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VITAMIN C, THIAMINE AND HYDROCORTISONE IN SEPTIC SHOCK: A RETROSPECTIVE ANALYSIS

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ABSTRACT: Background: Sepsis leads to approximately 11 million deaths annually. **Objectives:** We studied the effectiveness of using a combination of intravenous hydrocortisone (50mg QID), Ascorbic Acid (1.5g QID), and Thiamine (200mg BD) (HAT) to reduce mortality among septic patients compared to a historical control group. **Materials and Methods:** This retrospective, observational study was conducted between January 2016 – February 2018. Our hospital mortality for septic shock is 55%. According to published literature, hospital mortality decreased from 40.4% to 8.5% with the HAT protocol. To detect a 31.9% mortality difference with 95% confidence and 80% power, a minimum sample size of 27 patients would be required in each group. We included 62 patients (31 per group) with septic shock. In the experimental group, patients in septic shock received the HAT drugs within 6 hrs and continued for 4 days. They were compared with a propensity score-matched historical control group. **Results:** Nineteen (61.29%) and twenty-seven (87%) patients in the control group received steroid and vitamin supplements (non-Vitamin C), respectively. The mortality was 54.83% in the control group and 41.93% in the HAT group (p=0.65). Time to shock reversal was 59.64±25.59 h in the control group and 58.82±24.31 hr in the HAT group (p=0.88). There was no difference in change of SOFA score, duration of ICU or hospital stay, or need for mechanical ventilation or renal replacement therapy. **Conclusion:** In this study, the HAT protocol did not show a statistically significant reduction in mortality in patients with septic shock.

INTRODUCTION: The global burden of sepsis in 2017 was close to 49 million, of which approximately 11 million (22.5%) died, with almost 60% mortality in low and middle-income countries [1].

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A mortality rate of around 50% has been reported for septic shock in India [2, 3]. Given the high disease burden and mortality, novel therapeutic approaches are desperately required to combat this global burden of sepsis [4].

Emerging data suggest the beneficial impact of using Vitamin C for managing sepsis in acute care facilities [5]. Critically ill patients are found to have very low levels of Vitamin C. Uncontrolled inflammation, and overwhelming oxidative stress is believed to contribute to increased morbidity and mortality in sepsis by causing circulatory failure

and capillary leak leading to organ failure. Vitamin C plays an important role in scavenging oxygen free radicals and is an essential cofactor for many biochemical reactions, especially for iron and copper-containing enzymes. Vitamin C is also involved in preserving the integrity of human endothelium and thereby, the flow in the microcirculation.

In addition, it may also increase vasomotor responsiveness by increasing glyoxylate aminotransferase, which facilitates oxidation and synthesis of norepinephrine and vasopressin. Hydrocortisone is believed to improve the dysregulated immune response and hypotension. Preclinical studies confirm the beneficial effects of Vitamin C on preventing endothelial disruption and multi-system organ failure [6, 7].

Moreover, Vitamin C and hydrocortisone act synergistically to preserve endothelial integrity. Thiamine pyrophosphate is a coenzyme of glyoxylate (a metabolite of ascorbic acid) that oxidizes glyoxalate to carbon dioxide (instead of oxalate). Hence, thiamine is important to reduce the renal oxalate's crystallization risk. We studied whether a combination of Hydrocortisone, Vitamin C (Ascorbic Acid), and Thiamine (HAT Protocol) administration can decrease mortality in septic patients compared to a historical control group.

Aim: To evaluate the effectiveness of Hydrocortisone, Vitamin C (Ascorbic Acid), and Thiamine (HAT Protocol) compared to a retrospective control group of patients with septic shock. The primary objective was a reduction in all-cause in-hospital mortality. Secondary objectives included a reduction in the mean duration of vasopressor therapy, need for mechanical ventilation, duration of ICU stay, duration of hospital stay and need for renal replacement therapy. The ΔSOFA (sepsis-related organ failure assessment) score at 72 hr between experimental and control groups.

Study Design, Study Period and Setting: This is a retrospective, observational study that was conducted between January 2016 – February 2018 at an academic tertiary referral center in Kerala, India. The institutional ethics committee approved the study and waivered the need for informed consent. (IEC-AIMS-2018-ANES-163)

Study Population and Sepsis Management: Septic shock is associated with 55% mortality in our hospital. This is comparable to published data from India [2]. Based on the hospital mortality rate in the HAT group (8.5%) compared with in the control group (40.4%) observed in an existing article [5], the sample size was calculated to be at least 54 (27 in each group) to detect a 31.9% mortality difference with 95% confidence and 80% power. Our study included 62 patients (31 in each group). The study population consisted of control and experimental (HAT) groups. All adult patients (age >18 years) admitted to ICU during the study period with a primary diagnosis of septic shock as determined based on SSC 2012 guidelines were eligible. The exclusion criteria included (1) patients under 18 years of age, (2) pregnant patients, (3) patients with limitations of care (an advanced disease with malignancy), (4) burns, (5) acute liver failure.

The control group consisted of a similar propensity score matched cohort admitted between January 2016 and February 2017 who did not receive vitamin C. The treatment group consisted of patients admitted between March 2017 and February 2018 with septic shock who had received HAT protocol for 4 days. The HAT protocol consisted of 50mg intravenous hydrocortisone and 1.5g vitamin C (ascorbic acid) four times a day, and 200mg thiamine twice daily for 4 days, with the first doses of the intervention medications administered within 6 hr of established septic shock. A photolysis preventing infusion set was used to administer Vitamin C, over 30 min. Steroid use and nutritional supplements in the control group were as per clinicians' discretion, except for vitamin C. Management of sepsis was according to 2012 SSC guideline bundle. If hypotension persisted after adequate fluid resuscitation, invasive monitoring and norepinephrine were commenced to maintain a mean arterial pressure (MAP)$\geq$ 65 mmHg. Vasopressin was the second line vasopressor unless septic cardiomyopathy, as evidenced by decreased global contractility, is observed in transthoracic echocardiography. No changes were made to the sepsis management protocols in the hospital during the study period.

Data Collection: Data collection was carried out by reviewing patients' health record and a single

researcher collected it. All inpatients admitted with sepsis in ICU with sepsis diagnosis were identified from the hospital information system. The pharmacy consumption of IV Vitamin C during the study period was tracked from the hospital information system, and a cohort of patients with sepsis treated with IV vitamin C constituted the treatment arm. A retrospective chart review was conducted matched controls were taken from the cohort of sepsis patients in which Vitamin C was not used. Patients in control group were matched with HAT group for age, sex, mean arterial pressure, Glasgow Coma Scale, Lactate, White blood cell count, procalcitonin, initial SOFA score, initial inotrope score and 24 hr fluid balance. Variables such as demographic details, admission diagnosis, comorbidities, inotropic score, need for mechanical ventilation, hourly dosage of vasopressors, length of ICU stay, presence of AKI, positive blood cultures, laboratory investigations such as WBC, creatinine, platelet, bilirubin, lactate, CRP, procalcitonin (if available) and ΔSOFA at admission & at 72 hr were collected. Acute kidney injury (AKI) was defined as 'an increase in serum creatinine 0.3 mg/dL within 48 hr or a level 1.5 times the baseline value per Kidney Disease: Improving Global Outcomes (KDIGO) criteria [8]. If baseline serum creatinine is unknown and initial serum creatinine is > 1.5 mg/dL, they were regarded as having AKI. The Vasoactive-Inotropic Score is calculated based on the formula:

Inotrope Score (IS) = 'Dopamine dose (mcg/kg/min) + Dobutamine dose (mcg/kg/min) + 10^2 × Epinephrine dose (mcg/kg/min) [9]

Vasoactive-Inotropic Score (VIS) = 'Inotropic Score + 10 × Milrinone dose (mcg/kg/min) + 10^4 × Vasopressin dose (units/kg/min) + 10^2 × Norepinephrine dose (mcg/kg/min) [10]

Statistical Analysis: Statistical calculations were performed using IBM SPSS 20.0 (SPSS Inc, Chicago, USA). Continuous variables are summarized as mean ± SD and categorical variables as a percentage. Parametric and non-parametric data were analyzed using the independent two sample't' test and Mann Whitney u test, respectively. Chi-square test was used for categorical variables. Results were considered statistically significant when P-value < 0.05.

RESULT: Thirty-one patients were included in each group. The baseline characteristics of the two groups are presented in **Table 1.**

TABLE 1: BASELINE CHARACTERISTICS

Variable	Control (n= 31)	HAT (n=31)	p Value
Age , mean	56.23±15	56.45±14	0.95
Sex, male, No. (%)	22 (71%)	20 (68%)	0.58
Mean Arterial Pressure (mmHg)	67.2±12.6	64.6±12.8	0.42
GCS	12±3	11±4	0.26
Lactate (mmol/L)	3.5±2.7	3.7±2.3	0.75
WBC (x109)	16.70±10.7	15.81±8.86	0.72
Procalcitonin	18.08±33.5	27.02±37.5	0.32
Creatinine (mg/dl)	2.6±1.8	1.9±1.8	0.13
PaO2/FiO2	259.7±115	273.1±132.1	0.67
SOFA	8.87±3.9	8.84±2.7	0.97
Fluid resuscitation in first 24 hr(ml)	2976.1±1086.1	3113.0±1391.1	0.51
Comorbidities, No. (%)			
None	1 (3%)	2 (6%)	
Diabetes	18 (58%)	19 (61%)	
Hypertension	14 (45%)	15 (48%)	
CAD	9 (29%)	5 (16%)	
COPD	4 (13%)	4 (13%)	
Cirrhosis	11 (35%)	5 (16%)	
CVA	1 (3%)	2 (6%)	
CRF	8 (26%)	6 (19%)	
Primary Diagnosis, No. (%)			
Pneumonia	9 (29%)	18 (58%)	
Urosepsis	8 (26%)	6 (19%)	
Primary Bacteremia	5 (16%)	2 (6%)	
GI/Biliary	12 (39%)	5 (16%)	
Other	9 (29%)	9 (9%)	

Nineteen (61.29%) and twenty-seven (87%) patients in the control group received hydrocortisone and vitamin supplements (non-Vitamin C), respectively. The mortality was 54.83% in the control group and 41.93% in the HAT group (p=0.65). The time to shock reversal was 59.64±25.59 hr in the control group and 58.82±24.31 hr in the HAT group (P=0.88).

Fig. 1 shows the mean vasoactive inotropic score trends with time in the control and HAT groups. Eight (25%) patients in the HAT group and 12 (38.7%) in the control group required renal replacement therapy. Pneumonia (n=27 (32.5%) and UTI (n=14 (16.9%) were the commonest sources of sepsis.

Gram-negative organisms (Kleibsiella pneumonia, Acinetobacter, *E coli*) were the major causative pathogens in all the foci in both arms **Table 2.** The primary and secondary outcomes are depicted in **Table 3.**

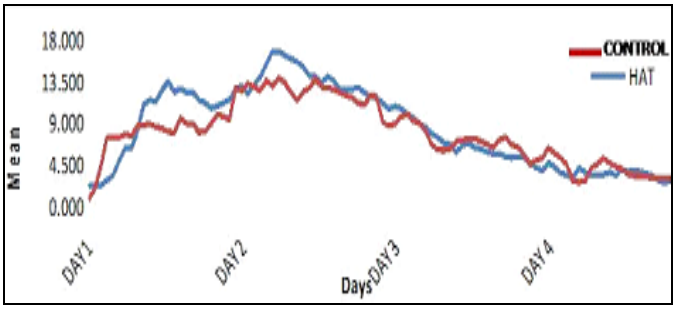

FIG. 1: MEAN VASOACTIVE INOTROPIC SCORE WITH TIME IN CONTROL AND HAT GROUP

TABLE 2: FOCUS OF INFECTION AND MICROBIOLOGICAL PROFILE AMONG CONTROL AND HAT

Focus of infection (MDR/NonMDR)	Control	HAT
Pneumonia	9	18
Klebsiella pneumoniae	3/0	7/1
Escherichia coli	1/0	0/0
Pseudomonas aeruginosa	1/2	2/1
Acinetobacter species	1/0	5/1
Serratia marcescens	1/0	0/0
Others	0/0	0/1
Urosepsis	8	6
Klebsiella species	3/1	3/1
Escherichia coli	0/0	0/1
Pseudomonas aeruginosa	1/0	0/0
Enterococcus sp	1/2	0/0
Others	0/0	0/1
Primary bacteremia	5	2
Klebsiella pneumoniae	1/0	1/1
Escherichia coli	2/1	0/0
Burkholderia	0/1	0/0
GI/Biliary	12	5
Klebsiella pneumoniae	1/1	1/0
Escherichia coli	4/0	2/0
Pseudomonas	1/0	0/1
Enterococcus	1/1	0/0
Others	1/2	0/1
Others	9	9
Klebsiella pneumoniae	2/0	2/1
Escherichia coli	1/0	0/0
Pseudomonas aeruginosa	1/1	1/1
Enterobacter species	1/1	1/0
Others	1/1	0/3

TABLE 3: OUTCOME VARIABLES

Variable	Control (n= 31)	HAT (n=31)	p Value
Mortality	54.83%	41.93%	0.65
Time to shock reversal (among survivors, in hr)	59. 64 ± 25.59	58.82±24.31	0.88
Need for Mechanical Ventilation	19 (61%)	22 (71%)	0.42
Average Length of ICU stay in days	16.39±13.25	19.23±16.75	0.46
Average Length of hospital stay in days	24.258±17.645	31.484±21.973	0.15
Renal replacement therapy	12 (38.7%)	8(25.8%)	0.27
ΔSOFA	0.58±3.7	0.71±2.9	0.87

DISCUSSION: There has been an increased interest in adopting metabolic resuscitation, in other words, Vitamin C, thiamine, and hydrocortisone, as an adjunct in the management of sepsis, both within and outside the context of the clinical trial, ever since the publication of Marik *et al.* in 2017 [5, 11]. He showed that this combination decreased death directly related to sepsis and reduced the vasopressor score.

Vitamin C is essential for the synthesis of endogenous stress hormones and also for adrenergic transmission. It is believed to restore vascular responsiveness to vasopressors, inhibit inducible nitric oxide and restore endothelial permeability barrier [12]. The animals that synthesize vitamin C tend to increase its production during stress- adrenocorticotropic hormone (ACTH) induces the release of Vitamin C - more like a "stress hormone" [12]. Our diet needs to supply Vitamin C, as we humans do not synthesize it. In humans, the temporal relationship for the decrease of vitamin C during sepsis is believed to be due to the metabolic uptake of the molecule, and reduced blood levels were associated with greater severity of organ failure. They increased mortality in many retrospective studies [13, 14]. In our study, we found that the use of HAT protocol did not significantly reduce in-hospital mortality rates. Although fewer deaths were observed in the HAT group, the difference did not attain statistical significance. Other secondary endpoints of time to shock reversal, duration of ICU and hospital stay, change in SOFA score, and need for renal replacement therapy and mechanical ventilation did not differ between groups.

Wani *et al.* was among the first to publish a randomized controlled trial on the use of HAT protocol in sepsis and septic shock. Although they found no difference in mortality, patients had a shorter duration for shock reversal [15]. A similar decrease in the use of vasopressors or earlier shock reversal was observed by Balakrishnan and Yanase in septic cardiac surgical patients and replicated in other Vitamin C trials like ORANGES, ViCTOR, and HYVCTTSSS [16 - 20]. The earlier shock reversal is possibly due to its protective effect in improving ejection fraction [21]. However, none of them, including other retrospective studies, showed no mortality benefit, even with slightly different doses and duration of the drugs of metabolic resuscitation [22-24]. The CITRIS-ALI study evaluated the use of Vitamin C in a specific subset of septic patients who developed acute lung injury. Although they did not find any difference in lung injury, the mortality benefit was observed in the group that received vitamin C [25].

It was postulated that to achieve adequate plasma levels and derive optimum benefit of metabolic resuscitation; high dose vitamin C should be administered at least 6-hourly, for a minimum 4 days, and early in the treatment of sepsis [26]. Our treatment group received 4 days of hydrocortisone, vitamin C, and thiamine, within 6 hr of established septic shock, in the doses used by Marik *et al.*, but without a mortality benefit [5]. In the VITAMINS and ViCTOR trials, the time from recognition of septic shock to the administration of HAT protocol was 12 and 6 hr, respectively. There was no significant mortality difference between the groups in both the trials, while the ViCTOR trial showed a decrease in vasopressor use in the intervention group [19, 27]. Lack of mortality benefit was observed in other recently published randomized controlled trials [28-30].

The reason for the higher mortality rates in our study could be multifactorial. The inclusion criteria were not sepsis but septic shock. Our cohort of patients had a high disease burden, as evidenced by a high initial SOFA score, with 65% of the isolates being multi-drug resistant **Table 2**. The mortality in our cohort is comparable to previously published literature from this part of the world [2].

We did not find any adverse events that could be attributable to vitamin C in our study. Although vitamin C levels can theoretically rise in renal failure, dose modification is not recommended in doses below 14g/day [12, 31]. Other human studies that used similar or even higher doses have not reported any side effects that could be attributable to Vitamin C [5, 7, 16, 17, 22, 25]. Our study adds to the growing body of evidence that metabolic resuscitation in the currently used doses, even when administered within 6 hr of the onset of septic shock for at least 4 days, does not decrease mortality or duration of shock [33, 34]. As ours was a retrospective study, we did not check the levels of vitamin C. Most of the sepsis and septic shock

trials looked at 7-14 day use of hydrocortisone [35]. We tried to replicate the findings of Marik *et al.* and, therefore, used hydrocortisone for 4 days only. It is possible that a shorter dose of steroids led to a relatively less decrease in inflammation. Hydrocortisone was stopped after 4 days and was not tapered as the dose and duration of hydrocortisone was relatively small. Patients in the control group received hydrocortisone during the treatment for sepsis, which could have provided mortality benefit by decreasing inflammation. Whether adding fludrocortisone or Vitamin D to HAT protocol improves shock reversal needs to be explored.

CONCLUSION: In conclusion, in this retrospective study, the HAT protocol did not reduce ICU mortality in septic shock. A well-controlled randomized trial is necessary to determine the therapeutic efficacy of HAT protocol in septic shock.

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CONFLICTS OF INTEREST: Nil

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