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Research Article

Analysis of ACTH Levels After High Dose and Long-Term Prednisone Therapy in Children with Steroid Sensitive Nephrotic Syndrome

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ABSTRACT

Background The use of high dose and long-term prednisone as glucocorticoid in steroid-sensitive nephrotic syndrome patients can cause the suppressive effect on endogenous steroid production, namely HPA axis suppression which is characterized by the decrease of ACTH levels. This can decrease cortisol levels so can affect metabolism process, immune response, and brain function. Objective To analyze ACTH levels in the induction and alternating phase, and to relate with the patient's condition both clinical and laboratory data. Methods ACTH levels were measured before and after induction phase and four weeks after alternating phase at 08.00-09.30 a.m. Results 15 patients consisted of 9 boys and 6 girls showed there were no significant differences between ACTH levels in each phase. ACTH levels were increased 23.6% from 22.2 ± 13.1 pg/mL to 27.4 ± 23.0 pg/mL during the induction phase ($p>0.05$) and alternating phase also showed that ACTH levels were increased 1.7% from 27.4 ± 23.0 pg/mL to 27.9 ± 22.2 pg/mL ($p>0.05$). The clinical manifestation of HPA axis suppression such as hypoglycemia, hypotension, weight loss, appetite loss, and acute dehydration were not found in the patients. Weakness, fatigue, nausea, vomiting, and abdominal pain were found only 7% after the induction phase. Conclusion HPA axis suppression did not occur after the high dose and long-term prednisone therapy in the induction and alternating phase which showed ACTH levels average in normal range. It was also supported by the absence of clinical and laboratory data that showed signs of HPA axis suppression.

Keywords: Nephrotic syndrome (NS), Adrenocorticotropic Hormone (ACTH), High-dose prednisone, HPA axis suppression, Pediatric.

INTRODUCTION

Nephrotic syndrome (NS) is a condition in which the glomeruli of the kidney leak protein from the blood into the urine[1]. It is characterized by the increased permeability of glomerular membrane with manifestations of massive proteinuria (50 mg/kg/day) or the ratio of protein/creatinine in urine >2 mg/mg or dipstick ≥2+) that causes hypoalbuminemia (<2.5 g/dL) and usually is accompanied by edema and hypercholesterolemia (>200 mg/dL)[2]. The worldwide incidence of NS in children is estimated to be 1-7 per 100.000[3]. The prevalence of idiopathic nephrotic syndrome in Asia 16 cases per 100.000 children and in Indonesia about 6 cases per 100.000 children less than 14 years with a ratio of boys and girls 2:1[2,4].

Nephrotic syndrome patients are given full dose of prednisone 2 mg/kg/day or 60 mg/m^2/day for 4 weeks to induce remission, followed by alternating dose prednisone 1.5 mg/kg/day or 40 mg/m^2/day.[2] Based on KDIGO consensus, it is called steroid-sensitive nephrotic syndrome if remission occurs at full dose prednisone for four weeks[5]. The use of high dose and long-term prednisone as glucocorticoid can cause the suppressive effect on endogenous steroid production, namely HPA axis suppression. HPA axis suppression occurs due to glucocorticoids endogenous and exogenous do negative feedback control that is short-loop feedback and long-loop feedback on the HPA axis by suppressing hypothalamic corticotropin-releasing hormone (CRH) production and adrenocorticotropic hormone (ACTH) secretion. It is characterized by the decrease of ACTH levels[6]. HPA axis suppression refers to the decreased or inadequate cortisol production that results from exposure of the HPA axis to exogenous glucocorticoids[7]. HPA axis suppression can cause hypotension, hypoglycemia, weakness/fatigue, nausea, vomiting, diarrhea, abdominal pain, headache (usually in the morning), fever, anorexia or weight loss, acute dehydration, psychiatric symptoms, mental status changes, consciousness loss, hyponatremia, seizure or coma[7,8]. Patients who experience with HPA axis suppression may require a prolonged period of recovery, which may extend even up to 1 year[9].

Prednisone 50 mg single dose can suppress the HPA axis during 1.25-1.5 days[10]. In another study, chemotherapy induction administration of dexamethasone 6 mg/m^2/day for 42 days in low or high risk acute lymphoid leukemia (ALL) patients showed that ACTH levels baseline, ACTH maximum concentration, and ACTH AUC

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Table 1: Baseline characteristics of patients

Patient Characteristics		Total Patients(N = 15) n (%)	Mean (SD)
Gender	Boys	9 (60)	-
	Girls	6 (40)	-
Age	< 2 years	0	-
	2- <6 years	4 (27)	3.5 (1.3)
	6- <12 years	8 (53)	7.5 (1.6)
	12-18 years	3 (20)	14.0 (1.0)
Weight	≤ 20.9 kg	8 (53)	16.4 (3.1)
	21-40.9 kg	5 (33)	26.9 (8.0)
	41-60 kg	2 (14)	48.5 (2.1)
Diagnosis	Initial attack nephrotic syndrome	4 (27)	-
	Infrequent relapses nephrotic syndrome	3 (20)	-
	Frequent relapse nephrotic syndrome	2 (13)	-
	Dependent steroid nephrotic syndrome	6 (40)	-
Duration of prednisone for 1 year prior to t=0	Not taking prednisone	5 (33)	0
	1-225 days	9 (60)	168 (54)
	226-450 days	1 (7)	229
	>450 days	0	-
Cumulative dose of prednisone for 1 year prior to t=0	Not taking prednisone	5 (33)	0
	1-5.000 mg	6 (40)	3132 (1393)
	5.001-10.000 mg	4 (27)	5939 (515)
	>6000 mg	0	-
ACTH levels t=0	1 week - 9 years (5-46 pg/mL)	11 (73)	19.3 (13.1)
	10-18 years (6-55 pg/mL)	4 (27)	22.5 (11.6)
Blood glucose[14]	<2 years (60-100 mg/dL)	0	-
	>2 years - adult (<200 mg/dL)	15 (100)	101 (22)
Blood pressure[15]	Normal (90-135/55-85 mmHg)	15 (100)	102/66 (13/11)
	Hypertension (>135/>85 mmHg)	0	-
Edema	Without edema	1 (7)	-
	Palpebra	4 (27)	-
	Extremity	1 (7)	-
	Anasarca	9 (60)	-
Meal frequency (x/day)	2	1 (7)	-
	3	12 (80)	-
	4	1 (7)	-
	5	1 (7)	-
Acute dehydration	Yes	0	-
	No	15 (100)	-
Weakness/fatigue	Yes	3 (20)	-
	No	12 (80)	-
Nausea/vomiting	Yes	4 (27)	-
	No	11 (73)	-
Abdominal pain	Yes	7 (47)	-
	No	8 (53)	-

Abbreviation: SD, standard deviation.

significantly decreased by >50% during therapy and tried to restore range normal ACTH levels after a few weeks of therapy discontinuation[11,12,13]. How far the impact and incidence of HPA axis suppression in children with nephrotic syndrome in Indonesia is unknown until now, so this study aims to analyze ACTH levels during the induction and alternating phase associated with the patient's condition from both clinical and laboratory data.

MATERIALS AND METHODS

This study conducted a prospective observational with a longitudinal design from May to October 2016 at Pediatric Department, Nephrology Division of Dr. Soetomo Teaching Hospital Surabaya. We included children aged <18 years who were diagnosed with steroid-sensitive nephrotic syndrome including initial attack, infrequent relapses, frequent relapse, and dependent steroid. Patients had received the high dose and long-term prednisone therapy (2 mg/kg/day or 60 mg/m^2/day for ± 4 weeks in induction phase and followed by alternating dose prednisone 1.5 mg/kg/day or 40 mg/m^2/day for ± 4 weeks. Patients were measured ACTH levels before and after induction phase, and four weeks after alternating phase at 08.00-09.30 a.m. We excluded

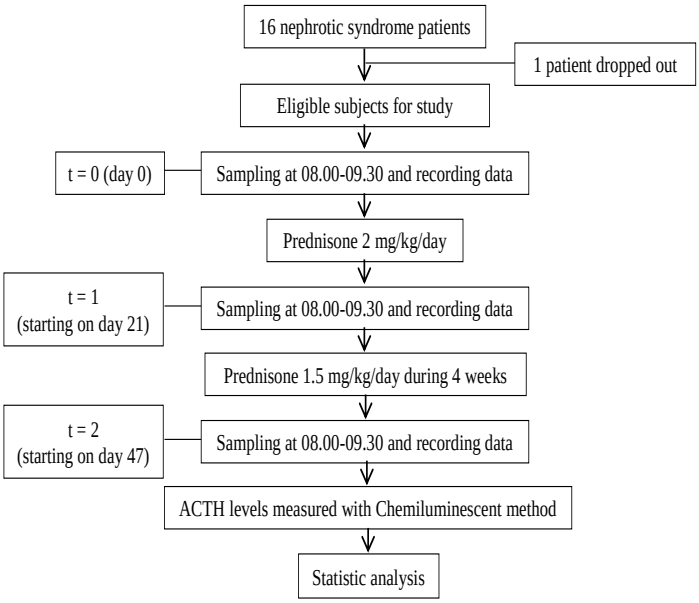

Figure 1: Study flow chart.

the patients who were diagnosed with steroid-resistant nephrotic syndrome. Steroid-sensitive nephrotic syndrome patients who changed the diagnosis, patients who resigned, and patients who died were dropped out during the study criteria.

Before starting the study, we explained the study methods, effects, and therapy of prednisone. A standard medical history, clinical, and laboratory data were collected from patient information and based on medical record. ACTH levels were measured with chemiluminescent (Immulite®1000) method. This study was approved by the Ethics Committee of the Dr. Soetomo Teaching Hospital Surabaya.

Nominal scale data described as frequency distribution and interval scale data were described as mean, deviations standard, and medians. Analysis data started with normality test with One Sample Kolmogorov-Smirnov. A comparative hypothesis test was performed to determine the differences of ACTH levels between phase with Paired Samples T-Test and General Linear Model Repeated Measures, and the differences of ACTH levels between diagnosis with One Way Anova. The test resulted significant statistically if probability (p) <0.05 with a confidence interval of 95%.

RESULTS

Table 1 showed the baseline characteristics of patients. The majority of children with nephrotic syndrome were female with age 6-<12 years and mean weight was 16.4 ± 3.1 kg. Based on sensitive-steroid nephrotic syndrome classification, dependent steroid nephrotic syndrome was most commonly found during this study. Based on infrequent relapses nephrotic syndrome definition was less than four relapses in one year and HPA axis suppression recovery duration might reach one year, then duration and cumulative dose of prednisone for one year prior to induction (t=0) was performed of classification[2,9]. The history of prednisone duration prior to one year at most for 1-225 days with cumulative doses was 1-5000 mg.

Based on age range and ACTH levels normal value, blood glucose, and blood pressure from literature, it was found that 15 patients had ACTH levels, blood glucose, and blood pressure within normal range. All patients did not experience acute dehydration such as eye and skin elasticity before induction (t-0). The majority of patients (80%) had a normal meal frequency, ie three times a day. 60% patients experienced anasarca edema accompanied by abdominal pain in some patients (47%) due to the clinical manifestations of massive proteinuria. Some patients (20-27%) also experienced weakness/fatigue and nausea/vomiting.

Table 2 showed ACTH levels changes in sensitive-steroid nephrotic syndrome patients. Three patients (MA, AR, and FH) had ACTH levels profile different from other patients which ACTH levels at t=0 lower than t=1. Figure 2 showed that there were no significant differences between ACTH levels in each phase. ACTH levels increased by 23.6% from 22.2 ± 13.1 pg/mL to 27.4 ± 23.0 pg/mL during the induction phase (p>0.05) and alternating phase also showed that ACTH levels increased by 1.7% from 27.4 ± 23.0 pg/mL to 27.9 ± 22.2 pg/mL (p>0.05). The clinical manifestation of HPA axis suppression such as hypoglycemia, hypotension, weight loss, appetite loss, and acute dehydration were not found in the patients in this study. Weakness, fatigue, nausea, vomiting, and abdominal pain were found only 7% after the induction phase.

DISCUSSION

Nephrotic syndrome is more common in boys than girls (ratio 3:2) in accordance with Paediatrics and Child

Table 2: ACTH Levels of Patients.

Patient Code	ACTH Levels (pg/mL) Normal Value [14,16]	t=0	t=1	t=2
Initial Attack Nephrotic Syndrome				
AI (B/14y) p	2-55	30.3	18.4	14.7
AM (G/3y)	5-46	9.5	11.1	11.1
DI (G/8y)	5-46	44.9	40.4	40.3
KY (B/2y)	5-46	10.8	11.0	10.8
Mean ± SD		23.9 ± 16.9	20.2 ± 13.9	19.2 ± 14.2
% Δ		-	↓ 15.3%	↓ 4.9%
Infrequent Relapses Nephrotic Syndrome				
JA (G/7y)	5-46	42.8	28.2	22.9
SR (G/7y)	5-46	11.0	10.6	11.3
MA (B/7y)	5-46	12.0	49.8	41.8
Mean ± SD		21.9 ± 18.1	29.5 ± 19.6	25.3 ± 15.4
% Δ		-	↑ 34.7%	↓ 14.2%
Frequent Relapse Nephrotic Syndrome				
AR (B/6y)	5-46	24.4	88.6	89.8
AP (B/11y) p	2-55	10.4	11.4	21.0
Mean ± SD		17.4 ± 9.9	50.0 ± 54.6	55.4 ± 48.6
% Δ		-	↑ 187.4%	↑ 10.8
Dependent Steroid Nephrotic Syndrome				
RF (B/15y) p	2-55	14.8	9.4	9.9
ND (B/4y)	5-46	21.5	16.6	25.5
RA (B/6y)	5-46	40.8	41.0	30.9
DA (G/5y)	5-46	11.2	11.0	15.8
NH (G/8y)	5-46	13.7	10.3	13.7
FH (B/13y)	6-55	34.3	53.1	58.3
Mean ± SD		22.7 ± 12.2	23.6 ± 18.8	25.7 ± 17.8
% Δ		-	↑ 3.7%	↑ 9.0%
Range(15 Patients)		9.5-44.9	9.4-88.6	9.9-89.8
Mean ± SD		22.2 ± 13.1	27.4 ± 23.0	27.9 ± 22.2
% Δ		-	↑ 23.6 %	↑ 1.7%

Abbreviation: B, boy; G, girl; p, pubertas; SD, standard deviation; y, years.

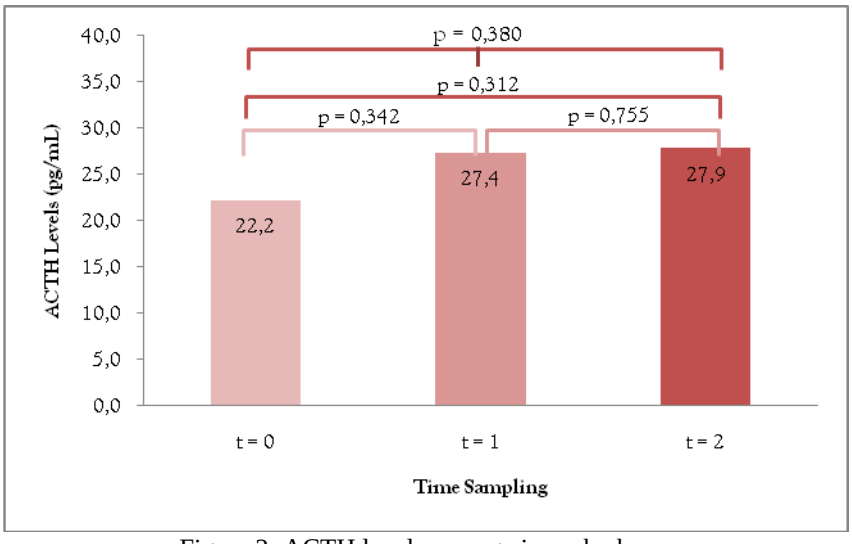

Figure 2: ACTH levels average in each phase.

Health reference. The relationship between male gender and nephrotic syndrome remains unclear. It has been established that pathogenesis of nephrotic syndrome involves T cell dysfunction. Abnormal T cell clones are predominantly located in the thymus and thymus disease is more common in boys than girls. Based on the WHO 2007 age range classification, nephrotic syndrome patients were the most aged of 6-<12 years because of the underlying disease condition (idiopathic)[17].

ACTH levels before induction (t=0) were in normal range due to patients taking prednisone when tapering off. The purpose of tapering off is to prevent steroid withdrawal

Table 3: Laboratory and Clinical Data of Patients (1).

Patient Code	Laboratory Data			Clinical Data								
	Blood Glucose (mg/dL)			Blood Pressure (mmHg)			Weight (kg)			Meal Frequency (x/day)		
	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2
AI	118	120	121	100/60	110/80	110/70	47.0	48.0	48.0	3	4-6	3
AM	96	111	117	90/60	90/60	90/60	11.8	10.5	11.0	3	5-6	5-6
DI	99	107	113	90/60	90/60	100/70	20.0	21.0	24.0	3	5-6	4-5
KY	126	102	112	95/50	100/60	90/50	12.3	14.0	14.0	3	4-5	3
JA	107	99	103	110/70	90/60	90/60	18.0	19.5	20.0	2-3	4-5	2-3
SR	116	73	110	90/60	90/60	110/70	21.8	19.5	19.0	3	4-5	4-5
MA	63	122	109	110/80	100/70	100/70	20.2	20.5	21.0	3-4	6-7	4-5
AR	78	114	116	90/60	90/60	80/50	16.1	17.0	17.0	3	4-5	3
AP	87	110	113	120/90	120/70	110/80	50.0	48.0	49.0	3	3-4	3
RF	147	106	85	110/80	100/70	100/70	29.7	28.0	30.0	3	4-5	3
ND	102	92	123	90/60	90/60	100/60	16.0	16.0	16.0	3	4-6	4-6
RA	122	123	112	90/60	90/60	90/60	17.0	14.5	14.5	4-5	4-6	4-5
DA	84	89	128	100/70	80/50	90/60	21.0	21.0	21.5	3	4-5	5
NH	88	118	87	110/60	90/60	80/50	22.0	21.0	21.0	3	4-5	3-4
FH	79	123	114	130/70	100/70	110/70	39.8	39.0	43.0	2	4-5	4-5
Range	63-147	73-123	85-128	90/50-130/90	80/50-120/80	80/50-110/80	11.8-50	10.5-48	11-49	2-5	4-7	3-6
Mean ± SD	101 ±22	107± 14	111± 12	102/66±13/11	95/63±10/7	97/63±11/9	24.2± 12.0	23.8± 11.8	24.6± 12.3	3±1	5± 1	4± 1

after the long-term prednisone therapy (>30 days). Based on other studies in acute lymphoid leukemia patients were induced using dexamethasone 6 mg/m^2/day for 28 days, ACTH levels returned to normal or increased after one month of glucocorticoid therapy was stopped[11,12,13]. Based on table 2, ACTH levels in three patients (MA, AR, and FH) before induction (t=0) was lower than after induction (t=1) due to the ACTH secretion and kinetics profile variation in each patient. The variations occured because of genetic variations in the resulting individual circadian rhythm. In addition, the CRH secretion waved different impact on synthesis and ACTH release. ACTH secreted followed circadian and ultradian rhythm under control the suprachiasmatic nucleus (SCN) of the anterior hypothalamus functions as the master circadian pacemaker[18]. Within this overall 24 hours diurnal cycle, periodic ACTH secretory bursts occured at a frequency modulation contributed to diurnal changes in ACTH profile[19]. This variation was demonstrated in a study of six healthy young men who carried out sampling every 7 minutes for 24 hours. This study illustrated ACTH pulse frequency amount variation, ACTH total secretion, and ACTH daily basal. This variation depends on in vivo hormone elimination rates, the degree of CRH synergism and ACTH priming of cortisol synthesis secretion, the amplitude and phase of the circadian rhythm, and dose-response parameters[20]. The autonomous and self-sustaining nature of the circadian timing system primarily depends on the presence of a genetic mechanism known as the molecular circadian clockwork (clock genes)[18].

8 nephrotic syndrome pediatric patients (AI, DI, JA, SR, RF, ND, DA, and NH) who experienced HPA axis suppression were characterized by the decrease of ACTH levels after induction therapy. HPA axis suppression occured due to endogenous and exogenous glucocorticoids to negative feedback control in the form short-loop feedback and long-loop feedback on the HPA axis by suppressing hypothalamic corticotropin-releasing hormone (CRH) and ACTH secretion. In short-loop feedback, CRH decrease caused CRH bonds with G protein-coupled receptor (GPCR) on the cell membrane of corticotroph cells decreased, resulting Gα activation decreased then the adenylyl cyclase stimulation and cyclic adenosine monophosphate (cAMP) decreased too. This caused PKA stimulation decreased and L-type Ca^{2+} channels activated thus led to the decrease in Ca^{2+} so ACTH exocytosis was decreased. Over a much longer time, CRH receptor activation decrease also led to the decrease of gene transcription and synthesis of the pro-priomelanocortin (POMC) thus ACTH synthesis was decreased[6].

Unlike 7 nephrotic syndrome pediatric patients (AM, KY, MA, AR, AP, RA, and FH) who had elevated ACTH level caused negative feedback. This negative feedback was a key component of most homeostatic control systems, so it could lead to differences in the ACTH levels pattern in each patient[21]. The negative feedback was controlled in the form HPA axis long-loop feedback by cortisol. In long-loop feedback, ACTH bond with MC2R decrease led to Gα activation decrease then the adenylyl cyclase stimulation and cAMP were decreased. This resulted in PKA stimulation decrease and then cortisol decrease[6]. Cortisol secretion was controlled by corticotrophin or ACTH, which was secreted by the anterior pituitary, which in turn was regulated by a hypothalamic hormone, corticotrophin-releasing hormone (CRH). Both ACTH and CRH were controlled by cortisol through a feedback mechanism, i.e., the greater the

Table 3: Laboratory and Clinical Data of Patients (2).

Patient Code	Clinical Data														
	Full Moon Face			Acute Dehydration			Weakness/Fatigue			Nausea/Vomiting			Abdominal Pain		
	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2	t = 0	t = 1	t = 2
AI	-	+	+	-	-	-	-	+	-	-	-	-	+	-	-
AM	-	+	+	-	-	-	-	-	-	-	-	-	-	+	-
DI	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
KY	-	+	+	-	-	-	+	-	-	+	-	-	+	-	-
JA	-	+	+	-	-	-	+	-	-	+	-	-	+	-	-
SR	-	+	+	-	-	-	-	-	-	-	-	-	+	-	-
MA	-	+	+	-	-	-	+	-	-	-	-	-	+	-	-
AR	-	+	+	-	-	-	-	-	-	2x	-	-	1x	-	-
AP	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
RF	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
ND	-	+	+	-	-	-	-	-	-	-	+	-	-	-	-
RA	-	+	+	-	-	-	-	-	-	-	-	-	+	-	-
DA	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
NH	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-
FH	-	+	+	-	-	-	-	-	-	1x	-	-	-	-	-
%	-	100	100	-	-	-	20	7	-	27	7	-	47	7	-

plasma cortisol concentration, less ACTH and CRH were released, and the lower the serum cortisol levels, the greater the amount of ACTH and CRH were released. ACTH levels were increased in three patients (MA, AR, and FH) in induction phase may be due to the stress factor (psichological and physical). Stress was defined as a state of threatened homeostatic[22].

Different test performed on the ACTH levels average in each sampling point showed that there were no significant differences between ACTH levels in each phase (p=0.380). This discrepancy might be due to the small sample size (15 patients) with considerable variation (SD ± 13.1 pg/mL at t=0, ± 23.0 pg/mL at t=1, and ± 22.2 pg/mL at t=2).

Clinical manifestations of massive proteinuria in nephrotic syndrome patients are edema. The edema is in accordance with the patient's condition that 60% experiences with anasarca. 27% patients experience with periorbital edema is noted first. Edema increases gradually and becomes detectable when fluid retention exceeds 3 to 5 percent of body weight[23]. The clinical manifestation of HPA axis suppression such as hypoglycemia, hypotension, weight loss, appetite loss, and acute dehydration were not found in the patients in this study. Weakness, fatigue, nausea, vomiting, and abdominal pain were found only 7% after the induction phase. Patients experienced weight loss in the induction phase because of the syndrome nephrotic patient's clinical condition improved, characterized by loss of anasarca (negative proteinuria). This is contrast to the patient condition that has an increased meal frequency when the induction phase is due to glucocorticoids effects may increase blood sugar levels through its action on glycogen, protein, fat metabolism. Meal frequency increased is not accompanied by an increase in blood sugar levels in all patients because insulin sensitivity in pediatric patients is still good. All patients experienced with full moon face in the induction and alternating phase due to body fat distribution increase[19]. Some patients experienced with weak/fatigue, nausea/vomiting, and abdominal pain before induction due to the rapid accumulation of fluid or peritonitis[23]. Weakness, fatigue, nausea, vomiting, and abdominal pain were found only 7% after the induction phase caused by prednisone side effect on the digestive tract. Corticosteroids alone become ulcerogenic only if treatment lasts longer than one month and the total administered dose exceeds 1000 mg. Corticosteroids can inhibit the biosynthesis of gastric cytoprotective prostaglandins while suppressing as well the production of gastric damaging leukotrienes. Both gastric mucus production and gastric bicarbonate secretion are impaired by steroid administration which results in a weakening of gastric mucosal defenses[24].

CONCLUCIONS

HPA axis suppression did not occur after the high dose and long-term prednisone therapy in the induction and alternating phase which was shown by ACTH levels average in the normal range. It was also supported by the absence of clinical and laboratory data that showed signs of HPA axis suppression.

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CONFLICT OF INTEREST

The authors report no conflicts of interest. This study is self-funded by the authors and they have no financial or proprietary interest in the subject matter or material

discussed. The authors themselves are responsible for the content and writing of the paper.

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