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Original Article

Efficacy of Granulocyte Colony Stimulating Factor (G-CSF) to Manage Neutropenia in Acute Lymphoblastic Leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL)

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ABSTRACT

Introduction: *Leukemia and NHL are the two most common malignancies in childhood. Nowadays children with malignant diseases have an excellent chance of survival around 75%. The incidence of neutropenia depends upon several factors including dose intensity, chemotherapy, the prior history of the patient, and the presence or absence of co-morbid condition.* ***Aim of the study:*** *This study aimed to assess the effect of G-CSF on neutropenia in patients of ALL and NHL and to see the duration of fever as compared to the control group.* ***Methods and Materials:*** *Children from 2 years to 12 years of age who had absolute neutrophil count (ANC) <500 /cumm, and attended in Paediatric Hematology and Oncology Department of DMCH, from July 2012 to July '13 were selected purposively. Data analysis was carried out with the help of SPSS (Statistical Package for Social Science) Windows software program.* ***Results:*** *Among 30 patients, 22 ALL patients and 8 NHL patients were included in group A, and 6 ALL patients and 4 NHL patients were included in group B. There was male predominance. The mean ANC was found 710.73±213.3/cumm in group A and 531±307.9/cumm in group B. The mean difference was statistically significant ($p<0.05$) between the two groups. groups. The mean duration of fever was found 11.07±3.08 days in group A and 13.6±4.03 days in group B which was*

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statistically significant (p<0.05) between the two groups. ***Conclusion:*** *This study concludes that G-CSF therapy significantly increases the absolute neutrophil count reduces the duration of fever and therefore lowers the infection rate.*

Keywords: *Granulocyte Colony Stimulating Factor (G-CSF), Neutropenia, Acute Lymphoblastic Leukemia (ALL), Non-Hodgkin's Lymphoma (NHL)*

INTRODUCTION

Leukemia and NHL are the two most common malignancies in childhood. Leukemia accounts for 31% of all malignancies that occur in children younger than 15 years of age and is an important cause of death in childhood. Acute lymphoblastic leukemia (ALL) accounts for about 77% of cases of childhood leukemia. Among lymphomas, non-Hodgkin's' Lymphoma accounts for 60% and 8-10% of all malignancies [1,2]. Nowadays children with malignant diseases have an excellent chance of survival, with an overall survival rate approaching 75% due to the intense chemotherapy regimens now employed to combat these diseases. Of those who do not survive, the cause of death is most often directly related to malignancy itself but one in 25 children with cancer die due to complications like infection, frequently presenting with neutropenia [3,4]. In our country death rate is even higher, because we can't provide the sterile environment needed for chemotherapy patients. So we have to maintain a high level of immunological compatibility. Neutropenia is either due to the direct result of the disease itself or due to chemotherapy which causes myelosuppression [5]. Studies showed that at least 40% of pediatric patients receiving cancer chemotherapy develop neutropenia and the risk of developing fever with severe neutropenia (ANC <500/cumm) following chemotherapy increases by approximately 10% per day [4,6]. The incidence of neutropenia depends upon several factors including dose intensity, chemotherapy, the prior history of the patient, and the presence or absence of co-morbid condition [5,7]. The occurrence of neutropenia often causes subsequent chemotherapy delays or dose reduction. It may also lengthen the hospital stay, increase monitoring, diagnostic, and treatment cost, and reduces patient's quality of life. As a result, dropouts from treatment protocol and failure to maintain treatment are happening frequently [5,6]. Different study was done to show the effect of granulocyte colony-stimulating factor (G-CSF) in the treatment of neutropenia [4-7]. They showed that G-CSF improves neutropenia faster and reduces neutropenia-related complications. On the other hand, some studies also demonstrate that the duration of neutropenia is the same in patients who received G-CSF for neutropenia, and hospital stay is only one day less and there is no significant change in culture-positive infections. Moreover, it is costly. So it should not be used [8-10]. G-CSF is an 18000 Dalton protein, produced in T-lymphocytes, monocytes, macrophages, endothelial cells, and fibroblasts in response to a variety of signals from substances associated with the infection including endotoxin, tumor necrosis factor-alpha (TNF), and interleukin 1. When it binds to receptors on committed granulocyte precursors, G-

CSF promotes the expansion of the neutrophil pool by stimulating the precursors' entry into the cell cycle and inhibiting apoptosis [11,12,14,15]. In addition G-CSF enhances certain functions of mature neutrophils, including phagocytosis, chemotaxis, and antibody-dependent cellular cytotoxicity. In the past decade, there have been many clinical trials investigating the potential benefits of colony-stimulating factors both to ameliorate or prevent profound neutropenia and its life-threatening consequences. From those studies, it is quite evident that the incidence of neutropenia in children receiving chemotherapy is high and G-CSF improves the condition. In Bangladesh, we are using G-CSF in different centers for neutropenia, but no such study has been done in the recent past to show its merits or demerits. This study will be directed to show the effect of G-CSF on neutropenia.

OBJECTIVE

General Objective

- To evaluate the effectiveness of G-CSF in neutropenia.

Specific Objectives

- To determine the incidence of infection.
- To see the age and gender distribution of the respondents.
- To assess the neutrophil count in the patients of both groups.

METHODS & MATERIALS

This Prospective study was conducted at the Department of Paediatric Hematology and Oncology Ward, Dhaka Medical College and Hospital, Dhaka, Bangladesh. The study duration was 12 months, from July 2012 to June 2013. Patients admitted to the Department of Paediatric Hematology and Oncology department of DMCH were included through a purposive sampling technique based on the following selection criteria.

Inclusion Criteria

- Children between 2 years to 12 years of age, who are diagnosed as ALL and NHL.
- All diagnosed children who are getting standard chemotherapy for the disease.
- Patients who are suffering from severe neutropenia that is absolute neutrophil count of <500/cumm.
- Patients who had given consent to participate in the study.

Exclusion Criteria

- Patients of age less than 2 years and more than 12 years.
- Patients who had known hypersensitivity to G-CSF.
- Patients with ANC more than 500/cumm after chemotherapy.
- Patients suffering from malignancies other than ALL and NHL.
- Patients who did not give consent to participate in the study.

Thirty patients who had absolute neutrophil count <500/cumm were included in Group-A, who received Inj. G-CSF cc subcutaneously once daily for consecutive 3 days along with Inj. antibiotics and other safety measures. 10 patients who had absolute neutrophil count <500/cumm were included in Group –B, who had given only blood transfusion, Inj.

antibiotics and other safety measures were taken. Then ANC of both groups was measured by CBC after 24 hours of treatment. They followed up for the following days whether the infection had occurred or not. Blood samples for blood C/S. Urine R/M/E and Chest X-ray were done for the screening of infection. CBC (Complete blood count) was done to see ANC. Infection screening was done by CBC, Blood for C/S, Urine R/M/E, and Chest X-ray. Data was entered and analyzed in the computer using SPSS for Windows version 16.0. Qualitative variables were presented as Mean ± standard deviation. For the comparison of differences between qualitative variables, the exact Fisher's test was used. Probability values of <0.05 were considered statistically significant for all results. Informed written consent was obtained from the respondents. Ethical clearance was taken from the local Ethical Committee to perform an investigation and study.

RESULTS

Table I: Distribution of the study patients by age (N= 40)

Age (in years)	***Group A (n=30)***		***Group B (n=10)***		***P value***
	n	**%**	**n**	**%**	
≤3	4	13.3	2	20.0	
4-5	3	10.0	2	20.0	
6-10	14	46.7	4	40.0	
>10	9	30.0	2	20.0	
Mean±SD	7.78±3.45		6.86±3.42		*0.468^{ns}*
Range (min-max)	2.5-12		3-12		
ns=not significant *P value reached from unpaired t-test*					

A total of 40 patients were included in this study, and it was observed that the majority of patients were aged belonged to 6-10 years in both groups. The mean age was found 7.78±3.45 years in group A and 6.86±3.42 years in group B. The difference was not statistically significant (p>0.05) between the two groups. [Table I]

Table II: Distribution of the study population by disease (N=40)

Disease	***Group A(n=30)***		***Group B(n=10)***		***P value***
	n	**%**	**n**	**%**	
ALL	22	73.3	6	60.0	*0.576^{ns}*
NHL	08	26.7	4	40.0	

ns=not significant
P value reached from Fisher's exact test

It was observed that ALL patients 22(73.3%) in group A and 6(60.0%) in group B. NHL patient 8(26.7%) in group A and 4(40.0%) in group B. The difference was not statistically significant (p>0.05) between the two groups. [Table II]

Table III: Sex distribution of the study population (N=40)

Sex	***Group A (n=30)***		***Group B(n=10)***		***P value***
	n	%	n	%	
Male	21	70.0	6	60.0	*0.414^{ns}*
Female	09	30.0	4	40.0	
ns=not significant *P value reached from Fisher's exact test*					

Males were predominant in both groups, which was 21(70.0%) in group A and 6(60.0%) in group B. The difference was not statistically significant (p>0.05) between the two groups. [Table III]

Table IV: Distribution of the study patients by ANC at the time of diagnosis (N= 40)

ANC(/cumm)	**Group A(n=30)**		**Group B(n=10)**		**P value**
	n	**%**	**n**	**%**	
≤100	18	60.0	5	50.0	
200-500	8	26.7	4	40.0	
>500	4	13.3	1	10.0	
Mean±SD	4232.33±4016.9		3825±3945.01		*0.781^{ns}*
Range(min-max)	100-13600		100-12200		
ns=not significant *P value reached from unpaired t-test*					

It was observed that the majority of patients had ANC <100/cumm in both groups. The mean ANC was found 4232.33±4016.97/cumm in group A and 3825±3945.01/cumm in group B. The mean difference was not statistically significant (p>0.05) between the two groups. [Table IV]

Table V: ANC of the Group-A (G-CSF group) patients before giving G-CSF (n=30)

CBC before starting G-CSF(ANC/cumm)	*N*	*%*
<100	12	*40.0*
200-500	18	*60.0*
>500	0	*0.0*
Mean±SD	181.48±108.12	
Range (min-max)	*10-390*	

It was observed that the majority of 18(60.0%) patients had ANC 200-500/cumm. The mean ANC was found 181.48±108.12/cumm. [Table V]

Table VI: ANC of the Group-B (non-G-CSF group) patients before giving other treatment (n=10)

CBC before starting Other treatment (ANC/cumm)	*N*	*%*
<100	4	*40.0*
200-500	6	*60.0*
>500	0	*0.0*
Mean±SD	175.4±124.75	
Range (min-max)	*4-410*	

It was observed that the majority of 6(60.0%) patients had ANC 200-500/cumm. The mean ANC was found 175.4±124.75/cumm. [Table VI]

Table VII: Distribution of the study patients by ANC after given G-CSF and not given G-CSF (N=40)

ANC(/cumm)	*Group A(n=30)*		*Group B(n=10)*		*P value*
	n	%	n	%	
<500	16	53.3	7	70.0	
500-1000	13	43.3	2	20.0	
>1000	1	3.3	1	10.0	
Mean±SD	710.73±213		531±307.9		*0.046^{ns}*

	.3				
Range (min-max)	90-2290		160-1200		
ns=not significant *P value reached from unpaired t-test*					

In this series, the majority of patients had ANC <500/cumm in both groups. The mean increase of ANC was found 710.73±213.3/cumm in group A and 531±307.9/cumm in group B. The mean difference was statistically significant ($p<0.05$) between the two groups. [Table VII]

Table VIII: Distribution of the study patients by presence of fever and duration of fever (N= 40)

Presence of fever	***Group A(n=30)***		***Group B(n=10)***		***P value***
	n	**%**	**n**	**%**	
No	03	10.0	1	10.0	*[a]0.744[ns]*
Yes	27	90.0	9	90.0	
Duration of fever (days)					
<10	8	26.7	1	10.0	
10-15	15	50.0	6	60.0	
16-20	4	13.3	1	10.0	
>20	0	0.0	1	10.0	
Mean±SD	11.7±3.08		13.6±4.03		*[b]0.044[s]*
Range (min-max)	6-17		9-22		
ns=not significant, s=significant *[a]P value reached from Fisher's exact test* *[b]P value reached from unpaired t-test*					

Fever was found 27(90.0%) in group A and 9(90.0%) in group B patients. The majority of patients had a fever for 10-15 days in both groups. The mean duration of fever was found 11.07±3.08 days in group A and 13.6±4.03 days in group B. The mean duration of fever difference was statistically significant ($p<0.05$) between the two groups. [Table VIII]

Table IX: Outcome of the patients on G-CSF therapy (n=30) and non-G-CSF therapy(n=10)

Outcome of the patients on G-CSF therapy	*Group A(n=30)*		*Group B(n=10)*		*P value*
	n	**%**	**n**	**%**	
Satisfactory	14	46.67	3	30.0	*0.014[s]*
Not satisfactory	16	53.33	7	70.0	
ns=not significant					
P value reached from Fisher's exact test					

14(46.67%) patients in group A and 3(30.0%) in group B patients satisfactory after G-CSF therapy. The P value was statistically significant (0.014) between the two groups. [Table IX]

DISCUSSION

The majority of patients were aged belonged to 6-10 years in both groups,14 (46.7%) in group A (G-CSF group) and 4(40%) in group B (non-G-CSF group). It was observed that male was predominant in both groups, which was 21(70.0%) in group A and 6(60.0%) in group B. The incidence of infection increases with the severity of neutropenia, during induction, CNS prophylaxis, and relapse in Leukaemia [16]. Depending on the chemotherapeutic regimen, profound neutropenia may persist at various intervals, seven days to six weeks. The level of circulating neutrophil is the most important factor in determining the prognosis of infection in neoplastic disease [17, 18]. In this study, the majority of patients had ANC <100/cumm in both groups, 18(60%) patients in group A and 5(50%) patients in group B at the time of diagnosis and before starting chemotherapy. This data coincides with the study in India where most patients had ANC < 200/cumm but it is contrary to the Western study where most patients had ANC 300-400/cumm [4,6]. The mean ANC was found 710.73±213.3/cumm in group A after giving Inj. G-CSF and 531±307.9/cumm in group B after other treatment. The mean difference was statistically significant ($p<0.05$) between the two groups, which coincides with the study held in India where the mean ANC was 850.73±113.3/cumm also similar to the western study where neutropenia improved after giving inj. G-CSF [4,6]. But did not coincide with the studies held in France and Pakistan where no marked improvement was shown in ANC count even after giving G-CSF therapy [8,9]. The presence of fever in the study patients was observed as a sign of infection. Fever was found 27(90.0%) in group A and 9(90.0%) in group B patients. The majority of patients had fever 10-15 days in both groups, 15(50%) in group A and 6(60%) in group B patients. The mean duration of fever was found 11.07±3.08 days in group A and 13.6±4.03 days in group B which was statistically significant ($p<0.05$) between the two groups. This figure correlates with the study in India where the

mean duration of fever was 8.2 days in the G-CSF group and 13.53 days in the control group ($p<0.05$) [4]. But in studies in Pakistan and in Western studies duration of fever did not reduce significantly [6,9]. The outcome was assessed based on the ANC count of these patients. ANC >500/cumm was assessed as a satisfactory outcome and ANC<500/cumm was denoted as non-satisfactory. Concerning the outcome of the patients on G-CSF therapy, it was shown that the outcome of 14(46.67%) patients in group A was satisfactory after G-CSF therapy, and 3(30.0%) in group B patients were satisfactory after conventional therapy. In another study by H. A. Engert et al, over 30 diagnosed cancer patients, who were given G-CSF due to neutropenia showed that it decreases the neutropenia and duration of fever [7]. This outcome s also similar to other studies [19,20]. Moreover, it is considered as an essential supportive therapy that reduces neutropenia complications and improves patient survival and quality of life [21].

Limitations of the Study

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. Moreover, CBC could not be seen every alternate day as it usually advocates, and repeated blood culture was not performed due to financial limitations.

CONCLUSION

This study concludes that G-CSF therapy significantly increases the absolute neutrophil count reduces the duration of fever and therefore lowers the infection rate.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

RECOMMENDATION

More broad-based studies may be done for further evaluation and to see the effect of the drug. This may be done with more patients within a longer period and also in multicenter.

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