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Original Research Article

Early administration of hydrocortisone vitamin C and thiamine in adult patients with septic shock: a randomized controlled clinical trial

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ABSTRACT

Background: Hydrocortisone, vitamin C and thiamine have been suggested as a possible treatment for sepsis and septic shock. However, many trials do not support their use therefore this RCT was conducted to evaluate the efficacy of early administration (within 12 hours of diagnosis) of triple therapy (hydrocortisone, vitamin C and thiamine) in patients of septic shock in north Indian population. The primary objective was to determine the effect of combination on all-cause mortality at day 14. Secondary objectives were change in sofa score at day 3 and day 7, time to shock reversal (in hours) and mean length of hospital stay.
Methods: This single centre double blinded RCT was conducted in LLR and Associated hospitals, Kanpur between June, 2023 and June, 2024. The patients were randomly assigned to either Interventional group (n=75) or PLACEBO group (n=75). Interventional group received inj. hydrocort 200 mg once a day, inj. vitamin C 1 gm iv 3 times a day, thiamine 200mg iv 2 times a day for 5 day or until ICU discharge, the patients were then followed up for 14 days.
Results: Delta sofa score at day 3 and 7 were not statistically significant (p values- 0.5, 0.241). Significant results were obtained in mean length of hospital stay (11.87 vs 14 days, p value 0.005) and Mean time to shock reversal (176.33 vs 204.40 hours, p value<0.001). Mortality at day 14 was lesser in the interventional group (34.67% vs 45.33%, p value 0.205, statistically insignificant).
Conclusions: Thus, in patients with septic shock early treatment (within 12 hours of diagnosis) with injection hydrocortisone, vitamin c and thiamine does not confer mortality benefit but it decreases the length of hospital stay and time to shock reversal.

Keywords: Hydrocortisone, Mortality, SOFA score, Septic shock, Thiamine, Vitamin C

INTRODUCTION

Sepsis is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. An increase in SOFA score of two points or more is indicative of organ dysfunction and is linked to an in-hospital mortality rate of more than 10%.

Septic shock should be defined as a subset of sepsis in which particularly profound circulatory, cellular and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone.[1] Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater and serum lactate level greater than 2 mmol/l (>18 mg/dl) in the absence of hypovolemia. Septic shock is associated with>40% hospital mortality.[3]

Forming a probable diagnosis, getting samples for culture, starting empirical antibiotic medication and achieving source control are the processes involved in the first management of infection but despite this the mortality in sepsis remains quite high.[4] In addition to normal therapy, novel techniques that focus on reducing the dysregulated

host response are expected to improve outcomes given the significant mortality and morbidity associated with septic shock.[5]

It has been observed that levels of thiamine and vitamin c are reduced in patients of sepsis in addition to HPA axis suppression, Vitamin C has potent antioxidant properties and contributes significantly to the production of vasopressors and increases their reactivity.[6,7]

Thiamine also acts as a cofactor in the Krebs cycle and has anti-oxidant properties. Corticosteroids act via two mechanisms: immune modulation and cardiovascular modulation.[8] Corticosteroids bind to nuclear factor kappa beta receptors and mitigate the vasoconstrictor response to vasopressor drugs.[6]

Previous retrospective studies have shown conflicting results regarding the effectiveness of triple therapy (vitamin C, thiamine and hydrocortisone) in preventing septicemic MODS.[9] Therefore, it is presumed that a beneficial effect can only be achieved if triple therapy is initiated at an early stage.

Therefore, we performed this RCT to evaluate the efficacy of early administration (within 12 hours of diagnosis) of triple therapy (hydrocortisone, vitamin C and thiamine) in patients of septic shock in north Indian population.

This study was conducted to find out the efficacy of early administration of hydrocortisone, vitamin c and thiamine in patients of septic shock.

Primary objective

To determine the effect of combination on all-cause mortality at day 14.

Secondary objective

Change in sofa score at day 3 and day 7. Time to shock reversal (in hours). Length of hospital stay.

METHODS

Study design

This single centre, double blinded RCT was conducted in LLR and Associated hospitals, KPS Institute of medicine, GSVM medical college, Kanpur between June, 2023 and June, 2024. A total of 204 patients were screened for this study out of which 160 patients got selected based on inclusion and exclusion criteria.

Out of 160 patients, 10 participants were lost to follow up. So effective sample size came out to be 150.The patients were randomly assigned using simple random sampling to either Interventional group (n=75) or placebo group (n=75). Ethics committee approval was taken before entering the study.

Study population

The patients who were more than 18 years of age and with a primary diagnosis of septic shock made within 12 hours were included in the study. Exclusion criteria included patients who have had received systemic corticosteroid therapy in the last 3 months or if the patient had cardiogenic, neurogenic or hypovolumic shock or if the patient is allergic to vitamin C, hydrocortisone or thiamine, known G6PD deficiency or hemochromatosis or if there was a refusal from the attending staff or family member.

Study methods

SEPSIS 3 standards were followed for the treatment of septic shock patients.[1] 30 ml/kg of iv crystalloid bolus was given in the first hour and if adequate blood pressure was not achieved the patient was put on vasopressor support where norepinephrine was the first choice.

Patients in the Interventional group received inj. hydrocort 200 mg once a day, inj. vitamin C 1 gm iv 3 times a day, thiamine 200 mg iv 2 times a day for 5 day or until ICU discharge.

All the three drugs were diluted in 100 ml of 0.9% NS and administered to the Interventional group. Equal amount of 0.9% NS was given in the placebo group. Patients were then followed up till 14 days of admission. Disease severity was assessed using SOFA score at day 1, 3 and 7. Duration of hospital stay, duration to shock reversal and ΔSOFA score at days 3 and 7 were the secondary endpoints, with all-cause mortality at day 14 served as the primary outcome.

RESULTS

Delta SOFA Score measures the change in SOFA scores from baseline, reflecting improvements or deterioration in organ function.

Table 1: Baseline characteristics of the study population.

Parameters	Interventional	Placebo	P value
Mean age	58.77	56.01	0.161
Sex			
Male %	65.33	54.67	0.091
Female %	34.67	43.33	0.091

Continued.

Parameters	Interventional	Placebo	P value
Co-morbidities			
None	20.00%	22.67%	0.345
CAD	22.67%	13.33%	0.068
HTN	36.00%	36.00%	0.500
T2DM	34.67%	40.00%	0.250
Hypothyroidism	6.67%	9.33%	0.274
Primary site of infection			
Urinary tract infection	16.00%	10.67%	0.168
Respiratory tract infection	33.33%	32.00%	0.431
Abdominal cavity infection	25.33%	24.00%	0.425
Meningitis	10.67%	14.67%	0.231
Cellulitis	14.67%	18.67%	0.256
Time from (in hours)			
Diagnosis to randomization	2.96	3.17%	0.075
Randomization to study drug administration	4.47	3.75%	0.001
Systolic bp (day 1)	71.65	67.84%	0.009
Diastolic bp (day 1)	45.76	41.84%	0.011
Mean arterial pressure (day 1)	54.39	50.51%	0.005
PAO2 (day1)	57.25	53.04%	0.006
GCS (day 1)	8.49	9.20%	0.010
Bilirubin (mg/dl day 1)	2.74	2.85%	0.330
Creatinine (mg/dl day 1)	2.6	2.76%	0.147
Sofa score (day 1)	13.6	15%	0.001

Table 2: Delta sofa score at day 3 and day 7.

Delta Sofa score at		Day 3	Day 7
Interventional	Mean±SD	1.95±4.09	3.29±5.59
Placebo	Mean±SD	1.95±4.31	2.60±6.45
P value (Interventional vs. placebo)		0.500	0.241

Table 3: Length of hospital stay and time to shock reversal in hours in the 2 groups.

	Interventional	Placebo	P value
	Mean±SD	**Mean±SD**	
Length of hospital stay (days)	11.87±3.37	14±6.26	0.005
Time to shock reversal (hours)	176.33±22.07	204.4±14.11	<0.001

Table 4: Mortality at day 14 in the 2 groups.

Mortality at day 14	Interventional		Placebo		P value
	N	**%**	**N**	**%**	
Alive	45	60.00	40	53.33	0.205
Dead	26	34.67	34	45.33	
Total	71	95	74	99	

Table 2 provides mean scores with standard deviations (SD) for each group and time point. The p values for Day 3 and Day 7 are both>0.05, suggesting that he differences in Delta SOFA scores between the two groups at these time points are not statistically significant.

Mean length of hospital stay (days) in Interventional group was 11.87 days while in the placebo group was 14 days (p value 0.005). Mean time to shock reversal was 176.33 hours in the Interventional group while it was 204.40 hours in the placebo group (p value<0.001). Both the results are statistically significant.

Mortality at day 14 was 34.67% in the Interventional group while it was 45.33% in the placebo group. P value for this observation was 0.205 (statistically not significant).

DISCUSSION

The study was conducted in KPS Institute of medicine, Kanpur where total 150 patients (75 patients in each group) were included in the study. All the physiological indicators, including blood pressure, pulse, respiration rate, temperature, oxygen saturation, and random blood sugar, were regularly measured as the patients underwent a thorough evaluation. The patients suffering from septic shock received an IV bolus of 30 ml/kg of crystalline fluid in the first three hours and then additive fluid therapy was given according to the hemodynamic status of the patient.[10] A target MAP of around 65 mmhg was used for titration of vasopressors. Appropriate routine microbiological cultures were sent before starting anti-microbial therapy. Appropriate empirical iv antibiotics were started as soon as possible within 1 hour of admission.[3]

The empirical broad-spectrum antibiotics were narrowed down once the pathogen is identified and clinical improvement was seen. Serum lactate levels, CBC, LFT, KFT, SE and other routine investigations were sent periodically.[11] Norepinephrine was the first-choice vasopressor while vasopressin and dobutamine were added as needed. Dopamine was used as an add on vasopressor in selected patients. Iv hydrocortisone 200 mg once a day, inj. vitamin c 3 times a day, thiamine 200 mg 2 times a day were given in the Interventional group while equal amount of 0.9% NS was given in the placebo group. Disease severity was assessed using SOFA score at day 1, 3 and 7.

Delta SOFA scores at day 3 and 7 in the Interventional group were 1.95 and 3.29 respectively while in the placebo group were 1.95 and 2.60 respectively. Delta sofa score was higher at day 7 in the interventional group however the p value for this observation was 0.241 (statistically not significant). Similar results were found by Weilan Na and his collegues who examined a lot of databases and included many RCTs assessing the efficacy of HAT therapies in sepsis and septic shock. They observed that the change in SOFA score at day 3 was significantly significant between the two groups (MD 0.65, 95% CI 0.30 to 1.00).[12]

However, Mahesh Balakrishnan and his colleagues randomized 24 patients suffering from septic shock into two groups: group 1 (who received a matching placebo daily for four days) and group 2 (who received triple therapy for four days). The main outcome was the amount of vasopressor administered over the course of four days of therapy; the secondary outcome was in-hospital death. Nonetheless, there was no variation in mortality or the SOFA score among the groups under investigation.[13]

The mean length of hospital stay (days) in Interventional group was 11.87 days while in the placebo group was 14 days (p value–0.005). Mean time to shock reversal was 176.33 hours in the Interventional group while it was 204.40 hours in the placebo group (p value<0.001). Both the results were statistically significant.

However conflicting results were obtained by Tomoko Fujii and his collegues. In their study the mean length of hospital stay in interventional and placebo groups were 12.3 (6.2 to 26.0) days and 12.3 (6.2 to 26.1) days respectively. P value was 0.75 (14). At day 14, the interventional group had a lower all-cause death rate than the placebo group (34% vs 45.33%). P value for this observation was 0.205 (not statistically significant). Conflicting results were obtained by Paul E Marik and his colleagues, they found that the hospital mortality was higher in the placebo group when compared to the interventional group (40.4% vs 8.5% respectively, p value<0.001).[14,15] The vitamins trial also showed that the 90 day mortality rate in the interventional group was 30/105 (28.6%), while in the control group, it was 25/102 (24.5%) (HR-1.18; 95% CI, 0.69-2.00).[14] The ORANGES trial also showed no 30 days mortality benefit.[16]

"ACTS randomized clinical trial" showed similar results with respect to all-cause mortality. Over the course of 72 hours, the SOFA score did not change statistically significantly (95% CI, -1.7 to 0.2; P =0.12). In terms of 30-day mortality, there was no statistically significant difference (34.7% vs. 29.3%; hazard ratio, 1.3; P =.26).[17]

CONCLUSION

In patients with septic shock early treatment (within 12 hours of diagnosis) with injection hydrocortisone, vitamin c and thiamine does bring a greater improvement in Mean arterial pressure and pa02 levels. The triple combination also decreases the length of hospital stay (11.87 days vs 14 days, p value-0.005) and the time to resolution of shock (176.33 hours vs 204.40 hours, p value<0.001). However, no significant change in all-cause mortality at day 14 was noted among the 2 groups. (34.67% vs 45.33%, p value 0.205). Consequently, more extensive research is required to evaluate the mortality advantage of starting early triple therapy in septic shock patients.

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