Effect of Early Administration of Hydrocortisone Combined with Vitamin C versus Hydrocortisone Alone on Hemodynamic Supports in Patients with Septic Shock: A Randomized Clinical Trial

Abstract

Background: Sepsis and septic shock result from a dysregulated immune response to infection, carrying high mortality. Current treatments focus on infection control and hemodynamic stabilization, yet adjuvant therapies to improve outcomes are urgently needed. **This study aims to** evaluate the efficacy of early hydrocortisone and vitamin-C combination therapy versus hydrocortisone alone in septic shock patients.

Methods: In a prospective, randomized, double-blind controlled trial, 120 septic shock patients in the intensive care unit (ICU) were randomly assigned to receive hydrocortisone alone (Group-I) or hydrocortisone with vitamin-C (Group-II). Vasopressor requirements within 24 hours were recorded as the primary outcome. Hemodynamic parameters, laboratory markers, Sequential Organ Failure Assessment (SOFA), duration on mechanical ventilation, ICU stay length, and 28-day mortality were recorded as secondary outcomes.

Results: Both groups showed insignificant difference regarding the dose and duration of vasopressors use after 24h. SOFA at day-three and mechanical ventilation duration were significantly improved in Group-II ($P=0.012$ and $P=0.002$) than Group-I. Heart rate, central venous pressure, and temperature were reduced significantly in both groups, while mean arterial pressure increasing significantly after 24 hours ($P<0.05$) compared to baseline. Lactate decreased significantly after 24h in Group II compared to Group I ($P=0.033$). No significant differences regarding ICU stay and 28-day mortality were observed.

Conclusion: The combination therapy with hydrocortisone and vitamin-C improved illness severity scores and lactate clearance more effectively without significant difference in vasopressors use than hydrocortisone alone in septic shock patients. These findings suggest potential benefits of vitamin C as an adjunct to standard sepsis care.

Keywords: Hydrocortisone; Vitamin C; Septic Shock; Hemodynamic Support; Randomized Clinical Trial.

Introduction

Sepsis is a critical condition resulting from a dysregulated immune response to infection, affecting approximately 49 million individuals and causing around 11 million related deaths annually worldwide (1). Septic shock, a severe form of sepsis, involves significant circulatory and metabolic disturbances that increase mortality risk. Currently, sepsis management focuses on the identification and treatment of infections with antibiotics and source control, alongside stabilizing hemodynamics through fluid resuscitation and vasopressors (2).

There is an urgent need for safe, effective, and affordable adjuvant therapies to complement standard care (2). A retrospective study suggested that early combination therapy with intravenous vitamin C and hydrocortisone might prevent organ dysfunction and reduce mortality in severe sepsis and septic shock, prompting interest in this treatment (3). However, more recent prospective randomized controlled trials have shown conflicting results regarding survival outcomes, highlighting a gap in specific data for septic shock patients (3-5).

The VITAMINS and ACTS trials, which enrolled patients diagnosed with septic shock within 24 hours, found no significant mortality differences between those receiving combination therapy and control groups, although early initiation of the therapy was presumed to yield benefits (3). Ascorbic acid (Vitamin C), an essential nutrient known for its antioxidant properties, is often deficient in critically ill patients, particularly those with acute respiratory infections and sepsis (6). High-dose ascorbic acid has shown promise in improving respiratory function, reducing edema, and lowering organ failure and intensive care unit (ICU) stay duration in critically ill patients (6).

Previous studies suggested that high doses could decrease the need for fluids and vasopressors in burn patients and improve hemodynamic parameters in those with severe sepsis (7). In light of this, a randomized controlled trial was conducted to assess the effectiveness of combination therapy with hydrocortisone and vitamin C in patients diagnosed with septic shock if administrated early (within 12 hours of diagnosis) , as

hydrocortisone is frequently used in such cases, despite its survival benefits being noted primarily in hypotensive patients who do not respond adequately to corticotropin.

Patients and methods

Design and population:

The study was a prospective, randomized, double-blinded controlled trial that included 120 patients admitted for septic shock in ICU. It began in September 2023 till September 2024 at Critical Care Medicine Department, Benha University. After approval of Research Ethics Committee of Benha University, Egypt (Approval Code: MS.29.8.2023). Informed consent was obtained from all patients' first-degree relatives after discussing the study aim and methods with each patient prior to enrolment.

Eligibility criteria:

Inclusion criteria were patients of both sexes with age of 18 or older, had a diagnosis of septic shock within 12 hours, clinical evidence of infection, evidence of a systemic response to infection, and the onset of shock within the previous 72 hours (as defined by a systolic blood pressure of <90 mm Hg despite adequate fluid replacement or a need for vasopressors for at least 1 hour). The exclusion criteria were patients who had received systemic corticosteroid therapy within the last three months prior to septic shock, those with immunosuppression, pregnancy, known glucose-6-phosphate dehydrogenase (G-6PD) deficiency, hemochromatosis, or known allergies to vitamin C or hydrocortisone. Patients were also excluded if anticipated death 90 days post-randomization, as determined by the enrolling physician, or if refusal was indicated by the attending staff or patient's family.

Randomization and Blindness:

Patients who met the inclusion criteria were randomized using a randomization computer software at a frequency of 1:1, with inter-sequencing dropping to allow free randomization. The randomization was stratified according to a table of computer-

generated random numbers. Patients were numbered according to their enrollment order, and the random results of each patient were concealed by the envelope method. Screening researchers opened the envelope based on the patient's enrollment number and then informed the treating nurse of the treatment plan. Finally, the designated nurse completed the medication according to the prescribed usage. Throughout the study, patients, clinical staff, and ICU residents responsible for data collection remained blinded to the allocated therapy, except for designated nurses. Blinding regarding the trial regimen was ensured by supplying the study drug and placebo in identical masked bags.

One hundred and twenty patients were distributed into two equal groups as follows:

Group I (Hydrocortisone alone): Patients received 100 mg of Solucortif® (dry powder, Pfizer, Egypt) as a continuous infusion of 200 mg daily over 24 hours, along with 50 mL of dextrose 5% in water (D5W) infused intravenously over 30 minutes every six hours for four consecutive days.

Group II (Hydrocortisone + vitamin C): Patients received the same dose of hydrocortisone along with vitamin C (Cevarol®, Amp, Memphis Company, Cairo, Egypt, 500 mg/5 mL), with a total of 1.5 g of vitamin C administered every six hours in 50 mL of D5W intravenously over 30 minutes for four consecutive days.

Intervention

All patients underwent a comprehensive assessment that included a full history taking, clinical examinations, laboratory investigations, and imaging studies (ECG, chest X-ray, echocardiogram, CT, MRI).

Upon diagnosis of septic shock, patients were treated according to the Surviving Sepsis Campaign guidelines, which included aggressive fluid resuscitation, appropriate antibiotics, and the use of vasoactive agents (8). Norepinephrine was the preferred vasoactive drug, with at least 30 mL/kg of IV crystalloid fluid administered within the first three hours. If a target mean arterial pressure (MAP) of 65 mmHg was not achieved, norepinephrine was started within the first hour of hypotension during or after fluid resuscitation, typically beginning at an infusion rate of 8 to 12 mcg per minute and titrated

to the desired pressure, with an average maintenance dose of 2 to 4 mcg per minute. The first dose of the study drug was given within two hours after randomization, with infusion continuing until the last dose was administered or until ICU discharge, study withdrawal, or death occurred, whichever came first.

Outcome measurements:

The primary outcome was measuring vasopressors requirements (duration and dose) and time for shock reversal. The secondary outcomes were hemodynamic parameters and laboratory markers after 24 hours of drug administration, sequential organ failure assessment (SOFA) scores and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores at baseline and after 3 days, Duration of mechanical ventilation, ICU and hospital length of stay, and 28-day mortality rate.

Sample size caluculation:

G*Power 3.1.9.2 (Universitat Kiel, Germany) was used for sample size calculation. Sample size was calculated based on the primary outcome of the study (time of shock reversal) reported by Lyu et al.(3) study utilizing an effect size equals to 0.530, with an α-error of 0.05 and an 80% study power, it was determined that a minimum sample size of 114 patients divided by two groups was required.

Statistical analysis:

Statistical analysis was done by SPSS v27 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD), while quantitative non-parametric data were presented as median and interquartile range (IQR) and were analyzed by unpaired student t-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate. A paired sample t-test is a statistical technique that is used to compare two population means in the case of two samples that are correlated. A two-tailed P value < 0.05 was considered statistically significant.

Results

Among 148 patients assessed for eligibility, 17 patients did not meet the included criteria (5 patients received steroids , 4 patients had late septic shock , 4 patient had allergy to medication used, 3 patients were pregnant, one patient had hemochromatosis) and 11 patients refused to participate in the study. The remaining 120 patients were randomized, followed-up and analyzed statistically. **Figure 1**

There were no significant differences in baseline characteristics such as age, sex, and BMI between the two groups, nor were there notable differences in comorbidities and the sources of infection. However, both groups exhibited a significant decrease in SOFA and APACHE II scores at three days compared to baseline ($P<0.05$). Notably, the SOFA and APACHE II scores at three days were significantly lower in group II compared to group I, with P-values of 0.012 and 0.046, respectively, despite no significant differences in baseline SOFA and APACHE II scores between the groups. **Table 1**

Regarding the primary outcomes (dose of vasopressors, the duration of its use, and shock reversal time), there were no statistical significant differences between both intervention groups. As well as, the need for MV, incidence of shock reversal, length of ICU stay, and hospital stay and 28-day mortality were insignificantly different between both groups. However, the duration of mechanical ventilation was significantly shorter in Group II compared to Group I. **Table 2**

In each group, heart rate (HR), central venous pressure (CVP), and temperature significantly decreased after 24 hours compared to baseline ($P<0.05$), while mean arterial pressure (MAP) significantly increased ($P<0.05$). However, there were no significant differences between both groups regarding HR, MAP, respiratory rates and temperature at both baseline and after 24 hours. The CVP significantly decreased in group II compared to group I ($P=0.012$) after 24 hours. Hemoglobin (Hb), platelet count (PLT), and prothrombin time (PT) showed no significant differences between baseline and after 24 hours in both groups, while C-reactive protein (CRP) significantly decreased after 24 hours compared to baseline. The total leukocyte count (TLC) was significantly lower after 24 hours in both groups. **Table 3**

In both groups, serum creatinine and bicarbonate (HCO3) levels significantly increased after 24 hours (P<0.001) compared to baseline values, with no significant difference in pH between baseline and after 24 hours. The serum lactate levels significantly decreased in group II compared to group I after 24 hours (P<0.033). There was no significant difference between the groups regarding fluid intake, fluid output after 24 hours, and fluid balance. **Table 4**

Discussion

Sepsis and septic shock result from a dysregulated immune response to infection, carrying high mortality (1). Current treatments focus on infection control and hemodynamic stabilization, yet adjuvant therapies to improve outcomes are urgently needed. Hence, this study aims to evaluate the efficacy of early hydrocortisone and vitamin C combination therapy versus hydrocortisone alone in septic shock patients (2).

The study primarily evaluated vasopressor requirements within 24 hours. Secondary outcomes included 28-day mortality, SOFA score progression, ICU and hospital stay durations, shock reversal, and various clinical measures, such as hemodynamics, oxygenation, renal function, and ventilation needs. In this study, application of high-dose ascorbic acid in association with hydrocortisone didn't affect significantly the requirements for vasopressor in terms of dose and duration in critically ill patients with septic shock. Several mechanisms including anti-oxidant, anti-inflammatory, nitric oxide (NO) synthase inhibitory, reversing vascular hyporesponsiveness to vasopressors, increasing cortisol and catecholamines synthesis, and enhancing the integrity properties of vascular endothelium may explain the ascorbic acid role in septic shock (9,10).

Inflammatory cascades and release of inflammatory cytokines are from known pathways in the pathogenesis of sepsis (8). In a recent phase I, randomized controlled trial in 24 patients with severe sepsis, intravenous infusions of high-dose vitamin C (200 mg/kg/ 24h) reduced the SOFA score rapidly and improved the hemodynamic parameters.

Vascular endothelial repair following reduction in the pro-inflammatory biomarkers such as C-reactive protein (CRP) and procalcitonin as well as decreasing the thrombomodulin level was suggested for ascorbic acid (9,11).

Our study indicated that the duration of vasopressor therapy typically ranged from 2 to 5 days, which is consistent with some authors (12) who examined the impact of stress doses of hydrocortisone on vasopressor duration in septic shock patients. Their prospective, randomized trial found that hydrocortisone significantly shortened the time required to discontinue vasopressor support compared to a placebo group. Additionally, other authors (13) investigated the timing of hydrocortisone administration and concluded that early treatment significantly reduced the time needed to stop vasopressors. Both studies highlight the potential benefits of hydrocortisone in managing vasopressor duration in septic patients.

Our study showed that the SOFA and APACHE II scores at day 3 were significantly lower in the group II compared to group I. This aligns with some authors (14) who found greater SOFA score improvements in patients receiving a combination of vitamin C, hydrocortisone, and thiamine versus hydrocortisone alone in septic shock patients. Similarly it was reported (15) that hydrocortisone, ascorbic acid, and thiamine (HAT) therapy improved SOFA scores. In contrast, a study found no significant differences in SOFA score changes in the CITRIS-ALI trial (16). Potentially due to variations in patient populations (septic shock vs. ARDS), timing of administration, and concurrent corticosteroid use, and the smaller sample size in CITRIS-ALI may have limited the study's statistical power (17).

Our study found no significant difference in the length of ICU stay between the two groups, which is consistent with the findings by some authors (18) in their meta-analysis of nine randomized controlled trials on the efficacy of vitamin C in sepsis and septic shock patients also reported no significant differences in ICU length of stay between the intervention and control groups.

Our study indicated that there was no significant difference in 28-day mortality between the two groups, a finding that aligns a published cohort study (19) in an ICU to

evaluate the effects of vitamin C combined with corticosteroids versus corticosteroids alone, this study reported no notable difference in hospital mortality rates between the groups receiving and not receiving vitamin C.

Our study found that the duration of mechanical ventilation was significantly shorter in Group II compared to Group I. In contrast, a multicenter, randomized, double-blind trial (20) examining the effects of a combination of vitamin C, thiamine, and hydrocortisone on ventilator and vasopressor-free days in sepsis patients and reported no significant reduction in ventilator days. The discrepancies between the studies may arise from differences in patient populations, underlying health conditions, and the specific interventions employed.

Although the noted results of our study have some limitations include its small sample size of 120 patients, which may restrict the generalizability of the findings to a larger population. Additionally, being a single-center study may further limit the applicability of the results to broader contexts. Furthermore, the study focused solely on short-term outcomes, such as vasopressor requirements and 28-day mortality, without assessing long-term survival or quality of life metrics.

Conclusion

The combination of hydrocortisone and vitamin C significantly improves SOFA and APACHE II scores compared to hydrocortisone alone in critically ill patients. Both treatment groups showed significant hemodynamic and laboratory improvements, such as reduced HR, increased MAP, and lower CRP levels, with no significant differences in other clinical parameters. These results suggest that hydrocortisone combined with vitamin C could offer an advantage in reducing the severity of illness, as reflected by SOFA and APACHE II scores, in patients with severe infections.

Author contribution

The authors contributed equally to the study.

Conflicts of interest

No conflicts of interest

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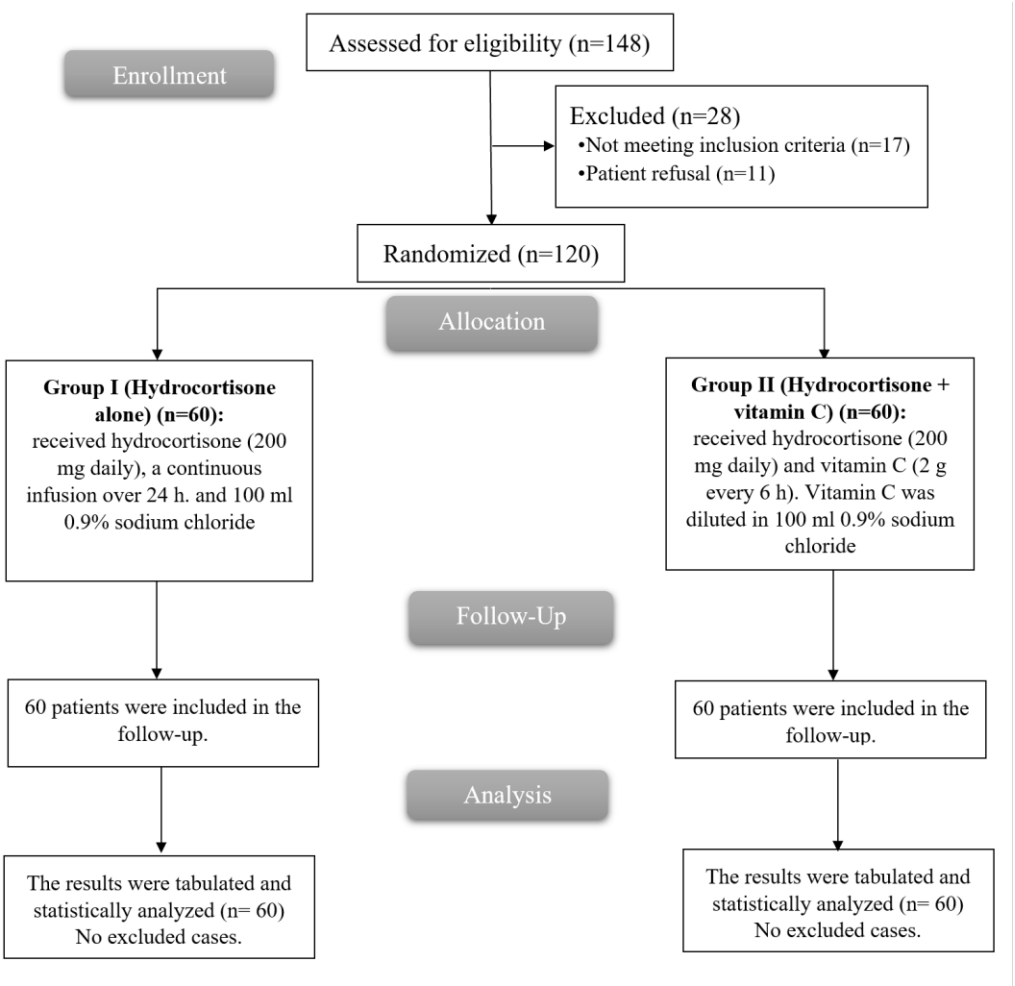

Figure 1: CONSORT flowchart of the enrolled patients

Table 1: Baseline characteristics, comorbidities, source of infection, and clinical scores of studied groups.

			Group I (Hydrocortisone alone) (n=60)	Group II (Hydrocortisone + vitamin C) (n=60)	P value
Age (years)		**Mean ± SD**	55.4±7.59	58±7.45	0.057
		Range	45-70	45-70	
Sex		**Male**	36 (60%)	39 (65%)	0.498
		Female	24 (40%)	21 (35%)	
BMI (kg/m^2)		**Mean ± SD**	26.7±3.26	27.3±2.96	0.255
		Range	21.26-31.89	22.32-32.24	
HTN			**37 (61.67%)**	**43 (71.67%)**	0.588
DM			**35 (58.33%)**	**27 (45%)**	
CAD			**14 (23.33%)**	**17 (28.33%)**	
COPD			**10 (16.67%)**	**13 (21.67%)**	
CKD			**4 (6.67%)**	**8 (13.33%)**	
Chronic liver disease			**1 (1.67%)**	**3 (5%)**	
Malignancy			**6 (10%)**	**10 (16.67%)**	
Pulmonary			**17 (28.33%)**	**12 (20%)**	0.106
Urinary tract			**11 (18.33%)**	**15 (25%)**	
Abdominal			**20 (33.33%)**	**23 (38.33%)**	
Skin-soft tissue infection			**12 (20%)**	**10 (16.67%)**	
SOFA score	**Baseline**	**Mean ± SD**	**10.9±1.96**	**11.1±1.68**	0.456
		Range	**8-15**	**9-14**	
	At 3 days	**Mean ± SD**	**6.8±3.01**	**5.5±2.7**	0.012*
		Range	**3-12**	**2-11**	
	P value within group		**<0.001***	**<0.001***	
APACHE II	**Baseline**	**Mean ± SD**	**17.7±1.74**	**17.8±2.11**	0.672
		Range	**15-20**	**14-21**	
	At 3 days	**Mean ± SD**	**11.4±4.96**	**9.7±3.84**	0.046*
		Range	**6-21**	**5-20**	
	P value within group		**<0.001***	**<0.001***	

BMI: body mass index. HTN: hypertension. DM: diabetes mellitus. CAD: coronary artery disease. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. SOFA: sequential organ failure assessment. APACHE II: acute physiology and chronic health evaluation. *: statistically significant.

Table 2: Outcome of the studied groups

		Group I (Hydrocortisone alone) (n=60)	Group II (Hydrocortisone +vitamin C) (n=60)	P value
Need for MV		19 (31.67%)	15 (25%)	0.417
Duration on MV	**Mean ± SD**	6.4 ± 1.4	5.1 ± 2.18	0.002*
	Range	5-9	4-9	
Reversal of shock		53 (88.33%)	55 (91.67%)	0.543
Time for shock reversal (days)	**Mean ± SD**	2.2 ± 1.07	1.9 ± 0.81	0.085
	Range	1-4	1-3	
Dose of vasopressors (ug/kg/h)	**Mean ± SD**	22.3 ± 7.56	21.0 ± 7.47	0.364
	Range	10-30	10-30	
Duration of vasopressors (days)	**Mean ± SD**	3.7±1.17	3.5±1.11	0.265
	Range	2-6	2-5	
Length of ICU stay (days)	**Mean ± SD**	7.7±3.78	7.1±3.42	0.363
	Range	3-16	2-15	
Length of hospital stay (days)	**Mean ± SD**	10.8±3.66	10.3±2.87	0.423
	Range	6-19	6-17	
28-day mortality		19 (31.67%)	12 (20%)	0.144

MV: Mechanical Ventilation, ICU: intensive care unit. *: statistically significant.

Table 3: Vital signs and Laboratory investigations of the studied groups

			Group I (Hydrocortisone alone) (n=60)	Group II (Hydrocortisone + vitamin C) (n=60)	P value
HR (bpm)	**Baseline**	**Mean ± SD**	115.2±9.76	117.8±10.67	0.175
		Range	100-135	100-135	
	After 24 h	**Mean ± SD**	101±9.89	97.3±12.38	0.072
		Range	82-125	73-121	
	P value within group		<0.001*	<0.001*	
RR (breath/min)	**baseline**	**Mean ± SD**	16.5±3.04	17.08±1.36	0.179
		Range	13-16	13-16	
	after 24 h	**Mean ± SD**	14.2±1.15	14.3±0.98	0.670
		Range	13-16	13-16	
	P value within group		0.10	0.13	
MAP (mmHg)	**Baseline**	**Mean ± SD**	70.6±2.39	70.4±2.38	0.620
		Range	67-74	67-74	
	After 24 h	**Mean ± SD**	79.8±3.23	80.2±4.17	0.575
		Range	72-88	71-89	
	P value within group		<0.001*	<0.001*	
CVP (mmHg)	**Baseline**	**Mean ± SD**	13.16±1.41	12.98±0.83	0.741
		Range	11-14	12-15	
	After 24 h	**Mean ± SD**	10.18±1.79	9.38±1.97	0.021*
		Range	8-12	7-11	
	P value within group		<0.001*	<0.001*	
Temperature (o C)	**Baseline**	**Mean ± SD**	37.8±0.27	37.8±0.34	0.660
		Range	37.3-38.2	37.3-38.4	
	After 24 h	**Mean ± SD**	37.79±0.33	37.3±0.33	0.879
		Range	36.8-37.8	36.8-38	
	P value within group		<0.001*	<0.001*	
Hb (mmHg)	**Baseline**	**Mean± SD**	10.5±0.74	10.5±0.88	0.653
		Range	9.2-12	9.2-12	
	After 24 h	**Mean ± SD**	10.8±0.88	10.7±0.96	0.625
		Range	9.2-12.4	9.2-12.7	
	P value within group		0.07	0.11	
PLT (*109/L)	**Baseline**	**Mean ± SD**	162.8±51.02	157.9±52.47	0.605
		Range	84-238	80-233	
	After 24 h	**Mean ± SD**	170.1±55.95	175.3±71.88	0.567
		Range	81-350	86-400	
	P value within group		0.48	0.20	
TLC (*109/L)	**Baseline**	**Mean ± SD**	16.1±0.94	15.3±0.87	0.757
		Range	13-18	13-17	
	After 24 h	**Mean ± SD**	6.1±1.07	5.8±1.07	0.130
		Range	4-8	4.1-8	
	P value within group		<0.001*	<0.001*	
CRP (mg/L)	**Baseline**	**Mean ± SD**	102.7±7.85	103.8±9.49	0.479
		Range	90.4-118.9	89.4-119.7	
	After 24 h	**Mean ± SD**	61.7±15.09	64.2±13.66	0.357
		Range	31.8-91.2	31.2-97.3	
	P value within group		<0.001*	<0.001*	
PT (sec)	**Baseline**	**Mean ± SD**	14.7±0.28	14.6±0.29	0.162
		Range	14.2-15.1	14.2-15.1	
	After 24 h	**Mean ± SD**	14.6±0.28	14.6±0.28	0.767
		Range	14.2-15.1	14.2-15.1	
	P value within group		0.310	0.919	

HR: heart rate. RR: respiratory rate. MAP: mean arterial blood pressure. CVP: central venous pressure. *: statistically significant. Hb: haemoglobin. PLT: platelets. TLC: total leukocyte count. CRP: C reactive protein. PT: prothrombin time.

Table 4: Serum levels of creatinine and lactate, arterial blood gas analysis (ABG), and fluid intake and fluid output after 24 hours of the studied groups

			Group I (Hydrocortisone alone) (n=60)	Group II (Hydrocortisone +vitamin C) (n=60)	P value
Creatinine (mg/dL)	**Baseline**	**Mean ± SD**	1.4±0.43	1.5±0.41	0.710
		Range	0.8-2.1	0.8-2.1	
	After 24 h	**Mean ± SD**	2.7±0.11	2.6±0.11	0.239
		Range	2.5-2.8	2.5-2.8	
	P value within group		<0.001*	<0.001*	
Lactate (mmol/L)	**Baseline**	**Mean ± SD**	3.2±0.55	3.2±0.54	0.777
		Range	2.3-4.1	2.3-4.1	
	After 24 h	**Mean ± SD**	2.8±1.36	2.4±0.89	0.033*
		Range	1.7-5.6	1.7-5.1	
	P value within group		0.060	<0.001*	
pH	**Baseline**	**Mean ± SD**	7.3±0.03	7.3±0.03	0.231
		Range	7.25-7.35	7.25-7.35	
	After 24 h	**Mean ± SD**	7.3±0.03	7.3±0.03	0.956
		Range	7.25-7.35	7.25-7.35	
	P value within group		0.485	0.609	
HCO3 (mEq/L)	**Baseline**	**Mean ± SD**	12.8±1.95	12.6±1.91	0.521
		Range	9.5-16.4	9.6-16.3	
	After 24 h	**Mean ± SD**	17.33±3.29	16.2±2.21	0.700
		Range	11.5-21.4	11.7-21.2	
	P value within group		<0.001*	<0.001*	
Fluid intake (mL)	**Mean ± SD**		2080.2±400.54	2088.8±388.23	0.904
	Range		1200-2700	1260-2730	
Fluid output (mL)	**Mean ± SD**		3652.3±143.39	3690.4±118.35	0.115
	Range		3400-3897	3500-3900	
Fluid Balance	**Mean ± SD**		-1572.15 ±-257.15	-1601.55 ±-269.88	0.540
	Range		-1197 - -2200	-1170 - -2240	

*: statistically significant. HCO3: Bicarbonate, ABG: arterial blood gas.