

## ANALYSIS OF INDUCTION PHASE GLUCOCORTICOID USE ON ADRENAL SUPPRESSION IN PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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### ABSTRAK

*Glukokortikoid memiliki peran penting dalam pengobatan leukemia limfoblastik akut (LLA). Namun, dosis suprafisiologis dapat menyebabkan supresi adrenal. Supresi adrenal menurunkan kadar kortisol yang menyebabkan tubuh rentan terhadap infeksi. Kejadian supresi adrenal sebelum dan sesudah terapi glukokortikoid masih belum jelas. Tujuan dari penelitian ini adalah untuk menganalisis perbandingan kadar kortisol pada penggunaan glukokortikoid selama fase induksi leukemia limfoblastik akut. Pasien yang memenuhi kriteria inklusi diberi terapi deksametason atau terapi prednison selama 7 minggu sesuai dengan protokol kemoterapi ALL Indonesia 2013. Kadar kortisol diukur pada hari ke 0, 14, 28, 42 dan 56 fase kemoterapi induksi. Jumlah pasien yang sesuai dengan kriteria inklusi sebanyak 24 anak di antara 31 anak yang menderita leukemia limfoblastik akut. Sebelum pengobatan, rerata kadar kortisol pasien sebesar 228,95 ng/ml pada kelompok risiko standar (prednison) dan 199,67 ng/ml pada kelompok risiko tinggi (deksametason). Pada pasien kelompok resiko biasa, supresi adrenal terjadi pada hari ke-56. Pada pasien kelompok resiko tinggi, penurunan kadar kortisol signifikan terjadi pada hari ke-14, hari ke-28, hari ke-42 terhadap hari ke-0 fase induksi ( $p=0,001$ ). Kedua kelompok memiliki puncak kortisol yang berbeda setelah 6 minggu fase induksi ( $p=0,028$ ). Deksametason mengakibatkan kadar kortisol yang lebih rendah dari prednison selama fase kemoterapi induksi. (FMI 2016;52:7-13)*

**Kata kunci:** glukokortikoid, leukemia limfoblastik akut, kadar kortisol, supresi adrenal

### ABSTRACT

*Glucocorticoids play an important role in the treatment of acute lymphoblastic leukemia (ALL). However, supraphysiological doses may cause suppression of the adrenal. Adrenal suppression resulting in reduced cortisol response may cause an inadequate host defence against infections, which remains a cause of morbidity and mortality in children with ALL. The occurrence of adrenal suppression before and after glucocorticoid therapy for childhood ALL is unclear. The aim of this study is to analysis the effect of glucocorticoid on cortisol levels during induction phase chemotherapy in children with acute lymphoblastic leukemia. A cross-sectional, observational prospective study was conducted to determine the effect of glucocorticoid on cortisol levels in children with acute lymphoblastic leukemia. Patients who met inclusion criteria were given dexamethasone or prednisone therapy for 49 days according to the 2013 Indonesian Chemotherapy ALL Protocol. Cortisol levels were measured on days 0, 14, 28, 42 and 56 of induction phase chemotherapy. There were 24 children, among 31 children recruited, who suffered from acute lymphoblastic leukemia. Before treatment, the means of cortisol levels were 228.95 ng/ml in standard risk group (prednisone) and 199.67 ng/ml in high risk group (dexamethasone). In standard risk group, the adrenal suppression occurs at about day 56. There was a significant decrement of cortisol levels in high risk group in days 14, 28, 42 against days 0 of induction phase ( $p=0.001$ ). Both groups displayed different peak cortisol levels after 6 week of induction phase ( $p=0.028$ ). Dexamethasone resulted in lower cortisol levels than prednisone during induction phase chemotherapy in children with acute lymphoblastic leukemia. (FMI 2016;52:7-13)*

**Keywords:** glucocorticoid, acute lymphoblastic leukemia, cortisol levels, adrenal suppression

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### INTRODUCTION

Acute lymphoblastic leukemia (ALL) is malignant diseases of blood cells are most commonly found in children. Reports from several studies showed mortality due to infection as a form of side effects of chemotherapy and high-dose steroids (Conter et al 2009, Prucker et al 2009, Silverman et al 2000, Pui et al 2000, Christensen et al 2005). One cause of mortality due to

infection in patients with LLA caused by glucocorticoids suppress adrenal inadequacy causing the body's defense against infection (Shulman et al 2007).

The incidence of patients who have adrenal suppression LLA vary from one protocol to another chemotherapy protocol. Each of these protocols used type, dose, duration of use, method of tapering and tapering off on different glucocorticoids (Gordijn et al 2012). Some

protocols reported incidence of adrenal suppression at 83-100% after the discontinuation of glucocorticoids given day for 21 days (Einaudi et al 2008, Rix et al 2005).

The high incidence of adrenal suppression provides an opportunity high incidence of febrile neutropenia in patients receiving glucocorticoids that would be associated with an increased incidence of infection and will impact on the cost of antibiotic therapy. Another impact resulting from the incidence of adrenal suppression is the occurrence of acute and chronic adrenal insufficiency and growth retardation in children (Shulman et al 2007, Ahmet et al 2011).

Glucocorticoids are used in the protocol LLA Indonesia in 2013 is dexamethasone and prednisone. Differences in the chemical structure of both cause differences in specificity and potency of action (Miller et al 2008). Comparison suppression of the hypothalamic-pituitary-adrenal between dexamethasone and prednisone was 17: 4 (Chrousos et al 2011). Both were granted for a period of time, ie for 49 days. The incidence of adrenal suppression that is reflected from the examination levels of cortisol in the induction phase has not been known until now.

**MATERIALS AND METHODS**

This study is a prospective, observational cross-sectional study design. The research sample is a whole new patients diagnosed as LLA ordinary risk and high risk that met the inclusion criteria. The inclusion criteria for this study is a new LLA patients 0-18 years of age and patients who have not received chemotherapy treatment of leukemia using LLA 2013 Protocol ordinary risk and high risk. Exclusion criteria for the study were patients receiving glucocorticoids on indications other than LLA and patients with critical condition.

Patients receiving chemotherapy protocols were at ordinary and high risk based on the criteria established by the Hematology Oncology Division of Indonesian Pediatrician Association. Ordinary risk patients receiving prednisone therapy of 60 mg/m<sup>2</sup> on day 0 until day 7 and then continued with a dose of 40 mg/m<sup>2</sup> on day 8 s.d 49th day. High-risk patients receiving therapy dexamethasone 6 mg/m<sup>2</sup> for 49 days including 14 days for tapering on and off tapering glucocorticoids. Blood samples were taken on day 0 (before treatment), day 14, day 28, day 42, and day 56 for inspection of the morning cortisol levels. Cortisol levels were measured by ELISA (DRG Cortisol ELISA-1887).

Data analysis included descriptive analysis and hypothesis testing. Shapiro-Wilk test was used to test the normality of the data obtained. Test the difference between cortisol levels in the prednisone and dexamethasone group using paired t-test when the normal data distribution or the Wilcoxon test when the distribution is not normal. Unpaired t test performed to test differences in cortisol levels between the dexamethasone group and prednisone group. The test results were statistically significant if p <0.05 with a confidence interval of 95%.

**RESULTS**

The number of patients who met the inclusion criteria were 24 patients. Patients usual risk groups and high risk groups respectively 9 and 15 patients. Based on patient characteristics (Table 1), there are no significant differences between the two groups. Changes in cortisol levels of patients LLA ordinary risk during the induction phase showed a significant difference in the mean levels of cortisol are found in the comparison of day 0 to day 56, day 28 to day 42, day 28 to day 56 and day 42 to day 56 after the use of prednisone (Table 2; Fig. 1).

Table 1. Characteristics of patients according to risk groups

Patients' characteristics		Moderate risk (n=9)	High risk (n=15)		p*
			<1 year	> 10 years	
Age (year, mean±SD)		4.22±2.49	0.75	12.20±0.84	
	(min-max)	(1-9)		(11-13)	
Sex	Male	5	1	10	0.412
	Female	4	0	4	
BMP morphology results	L1	9	0	12	0.266
	L2	0	1	2	
Hemoglobin (g/dL, median (min-max))		8 (3.3-12.9)	4.2	7.6 (4.2-14.70)	
Leukocyte (/μL, median (min-max))		8.240 (760-36.900)	45.600	172.600 (2.880-672.000)	
Thrombocyte (/μL, median (min-max))		32.000 (1.000-247.000)	128.000	58.000 (3.000-146.000)	

Notes: \*) significant at p <0.05 with a statistical test of Fisher's exact test

Table 2. Levels of cortisol LLA risk patients before and after treatment ordinary prednisone

Patients' initials	Cortisol level (ng/ml)				
	Day0	Day 14	Day 28	Day 42	Day 56
MI	339.04	10.59	1.07	18.04	—
VS	252.43	568.13	523.43	600.87	65.64
FV	299.83	0.81	545.32	550.05	2.26
MA	49.63	8.70	394.54	500.012	9.01
AF	121.24	563.49	472.47	626.38	47.47
FeAd	568.13	476.36	†	†	†
VD	97.44	555.80	527.65	582.51	8.04
RR	300.76	600.87	12.95	4.05	72.94
MR	32.08	445.34	†	†	†
Mean ±	228.95±172.38	358.89±472.47	353.91 ±242.22	411.70 ±276.63	34.23 ±31.63
SD	(32.08-568.13)	(0.81-600.87)	(1.07-545.32)	(4.05-626.38)	(2.26-72.94)
% Δ against Day 0		↑ 57%	↑ 55%	↑ 80%	↓ 85%
% Δ against Day 42					↓ 92%

Notes:

†: The patient died

(-) There is no data because the patient does not control after the induction phase

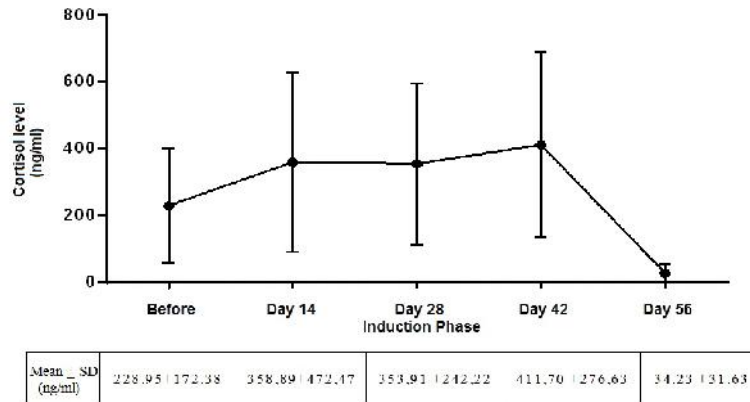


Fig. 1. Changes in cortisol levels LLA risk patients before and after treatment ordinary prednisone

Table 3. Cortisol levels LLA high-risk patients before and after therapy dexamethasone

Patients' initials	Cortisol level (ng/ml)				
	Day 0	Day 14	Day 28	Day 42	Day 56
CA	166.89	0.79	0.49	0.57	†
BB	268.43	0.96	0.96	4.09	361.05
TA	3.43	1.59	1.78	1.42	17.17
AP	339.21	92.50	1.06	1.39	104.81
DY	282.79	2.77	2.43	1.61	140.828
ArPu	94.94	2.30	†	†	†
YS	124.25	178.19	†	†	†
FeAy	208.21	106.34	192.62	†	†
FaAh	222.32	1.48	0.38	2.42	—
IA	74.76	1.54	0.62	3.81	†
SA	256.20	1.46	1.66	1.78	47.47
FaAk	171.70	0.55	0.96	1.47	308.88
AA	108.67	4.88	4.63	3.16	374.013
AZ	82.08	10.64	PP	PP	PP
RE	591.57	1.53	1.21	1.17	—
Mean ± SD	199.67±142.12	27.17±59.92	17.40±55.19	2.08 ±1.15	193.46 ±151.12
% Δ against Day 0		↓ 86%	↓ 36%	↓ 88%	↓ 3%
% Δ against Day 42					↑ 92%

Information:

†: The patient died

PP: Patients return Forced

(-) There are no data for patients not/do not control after the induction phase

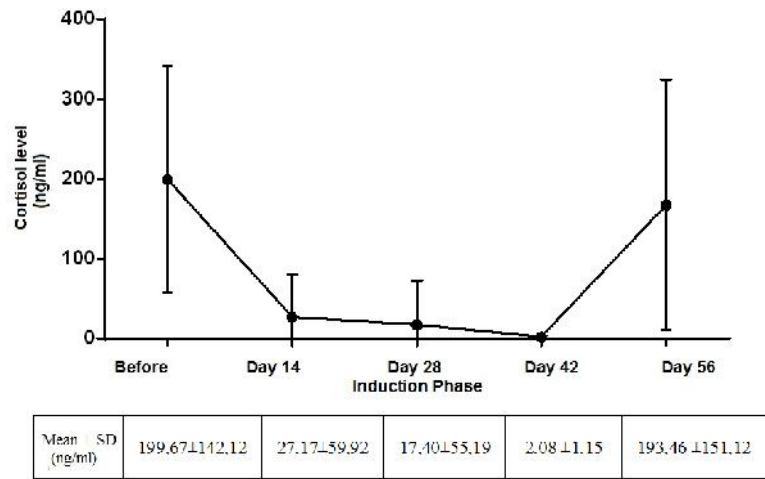


Fig. 2. Changes in cortisol levels LLA high-risk patients for phase induction chemotherapy LLA

Table 4. Statistical analysis the difference between the levels of cortisol patient therapy LLA ordinary risk and high-risk patients

Group comparison	n	Mean ± SD	Cortisol level comparison Prednisone: Dexamethasone	p values
H0 Moderate risk	9	228.95±172.38		
High risk	15	199.67±142.12		0.656*
H1 Moderate risk	9	358.89±472.47	13:1	
4 High risk	15	27.17±59.92		0.004#
H2 Moderate risk	7	353.91 ±242.22	20:1	
8 High risk	12	17.40±55.19		0.002#
H4 Moderate risk	7	411.70 ±276.63	198:1	
2 High risk	11	2.08 ±1.15		0.000#
H5 Moderate risk	6	26.48 ±28.30		
6 High risk	7	167.88 ±156.83		0.028*

Notes:  
 \*) Significant at p <0.05 by unpaired t test  
 #) Significant at p <0.05 by Mann-Whitney test

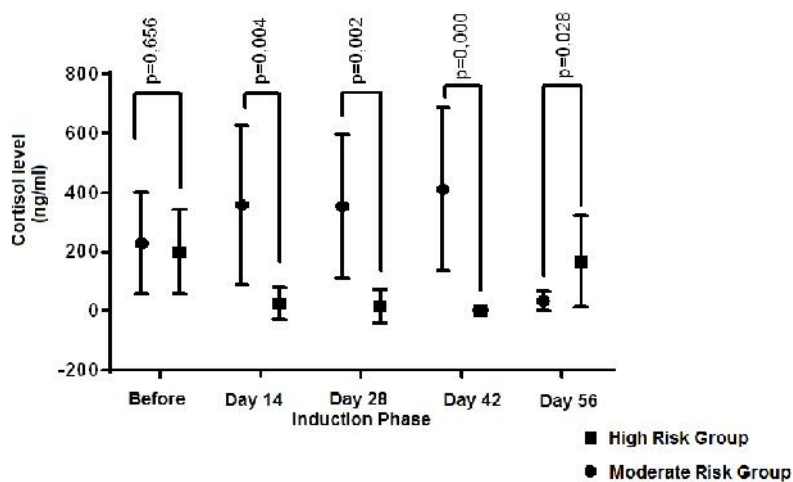


Fig. 3. Comparison cortisol levels LLA patients ordinary and higher risk during phase induction

Changes in cortisol levels of patients LLA high risk during the induction phase showed a significant difference in mean cortisol levels in comparison day 0 to day 14, day 0 to day 28, day 0 to day 42, day 14th to the 56th, day 28 to day 56 and day 42 to day 56 after the use of dexamethasone (Table 3; Fig. 2). Cortisol levels reached a nadir on day 42. Cortisol levels increase after a period tapering week off and recovery. Statistical analysis comparing the cortisol levels between the ordinary risk and high risk showed a significant difference was found in the comparison of day 14, day 28, day 42, day 56 (Table 4; Fig. 3).

## DISCUSSION

Glucocorticoids play an important role in the induction phase of treatment LLA, but suprafisiologis dose given during the administration of glucocorticoids can suppress adrenal disorder that occurs in response to stress and inadequate body's defense against infection. The incidence of patients who have adrenal suppression LLA differs from chemotherapy protocols with other chemotherapy protocols. This is due to the dosage and type of glucocorticoids as well as the method and duration of cessation of glucocorticoids are different from one protocol chemotherapy to another (Gordijn et al 2012).

Patients fit inclusion criteria to judge the cortisol levels before and after glucocorticoid therapy. The level of cortisol performed 5 times, ie before, day 14, day 28, day 42, and day 56 glucocorticoid therapy. Blood sampling performed at 08:00 to 09:00 o'clock in the morning because the peak cortisol levels are in the morning. Cortisol is a glucocorticoid synthesized by the adrenal cortex. Cortisol secretion is controlled by the hypothalamic-pituitary and adrenal. Stimulation of secretion is influenced by the state of stress, tissue damage, hypoxia, hypotension and hypoglycemia (Venkatesh & Cohen 2008). Stress conditions lead to increased production of cytokines, ie networks of signaling molecules that combine work macrophages/monocytes, lymphocytes T and B lymphocytes to the immune response that continues to rise. Among these cytokines, interleukin (IL-1), IL-6 and tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) stimulate the HPA axis. IL-1 stimulates the release of CRH by hypothalamic neurons, interact directly with the pituitary to increase the release of ACTH, and directly stimulates the adrenal gland to produce glucocorticoids (Schwimmer & Funder 2011). The state of the decrease cortisol production or inadequacy result of exposure to the hypothalamic-pituitary-adrenal (HPA) on exogenous glucocorticoid defined as adrenal suppression (Fauci et al 2008, Miller et al 2008).

Ordinary risk group and high risk group showed the incidence of different adrenal suppression. In the high risk group, the incidence of adrenal suppression has been apparent on the 14th day and reached a nadir on day 42 use glucocorticoids. In contrast, the group receiving the new prednisone therapy demonstrated adrenal suppression effect after 7 days of discontinuation of glucocorticoids. The adrenal suppression effect in terms of a decrease in basal cortisol levels based on the normal range of child cortisol levels.

Ordinary risk group patients receiving prednisone therapy during the induction phase. In the usual risk groups, there was an increase and a decrease in cortisol levels in the normal range from day 0 to day-to-56 induction phase. Adrenal suppression effect began to be seen during the week tapering off and recovery with decreased cortisol levels by 92% on the cortisol levels 42nd day. High risk group patients receiving dexamethasone therapy during the induction phase. In the high-risk groups, cortisol levels decreased from day 0 to day-to-42 induction phase. Dexamethasone has given adrenal suppression effect from day 0 up to day 42. Adrenal suppression effect was not looked after tapering off and recovery week with a 92% increase in cortisol levels of cortisol levels 42nd day.

One predictor of HPA axis suppression due to the use of glucocorticoids is the type and potency steroids used (Kaltkas & Alexandraki 2012). Based on the half-life, prednisone and dexamethasone provides biological half-life, each for 18-36 hours and 36-54 hours. Therefore, prednisone classified in glucocorticoid dexamethasone while the action is being classified in long action. HPA axis suppression effects comparison between prednisone and dexamethasone was 4:17 (Chrousos et al 2011). It means giving suppressive effect of dexamethasone 4 times greater than prednisone. Different molecular dexamethasone with prednisone only by the addition of fluorine atom at position 9 $\alpha$  in ring B and the methyl group at C16 position on the ring D. The difference of these structures result in different pharmacodynamics and pharmacokinetics of both (Siswandono & Purwanto 2000). Parameter pharmaco-dynamics showed that dexamethasone-glucocorticoid receptor complex is more stable than prednisone-receptor complex. Affinity of dexamethasone as an agonist of the glucocorticoid receptor was 8.1 to 9.0 while the prednisone only amounted to 6.28 (Strehl et al 2011). In this study, dexamethasone is known to have effects adrenal suppression in the form of decreased cortisol levels on day 14, while the new prednisone provide to that effect between the 42nd to 56th. Thus, it can be described that difference prednisone and dexamethasone is located on the biological activity of prednisone lower compared with dexamethasone in adrenal suppression effect.

Supraphysiological dose dexamethasone can suppress the secretion of hypothalamic corticotrophin-releasing hormone (CRH). This dose will decrease the levels of mRNA and disposal resulting in decreased secretion of CRH. In the anterior pituitary, CRH binds to the CRH receptor. A decrease in the secretion of CRH neurons that store the result in CRH in secretory vesicles located at the synapse end of the median eminence of the hypothalamus causes a decrease in the release of ACTH stimulation, also known as corticotropin from the anterior pituitary. This is due to lack of CRH were up on the anterior pituitary resulting in a reduced number of binding with G protein-coupled receptor (GPCR) on the cell membrane of the cell corticotrop. The decline lowered the bonding hormone activation G which activates adenylate adenilil thus reducing the load of cyclic Adenosine Monophosphate (cAMP). Stimulation of protein kinase A (PKA), which is less thereby decreasing the amount of L-type Ca<sup>2+</sup> channels are active so that the lower the concentration of Ca<sup>2+</sup>. The decrease Ca<sup>2+</sup> resulted in a decrease in ACTH exocytosis. Suppression of ACTH release is also caused by resistance POMC synthesis (White 2010, Moisiadis & Matthews 2014, Barrett 2012).

At the adrenal cortex, ACTH reduced bond with melanocortin-2 receptor (MC2R) in the plasma membrane of the cell and reticular fasciculata zone resulted in the synthesis of cortisol. Lack MC2R number of bonds paired with G proteins will reduce the number of adenilil cyclase activated. The result is a decrease in the charge cAMP, decreased activation of PKA will phosphorylate a variety of proteins. The result is a decrease in the stimulation of rate-limiting step (limiting step rate) on the formation of cortisol through the conversion of cholesterol to pregnenolone which is catalyzed by the enzyme side-chain cleavage/SCC (breaker side chains) cholesterol (White 2010, Moisiadis & Matthews 2014, Barrett 2012).

At the 6th week induction phase of high-risk groups, cortisol levels increased to 167.88 ± 156.83 ng/ml. Increased cortisol levels showed that on average patients who received dexamethasone therapy did not experience adrenal suppression when the patient continued chemotherapy in a consolidation phase. Some of these studies indicate that the incidence of adrenal suppression occurs after a period of at least tapering off in patients with ALL. Research by Kuperman (2001) reported an incidence of 4/15 patients experienced adrenal suppression when dexamethasone 6 mg/m<sup>2</sup>/day is stopped suddenly (Kuperman et al 2001) Genesis adrenal suppression is observed for 4/20 patients who received a cumulative dose dexamethasone 246.25 mg/m<sup>2</sup> on AIEOP protocol ALL 2000 (Einaudi et al 2008). The research report that uses the protocol

NOPHO ALL-92 reported an incidence of 1/5 patients experienced adrenal suppression after a 9-day period tapering off with a cumulative dose dexamethasone 236.25 mg/m<sup>2</sup> (Rix et al 2005).

The results of this study indicate that among the two groups there was no significant difference in mean cortisol levels before glucocorticoid therapy (p=0.656). Meaningful comparisons between groups of ordinary risk and high-risk occurs on day 14, day 28, day 42 and day 56. Thus, dexamethasone and prednisone effect of different adrenal suppression during the induction phase with a ratio of 198: 1 on day 42. Research by Kuperman (2012) compare the mean levels of cortisol in the LLA 16 patients who received prednisone therapy (40 mg/m<sup>2</sup>/day) and 13 patients who received the therapy LLA dexamethasone (6 mg/m<sup>2</sup>/day) for 28 days induction phase. Significant differences were not found in the study due to individual variations in producing adrenal cortisol (Kuperman et al 2012).

## CONCLUSION

Adrenal suppressive effect on the use of prednisone began to look at the past week tapering off and recovery with decreased cortisol levels by 92% whereas the effects of adrenal recovery occurs after tapering week off and recovery with increased cortisol by 92%. Dexamethasone provides faster adrenal suppression effect during the induction phase with decreased cortisol levels by 198 times compared with prednisone.

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