Original Article

Clinical and laboratory effects of exchange transfusion in pediatric acute lymphoblastic leukemia with hyperleukocytosis

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Abstract

Background Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Emergency complications such as hyperleukocytosis can arise as the disease develops. Exchange transfusion is one of many cytoreductive modalities to resolve the condition.

Objective To analyze the clinical and laboratory effects of exchange transfusion in childhood acute lymphoblastic leukemia patients with hyperleukocytosis.

Methods This analytical retrospective cohort study with a pre- and post-test design used secondary medical record data. The obtained characteristics were the incidences of dyspnea, tachypnea, headache, intracranial bleeding, hepatomegaly, splenomegaly, lymphadenopathy, abdominal pain, fever, pallor, nausea/vomiting, and skin or mucosal bleeding; hemoglobin, white blood cell, and platelet counts; and serum potassium, sodium, calcium, phosphate, blood urea nitrogen, and creatinine levels.

Results A total of 16 patients underwent exchange transfusion; they had significant reductions of the incidence of dyspnea, tachypnea, hepatomegaly, and pallor and significant improvement in the form of elevation of hemoglobin level and decrease in white blood cell counts (P<0.05 for all) compared to pre-treatment. The remainder of the variables were not significantly different between pre- and post-treatment, but a general decrease in all clinical manifestations except intracranial bleeding was observed.

Conclusion Exchange transfusion has the beneficial effect of resolving hyperleukocytosis and its manifestations, although correction in laboratory outcomes that remained abnormal are still needed. [Paediatr Indones. 2023;63:464-71; DOI: https://doi.org/10.14238/pi63.6.2023.464-71].

Keywords: *acute lymphoblastic leukemia; childhood ALL; pediatric; exchange transfusion*

Acute lymphoblastic leukemia (ALL) is the most prevalent malignancy in children worldwide. Children aged 0-14 years comprise 80% of cases and adolescents aged 15 to 19 years comprise 56% of cases.[1] ALL emerges from abnormal proliferation of lymphoid progenitor cells as a result of somatic mutation in one of the developmental phases.[1,2] The growth of immature lymphoid cells in the bone marrow, peripheral blood, and other organs is the hallmark of this heterogeneous hematologic illness.[3] Some factors have been linked to an increased risk of ALL, including prenatal exposure to X-rays, genetic conditions (Down syndrome, comprising a cumulative risk of approximately 2.1% by 5 years of age and increasing to 30 years of age), and exposure to high doses of radiation or chemotherapy.[4-7] With the recent advances in the understanding ALL pathophysiology, treatments have demonstrated greater success and efficacy. Studies have shown improved 5-year overall survival rates exceeding 90%, and the current

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treatment is considered to be well-tolerated and does not impair survivors' quality of life.[8,9] Even with such significantly satisfactory outcomes, complications and emergencies in ALL still require immense consideration. Hyperleukocytosis, reported in 9-13% of children with ALL, is one of the complications and a risk factor for early morbidity and mortality, as well as poor outcomes.[10,11] Hyperleukocytosis has an event-free survival rate as low as 63.3%, *vs.* 100% in patients with a white blood cell (WBC) count below $100x10^9$/L.[11-13] Patients who initially present with hyperleukocytosis are also at risk of developing early problems, resulting in a 20% death rate during remission induction treatment.[12-14] Nevertheless, very few studies, notably in Surabaya, Indonesia, have attempted to address this problem.

Hyperleukocytosis can be defined as a condition in which the peripheral leukocyte count exceeds $100x10^9$/L. High leukemic blast counts in the blood can induce increased blood viscosity, leukocyte aggregation, as well as microvascular clumping and obstruction. All of these conditions can lead to further life-threatening issues for the patient, such as leukostasis and tumor lysis syndrome (TLS).[10,13] Leukostasis, which manifests as respiratory and neurologic complications, is present in <10% of patients with a leukocyte count below $400x10^9$/L.[12] This syndrome, which presents as hyperkalemia, hyperphosphatemia, and hypocalcemia, is the result of rapid cancer cell turnover that releases intracellular ions. ALL is classified as "high-risk tumors" on account of its TLS prevalence, ranging from 5.2 to 23%.[15] Hyperleukocytosis, especially if complicated with leukostasis or TLS, can lead to rapid deterioration of the patient's condition and constitutes a hematologic emergency requiring immediate cytoreductive treatment besides hyperhydration and alkalinization therapy, in order to promptly reduce lymphoblast count.[16] Exchange transfusion is one of the cytoreduction modalities that can reduce blast count from peripheral circulation up to 85%, compared to leukopheresis, which only causes a 30-60% reduction.[17] Other studies also reported that blast reduction was shown earlier in exchange transfusion, which can benefit coagulation abnormalities and anemia correction.[18,19] We aimed to evaluate the clinical and laboratory response of exchange transfusion therapy in childhood ALL patients with hyperleukocytosis. The results of this study are expected to lead to recommendations for management of hyperleukocytosis to improve prognosis and prevent further morbidity and mortality in ALL.

Methods

This retrospective, observational study compared patient variables, pre- and post-exchange transfusion, to evaluate for significant clinical or laboratory changes. The study was conducted in the Pediatric Department of RSUD. Dr. Soetomo, Surabaya, East Java, on children with ALL admitted from January 2019 to July 2021. The data were obtained from medical records of all childhood ALL patients presenting with hyperleukocytosis to our facility and who underwent exchange transfusion within the time frame specified. The inclusion criteria were ALL patients aged 0-19 years with leukocyte counts above $100x10^9$/L, treated with exchange transfusion, and complete medical records of the pre- and post-therapy clinical and laboratory data. The exclusion criteria was medical records that lacked data outcomes., death before the exchange This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Airlangga.

The observed variables consisted of a dependent variable which was exchange transfusion, and independent variables, such as clinical manifestations (the presence of dyspnea, tachypnea, headache, intracranial bleeding, organ enlargement, abdominal pain, fever, pallor, nausea/vomiting, or skin and mucosal bleeding) and laboratory findings (hemoglobin, WBC, platelets, uric acid, potassium, sodium, phosphate, calcium, serum BUN, and serum creatinine level). The data were then pooled in Microsoft Excel and analyzed in *SPSS version 19* (*IBM, USA*) software using parametric and non-parametric tests, according to the data type and distribution, which were Wilcoxon test or paired T-test and McNemar test, respectively.

Results

This study was conducted in 16 patients who underwent exchange transfusion: 10/16 patients

were treated once, 2/16 patients twice, 2/16 patients four times, one of 16 patient five times, and 1/16 patient six times. Of the potentially elgible 72 patients examined for eligibility, 42 were confirmed eligible, 26 were excluded due to exclusion criteria, and the remaining 16 were included and analyzed further. From 16 subjects, the total number of exchange transfusion episodes was 33.

Demographic characteristics of subjects are displayed in **Table 1**. The majority of patients were aged 1 to 10 years. The youngest patient was 1 year 7 months, and the oldest patient was 16 years 1 month, with a female: male ratio of of 1: 2.2. The most common type of ALL in patients was type L1 (13/16 subjects).

Clinical response data were analyzed by McNemar test (**Table 2**). In 21/33 pisodes, new clinical manifestations presented post-exchange therapy that were not present pre-exchange therapy (headache, hepatomegaly, abdominal pain, fever, nausea/vomiting, as well as skin and mucosal bleeding), with the rest being a continuation of symptoms from pre-exchange therapy. The most significant decrease in frequency and percentage was in the clinical manifestation of tachypnea, from 18/33 episodes to 6/33 episodes. Skin and mucosal bleeding in the above data included petechiae in skin, bleeding and epistaxis, subconjunctival bleeding, and gum, as well as mucosal bleeding. McNemar test revealed statistically significant differences in four clinical manifestations: dyspnea, tachypnea, hepatomegaly, and pallor.

Laboratory response of each laboratory parameter were analyzed by paired T-test for normally distributed data and the Shapiro-Wilk test for non-normally distributed data, as shown in **Table 3**. Significant differences between pre- and post-treatment were found in increased hemoglobin levels (P=0.002) and decreased WBC counts (P=0.001).

Discussion

Most of our subjects ranged in age from 1-10 years (12/16). Similarly, another study reported that 69.8% of their total sample of children with all were aged 1-10 years.[20] Studies in 184 countries also showed

Table 1. Demographic characteristics of subjects

Characteristics	(N=16)
Age group, n	
<1 year	0
1-10 years	12
>10 years	4
Sex, n	
Male	11
Female	5
ALL type, n	
L1	13
L2	2
L3	1

Table 2. Clinical manifestations pre- and post-exchange transfusion in childhood ALL with hyperleukocytosis (N=33)

Clinical manifestations, n	Pre	Post	P value
Dyspnea	8	1	0.016[a]
Tachypnea	18	6	0.000[a]
Headache	18	11	0.210
Intracranial bleeding	1	1	[b]
Splenomegaly	3	0	0.250
Hepatomegaly	10	3	0.039[a]
Lymphadenopathy	3	1	0.500
Abdominal pain	7	2	0.180
Fever	13	8	0.227
Pallor	11	1	0.002[a]
Nausea/vomiting	4	2	0.625
Skin or mucosal bleeding	9	3	0.146

[a]P<0.05 indicates statistical significance; [b]data were not sufficient to be analyzed

Table 3. Laboratory parameters pre- and post-exchange transfusion in childhood ALL with hyperleukocytosis

Laboratory parameter	Pre Mean (SD)	Post Mean (SD)	P value
Hb count, g/dL	9.07 (2.04)	10.75 (1.44)	0.002[a]*
WBC count, /mm³	274.33 (211.93)	179.27 (147.02)	0.001[a]
Platelet count, /mm³	60.37 (47.35)	48.20 (26.28)	0.247
Uric acid level, mg/dL	7.74 (5.16)	7.49 (4.11)	0.665
Serum potassium level, mEq/L	3.29 (0.64)	3.39 (1.33)	0.767
Serum sodium level, mEq/L	136.44 (7.17)	138.41 (4.10)	0.269
Serum calcium level, mEq/L	9.10 (1.97)	8.76 (1.27)	0.105
Serum phosphate level, mEq/L	3.93 (1.53)	3.4 (1.26)	0.083
Serum blood-urea-nitrogen level, mg/dL	12.13 (13.09)	12.03 (13.96)	0.473
Serum creatinine level, mg/dL	0.70 (0.46)	1.53 (4.23)	0.539

[a]P <0.05 indicates statistical significance; *P value was obtained with paired T-test

peaks in the 0-4 year range, but the exact etiology of these findings has not been found, and no studies have discussed it.[21,22] However, there is a hypothesis that the mechanism of infection as a secondary stimulator of preleukemic genetic alterations leads to development of ALL; infections are common in early childhood.[23] In our study, the female: male ratio was 1: 2.2. Other studies also noted high prevalences of ALL in males.[21,22,24] This may be due to mutations in tumor suppressor genes on the X chromosome that lead to gender predisposition in some cancers.[25,26] Mutations of tumor suppressor gene H3K27me3 demethylase UTX, and PHF6 that contribute to ALL formation are linked to the X chromosome. Males have a single X chromosome, but females have two of them so they are less susceptible to X chromosome inactivation than males.[26,27] In addition, another study that examined SNPs in pediatric ALL reported that two ARID5B (AT-rich interactive domain 5b) SNPs (rs10994982 [P = 0.01] and rs10740055 [P = 0.03]) had statistically significant male-specific risk.[28] In our study, the most common morphology type was L1. This morphologic classification of FAB has no relationship or clinical significance to the ALL disease.[29]

The high leukocyte count in ALL patients with hyperleukocytosis can lead to hyperviscosity of the blood and infiltration of leukemic blast cells into other organs. In our study, the symptoms of pulmonary leukostasis included tachypnea (18/33) and dyspnea (8/33). Pulmonary leukostasis, which is the most common complication causing death in leukemia patients, is a condition in which the patient's

WBC count exceeds 100x10⁹/L and the presence of clinical respiratory symptoms include fever, dyspnea, tachypnea, and hypoxia with a degree of severity ranging from mild breathing difficulties to acute respiratory failure and death.[30] The number of blast cells and blast cell attachment to the endothelium are influential in leukostasis; blast cells have a more rigid shape compared to normal white blood cells, and this decreased deformability can lead to microvascular occlusion which results in reduced blood flow and can end in hypoxia of the affected tissue. Exchange transfusion therapy, a cytoreductive measure, reduces respiratory manifestations such as dyspnea and tachypnea and corrects the hyperleukocytosis (P=0.016 and P=0.000, respectively). Previous studies reported that of three pediatric patients with acute leukemia and symptoms of pulmonary leukostasis, all experienced clinical (tachypnea and hypoxemia) and radiologic (presence or absence of pulmonary infiltration) improvement after cytoreductive measures in the form of leukapheresis or exchange transfusion therapy.[18,31] Reduced WBC count is consistent with improvement of complications within 24 to 120 hours after leukapheresis or exchange transfusion therapy.[18] One study noted that respiratory status by arterial-to-alveolar oxygen tension (a/APO₂) ratio improved in ALL patients receiving exchange transfusion therapy, and immediate respiratory support device usage decreased.[32] Large number of WBC require oxygen and can cause a direct decrease in PO2 in the blood.[33]

Coagulation disorders and bleeding are

commonly found in ALL patients as intracranial hemorrhage, as well as skin and mucosal bleeding. Severe menorrhagia and gum bleeding for two weeks stopped after patients received exchange transfusion therapy from six donors.[34] The cessation or reduction of bleeding may be a beneficial effect of new blood with relatively normal leukocyte and platelet counts. In ALL patients, platelet counts are suppressed by the proliferation of immature WBC, such that thrombocytopenia may occur, not only from the pathophysiology of the disease but also from cytotoxic chemotherapy treatment regimens.[34] In addition, the cytoplasm of leukemic blast cells contains procoagulant substances, which can cause thrombin dysfunction and aggravate thrombocytopenia with acute bleeding or thrombosis.[35] Coagulation abnormalities and bleeding improved after several days of exchange transfusion therapy and corresponded to decreased WBC counts. Blood D-dimer, prolonged prothrombin time, and fibrinogen mark the improvement of coagulation-fibrinolysis.[18,31,32]

The clinical manifestations of fever, headache, pallor, and nausea/vomiting are symptomatic sequelae and aggravate of ALL disease. The classic symptoms of leukemia, including high fever, fatigue, pallor, bone pain, and arthralgia, reflect the abnormalities of hematologic insufficiency caused by infiltration of the bone marrow by leukemic blast cells.[36,37] Fever that appears in ALL has no clear pathogenesis. Some hypotheses for the cause of fever include leukemia mechanisms that inhibit the maturation and suppression of erythroid and megakaryocytic cells, causing a decrease in the number of WBC/neutrophils, which makes patients more susceptible to infection and leading to fever; damaged tissue that causes cell death will release endogenous lipopolysaccharide contents which interact with polymorphonuclear cells and produce endogenous pyrogens, and inflammatory responses mediated by Kuffner cells in the liver sinuses, producing interleukin-1 as a pyrogen.[38,39] The decrease in the prevalence of febrile manifestations (P=0.227) may have been due to the decrease in inflammatory cells and cytokines due to blood turnover, but the difference was still not significant because some patients developed fever post-procedure; this could be due to post-action complications or unresolved underlying disease.[35,40]

Headache can be caused by several mechanisms,

one of which is anemia caused by the suppression of erythroid cells and lower oxygen levels reaching the brain. Low oxygen levels in the brain stimulate the surrounding arteries to dilate, thus producing headaches. Mean Hb levels in **Table 3** increased from moderate to mild anemia [9.07 (SD 2.04) and 10.75 (SD 1.44), respectively]. Anemia in patients affects the clinical manifestation of pallor (P=0.002), the development of which can occur acutely and accurately corresponds to the patient's anemic condition.[42] Headaches can also be caused by leukemic blast cell infiltration into the central nervous system and superior vena cava (SVC) syndrome caused by thymus enlargement, affecting blood flow to the brain.[43] However, treatment of ALL can also cause long-term headaches from neurotoxicity and neurological complications. Of 4151 survivors of ALL, 21% experienced persistent headaches.[44,45]

Acute lymphoblastic leukemia is an infiltrative disease. The high number of circulating leukemic blast cells causes their infiltration into organs and subsequent enlargement of these organs, such as in hepatomegaly, splenomegaly, and lymphadenopathy.[46] The size of lymph nodes correlates with the peripheral blood granulocyte count--the higher the white blood cell count, the larger the lymph nodes.[47] High blood turnover of leukemic blast cells with exchange transfusion therapy decreases organ infiltration and reduces hepatomegaly, splenomegaly, and lymphadenopathy (P=0.039; 0.250; 0.500, respectively). The increase in abdominal mass can also cause abdominal discomfort and pain.[46]

Secondary nausea and vomiting come from previous symptoms, such as anemia and leukemic blast cell infiltration, which can cause headaches, blurred vision, as well as liver and lymph enlargement, which causes a feeling of fullness in the stomach, and the occurrence of inflammatory processes by cytokines and the immune system, all three of which lead to nausea and vomiting.[48-50] Abnormalities in electrolyte and metabolic levels, namely hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia, can also cause clinical manifestations of nausea and vomiting.[51,52] Serum potassium levels tended to be low and were not significantly different pre- and post-exchange transfusion therapy (**Table 3**). Mean serum phosphate and serum calcium levels were also normal, but serum uric acid levels were

elevated (hyperuricemia). Serum uric acid levels decreased post-therapy, but not significantly, and remained in the hyperuricemia range. In addition to the above causes, nausea and vomiting can also arise from the short- and long-term effects of therapy for acute lymphoblastic leukemia, such as chemotherapy-induced nausea-vomiting (CINV) side effects.[53] In studies of blood electrolyte and metabolic abnormalities, improvements were found after exchange transfusion therapy or leukapheresis.[18] This finding may have been due to exchange transfusion therapy that reduces leukemic blast cells and substitutes plasma with normal new plasma that can support electrolyte and metabolic correction.[18,54] This is an advantage of exchange transfusion therapy over leukapheresis or other cytoreductive therapies, as anemia and metabolic abnormalities will be corrected along with leukocyte reduction.[18]

A limitation of our study was that our clinical manifestation data was obtained from medical records, so it was prone to subjectivity in observation and documentation. Also, our study was limited to immediate outcomes, so further study should be conducted on long-term effects.

In conclusion, exchange transfusion can improve clinical and laboratory manifestations of childhood ALL with hyperleukocytosis. Moreover, exchange transfusion produces statistically significant reductions in the incidence of dyspnea, tachypnea, hepatomegaly, and pallor, while increasing hemoglobin level and decreasing WBC count as an immediate response. A prospective study should be conducted, and a comparison with other cytoreductive modalities is needed.

Conflict of interest

None declared.

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