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Efficacy of Marik Protocol in the Treatment of Septic Shock (Hydrocortisone, Ascorbic Acid and Thiamine)

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ABSTRACT

Background: Septic shock is a life-threatening state characterized by inability of the organism to maintain sufficient blood pressure and thus end-organ perfusion because of sepsis. The cornerstones of treatment of sepsis and septic shock largely consist of early diagnosis of sepsis, control of infection source, early antimicrobials and supportive treatment with adequate hydration and vasopressor drugs.

Objective: The current study aimed to evaluate the efficacy of Marik protocol treatment for septic shock.

Patients and Methods: This was a prospective study that included 100 patients with septic shock who arrived to Emergency Departments of both Al-Azhar and Al-Mansoura University Hospitals over one year (January 2021-December 2021). Entire subjected were divided into a control group who administered a standard treatment and a treatment group who administered IV vitamin C, thiamine and hydrocortisone within 24 h after intensive care unit (ICU) admission.

Results: Marik group was linked to a significant decrease in hospital mortality 4 (8%) and ICU mortality rate 45 (90%) in comparison with controls (P<0.001). A significant decrease in SOFA score was recorded among Marik group in comparison with control subjects (P<0.05). A statistically reduction in lactate co concentration during follow-up was recorded in Marik group only.

Conclusion: Marik group was linked to a significant reduction in hospital and ICU mortality rate. A significant reduction in SOFA score was recorded among Marik group.

Keywords: Coronavirus disease 2019, Procalcitonin, Septic shock, Vitamin C, Hydrocortisone, Thiamine, Marik protocol.

INTRODUCTION

Septic shock is an inflammatory condition with life-threatening organ dysfunction causing inability of the organs to maintain sufficient blood pressure and end-organ perfusion because of sepsis –a dysregulated inflammation caused by the infection from a dysregulated host response to it [(1)]. Sepsis mortality is still remarkably high, it is highly prevalent in ICU and carries a significant morbidity and mortality worldwide. Sepsis-associated mortality is about 15% whereas septic shock is responsible for 40% in-hospital mortality [(2)].

Current treatment approaches for sepsis include rapid adequate fluid resuscitation, early antimicrobials, haemodynamic support using vasopressor agents, along with identifying and controlling the infected sites [(3)]. Recently, it was demonstrated that a significant reduction in the mortality of cases with sepsis that administer a "cocktail" of IV ascorbic acid, corticosteroids, and thiamine [(4)]. Furthermore, a patient receiving the cocktail had substantially shorter time to vasopressors independence, less necessity for renal replacement therapy (RRT), and a higher reduction in Sepsis-Related Organ Failure Assessment (SOFA) score. The study showed that early starting of IV vitamin C, steroids, and thiamine was effective for the prevention of significant organ dysfunction, such as acute kidney injury (AKI), and for decreasing mortality among cases with severe sepsis [(5)]. This study aimed at evaluating the efficacy of Marik protocol treatment for patients with septic shock.

PATIENTS AND METHODS

This prospective study enrolled a total of 100 cases with septic shock that were admitted to the ICU at both Al-Azhar and Mansoura University Hospitals over a period of one year from January 2021 to December 2021. The included patients aged from 18 to 60 years old and were admitted to ICU for less than 24 h, they were hypotensive in spite of a fluid administration of 30 mL/kg and required pressor of 5 mcg/min of norepinephrine or equivalent to keep MAP > 65 mmHg. Additionally, hydrocortisone 50 mg IV Q 6hrs, were started.

Exclusion criteria:

Patients with contraindication to corticosteroids, thiamine, or vitamin C, pregnant females, patients with a fatal pre-existing disease who was not likely to survive to hospital discharge, patients with acute cerebral vascular event, acute coronary syndrome, active GI hemorrhage, burns or trauma, patients needed immediate surgical interference and mechanically ventilated patient.

Each patient was subjected to the basic blood tests as complete blood count, C-reactive protein (CRP), lactate, procalcitonin (PCT), blood culture, and liver and renal function tests. The patients were divided into

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two groups: (1) Control group: received a standard treatment care. (2) Treatment Group: received IV vitamin C, thiamine and hydrocortisone within 24 h following ICU admission.

Marik cocktail:

Marik cocktail consisted of several medications due to their significant synergism and looked at their effects on sepsis-related mortality. It consisted of ascorbic acid, thiamine and stress dose hydrocortisone [(6)]. Single high dose of vitamin C protects against capillary blockage and another further dose, might also help open of blocked capillaries. Notably, such advantageous effects lasted for up to 24 h. Large dose vitamin C might be potentially life-saving in sepsis [(7)]. In addition, thiamine was significantly used in sepsis since many reports revealed thiamine deficiency among critically ill patients particularly those with lactic acidosis, which may be due to thiamine deficiency in sepsis. Corticosteroids were often well-tolerated and they work in synergism with vitamin C to decrease inflammation, enhance catecholamines production, improve endothelial function, and enhance sensitivity to vasopressors [(8)]. The combination doses were given like that in figure (1).

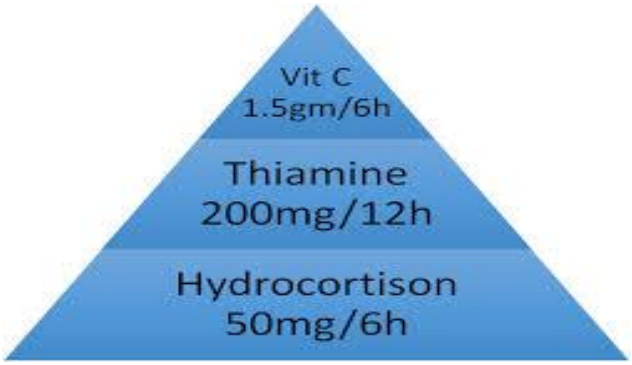

Figure (1): Marik cocktail [(4)].

Outcomes:

Primary outcome: Hospital mortalities.

Secondary outcome: Mean duration of vasopressors, necessity for RRT among those with AKI, PCT clearance (initial PCT minus PCT at 72 h divided by initial PCT x 100) and 72-h delta SOFA score (difference between subsequent scores).

Ethical consideration:

The study was approved by the by The Local Research Committee and The Studies Committee as well as The Research Ethics Committee of Al-Azhar and Mansoura University. Informed written consents were obtained from all study population. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

Data were analyzed by IBM Statistical Package for Social Sciences software (SPSS), 20st edition (IBM, United States). Data were expressed as frequencies and percent for qualitative data and means, standard deviations and ranges for quantitative data with parametric distribution and median with inter quartile range for quantitative data with non- parametric distribution. Comparing different methods utilizing the chi-square test for categorical variables and students test for continuous variables. Variables presenting significant differences between methods in univariate comparison were entered in step wise Logistics regression analysis. P-value $\leq$ 0.05 is considered statistically significant.

RESULTS

This study enrolled 100 cases with septic shock that arrived to Emergency Departments of both Al-Azhar and Al-Mansoura University Hospitals over one year (January 2021 - December 2021) to assess the effectiveness of Marik protocol in cases with septic shock. A non-statistically significant difference existed between the study groups regarding socio-demographic characteristics (age and sex) **(P>0.05),** while as regards medical history, there were significant differences among AKI, DM and COVID-19 between the study groups **(Table 1).**

Table (1): Socio-demographic data and medical history of study groups

	Marik group N=50	**Control group N=50**	**Test of significance**
Age (years)	47.80 ± 10.67	44.08 ± 10.62	t=1.75 p=0.084
Sex Male Female	 36 (72.0) 14 (28.0)	 40(80) 10(20)	 X^2=0.877 P=0.349
AKI -VE +VE	 18 (36) 32 (64)	 4 (8) 46 (92)	 X^2=11.42 P=0.001*
COVID-19 -VE +VE	 47(94) 3 (6)	 34 (68) 16 (32)	 X^2=10.98 P=0.001*
DM -VE +VE	 28(56) 22 (44)	 14 (28) 36 (72)	 X^2=8.05 P=0.005*
Hypertension -VE +VE	 20 (40) 30 (60)	 17 (34) 33 (66)	 X^2=0.386 P=0.534

X^2=Chi-Square test, t: Student t test *statistically significant, AKI: Acute kidney Injury, DM: Diabetes mellitus COVID-19: coronavirus disease 2019.

There were highly significant increases in mortality rate among the control group compared to Marik group as regards both hospital and ICU mortality. Marik group significantly reduced the duration of vasopressors in comparison with controls (18.96 vs. 59.82) **(P<0.001).** A non-significant difference was recorded among both groups regarding PCT value (P>0.05) (Table 2).

Table (2): Hospital mortality, Duration of vasopressor, and PCT distribution among studied groups

	Marik group N=50	**Control group N=50**	**Test of significance**
Hospital mortality (N-%)	4(8)	20(40)	X^2=14.035 P<0.001*
ICU Mortality (N-%)	45(90)	20(40)	X^2=27.47 P<0.001*
Duration of vasopressor/hours	18.96±3.57	59.82±14.16	t=14.90 p<0.001*
PCT	1.06±0.24	0.981±0.22	t=0.846 p=0.399

X^2=Chi-Square test, *statistically significant; ICU: Intensive Care unit, mean ±SD PCT: Procalcitonin.

There was a significant decrease in **SOFA** score among Marik group in comparison with control either at baseline or during follow-up. However, no significant differences were recorded before and after follow-up in both groups **(P > 0.05).** A significant reduction in **WBCs** was found at follow-up period in the control group regarding the baseline value as well as regarding Marik group (P<0.05). No significant difference was recorded regarding **PLT** among both groups at baseline and during follow-up **(P>0.05).** However, there was a significant decrease in **PLT** during follow-up in controls **(P<0.05).** A non-significant difference existed among both groups for **lactate** at baseline, while there was a significant decrease in **lactate** level during follow-up in Marik group only (P<0.05). **Regarding** HB at baseline and during follow up between studied groups, no significant differences were recorded among both groups at baseline and during follow-up **(P>0.05).** However, there was a highly significant decrease in HB during follow-up in Marik group only **(P<0.001).** Regarding **CRP** at baseline and during follow-up between studied groups, no significant differences were recorded among both groups at baseline and during follow-up (P>0.05). However, there were significant reductions in **CRP** in the two groups during follow-up compared to the baseline value **(P<0.05) (Table 3).**

Table (3): Comparison of SOFA score, WBC, PLT, Lactate, HB, CRP at baseline and during follow up between studied groups

	Marik group N=50	**Control group N=50**	**Test of significance**
SOFA 1	10.44±1.79	11.44±2.70	t=2.18 p=0.032*
SOFA 2	10.24±1.58	11.62±2.32	t=3.47 p=0.001*
Paired t test	t=1.43 p=0.159	t=1.70 p=0.095	
WBC1	22.78±4.22	22.07±5.60	t=0.582 p=0.562
WBC2	22.78±5.12	19.38±4.82	t=2.40 p=0.018*
Paired t test	t=0.007 p=0.955	t=4.81 p<0.001*	
PLT1	284.0±70.45	276.92±67.91	t=0.251 p=0.802
PLT2	278.1±66.54	242.6±58.27	t=1.39 p=0.167
Paired t test	t=0.45 p=0.654	t=2.89 p=0.006*	
Lactate 1	2.73±0.61	2.38±0.55	t=0.718 p=0.474
Lactate 2	2.21±0.51	2.36±0.53	t=0.411 p=0.682
Paired t test	t=2.294 p=0.005*	t=0.191 p=0.849	
HB1	9.56±2.25	9.44±2.1	t=0.276 p=0.783
HB2	8.99±2.18	9.36±2.13	t=0.834 p=0.406
Paired t test	t=3.85 p<0.001*	t=0.762 p=0.449	
CRP1	230.16±55.73	215.52±51.58	t=0.713 p=0.478
CRP2	218.52±52.11	207.28±50.12	t=0.609 p=0.544
Paired t test	t=3.22 p=0.002*	t=2.04 p=0.047*	

t: Student t test; SOFA: Sepsis-Related Organ Failure Assessment. *statistically significant

Table (4) and figure (2) demonstarted validity of laboratory parameters in differentiation between cases and control. At cut off 20.4, **WBC 1** had the ability to differentiate between cases and control with 80% sensitivity and 52% specificity. At cut off 16.5, **WBC 2** had the ability to differentiate between cases and control with 84% sensitivity and 40% specificity. At cut off 1.8, **Lactate 1** had the ability to distinguish patients from controls with sensitivity and specificity of 60% and 56% respectively. At cut off, 1.75 **Lactate 2** had the ability to differentiate between patients and controls with sensitivity and specificity of 56% and 36% respectively. At cut off 8.45 **Hb 1** had the ability to distinguish patients from controls with sensitivity and specificity of 56% and 36% respectively. At cut off 8.4 **Hb 2** had the ability to distinguish patients from controls with sensitivity and specificity of 48% and 42% respectively. At cut off 231.5, **CRP 1** had the ability to distinguish patients from controls with sensitivity and specificity of 50% and 52% respectively. At cut off 225, **CRP 2** had the ability to distinguish patients from controls with sensitivity and specificity of 50% and 52% respectively.

Table (4): Validity of laboratory parameters in differentiation between cases and control

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval		cut off point	Sensitivity%	Specificity %
				Lower Bound	Upper Bound			
WBC1	.545	.062	.440	.422	.667	20.4	80.0	52.0
WBC2	.632	.057	.023	.521	.743	16.5	84.0	40.0
Platelet 1	.543	.059	.457	.428	.658	215.5	68.0	44.0
Platelet 2	.562	.058	.282	.448	.677	210.5	60.0	56.0
Lactate 1	.625	.057	.031	.514	.736	1.8	60.0	56.0
Lactate 2	.537	.058	.526	.422	.651	1.75	56.0	36.0
Hb1	.507	.059	.907	.392	.622	8.45	56.0	36.0
Hb2	.442	.058	.321	.329	.556	8.4	48.0	42.0
CRP 1	.531	.058	.596	.417	.645	231.5	50.0	52.0
CRP 2	.555	.058	.345	.441	.668	225	50.0	52.0

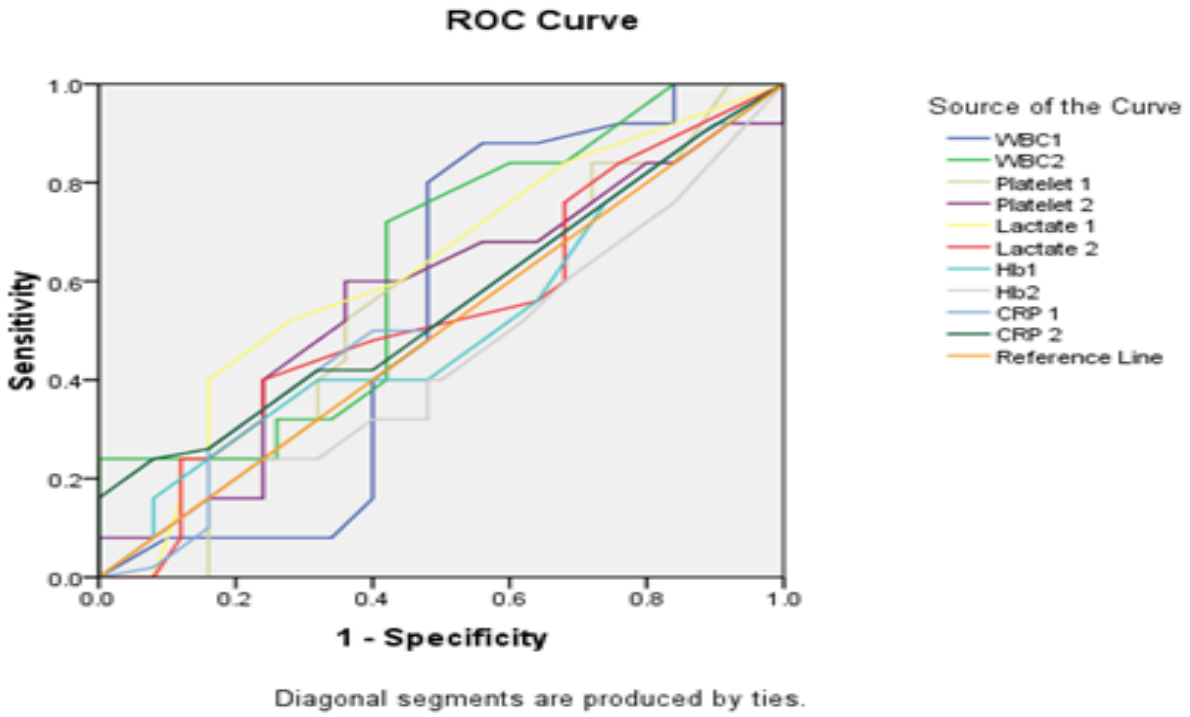

Figure (2): ROC curve of laboratory parameters in differentiation between cases and control.

DISCUSSION

The cornerstones of treating sepsis and septic shock mainly involve early diagnosis of sepsis, control of infection source, early antimicrobials and supportive treatment with IV fluids and vasopressor drugs [(8)]. Efforts performed for identification of effective treatments that target the inflammatory responses of sepsis have generally been not effective [(9)].

This prospective study included 100 patients with septic shock who arrived to Emergency Departments of both Al-Azhar and Al-Mansoura University Hospitals over one year (January 2021 - December 2021) to assess the effectiveness of Marik protocol for patients with septic shock. Entire subjected were divided into a control group who administered a standard care and a Marik group who administered IV vitamin C, thiamine and hydrocortisone within 24 h following ICU admission.

As regards, demographic features, no statistically significant differences were recorded among both groups as regards socio-demographic features (age and sex) (P>0.05). Such fact indicated that both groups were comparable and such parameters were not interfering with the net results of our study. In the context of hospital mortality, our study displayed that Marik group was linked to a significant reduction in

hospital and ICU mortality rate in comparison to controls (P<0.001). This comes in accordance with **Marik and his colleagues** [4] who conducted a retrospective study that compared the outcomes and clinical course in septic patients who received IV vitamin C, hydrocortisone, and thiamine during a 7-month period (treatment group) with control individuals treated in ICU over the preceding 7 months. They have displayed that hospital mortality was 8.5% in the treatment group in comparison to 40.4% in controls (P < .001). The propensity adjusted odds of mortality among cases that received ascorbic acid was 0.13 (P = 0.002). SOFA score was reduced in the treatment group, and none of patients developed severe organ failure. In the same line, **Muhammad and his colleagues** [10] have displayed that in patients received vitamin C, a significant decrease in mortality (p = 0.016), SOFA (p < 0.001), and duration of vasopressors need (p = 0.001). Non-significant differences existed in the hospital and ICU length of stay. On the contrary, **Litwak and his colleagues** [11] have displayed that no significant difference in hospital mortality was observed among treatment group and controls (both were 40.4%). Besides, a non-significant difference was reported as regards secondary outcome, including ICU mortality. Also, **Chang and his colleagues** [12] have reported that in septic cases, the triple therapy did not decrease mortality in comparison to placebo. Such alterations could be explained by the associated comorbidities (hypertension and diabetes mellitus), which may interfere with the overall prognosis of the studies.

Thiamine is a coenzyme for multiple pathways including glucose metabolism, citric acid cycle, as well as ATP production. in addition, its lack is common among critically ill patients and could result in lactic acidosis as pyruvate is unable to enter citric acid cycle [13]. Administration of 200 mg IV thiamine twice a day was found to significantly reduce lactic acid concentrations among those who are critically ill with thiamine deficiency [14]. Together with ascorbic acid and thiamine, these 3 drugs can theoretically work in synergism to decrease endothelial barrier alterations mediated by septic shock and protect against AKI linked to increased production of oxalates [15].

Concerning SOFA score, our study reported that there was a significant decrease in SOFA score among Marik group in comparison with control group during follow-up compared to baseline group. However, no significant differences were recorded before and after follow-up in both groups (P>0.05). In the same line, **Balakrishnan and his colleagues** [16] did not report any difference in SOFA score among the treatment group (vitamin C, thiamine and hydrocortisone daily for four days) and controls (P>0.05). While, **Marik and his colleagues** [4] have recorded that SOFA score reduced in treatment group, and none developed serious organ failure including AKI. In addition, **Muhammad and his colleagues** [10] have demonstrated that vitamin C treatment reduced SOFA score in comparison with controls. Moreover, pooled results from randomized clinical trials showed that hydrocortisone, vitamin C, and thiamine significantly decreased SOFA (p<0.00) [17].

With regard to duration of vasopressor distribution, the current study demonstrated that treatment group had significantly lower duration of vasopressor in comparison with controls (18.96 versus 59.82) (P<0.001). Likewise, **Marik and his colleagues** [4] have reported that all cases in treatment group underwent weaning off vasopressor drugs, a mean of 18.3 ± 9.8 hour after initiating ascorbic acid protocol. The mean duration of vasopressors infusion was 54.9 ± 28.4 hour in controls (P < .001). Also, the study by **Wani and his colleagues** [18] included 100 cases with sepsis/septic shock that received either standard of care alone (controls) or Marik protocol (treatment group). They reported a significant difference in duration of vasopressors infusion. On the contrary, **Litwak and his colleagues** [11] did not report any significant difference in time to vasopressor independence.

In terms of PCT, the current study showed that a non-significant difference was reported among both groups regarding PCT value (P>0.05). However, **Balakrishnan and his colleagues** [16] have reported that PCT values on the third day (68.11 ± 33.64 versus 33.2 ± 27.55 ng/mL; P = 0.0161) and on fourth day (70.03 ± 29.74 versus 26.3 ± 23.08 ng/mL; P = 0.0009) were significantly lower among patients in treatment group in comparison with controls. Likewise, **Guirguis and his colleagues** [19] have displayed that high dose of IV vitamin C improved SOFA scores, reduced CRP and PCT values, and decreased vasopressors use. As a retrospective study, their analysis had a limitation which was that a large number of PCT levels were missing. PCT was elevated from day 1 to 4 in the 2 groups in spite of administering sepsis therapy. This could be clarified partially by inadequate lab values, which might have incorrectly represented the overall group's PCT alterations. Inappropriate empiric antibiotics was noticed in about 30% of cases overall, which could have also caused a rise in PCT [11].

regarding lactate, at baseline, no significant difference was recorded among both groups, while there was a significant decrease in lactate level during follow-up in Marik group only (P<0.05). Similar outcomes were recorded also by **Wani and his colleagues** [18] who have displayed that lactate clearance (controls: 41.81% versus treatment group: 56.83%, p value =.031) had no significant difference among both groups. Likewise, **Guirguis and his colleagues** [19] have displayed that high dose of IV ascorbic acid together with starting thiamine reduced lactic acid concentrations among cases with thiamine deficiency in one study and displayed more rapid lactate clearance and lower 28-day mortality in another study. At cut off 1.8, Lactate 1 had the ability to distinguish cases from controls with sensitivity and specificity of 60% and 56% respectively. At cut off, 1.75 Lactate 2 had the ability to distinguish

cases from controls with sensitivity and specificity of 56% and 36% respectively. At cut off 231.5, CRP 1 had the ability to distinguish cases from controls with sensitivity and specificity of 50% and 52% respectively. At cut off 225, CRP 2 had the ability to distinguish cases from controls with sensitivity and specificity of 50 and 52% respectively.

CONCLUSION

Marik treatment significantly decreased hospital and ICU mortality rate. A significant decrease in SOFA score and duration of vasopressors were recorded among Marik group. A statistical reduction in lactate level during follow-up was recorded in Marik group.

RECOMMENDATIONS

Utilization of Marik protocol in cases with septic shock. Further studies have to be conducted on large number of cases.

Conflict of interest: None.
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