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Original Article

The effect of physiologic dose of intravenous hydrocortisone in patients with refractory septic shock: a randomized control trial

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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.

Methods: This was a prospective, randomized-controlled, two-group assignment study. Patients referred to Imam Reza (AS) hospital in Mashhad 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

Introduction

Septic shock is a systemic response to infection which is accompanied with tissue hypoperfusion. It does not respond to fluid therapy and eventually leads to organ dysfunction and death (1). Septic shock is considered as an emergency. It is noteworthy that the tenth cause of death in the United States is septic shock (2). Many efforts are done to improve the prognosis and reduce mortality due to septic shock. Antimicrobial drugs are considered as the main treatment. In addition, vasopressin, anti-inflammatory drugs, gram-negative bacteria endotoxin neutralizing materials and anticoagulant therapy and supportive cares are used as additives to prevent damage to other organs. One of the treatments under investigation is the use of corticosteroids in the management of septic shock (3). Despite numerous studies on using steroids in the treatment of septic shock, controversies still exist (4). It is proven that a high dose of corticosteroids has harmful effects in the management of septic shock (5). However, lots of debates for using low dose corticosteroids in refractory septic shock exist (6). These controversies are often about the type of steroid, dose and duration of administration.

Incidence of adrenal insufficiency in septic shock is about

50%. Adrenal insufficiency means partial or no systemic response to cortisol which is called CIRCI (critical illness related corticosteroid insufficiency) (7). The adrenal insufficiency in septic shock means level of serum cortisol less than 9 μg/dL after administration of 250 μg adrenocorticotropic hormone (ACTH) or random serum cortisol level less than 10 μg/dL (8). It was demonstrated that there is a relationship between cortisol level and response to ACTH stimulation test and the survival rate of septic shock in patients (9).

In a randomized controlled trial (RCT) study, intervention group received 100 mg hydrocortisone every 8 hours for 5 days and the control group received placebo. The mortality rate and return of shock were statistically significant in intervention group (10). In a RCT conducted in Turkey intravenous prednisolone was used. In this study, there was no relationship between age, underlying disease, corticosteroid treatment, serum cortisol, response to cosyntropin and finally mortality (11). In another RCT study 50 mg hydrocortisone followed by 0.18 mg/kg/h was given to the intervention group. Mortality rates, return of the shock, and response to cosyntropin test was not different in two groups (12). In an RCT study in 2008, 50 mg intravenous hydrocortisone was used every 6 hours for 5 days. There was no significant difference in mortality in those who did not respond or responded to cosyntropin test in two groups in 28 days. Mortality also did not show a difference in two groups. Return of shock in patients receiving hydrocortisone happened faster than placebo and it was statistically significant, but return of shock rate was not significant (13). In another study, 28-day mortality did not show significant difference between the intervention and placebo groups (14). There are still lots of debates for using low dose corticosteroid septic shock in the treatment of patients. For better treatment of refractory septic shock, we designed a study to evaluate the effect of low-dose hydrocortisone in mortality of septic shock.

Methods

This randomized, double-blind, clinical trial study was conducted in Imam Reza hospital (a referral hospital in the second most populated city of Iran) in Mashhad from August 2014 to April 2015. We enrolled (*a*) Patients >18 years old referred to Imam Reza (AS) hospital in Mashhad 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 patients' venous sample. Then 250 mg ACTH was administered intramuscularly. After 30-60 minutes, venous cortisol level was checked to evaluate the response to ACTH. Adrenal insufficiency means serum cortisol level less than 9 μg/dL after administration of 250 μg ACTH or random serum cortisol level less than 10 μg/dL.

One group was treated with administration of 50 mg hydrocortisone intravenously every 6 hours and another group was treated with placebo (saline in the same volume) for 7 days. Then return of shock and mortality at 28 days in both groups were determined. Response to hydrocortisone is defined as no need to vasopressor therapy for at least 6 hours in patients with diagnosis of septic shock.

The sample size was obtained based on Bollaert et al study (10), in terms of type I error (or $\alpha = 0.05$). Also, to have 90% power for comparing the mortality in 28 days in two groups, we had the maximum sample size of 80 patients in each group.

Analyzing the data was done by SPSS version 16. For normally distributed variables, a *t* test was used for comparisons. Concerning qualitative variables, the chi-square test or Fisher exact test were applied. Spearman correlation was used for comparison of two non-normally distributed quantitative variables. A P value <0.05 was regarded as statistically significant.

Results

As it is demonstrated (Table 1), distribution of basic characteristics was normal. The most prevalent underline disease in intervention group was pulmonary disease and diabetes and in control group it was diabetes. The least prevalent disease belonged to liver disease in both control and intervention groups. In general, diabetes was the most common underlying disease (40%). Pulmonary diseases here included chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). Neurologic diseases encompassed history of cerebrovascular accidents and cerebral palsies and patients who were under the treatment of epilepsy.

The difference was not significant in mortality in intervention group with cosyntropin positive and negative test ($P = 0.259$). The difference was not also significant in mortality in control group with cosyntropin positive and negative test ($P = 0.597$).

Outcome in intervention and control groups is demonstrated in Table 2. Mortality according to underline disease in intervention group and control group is illustrated in Table 3.

In general, there were significant differences in mortality rate in septic shock patients with and without diabetes

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

($P<0.001$), renal failure ($P=0.012$) and liver failure ($P=0.029$) (Table 4).

Mortality had a statistically significant difference in patients with and without diabetes in both groups. Mortality also had a significant difference in intervention group with renal failure ($P=0.04$). Patients with renal failure who received hydrocortisone had a higher significant mortality (Table 3).

Discussion

In this study, we could not find any significant difference in 28-day mortality and return of shock in 7 days in intervention group and control group. Mortality in patients with positive cosyntropin test and negative cosyntropin test (in subgroups who had received or not received hydrocortisone) did not differ significantly. The results of this study have some similarities and differences with previous studies.

In the meta-analysis in 2014 in China, 28-day mortality did not differ significantly by administration of hydrocortisone. The return of the shock at 7 days in both groups was significant ($P<0.0001$). In this meta-analysis, secondary infection caused by hydrocortisone was also evaluated. In this study, hyperglycemia in two groups was significant (15). In a systemic review in 2012, a statistically significant reduction in mortality was observed in intervention group. The return of the shock rate had no significant difference. But, duration time of shock return differed significantly (3.3 versus 5.8 days). The point in these articles was new septic shock in patient who received hydrocortisone (16). In a RCT in 2008, 50 mg hydrocortisone was used every 6 hours. Mortality in hydrocortisone group was 3% more, but did not differ significantly. Mortality also did not differ in subgroups with and without response to cosyntropin test. In both groups, the rate of return of shock did not differ significantly. But in hydrocortisone group, the return of shock occurred faster (13). In a study on patients with refractory septic

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)	

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)	

shock which were given low dose of hydrocortisone, the mortality rate differed significantly (17). In a retrospective study on refractory septic shock with 28-day mortality of 55%, they concluded that higher basal cortisol level was related with higher mortality and response to cosyntropin test did not relate to outcome (18). In the last version of international guidelines for management of severe sepsis and septic shock, there is no recommendation for hydrocortisone administration in septic shock. There is only recommendation for hydrocortisone when it is refractory to vasopressors (level 2c) (19).

In previous studies, type of steroid (methylprednisolone and hydrocortisone) and method of administration (divided doses versus infusion) did not alter the prognosis and mortality (11-13). In a study in China, slow intravenous infusion was compared with continuous intravenous infusion of hydrocortisone. It was demonstrated that continuous intravenous infusion could maintain metabolic balance and blood glucose levels. But there was no significant difference in 28-day mortality (20). Currently, recent research show that patients with acute respiratory distress syndrome or burns or community-acquired pneumonia respond well to low dose hydrocortisone and it can reduce the morbidity rate (21). In a few studies, source of infection was considered and mortality was obtained according to the source. Low-dose corticosteroid therapy was associated with reduced mortality in patients with refractory septic shock after emergency laparotomy of lower intestinal perforation (22). In patients with severe community-acquired pneumonia, the use of methylprednisolone decreased treatment failure in compare with placebo group (23). Maybe classification of septic shock according to the source of the infection and application of steroids could lead to better results.

In our study mortality rate was 70%. Hydrocortisone group had a slightly lower mortality, but it was not significant (67.5% versus 72.5%). Return of shock in intervention group was higher (33.8% versus 25%). This difference was not significant. The rate of response to cosyntropin test was more in patients who received hydrocortisone, but it was not significant. Higher response to cosyntropin test does mean that adrenal insufficiency was less common in hydrocortisone group, therefore, fewer patients needs hydrocortisone in this group. Maybe this is the reason of no difference in mortality in two groups.

In some studies, complications of hydrocortisone such as gastrointestinal bleeding, new infection, hyperglycemia and hypernatremia were taken into account. In our study, we considered underlying diseases (Table 3). The most common underline disease in intervention group was pulmonary disease and in control group it was diabetes. The least common in both groups was liver failure. Few studies considered underline disease and its relationships to death. In a systemic review and meta-analysis which was done in 2015, a total of 35 articles were assessed. It included 4682 patients and there was no relation between steroid doses and mortality (24). Death in patients with and without diabetes had a significant difference. It can be concluded that patients with septic shock who had diabetes have worst prognosis. Mortality in patients with and without renal failure and liver failure was significant. Renal failure patients in intervention group had a statistically significant difference in mortality. It can be concluded that in a renal failure patient with septic shock, hydrocortisone is not suitable. More study is needed to determine the role of underline disease in prognosis of septic shock.

Conclusion

Despite numerous studies in different parts of the world, different results have been obtained (mortality rate, return of shock rate and duration of shock). These diversities could be attributed to high heterogeneity of groups. It is recommended that in future studies underline disease or source of the infection be considered and indices be evaluated in more differentiated groups.

Ethical issues

The study procedure was approved by the Research Council Ethics Committee of Mashhad University of Medical Sciences (No. 920688) and all participants were required to fill out an informed consent form prior to study entrance. Also, this study was registered in the Iranian Registry of Clinical Trials ((identifier: IRCT2014080211956N2, http://irct.ir).

Authors' contributions

MTD supervised the whole project. AMG and MJ collected the data. MS participated in the design of the

study and performed the statistical analysis. HR conceived the idea of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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