Original Article

Critical illness-related corticosteroid insufficiency in children: A single center, prospective, cohort study

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ABSTRACT

Background: Although guidelines for diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in adults are developed, there is a paucity of data on CIRCI in children. **Objective:** To study the incidence, risk factors, mechanism, and associations of CIRCI in children using adrenocorticotropic hormone (ACTH) stimulation test. **Materials and Methods:** Single-center prospective cohort study was conducted in eight bedded pediatric intensive care unit of teaching hospital over a period of 1 year. Serum total cortisol concentration was measured in 110 critically ill children before and after stimulation with 250 μg ACTH. CIRCI was defined by post-ACTH increment in serum cortisol ≤9 μg/dl. Children with and without CIRCI were compared. **Results:** Incidence of CIRCI was 38.2%. Children with CIRCI had higher median age (34 vs. 18 months), higher pediatric risk of mortality score (17.79±2.60 vs. 16.37±3.68), and significantly higher basal cortisol levels (27.37±11.64 vs. 22.02±7.26) (p=0.004) than those without CIRCI. There was a significantly higher (p=0.000) requirement of catecholamines (2.71±0.457 vs. 2.00±0.792) and higher additional fluid boluses (15.79±4.7 vs. 10.65±4.60) in children with CIRCI. However, duration of catecholamine use was not significantly different between two groups. The presence of CIRCI was not found to be an independent risk factor for mortality. For each additional use of catecholamine, the risk of CIRCI increased to 5.6 times; and for each extra fluid bolus, the risk increased to 1.2 times. **Conclusion:** CIRCI occurs in a wide spectrum of diseases in critically ill children associated with increased need for catecholamine and fluids. CIRCI is likely to be multifactorial in etiology and associated with high basal cortisol levels.

Key words: *Adrenal function, Adrenocorticotropic hormone, Cortisol, Critically ill children*

Survival in critical illness depends on the adequate adrenocortical function. The levels of plasma cortisol are elevated in the majority of critically ill patients. Increased release of cortisol from the adrenal cortex during severe illness and stress reflects the enhanced activity of the hypothalamic-pituitary-adrenal axis (HPA) [1,2]. However, in many patients who are critically ill, there may be impaired homeostasis and adaptation [3]. These patients have an inadequate production of cortisol leading to relative or functional adrenal insufficiency (AI) in relation to increased demand during periods of severe stress. AI is a clinical condition associated with hypotension that can be resistant to fluid and catecholamine therapy and, if untreated, can result in increased mortality [4-6]. The larger fluid volumes needed to be given as well as the greater need for catecholamines in patients with unrecognized AI may result in a longer requirement for mechanical ventilation [7,8] and a prolonged need for invasive monitoring and vascular access in adult patients [8].

Multiple different definitions were used for the diagnosis of AI in many pediatric studies, focused almost exclusively on patients with septic shock [9-19], did not conduct corticotropin stimulation tests on all patients (only obtained random cortisol levels) [20-22], and used different doses for the corticotropin tests [11,14,15,19,22]. As a result, the reported prevalence of AI varies from 10% to 100% [21,22]. Very few studies identified risk factors for the development of AI and were adequately powered to assess associations with outcomes or studied both the high- and low-dose corticotropin tests [9,23]. Furthermore, the majority of studies did not measure adrenocorticotropic hormone (ACTH) levels [11,12,15,16].

The term "critical illness-related corticosteroid insufficiency (CIRCI)" was introduced recently [24]. Recommendations for the diagnosis and management of this condition in adults were published by an international task force of the American College of Critical Care Medicine and have asked to avoid the term "relative AI" [25]. However, there

is less agreement regarding diagnostic criteria and prevalence of this condition among intensivists and endocrinologists in the pediatric population [26].

The objectives of this study were to determine prospectively the incidence of CIRCI, risk factors, mechanisms for its development and association with clinically important outcomes using ACTH stimulation test in critically ill children

MATERIALS AND METHODS

This study was conducted as a prospective single-center cohort study in the pediatric intensive care unit (PICU) of a tertiary care teaching hospital, over a period of 1 year from August 2012 to July 2013. Patients were eligible if they were 1 month to 17 years of age and had arterial or central venous catheter and enrolled within 24 h of admission. Neonates and patients with known or suspected adrenal, pituitary or hypothalamic disease, patients who had received systemic steroid for more than 10 days in previous month or had more than one dose of systemic steroid within 24 h before admission and those who were expected to have care withdrawn or were transferred from another ICU were excluded from the study. Suspected or diagnosed cases of asthma or allergic diseases were also excluded. None of the patients received etomidate. Approval from research ethics committee of the hospital was obtained. Written informed consent was obtained from all parents of study participants just after admission in PICU.

Random serum total cortisol, ACTH, glucose, and electrolytes were measured for all the patients after enrollment. Patients were given 250 μg of cosyntropin (Cortrosyn, Mylan Institutional LLC-Gland Pharma, India) intravenously with a repeat cortisol level measured at 30 min. This ACTH stimulation test was performed within 1 h after admission. After centrifugation, samples were preserved within ice packs in PICU and were transported to the central lab with ice packs. In lab, they were stored at −20°C in the deep freezer before processing. Plasma cortisol levels were measured using chemiluminescence immunoassay (Unicel Dxl 600) (measurement range: 0.4-60 μg/dl, coefficient of variation: Kit insert CV% 7.9%), and serum ACTH were measured using chemiluminescence immunoassay (Immulite 2000 xpi) (measurement range: 5-1250 pg/ml, coefficient of variation: Kit insert CV% 10%).

CIRCI was defined as an increment in serum total cortisol (delta cortisol) ≤9 μg/dl after ACTH stimulation test as recommended by consensus statements from international task force by American College of Critical Care Medicine 2008 [25]. We documented baseline characteristics including diagnosis, age, and the pediatric risk of mortality score (PRISM-III) [27] in all patients. PRISM-III score was calculated using an online calculator. Institutional protocols were used for treating all patients admitted to PICU independent of study participation. The treating PICU team was kept unaware of the results of cortisol and ACTH so as not to influence the patient's treatment.

Fluid boluses were calculated from the arrival time in PICU. The amount of fluid used for the resuscitation in the emergency room (20-40 ml/kg) before shifting to PICU was not included, and requirement of only additional fluid boluses received in PICU was correlated. Furthermore, fluids given after ACTH test were not included as it was not part of the study. These fluid boluses were apart from the maintenance fluids, replacement fluids, or medications. As a protocol of this study, we have calculated only number of catecholamines used (dopamine, dobutamine, noradrenaline, and adrenaline) and not their mean doses. Catecholamines were chosen and added in a graded fashion depending on the type and severity of shock. If one drug at maximum dose was not able to correct hypotension, second or third drug was added. Higher number of catecholamines suggests more severe hypotension.

The primary objective of this study was to determine the incidence of CIRCI on the day of admission. Secondary objectives were to identify possible risk factors for CIRCI, including age, diagnosis, and severity of illness, to determine the association of CIRCI with the need of catecholamines, fluid boluses, and PICU mortality.

Statistical analysis was made with IBM SPSS 19.0 version. Data were expressed as median (range) or mean (±standard deviation) according to data distribution. Patients were grouped according to presence or absence of CIRCI. Mann–Whitney U-test or Student's t-test for continuous variables while Fisher's exact test for categorical variables was used to compare two groups. Cortisol concentrations at baseline and after ACTH stimulation test were compared by paired t-test. Associations between variables were assessed by Spearman's correlation test. After determination of association of individual factors with CIRCI by univariate analysis, a binary logistic regression model of significant factors was developed. The results of regression model were presented as adjusted odds ratio. Wald's Chi-square value was used to test unique contribution of each predictor. $p<0.05$ was considered significant.

RESULTS

During the study period of 1 year, total 268 children were admitted to the PICU. Eligibility criteria were met by 158 (58.9%) patients. Of those 110 excluded patients, 39 (35.5%) patients had received more than one dose of steroid within the previous 24 h (reasons for steroid use were not recorded), 31 (28.2%) had received more than 10 days of systemic steroid in the previous month, 24 (21.8%) expired within 24 h, and 16 (14.5%) were either referred to other center or discharged against medical advice. Of the eligible patients, in 21 (13.3%) consent could not be obtained in time and 23 (14.55%) had parents or guardian who declined consent. Finally, remaining 110 (42.6%) patients were enrolled in the study.

For the given effect size population, mean of basal cortisol (27.37±11.64 vs. 22.02±7.26), sample size (42 and 68), and alpha (0.05, two-tailed) statistical power was 0.84. Overall patient cohort had median age of 30 months (interquartile range [IQR], 1.5-156.0), median weight 11 kg (IQR, 2-32), 69.1% were male and on admission, median PRISM score of 17 (IQR, 11-23). On the day of admission, 42 (38.2%) had CIRCI using ACTH stimulation test. Baseline characteristics between patients with or without CIRCI are shown in Table 1. Patients with CIRCI had significantly higher median age (34 vs. 18 months) and higher PRISM score (17.79±2.60 vs. 16.37±3.68) (Table 1). The prevalence of CIRCI was highest (30.9%) in patients with septic shock followed by 21.4% in patients with acute lung injury or acute respiratory distress syndrome (ALI/ARDS) (Table 2).

The baseline cortisol and corresponding ACTH levels in patients with CIRCI are shown in (Table 3). 3 (7.1%) of CIRCI patients had baseline cortisol levels >36 μg/dl and high ACTH levels. Almost 16.7% (7/42) of patients had very low baseline cortisol levels (<18 μg/dl) and normal or high ACTH levels suggestive of primary adrenal dysfunction, while majority 61.9% (26/42) of the patients had normal to high cortisol with low or normal ACTH levels suggestive of secondary adrenal dysfunction.

The distribution of serum cortisol levels, pre- and post-ACTH stimulation, is provided in Table 4. Basal cortisol levels (27.37±11.64 vs. 22.02±7.26) were significantly (p=0.004) higher while post-ACTH stimulation cortisol levels (32.55±12.26 vs. 52.94±77.23) and cortisol increment (Δ) levels (5.19±2.85 vs. 31.76±79.59) were significantly lower in patients with CIRCI. There was no significant difference in basal ACTH levels between the two groups (Table 4). The requirement of ventilation (46.6% vs. 53.4%) and duration of ventilation (56.27±19.53 vs. 59.95±23.51) in two groups were not significantly different (Table 5). There was significantly higher (p=0.000) requirement of catecholamines (as shown by number of catecholamines used) (2.71±0.457 vs. 2.00±0.792) and extra fluid boluses in PICU (15.79±4.7 vs. 10.65±4.60) in patients with CIRCI but the duration of catecholamine use was not significantly different between two groups (Table 5).

Although mortality (52.3% vs. 7.8%) in CIRCI group was significantly higher (p=0.000), the duration of PICU stay did not differ from that of the other group. In the regression analysis, age, disease severity measured by PRISM score, and duration of catecholamine use were not found to be independent risk factors for CIRCI; however, use of higher number of additional fluid boluses (p=0.002) and higher number of

Table 1: Comparative demography and clinical characteristics in study population

Parameter	CIRCI (n=42)	No CIRCI (n=68)	p value
Age in months, median (IQR)	34 (1.5-156)	18 (2-144)	0.0258
Weight in kg, median (IQR)	12 (2-32)	11 (2.5-27)	0.267
Male/female	27/5	49/19	0.404
PRISM score, mean±SD	17.79±2.60	16.37±3.68	0.020
Serum albumin, median (IQR)	3.2 (1.9-3.9)	3.1 (2.1-3.9)	0.82

PRISM: Pediatric risk of mortality, IQR: Interquartile range, SD: Standard deviation, CIRCI: Critical illness-related corticosteroid insufficiency

Table 2: Distribution of study population according to primary systemic diagnosis

Systemic diagnosis	CIRCI (n=42)	No CIRCI (n=68)	p value
Status epilepticus	4 (1)*	10	0.567
Head injury	3 (1)*	13	0.101
Congestive cardiac failure	4 (1)*	4 (1)*	0.478
Severe gastroenteritis	3 (1)*	7	0.739
Acute liver failure	3 (2)*	1 (1)*	0.155
ALI/ARDS	9 (5)*	8	0.186
Poisoning/bites	3 (1)*	5	1.000
Septic shock	13 (10)*	10 (4)*	0.054

***Indicates number of deaths, ALI: Acute lung injury, ARDS: Acute respiratory distress syndrome, CIRCI: Critical illness-related corticosteroid insufficiency**

Table 3: Basal cortisol and ACTH levels in patients with adrenal insufficiency

ACTH (pg/dl)	Cortisol (μg/dl)		
	<18	18.1-36	>36.1
Low (<5.9)	1	1	0
Normal (6-56.7)	6	13	12
High (>56.8)	1	5	3

ACTH: Adrenocorticotropic hormone

Table 4: Cortisol and ACTH levels in study population

Parameter	CIRCI (n=42)	No CIRCI (n=68)	p value
Basal cortisol level (mg/dl)	27.37±11.64	22.02±7.26	0.004
Post-ACTH cortisol level (mg/dl)	32.55±12.26	52.94±77.23	0.036
Cortisol (Δ) level (mg/dl)	5.19±2.85	31.76±79.59	0.008
ACTH levels (pg/dl)	29.18±15.52	28.37±8.23	0.725

ACTH: Adrenocorticotropic hormone, CIRCI: Critical illness-related corticosteroid insufficiency

catecholamines (p=0.003) had independently increased the risk of CIRCI. For each additional use of catecholamine, the risk of CIRCI increased to 5.6 times; and for each extra fluid bolus, the risk increased to 1.2 times (Table 6). The presence of CIRCI was not found to be an independent risk factor for mortality.

DISCUSSION

In this single center prospective study, the incidence of CIRCI by definition of cortisol increment <9 μg/dl after ACTH stimulation was 38.18%. This incidence was consistent with prior studies [9,11,13,18,21,22] by similar definition of AI. Age, sex, weight, and disease severity were not found to be independent risk factors for the development of CIRCI. There was no significant difference in the incidence of CIRCI related to any specific disease condition. Despite of long standing focus in the literature on adrenal function in sepsis [12,15-18], we could not find the increased risk of CIRCI in the presence of sepsis. Menon et al. and Balbão et al. also had similar observations [9,28].

Table 5: Comparative outcome in study population

Parameter	CIRCI (n=42)	No CIRCI (n=68)	p value
Hours on catecholamines	81.93±42.08	71.71±24.01	0.107
Additional fluid boluses ml/kg	15.79±4.7	10.65±4.60	0.000
Number of catecholamines	2.71±0.457	2.00±0.792	0.000
Ventilation required n (%)	27 (46.6)	31 (53.4)	0.077
Duration of ventilation in hours	56.27±19.53	59.95±23.51	0.109
Length of PICU stay in days	68.90±18.63	67.17±25.43	0.652
Mortality n (%)	22 (52.3)	6 (7.8)	0.000

ACTH: Adrenocorticotropic hormone, CIRCI: Critical illness-related corticosteroid insufficiency, PICU: Pediatric intensive care unit

Table 6: Multivariate analysis of factors associated with CIRCI by logistic regression

Variable	Wald	df	p value	Odds ratio
Age	0.08	1	0.928	0.999
PRISM score	1.295	1	0.255	0.864
Duration of catecholamine use	0.102	1	0.749	1.002
Additional fluid boluses	9.687	1	0.002	1.216
Number of catecholamines	9.131	1	0.003	5.565

PRISM: Pediatric risk of mortality, df: Degree of freedom, CIRCI: Critical illness-related corticosteroid insufficiency

The CIRCI was associated with more use of catecholamine (odds ratio 5.565, p=0.003) and higher additional fluid boluses (odds ratio 1.216, p=0.002) independently. Similar findings were observed by Menon et al. [9]; however, Balbão et al. [28] could not find such association. High mortality in our study population can be contributed by higher PRSIM score. Although mortality in children with CIRCI was significantly higher, CIRCI was not found to be an independent risk factor for mortality. This finding was consistent with prior studies [9,13,23,28].

Many factors lead to dysfunction of the HPA axis during illness. These include a decreased production of the corticotropin-releasing hormone, ACTH and cortisol and dysfunction of their receptors. Some patients may have structural damage and peripheral resistance to glucocorticoids can also aggravate an inadequate response of the HPA axis to stress [21,23]. The decreased activity of glucocorticoids is probably caused by different interacting mechanisms. Of them, one is a reduction of glucocorticoid receptors [29] and the other, an increase in the conversion of cortisol to inactive cortisone by enhanced activity of 11-β-hydroxysteroid dehydrogenase stimulated by interleukin(IL)2, IL4, and IL13 [30].

Our study suggests that the mechanism for adrenal dysfunction in critically ill children may be highly variable and multifactorial. Many threshold levels for random cortisol in acute illness were proposed, but none was satisfactory. We have chosen the cutoff values, which were used in past studies by Menon et al. and Cooper and Stewart [26,31]. In the majority of patients with CIRCI, baseline cortisol levels were >18 μg/dl but did not increase with exogenous ACTH stimulation. This finding was consistent with prior studies. This may be because of the inability of adrenal gland to mount an adequate response despite a normal baseline cortisol levels during critical illness, or the definition of CIRCI may be simply a marker of the need for catecholamine and fluid or a reflection of end organ resistance [31,32] in critically ill children.

Almost 30% (14/42) of our CIRCI patients had baseline cortisol levels between 18 μg/dl and 36 μg/dl and inappropriately normal or low ACTH levels suggestive of HPA axis dysfunction. Although patients with baseline cortisol levels >36 mg/dl may still have dysfunction of HPA axis, they may not respond to exogenous glucocorticosteroids as plasma cortisol levels achieved by 1-2 mg/kg of exogenous hydrocortisone may not be significantly higher than those already present in these patients [33]. There are no large randomized controlled trials on the use of steroid in critically ill children, yet many intensivists report using steroid to treat catecholamine and fluid-resistant shock [25], and steroids have been recommended in the guidelines for the treatment of catecholamine-resistant shock in children [34]. We have studied cortisol levels only on day 1 and follow-up levels during further hospital stay were not studied, so it is beyond the scope of this study to comment whether

these children with CIRCI would have been helped for their better outcome.

This study has many strength. To the best of our knowledge, this is the only Indian critical care trial to examine the incidence of AI in a wide spectrum of diseases. Furthermore, it is the only Indian study to explore the potential mechanisms of CIRCI in the critically ill population using ACTH stimulation testing as well as measurement of ACTH levels. The majority of our patients had secondary AI or HPA axis suppression and very few had primary AI. A potential limitation of our study is that we have not measured free cortisol levels. Serum albumin levels were comparable between children with or without CIRCI. The increment in cortisol level is independent of serum protein levels, and free cortisol measurements are available only in research laboratories, thereby limiting their usefulness. This study included only patients with existing vascular access and likely represents sicker children within the PICU. However, the clinical significance of this fact is unclear as disease severity was not found to be associated with CIRCI [9,12,21].

CONCLUSION

CIRCI occurs in a wide spectrum of diseases in critically ill children associated with increased need for catecholamine and fluids. CIRCI is likely to be multifactorial in etiology and associated with high basal cortisol. Further research is necessary to determine which of these critically ill children are truly cortisol deficient and who will be benefited by exogenous steroids.

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