Hydrocortisone-Ascorbic Acid-Thiamine Use Associated with Lower Mortality in Pediatric Septic Shock

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Impact: Our study highlights a potentially valuable metabolic adjuvant therapy for children who are critically ill. This is the first pediatric study to show that the relatively inexpensive

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combination of parenteral hydrocortisone, ascorbic acid and thiamine may be associated with reduced mortality in children with septic shock.

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To the Editor:

Septic shock is one of the leading causes of death in critically ill children (1). The combination of hydrocortisone, intravenous (IV) ascorbic acid (vitamin C), and thiamine ("HAT therapy"), has been proposed as adjunctive therapy in adults, primarily targeting the oxidative stress observed in septic shock (2).

Numerous studies have shown the potential benefits of IV ascorbic acid use in sepsis (2-7). Ascorbic acid aids in the production of catecholamines and its effects on redox-sensitive pathways protect the microvasculature by preserving capillary blood flow and arteriolar responsiveness to vasoactive medications (3). Both high-dose IV ascorbic acid and HAT therapy have been associated with earlier recovery from organ failure, earlier reversal of shock, and lower mortality in adults with sepsis and septic shock (2, 6, 7). Given these results, we developed a protocol for the use of HAT therapy in children with septic shock. We hypothesized that children receiving HAT therapy would have decreased mortality when compared to similar patients not receiving the treatment.

METHODS

We conducted a retrospective, propensity score-matched cohort study of patients with septic shock admitted to our pediatric intensive care unit (PICU) between 1/2014 and 2/2019. Patients with septic shock were defined as those with a suspected or confirmed infection who required vasoactive infusions within 24 hours of admission. Stress-dose hydrocortisone therapy ("hydrocortisone only") and HAT therapy were initiated at the discretion of the bedside physicians. HAT therapy was first used in May 2017; this protocol consists of IV ascorbic acid (30 mg/kg/dose every 6 hours for 4 days; maximum 1500 mg/dose), IV hydrocortisone (50 mg/m2/day divided every 6 hours) and IV thiamine (4 mg/kg/day for four days; maximum 200

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mg/dose). Patients were considered treated with these therapies if they were started within 24 hours of vasoactives initiation.

We performed two propensity score-matched analyses: (1) patients who received HAT therapy matched with untreated controls; (2) patients who received HAT therapy matched with patients who received hydrocortisone only. Patients were matched 1:1 without replacement using the nearest neighbor approach with a caliper of 0.5 standard deviations. We matched patients based on the propensity to use HAT therapy according to age, immunocompromised state, the presence ≥2 complex chronic conditions (8), and the following variables in the first 24 hours of admission: peak vasoactive inotrope score (9), peak serum lactate level, need for mechanical ventilation, and lowest PaO_2/FiO_2 ratio. Patients without a PaO_2 recorded had a PaO_2/FiO_2 ratio estimated based on their lowest SaO_2/FiO_2 ratio (10). Missing variables were assumed to be normal. We performed two sensitivity analyses using the entire cohort: (1) an inverse probability treatment weighting (IPTW) analysis with the same covariates and a time epoch to increase the weight of patients in the post-HAT era; and (2) a Cox regression analysis of time-to-death with HAT therapy as a predictor and the same covariates as confounders. The primary outcome was 30-day mortality. This study was approved by the local Institutional Review Board.

RESULTS

There were 557 patients included and 64 (11.5%) died within 30 days of PICU admission. Clinical characteristics of the three treatment groups are presented in Table 1. Patients were started on vasoactive infusions a median of 0.5 hours (interquartile range [IQR] - 0.4–6 hours) from PICU admission and those treated with HAT therapy received IV ascorbic acid a median of 12 hours (6–19 hours) after PICU admission. Propensity score matching reduced the standardized differences between the treatment groups, as seen in Figure 1A.

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Patients who received HAT therapy had significantly lower 30-day mortality than matched controls and matched hydrocortisone only patients ($p \leq 0.03$). There were no differences in vasoactive inotrope-free days or hospital-free days (Table 1). Figure 1B shows the Kaplan-Meier survival curve for the matched groups.

In the sensitivity analysis using IPTW with a time epoch, 30-day mortality was again lower in septic shock patients who received HAT therapy compared to untreated controls ($p=0.006$) and hydrocortisone only patients ($p=0.014$). In the Cox regression analysis, HAT therapy was independently associated with a lower hazard ratio for death (0.3; 95% confidence interval: 0.1-0.9).

DISCUSSION

In our retrospective propensity score-matched analysis, children with septic shock who received HAT therapy experienced decreased mortality when compared to children who received hydrocortisone only or neither of these adjunctive therapies. To our knowledge, this is the first study to examine clinical outcomes associated with the use of HAT therapy in children with septic shock.

The improvement in mortality observed appears to be primarily associated with reduced early deaths. Previously, investigators have found that up to one-third of children with septic shock die early from refractory shock (11). A possible explanation of our results is that HAT therapy reduces the incidence and duration of refractory shock and thus reduces early deaths. This may explain the observed improvement in survival without concomitant increases in vasoactive-free days, as once the early shock phase is resolved in any survivor, the need for vasoactive support is drastically reduced.

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We hypothesize that the observed benefit of HAT therapy is due to the administration of IV ascorbic acid, followed by the synergistic effects of hydrocortisone and thiamine. Sepsis is associated with the depletion of ascorbic acid in critically ill patients and this has been associated with poor outcomes (3). Parenteral administration of ascorbic acid raises plasma and cellular levels and may ameliorate the pathologic changes that occur during sepsis, resulting in improved clinical outcomes (2-4, 6, 7). Thiamine, a co-factor in energy production pathways, prevents formation of renal oxalate crystals that may occur with high-dose ascorbic acid administration (2, 12). Potential pitfalls of ascorbic acid use include pro-oxidant effects, excess iron absorption, and interference with blood glucose measurements. Avoiding this therapy is prudent in patients with oxalate nephrolithiasis, glucose-6-phosphate dehydrogenase deficiency, and paroxysmal nocturnal hemoglobinuria (4).

Our study is a single-center, retrospective investigation; accordingly, further validation is needed. Propensity score matching, IPTW, and Cox regression were used to reduce treatment-selection bias, but unmeasured confounding variables may have been present. Additionally, untreated controls and hydrocortisone only patients from both the pre-HAT and post-HAT epochs were used to capture sufficiently similar patients for the matching analysis. However, the 30-day mortality of untreated controls did not change significantly between epochs, making changes in baseline mortality an unlikely contributor to our results. Finally, survival bias may have confounded our results; however, median time-to-death in untreated controls significantly exceeded the median time-to-HAT therapy, making this unlikely.

In summary, children with septic shock treated with HAT therapy had an associated lower mortality when compared to matched untreated control patients and matched hydrocortisone only therapy patients. Larger, multi-center studies in children with septic shock are needed to confirm our findings.

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Unmatched Patients	**Untreated Controls**	**Hydrocortisone Only Therapy**	**HAT Therapy**
Total No. (%)	333 (60%)	181 (33%)	43 (8%)
Age, years (IQR)	10.1 (3, 15)	10.5 (4, 15)	8.4 (4, 14)
Male, No. (%)	160 (48)	96 (53)	26 (60)
Immunocompromised, No. (%)	114 (34)	88 (47)	15 (35)
≥2 Complex Chronic Conditions, No. (%)	253 (76)	162 (90)	43 (100)
Clinical Characteristics in first 24h			
Mechanical Ventilation, No. (%)	166 (50)	101 (56)	35 (81)
Lowest PaO2/FiO2 median (IQR)	168 (93, 290)[a]	128 (69, 230)[a]	149 (109, 318)
Highest Vasoactive Inotrope Score median (IQR)	7 (5, 12)	15 (6, 30)	19 (10, 38)
Highest Serum Lactate, mmol/L median (IQR)	1.8 (1, 3.8)[b]	3.3 (1.5, 6.9)[b]	2.9 (1.9, 6.6)
Microbiological Characteristics			
Organisms isolated:			
Gram-positive bacteria, No. (%)	72 (22)	43 (24)	12 (28)
Gram-negative bacteria, No. (%)	98 (29)	74 (41)	21 (49)
Other bacteria, No. (%)	14 (4)	3 (2)	0 (0)
Viruses, No. (%)	61 (18)	37 (20)	7 (16)
Fungi, No. (%)	10 (3)	14 (8)	8 (19)
No organism isolated, No. (%)	150 (45)	76 (42)	10 (23)
Infection source:			
Bloodstream, No. (%)	62 (19)	62 (34)	16 (37)
Respiratory tract, No. (%)	120 (36)	65 (36)	23 (53)
Cerebral spinal fluid, No. (%)	0 (0)	3 (2)	0 (0)
Genitourinary tract, No. (%)	43 (13)	21 (12)	4 (9)
Other, No. (%)	5 (2)	20 (11)	4 (9)
Outcomes			

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Vasoactive inotrope-free days at 30 days median (IQR)	28 (27, 29)	28 (24, 29)	26 (22, 28)
Hospital-free days at 30 days median (IQR)	18 (6, 24)	12 (0, 22)	0 (0, 11)
Mortality at 30 days (%)	27 (8)	33 (18)	4 (9)
Mortality at 90 days (%)	30 (9)	39 (22)	6 (14)
Matched Patients	**Matched Controls**	**Matched Hydrocortisone Only**	**HAT Therapy**
Clinical Characteristics in first 24h			
Total No.	43	43	43
Age, years (IQR)	7.8 (1.5, 16.5)	8.6 (3, 16)	8.4 (4, 14)
Male, No. (%)	17 (40)	29 (67)	26 (60)
Immunocompromised, No. (%)	11 (26)	15 (35)	15 (35)
≥2 Complex Chronic Conditions, No. (%)	43 (100)	43 (100)	43 (100)
Mechanical Ventilation, No. (%)	38 (88)	36 (84)	35 (81)
Lowest PaO2/FiO2 median (IQR)	159 (89, 459)	165 (76, 284)	149 (109, 318)
Highest Vasoactive Inotrope Score median (IQR)	13 (8, 20)	19 (7, 35)	19 (10, 38)
Highest Serum Lactate, mmol/L median (IQR)	3.9 (1.9, 6.2)	3.4 (1, 7.1)	2.9 (1.9, 6.6)
Outcomes			
Vasoactive inotrope-free days at 30 days median (IQR)	25 (2, 28)	27 (11, 28)	26 (22, 28)
Hospital-free days at 30 days median (IQR)	2 (0, 15)	0 (0, 16)	0 (0, 11)
Mortality at 30 days No. (%)	12 (28)[a]	13 (30)[b]	4 (9)[a,b]
Mortality at 90 days No. (%)	15 (35)[c]	16 (37)[d]	6 (14)[c,d]

Table 1. Comparison of baseline clinical characteristics in the first 24 hours and outcomes of patients with septic shock based on treatment group for both unmatched patients (top) and propensity score-matched patients (bottom). 168 patients (49%) in the unmatched control group and 99 patients (55%) in the unmatched hydrocortisone only group had PaO_2/FiO_2 measurements or a SaO_2/FiO_2 ratio to convert. 232 patients (70%) in the unmatched control group and 134 patients (74%) in the unmatched hydrocortisone only group had serum lactate measurements. Baseline clinical characteristics of matched patients were compared using Mann-Whitney U and Chi-squared tests and were not statistically different (p=0.08 for age and p=0.13 for vasoactive inotrope score in the matched control-HAT therapy comparison, otherwise p≥0.29). Comparison of outcomes were as follows: Vasoactive inotrope-free days and hospital-free days at 30 days were not statistically different (p≥0.64). Mortality at

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30 days and 90 days were significantly lower in HAT therapy patients: [a]p=0.03; [b,d]p=0.01; [c]p=0.02.
HAT, hydrocortisone-ascorbic acid-thiamine; *IQR*, interquartile range.

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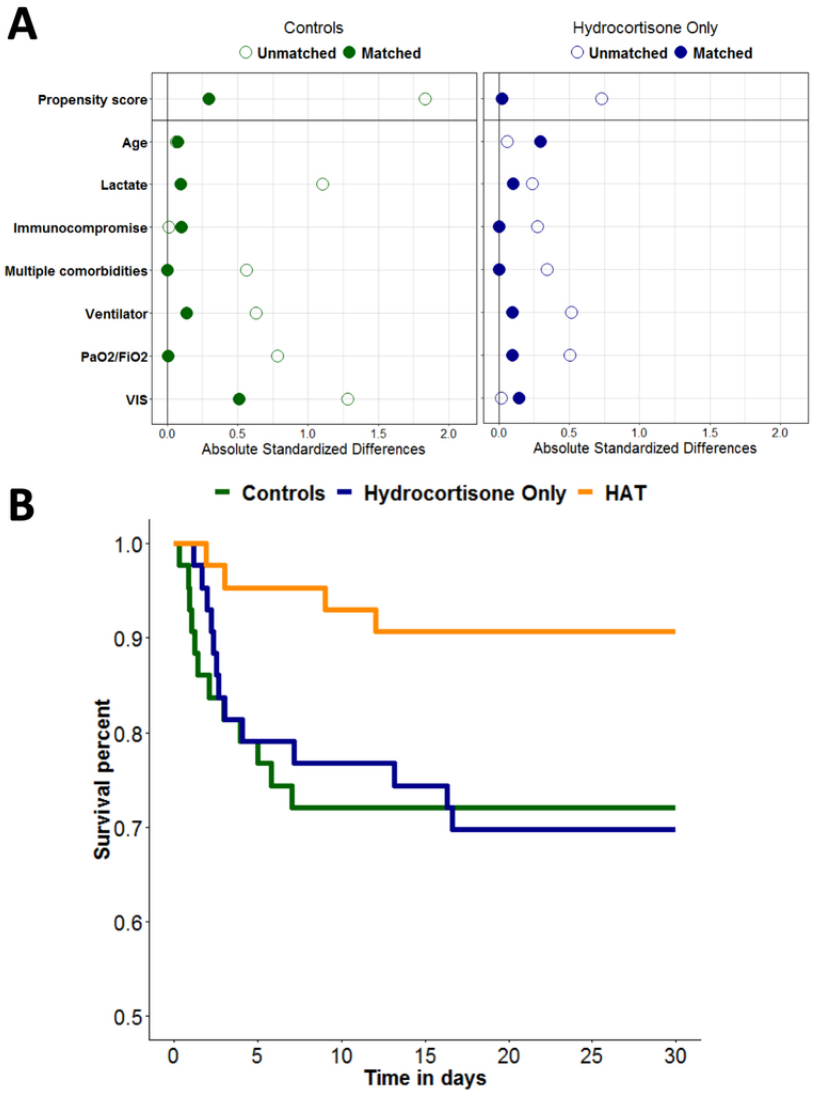

Figure 1. (A) Absolute mean standardized differences between HAT and controls (left) and hydrocortisone only (right) before and after matching; and (B) Kaplan-Meier survival curves of matched patients who received HAT therapy (orange), hydrocortisone only (blue), and untreated controls (green). Median time-to-death in matched untreated controls was 1.8 days, in matched patients with hydrocortisone only therapy was 2.4 days, and in patients receiving HAT therapy was 6 days. VIS, vasoactive inotrope score; HAT, hydrocortisone-ascorbic acid-thiamine

68x95mm (300 x 300 DPI)

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