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Original Article

Vincristine induced peripheral neuropathy in children undergoing chemotherapy for acute lymphoblastic leukaemia during induction

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ABSTRACT

Background: Vincristine is an anticancer agent administered to all children with acute lymphoblastic leukemia (ALL), and peripheral neuropathy is the major dose-limiting toxicity of this therapy. As cure rates of childhood ALL exceeds 80%, therefore treatment-related toxicities need to be reduced. Thus, the aim of this study was to determine the prevalence and risk factors of vincristine-induced peripheral neuropathy (VIPN) in children with ALL undergoing induction chemotherapy.

Methods: A case-control study was conducted from September 2017 to August 2018 in the Department of Paediatric Haematology and Oncology at Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Eighty newly diagnosed ALL and 35 acute myeloid leukemia (AML) cases aged 5 to 17 years with no pre-existing neurological abnormality were recruited. To assess the peripheral neuropathy, we used pediatric-modified total neuropathy score and National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI-CTCAE), version-04 grade.

Results: Among ALL patients, 29.2% developed peripheral neuropathy compared to 10% in AML control group (P=0.04). Higher proportion (57.1%) of peripheral neuropathy was found in age below 10 years (P<0.001). There was no significant association of peripheral neuropathy with sex and body mass index of the patients.

Conclusion: Almost 3 in 10 patients developed VIPN during the induction therapy which is significantly higher in age below 10 years compared to ≥ 10 years.

Keywords: peripheral neuropathy, risk factors, acute lymphoblastic leukemia, induction remission chemotherapy, pediatric-modified total neuropathy score

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common pediatric malignancy. ALL represents 25-30% of all childhood cancers and approximately 75% of all cases of childhood leukemia. The reported incidence of childhood cancer in Bangladesh is 7.8 per million per year, with leukemia (28%) and ALL accounting for 84% of leukemias[1]. Typically, ALL is treated by chemotherapy in different phases such as induction therapy, consolidation, central nervous system directed therapy, and maintenance.[2] However, ALL therapy continues to pose significant morbidity. Now it becomes increasingly important to mitigate acute and chronic toxicities of treatment that adversely affect the quality of life and longevity. Vincristine is one of the most commonly employed and effective anticancer agents for the treatment of leukemia.[3, 4]

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HIGHLIGHTS

1. **Vincristine induced peripheral neuropathy (VIPN) is slightly common during induction chemotherapy.**
2. **Younger children (5-10 years) suffer more from neuropathic pain.**
3. **Female patients present more symptoms of VIPN than male.**

Vincristine exerts its cytotoxic effects by inhibiting microtubule formation and mitotic spindle dynamics, thereby causing mitotic arrest and cell death.[5,6] Vincristine's dose-limiting toxicity is peripheral neuropathy[7], which is characterized by neuropathic pain and sensory and motor dysfunction (such as impaired manual dexterity, balance, deep tendon reflexes, and altered locomotion). A substantial percentage of patients develop neuropathy that causes considerable morbidity and often disrupts curative treatment.[8]

Common signs and symptoms of VIPN include numbness and tingling in the hands and feet with associated neuropathic pain, asymptomatic hyporeflexia, constipation, and muscle weakness, and less commonly, impaired balance, jaw pain, and orthostatic hypotension.[9-13] Refractory peripheral neuropathy and associated neuropathic pain are significant health problems due to their undeniable negative influence on functional status, patient safety, quality of life, and cost of care.[14-16] In addition, VIPN often necessitates chemotherapy dose reductions, possibly compromising the efficacy of potentially life-saving treatment. Therefore, efforts to prevent or minimize VIPN are critically important. Not much is known about the risk factors and natural history of VIPN. Data regarding the same from the Bangladeshi population is also lacking.

Thus, the objective of this study is to ascertain the prevalence and risk factors of VIPN in children undergoing chemotherapy for ALL during induction period.

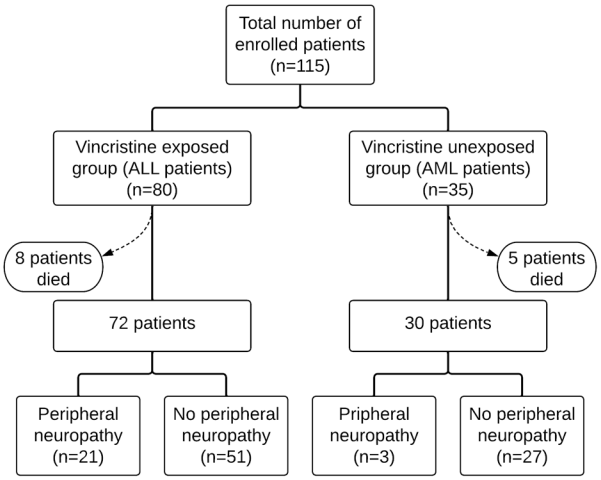
METHODS

Study design and participants

The present single-centered, case-control study was done from September 2017 to August 2018 in the Department of pediatric hematology and oncology at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. All newly diagnosed patients of ALL and acute myeloid leukemia (AML) between the age of 5 to 17 years with no pre-existing neurological abnormality were included in this study.

Recruitment of the cases and controls

The diagnosis of ALL and AML were obtained based on history, clinical examination, complete blood count with peripheral blood film, examination and bone marrow aspiration, study for morphology, and immunophenotyping. Baseline investigations were done prior to the initiation of therapy. Chemotherapy had been given to all patients with ALL according to the modified UK acute lymphoblastic leukaemia 2003 protocol after risk stratification. Patients who were between the ages of 5 to 9 years with an initial white blood count of less than 50,000 cells per cubic millimeter (cmm) were considered as standard risk. Patients who were between the ages of 10 years or more with an initial white blood count of more than 50,000/ cmm were considered intermediate risk.



A total of 80 children with ALL who were exposed to vincristine and 35 children with AML who were not exposed to vincristine were included in this study. Eight patients died in vincristine exposed ALL group and five patients died in vincristine unexposed AML

group, and they were excluded from the study. Finally, data of 102 patients (72 patients in vincristine exposed ALL group and 30 in vincristine unexposed AML group) were analyzed **(FIGURE 1).**

Treatment protocols

Regimen-A had been given to the standard-risk group and regimen-B was specified for intermediate-risk group. The induction phase is the first phase of the protocol, which comprises 35 days. For regimen-A, the chemotherapeutic agent was used in the induction phase including oral dexamethasone (dose: 6-10 mg/m^2 on days 1-35), vincristine (dose: 1.5 mg/m^2, intravenous on days 2, 9, 16, 23 and 30), L-asparaginase (dose: 6,000 IU/m^2, intramuscular on days 4, 6, 8, 10, 12, 14, 16, 18, 20), 6-mercaptopurin (75 mg/m^2 on days 28-35), and intrathecal methotrexate, hydrocortisone and/or cytosine-arabinoside. However, in regimen-B daunorubicin (25 mg/m^2 on days 2, 9, 16 and 23) was added.

All patients who were diagnosed with AML had been treated according to the Medical Research Council's 12–point protocol. The induction phase was the first phase of the protocol, consisting of injection daunorubicin (50 mg/m^2 body surface area on days 1, 3, 5), injection etoposide (100 mg/m^2 body surface area on days 1 to 10), injection cytarabine (100 mg/m^2 body surface area/ day- 12 hourly on days 1 to 10), and intrathecal chemotherapy with cytarabine on day 1. These drugs were used both during the induction and reinduction phases. General supportive management like hydration, alkalinization, allopurinol, phosphate binder, oral care, anal care, etc. were administered to all patients.

Follow up of patients

All patients were followed up for neuropathic pain using the pediatric-modified total neuropathy score, National Cancer Institute- Common Terminology Criteria for Adverse Events version 4.0 at baseline (day 1) and on each subsequent day of vincristine treatment prior to vincristine administration (that is on day 9, day 16, day 23, and day 30).

Data collection

Consent was taken from the parent or legal guardian, and assent was taken from the participants at the time of enrollment to the study. Data were collected using a questionnaire. Peripheral neuropathy was assessed by using pediatric-modified total neuropathy score and National Cancer Institute- Common Terminology Criteria for Adverse Events version 4, grade.

Statistical analysis

All data were recorded systematically in data collection form. Statistical analysis was performed by using Statistical Package for the Social Sciences (SPSS) for windows version 22.0. Descriptive statistics (numbers and percentages) were calculated for all variables, and Chi-square test was used to find associations between the variables. $P<0.05$ was considered statistically significant. Risk estimation was calculated by using the odds ratio through cross tabulation with 95% confidence intervals (CI).

RESULTS

The mean (standard deviation) age of the patients were 8.3 (2.6) years and 8.4 (2.5) years in vincristine exposed and unexposed groups, respectively. Eight in ten (80.6%) patients in vincristine exposed group and seven in ten (76.7%) patients in vincristine unexposed group were below 10 years. More than half of the patients in vincristine exposed group (58.3%) and vincristine unexposed group (56.7%) were male. The mean body mass index in vincristine exposed and unexposed groups were similar 14.3 kg/m^2 and 14.0 kg/m^2, respectively **(TABLE 1)**. A higher prevalence of peripheral neuropathy (P=0.04) was found in vincristine exposed group (29.2%) compared to the non-exposed group (10.0%) **(TABLE 2)**. In the group of vincristine-exposed, patients who developed peripheral neuropathy, 12 (57.1%) received regimen B and 9 (42.9%) received regimen A. In contrast, only three

TABLE 1 Age and sex distribution between cases and controls (n=102)

Characteristics	Cases (n=72)	Controls (n=30)	P*
	Number (%)	Number (%)	
Age category			
Less than 10	58 (80.6)	23 (76.7)	0.66
10 or more	14 (19.4)	7 (23.3)	
Sex			
Male	42 (58.3)	17 (56.7)	0.88
Female	30 (41.7)	13 (43.3)	

*Chi-square test

TABLE 2 Development of peripheral neuropathy in between vincristine exposed and unexposed groups (n=102)

Peripheral Neuropathy	Cases (n=72)	Controls (n=30)	*P**
	Number (%)	Number (%)	
Yes	21 (29.2)	3 (10.0)	
No	51 (70.8)	27 (90.0)	0.04

*Fisher's exact test

patients in the vincristine-unexposed group who developed peripheral neuropathy received the MRC AML 12 regimen. We found that older age group (≥10 years) have high risk neuropathy (OR: 6.9; 95% CI 1.9 – 24.4) **(TABLE 3)**.

DISCUSSION

ALL is the most common pediatric malignancy. ALL represents 25% to 30% of all childhood cancers and approximately 75% of all cases of childhood leukemia. Chemotherapy is the main treatment for ALL and the 5-year overall survival rate for children with ALL has greatly increased over time and is now more than 85%. One of the most widely used and effective anticancer agents for treating leukemias is vincristine.[3,4] For improved survival, adequate vincristine dosing is crucial. Because some children experience only mild VIPN, it is important that our assessment could detect a broad range of VIPN severity. It is hypothesized that children with a disease that carries a particularly high risk and who can tolerate a dose increase of vincristine may benefit from a more effective disease management if they receive higher doses of this crucial medication. In contrast, minors at high risk for severe VIPN may benefit from early or preventative dose modification or even elimination of vincristine.

Lopez-Lopez et al., like our study reported that 30% of patients developed neurotoxicity during induction phase.[19] Bradfield S.M. et al. also observed in their study that 30% of patients are affected by vincristine associated neurotoxicity.[20] Similarly, Cooper et al. in their study reported 25.4% peripheral neuropathy during induction.[21] Anghelescu et al. in their study also found that about 34.9% of ALL patients experience neuropathic pain during treatment.[22] Gilchrist et al. in their study reported that the prevalence of peripheral neuropathy ranges between 55 - 87% using paediatric-modified total neuropathy score.[23-25] Similar findings were reported by Anghelescu et al. [22]

Higher frequency of peripheral neuropathy was found in young patients by Similarly, Vainionpaa et al.[10] However, Lavoie Smith et al. and Diouf et al. reported a significantly higher prevalence in older children.[18,26] On the other hand, a few studies did not find an association between age and VIPN in children.[19,21]

TABLE 3 Measurement of risk factors for vincristine induced peripheral neuropathy in children with acute leukaemia (n=72)

Risk factors	Peripheral neuropathy		
	Yes (n=21)	No (n=51)	OR (95% CI)
	n (%)	n (%)	
Gender			
Male	9 (42.9)	33 (64.7)	0.4 (0.2 - 1.2)
Female	12 (57.1)	18 (35.3)	
Age group			
≥ 10 years	9 (42.9)	5 (9.8)	6.9 (1.9 - 24.4)*
<10 years	12 (57.1)	46 (90.2)	
Initial white blood cell count			
>50000	7 (33.3)	15 (29.4)	1.2 (0.1 - 3.6)
<50000	14 (66.7)	36 (70.6)	
Immunophenotype			
B- ALL	20 (95.2)	43 (84.3)	3.7 (0.4 - 31.8)
T- ALL	1 (4.8)	8 (15.7)	
Acute myeloid leukemia			
Types of chemotherapy			
Regimen-A	9 (42.9)	30 (58.8)	0.5 (0.2 - 1.5)
Regimen-B	12 (57.1)	21 (41.2)	
Medical Research Council Regimen 12			
Acute lymphoblastic leukaemia risk group			
Standard	9(42.9)	30(58.8)	0.5 (0.2 - 1.5)
High	12(57.1)	21(41.2)	

*Statistically significant

The relationship of sex with VIPN is confusing. Some observed female predominance[27,31] while other observed male predominance[33] and some found no relationship.[18,22]

Although higher frequency of peripheral neuropathy was observed in patients receiving regimen B in our study but not significant. However, cautious interpretation is needed because of the inability to establish a blinded design, and the relatively small

study sample of our study. So, more comprehensive evaluations including larger population groups are required in confirming the findings. Some adverse clinical outcomes like malnutrition, impaired quality of life and treatment delay associated with peripheral neuropathy were not studied. Future studies addressing this issue with peripheral neuropathy can be done.

Conclusion

Higher frequency of VIPN was found during induction period in the present study. However, VIPN was observed with higher frequency in girls. Age below 10 years was found to be more associated with VIPN. Thorough neurological examination should be an integral part of patient's routine follow up during induction of remission. Our study could not achieve enough sample size for ALL. Large-scale studies are needed to establish the fact and to find out any association between outcomes of the patients.

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Author Contributions

- Conception and design: NS, CYJ
- Acquisition, analysis, and interpretation of data: NS, SAS, ATMRM, MNIM
- Manuscript drafting and revising it critically: NS, CYJ, ATMAR
- Approval of the final version of manuscript: NS, CYJ, ATMAR, SAS, MNIM, AHMRM
- Guarantor accuracy and integrity of the work: CYJ

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Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical approval

This study was approved by the Institutional Review Board of BSMMU (memo number Bangabandhu Sheikh Mujib Medical University/2017/13323, date:13 Nov 2017).

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