

Efficacy and Safety of Levofloxacin Prophylaxis during Induction Therapy for Childhood Acute Lymphoblastic Leukemia

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Abstract

Background: Infection related complications represent an important cause of morbidity and mortality in pediatric cancer patients, especially in those receiving chemotherapy. Although antibiotic prophylaxis is used in adult leukemic patients, but it is less practiced in pediatric cancer patients. The aim of this study was to evaluate the efficacy and safety of Levofloxacin prophylaxis to reduce infection which occur during induction phase of chemotherapy among pediatric Acute Lymphoblastic Leukemia (ALL) patients.

Materials and methods: This single centered, pilot study in RCT design was conducted in Pediatric Hemato-Oncology Department of Chittagong Medical College Hospital (CMCH). Sixty newly diagnosed ALL patients admitted for chemotherapy were randomly allocated to two groups 30 in each: one group received Levofloxacin prophylaxis (Intervention group) and other group did not receive prophylaxis (Control group). During the whole period of induction, clinical and laboratory features of infection, fever and neutropenia were observed and adverse effects were noted in both groups.

Results: In induction phase of chemotherapy of ALL, significantly lower proportion of patients developed fever in the intervention group than in the control group [(18/30, 60.00%) versus (26/30, 86.67%)]. Incidence of infection was significantly less in intervention group compared to control group (60% versus 86.7%, $p=0.039$). Also, incidence of febrile neutropenia was significantly less in intervention group compared to control group ($p=0.039$). No major adverse effects were observed in any of the levofloxacin prophylaxis group except only two patients reported mild lower limb pain.

Conclusion: It may be concluded from this pilot study that, Levofloxacin prophylaxis in children with ALL during the induction phase of chemotherapy is effective in reducing infection, febrile episodes and febrile neutropenia.

Key words : ALL; Febrile neutropenia; Levofloxacin.

Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common childhood cancer globally.¹ The outcome of children with leukemia has improved substantially since the introduction of “total therapy” at St. Jude Children Research Hospital in 1972.² Earlier, no remission was achieved in children with hematologic malignancies, and they all died within months of diagnosis. Since early 1980s, the 5-year Event Free Survival (EFS) of ALL has increased from 57% to 78% in the European countries.³

Treatment of children with ALL is divided into several stages: remission of induction, consolidation or intensification and maintenance (Continuation) therapy with central nervous system (CNS) prophylaxis therapy generally provided in each stage. The goal of induction therapy is to bring the disease into remission, that is patient’s blood counts return to normal and bone marrow shows no signs of disease. Usually induction therapy using vincristine, prednisolone/dexamethasone, plus L-asparaginase in conjunction with intrathecal chemotherapy results in complete remission rates of greater than 95%.^{4,5}

Chemotherapy-Induced Neutropenia (CIN) is the most serious hematological toxicity of cancer chemotherapy.⁶ CIN is associated with the risk of life-threatening infections, as neutropenia blunts the inflammatory response, allowing bacterial multiplication and invasion.⁷ Infection in a neutropenic patient is very difficult to evaluate because the normal inflammatory response to the infecting microorganism is blunted. Fever may be the only presenting sign of infection. The onset of fever in a neutropenic patient is an indication for empiric initiation of high dose parenteral, broad-spectrum antibiotic therapy to control the illness and reducing the chance of morbidity due to infection.

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Primary antibacterial prophylaxis during chemotherapy related neutropenia in adults reduces Clinically Documented Infection (CDI) Microbiologically Documented Infection (MDI) and infection related mortality.⁸ The US National Comprehensive Cancer Network recommends antibacterial prophylaxis with levofloxacin, a broad-spectrum fluoroquinolone, for adult patients with acute leukemia.

In the pediatric ALL population data supporting the efficacy and safety of primary antibacterial prophylaxis is insufficient. There are a few published studies of antibacterial prophylaxis with fluoroquinolones for pediatric ALL patients. Wolf et al. examined the effects of primary antibacterial prophylaxis with Levofloxacin on serious infections and antibiotic exposure in children underwent induction therapy for ALL.⁹ They observed that, all prophylaxis regimens, including Levofloxacin, reduced the risk of febrile neutropenia and systemic infection, but Levofloxacin prophylaxis also shifted antibiotic use away from agents typically used to treat infection and dramatically reduced the risk of enterocolitis and *C. difficile* infection.

Study regarding antibiotic prophylaxis in pediatric ALL patients, with Levofloxacin is limited in Bangladesh. Rahman & Khan conducted a prospective, randomized, placebo controlled, single-blinded study to assess the efficacy and safety of prophylaxis with oral levofloxacin in chemotherapy-induced febrile neutropenic adult patients during July 2006 to October 2007.¹⁰ They found that, Levofloxacin reduced the bacterial infections and delays the onset of fever in CIN especially in short duration. Shireen carried out a study in children with cancer to see the efficacy of prophylactic oral levofloxacin in reducing the bacterial infection. The author reported that, Levofloxacin prophylaxis in children with ALL or NHL during the intensive chemotherapy was effective and well tolerated.¹¹

Fluoroquinolones have a very good spectrum of activity. Levofloxacin belongs to fluoroquinolones groups. It has drawn much interest because of their broad antimicrobial spectrum, systemic bacterial activities, and tolerability, bioavailability, high therapeutic index and lack of myelosuppression. They are active against several clinically important aerobic Gram-negative bacilli

like those belonging to Enterobacteriaceae (e.g. *E. coli* and *Pseudomonas aeruginosa*). They are also active against Gram positive cocci like *S. pneumoniae*, *S. aureus* and beta haemolytic streptococci. *H. influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumoniae* are also susceptible but anaerobic cover is limited. It is also cheap and has less adverse effects.¹² Therefore, it is expected that, addition of levofloxacin as prophylaxis from the beginning of chemotherapy protocol would reduce the rate of infection and morbidity and mortality as well.

In this context, the current study was aimed to identify the effects of antibacterial prophylaxis with Levofloxacin in preventing the infection related morbidity and mortality during the induction phase of chemotherapy in pediatric ALL patients. And to observe any adverse effects of levofloxacin prophylaxis on pediatric ALL patients.

Materials and methods

This pilot study with randomized control trial design was conducted in the department of Pediatric Hemato-Oncology, Microbiology, Pharmacology & Therapeutics of Chittagong Medical College Hospital (CMCH) Chattogram, from May 2019 to April 2020. Sixty newly diagnosed ALL patients admitted for induction chemotherapy during the study period were included in the study. All the consecutive ALL patients were screened by the following criteria to select eligible patients for randomization.

Inclusion criteria:

- i) Newly diagnosed ALL patients admitted for induction chemotherapy.
- ii) Age 1 to 12 years and of both sexes.

Exclusion criteria:

- i) Patients with a known history of hypersensitivity to fluoroquinolones.
- ii) Patients with history of chronic arthritis or suffering from chronic active arthritis.
- iii) Patients or guardian refused to participate the study.

The study was conducted with the prior approval of the Ethical and Review Committee of Chittagong Medical College. Prior written informed consent was taken from the guardians. In case of older children, assent was also taken. It was an open-label pilot study and both the researcher and the subject were aware about the

drugs what they received. Children with an age range of 1-12 years diagnosed as ALL and scheduled to receive induction therapy as per UKALL protocol at Pediatric Hemato Oncology Department of, CMCH during the study period were enrolled consecutively in this study. After enrolment, detailed history and physical examination findings were recorded in Case Record Form (CRF). Eligible individuals were recruited consecutively and randomly assigned in 1:1 ratio (Block size of two) with a computer-generated randomization list, to one of the two treatment arms.

For Intervention Group (With Levofloxacin):

The newly diagnosed pediatric ALL patients for the intervention group (received levofloxacin) were given Levofloxacin orally at the dose 10 mg/kg body weight/day (Maximum 750mg/ day) as a single daily dose from the same day of starting chemotherapy. Chemotherapy induced neutropenia usually recovers by about 14 days from the beginning of therapy. So, levofloxacin was continued for 14 days or until the Absolute Neutrophil Count (ANC) increased $> 0.5 \times 10^9/l$, whichever took longer. In this period no other antibiotics were added except treatment of any infection is needed as per protocol.

For Control Group (Without Levofloxacin):

The control group did not receive prophylactic antibiotic (Levofloxacin) during their induction phase of chemotherapy. According to protocol, all the children with ALL received twice weekly oral co-trimoxazole (As prophylaxis for Pneumocystis jiroveci) during their chemotherapy. This was not taken as exclusion criteria.

After enrolment of patients of both the group were routinely followed up twice daily. Clinical course of the patients was followed up meticulously, regarding development of fever or any sign of infection by attending physician. Cases where fever or infection developed in spite of giving prophylaxis in intervention group and in control group were managed according to protocol. Blood for CBC was carried out routinely by automated hematology analyzer (XS-800i, Sysmex, Japan) in the Hematology lab of the department of pediatric Hematology Oncology. When there is any clinical features of infection or fever blood culture for bacteria were sent to microbiology lab, where culture done by automated (BACTEC) blood culture system (Organon Teknika, USA). Antibiotic susceptibility testing was interpreted by disc diffusion method.

Levofloxacin was stopped when clinical condition of the patient necessitated the initiation of empirical broad-spectrum antibiotic. Depending on the clinical condition of the patient, chemotherapy was stopped temporarily, when necessary.

When fever or infection was encountered, either in study group or in control group, same points were to be noted down. Total duration of neutropenia and duration of fever were compared in both groups. Antibiotics were added according to the protocol of the department. Total antibiotic days required for both the groups were documented and compared. In this study duration of induction period were also to be compared in both groups during chemotherapy.

All the necessary information and clinical data were collected from each of the study population and were recorded systematically in a predesigned questionnaire. After filling data sheet data were analyzed and prepared for calculation. Then they were entered into Microsoft Excel to generate a master sheet. Next, they were fed into SPSS (Statistical package for social science) version 23 for processing and analysis. Descriptive statistics were used to summarize observations and to describe the characteristics of the study subjects. Categorical variables were expressed as frequency and percentage. Continuous data were expressed either in mean (\pm SD) or median (Interquartile range: 25th percentile-75th percentile) as appropriate according to their distribution. Chi-square test and Fisher's exact test was used to compare qualitative variables between groups. Independent sample t-test was used to compare quantitative variables between both groups. Mann Whitney test was used instead of t test in nonparametric data. Relative risk, risk reduction analysis and mean differences were calculated as a measure of treatment effect with their 95% confidence interval. Statistical significance was defined at $p < 0.05$.

Results

Intervention group (With Levofloxacin): They were given prophylactic oral Levofloxacin, once daily at a dose of 10mg/kg body weight /day. Control group (Without prophylaxis): They did not receive levofloxacin as prophylactic antibiotic during their chemotherapy.

Age distribution of the intervention and control group children shown in Table -I :-

Table I Age distribution of the patients in intervention and control group

Age (Years)	Intervention group (n=30)	Control group (n=30)	p value
Median (IQR)	5 (3-10)	5 (3-11)	0.98*
Age group			
1-2 years	1 (3.33%)	0 (0%)	0.67†
2-5 years	16 (53.33%)	16 (53.33%)	
5-10 years	10 (33.33%)	9 (30.00%)	
10-12 years	3 (10.00%)	5 (16.67%)	

Abbreviations: IQR, interquartile range.

Data represent frequencies (%) of patients if not otherwise specified.

p value was obtained either by †Chi-square test or *Mann-Whitney U test.

Table- I shown that, majority of the children (53.33%) were between 2-5 years in both groups. Next common age group was 5-10 years. Both the groups were similar in terms of the age distribution.

Table II Development of fever in intervention and control group

Fever	Intervention Group (n=30)	Control group (n=30)	Relative risk (95% CI of RR)	p value‡
No fever	12 (40.00)	4 (13.33)	0.69	0.039
Fever	18 (60.00)	26 (86.67)	(0.50-0.96)	

Data represent frequencies (%) of patients. ‡p value was obtained from Fisher exact test.

Table II shown that, a significantly lower proportion developed fever in the intervention group than in the control group [(18/30, 60.00%) versus (26/30, 86.67%)]. This difference was statistically significant (p=0.039). NNT (Benefit): 3.75 (2.08-18.77).

Table III Febrile neutropenia and profound neutropenia in intervention and control

Neutropenia	Intervention group (n=30)	Control group (n=30)	Relative risk (95% CI of RR)	p value
Febrile neutropenia	18 (60.00)	26 (86.67)	0.69(0.50-0.96)	0.039
Profound neutropenia	6 (20.00)	13 (43.33)	0.46 (0.20-1.05)	0.052

Data represent frequencies (%) of patients.

‡p values were obtained from Chi-square test.

Table III shown incidence of febrile neutropenia was significantly less in intervention group compared to control group (p=0.039). NNT (Benefit): 3.75 (2.08-18.77).

Profound neutropenia is also near to statistical significance limit as shown in the table III (p=0.052). NNT: 4.28.

Table IV Presence of Infections in Intervention group and Control group

Infection	Intervention group (n=30)	Control group (n=30)	Relative risk (95% CI of RR)	p value
Present	18(60.00)	26.(86.67)	(0.50-0.96)	0.69
Absent	12 (40.00)	4 (13.33)		0.039

Table IV shown incidence of infection was significantly less in intervention group compared to control group (p=0.039). NNT (Benefit): 3.75 (2.08-18.77).

Table V Types of infections in intervention and control group

Types of infection	Intervention group (n=30)	Control group (n=30)	Relative risk (95% CI of RR)	p value
CDI	15 (50.00)	25 (83.33)	0.60 (0.41-0.89)	<0.001†
MDI	3 (10.00)	1 (3.33)	3.00 (0.33-27.34)	0.268‡

Data represent frequencies (%) of patients. p values were obtained from either †Chi-square test.

Table V Shown most of the infections were Clinically Documented Infection (CDI) and only in four cases (Three in prophylaxis group and one in without prophylaxis group) were Microbiologically Documented Infection (MDI).

It was found highly significant. NNT (Benefit): 3.0 (1.79-9.08)

Table VI Adverse events observed in Intervention group and Control group

Adverse events	Intervention group (n=30)	Control group (n=30)	p value
Rash	0 (0%)	0 (0%)	NA
Limb pain	2 (6.67%)	1 (3.33 %)	0.491

Data represent frequencies (%) of patients. *p value was obtained from Fisher's exact test.

Table VI shown adverse events related to levofloxacin treatment were infrequently observed in the study. Only two patients reported to had lower limb pain in the levofloxacin prophylaxis group (p value is 0.491).

Discussion

For this purpose 60 children with ALL were randomized in two groups: half of them received levofloxacin prophylaxis and other half was the control group of the study who did not receive this levofloxacin prophylaxis during induction phase. Previous studies done on this topic in Bangladesh

was either conducted in adults used ciprofloxacin as antibacterial agent or was an intervention study using historical data as control^{10,11,13}.

Majority of the ALL children were between 2 - 5 years with a median age of 5 years in male predominance in both groups (Table-I). This age and sex distribution of ALL children hospitalized in Bangladesh is in agreement with the previous studies.^{11,14} Age and sex distribution of ALL in the study and control group are almost similar to the international findings.¹⁵

Regarding incidence of fever current study demonstrated that, fever is less in levofloxacin group than the control group. Sixty percent (60%) of patients in levofloxacin prophylaxis group developed fever, compared to 86.67% in the without levofloxacin group (Table-II). This difference was statistically significant ($p=0.039$). This is important observation as neutropenic patients are unable to mount robust inflammatory responses, serious infection can occur with minimal symptoms and signs. In such patients, fever is often the only sign of infection. Wolf et al. & Lehrnbecher et al., from their large series also reported similar pattern of infection in levofloxacin and without levofloxacin prophylaxis group.^{9,16}

Incidence of febrile neutropenia was significantly less in levofloxacin prophylaxis group compared to control group (Table-III). Children in levofloxacin prophylaxis group had lower risk of developing infection in the present study compared to control group (RR:0.69; 95% CI:0.50-0.96) (Table-IV). Similar pattern was also reported by Gafter-Gvili et al., Shireen, Reuter et al.^{8,11,17} Regarding documented infection most of them were clinically documented and only in four cases (Three in prophylaxis group and one in no prophylaxis group) infections were confirmed microbiologically in the present study.

Levofloxacin was well tolerated and related serious adverse events were rare. There was always some hesitancy to use fluoroquinolones, including levofloxacin in children largely because studies in juvenile laboratory animals suggest there may be an increased risk of fluoroquinolone associated cartilage lesions. But in the study by Noel et al in 2007 on 2523 children, authors found levofloxacin to be well tolerated during and for 1 month after therapy as evidenced by similar

incidence and character of adverse events compared with non fluoroquinolone antibiotics.¹⁸ In the present study, only two patients from levofloxacin prophylaxis group and one patient from control group reported to had mild limb pain, no joint or bone related side effects were noted in either group. This limb pain could be due to routine use of steroid in the treatment of ALL. Another similar study from Dhaka, Bangladesh also did not find adverse effect of Levofloxacin in their subjects.¹¹

Limitations

This was a pilot study with small sample size. So, conclusion may not be consistent with similar large sample sized studies. Patients were collected from a single center. So, the results of the study do not represent the exact picture of the country. Only induction phase of chemotherapy patients was taken as sample, it would have been better if all the phases of chemotherapy patients would be included in study.

Conclusion

This study provides suggestive evidence that prophylactic levofloxacin, given during induction phase of chemotherapy in children with ALL, may reduce the febrile episode, and febrile neutropenia. Levofloxacin prophylaxis also reduce number of infectious episodes and it is safe in children. Thus, larger study with levofloxacin prophylaxis is important to generate evidence about usefulness of levofloxacin prophylaxis in children with ALL.

Recommendations

As this small study shown hope on efficacy as prophylaxis of levofloxacin on ALL children without significant adverse effects, so further double blinded placebo controlled trial in multiple pediatric Hemato oncology center is necessary to establish the efficacy & safety of levofloxacin prophylaxis.

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Contribution of authors

RU-Conception, Literature review, data collection, manuscript writing and final approval.

M-Design, critical revision and final approval.

ND-Conception, drafting final approval.
QSS-Interpretation of data, drafting final approval.
AKM RK-Data collection, critical revision final approval.
SMJ-Data analysis, critical revision final approval.
RS-Design, critical revision final approval.

Disclosure

All the authors declared no competing interest.

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