Hydrocortisone, Vitamin C, and Thiamine for Treatment of Sepsis and Septic Shock: A Single Centre Retrospective Comparative Study

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Background: The global burden of sepsis is estimated to be 19 million cases annually, with mortality rate approaching 26 % in high-income countries and 50% in low-income countries

Methods: In this retrospective comparative study we looked at the outcome of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine over 6 months duration (treatment group) with a control group treated in our ICU (Intensive Care Unit) during preceding 6 months. The primary outcome was hospital mortality.

Results: There were 24 patients in treatment group and 30 patients in control group with no significant difference in baseline characteristics between the two groups. The hospital mortality of sepsis was 7.7% (1 of 13 patients) in the treatment group compared with 13.3 % (2 of 15 patients) in the control group (P value = 0.63) and hospital mortality of septic shock was 27.3% (3 of 11 patients) in the treatment group compared with 40% (6 of 15 patients) in the control group (P value = 0.52)

Conclusion: Our results suggest that there was no statistically significant reduction in mortality with early use of intravenous vitamin C, hydrocortisone and thiamine in sepsis and septic shock.

Keywords: hydrocortisone, sepsis, septic shock, thiamine, vitamin C.

The global burden of sepsis is enormous with an estimated 19 million cases per year, majority of these cases occurring in low-income countries.[1] With timely diagnosis and improvement in supportive care, the 28-day mortality of sepsis in high income countries has declined to about 26%.[1] But it remains very high in low-income countries, approximately 50 %.[2, 3]

Over the last three decades, more than 100 phase 2 and phase 3 clinical trials have been performed testing various novel pharmacological agents and therapeutic interventions to improve the outcome of sepsis and septic shock; all these efforts ultimately failed to produce a novel pharmacological agent that improved the outcome of sepsis.[4]

Marik PE and colleagues have shown in their before and after study that early use of intravenous vitamin C, hydrocortisone and thiamine in sepsis reduced mortality from 40.4% to 8.5% (P<0.001).[5] This study was conducted to find out whether early use of intravenous hydrocortisone, vitamin C and thiamine reduced mortality in sepsis and septic shock in our setup.

Methods

This study was done in B and B Hospital, Kathmandu, from June 2017 to June 2018. Patient consent was taken. All patients more than 14 years of age admitted to ICU (Intensive Care Unit) from January 2018 to June 2018 with a primary diagnosis of sepsis and septic shock were treated with intravenous hydrocortisone, vitamin C and thiamine within 24 hours of ICU admission (treatment group). The control group consisted of consecutive patients above 14 years of age admitted in the ICU between June 2017 and December 2017 with primary diagnosis of sepsis and septic shock. During control period, patients with sepsis did not receive intravenous vitamin C or thiamine. The diagnosis of sepsis and septic shock were based on the 2016 The Third International Consensus Definition for Sepsis and Septic Shock. [6]

The overall treatment of sepsis and septic shock during control and treatment periods was similar except for the administration of combination of vitamin C, hydrocortisone, and thiamine during the treatment period. During control period, patients received hydrocortisone (50 mg I.V every 6 hours) at the discretion of attending physician. During the treatment period, all patients with primary diagnosis of sepsis and septic shock were treated with intravenous vitamin C (1.5gm every 6 hours for 5 days), hydrocortisone (50 mg every 6 hour for 7 days which was tapered over 3 days), and intravenous thiamine (200 mg every 12 hours for 5 days).

The demography, etiology and outcome of

the patients between the two groups were analyzed. The end point of the study was discharge from the hospital. All the categorical variables were expressed in number and percentage, while continuous variables were expressed in mean ± SD or median (range). Statistical analysis was done using SPSS 14.0 for windows.

Results

There were 24 patients in the treatment group and 30 patients in the control group. The baseline characteristics of the two groups are given in **Table 1**. There were no significant differences in baseline characteristics between the two groups. Most patients had multiple co-morbidities. The causes of sepsis were similar in both the groups, chest infection being the commonest. The hospital mortality of sepsis was 7.7% (1 of 13 patients) in the treatment group compared with 13.3 % (2 of 15 patients) in the control group (P value = 0.63). And the hospital mortality of septic shock was 27.3 % (3 of 11 patients) in the treatment group compared with 40% (6 of 15 patients) in the control group (p value = 0.52). **(Table 2) (Figures 1 and 2)**.

Variables	**Treatment group (n=24)**	**Control group (n=30)**	**p value**
Age, mean ± SD years	58.9 ± 18.3	60.9 ± 18.7	0.69
Gender, No (%)			0.41
Male	10 (41.7%)	17 (56.7 %)	
Female	14 (58.3%)	13 (43.3%)	
Co morbidities, No (%)			
Hypertension	14 (58.3 %)	14 (46.7%)	0.40
COPD	16 (66.7 %)	16 (53.3 %)	0.32
Diabetes mellitus	10 (41.7 %)	10 (33.3 %)	0.53
CKD	3 (12.5 %)	5 (16.7 %)	0.67
Heart Failure	2 (8.33 %)	4 (13.3 %)	0.56
Primary Diagnosis, No (%)			
Chest Infection	14 (58.3 %)	17 (56.7 %)	0.91
Urosepsis	5 (20.8 %)	7 (23.3 %)	0.83
Intra-abdominal sepsis	0 (0 %)	3 (10 %)	0.11
Skin and soft tissue infection	3 (12.5 %)	0 (0 %)	0.05
Tropical Sepsis	2 (8.3%)	3 (10 %)	0.83

Table 1: Baseline Characteristics of patients in Treatment and Control groups

Outcome	Treatment Group (n=24)	Control Group (n=30)	p value
Sepsis, n (%)	13 (54.2%)	15 (50%)	NA*
Mortality in sepsis, n (%)	1 (7.7%)	2 (13.3%)	0.63
Septic shock, n (%)	11 (45.8 %)	15 (50%)	NA*
Mortality in septic shock, n (%)	3 (27.3 %)	6 (40%)	0.52

Table 2: Outcome of patients in treatment group and control group

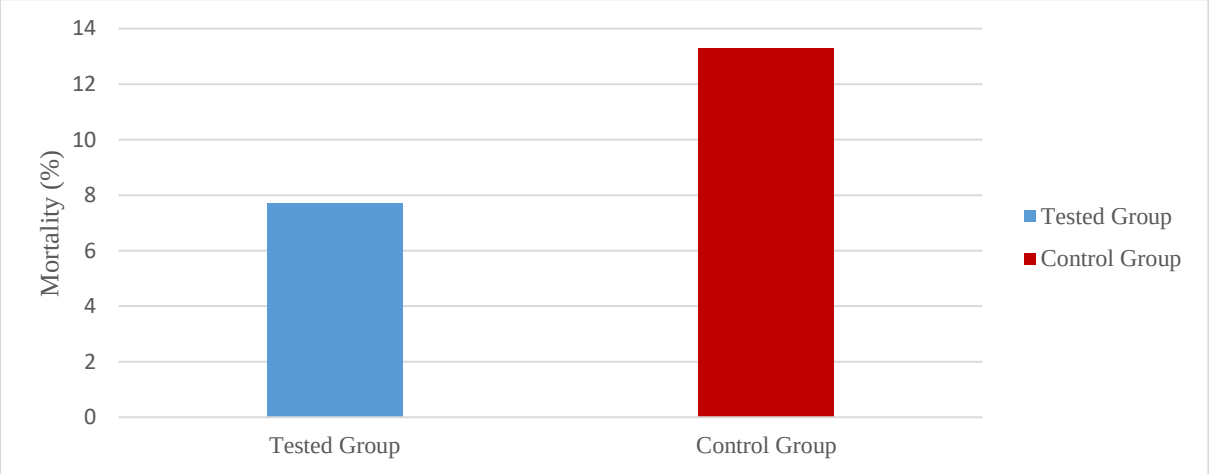

Figure 1: Mortality of sepsis in the treated and control group

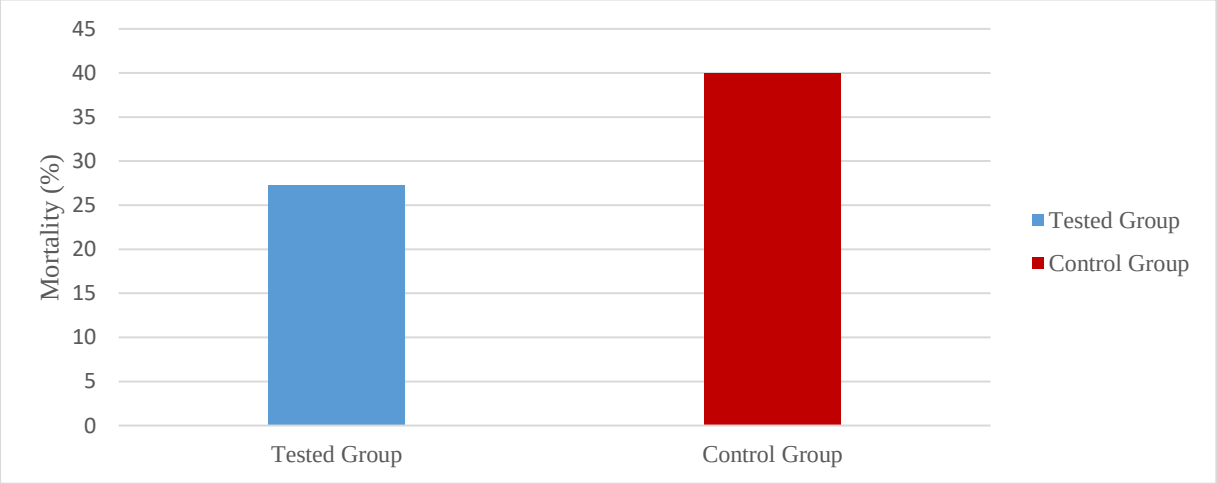

Figure 2: Mortality of septic shock in the treated and control group

Discussion

Critically ill patients, including septic patients, have critical illness related corticosteroid insufficiency (CIRCI).[7] Steroid has multiple beneficial effects in sepsis. It inhibits Nuclear Factor - kappa B, the excessive stimulation of which causes cytokine storm in sepsis. It recruits microcirculation and re-sensitizes catecholamine receptors.[8] But, hydrocortisone did not improve survival in septic shock in CORTICUS[9] and

ADRENAL[10] trials. Steroid alone does not work well in sepsis, as steroid receptor gets oxidized in oxidative state like sepsis and the receptor loses its affinity for agonistic ligand and binds with the antagonistic ligand. This brings about a conformational change in the receptor, because of which steroid cannot bind with the receptor to exert its effect.[11] Vitamin C reduces the cysteine thiol groups of steroid receptors and displaces the antagonistic ligand and primes the receptor.[12]

Vitamin C also acts through multiple pathways in sepsis and has multiple overlapping effects with steroid.[13] It is required for synthesis of catecholamines and corticosteroids in the adrenal glands. It is required for synthesis of vasopressin and neurotransmitters. It is required for the functioning of T - cells and macrophages; it is an inhibitor of Nuclear Factor - kappa B and it maintains the integrity of tight junction. [14,15,16] Almost all septic patients have vitamin C deficiency, [17,18] but oral administration of vitamin C as high as 1.5 gm/day cannot restore vitamin C levels in patient with sepsis due to saturable gastro-intestinal transporter, sodium - vitamin C co-transporter 1 (SVCT - 1).[19] To achieve normal vitamin C levels in critically ill patients, a daily dose of more than 3 gm is required.[17, 20, 21]

Thiamine deficiency is common in septic patients and is associated with an increased risk of death.[22] Hyperoxaluria sometimes results in patients with renal impairment receiving megadose of vitamin C [23] and thiamine diverts metabolism away from oxalic acid synthesis.[24]

Although Paul E. Marik and colleagues have shown that early use of intravenous vitamin C, hydrocortisone and thiamine in sepsis reduced the mortality of sepsis from 40.4 % to 8.5 % ($P < 0.001$)[5], our study has shown that there was a decline in mortality rate of sepsis from 13.3 % to 7.7% ($p= 0.63$) and septic shock from 40% to 27.3% ($p = 0.52$), but it did not achieve statistical significance.

There are three ongoing large multi centric trials, VITAMINS[25], ACTS[26] and VICTAS[27]. VITAMINS is a multi-centric Australasian study comparing intravenous vitamin C, hydrocortisone, and thiamine with intravenous hydrocortisone alone in septic shock with vasopressor free days as the primary end point and 90-day mortality as the key secondary end point. ACTS is a multi-centric US study comparing intravenous ascorbic acid, hydrocortisone, and thiamine with placebo in septic shock with change in SOFA[28] (sequential organ failure assessment) score at 72 hours as the primary end point and incidence of kidney failure and 30-day mortality as the key secondary end points. VICTAS is a multi-centric US study comparing the combination of intravenous vitamin C,

hydrocortisone, and thiamine with placebo in sepsis with ventilator- and vasopressor-free days as the primary end point and 30-day mortality as the key secondary end point. We need to wait for the results of these RCTs for concrete evidence.

Conclusion

The result of our study suggests that there was no statically significant reduction in mortality with early use of intravenous vitamin C, hydrocortisone and thiamine in sepsis and septic shock. However, larger multicentric studies are required to confirm our results.

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