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*Original Article*

# EFFECTIVENESS OF DEXAMETHASONE COMPARED WITH PREDNISOLONE IN INDUCTION THERAPY OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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## Abstract:

**Background: Corticosteroids are an essential component of treatment for acute lymphoblastic leukemia (ALL). Prednisolone is the most commonly used steroid. There is increasing evidence that, even in equipotent dosage for glucocorticoid effect, dexamethasone has enhanced lymphoblast cytotoxicity and penetration of central nervous system compared with prednisolone.**

**Objectives: To determine the effect of dexamethasone and prednisolone and to compare them in induction therapy of ALL in Children.**

***Material & Methods*: A total of 60 newly diagnosed cases of ALL confirmed by bone marrow study, children of either sex with age >1 year were included in this study. Variables studied were age, sex, presenting features, neutrophil count, blast cell count, platelet count, bone marrow status at diagnosis, on D15 & D29 of induction and side effects.**

***Results:* Mean age of the patients of group A was 6.28 years & that of group B was 7.2 years. Out of all patients of group A 19 (63.3%) were male and 11 (36.7%) were female. In group B 21 (70.0%) patients were male and rests 9 (30.3%) were female. No statistically significant difference was observed in both groups in terms of age, sex & presenting features. After induction significant difference was observed in liver & spleen size at day 7 and day 15. All patients of both groups had M3 marrow status at diagnosis. Overall, in group A 93.3% patients achieved M1 marrow status (fewer than 5% blasts) and 6.7% had M2 marrow status (5-25% blasts) at day 15 of induction. On the other side 66.7% patients of group B achieved M1 status and 33.3% M2 status at day 15. Statistically significant difference was observed between groups on day 15 in term of achieved marrow status ($p<0.05$). No statistically significant difference was observed between groups in term of infection in difference days of induction. On day 16 of induction maximum incidence of infection was observed in both groups.**

**Conclusion: Dexamethasone may be an effective alternative option to prednisolone for the treatment of acute lymphoblastic leukemia in children.**

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## Introduction:

Leukemia is a disease resulting from the neoplastic proliferation of hemopoietic or lymphoid cells. It results from a mutation in a single stem cell, the progeny of which form a clone of leukemic cells. Often there is a series of genetic alterations rather than a single event. Genetic events contributing to malignant transformation include inappropriate expression of oncogenes and loss of function of cancer suppressor genes. The cell in which the leukemic transformation occurs may be a lymphoid precursor, a myeloid precursor or pluripotent stem cells capable of differentiating into both myeloid and lymphoid cells[1].

The vast majority of childhood leukemia are acute, accounting almost one third of childhood malignancies[2]. The most common subtype, acute lymphoblastic leukemia (ALL) accounts for 70%-80% of all cases, with acute myeloid leukemia (AML) comprising approximately 20% and chronic myeloid leukemia (CML) 2% of cases. Substantial geographic variation exists in childhood leukemia incidence rate. Annual incidence of childhood ALL range from 9 to 47 per million for male and 7 to 43 per million for females worldwide. Incidence rate for ALL are highest in Israel, United States, Australia, Costa Rica & Germany and lowest in India[3].

Acute leukemia are characterized by a defect in maturation leading to an imbalance between proliferation and maturation; since cells of the leukemic clone continue to proliferate without maturing to end cells and dying, there is continued expansion of the leukemic clone and immature cells predominate[1]. The clinical presentation of ALL is determined by the degree of marrow failure, caused by the infiltration of lymphoblast and extramedullary organ infiltration. About two thirds of children with ALL will have signs and symptoms of disease for less than 4 weeks at the time of diagnosis. However, a history of some months is to compatible with the diagnosis of ALL. The first symptoms are usually nonspecific and include lethargy, rapid exhaustion or lack of appetite. More specific symptoms such as anemia, hemorrhage and infection are the consequences of lymphoblast occupying the bone marrow and disturbing the residual normal hematopoiesis[4].

The WBC (white blood corpuscles) count at presentation is a highly significant prognostic variable with the recognition of distinct prognostic subgroups, contemporary protocols stratify children with ALL into groups designated “high-risk”or “standard-risk”. Risk classification is based, in part, on clinical features, the most important of which are presenting age and leukocyte count[5].Participants of a workshop sponsored by the National Cancer institute defined standard-risk ALL cases with age between one and ten years and an initial leukocyte count of less than $50x10^9$/L . Childhood ALL is not a single disease, but a group of diseases with a variety of genetic aberrations in the leukemic blasts, leading to a wide range of clinical presentations and outcomes. The first features used in risk classification were WBC count (leukemia burden) at diagnosis and the age of the patient. These features are still included in the modern risk assessment. In the future, immunologic and genetic markers of the disease may possibly replace WBC and age[6].

The tumor burden of leukemia is also a marker of its biological characteristics. Children with high WBC at the first presentation have a rapid disease with high proliferation rates of the leukemic blasts. In contrast children with low WBC count at diagnosis may have low hemoglobin and platelets level, which have for a long time interfered with the production of normal precursors of blood cells [6].

Risk adapted polychemotherapy for children with acute lymphoblastic leukemia is the basis of success stories in modern clinical oncology. Identification of risk factors therefore, is very important. There are some recognized risk factors in childhood ALL. Some of the recent studies showed that early response to induction therapy is a predictor of disease free survival (DFS) and late recurrence of childhood acute lymphoblastic leukemia[7].

For many years high leukemic tumor burden has been recognized as one of the most important independent risk factors. Recently many studies have suggested that the rapidity of response in initial induction therapy in childhood acute lymphoblastic leukemia, as determined by the degree of lymphoblast cytoreduction in first 1 to 2 weeks of treatment,is an important predictor of disease free survival ( DFS ) in patients achieving complete remission[8].Literature search reveals that persistence of circulating blasts after 1 week of multiagent chemotherapy confers a poor prognosis in childhood acute lymphoblastic leukemia[9].

Corticosteroids are an essential component of treatment for ALL. Prednisolone is the most commonly used steroid. Therefore the importance of the rapidity of cytoreduction on initial tumor load was felt. There is increasing evidence that, even in equipotent dosage for glucocorticoid effect, dexamethasone has enhanced lymphoblast cytotoxicity and penetration of central nervous system compared with prednisolone[10].

In CCG-1922, two hypotheses were tested. The first hypotheses was that dexamethasone will be superior

to prednisolone in preventing central nervous system (CNS) relapse and provide better event-free survival (EFS). Although in terms of conventional glucocorticoid activity, dexamethasone is only 6.25 times more potent than prednisolone; the MTT (3-2. 5- diphenyltetrazolium bromide) assay suggests a 16-fold gain in potency against lymphoblasts[11]. In addition, it has been suggested that dexamethasone has better penetration of the central nervous system (CNS)[12] and there is clinical evidence that substitution of prednisolone by dexamethasone result in a lower incidence of meningeal leukemia[13]. For example, the Dutch ALL study VI substituted dexamethmsone for prednisolone with major gains in EFS compared with their historical experience (3-years EFS 66% for the comparable study V vs. 80% for patients entered into study VI)[14]. The cancer and Leukemia Group B (CALGB), also in a historical comparison, found that children assigned to dexamethasone had a lower CNS relapse rate than those assigned to prednisolone, although the EFS for the two groups was similar.

Treatment of ALL in children still remains very complicated. For many years, different centers all over the world are trying to adopt simplified and uniform measures to treat ALL. Until now, with the advent of a number of new chemotherapeutic agents, as well as different treatment schedules, a great success has been achieved. To reach the ultimate goal, stratification on the basis of prognosis is a very important aspect. However, still we have to find out suitable strategy of stratification, which should be simple, effective, easily available and applicable.

Most of the authors used prednisolone in induction of childhood ALL, very few in the past, were seen using dexamethasone in induction chemotherapy of childhood ALL. It is universally accepted that response to chemotherapy in induction of remission is a vital one to affect the outcome of ALL chemotherapy. But studies are hardly available to have comparison between the effects of dexemethasone with that of prednisolone in induction of remission in ALL in children. No such study has yet been done in Bangladesh. Therefore, it was decided to carry out a randomized controlled trail to compare the effectiveness of dexamethasone with that of prednisolone in induction therapy of childhood acute lymphoblastic leukemia.

**Methodology:**

This was a randomized controlled trial study conducted in the Pediatric Hematology & Oncology Unit of Department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU), from March 2006 to March 2007.

Newly diagnosed cases of ALL (Acute lymphoblastic leukemia) Confirmed by bone marrow study and children of either sex with age >1 year were included in this study.CNS diseases at diagnosis, very sick child requiring immediate medical care, Parents refusal to be included in the study were excluded. A total of sixty (60) Patients of ALL were enrolled in this study, placed in either group randomly. “Group A” received dexamethasone, 6.5 mg/$m^2$ /day in divided doses. “Group B” received prednisolone, 60 mg/$m^2$ / day in divided doses.

Other medications of induction of remission of ALL started according to a standard protocol in both groups. Variables considered were age, sex, presenting features, liver & spleen size, hemoglobin level, neutrophil count, peripheral blast cell count, platelet count , marrow status at diagnosis, on D15 & D29 of induction, FAB type, side effects like infections, hemorrhage and neutropenia. Patients were followed up clinically daily for pallor, skin bleeding, mucus membrane bleeding, liver & spleen size ; laboratory investigations for hemoglobin level , neutrophil count , platelet count , peripheral blast cell count etc. on D8, D16, D22 & D28 of induction and bone marrow status at diagnosis, on D15 & D29. All the finding were recorded in data sheet.

All the data were subjected to statistical analysis according to standard procedure. SPSS version 13.0 was used for statistical analysis.

To identify the correlation between two groups of values Pearson’s bivariate correlation test was performed. To compare the mean and SEM of two different groups of ALL, independent sample t-test or paired sample t-test was done, as required. Pearson’s Chi-square test was used to analysis the relationship of response of ALL to chemotherapy dexamethasone with (i) initial WBC count, (ii) initial blast cell count and (iii) response to chemotherapy. The test (Pearson’s Chi-square test) was also done to analyze the relationship of initial WBC count and response to induction chemotherapy. P value less than 0.05 and 95% confidence interval (CI) were used as the level of significance.

**Results:**

Out of all patients of group A 19 (63.3%) were male and 11 (36.7%) were female. In group B 21 (70.0%) patients were male and rests 9 (30.3%) were female. Mean age of the patients of group A was 6.28 years with a standard deviation of ±3.23 years. In group B mean age was 7.2 years with a standard deviation of ± 3.43 years . Maximum (53.4%) patients of group A were belonged to 1 to 6 years age range whereas in group B maximum (60%) patients were 6 to 9 years age range. Maximum presenting feature of patients of both groups was pallor. 96.7% patient of group A and similar number from group B had pallor. Next highest presenting feature was fever, 86.7% for group A and 83.3% for group B, followed by organomegaly (76.7% VS. 73.3%), skin rash (63.3% vs. 70.0%), and bony tenderness (33.35% vs. 26.7%). Other features were mucus membrane bleeding, gum bleeding and edema. Maximum patients of group A (53.3%) and group B (4.7%) had 3 to 5 cm enlarged liver. During induction liver size of the patients of both groups had gradually decreased, but statistically significant difference was observed at Day 7 and Day 15. At Day 22 liver sizes of all patients of both groups were found normal (not enlarged). 26.7 % patients of group A and 36.7 % of group B had 3 to 5 cm enlarged spleen at diagnosis. During induction, spleen size of the patients of both groups had gradually decreased but statistically significant difference was observed at Day 7 and Day 15.

All patients of both groups had M3 marrow status at diagnosis. Overall, in group A 93.3% patients achieved M1 marrow status (fewer than 5% blasts) and 6.7% had M2 marrow status (5-25% blasts) at day 15 of induction. On the other side 66.7% patients of group B achieved M1 status and 33.3% M2 status at day 15. Statistically significant difference was observed between groups on day 15 in term of achieved marrow status ($p<0.05\%$). No statistically significant differences were observed between groups in term of infection in difference days of induction. On day 16 of induction maximum incidence of infection was observed in both groups. On that day 23.3% of group A and 40.0% of group B patients had infection.

Hemorrhage was observed more on day 16 of induction 3.3% patient of group A and 13.3% of group B had hemorrhage.

**Table-I**

*Sex distribution of the patients.*

| Sex | Group | |
|---|---|---|
| | Gr. A (Dexamethasone) | Gr. B (Prednisolone) |
| Male | 19 (63.3)* | 21 (70.0) |
| Female | 11 (36.7) | 9 (30.0) |
| Total | 30(100.0) | 30(100.0) |

**Table II**

*Age distribution of the patients.*

| Age range of the Patients yrs | Group Gr.A Dexamethasone | Gr.B PredniSone |
|---|---|---|
| 1-3 | 8 (26.7)# | 5 (16.7) |
| 3-6 | 8 (26.7) | 7 (23.3) |
| 6-9 | 8 (26.7) | 9 (30.0) |
| 9-13 | 6 (20.0) | 9 (30.0) |
| Total | 30 (100.0) | 30 (100.0) |
| Mean ±SD range) | 6.28±3.23 (1.5-13) | 7.2±3.432-13)* |

**Discussion:**

Glucocorticoids are highly cytotoxic to lymphoblasts and thus have been a key component of treatment regimens for acute lymphoblastic leukemia (ALL) for many decades. Prednisone has been the most commonly used of these compounds in ALL therapy. Among other oral synthetic glucocorticoids, dexamethasone may be more effective because of its increased half life, longer duration of biologic action and higher CSF to-plasma ratio[15]. Glucocorticoids differ considerably in their estimated glucocorticoid and mineralocorticoid potencies and plasma half life. The determination of bioequivalence among corticosteroid congeners has often yielded discordant results. Generally, 1 mg of dexamethasone has been considered to be equivalent to 5 to 10 mg of prednisone, and a single dose of dexamethasone appears to be six to nine times more potent than prednisone (or its biologically active metabolite prednisolone) in reducing inflammation. Recently, studies with the 3-2.5-diphenyl tetrazolium bromide (MTT) assay indicated that the relative antileukemic activity of dexamethasone was considerable greater

than would be predicted from the anti inflammatory effects, that is, a single dose of dexamethasone had a median of 38 times the antieukemic potency of prednisolone. Thus, dexamethasone administered at currently recommended dosages possesses greater antieukemic potency than prednisone, which would account for the better clinical responses observed by some investigators. Conceivable much lower doses of dexamethasone could produce clinical responses similar to those obtained with prednisone, with fewer adverse side effects[16].

In present study randomly enrolled 60 patients in whom 30 were in group A for dexamethasone and 30 in group B for prednisolone. All patients were 1.5 to 13 years age range. Mean age of the patients of group A was 6.28±3.23 years and group B was 7.2 ± 3.43. Maximum patients of both groups were male with a male and female ratio in group A was 1.73: 1 and group B was 2.33:1. No significant difference was seen in both groups.

The most common presenting symptom of this study subjects was pallor. 96.7% patient of group A and similar number from B had pallor. Next highest presenting feature was fever, 86.7% for group A and 83.3% for group B, followed by organomegaly (76.7% VS. 73.3%), skin rash (63.3% vs. 70.0%), and bony tenderness (33.35% vs. 73.3%). Other features were mucus membrane bleeding, gum bleeding and edema.There was no significance diferance was seen in both groups.

In present series at diagnosis 7 (23.3%) patients of group A and 3 (10%) patients of group B had normal liver (not enlarged ). Rests had enlarged liver of varying size. Maximum patients of group A (53.3%) and group B (46.7%) had 3 to 5 cm enlarged liver. During induction liver size of the patients of both groups had gradually decreased but statistically significant difference was observed at Day 7 and Day 15 with a p value of 0.04 and 0.011 respectively. At Day 22 liver sizes of all patients of both groups were found normal (not enlarged). No further enlargement was observed at Day 29. At diagnosis 15 (50.0%) patients of group A and 11(36.7%) patients of group B had normal spleen (not enlarged). Rests had enlarged spleen of varying size. 26.7% patients of group A and 36.7% of group B had 3 to 5 cm enlarged spleen at diagnosis. During induction of remission spleen size of the patients of both groups had gradually decreased, but statistically significant difference was observed at Day 7 and Day 15. At Day 22 spleen sizes of all patients of both groups were found normal (not enlarged). No further enlargement was observed at Day 29.

In this study it was observed that during induction of remission Hb level of both groups were gradually increased. However this initial rise of Hb level in both groups were due to packed cell transfusion. As 9 patients of groups A and 7 patients of Group B received transfusion before Day 8 of induction. At diagnosis mean total count of WBC of group A was 39.13±45.46 ($x10^9$/L) and group B was 42.42±35.38($x10^9$/L). During induction of remission total counts was sharply declined at Day 8 and continued up to last follow-up. No significant differences were observed between groups at different follow-ups day ($p>0.05$).

At diagnosis no statistically significant difference of neutrophil count was observed in patients of both groups. Mean neutrophil count at diagnosis was observed in patients of both groups. Mean neutrophil count at diagnosis was 17.83±6.65 in group A and 14.83±5.33 in group B. During induction significant difference was observed in both groups in all follow-ups in terms of neutrophil count. Mean blast cell of group A was 40.4±19.14 and group B was 50.0±20.29 at diagnosis . At Day 8 mean blast cell of group A was 1.1±2.44 and group B was 4.43±4.31 ($p<0.05$). No blast cell was found on subsequent follow-ups.

The benefit was apparent in present series for Day 15 M1,M2 & M3 marrow status of patients of group A who were treated with dexamethasone. All patients of both groups of present study had M3 marrow status at diagnosis. Overall, in group A (Dexamethasone) 93.3% patient achieved M1 marrow status (<5% blasts) and 6.7% had M2 Marrow status (5%-25% blasts) at Day 15 of induction. On the other side 66.7 % patients of groups B (prednisolone) achieved M1 status and 33.3% M2 status at Day 15. Statistically significant difference was observed between groups on Day15 in term of achieved marrow status ($p<0.05$). At the end of induction (at Day 29) all patients of both groups had M1 marrow status.

Blast percentage in marrow was determined by Bostrom et al (2003)[17]which was nearly consistent with findings of present study. Overall, 53% of all patients achieved M1 marrow status (fewer than 5 % blasts); 25% of patients had M2 marrow status (5%-

25% blasts); and 22% had M3 status (>25% blasts). There was no difference in Day 7 marrow response or induction end marrow status by randomized steroid. At the end of the induction phase, 99% of patients had M1 marrow status, 10 had M2 marrow status and one had M3 marrow status.

Marrow response on Day 7 of therapy also was a significant prognostic factor (p= 0.002). Bostrom et al[17] found worse outcome for patients with M2 (RR= 1.59) or M3 (RR= 1.82) versus M1 marrow status. Dexamethasone was found superior to prednisone for patients with Day 7 M1 marrow status, M2 marrow status and M3 marrow status.

The CCG-141 trial accrued infants, children and adolescents with ALL of all prognostic strata between 1974 and 1978. Miller et al. (1983)[10] reported that 22% of children who had >25% marrow blasts (marrow rating: M3) on Day 14 of treatment with vincristine, prednisone and L-asparaginase (VPL) failed to achieve remission on Day 28 versus 3 % and 6 % of children with <5 % (marrow rating: M1) and 5-25% (marrow rating: M2 ) marrow blasts, respectively, on Day 14. Children with an M3 marrow on Day 14 who nonetheless achieved remission by Day 28 still had a worse subsequent DFS than children with M1 or M2 marrows on Day 14.

In a study Steinherz et al (1996)[18] stated that on the New York (NY) regimen, 68%, 14% and 18%, and on the Berlin-Frankfurt-Munster (BFM) regimen, 56%,15% and 29% of patients had M1 (<5% blasts), M2 (5%-25%), or M3 (>25%) responses on Day 7 (p= .075). On Day 14, the corresponding values were 87%, 6%, 7% on NY and 84%, 8%, 8% on BFM. For patients who achieved remission by Day 28 and a Day 7 marrow rating of M1, M2, or M3, the 6-year EFS rate was 78%, 61%, and 49% (p< .001). The day14 ratings predicted for a 72%, 32%, or 40%EFS (p<.001). Patients with 5% to 10% blasts on Day 7 had three times as many events as those with less 5% and had no better EFS than those with 11% to 25% blasts. They concluded that marrow aspiration on Day 7 of therapy provided more useful information than that on Day 14. However, Day 14 marrow provided additional information for patients with a poor Day 7 response. The rate of cytoreduction is a powerful, independent prognostic factor that can identify patients with a slow early response who are at risk for short remission duration.

Common side effects observed in present series were infection, haemorrhage, neutropenia. No statistically significant difference were observed between groups in terms of these side effects. However psychological assessment of the patients was not done and no complaints about avascular necrosis of femoral head found.

Patients assigned to dexamethasone or prednisone had identical incidence of bacteremia during induction (13%) as described by Bostrom et al[17] was consistent with findings of this study.

But result of present study was different from Mitchell et al[10]. They found significant excess of overall toxicity in the dexamethasone group (11% vs. 5% with prednisolone). This consisted principally of an excess of behavioral problems, myopathy, osteopenia and other toxicity (especially excess weight gain and acute liver enlargement). Treatment was changed from dexamethasone to prednisolone in 6% of patients because of unacceptable side effects.

Hurwitz et al[19] described an increased incidence of gram-negative bacteremia and induction death in a group of patients who received dexamethasone during induction compared with historical controls who received prednisone. In contrast, in present study there was no difference in infectious complication during induction. Hurwitz et al[19] used doxorubicin during induction, unlike this trial, which might have deepened neutropenia and delayed neutrophil recovery.

**Conclusion:**

Dexamethasone may be an effective alternative option for the treatment of acute lymphoblastic leukemia in children. Early response with no statistical significant difference in side effects makes this steroid in comparison with prednisolone as a better addition to the therapeutic armamentarium for childhood acute lymphoblastic leukemia.

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