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Research Article

ANALYSIS OF CORTISOL LEVEL AFTER HIGH-DOSE AND LONG-TERM PREDNISONE EXPOSURE IN CHILDREN WITH STEROID-SENSITIVE NEPHROTIC SYNDROME

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ABSTRACT

Objective: The objective of this study is to analyze the cortisol levels in induction and alternate phases associated with the clinical manifestation in the developing of adrenal suppression.

Methods: An observational, longitudinal study which had been approved by the ethical committee of Dr. Soetomo Teaching Hospital Surabaya was conducted from June to October 2016. The cortisol levels were measured before induction phase (t=0), after induction phase (t=1), and after alternate phase (t=2). The venous blood samples were obtained in the morning at 08.00–09.00 am. The data were analyzed using student's t-test.

Results: A total of 15 patients were included, but 6 patients were excluded because of cross-reactivity with prednisone when using ADVIA Centaur Cortisol Assay. 9 patients (55.56% boys) had a mean age 6–< 12 years old and 33.33% were initial attack and dependent steroid nephrotic syndrome. 8 of 9 patients had a normal cortisol level at baseline (t=0). The cortisol level decrement in the induction phase was 72.92% (11.79±10.66 mcg/dL–1.75±1.08 mcg/dL) (*p=0.024). After alternate phase, the cortisol levels increased 417.60% (1.75±1.08 mcg/dL to 5.95±3.33 mcg/dL (*p=0.007). The clinical manifestation as nausea/vomiting and abdominal distension only appeared in 11.11% of patients in the induction phase but not in the alternate phase.

Conclusions: Hypothalamus-pituitary-adrenal (HPA) axis suppression could develop after induction phase which was indicated by low cortisol levels. High-dose and long-term prednisone exposure decreased the cortisol levels reversibly. The clinical manifestation of adrenal suppression as weakness, nausea/vomiting, acute dehydration, and abdominal distension almost did not manifest in all patients.

Keywords: Cortisol, Nephrotic syndrome, Sensitive steroid nephrotic syndrome, Prednisone, High-dose prednisone, Long-term prednisone, Hypothalamus-pituitary-adrenal axis suppression, Children.

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INTRODUCTION

Nephrotic syndrome (NS) is a glomerular disease characterized by heavy protein urine (≥40 mg/m^2/h or more than 50 mg/kg/day or dipstick ≥2+), hypoalbuminemia (≤2.5 g/dL), and edema and may accompanied by hypercholesterolemia (>200 mg/dL) [1-5]. The incidence of this disease in America and Europe was occurred in 1–3/100,000 in children with the mean age of <16 years old. The cumulative incidence was 16/100,000 with the ratio between boy and girl 3.8:1 [5,6]. In Indonesia, the prevalence of this disease was 6 cases per 100,000 children each year with the ratio between boy and girl 2:1 [1,4].

The regimen therapy of NS was prednisone of 60 mg/m^2 or 2 mg/kg/day for 4 weeks or until remission (relapse) for 3–4 weeks followed by the alternate-day prednisone of 40 mg/m^2 or 1.5 mg/kg/day for 4–12 weeks. There was a difference among guidelines for the duration of prednisone therapy, some guidelines recommended longer prednisone therapy for 3–6 months including full dose, and alternating dose could decrease risk relapse than therapy for 2–3 months [4,5,7]. The main effect of high-dose and long-term prednisone was hypothalamus-pituitary-adrenal (HPA) axis suppression. It could suppress endogenous cortisol production through suppression adrenal cortex [8,9].

The mechanism of HPA axis suppression was occurred by short- and long-loop feedback in corticotropin-releasing hormo*ne* (CRH) neuron. The suppression of CRH neuron decreased the production of CRH mRNA, CRH, and ACTH. The net result of HPA axis suppression was decreasing cortisol production level in the adrenal cortex, especially in fasciculate zone [10,11]. The adrenal cortex suppression caused acute and chronic adrenal insufficiency which indicated by acute dehydration, hypotension, hypoglycemia, altered mental status, fatigue/weakness, anorexia, nausea, vomiting, loss of appetite, weight loss, and abdominal pain [12-14]. The children with NS who exposure to prednisone could develop adrenal suppression. The recovery period of it was not completely determined, but it could last up to 1 year [15].

Study-related HPA axis suppression was conducted since 1965 by measuring cortisol level after giving synacthen test. The result showed HPA axis suppression which indicated by decrease cortisol level [16-18]. The current study conducted in children with NS showed that there were possibilities in developing HPA axis suppression which was indicated by decrease cortisol level and increasing risk relapse [19]. Another study with different regimens conducted in adult showed the same result as in children [20]. However, how far the effect of prednisone therapy in children with sensitive NS in Dr. Soetomo Teaching Hospital Surabaya has not been determined. Therefore, to monitor cortisol level during high dose and long term prednisone therapy in nephrotic syndrome is necessary.

METHODS

We conducted a prospective, observational, and longitudinal study from June to October 2016 at the Pediatric Nephrology Department of Dr. Soetomo Teaching Hospital Surabaya. We recruited 16 children who diagnosed as steroid-sensitive NS, aged <18 years old, and followed this study until finish. We excluded patients who diagnosed as steroid-resistant NS and took prednisone <24 h. We dropped outpatient who changed diagnose during study, did not followed the study completely,

Table 1: Baseline characteristics of nephrotic syndrome patients

Patient characteristics	Total patients n=9 (%)	Mean±SD
Gender		
Boys	5 (55.56)	-
Girls	4 (44.44)	-
Age (Years)		
<2	0 (0)	-
2–<6	4 44.44)	3.50±1.29
6–<12 tahun	5 (55.56)	7.80±1.92
12–18 tahun	0 (20)	-
Body weight		
0–20.9 kg	7 (77.78)	16.47±3.38
21–40.9 kg	1 (11.11)	21.00
41–60 kg	1 (11.11)	50.00
Blood pressure		
Normal (90–135/55–85 mmHg)	9 (100)	98.33/6667±10.61/12.25
Hypertension (>135/>85 mmHg)	0 (0)	-
Blood glucose		
<2 years (60–100 mg/dL)	0 (0)	0
>2 years–adult (<200 mg/dL)	9 (100)	98.44±19.37
Diagnose		
Initial attack (NS)	3 (33.33)	-
Infrequent relapses (NS)	2 (2.22)	-
Frequent relapses (NS)	1 (11.11)	-
Dependent steroid (NS)	3 (33.33)	-
Cortisol level t=0		
<3 mcg/dL	1 (11.11)	2.79
3–<10.164 mcg/dL	4 (44.44)	5.91±2.49
10.164–21 mcg/dL	3 (33.33)	14.25±3.43
>21 mcg/dL	1 (11.11)	36.89
Cumulative dose of prednisone 1 year prior t=0		
Not taking prednisone	3 (33.33	0±0
1–5.000 mg	3 (33.33)	3.835.0±967.97
5.001–10.000 mg	3 (33.33)	5.888.3±618.92
>10.000 mg	0 (0)	-
Duration of prednisone 1 year prior t=0		
Not taking prednisone	3 (33.33)	0±0
1–225 days	5 (55.56)	183.40±33.25
226–450 days	1 (11.11)	229
>450 days	0 (0)	0±0
Edema		
Without edema	1 (11.11)	-
Palpebrae	2 (22.22)	-
Extremity	1 (11.11)	-
Anasarca	5 (55.56)	-
Meal frequency (x/day)		
2	0 (-)	-
3	7 (77.78)	-
4	1 (11.11)	-
5	1 (11.11)	-
Acute dehydration		
Yes	0 (0)	-
No	9 (100)	-
Weakness/fatigue		
Yes	3 (33.33)	-
No	6 (66.67)	-
Nausea/vomiting		
Yes	2 (22.22)	-
No	7 (77.78)	-
Abdominal pain		
Yes	4 (44.44)	-
No	5 (55.56)	-

NS: Nephrotic syndrome

and died. Patients received full-dose prednisone of 2 mg/kg/day or 60 mg/m^2/day for ±4 weeks and followed by alternate-day prednisone of 1.5 mg/kg/day or 40 mg/m^2 for ±4 weeks. The cortisol level measured before induction phase, after induction phase, and after alternating phase at 08.00–09.00 a.m.

This study had been approved by the ethical committee of Dr. Soetomo Teaching Hospital Surabaya. We had explained everything about this study in detail before starting. All data were collected from patient medication report and direct interview with patients. ADVIA Centaur Cortisol Assay was used to determine cortisol level.

Normality test performed in interval scale data using One-sample Kolmogorov–Smirnov. Student's t-test was used to compare the cortisol level in the induction phase and alternating phase. Statistical analysis was performed using the computer program package

Table 2: Cortisol levels of nephrotic syndrome patients

Inisial pasien	Normal value (mcg/dL)	Cortisol levels (mcg/dL)				
		t=0	t=1	t=2	$\Delta_{t=1-t=0}$	$\Delta_{t=2-t=1}$
AM (G/3 y)	3–21	10.41	1.6	3.12	−8.81	1.52
DI (G/8y)	3–21	6.15	0.62	4.92	−5.53	4.3
KY (B/2y)	3–21	15.36	2.51	1.18	−12.85	−1.33
JA (G/7y)	3–21	9.35	2.67	4.22	−6.68	1.55
MA (B/7y)	3–21	16.99	0.99	8.56	−16	7.57
AP (B/11y)	3–21	4.23	3.9	10.88	−0.33	6.98
ND (B/4y)	3–21	3.92	0.62	9.83	−3.3	9.21
RA (B/6y)	3–21	36.89	1.32	3.5	−35.57	2.18
DA (G/5y)	3–21	2.79	1.56	7.34	−1.23	5.78
Mean±SD		11.79±10.66	1.75±1.08	5.95±3.33	−10.03±10.87	4.19±3.46

SD: Standard deviation

Table 3: Clinical and laboratory manifestation of adrenal suppression

Patients' code	AM	DI	KY	JA	MA	AP	ND	RA	DA	Mean±SD
Blood glucose	96	99	126	107	63	87	102	122	84	98.44±19.37
	111	107	102	99	122	110	92	123	89	106.1±11.92
	117	117	112	103	109	113	123	112	128	114.89±7.44
Blood pressure	90/60	90/60	95/50	100/70	110/80	120/90	90/60	90/60	100/70	98.33±10.61
										66.67±12.25
	90/60	90/60	100/60	90/60	100/70	120/70	90/60	90/60	80/50	94.44±11,30
										61.11±6.01
	90/60	100/70	90/50	90/60	100/70	110/80	100/60	90/60	90/60	95.56±7.26
										63.33±8.66
Body weight	12	20	12	18	20	50	16	17	21	20.70±11.47
	11	21	14	20	21	48	16	15	21	20.56±10.93
	11	24	14	20	21	49	16	15	22	21.22±11.24
Meal frequency	3	3	3	3	4	3	3	5	3	3.13±0.64
	6	6	5	5	7	4	6	6	5	5.4±0.74
	6	5	3	3	5	3	6	5	5	4.3±1.16

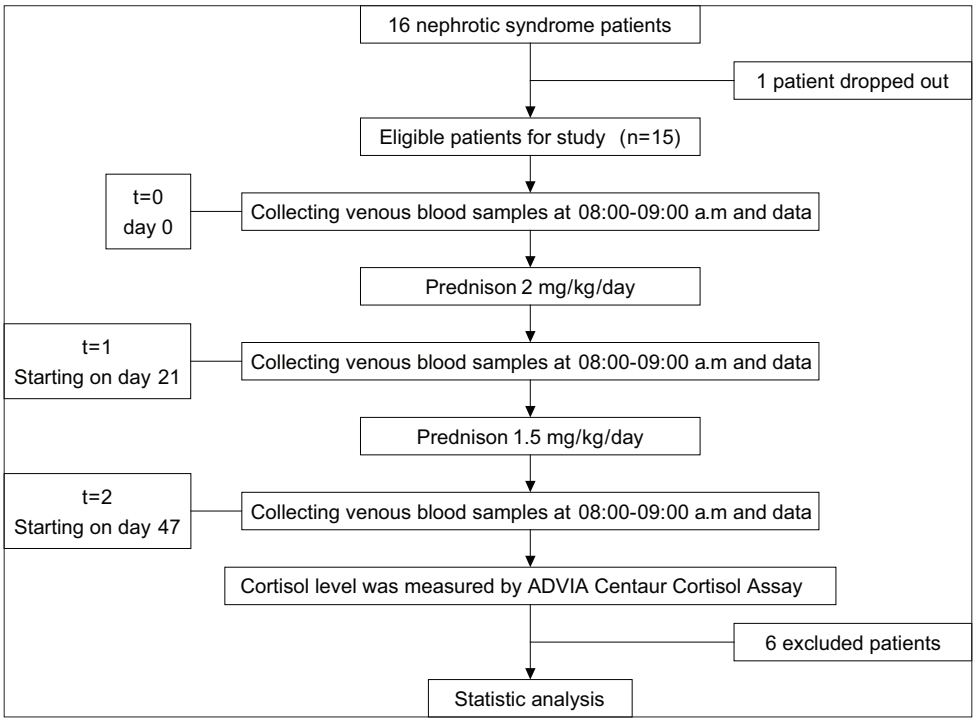

Fig. 1: Study flow chart

SPSS (version 20.0). Nominal data scale presented as a frequency distribution.

Overview of this cohort study was shown in Fig. 1.

RESULTS

The boy had higher percentage (55.56%) than girl with the mean age of 6–<12 years old (55.56%). The mean weight was 16.47±3.38 kg.

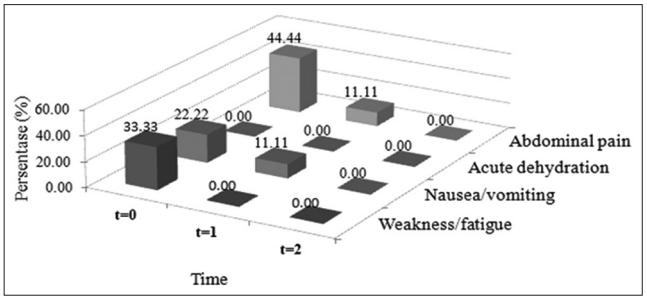

Fig. 2: Clinical manifestation of adrenal suppression

Based on diagnosis of patient, both initial attack and dependent steroid NS had the same percentage (33.33%). History of duration and cumulative dose were determined as HPA axis suppression could last up to 1 year and relapse of infrequent relapse NS was <4 relapses in 1 year [4,15]. Baseline characteristics of all patients are showed in Table 1.

The majority cortisol level at t=0 was normal (44.44%), except one patient had cortisol subnormal (<3 mcg/dL) and one patient had the cortisol level higher than normal range (>21 mcg/dL). The cortisol level decreased into subnormal at t=1 and increased at the end of the alternating phase (t=2). However, AP still had normal cortisol level at t=1. Table 2 shows the cortisol level of NS patients.

Statistical analysis of normality showed that all data were normally distributed. The duration and cumulative dose of prednisone a year before the study showed no correlation with the cortisol level at t=0. Student's t-test to compare the cortisol level at t=0 and t=1 and t=1 and t=2 showed that there was a significant difference with*p=0.024 and *p=0.007, respectively. Student's t-test also used to compare the delta cortisol level during each phase. The results showed significant difference between the delta cortisol level at the end of t=1 and at the end of t=2 (*p=0.003).

Clinical and laboratory finding associated with HPA axis suppression almost did not find in patients as shown in Table 3 and Fig. 2.

DISCUSSION

A total of 15 eligible patients were recruited in this study. The diagnosis of one patient was changed to be lupus nephritis. Cross-reactivity was occurred in 6 patients when measured by ADVIA Centaur Cortisol Assay. It was caused by similarity structure between cortisol and prednisone [21].

The mean cortisol level at t=0 in some patients was lower than others. It was occurred because of genetic variation in HPA axis and receptor variation. Another variation could find in some points of HPA axis system such as at CRH or ACTH synthesis [22]. The history duration and cumulative dose of prednisone were analyzed using Pearson correlation. It showed no significant correlation between the history duration and cumulative dose of prednisone and the cortisol level at t=0 (*p>0.05). It was occurred because some patients were in alternating phase. Therefore, their cortisol level reached to the normal range [10,22]. One patient had subnormal cortisol level at t=0 because she took 30 mg of prednisone before admission. Another patient had cortisol level higher than normal because he was stress (crying and anxious). Acute stress could induce the releasing of CRH and cortisol as the end product of HPA axis circuit [9,23].

The mean cortisol level at t=0 and t=2 was 11.79±10.66 mcg/dL and 1.75 mcg/dL or decreased 72.92%. Statistical analysis of the cortisol level at t=0 and t=1 showed significant difference with *p=0.024. The suppression was occurred through negative feedback in hypothalamic which suppressed expression of proopiomelanocortin gene at hypophyse and pro-CRH gene at hypothalamic, so releasing of ACTH was inhibited. The deficiency of ACTH caused atrophy of the adrenal gland [9,24]. The decrease cortisol level at t=1 indicated adrenal suppression which could develop if the morning cortisol level <3 mcg/dL [13,25,26]. However, the cortisol level at t=2 increased up to 417.60% from t=1 (5.95±3.33 mcg/dL). Statistical analysis showed significant difference with *p=0.007. The alternating-day regimen could increase cortisol level to normal range or the adrenal suppression at t=1 was reversible. Except in patient with inisial (KY), cortisol level lower than at t=1 received devided dose regimen which suppressed HPA axis higher than single dose [9,23]. Statistical analysis also was used to compare the delta cortisol level at the end of induction phase and the end of alternate phase with *p=0.003.

The clinical manifestation such as hypoglycemia, hypotension, weight loss, loss of appetite, and acute dehydration was not found in the patients in this study. Nausea/vomiting and abdominal pain were only found in 7% after the induction phase caused by prednisone side effect on the digestive tract [27,28].

The limitation of this study was that some patients had cross-reaction with prednisone when using ADVIA Centaur Cortisol Assay. We had to make sure the compliance of patient not to taking prednisone before collecting the sample. Another limitation was that the incidence of NS was rare, so it was difficult to find the subject in short period.

CONCLUSIONS

HPA axis suppression was occurred in the induction phase which indicated by the decrease of cortisol level 72.92%. The suppression was reversible which was indicated by the increase of the cortisol level at the end of the alternating phase 417.60%. The clinical manifestation only such as nausea/vomiting only found in 11.11%. However, we need do the longer study with many patients to support the result in this study, and further discussion will be needed.

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CONFLICTS OF INTEREST

No conflicts of interest, financial, or otherwise are declared by authors.

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