EFFECT OF CORTICOSTEROIDS IN PEDIATRIC PATIENTS WITH VASOACTIVE DRUG-DEPENDENT SEPTIC SHOCK

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Abstract. Increased cortisol level is known to be an adaptive process for maintaining cardiac contractility, vascular tone, and blood pressure. However, the benefit of adjunctive corticosteroids in septic shock remains inconclusive. Additionally, the adverse effects of corticosteroids are often under-recognized and can be harmful. The aim of this retrospective study was to investigate the effect of adjunctive corticosteroid therapy in children with septic shock that required vasoactive support. Hemodynamic variables, inotrope score, time to cessation of vasoactive drug, mortality, and length of stay were compared between patients who received corticosteroid therapy and those who did not. Ninety-five patients met the inclusion criteria, and 32 (33.6%) of those received corticosteroids. Illness severity, as measured by median PIM II scores, was similar between the two study groups. Median inotrope scores were higher in the corticosteroid group than in the no corticosteroid group at 4 hours (20 *vs* 10; p=0.007), 8 hours (20 *vs* 10; p=0.007), and 12 hours (19 *vs* 9; p=0.004) after initiation of vasoactive support. There was a trend toward longer median time to cessation of vasoactive drug in the corticosteroid group, as compared to the no corticosteroid group (48.7 *vs* 37.0 hours; p=0.051). There were no differences between groups for ICU mortality, 28-day mortality, or ICU length of stay. In summary, no definite outcome improvement can be attributed to adjunctive corticosteroid therapy in our study patients. Further well-designed randomized controlled trials are needed to prove the benefit of this intervention in clinical practice.

Keywords: corticosteroids, septic shock, children, vasoactive drug

INTRODUCTION

Glucocorticoids play an important role in maintaining cardiovascular homeostasis, including maintenance of vascular tone, endothelial integrity, and distribution of fluids within the vascular compartment. Dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis has been described in patients with septic shock, including abnormalities in glucocorticoid receptors and decreased production of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and cortisol (Levy-Shraga and Pinhas-Hamiel, 2013).

However, the efficacy of the empirical treatment with corticosteroids in septic shock patients continues to be debated. Many studies in both adults and children reported hemodynamic benefits in terms of time to resolution of shock or weaning off of vasoactive support (Annane *et al*, 2002; Charles *et al*, 2008; Hebbar *et al,* 2011). In contrast, overall data from recent systematic reviews and meta-analyses

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revealed lack of mortality reduction from this adjunctive treatment in septic shock (Menon *et al,* 2013; Wang *et al,* 2014; Volbeda *et al,* 2015). In addition, possible adverse effects of corticosteroids were noted among critically ill children, including hospital-acquired infections secondary to immune suppression, ICU-acquired weakness secondary to lean body catabolism, hyperglycemia, and delirium (Zimmerman, 2015).

Based on these inconclusive outcomes and in an attempt to elucidate the effectiveness of this adjuvant therapy, we set forth to examine the effect of corticosteroids in children with septic shock who required vasoactive support for shock resuscitation in our critical care setting.

MATERIALS AND METHODS

The protocol for this retrospective study was approved by the Siriraj Institutional Review Board (SIRB), Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (approval no. *Si*117/2016).

Subjects

This retrospective study included children aged 1 month to 18 years admitted with vasoactive drug-dependent septic shock to the 12-bed multidisciplinary pediatric intensive care unit (PICU) of Siriraj Hospital during the January 2013 to December 2015 study period. Patients that had pulmonary hypertension, pulmonary embolism, primary cardiogenic shock, left ventricular dysfunction [left ventricular ejection fraction (LVEF) <50%], or left ventricular outflow tract obstruction were excluded.

Definitions

Pediatric septic shock and organ dysfunction were defined according to criteria established by the International Pediatric Sepsis Consensus Conference (Goldstein *et al,* 2005). Absolute adrenal insufficiency (AI) was defined as a random total cortisol result of <18 µg/dl (Dellinger *et al,* 2008). Children at risk for absolute AI include those with septic shock and purpura, those having previous steroid therapies for chronic illness, and those with pituitary or adrenal abnormalities (Dellinger *et al,* 2013).

Data collection

The following data were recorded and included in the final analysis: (1) general characteristics, including underlying disease and site of infection; (2) severity of illness assessed by Pediatric Index of Mortality II (PIM II) score (Slater *et al,* 2003) and organ dysfunction; (3) interventions, including volume of fluid resuscitation, respiratory support, and time to administration of antibiotics; (4) primary outcome variables, including heart rate (HR), blood pressure (BP), and inotrope dose (quantified by inotrope score) (Hoffman *et al,* 2003) and duration; (5) secondary outcome variables, including duration of mechanical ventilation, PICU length of stay, hospital length of stay, and mortality; and, (6) dose and duration of hydrocortisone therapy. Inotrope score was calculated as follows:

Total inotrope score = dopamine (mcg/kg/min) x 1 + dobutamine (mcg/kg/min) x 1 + adrenaline (mcg/kg/min) x 100 + noradrenaline (mcg/kg/min) x 100

Statistical analysis

Categorical data are expressed as number and percentage. Normally distributed continuous data are shown as mean ± standard deviation, non-normally distributed continuous data are shown as median and 25% to 75% interquartile range. Categorical variables were analyzed using chi-square test. *T*-test and Mann-Whitney *U* test were used to analyze continuous normally distributed and continuous non-normally distributed variables, respectively. Kaplan-Meier analysis was used to compare time to cessation of vasoactive support between groups. A p-value<0.05 was regarded as being statistically significant. Data analysis was performed using SPSS Statistics version 19 (IBM, Armonk, NY).

RESULTS

A total of 95 patients met the inclusion criteria, of whom 32 (33.7%) patients received stress dose corticosteroids as adjunctive therapy for septic shock. Patient demographic and clinical characteristics are presented in Table 1. Hydrocortisone was the type of corticosteroids used as an adjunctive treatment for septic shock in our PICU. Median duration and median accumulative dose of corticosteroid therapy was 5 days [IQR: 3-8] and 247.5 mg/m^2 [IQR: 300-570], respectively. Patients who received corticosteroids had a higher vasoactive support requirement compared to those who did not, as indicated by inotrope score at 4 hours (20 *vs* 10; *p*=0.007), 8 hours (20 *vs* 10; *p*=0.007), and 12 hours (19 *vs* 9; *p*=0.004) after initiation of vasoactive drug (Fig 1). Duration of vasoactive support was longer among patients in the corticosteroid group, but the difference between groups did not achieve statistical significance (Fig 2). Median time to cessation of vasoactive support was 48.7 hours (95% CI: 23.6-73.7) in the corticosteroid group,

Table 1
Demographic and clinical characteristics of children with vasoactive drug-dependent septic shock.

Characteristics	No corticosteroid therapy (*n*=63)	Corticosteroid therapy (*n*=32)	*p*-value
Age (y), median [IQR]	2.6 [0.7-12.4]	9.3 [5.5-13.4]	0.090
Male gender, *n* (%)	41 (65.1)	17 (53.1)	0.259
Underlying disease, *n* (%)			
Heme-onc disease	8 (12.7)	17 (53.1)	**<0.001**
Solid organ tumor	5 (7.9)	2 (6.3)	0.766
Connective tissue disease	0 (0)	2 (6.3)	**0.045**
Congenital heart disease	4 (6.3)	0 (0)	0.145
Neurologic disease	11 (17.5)	6 (18.8)	0.877
Hematologic disease	3 (4.8)	3 (9.4)	0.382
GI and liver disease	4 (6.3)	0 (0)	0.145
Other	4 (6.3)	1 (3.1)	0.506
Site of infection, *n* (%)			
Respiratory tract	23 (36.5)	7 (21.9)	0.147
Urinary tract	7 (11.1)	2 (6.3)	0.444
Gastrointestinal tract	11 (17.5)	13 (40.6)	**0.014**
Skin and soft tissue	6 (9.5)	2 (6.3)	0.587
Central nervous system	4 (6.3)	1 (3.1)	0.506
CRBSI	2 (3.2)	2 (6.3)	0.481
DSS	4 (6.3)	1 (3.1)	0.506
Other	2 (3.2)	1 (3.1)	0.349
Unknown	12 (19.0)	6 (18.8)	0.972
Number of infection sites, *n* (%)			
1 site	57 (90.5)	29 (90.6)	0.981
>1 site	6 (9.5)	3 (9.4)	0.646
Positive culture, *n* (%)	31 (49.2)	25 (78.1)	**0.007**

Characteristics	No corticosteroid therapy (*n*=63)	Corticosteroid therapy (*n*=32)	*p*-value
Type of organism, *n* (%)			
Gram-positive bacteria	12 (19.0)	5 (15.6)	0.681
Gram-negative bacteria	23 (36.5)	20 (62.5)	**0.016**
Fungus	2 (3.2)	1 (3.1)	0.990
Virus	6 (9.5)	1 (3.1)	0.259
Mixed	12 (19.0)	7 (3.1)	0.745
Time to appropriate antibiotics from shock onset (h), median [IQR]	0.8 [0.3-1.5]	0.3 [0-0.9]	**0.010**
Non-invasive respiratory support, *n* (%)	41 (65.0)	19 (59.4)	0.204
Nasal cannula	27 (42.2)	9 (29.0)	
Non-rebreathing mask	11 (17.5)	10 (31.1)	
HFNC	2 (3.2)	0 (0)	
BiPAP	1 (1.6)	0 (0)	
Mechanical ventilation, *n* (%)	22 (34.9)	13 (40.6)	0.811
Duration of mechanical ventilation (d), median [IQR]	5.5 [4-12]	4.0 [3-22]	0.539
Fluid resuscitation (ml/kg), median [IQR]	50 [40-60]	50 [30-68]	0.904
PIM II score (%), median [IQR]	1.1 [0.9-3.9]	4 [0.9-8.7]	0.420
Number of dysfunctional organs on day 0-1, median [IQR]	2 [1-2]	2 [2-3]	**0.009**
Organ dysfunction, *n* (%)			
Respiratory	37 (58.7)	22 (68.8)	0.341
Neurologic	4 (6.3)	1 (3.1)	0.506
Hematologic	13 (20.6)	17 (53.1)	**0.001**
Renal	7 (11.1)	5 (15.6)	0.531
Hepatic	4 (6.3)	2 (6.3)	0.985
Time to vasoactive support from shock onset (h), median [IQR]	1.42 [0.92-2.25]	1.00 [0.44-2.07]	0.059

BiPAP, bilevel positive airway pressure; CRBSI, catheter-related blood stream infection; DSS, dengue shock syndrome; Heme-onc disease, hematologic-oncologic disease; HFNC, high-flow nasal cannula; IQR, interquartile range; GI, gastrointestinal; PIM II score, Pediatric Index of Mortality II score.

as compared to 37.0 hours (95% CI: 21.0-52.9) in the no corticosteroid group (p=0.051). No differences in hemodynamic variables [HR, systolic BP, and mean arterial pressure (MAP)] stratified by age were observed between groups. Resource utilization, including mechanical ventilation and ICU length of stay, was not different between groups. However, hospital length of stay was longer in the corticosteroid group. There were no differences in ICU mortality or 28-day mortality between the two study groups.

DISCUSSION

The current Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis recommends timely adjunctive corticosteroids in children with fluid-refractory, catecholamine-resistant shock, and suspected or proven absolute adrenal insufficiency (grade 1A) (Dellinger *et al,* 2013). However, questions remain regarding the strict definition of adrenal insufficiency and the risk/benefit of this phar-

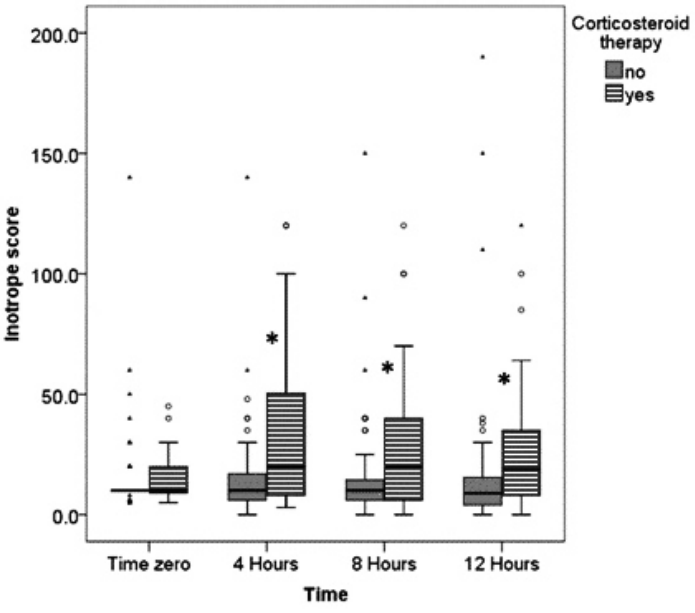

Fig 1– Box plot of inotrope score in children with vasoactive drug dependent septic shock over time. Inotrope scores of corticosteriod group were significantly higher than those of the no corticosteriod group after initiation of vasoactive support at 4 hours (p = 0.007), 8 hours (p = 0.007) and 12 hours (p = 0.004), respectively.

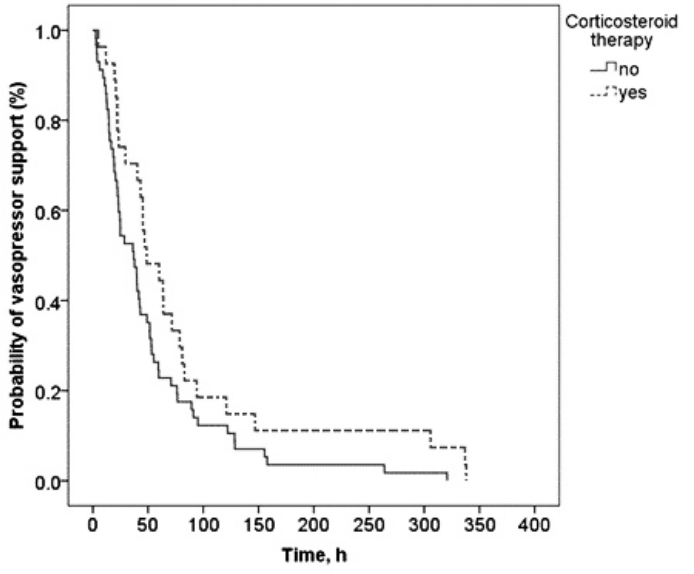

Fig 2– Kaplan-Meier curves for the time cessation of vasoactive support. The median time to cessation of vasoactive support tended to be longer in the corticosteriod group than in the no corticosteroid group; 48.7 hours (95%CI:23.6-737) *versus* 37.0 hours (95%CI: 21.0-52.9) (p = 0.051).

macological intervention. In this study, we set forth to investigate the effect of this adjunctive therapy in children with septic shock who required vasoactive support in our PICU.

A significant increase in dose and a trend toward increased duration of vasoactive support were found in corticosteroid group patients compared to no corticosteroid group patients with the same illness severity according to admission PIM II score. We also found similar outcomes between groups regarding mortality and PICU resource utilization, as documented by days of mechanical ventilation and PICU length of stay. Hospital length of stay was longer among subjects who received corticosteroids, but the relevance of this isolated observation is not clear. The findings from this study suggest that there is no proof of corticosteroid benefit in pediatric patients with this condition. These results are consistent with those from 2 large retrospective studies (Markovitz *et al,* 2005; Zimmerman and Williams, 2011) and the results of a meta-analysis in a systematic review (Menon *et al,* 2013). Results that conflict with our findings have also been reported. A trend toward earlier reversal of shock and lower inotrope requirement with similar mortality were reported by Valoor *et al* (2009). That study is the only RCT in adjuvant corticosteroid to be conducted in pediatric septic shock patients within the last 10 years. Similarly, a decrease in time to resolution of shock was demonstrated in 2 large adult RCTs (Annane *et al*, 2002; Charles *et al*, 2008), but no mortality benefit was found in accumulated data analyzed by systematic review and meta-analysis (Wang *et al,* 2014; Volbeda *et al,* 2015).

We cannot provide a clear explanation for the findings in our study. It is possible that subjects in the corticosteroid group were more severely ill than our no corticosteroid patients, and that PIM II score might not be sensitive enough to stratify illness severity. Since PIM II score was designed to assess general illness severity, its accuracy in subgroups of septic shock patients can be called into question. Development of disease-specific scoring systems should be further investigated. It should be noted that the number of dysfunctional organs on day 0-1 was higher in the corticosteroid group. Additionally, the definition of AI in terms of biochemical parameters is still inconclusive. The subjects with a biochemical diagnosis of AI in our study, which was defined as a random total cortisol result of <18 μg/dl (Dellinger *et al,* 2008), may have been overdiagnosed with AI and then received corticosteroids as a result. This possible overprescribing of hydrocortisone may have led to unexpected consequences. Potential adverse events from corticosteroids are usually underrecognized among critically ill children, but can be associated with increased risk of morbidity and mortality (Zimmerman, 2015).

This study has several mentionable limitations. First, this was a retrospective study with single-center experience and study population. Second, no standard protocol has been established that addresses dose and duration of corticosteroid therapy in pediatric septic shock. As such, decision-making regarding this adjuvant treatment is based on the experience and discretion of the attending physician. This acknowledged potential variation in treatment makes outcome assessment difficult. Finally, the adverse effects of corticosteroids have been insufficiently studied; thus, we have inadequate data to suspect or confirm corticosteroid-associated morbidity.

In conclusion, the findings of this study strongly suggest that there is insufficient data to support the benefit of adjunctive corticosteroids in children with catecholamine-dependent septic shock. Moreover, potential adverse effects can develop from this concurrent therapy. Further well-designed, adequately powered studies to clarify the definition of adrenal insufficiency and to examine the safety and efficacy of corticosteroids in pediatric septic shock are warranted.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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