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ORIGINAL STUDY

Evaluation of the Effect of Using Vitamin C, Thiamine, and Hydrocortisone in Treatment of Sepsis

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Abstract

Objectives: **To explore the effect of adding vitamin C, thiamine, and hydrocortisone to traditional treatment in treatment of sepsis.**

Background: **Sepsis is a life-threatening syndrome of a dysregulated host response to infection. Sepsis remains a significant cause of morbidity and mortality, despite advances in diagnosis and treatment. Using vitamin C, thiamine, and hydrocortisone to traditional treatment (Marik protocol) may play a key role in treatment of sepsis.**

Patients and methods: **This case−controlled study was conducted on 44 Egyptian patients diagnosed with sepsis according to sequential organ-failure assessment score then divided into two equal groups, half of them treated with traditional treatment with sepsis for 5 days and the other half treated with Marik treatment that added on traditional treatment for 5 days, all patients undergo quick sequential organ-failure assessment, daily also close-monitoring vital data and sepsis markers (C-reactive protein, lactate, and procalcitonin), the need to mechanical ventilation and vasopressors, and then prognosis.**

Results: **There was a statistically significant improvement in the level of sepsis markers and vital data in patients receiving Marik treatment. Also, there was a highly statistically significant difference between both treatments in using mechanical ventilation, vasopressors, and prognosis of patients.**

Conclusion: **Marik treatment added to traditional treatment has a superiority over traditional treatment of sepsis. We recommended that addition of vitamin C, thiamine, and hydrocortisone to the traditional treatment of sepsis seems to improve the prognosis of patients with sepsis.**

Keywords: Hydrocortisone, Marik treatment, Sepsis, Thiamine, Vitamin C

1. Introduction

Sepsis is a life-threatening syndrome of a dysregulated host response to infection [1]. Over the course of the 20th century, numerous experimental and clinical trials demonstrate the importance of the host immune response to the manifestations of sepsis. However, the heterogeneity of the disease process posed serious difficulties in recognizing, treating, and studying sepsis [2]. Following diagnosis, successful sepsis-management hinges on prompt treatment of infection and correction of organ dysfunction. Suspected or documented infection and an acute increase of more than or equal to two sequential organ-failure assessment (SOFA) points of the task force considered that positive quick SOFA (qSOFA) criteria should also prompt consideration of possible infection in patients not previously recognized as infected. qSOFA criteria: altered mental status (GCS score <15), systolic blood pressure (BP) less than 100 mmHg, and respiratory rate more than 22 breaths per min [3]. Many clinicians now use track-and-trigger early warning score systems as a standard of care to identify patients at risk of deteriorating. Two examples of these scores are the National Early Warning Score (NEWS) and the Modified Early Warning Score (MEWS) used in the United Kingdom. These scores are validated tools for

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predicting poor outcomes and are commonly used in healthcare facilities [4]. Rapid recognition and resuscitation of patients with sepsis is therefore key to the effective management of sepsis. Deteriorating patients with a raised early warning score (such as a raised aggregate early warning score of 5 or above) should therefore be screened for infection [5]. Traditional sepsis-care bundles: bundles are a group of treatments that are built around the best evidence, and they are known to produce greater benefit when implemented together than as individual therapies [6]. Surviving Sepsis Campaign guidelines in 2008 incorporated sepsis-resuscitation bundle to be achieved in 6 h and sepsis-management bundle to be achieved in 24 h. In 2012, the 6-h resuscitation bundle was modified into two bundles, the severe-sepsis 3-h resuscitation bundle and the 6-h septic-shock bundle, which contain all therapeutic goals to be completed, respectively, within 3 and 6 h of presentation with septic shock [7]. Three-hour resuscitation bundle: measure initial serum lactate, obtain blood cultures prior to antibiotics, administer broad-spectrum antibiotics, and administer 30 ml/kg crystalloids for hypotension or lactate more than or equal to 4 mmol/l. Six-hour septic-shock bundle: apply vasopressors (for hypotension unresponsive to initial fluid resuscitation) to maintain mean arterial pressure more than or equal to 65 mmHg. In the event of persistent hypotension, despite fluid resuscitation (septic shock) or lactate more than or equal to 4 mmol/l, measure central venous pressure (CVP) and $ScvO_2$ [8]. Dr Marik and his group used a very intelligent idea. They used a mixture of drugs assuming their perfect synergism and looked at their effect on sepsis mortality [9]. The magic cocktail contains vitamin C, thiamine, and stress dose hydrocortisone. Thus, the aim of this study was to explore the effect of adding vitamin C, thiamine, and hydrocortisone to traditional treatment in treatment of sepsis.

2. Patients and methods

This is a prospective observational study that was carried out on 44 adult patients aged above 18 years old from both sexes with different sources of sepsis (surgical and nonsurgical sources) who attended to ICU at Menoufia University Hospital and Shebin El Kom Teaching Hospital, El Menoufia, Egypt during the period from 2020 to 2021.

A written consent was taken from all enrolled patients or their relatives, and the study was approved by the medical ethical committee of the hospital and by the research ethics committee of Menoufia Faculty of Medicine, Egypt.

The participants were diagnosed with SOFA score and were divided into two groups. Each study group consisted of 22 patients. For the first group, we started on the traditional treatment of sepsis, which included the following steps: antibiotics, drain pus, or remove infected tissues, giving intravenous fluids, and life-support measures, such as mechanical ventilation, dialysis, and pressor medications. Nutrition therapies were often given through a nasogastric tube or orogastric tube. The second group was managed with Marik protocol added to traditional treatment of sepsis, which included treatment as in the first group, plus vitamin C, intravenously 1500 mg every 6 h, hydrocortisone, intravenously 50 mg every 6 h, and thiamine, intravenously 200 mg every 12 h. Every patient was calculated for the qSOFA score daily, venous and arterial blood samples were obtained directly, and then the biochemical parameters were performed. Laboratory tests were investigated daily: complete blood count (hemoglobin, white-blood cells, and platelets), serum albumin, blood urea and serum creatinine, liver-function tests like alanine aminotransferase and aspartate aminotransferase, arterial samples obtained to measure arterial blood gases (pH, PCO_2, and HCO_3), serum electrolytes like Na, K, Ca, and Cl, glucose, serum procalcitonin (PCT), C-reactive protein (CRP), and serum lactate. We followed each patient state daily in two ways: laboratories: we have measured daily serum PCT, CRP, and serum lactate as a biomarker of sepsis. Clinical data: we have monitored patient vital sign and their improvement, then showed the effect of Marik treatment in early weaning from vasopressors, mechanical ventilation, decreased the mortality rate in patients with sepsis, and decreased the time of stay in the ICU.

2.1. Primary outcome

To assess the efficacy of vitamin C, hydrocortisone, and thiamine.

2.2. Secondary outcome

Reporting the time needed for weaning patients with sepsis from vasopressors and mechanical ventilation, the length of stay in the ICU, and the mortality rate.

2.3. Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA). Qualitative data

were described using number and percent. The Kolmogorov–Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, SD, median, and interquartile range. Significance of the obtained results was judged at the 5% level. The used tests were c^2 test: for categorical variables, to compare between different groups. Mann–Whitney test: for abnormally distributed quantitative variables, to compare between two studied groups.

3. Results

In the current study, there was no significant difference in age ($P = 0.430$) and sex ($P = 1.000$) between both groups. The percent distribution of all 44 patients included in our study have different comorbidities of sepsis, most causes are chest infection with value 27.3% for each group, then intestinal obstruction with value 22.7% for each group, then urology cause (urinary-tract infection, pyelonephritis, etc.) with value 13.6% for each group, then diabetic foot and neurosurgical cause (bacterial meningitis, etc.) and Fournier gangrene and central nervous system cause of sepsis with the same value for each cause about 9.1% for each group, and then finally hepatic cause (spontaneous bacterial peritonitis, etc.) with value 4.5% for each group. There were no significant changes between the two study groups as all patients according to SOFA score have more than 2 with mean values 7.23 ± 2.45, 7.50 ± 2.39, respectively, with P value 0.652 (Table 1).

There was improvement in mean arterial BP. The approximately pretreatment mean value of mean arterial BP of both study groups had the same value 57.92 ± 5.43, 56.86 ± 6.10, respectively, with P value 0.647, then from the first day of treatment, there was improvement of mean arterial BP in both groups over the first 5 days from treatment beginning with mean values 63.23 ± 9.99, 68.29 ± 12.96, 73.07 ± 15.90, 76.86 ± 18.19, and 77.60 ± 20.24, respectively, in traditional treatment, and the mean values of Marik protocol were 76.53 ± 10.56, 77.80 ± 10.66, 80.69 ± 11.29, 85.63 ± 12.67, and 87.0 ± 12.51, with P values 0.002, 0.039, 0.149, 0.144, and 0.139 (Table 2).

Both groups had a low pretreatment CVP, mainly in Marik group with P value 0.283, and after we start treatment, we found great improvement in CVP in both study groups, mainly in Marik group, with P values 0.263, 0.443, 0.915, 0.670, and 0.390. There were no significant changes in the level of SaO_2 after start treatment of sepsis with the two study groups as pretreatment P value was 0.212, and after start treatment, P values were 0.301, 0.941, 0.824, 0.477, and 0.163, respectively. Both regimens of treatment have improved the level of heart rate and respiratory rate with low time needed mainly in Marik protocol with P values (heart rate: 0.483, 0.412, 0.139, 0.131, 0.077, and 0.069) (respiratory rate: 0.095, 0.095, 0.040, 0.021, 0.027, and 0.006). Also, there were no significant changes between two regimens on the

Table 1. Comparison between the two studied groups according to demographic data, the classification of patients according to their comorbidities.

Variables	Group I ($N = 22$) [n (%)]	Group II ($N = 22$) [n (%)]	Test of significance	P
Sex				
Male	11 (50)	11 (50)	$\chi^2 = 0.000$	1.000
Female	11 (50)	11 (50)		
Age (years)				
Mean ± SD	53.64 ± 12.25	49.91 ± 18.15	$t = 0.798$	0.430
Diabetic foot	2 (9.1)	2 (9.1)	$\chi^2 = 0.000$	$^{FE}P = 1.000$
Fournier gangrene	2 (9.1)	2 (9.1)	$\chi^2 = 0.000$	$^{FE}P = 1.000$
Intestinal obstruction	5 (22.7)	5 (22.7)	$\chi^2 = 0.000$	1.000
Neurosurgical cause	2 (9.1)	2 (9.1)	$\chi^2 = 0.000$	$^{FE}P = 1.000$
Urology	3 (13.6)	3 (13.6)	$\chi^2 = 0.000$	1.000
Chest infection	6 (27.3)	6 (27.3)	$\chi^2 = 0.000$	1.000
Hepatic disorders	1 (4.5)	1 (4.5)	$\chi^2 = 0.000$	$^{FE}P = 1.000$
CNS infection	2 (9.1)	2 (9.1)	$\chi^2 = 0.000$	$^{FE}P = 1.000$
SOFA score				
Not sepsis (≤2)	0	0		
Sepsis (>2)	22 (100)	22 (100)	–	–
Mean ± SD	7.23 ± 2.45	7.50 ± 2.39	$U = 223.0$	0.652
Median (minimum–maximum)	7 (3–12)	7 (3–11)		

χ^2, χ^2 test; CNS, central nervous system; FE, Fisher exact; SOFA, sequential organ-failure assessment; t, Student t test; U, Mann–Whitney test.
Group I: traditional treatment.
Group II: traditional treatment + Marik protocol.
P value >0.05 is non significant.

Table 2. Comparison between the two studied groups according to mean arterial blood pressure.

	Pretreatment	$N = 12$	$N = 14$		
	Mean ± SD	57.92 ± 5.43	56.86 ± 6.10	$t = 0.464$	0.647
	D1	$N = 13$	$N = 15$	$t = 3.407$*	0.002*
MAP≥65	Mean ± SD	63.23 ± 9.99	76.53 ± 10.56		
	D2	$N = 14$	$N = 15$	$t = 2.166$*	0.039*
	Mean ± SD	68.29 ± 12.96	77.80 ± 10.66		
	D3	$N = 14$	$N = 16$	$t = 1.493$	0.149
	Mean ± SD	73.07 ± 15.90	80.69 ± 11.29		
	D4	$N = 14$	$N = 16$	$t = 1.511$	0.144
	Mean ± SD	76.86 ± 18.19	85.63 ± 12.67		
	D5	$N = 15$	$N = 15$	$t = 1.530$	0.139
	Mean ± SD	77.60 ± 20.24	87.0 ± 12.51		

MAP, mean arterial blood pressure; *t*, Student *t* test; *U*, Mann–Whitney test.
*Statistically significant at *P* value less than or equal to 0.05.

level of serum glucose as they showed mild improvement in RBG with *P* values 0.370, 0.687, 0.771, 0.925, 0.573, and 0.301. There was significant change on urinary output after start of treatment over the first 5 days with *P* value pretreatment: 0.968, and once treatment started with respect to 0.449, 0.805, 0.897, 0.770, and 0.970, with no superiority for each regimen on other regimens (Table 3).

Our results show no significant improvement in the result of serum PCT in traditional treatment group with mean of serum PCT (25.54 ± 24.73, 24.60 ± 24.40, 23.38 ± 22.82, 22.77 ± 23.34, and 22.47 ± 23.24, respectively), but we have slight improvement in the result of PCT in Marik group with mean of serum PCT (18.15 ± 16.29, 16.25 ± 13.26, 15.02 ± 11.13, 13.76 ± 9.07, and 12.64 ± 9.54, respectively), with no significant difference between two groups with *P* values 0.318, 0.405, 0.460, 0.474, and 0.342. There was no significant improvement in the result of serum lactate in traditional group with mean of serum lactate (13.66 ± 12.81, 13.31 ± 12.39, 12.31 ± 10.85, 12.26 ± 10.39, and 13.04 ± 11.46), but we have slight improvement in the result of serum lactate in Marik group with mean of serum lactate (7.68 ± 6.69, 6.79 ± 5.96, 6.33 ± 5.56, 5.17 ± 4.08, and 4.80 ± 4.36, respectively), with *P* values 0.098, 0.084, 0.049, 0.046, and 0.014. There was slight improvement in the result of CRP in traditional group with a mean of CRP (82.83 ± 56.42, 76.26 ± 49.89, 71.89 ± 41.90, 61.14 ± 41.43, and 59.46 ± 42.24), respectively, but we have gradual and significant improvement in the result of CRP in Marik group with a mean 67.05 ± 45.39, 62.73 ± 29.61, 50.18 ± 23.90, 42.0 ± 21.83, and 37.36 ± 30.65, respectively, with *P* values 0.468, 0.637, 0.122, 0.303, and 0.100 (Table 4).

Regarding the effect of traditional treatment and Marik protocol in treatment of patient sepsis and their length of stay in the ICU either improved or died, no significant difference in the two regimens with a result 9.36 ± 4.27 and 9.14 ± 3.99, respectively, with *P* value 0.953. There was no significant difference between the two groups as in traditional-treatment group, about 15 patients from 22 patients needed mechanical ventilation with a mean mechanical ventilation day 8.80 ± 4.43, but in Marik protocol group, about 11 patients from 22 patients needed additive treatment with mechanical ventilation with a mean mechanical ventilation day 7.0 ± 4.43 and *P* value between these two regimens is 0.219. There was no significant difference between the two groups. The traditional-treatment group had a mean duration of use of inotrope vasopressors of 7.09 ± 3.99, while in Marik group, the result was 5.50 ± 3.41 and *P* value was 0.119. There was a significant improvement in the number of deaths in Marik group as only five (22.7%) patients died, meanwhile, in the traditional group, the number of deaths is 13 (59.1%) of the patients included in the group (Table 5).

4. Discussion

Despite years of research and advances in therapy, sepsis and septic shock continue to be among the most common causes of ICU admissions. Recent trials have investigated the treatment of patients with sepsis using the combination of vitamin C, thiamine, and hydrocortisone. The combination was first proposed by Marik et al. [10], for use in septic-shock patients. Thus, the purpose of this case–controlled study was to explore the effect of adding vitamin C, thiamine, and hydrocortisone to traditional treatment in treatment of sepsis. Forty-four Egyptian patients diagnosed with sepsis according to SOFA score.

In agreement with Hussein et al. [11], who studied 94 patients who were divided into two groups: group I was given hydrocortisone 50 mg/6 h intravenously

Table 3. Comparison between the two studied groups according to central venous pressure, SaO_2, and urinary output.

Pretreatment	Group I ($N = 22$)	Group II ($N = 22$)	Test of significance	P
CVP ≥8 cmH_2O				
Mean ± SD	−0.5 ± 2.9	−1.4 ± 2		
Median (minimum−maximum)	0 (−5−5)	−1 (−5−1)		
D1				
Mean ± SD	0.8 ± 3.6	−0.5 ± 2.2	$U = 195.0$	00.263
Median (minimum−maximum)	0 (−5−10)	0 (−5−3)		
D2				
Mean ± SD	1.8 ± 4	0.7 ± 2.7	$U = 209.50$	00.443
Median (minimum−maximum)	1 (−5−9)	0.5 (−3−7)		
D3				
Mean ± SD	3.2 ± 4.7	2.4 ± 3	$U = 237.50$	00.915
Median (minimum−maximum)	1.5 (−2−12)	2.5 (−2−7)		
D4				
Mean ± SD	4 ± 5.3	3.9 ± 3.5	$U = 224.0$	00.670
Median (minimum−maximum)	2 (−3−12)	3 (−3−10)		
D5				
Mean ± SD	4.1 ± 5.8	5.4 ± 4.5	$U = 205.50$	00.390
Median (minimum−maximum)	2.5 (−5−14)	5 (−5−11)		
SaO_2>92%				
Pretreatment				
Mean ± SD	91.8 ± 4.2	90.1 ± 4.8	$t = 1.268$	00.212
Median (minimum−maximum)	91.5 (81−97)	90.5 (75−99)		
D1				
Mean ± SD	92 ± 3.7	90.8 ± 4.3	t = 1.047	00.301
Median (Min.−Max)	92.5 (83−97)	92 (77−97)		
D2				
Mean ± SD.	92.5 ± 4.2	92.6 ± 3.9	$t = 0.074$	00.941
Median (minimum−maximum)	93 (79−97)	93 (81−97)		
D3				
Mean ± SD	93.4 ± 3.8	93.6 ± 2.9	$t = 0.224$	00.824
Median (minimum−maximum)	94 (80−98)	94.5 (89−97)		
D4				
Mean ± SD	93.9 ± 3.9	94.6 ± 2.7	$t = 0.717$	00.477
Median (minimum−maximum)	95 (82−98)	95 (90−99)		
D5				
Mean ± SD	93.6 ± 3.6	95 ± 2.7	$t = 1.418$	00.163
Median (minimum−maximum)	94.5 (84−98)	95.5 (90−99)		
UOP>0.5 ml/dl				
Pretreatment				
Mean ± SD	772.7 ± 533.1	705.3 ± 295.3	$t = 207.50$	00.968
Median (minimum−maximum)	700 (100−2100)	700 (200−1100)		
D1				
Mean ± SD	1047.3 ± 660.3	802.4 ± 334.8	$t = 200.0$	00.449
Median (minimum−maximum)	900 (100−2500)	780 (100−1300)		
D2				
Mean ± SD	1261.4 ± 748.5	1056.8 ± 389.8	$t = 231.50$	00.805
Median (minimum−maximum)	925 (300−3000)	1100 (300−1700)		
D3				
Mean ± SD	1343.6 ± 873.6	1252.3 ± 475.2	$t = 236.50$	00.897
Median (minimum−maximum)	1195 (200−3000)	1200 (600−2100)		
D4				
Mean ± SD	1553.3 ± 872.9	1561.4 ± 557.6	$t = 219.0$	00.770
Median (minimum−maximum)	1500 (370−3100)	1700 (500−2300)		
D5				
Mean ± SD	1796.5 ± 935.1	1725 ± 766.8	$t = 218.50$	00.970
Median (minimum−maximum)	1775 (290−3500)	1900 (500−3000)		

CVP, central venous pressure; *t*, Student *t* test; *U*, Mann−Whitney test; UOP, urinary output.

Table 4. Comparison between the two studied groups according to serum procalcitonin (normal >5 ng/dl), serum lactate (normal: <2 mmol/l), and C-reactive protein (normal <6 mg/l).

Variables	Group I ($N = 22$)	Group II ($N = 22$)	U	P
Procalcitonin				
Day 1				
Mean ± SD	25.54 ± 24.73	18.15 ± 16.29	199.50	0.318
Median (minimum–maximum)	15.15 (3.50–100)	11.50 (3.30–55)		
Day 2				
Mean ± SD	24.60 ± 24.40	16.25 ± 13.26	206.50	0.405
Median (minimum–maximum)	13.35 (2.50–96.70)	9.65 (3.10–49)		
Day 3				
Mean ± SD	23.38 ± 22.82	152 ± 11.13	210.50	0.460
Median (minimum–maximum)	12.50 (2.50–90.70)	10.50 (2.70–40.30)		
Day 4				
Mean ± SD	22.77 ± 23.34	13.76 ± 97	211.50	0.474
Median (minimum–maximum)	12.60 (25–100)	11.60 (2.10–35.40)		
Day 5				
Mean ± SD	22.47 ± 23.24	12.64 ± 9.54	201.50	0.342
Median (minimum–maximum)	12.35 (1.90–95.70)	11.75 (1.30–33.20)		
Serum lactate				
Day 1				
Mean ± SD	13.66 ± 12.81	7.68 ± 6.69	171.50	0.098
Median (minimum–maximum)	9.50 (1.90–45)	4.15 (1.20–235)		
Day 2				
Mean ± SD	13.31 ± 12.39	6.79 ± 5.96	168.50	0.084
Median (minimum–maximum)	10.70 (1.90–43.30)	3.70 (1.50–21.19)		
Day 3				
Mean ± SD	12.31 ± 10.85	6.33 ± 5.56	158.0[a]	0.049[a]
Median (minimum–maximum)	10.35 (1.80–38.50)	3.10 (1.80–20.71)		
Day 4				
Mean ± SD	12.26 ± 10.39	5.17 ± 48	157.0[a]	0.046[a]
Median (minimum–maximum)	125 (1.50–33.90)	3.35 (1.50–16.30)		
Day 5				
Mean ± SD	134 ± 11.46	4.80 ± 4.36	137.0[a]	0.014[a]
Median (minimum–maximum)	13.55 (1.10–35.70)	3.50 (1.10–15)		
CRP				
Day 1				
Mean ± SD	82.83 ± 56.42	675 ± 45.39	211.50	0.468
Median (minimum–maximum)	72 (12–205)	48 (6–148)		
Day 2				
Mean ± SD	76.26 ± 49.89	62.73 ± 29.61	222.50	0.637
Median (minimum–maximum)	72 (12–195)	48 (12–96)		
Day 3				
Mean ± SD	71.89 ± 41.90	50.18 ± 23.90	178.0	0.122
Median (minimum–maximum)	48 (24–171)	48 (12–96)		
Day 4				
Mean ± SD	61.14 ± 41.43	42 ± 21.83	199.0	0.303
Median (minimum–maximum)	42 (12–148)	36 (12–96)		
Day 5				
Mean ± SD	59.46 ± 42.24	37.36 ± 30.65	173.0	0.100
Median (minimum–maximum)	48 (6–140.90)	24 (6–96)		

CRP, C-reactive protein; U, Mann–Whitney test.
Group I: traditional treatment.
Group II: traditional treatment + Marik protocol.
[a] statistically significant at P value less than or equal to 0.05.

for a period of 7 days or until ICU discharge, this was followed by tapering in cases of sooner discharge. Group II was given hydrocortisone 50 mg/6 h intravenously for a period of 7 days or until discharge from the ICU, after which tapering followed, as well as vitamin C 1.5 g/6 h intravenously for a period of 4 days, or until discharged from the ICU, and thiamine 200 mg/12-h intravenously for 4 days, or until discharged from the ICU. They found that the two study groups were comparable and showed a nonsignificant difference regarding demographic data. Also, Litwak et al. [12] found no significant difference between the two groups regarding age and sex.

Table 5. Comparison between the two studied groups according to ICU length of stay (days), use of mechanical ventilation (days), and mortality rate.

Variables	Group I ($N = 22$)	Group II ($N = 22$)	Test of significance	P
ICU stay (days)				
Mean ± SD	9.36 ± 4.27	9.14 ± 3.99	$U = 239.50$	0.953
Median (minimum–maximum)	7 (5–20)	8.50 (5–20)		
Mechanical ventilation (days)	15 (68.2)	11 (50)	$\chi^2 = 1.504$	0.220
Mean ± SD	8.80 ± 4.43	7 ± 4.43	$U = 59.0$	0.219
Median (minimum–maximum)	7 (4–19)	6 (2–15)		
Use of inotropes (days)				
Mean ± SD	79 ± 3.99	5.50 ± 3.41	$U = 176.0$	0.119
Median (minimum–maximum)	7 (2–19)	4 (1.50–13)		
Mortality rate				
Improved	9 (40.9)	17 (77.3)	$\chi^2 = 6.017$[a]	0.014[a]
Died	13 (59.1)	5 (22.7)		

χ^2, χ^2 test; FE, Fisher exact; *t*, Student *t* test; *U*, Mann–Whitney test.
Group I: traditional treatment.
Group II: traditional treatment + Marik protocol.
[a] Statistically significant at *P* value less than or equal to 0.05.

The present study showed that the most common causes of sepsis were chest infection in 27.3% of each group, then intestinal obstruction in 22.7% of each group, and then urology cause in 13.6% of each group. In the same line, according to Hwang et al. [13], the most common site of infection was intra-abdominal, followed by the respiratory tract. Another study by Litwak et al. [12] reported that the most common infection in both groups was pneumonia (TT 46.8% vs. SC 38.3%, $P = 0.404$), followed by gastrointestinal and biliary infection (TT 21.3% vs. SC 31.9%, $P = 0.243$). Sixteen (34%) patients in the treatment group and 18 (38.3%) patients in the SC group had positive blood cultures ($P = 0.668$). The study of Kim et al. [14] only included ICU patients with severe pneumonia, while the study of Vail *et* al. [15] analyzed the records of all patients with ICD-10 codes for infection and organ dysfunction.

In this study, both regimens of treatment have improved the level of heart rate and respiratory rate with low time needed mainly in Marik protocol. There was no significant difference between the two groups pretreatment and after treatment regarding heart rate. While, according to respiratory rate, there was no significant difference prior to and posttreatment in both groups. Also, no significant changes were found between the two regimens on the level of serum glucose. In agreement, Hwang et al. [13] found no significant difference between the two groups regarding heart rate and respiratory rate.

In agreement, Litwak et al. [12] reported an increase in serum PCT from day 1 to day 4 in both groups, despite receiving sepsis treatment. This can be explained in part by insufficient laboratory values that may have inaccurately represented the overall group's PCT-score and SOFA-score changes. Inappropriate empiric antibiotic selection was observed in nearly 30% of patients overall, which could have also contributed to the increase in PCT. Also, in agreement, Hwang et al. [13] found no significant difference between the two groups regarding PCT. On the other hand, Hussein et al. [11] found a significant difference between the two groups regarding PCT values 72 h after being included in the study. By comparing before and after PCT values within the same group, it was found that the intervention group had a significant decline in PCT values. Also, Dey and Bishayi [16] and Bone et al. [17] found that PCT, which is a more specific infection marker, showed a significant reduction in the intervention group. This opens the possibility of the synergistic effect of vitamin C with antibiotics and its direct antimicrobial effect. Sepsis-marker improvement may be related to the lower duration of vasopressors needed in the intervention arm where norepinephrine exerts a bacterial growth-promoting effect and increasing the risk of secondary infections, which may delay sepsis resolution [18].

In the present study, there was no significant improvement in the results of serum lactate after use of traditional treatment, but we have slight improvement after use of Marik protocol. The results showed no significant difference between the two groups at the first and second days of treatment, but showed a significant increase among group II than group I at third, fourth, and fifth days of treatment. In agreement, Axelrod [19] and Keh et al. [20] demonstrated that lactate was slightly improved in the intervention group but insignificantly. These findings can be explained by the anti-inflammatory effect of hydrocortisone, which was present in the two groups, and was responsible for this similarity. Also, in the study by Litwak et al. [12], Fujii et al. [21], and Moskowitz et al. [22], thiamine showed a statistically significant difference at lowering the

lactate level compared with the control group and, therefore, possible reduction in overall mortality. As well, Donnino et al. [23] reported that in the subgroup with thiamine deficiency, patients who were treated with thiamine had significantly lower lactate level at 24 h and a possible decrease in mortality over time compared with the placebo group.

The present study demonstrated that there was slight improvement in the results of CRP after use of traditional treatment, while there was a gradual and significant improvement after use of Marik protocol, with no significant difference between the two groups. In agreement, Axelrod [19] and Keh *et a*l. [20] demonstrated that CRP slightly improved in the intervention group but insignificantly. Also, in agreement, Hwang *et a*l. [13] found no significant difference between the two groups regarding CRP.

There were no significant differences between the two groups according to SOFA score with mean values of 7.23 ± 2.45 and 7.50 ± 2.39 in group I and group II, respectively. According to qSOFA score, there were no significant differences between the two groups pretreatment, and first, second, and third days after treatment. Meanwhile, there were significant differences at fourth and fifth days after treatment. Also, no significant differences were found regarding ICU stay, mechanical ventilation, and use of inotropes. On the other hand, there was significant reduction in mortality rate among group II compared with group I. In agreement, Zayed et al. [24] reported that the use of vitamin C, thiamine, and hydrocortisone was not associated with a significant reduction of long-term and ICU mortality, ICU, or hospital length of stay. Our results are consistent with Wald et al. [25], who combined treatment with vitamin C, hydrocortisone, and thiamine, which did not show reductions in SOFA score, ICU-free days, shock-free days, or ventilator-free days. Also, Marik et al. [10], Sadaka et al. [26], and Wald et al. [25] demonstrated a reduction in mortality among those who received this combination. In addition, Hussein et al. [11] showed that the intervention group showed a nonsignificant reduction in SOFA score compared with the control group at the different cutoff points. It was shown that patients in the control group were likely to get 0.57 more in SOFA score relative to those in the intervention group adjusted for other predictors in the model, but this was not statistically significant. Also, there was no significant difference between the two groups with respect to the number of patients who needed mechanical ventilation during their ICU stay, including those who needed it during the first 72 h of the ICU stay. On the contrary, Zayed et al. [24] found a significant reduction in the SOFA score at day 3 postrandomization in the intervention group in comparison with the control group. Also, Fujii et al. [21] and Chang et al. [27] trials have shown significant reduction in SOFA score on day 3 postrandomization in patients treated with vitamin C, thiamine, and hydrocortisone. As well, Hussein et al. [11] revealed that Marik protocol offered in significantly lower vasopressor dose and lower length of stay, whether in the ICU or hospital. However, it is vital to report that our results are inconclusive and could be secondary to a type-II error as a result of insufficient sample size to say that there was sufficient power to exclude benefit from the intervention. Moreover, the difference in the results may be due to different inclusion criteria among the cohort studies.

Also, Moskowitz et al. [22] revealed that the combined treatment with vitamin C, hydrocortisone, and thiamine did not show reductions in mortality.

Our results should be interpreted in the light of the study's limitations. First, we calculated the required sample size to identify improvements in organ function, but larger samples may be required to estimate the effects of vitamin C and thiamine treatment on mortality. Second, chest infection and intestinal obstruction accounted for almost half of the cases of septic shock. These baseline characteristics might affect our results. Third, the treatment and control periods occurred during different seasons. Finally, the safety of hydrocortisone, vitamin C, and thiamine is supported by more than 50 years of clinical experience. Because of the inherent safety of the combination of hydrocortisone, vitamin C, and thiamine, we believe that this treatment strategy can be adopted pending the results of further clinical trials. We believe that the results of our study provide sufficient information for the design of an adequately powered, high-quality pragmatic trial to confirm the findings of our study.

4.1. Conclusions

Vitamin C, thiamine, and hydrocortisone in combination with traditional treatment showed significant reduction in mortality rate compared with traditional treatment, but had no significant effect on ICU stay and mechanical ventilation. There was slow improvement in the results of serum PCT after use of traditional treatment, but we have significant improvement after use of Marik protocol with no significant difference between the two groups. Also, there was slow improvement in the results of serum lactate after use of traditional treatment, but we have significant improvement

after use of Marik protocol. Further studies with larger numbers of patients are needed to provide stronger evidence. In addition, further studies are needed to emphasize the role of vitamin C, thiamine, and hydrocortisone in the treatment of septic shock, and whether there are certain groups of patients who might have beneficial effect.

4.2. Limitations

Namely the small sample size, single-center design, and the participation of nonconcurrent controls.

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Conflicts of interest

There are no conflicts of interest.

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