crystalloid fluid in cases of hypotension or when lactate levels exceeded 4 mmol/L.
5. Perfusion evaluation utilizing CVP and oxygen saturation at prominent venues.
6. In the case of persistent hypotension, a vasopressor (norepinephrine was administered) was utilized to ensure that the mean arterial pressure remained at or above 65 mmHg.
7. Patients diagnosed with sepsis, who exhibited continuous hemodynamic instability after receiving sufficient fluid resuscitation and vasopressor therapy, were subjected to further treatment including the administration of hydrocortisone at a dosage of 200 mg intravenously each day).
8. Glycemic control was achieved through the administration of insulin when the patient's blood glucose level surpassed 180 mg/dL.

Treatment regimen in group 1 [4]

For four days, 200 mg of thiamine IV every 12 hours was administered, in addition to 1.5 g of vitamin C every six hours. The physician established the hydrocortisone dosage as follows: 50 mg IV every 6 hours, 100 mg IV every 8 hours, or 10 mg continuously IV infusion. Following the administration of steroids for a period of seven days, they were tapered off progressively over the subsequent three to five days.

The ICU mortality rate was the principal outcome. Length of stay in the intensive care unit, need for any subsequent supportive measures, duration of ventilatory support, duration of vasopressor therapy, renal replacement therapy (RRT) necessity in patients with acute kidney injury (AKI), and changes in serum creatinine, lactate, and SOFA scores were categorized as secondary outcomes.

Statistical analysis

The statistical analysis was performed using SPSS v26 (IBM Inc., Chicago, IL, USA). The mean and standard deviation (SD) were used to depict the quantitative variables. A one-sample Student's t-test was used to assess the disparities between the two groups with respect to these factors. The qualitative variables were expressed as frequencies and percentages (%) and assessed using either Fisher's exact test or the Chi-square test, depending on the appropriateness of each test. The research used univariate and multivariate logistic regression analysis to identify the risk factors associated with predicting a categorical outcome variable. A two-tailed P value below 0.05 was considered to indicate statistical significance.

Results

Regarding source of sepsis, age, sex and comorbidities, there was no significant difference in both groups. Table 1.

Table 1: This table shows the source of sepsis, demographic data and comorbidities in the all groups

		Group I (Treatment group) (n= 30)	Group II (Control group) (n= 30)	P value
Age (years)		50.63±10.91	53.20±8.49	0.992
Sex	Male	20 (66.7%)	21 (70%)	0.781
	Female	10 (33.3%)	9 (30%)	
Comorbidities				
DM		16 (53.3%)	11 (36.7%)	0.194

HTN	10 (33.3%)	17 (56.7%)	0.069
Chronic kidney disease	6 (20%)	7 (23.3%)	0.745
Chronic liver diseases	8 (26.7%)	3 (10%)	0.095
COPD	4 (13.3%)	1 (3.3%)	0.161
Thyroid disorders	5 (16.7%)	2 (6.7%)	0.228
Source of sepsis			
RTI	12 (40%)	11 (36.7%)	0.648
UTI	8 (26.7%)	6 (20%)	0.779
bed sores	3 (10%)	1 (3.3%)	0.514
blood infection	2 (6.7%)	4 (13.3%)	0.638
cellulitis	2 (6.7%)	3 (10%)	0.647
intrabdominal sepsis	3 (3.3%)	5 (16.7%)	0.061

Data are demonstrated as average ± SD or frequency (%). DM, COPD, UTI, RTI

Regarding MAP, SOFA and vital signs, there was no significant difference in both groups along study duration. There was high significant difference in MAP with time in each group. Table 2.

Table 2: This table shows SOFA, vital signs and MAP along the study duration in the all groups

Variables	Group I (Treatment group) (n= 30)	Group II (Control group) (n= 30)	P value
SOFA score			
Day 1	12.03±4.36	12.90±5.36	0.613
Day 2	12.67±4.10	13.47±5.13	0.704
Day 3	12.77±3.62	13.10±4.34	0.819
Day 4	12.37±3.30	12.77±4.07	0.787
Day 5	12.43±3.17	12.59±4.16	0.652
Day 6	12.24±3.8	12.36±4.16	0.718
Day 7	12.3±4.01	12.46±4.23	0.686
Repeated measures ANOVA	0.251	0.251	
Vital signs			
Temperature	38.25±0.63	38.39±0.53	0.174
HR	125.18±11.71	124.25±10.73	0.650
RR	31.68±2.97	31.62±3.28	0.907
MAP			
Day 1	64.33±15.68	61.64±13.09	0.118
Day 2	80.50±12.3	79.67±10.88	0.794
Day 3	81.25±10.02	80.75±11.7	0.730
Day 4	86.95±11.91	86.42±12.36	0.876
Day 5	89.49±11.5	87.17±11.51	0.420
Day 6	88.02±12.97	86.91±12.07	0.384
Day 7	86.98±13.65	84.64±12.19	0.390
Repeated measures ANOVA	F= 19.058 $p<0.001^*$	F= 21.114 $p<0.001^*$	--

Data are demonstrated as mean ± SD or frequency (%). SOFA, ANOVA, HR, PR, MAP, F: repeated measures ANOVA

There was no significant difference in both groups, regarding analysis of ABG and laboratory data. Table 3.

Table 3: This table shows laboratory data and analysis of ABG in the all groups

Variables	Group I (Treatment group) (n= 30)	Group II (Control group) (n= 30)	P value
Hemoglobin(HB) (gm./dl)	9.79±1.81	9.29±1.85	0.139
White blood cells (*103/L)	16.62±4.71	15.39±3.35	0.102
Platelets (*103/microliter)	158.20±40.59	163.03±38.60	0.505
Serum Creatinine (mg/dl)	2.75±1.67	2.85±1.68	0.791
Serum urea (mg/dl)	124.62±53.39	127.18±52.47	0.755
Serum Na (mEq/L)	131.05±9.74	133.05±9.34	0.253
Serum Potassium (mEq/L)	4±0.97	4.21±.84	0.207
SGOT (IU/l)	111.55±91.95	89.50±60.52	0.123
SGPT (IU/l)	118.88±86.93	95.10±57.45	0.080
Serum bilirubin (mg/dl)	1.58±1.03	1.35±0.54	0.127
CRP	186.25±24.19	193.17±30.08	0.326
ESR	47.58±12.37	50.18±13.66	0.132
ABG			
PH	7.32±0.05	7.31 ±0.04	0.198
PCO2	41.12±17.24	37.53±14.61	0.222
PO2	104.96±51.26	113.65±46.96	0.335
HCO3	15.21±4.58	15.01±3.47	0.796

Data are presented as mean ± SD or frequency (%), SGOT, SGPT, CRP, ESR, ABG, PCO_2: carbon dioxide, PO_2: partial pressure of oxygen, HCO_3: byproduct of your body's metabolism

Regarding primary and secondary result, there was no significant difference in both groups. Table 4.

Table 4: This table shows final primary and secondary results in the all groups

Variables	Group I (Treatment group) (n= 30)	Group II (Control group) (n= 30)	P value
Died	14 (46.7%)	19 (63.3%)	0.194
Survived	16 (53.3%)	11 (36.7%)	
Vasopressor dose (Norepinephrine) (mcg/kg/minute)	0.35±0.08	0.38±0.10	0.124
length of stay (days)	10 (8-16)	11 (8-15)	0.098
Ventilator free days	8 (7-11)	9 (7-12)	0.909
Vasopressor free days	9 (7-14)	10 (7-13)	0.672

Data are demonstrated as mean ± SD or frequency (%) or median (IQR)

There was significant difference (age, HTN, CKD, SOFA, SBP, DBP, PH, PCO_2, PO_2, HCO_3 and CRP) and there was no significant difference (DM, CLD, COPD and thyroid disorders), regarding univariate regression analysis.

Regarding multivariate regression analysis, there were significant difference (HTN and DBP) and there were no significant difference(Age, DM, CKD, CLD, COPD , thyroidd disorders, SOFA,SBP,pH, PCO_2, PO2, HCO3 and CRP). Table 5.

Table 5: This table shows univariate and multivariate regression analysis of predictors for mortality (n= 33)

Variables	Univariate analysis	Multivariate analysis		
		OR	95% CI for OR	P value
Age	0. 29*	1.113	0.937-1.332	0.211
DM	0.0273	--	--	--
HTN	0.012*	0.746	0.514-0.927	0.035*
CKD	0.038*	0.482	0.274-0.728	0.122
CLD	0.142	--	--	--
COPD	0.396	--	--	--
Thyroid disorders	0.267	--	--	--
SOFA	0.038*	0.482	0.274-0.728	0.122
SBP	< 0.001*	1.007	0.999- 1.014	0.071
DBP	< 0.001*	1.047	1.005-1.91	0.027*
PH	0.001*	1.004	0.787-1.28	0.973
PCO_2	0.021*	0.692	0.340-1.407	0.309
PO_2	0.008*	1.004	0.991-1.017	0.561
HCO_3	0.002*	1.186	0.694-2.07	0.532
CRP	0.001*	1.040	0.952-1.136	0.831

Data are presented as number, DM: diabetes mellitus, HTN, CKD, CLD: chronic liver disease, COPD, SOFA: sequential organ failure assessment, SBP, DBP, PCO_2: carbon dioxide, PO_2: partial pressure of oxygen, CRP

Discussion

Septic shock and sepsis are major contributors to worldwide mortality. Sepsis is the primary cause of mortality in non-cardiac patients in critical care units, as stated by the Centres for Disease Control and Prevention [9].

Critically ill patients frequently experience thiamine deficiency, which can result in lactic acidosis as pyruvate is unable to access the Krebs cycle [10]. Research has demonstrated that administering 200 mg of IV thiamine every 12 hours can effectively reduce lactate levels in critically ill patients who have a pre-existing thiamine deficiency [7].

In the present investigation, upon conclusion of the research, it was observed that 34 out of 60 instances experienced fatality, resulting in an incidence rate of 55%. The death rate seen in our research was found to be comparable to the findings published by Hassan et al. [11] at Assiut University, where the mortality rate was documented as 64.7%. Nevertheless, the prevalence indicated in another Egyptian research conducted by Amer et al. (39%) was lower than the aforementioned [12].

Throughout the entirety of the present investigation, the treatment group exhibited a lower SOFA score than the control group; however, this disparity did not attain statistical significance.

This finding is consistent with the results reported by Marik et al. [3], which indicated a marginal improvement in the QSOFA score for the treatment group over the control group within 72 hours (3.5±3.3 vs. 1.8±3.0, respectively; P=0.02).

In the current study, the mortality rate was lower in the treatment group compared to the control group (46.7% and 63.3%), however, it didn't reach a significant value (p=0.194).

According to Sevransky et al. [13], there was a difference of 2.7% (95% CI, −11.3% to 5.8%), with death rates of 40.5% and 37.8% in the intervention and control groups, respectively, after 180 days. This was in accordance with Litwak et al. [14] who showed that the mortality rate for septic patients receiving triple therapy did not differ statistically significantly from that of those receiving standard medical treatment. This finding contradicted with the finding of Marik et al. [3], who showed that the hospital rate of mortality in the treatment group was 8.5% (4 out of 47 patients), even though it was 40.4% (19 out of 47 patients) in the control group (p<.001).

In the current study, the mean required dose of Norepinephrine as a vasopressor was 0.35±0.08 mcg/kg/minute in the treatment group and 0.38±0.10 mcg/kg/minute in the control group. Decreasing the dose in the treatment group, but without achieving a statistically significant value (p= 0.124). Within the same line, the research carried out by Marik et al. [3] shown that, on

average treatment group patients were successfully withdrawn off vasopressors within a mean duration of 18.3±9.8 hours after the initiation of therapy using the vitamin C regimen. Vitamin C administration cause a predictable decrease in the dosage of pressors within the time frame of 2 to 4 hours after the first infusion. In the control group, the average duration of vasopressor usage was found to be 54.9±28.4 hours, which was statistically significant ($p <$ .001). It is important to note that in the control group 9 patients experienced rising dosages of vasopressors and ultimately succumbed to refractory septic shock.

People in the control group were in the hospital for 11 (8-15) days, while people in the treatment group were there for 10 (8–16) days. Among the 2 groups, there was no statistically significant difference (p= 0.098). The findings of Chang et al. [15] were consistent with this. In the treated group, the average length of stay in the intensive care unit was 7.5 days (4-12.8), while in the control group, it was 7.5 days (4-11.8). The disparity was not significant. This aligns with the findings of Marik et al [3]. According to them, the median ICU stay in the treatment group was 4 (3-5) days, whereas in the control group it was 4 (4-10) days, which was not a significant difference. The present study observed that patients in the treatment group necessitated vasopressors and mechanical ventilation for a reduced duration. However, this difference did not reach statistical significance ($p > 0.05$, 0.909). The findings of the study are consistent with those of Fujii et al. (16), which indicated that between the intervention group and the control group, there was no statistically significant difference in the duration of survival without the need for vasopressors until day 7 (168 hours) following randomization. The intervention group had a median length of 122.1 hours (interquartile range [IQR], 76.3-145.4 hours), while the control group had a median duration of 124.6 hours (IQR, 82.1-147.0 hours). The median of all paired differences between the *2* groups was -0.6 hours (95% confidence interval [CI], -8.3 to 7.2 hours), and the p-value was 0.83. Within the same line, Chang et al. [15] revealed that the median duration of mechanical ventilation did not differ significantly between the 2 groups. (126.5 h; 63.5-239.3 vs 94.5 h; 39.8-211).

In the current study, with univariate regression analysis, increasing age, presence of HTN, presence of CKD, increasing SOFA score, lower SBP, lower DBP, lower PH, higher PCO_2, lower PO_2, lower HCO_3 and increasing CRP were shown as risk predictors for mortality. However, the results of multivariate regression analysis demonstrated that decreased DBP and the presence of hypertension were independent risk factors for mortality.

In accordance with the findings of the current study, a previous study [17] reported that the non-survivor group had a higher mean age of 78 years (with a range of 73.8 to 83 years) and consisted of 52.8% males. Orak et al. [18] found that the age of individuals in the dead group was considerably higher compared to the non-died group (67.78 vs. 52.94 years, $p < 0.001$). This finding is consistent with the findings of the aforementioned investigation. According to the study conducted by Angus et al. [19], a positive correlation was seen between older age and death rates among septic patients, particularly in the elderly population. In contrast, an alternative investigation found no statistically significant difference between the cohorts of survivors and non-survivors (61.17 vs. 61.70 - p = 0.82). According to the

findings of Orak et al. [18], there was a greater incidence of diabetes and HTN among those who did not survive. The prevalence of HTN was shown to be 20.1% among those in the non-survivor group, while it was only 7.2% among survivors (p = 0.002). However, there was no significant difference seen in the prevalence of chronic renal disease between the two groups (p = 0.189).

In a separate investigation, the prevalence of HTN was shown to be 58.7% among non-survivors and 57.5% among survivors [21].

In the current study, decreasing the SBP and DBP on admission was associated with risk of mortality.

The findings of the current study exhibited partial concurrence with the research conducted by Shaikh and Yadavalli [22]. Their investigation revealed that non-survivors had greater average heart rate and breathing rate, whereas survivors exhibited lower mean systolic blood pressure and DBP. The findings of the present investigation are in contrast to a previous study that found no statistically significant change in mean arterial pressure (p = 0.465) [21].

Among the participants in the current study, a considerable correlation was found between the increase in SOFA score and mortality. This discovery aligns with the outcomes documented by Salem et al. [23], wherein they illustrated that the mean SOFA score for survivors was 9.6±1.8, whereas it was 10.5±2.2 for non-survivors. Between the 2 groups, a statistically significant difference in SOFA scores was also noted (p=0.005), according to the study. Recent research has confirmed that, among the variables recorded on day one, independent correlations exist between SOFA scores and the 28-day mortality and the severity of sepsis [24, 26]. Within the current study, CRP levels increasing were associated with increasing risk for mortality ($p > 0.05$, 0.326).

With respect to the arterial blood gas analysis, the present study identified lower pH, higher PCO2, lower PO2, and lower HCO3 as mortality risk predictors (p = 0.222, p = 0.335, p = 0.796, respectively). Similar findings were published in the study by Kim et al. [27]. The PH of survivors was 7.43 compared to 7.37 in non-survivors (p = 0.01). There was no difference in the bicarbonate concentration between the two groups, however (p = 0.093). Our study was limited by a small sample size, the fact that all patients were enrolled in multiple medical centres, which restricted the generalizability of the results, and our inability to assess the impact of renal dysfunction and hypoxemia on MPV elevations.

Conclusion
The use of mentioned drugs before did not provide a hastened recovery of septic shock as compared to traditional therapeutic approaches.

Financial support and sponsorship: Nil.

Conflict of Interest: Nil.

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