Paediatrica Indonesiana

VOLUME 54 November • 2014 NUMBER 6

Original Article

Hypertension, high-dose corticosteroids, and renal infiltration in children with acute lymphoblastic leukemia

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Abstract

Background Hypertension is a rarely recognized complication of acute lymphoblastic leukemia (ALL). The incidence of hypertension in ALL patients in Indonesia remains unknown, but the most common risk factors are corticosteroid use during induction-phase chemotherapy and renal leukemic infiltration.

Objective To determine the incidence of hypertension in children with ALL, and to assess for associations of high-dose corticosteroids, renal infiltration, and hyperleukocytosis to hypertension.

Methods This was a cross-sectional study involving 100 children aged 2-18 years. Subjects were newly diagnosed ALL patients and those underwent induction-phase chemotherapy in the Pediatric Ward or Outpatient Clinic at Cipto Mangunkusumo or Dharmais Hospitals.

Results Hypertension occurred in 6 (10%) of 60 newly diagnosed ALL patients and 8 (20%) of 40 patients who had received high-dose corticosteroids, but the difference was not statistically significant (OR=2.25; 95%CI 0.72 to 7.07; P=0.239). Hypertension was reported in 8 of 29 subjects who received dexamethasone, but in none of the subjects who received prednisone. However, the difference in these subgroups was also not statistically significant. Renal enlargement was found in 1 of 14 hypertensive patients, but it was not associated with hypertension (OR=0.80; 95%CI 0.52 to 1.24; P=0.417). Hyperleukocytosis was also not associated with hypertension (OR= 0.79; 95% CI 0.20 to 3.11; P=1.000).

Conclusion The incidence of hypertension in ALL patients was 14%. Hypertension is not associated with renal infiltration or hyperleukocytosis. Furthermore, hypertension is not associated with corticosteroid dose, though is found only in subjects who receive dexamethasone. **[Paediatr Indones. 2014;54:372-6.]**

Keywords: *acute lymphoblastic leukemia, hypertension, corticosteroid, renal infiltration, hyperleukocytosis*

Hypertension is one of the adverse effects in patients undergoing chemotherapy, especially those who receive high-dose corticosteroids. Corticosteroid treatment induces apoptosis of leukemic cells, therefore, it is the backbone of induction-phase chemotherapy for acute lymphoblastic leukemia (ALL) and cannot be omitted from the ALL protocol.[1,2] Other risk factors for hypertension in ALL are hyperleukocytosis and tumor lysis syndrome, as well as renal leukemic infiltration, and sepsis.[3,4] Electrolyte imbalance and hyperuricemia in tumor lysis syndrome leads to renal injury and hypertension.[5] Renal leukemic infiltration can be detected as renal enlargement by ultrasound examination, and is usually found in newly diagnosed ALL patients.[4,6] Reported incidences of hypertension in children with ALL or lymphoma varies between centers, ranging from 46% to 67.3%,[6,7] significantly higher than the incidence of hypertension in the general pediatric population, 1-3%.[8,9]

The incidence of hypertension in pediatric ALL patients in Indonesia is unknown, and hypertension

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itself and its risk factors are not of great interest nowadays. The purpose of this study was to assess for the incidence of hypertension in pediatric ALL patients, and to assess for associations of hypertension to renal leukemic infiltration, high-dose corticosteroids, and hyperleukocytosis.

Methods

This cross-sectional study was conducted in the Pediatric Wards and Outpatient Clinics of Cipto Mangunkusumo and Dharmais Hospitals from August to December 2012. Subjects were children aged 2 to 18 years with newly diagnosed ALL, or ALL patients who underwent induction-phase chemotherapy. Subjects were also cooperative during blood pressure measurements and their parents agreed to participate in the study. Diagnoses of ALL were established based on microscopic evaluation and immunophenotyping of bone marrow aspirates. We excluded patients who had previously known hypertension or kidney diseases, received anti-hypertensive drugs, consumed corticosteroids prior to ALL diagnosis, or had relapsed ALL. The minimum required sample size was 95, calculated with a formula of single proportion. Subjects (100 total) were recruited by consecutive sampling.

This study was approved by the Ethics Commitee of the Medical Faculty at the University of Indonesia. A complete explanation of the study was given to all participating subjects and parents provided written informed consent. Subjects' baseline characteristics were recorded, including birth date, gender, body weight and height, date of diagnosis, white blood cell (WBC) count at the time of diagnosis, ALL classification, date of chemotherapy onset, corticosteroid dosage, and completed weeks of induction phase.

In an unblinded manner, blood pressure was measured 3 times in the morning or afternoon using a mercury sphygmomanometer (*Riester*®) and stethoscope (*Litmann*®). An average of the 3 measurements was recorded for later analysis. Urinary tract ultrasound was performed on subjects with hypertension. Corticosteroid consumption was recorded as the cumulative dose (mg) and total duration (days) from first day of corticosteroid windows to the day of blood pressure measurement. Chi-square and Fisher's exact test with a significance level of $P < 0.05$ were used to assess for associations between risk factors and hypertension. Statistical analysis was performed using *SPSS 20.0* for *Windows*.

Results

A total of 100 children with ALL fulfilled the study criteria and participated in the study. The numbers of male and female subjects were comparable at a ratio of 1.08:1. Most subjects were aged 2 to 10 years (77%) and had WBC count <50,000/uL (75%). Only 40% of subjects had started induction-phase chemotherapy and received corticosteroids, as shown in **Table 1**.

Elevated blood pressure was detected in 6 (10%) of 60 subjects with newly diagnosed ALL and 8 (20%) of 40 subjects who had undergone induction phase chemotherapy. There was 1 subject with hypertensive crisis who presented with seizure and decreased consciousness. He was the only hypertensive subject treated with antihypertensive agents: nifedipine, captopril, and clonidine. Hypertension was detected in 8 of 29 subjects who received dexamethasone, and in no subjects who received prednisone, but the difference was not statistically significant. There was no association between hypertension and corticosteroid administration or age group (**Table 2**).

Renal ultrasound was performed on 12 of 14 subjects with hypertension. The remaining two did not return for an ultrasound examination follow-up visit. Renal enlargement was found in 1/12 subject and there was no association between renal enlargement and chemotherapy status in this study (**Table 3**).

Table 1. Baseline characteristics of subjects

Characteristics	n=100
Gender, n (%)	
Male	52 (52)
Female	48 (48)
Age, n (%)	
2-10 years	77 (77)
>10 years	23 (23)
Corticosteroid use, n (%)	
None	60 (60)
Dexamethasone	29 (29)
Prednisone	11 (11)
WBC count at the time of diagnosis, n (%)	
<50,000/µL	75 (75)
≥50,000/µL	25 (25)

We could not evaluate the role of corticosteroid dose on the incidence of hypertension because of the absence of cumulative steroid dose data. **Table 4** describes corticosteroid usage based on type, duration, and cumulative dose in subjects with and without hypertension.

Hypertension was detected in 3 of 25 subjects with white blood cell (WBC) counts of more than 50,000/uL. Eleven of 75 subjects who had lower WBC counts, had hypertension, but the difference was not statistically significant (P=1.000) (**Table 5**).

Table 2. Distribution of hypertension and its related factors in children with ALL (n = 100)

	Hypertension	No hypertension	OR	95% CI	P* value
Chemotherapy status					
Not started	6	54	2.250	0.72 to 7.07	0.239
Induction phase	8	32			
Age					
2 – 10 years	12	65			
>10 years	2	21	0.516	0.11 to 2.49	0.512
Corticosteroid type					
Dexamethasone	8	21			0.08
Prednisone	0	11			
None	6	54			

* Fisher's exact test, with statistical significance level of P<0.05
OR= odds ratio; 95% CI= 95% confidence interval

Table 3. Role of renal enlargement in children with ALL and hypertension (n=12)

Chemotherapy status of ALL children with hypertension	Renal enlargement	No renal enlargement	OR	95% CI	P value*
Not started	1	4	0.80	0.52 to 1.24	0.417
Induction phase	0	7			

* Fisher's exact test, with statistical significance level of P<0.05

Table 4. Distribution of hypertension and corticosteroid use in children with ALL (n=40)

Corticosteroid	Hypertension	No hypertension	Total n=40
Types, n			
Dexamethasone	8	21	29
Prednisone	0	11	11
Duration, n			
Dexamethasone			
1-5 days (windows)	1	4	5
8-14 days (week I)	2	6	8
15-21 days (week II)	1	3	4
22-28 days (week III)	1	5	6
29-35 days (week IV)	0	1	1
36-42 days (week V)	1	5	6
43-49 days (week VI)	2	8	1
Cumulative dose, n			
Dexamethasone			
≤ 27 mg/m^2	1	4	5
>27-69 mg/m^2	2	6	8
>69-111 mg/m^2	1	3	4
> 111-153 mg/m^2	1	5	6
> 153-195 mg/m^2	0	1	1
> 195-237 mg/m^2	1	5	6
> 237 mg/m^2	2	8	10

Table 5. White blood cell count and hypertension in children with ALL (N = 100)

WBC count (/uL)	Hypertension	No hypertension	OR	95% CI	P value*
< 50,000	11	64	0.79	0.20 to 3.12	1.000
≥ 50,000	3	22			

* Fisher-exact test, with statistical significance level of 0.05

Discussion

Hypertension is a rarely recognized complication of ALL. This is the first study to define the incidence of hypertension and its risk factors in Indonesian children with ALL. Several limitations of this study were its cross-sectional design, which allowed for only one-time rather than daily blood pressure measurements of a cohort design, and its imbalanced proportion of newly diagnosed ALL subjects and ALL subjects who underwent induction-phase chemotherapy (ratio 1.5:1).

The incidence of hypertension in our study was 14%, 10 times higher than the incidence in the general pediatric population (1-3%).[8-12] This finding was similar to Belgaumi *et al*. who reported hypertension in 18 (10.7%) of 156 children with ALL,[13] but much lower than the 46% in a study by Attard-Montalto *et al*.[6] This difference may have been due to the design limitation of our study. Attard-Montalto *et al.* used a prospective design with daily blood pressure measurements for 28 days of induction-phase chemotherapy, while our study recorded blood pressure measurements only a single time. Therefore, our results do not reflect overall blood pressure patterns in ALL patients before and during chemotherapy. A higher incidence of hypertension was found in the 2 to 10-year-old age group (21%) compared the >10 year-old age group (8%), although the difference was not statistically significant. Similarly, Louis *et al*.[7] and Olgar *et al*.[4] reported mean ages of children with hypertension to be 4.2 and 8.9 years, respectively. Those studies did not explain the possible cause of the findings. The incidence of hypertension in subjects who underwent chemotherapy was 2 times higher than in newly diagnosed, untreated ALL subjects. Although statistics showed no significant difference, this finding was clinically significant. Subjects who underwent chemotherapy had 2 times higher risk of developing hypertension than newly diagnosed ALL subjects (OR 2.25; 95%CI 0.72 to 7.07).

Dexamethasone use in the induction phase resulted in 8/29 (27.5%) of subjects with hypertension, while no hypertension was reported in subjects who received prednisone in our study. In contrast, Belgaumi *et al*. reported 10% and 12.2% incidences of hypertension in subjects who received dexamethasone and prednisone, respectively.[13] This difference may have been due to varying prednisone doses in these studies. Sixty-three of 106 subjects who received prednisone in the Belgaumi *et al*. study underwent high-risk protocols, therefore, they received a higher prednisone dose (60 mg/m^2) than in our study (40 mg/m^2). Dexamethasone is more potent than prednisone. The anti-inflammatory effect of 1 mg of dexamethasone is equal to 5-10 mg of prednisone, and an equivalent biological effect is reached in a prednisone (mg)/dexamethasone (mg) ratio [P/D] of 5-10. A P/D ratio of less than 7 results in higher remission rates with dexamethasone, in accordance with increased toxic effects.[2] The P/D ratio in our ALL protocol was 6.6 (40 mg/m^2/day prednisone in the standard-risk protocol compared to 6 mg/m^2/day dexamethasone in the high-risk protocol). This ratio contributed to a higher incidence of toxic effects in subjects who received dexamethasone compared to prednisone in our study. Theoretically, a higher cumulative dose of corticosteroids leads to higher incidence of hypertension in ALL patients undergoing chemotherapy,[2] but we did not observe this pattern in our study. The cross-sectional design of our study may contribute to this finding. Hypertension may not have been detected during the single, blood pressure measurement, but may have occurred later.

We used renal enlargement as a parameter for renal involvement in ALL. Renal ultrasound was performed on 12 of 14 patients with hypertension. Renal enlargement was detected in 1/12 of subjects, much lower than the 23.8% incidence of hypertension caused by renal infiltration in a study by Olgar *et al*.[4] They performed renal ultrasounds on every patient before chemotherapy onset and monitored daily blood

pressure during the induction phase, therefore, renal infiltration could be optimally detected in their ALL patients.

Hyperuricemia in tumor lysis syndrome may result in renal injury and hypertension in ALL patients with hyperleukocytosis.[5,14,15] We did not find a significant association between WBC count and hypertension. The incidence of hypertension was higher in subjects with WBC count <50,000/uL at the time of diagnosis than in subjects with WBC count >50,000/uL. In contrast, Olgar *et al.* showed a 28.6% incidence of tumor lysis syndrome in hypertensive subjects, much higher than the 11.5% incidence in normotensive subjects.[4] We found two subjects with hypertension at the time of diagnosis who had hyperleukocytosis with WBC counts of 384,000/uL and 627,000/uL, respectively. The latter subject had an enlarged kidney, which may have indicated hypertension due to renal infiltration. Of 8 patients with hypertension during the induction phase, only 1 subject had hyperleukocytosis with a WBC count of 362,320/uL at the time of diagnosis. It is possible that hypertension in this study was mainly caused by corticosteroid use rather than hyperleukocytosis. Subjects who had high blood pressure at the time of diagnosis may have had the condition previously, while in subjects with hyperleukocytosis, high WBC count may have contributed to high blood pressure.

In conclusion, the incidence of hypertension in pediatric ALL subjects is 14%, ten-times higher than the incidence in the general pediatric population aged 2-18 years (1-3%). We find no significant associations between hypertension and high-dose corticosteroid use, renal infiltration, or hyperleukocytosis. Hypertension is seen in subjects who receive dexamethasone, but not in subjects who receive prednisone. Routine blood pressure measurements should be done in ALL patients at the first visit, daily during induction-phase chemotherapy, and at every follow-up visit. Prednisone should be the preferred corticosteroid, over dexa-methasone, in induction-phase chemotherapy. We suggest a future cohort study to evaluate renal infiltration and the role of corticosteroid use in pediatric ALL patients with hypertension.

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Acknowledgments

The Editorial Board would like to thank the following physicians and other healthcare professionals for contributing their time and expertise to the review of manuscripts submitted to Paediatrica Indonesiana from January 2014 to November 2014.

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Erratum

Issue : Vol. 52 No. 2 March 2014
Title : Anemia among children and adolescents in a rural area
Author : Ivan Riyanto Widjaja[1], Felix Firyanto Widjaja[2], Lucyana Alim Santoso[2], Erick Wonggokusuma[1], Oktaviati[1]
Page : 89
Erratum : The Mentzer[15] (MCV/RBC) and England & Fraser indices[16] (MCV-RBC-5*Hb) should **be MCV-RBC-(5xHb)-3.4**
For the Mentzer index a score of ≥3 was considered to be IDA.[15] should be a score of **>13**