

# Metabolic Resuscitation Using Hydrocortisone, Ascorbic Acid, and Thiamine: Do Individual Components Influence Reversal of Shock Independently?

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## ABSTRACT

**Aims and objective:** To study the effects of various components of “metabolic resuscitation” on the shock reversal among patients with septic shock

**Introduction:** Sepsis is characterized by dysregulated host response to infection. Mitochondrial dysfunction which occurs early in sepsis is associated with multiorgan dysfunction. Therapies such as adequate resuscitation, early administration of antibiotics, and aggressive monitoring reduced mortality substantially but it still remains high for those with septic shock. Combination of vitamin C, hydrocortisone, and thiamine improved outcome in a retrospective study, but how effective is this therapy in isolation compared to combination has to be known before implementation.

**Materials and methods:** This study is single-center, prospective, randomized nonblinded trial done in septic shock patients admitted to the medical intensive care unit. Subjects were randomized to three groups of hydrocortisone (H), hydrocortisone, ascorbic acid (HA), hydrocortisone, ascorbic acid, thiamine (HAT). Following randomization, they received hydrocortisone 200 mg over 24 hours as infusion, intravenous ascorbic acid 1.5 g every 6 hours, thiamine 200 mg twice daily as allotted and continued till shock reversal or death. Primary outcome is time to shock reversal and secondary outcome is time to vasopressor dose reduction from hemodynamic SOFA score 4–3.

**Results:** Twenty seven subjects were randomized into 3 groups of 9 each, of which 17 (63%) patients met primary outcome and secondary outcome has been studied in 16 (59%) patients. Eight patients (29.5%) died and did not meet either outcome and two patients (7.5%) met secondary outcome but not primary outcome because of discharge to other hospital. There is no difference in time to shock reversal [mean, SD in H (7422, 8348), HA (2528, 3086), HAT (1860, 749), *p* value 0.17]. There is no difference in time to shock reversal from hemodynamic SOFA 4–3 [mean, SD in H (4935, 6406), HA (2310, 2515), HAT (1800, 1282), *p* value 0.35].

**Conclusion:** In patients with septic shock, there is no difference in time to shock reversal comparing individual components of metabolic resuscitation.

**Keywords:** Adenosine triphosphate, Hydrocortisone, Metabolic resuscitation, Septic shock, Thiamine, Vitamin C.

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## INTRODUCTION

Sepsis is associated with multiorgan dysfunction syndrome (MODS) which represents adaptive, protective, and reactive response to overwhelming inflammation triggered by systemic infection.<sup>1</sup> It is usually the result of host-response to infecting pathogen. Early use of antibiotics, appropriate fluid resuscitation, and better monitoring reduced the mortality in sepsis significantly. Mitochondrial dysfunction occurs early in sepsis and has a central role in MODS development.

Exposure to bacterial endotoxins lead to expression of genes regulating cytokines, chemokines, adhesion molecules, enzymes, clotting factors, and stress proteins.<sup>2</sup> These mediators are involved in vasoplegic shock, myocardial dysfunction, altered microvascular flow, and endothelial injury. In addition, reactive oxygen species (ROS) are produced by xanthine oxidase, lipoxigenase, and cyclooxygenase which underlie many pathologic process characteristic of sepsis. Mitochondria are the source and target of ROS in sepsis. This unbalanced production of ROS impairs mitochondrial structure, function, an cellular integrity resulting in multiorgan dysfunction.<sup>3</sup> The recovery of mitochondrial function is associated with MODS recovery and survival.

Mortality from sepsis still remains high and targeting therapy to improve mitochondrial function termed as “metabolic resuscitation” mitigates MODS and reduces mortality.

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## Role of Vitamin C

In acutely ill and sepsis patients, vitamin C levels are low due to increased oxidation, decreased absorption, and increased urinary losses. These low levels correlate with increased vasopressor requirement, multiorgan failure, and death.<sup>4,5</sup>

Vitamin C is required for the synthesis of catecholamines and cortisol. It is also required for the endothelial function. It has antithrombotic effect by decreasing platelet activation, enhances immune function, and promotes wound healing. Its deficiency

leads to low catecholamine levels, thereby resulting in failure of sympathetic nervous system. It is involved in the regulation of macrophage function, reduction of inflammatory mediators, and has bacteriostatic effect at higher concentration.<sup>6,7</sup> It reduced the resuscitation fluid requirement during the first 24 hours after thermal injury.<sup>8</sup>

Patients treated with vitamin C showed improvement in SOFA scores, reduced vasopressor requirement, and reduction in mortality.<sup>9,10</sup>

The prooxidant effect of vitamin C is seen at very high doses (>100 g) in the absence of free iron but can occur at dose >300 mg/kg in ischemia/reperfusion due to free iron. This narrow dose response curve is rationale for administering high-dose vitamin C (6 g/day) for four days followed by continuation in low nutritional doses to allow generation of low concentration of ROS which are essential for physiological signaling and repair.

Vitamin C metabolizes into oxalic acid leading to calcium oxalate nephropathy. This has been reported at much higher doses >40 g/day.<sup>11</sup> The concurrent use of thiamine reduced conversion of vitamin C to oxalate.

### Role of Thiamine

Thiamine as a precursor of thiamine pyrophosphate (TPP) is involved in glucose metabolism, Krebs's cycle, production of NADPH, and generation of ATP and is an essential cofactor for pyruvate dehydrogenase without which anaerobic metabolism ensues and lactic acidosis occurs. It plays an important role in cellular energy metabolism, brain function, and interneuronal communication.<sup>12</sup> It has a role in the uptake of serotonin thereby affecting the activity of cerebellum, hypothalamus, hippocampus.

Hypermetabolic state in critical illness predisposes individuals to thiamine deficiency. So its deficiency leads to decreased activity of thiamine-dependent enzymes causing energy compromise, decreased ATP production, and increased ROS generation.<sup>13,14</sup> Its deficiency compounds mitochondrial injury caused by vitamin C depletion and its supplementation to patients with septic shock who are thiamine-deficient reduces mortality and lactate levels.<sup>15–20</sup>

### Role of Steroid

Glucocorticoids have anti-inflammatory action through multiple mechanisms repressing large number of proinflammatory genes encoding cytokines, chemokines, cell adhesion molecules, and inflammatory enzymes. Using short course of low-dose steroids is well-tolerated and unlikely to exacerbate infection.<sup>21</sup> Stress dose steroids cause fewer side effects than giving same dose to healthy person due to sepsis-induced glucocorticoid resistance.<sup>22</sup> Further steroid supplementation leads to early shock reversal.<sup>23</sup> Another study published in the same year where hydrocortisone was used with fludrocortisone showed reduction in mortality.<sup>24</sup>

### Rationale for Combination

Rationale for combining vitamin C and steroid is that they work synergistically as antioxidants, anti-inflammatory agents, further steroid sensitivity is increased by vitamin C and both in combination but not in isolation found to preserve endothelial integrity against challenge from lipopolysaccharide.<sup>1,25–27</sup> The antiinflammatory and immune-enhancing effects of steroids and vitamin C limit immunosuppression in sepsis. Both thiamine in synergism with steroid and vitamin C limiting mitochondrial injury restore

mitochondrial function and energy production. It also decreases the oxalate production.

But do individual components of “metabolic resuscitation” influence the reversal of shock independently? To be addressed.

## MATERIALS AND METHODS

### Study Population

Patients admitted to intensive care unit (ICU) with diagnosis of septic shock and age more than 18 years are included in the study. A rise in SOFA score of 2 with persistent hemodynamic instability despite fluid resuscitation and requiring vasopressors criteria should be met. We did not include pregnant patients and those with new onset acute coronary syndrome along with sepsis.

### Study Design, Randomization, and Treatment

This study is single center, prospective, randomized nonblinded clinical trial. Randomization done alternatively using sequential randomization. Three groups were identified a priori: the hydrocortisone (H) alone group, the hydrocortisone, and ascorbic acid group (HA), and hydrocortisone, ascorbic acid, and thiamine (HAT) group. Baseline APACHE and SOFA scores were recorded at randomization.

Ethical approval was obtained from ethics committee. Hydrocortisone was administered as 200 mg over 24 hours infusion in all 3 groups, ascorbic acid in dose of 1.5 g IV every 6 hour in HA, HAT group and thiamine dose of 200 mg IV every 12 hours in HAT group. The primary outcome measured is the time from initiation of therapy to shock reversal and the secondary outcome measured is time from initiation of therapy to vasopressor dose reduction from hemodynamic SOFA 4–3. This resuscitation continued till shock reversal or death. Vasopressor dose was titrated and tapered targeting MAP of 65 mm Hg. Shock reversal is labeled if they are off vasopressors for more than 24 hours. If hydrocortisone was administered for more than 5 days, it is tapered over 4 days.

### Statistical Analysis

Based on admission in the last year, for a population of 400, expected sample size is 198 for 5% margin of error and 95% confidence limits. We limited our sample size to 27 as we want to generate hypothesis for a larger study.

Data entry done in excel and analyzed using socscistatistics.com. Continuous variables were expressed as mean and standard deviation. Significance of difference in means assessed by one-way ANOVA as there are 3 comparison groups.

## RESULTS

A total of 27 patients randomized into 9 in each group of which men constituted 63%. Eight patients (29.5%) died and did not meet either outcome and 2 patients (7.5%) met secondary outcome but not primary outcome because of discharge to other hospital. Seventeen (63%) patients were analyzed for primary outcome. The secondary outcome has been analyzed in 16 (59%) patients

Baseline characteristics were comparable and there is no difference in age, mean APACHE, and SOFA scores on admission. Mean time to shock reversal is longer in H group compared to others [mean, SD in H (7422, 8348), HA (2528, 3086), HAT (1860, 749), *p* value 0.17]. Time to shock reversal from hemodynamic SOFA 4–3 is also longer in H group [mean, SD in H (4935, 6406), HA (2310, 2515), HAT

**Table 1:** Baseline patient characteristics

Characteristics	H group (n = 7)	HA group (n = 7)	HAT group (n = 5)	p value
Age (Y), mean (SD)	55.4 (12.3)	56.5 (12)	53.8 (11)	0.6
Sex no. (%) male	3 (15.7)	3 (15.7)	4 (21)	
APACHE score, mean (SD)	21.2 (6.5)	17 (3.8)	18.4 (2.5)	0.26
SOFA score, mean (SD)	8.8 (2.9)	11 (3.4)	9.2 (0.4)	0.34
Time to metabolic resuscitation (minutes), mean (SD)	762 (480)	1,935 (2,403)	786 (424)	0.29
Source of infection, no. (%) pulmonary	3 (42.8)	0	1 (20)	
Gastrointestinal	1 (14.3)	4 (57.1)		
Urinary	2 (28.6)	2 (28.6)	2 (40)	
Skin and soft tissue	1 (14.3)	0		
Unknown	0	1 (14.3)	2 (40)	

**Table 2:** Primary and secondary outcome

Outcome (no)	H group (5)	HA group (7)	HAT group (5)	p value
Primary outcome	7,422 (8,348)	2,525 (3,086)	1,860 (749)	0.17
Time to shock reversal (minutes), mean (SD)				
Secondary outcome (no.)	H group (6)	HA group (5)	HAT group (5)	p value
Time to vasopressor reduction (minutes) from SOFA (h) 4–3 mean (SD)	4,935 (6,406)	2,310 (2,515)	1,800 (1,282)	0.35

(1800,1282), *p* value 0.35]. Mean time to metabolic resuscitation was 762 minutes (SD 480) in H, 1935 minutes (SD 2403) in HA, and 786 minutes (SD 424) in HAT.

Other data can be seen in Tables 1 and 2.

## DISCUSSION

This prospective nonblinded trial in septic shock was conducted in patients admitted to medical intensive care unit (MICU) in the tertiary care hospital. The mean time to complete shock reversal and shock reversal from hemodynamic SOFA 4–3 is higher in H group compared to other groups but not significant statistically. This could be due to small sample size. There is no significant difference in time to initiation of metabolic resuscitation among groups. APACHE and SOFA scores are comparable. In our study, 64% of patients are with urinary tract and gastrointestinal tract infection. All patients received their first dose of antibiotic in the emergency department. Few patients in H, HA groups received thiamine for other indications, but dose was 100 mg/day.

A before and after study showed early shock reversal with metabolic resuscitation.<sup>26</sup> Similar results were reproduced in a recent study.<sup>28</sup> While previous trials compared hydrocortisone with all three components (hydrocortisone, ascorbic acid, thiamine), this study aimed to detect individual components' role and to generate hypothesis.<sup>26,29</sup> We included 1 patient with >24 hours after onset of shock unlike VITAMINS trial where shock duration of <24 hours only is included in their study.<sup>29</sup> We did not include the length of stay, ventilator-free days, and mortality in our outcomes.

## Limitations

- This is nonblinded study
- Small sample size
- Not powered to detect statistical difference
- Single-center study.

## CONCLUSION

In septic shock patient resuscitation with hydrocortisone or in combination with ascorbic acid, thiamine did not show any

difference in time to shock reversal. If larger doses of these antioxidants or continuation for longer duration plays any role to be addressed. A larger clinical trial may give further information about individual components' role–dose, timing, and duration of therapy.

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