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A RANDOMIZED CONTROL TRIAL ON THE EFFECT OF PHYSIOLOGIC DOSE OF INTRAVENOUS HYDROCORTISONE IN PATIENTS WITH REFRACTORY SEPTIC SHOCK

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Abstract:

Objective: *Septic shock is a response to infection and tissue hypoperfusion which does not respond to fluid therapy and eventually leads to organ dysfunction. Aggressive treatment of a broad-spectrum antimicrobial and supportive measures are the cornerstones of successful treatment. In addition to the main treatment, there are adjunctive therapies. Steroids are one of the treatments which have been studied in the management of refractory septic shock. Despite numerous studies on the role of steroids in the mortality of severe sepsis and septic shock, still lots of controversies exist. These conflicts are often about the steroid dose and duration of administration.*

Place and Duration: *This randomized, double-blind, clinical trial study was conducted in the Emergency department of Mayo Hospital Lahore for one-year duration from March 2019 to March 2020.*

Methods*: This was a prospective, randomized-controlled, two-group assignment study. Patients who had refractory septic shock criteria were randomly divided into two groups: 80 patients were included in each group. After obtaining the baseline cortisol level and cosyntropin test, one group was treated with intravenous hydrocortisone, and the other group was treated with placebo. The response to hydrocortisone, the return of shock duration, and mortality at 28 days were investigated. The data were analyzed using SPSS version 16. For the normally distributed variables, a t test was used for comparisons. Concerning qualitative variables, the chi-square test or Fisher exact test were applied accordingly.*

Results: *The return of shock duration and mortality in intervention group patients was more than control group, but it was not statistically significant.*

Conclusion: *Despite numerous studies in this field, there are various outcomes (mortality rate, rate of return of shock, time of return of shock). These differences can be attributed to high degree of heterogeneity. Perhaps considering the underlying disease and more differentiation could change the return of shock and mortality rate.*

Keywords: *Hydrocortisone, Septic shock, Adrenal insufficiency, Cortisol*

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INTRODUCTION:

Septic shock tissue is a systemic response to infection along with hypoperfusion. It does not respond to fluid treatment and ultimately leads to organic dysfunction and death. Septic shock is considered urgent. It should be noted that the tenth cause of death in the United States is septic shock. Many efforts have been made to improve the prognosis and reduce mortality due to septic shock. Antimicrobial drugs are considered the main treatment. In addition, anti-inflammatory drugs, gram-negative neutralizing substances and anticoagulants and supportive therapy are used as additives to prevent damage to other organs. One of the treatments studied is the use of corticosteroids in the treatment of septic shock. Despite numerous studies on steroid use in the treatment of septic shock, discussions still exist. However, there is a lot of discussion about the use of low doses of corticosteroids resistant to septic shock. These discussions are usually about the type of steroid dosage, dosage and duration of use.

Adrenal insufficiency in septic shock is about 50%. Adrenal insufficiency means that there is no partial or no systemic response to a cortical corticosteroid (corticosteroid deficiency due to a critical disease). Adrenal failure in septic shock means that serum cortisol levels are less than 9 g/dl when serum cortisol levels are applied below 250 g of adrenocorocritropic hormone (ACTH) or 10 g/dl. Cortisol levels have been shown to be associated with response to ACTH stimulation and septic shock survival in patients.

In a randomized controlled trial (RCT), the intervention group took 100 mg of hydrocortisone every 8 hours for 5 days and placebo in the control group. Mortality and the return of shocks in the intervention group were statistically significant. In this study there was no treatment for corticosteroids, serum cortisol response and finally mortality. Another RCT study used 50 mg hydrocortisone followed by 0.18 mg/kg/intervention group. Mortality, shock return and response to the cosyntropin test did not differ in both groups. In a 2008 RCT study, 50 mg of intravenous hydrocortisone was used every 6 hours for 5 days. Within 28 days, there was no significant difference in mortality in the two groups for those who were unable to respond to or respond to the cosyntropin test. Mortality also did not differ in both groups. The return of shock in patients receiving hydrocortisone occurred faster than placebo and was statistically significant, but the return of the shock rate was not significant. Another study showed no significant difference between 28-day mortality and placebo groups. There is still a lot of discussion about the use of low-dose corticosteroid septic shock in the treatment of patients. In order to better treat refractory septic shock, we have developed a study evaluating the effect of low-dose hydrocortisone on septic shock mortality.

METHODS:

This randomized, double-blind, clinical trial study was conducted in the Emergency department of Mayo Hospital Lahore for one-year duration from March 2019 to March 2020. We enrolled (a) Patients >18 years old and (b) patients with septic shock criteria that did not respond to vasopressor therapy for more than 60 minutes. We excluded (a) patients who had documented adrenal insufficiency before admission, (b) patients with tuberculosis, and (c) patients treated with ketoconazole or estrogen. This was a prospective, randomized-controlled, two group assignment study. Using concealed envelopes marked in advance, study participants were randomized in a 1:1 ratio by simple method randomization following screening, fulfilling the inclusion criteria, and signing an informed consent form. In total, 160 patients were selected randomly. They were divided into study group (80 patients) and control group (80 patients). First, basal cortisol levels were evaluated in samples of sorry patients. Then 250 mg ACTH was administered intramuscularly. After 30-60 minutes, the level of venous cortisol was checked to assess the response of the ACTH. Adrenal insufficiency means that after applying ACTH 250g, serum cortisol concentrations are less than 9 g/dl or a random serum cortisol level below 10 g/dl.

One group was treated intravenously with 50 mg hydrocortisone every 6 hours, while another group was treated with placebo (salt of the same volume) for 7 days. Then, 28 days of concussion and mortality were determined in both groups. Hydrocortisone response is not required for the treatment of vasopressor for at least 6 hours in patients diagnosed with septic shock.

The data was analyzed using SPSS version 16. The T test is used to compare variables that are typically deployed. In terms of quality variables, a Chi-square test or a Fisher test was conducted. Spearman's correlation was used to compare two abnormal quantitative variables. The P value is considered to be <0.05 statistically significant.

RESULTS:

As shown in figure (Table 1), the distribution of key properties was normal. The most common subsection in the intervention group were lung disease and diabetes in the control group. The less common disease belonged to liver diseases in the control and intervention groups. Diabetes is usually the most common underlying disease (40%). Lung diseases were chronic obstructive pulmonary

disease (COPD) and interstitial lung disease (EDE). Neurological diseases include patients with stroke and cerebral palsy and epilepsy treatment.

The results in the intervention and control groups are shown in Table 2. Mortality according to the disease highlighted in the intervention group and the control group is shown in Table 3.

Table 1. Basic characteristic of intervention and control groups

Basic characteristic	Intervention group	Control group	*P*
Gender, No. (%)			0.749
Male	47 (58.8)	33 (41.3)	
Female	45 (56.3)	35 (43.8)	
Mean age	67.13±10.92	66.93 ±11.24	0.909
Response to cosyntropin test, No. (%)	44 (55)	42 (52.5)	0.751
Underline disease, No. (%)			
Pulmonary disease	33 (41.33)	28 (35)	0.416
Hypertension	22 (27.5)	18 (22.5)	0.465
Diabetes	32 (40)	32 (40)	>0.99
Renal failure	17 (21.3)	16 (20)	0.845
Malignancy	24 (30)	28 (35)	0.500
Heart failure	26 (32.5)	24 (30)	0.733
Neurologic disease	10 (12.5)	10 (12.5)	>0.99
Liver failure	7 (8.8)	9 (11.3)	0.598

Table 2. Outcome in intervention and control groups

Outcome	Intervention group No. (%)	Control group No. (%)	*P*
Return of shock	27 (33.8)	20 (25)	0.224
Mortality	54 (67.5)	58 (72.5)	0.490

Table 3. Mortality according to underline disease in intervention group and control group

		Intervention group No. (%)	P value	Control group No. (%)	P value
Pulmonary disease	Patients with disease	23 (69.7)	0.752	24 (87.5)	0.052
	Patients without disease	31 (66)		34 (65.4)	
Hypertension	Patients with disease	15 (68.2)	0.936	12 (66.7)	0.529
	Patients without disease	39 (67.2)		46 (74.2)	
Diabetes	Patients with disease	28 (87.5)	0.002	30 (93.8)	0.001
	Patients without disease	26 (54.2)		28 (58.3)	
Renal failure	Patients with disease	15 (88.2)	0.04	14 (87.5)	0.133
	Patients without disease	39 (61.9)		44 (68.8)	
Malignancy	Patients with disease	19 (66.7)	0.917	19 (67.9)	0.495
	Patients without disease	38 (67.9)		39 (75)	
Heart failure	Patients with disease	14 (53.8)	0.07	19 (79.2)	0.382
	Patients without disease	40 (74.1)		39 (69.6)	
Neurologic disease	Patients with disease	8 (80)	0.367	7 (70)	0.850
	Patients without disease	46 (65.7)		51 (72.9)	
Liver failure	Patients with disease	7 (100)	0.055	8 (88.9)	0.242
	Patients without disease	47 (64.4)		50 (70.4)	

Overall, significant differences in mortality were detected in patients with diabetes mellitus and diabetes mellitus (P 0.001), renal insufficiency (P - 0.012) and hepatic impairment (P - 0.029) (Table 4).

Table 4. Mortality according to underline disease in total patients

		Total patients	*P*
Pulmonary disease	Patients with disease	47 (77)	0.127
	Patients without disease	65 (65.7)	
Hypertension	Patients with disease	27 (67.5)	0.690
	Patients without disease	85 (70.8)	
Diabetes	Patients with disease	58 (90.6)	0.000
	Patients without disease	54 (56.3)	
Renal failure	Patients with disease	29 (87.9)	0.012
	Patients without disease	83 (65.4)	
Malignancy	Patients with disease	35 (67.3)	0.606
	Patients without disease	77 (71.3)	
Heart failure	Patients with disease	33 (66)	0.457
	Patients without disease	79 (71.8)	
Neurologic disease	Patients with disease	15 (75)	0.602
	Patients without disease	97 (69.3)	
Liver failure	Patients with disease	15 (93.8)	0.029
	Patients without disease	97 (67.4)	

Both groups found a statistically significant difference in patients with diabetes and diabetes. There was also a significant difference in the intervention group with renal insufficiency (P-0.04). Significant mortality was higher in patients with renal insufficiency in the hydrocortisone area (Table 3).

DISCUSSION:

In this study, we found no significant difference in 28-day mortality and 7-day shock return in the intervention and control groups. In a 2014 meta-analyze in China, 28 days of mortality was not significantly different from hydrocortisone. In both groups, the return of the shock within 7 days was significant (P <0.0001). This meta-analysis also looked at secondary infection caused by hydrocortisone. In this study, hyperglycemia was significant in two groups. In the 2012 system review, a statistically significant reduction in mortality in the intervention group was observed. The return of the concussion rate had no significant difference. However, the recovery time was much different (3.3 to 5.8 days). In these articles the patient received a hydrocortisone point was a new septic shock. In 2008, 50 mg of hydrocortisone was used every 6 hours in RCT. Mortality was 3% higher in the hydrocortisone group, but there was no significant difference. In response to the cosyntropin test, the mortality rate in unanswered subgroups was no different. The rate of shock return in both groups did not differ significantly. But in the hydrocortisone group, the return of the shock occurred faster. Mortality varied significantly in patients with refractory septic shock and low doses of hydrocortisone. A retrospective septic shock-resistant study found that basal cortisol levels were associated with higher mortality rates of 55 to 28% of the day's mortality, and that the response to the cosyntropin test was not related to the outcome. In the latest version of the international guidelines for severe sepsis and septic shock management, there is no suggestion of the use of septic shock hydrocortisone. Vasopressors are recommended only for hydrocortisone when resistant (level 2c).

In previous studies, the type of steroid (methylprednisolone and hydrocortisone) and the method of use (infusion against split dose) did not alter prognosis and mortality. In a study conducted in China, slow intravenous infusion of hydrocortisone was compared with continuous intravenous infusion. Continuous intravenous infusion has been shown to maintain metabolic balance and blood sugar levels. But there was no significant difference in 28-day mortality. Recent studies show that low doses of hydrocortisone can reduce good response and morbidity in patients with acute respiratory distress syndrome or community-acquired pneumonia or pneumonia. Some studies have considered the source of infection and achieved mortality according to the source. Low-dose corticosteroid treatment was associated with reduced mortality in patients with refractory septic shock after sudden laparotomy with lower intestinal perforation. In patients with severe pneumonia born in the community, the use of methylsolone decreased compared to the placebo group. Perhaps the classification of septic shock depending on the source of infection and steroid use may have better consequences.

In our study, mortality was 70%. Mortality in the hydrocortisone group was slightly lower, but was not significant (compared to 67.5%). The rate of

return was higher in the venture group (compared from 33.8% to 25%). This difference did not matter. In patients receiving hydrocortisone, the response rate to the cosyntropin test was higher, but it made no sense.

Some studies have taken into account complications of hydrocortisone, such as gastrointestinal bleeding, a new infection, hyperglycemia and hypernatremia. In our study, we investigated underlying diseases (Table 3). Lung disease is the most common infrastructure disease in the intervention group, and diabetes in the control group. The least common liver disorder in both groups was. Few studies have considered their relationship to disease and death. A total of 35 articles were evaluated in 2015 as part of a systemic study and meta-investigation. It included 4,682 patients and had no link between steroid dosages and mortality. Death in patients with diabetes and diabetes has changed significantly. It can be concluded that patients with septic shock had the worst prognosis. Mortality was significant in patients with renal insufficiency and without renal failure. A statistically significant difference in mortality was detected in patients with renal insufficiency in the intervention group. In a patient with impaired renal function with this septic shock, it can be concluded that hydrocortisone is not enough. More work is needed to determine the role of the disease, which highlights the prognosis of septic shocks.

CONCLUSION:

Despite numerous studies conducted in different parts of the world, different results were achieved (mortality, return of the shock rate and shock time). This diversity can be attributed to high heterogeneity groups. It is recommended that future studies consider the source of the disease or infection and evaluate the indicators in different groups.

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