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Original Research Article

Risk factors of asparaginase-associated pancreatitis in children with acute lymphoblastic leukaemia

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ABSTRACT

Background: Acute lymphoblastic leukaemia (ALL) is the top childhood cancer, with survival rates of 80–85%. Attention now focuses on treatment complications. Pancreatitis, linked to Asparaginase in ALL therapy, remains poorly understood despite its recognition. The main objective of the study was to identify the risk factors of pancreatitis in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy.
Methods: A prospective observational study was conducted at BSMMU's Paediatric Haematology and Oncology Department from March 2018 to February 2019. Newly diagnosed ALL cases in children aged 1 to 17.9 years were included, excluding those <1 or >18 years, with prior pancreatitis, or relapsed cases. Informed consent was obtained from parents/legal guardians. Diagnosis relied on clinical, CBC, bone marrow and immunophenotyping. Induction chemotherapy followed the UK ALL 2003 protocol for 35 days, with regular follow-ups monitoring abdominal symptoms and laboratory markers. USG of the abdomen was performed if pancreatitis symptoms or elevated serum amylase/lipase occurred post-L-asparaginase administration.
Results: Among 80 patients, pancreatitis affected 3 (3.8%) after the 2nd, 3rd and 7th doses of L-asparaginase, independent of individual or cumulative dosing, induction phase or concomitant medications. Age, sex, initial WBC count, ALL lineage, treatment regimen and CNS status were not statistically linked to pancreatitis incidence. Clinical manifestations included abdominal pain, tenderness, nausea, vomiting and fever, alongside elevated serum amylase and lipase levels, supported by consistent ultrasonographic findings. Despite these symptoms, no pancreatitis-related mortalities were observed, however, overall mortality during induction therapy reached 20%, unrelated to pancreatic complications.
Conclusions: In this study no significant risk factor could be identified for developing pancreatitis in ALL patients treated with asparaginase. Further studies with large sample size are required to predict who will develop pancreatic toxicity from asparaginase.

Keywords: Asparaginase, Associated pancreatitis, Acute lymphoblastic leukemia

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood accounting for 25% of all childhood cancers.[1] At our center, Department of Paediatric Haematology and Oncology of BSMMU, 58% cases of ALL among 455 newly diagnosed children with malignancy were recorded in one year.[2] Given that overall survival rates for all are 80–85% on contemporary protocols, attention is now increasingly turning towards treatment-related morbidity and mortality and genetic predispositions accounting for side.[3]

Asparaginase is a bacterially derived enzyme which is a universal component of all chemotherapeutic regimens for childhood acute lymphoblastic leukemia (ALL). Asparaginase was first administered as a single agent to patients with ALL in the 1960s and was effective in inducing complete remission in up to 60% of cases.[4]

The incorporation of L-asparaginase has significantly improved event-free survival in children with ALL and failure to complete planned L-asparaginase treatment has been linked to increased relapse rate.[5,6] Unlike healthy human cells, malignant lymphoblasts are not capable of synthesizing asparagine. The resulting deficiency in protein synthesis causes apoptosis of lymphoblasts.[5,7]

The toxicities of asparaginase are considerable. These include hypersensitivity reactions, severe hyperlipidaemia, liver dysfunction, coagulopathy, hypoinsulinemia with resulting hyperglycemia, and pancreatitis.[8,9] One of the most serious adverse events of L-asparaginase treatment is acute pancreatitis, and it is also among the most common reasons for stopping treatment with L-asparaginase.[10-13]

Although cases of asparaginase-associated pancreatitis (AAP) were first reported in the 1970s, little progress has been made in our understanding of this important problem. Although a long-recognized toxicity, the pathophysiology of asparaginase-associated pancreatitis remains unclear.[10,12,14] Who developing pancreatitis following asparaginase is unpredictable, but would be important to predict.

Even though there are numerous case reports in the literature highlighting pancreatitis following asparaginase, there are neither large trials nor large case series. The reported incidence of AAP ranges from 0.7%–18%.[15] There has been no proven relationship linking dose, duration or formulation of asparaginase and the development of pancreatitis.

The present study focused on exploring the potential impact of asparaginase and determining the associated risk factors for developing pancreatitis in children with newly diagnosed ALL during induction period. To identify the risk factors of pancreatitis in children with acute lymphoblastic leukemia receiving L-Asparaginase during induction chemotherapy.

METHODS

Study design

Prospective observational study.

Duration of study

The study period was from March 2017 to February 2018.

Study place

The study was conducted at Department of Pediatric Hematology and Oncology, BSMMU.

Study population

Newly diagnosed cases of ALL aged 1 to 17.9 years who were admitted in department of Paediatric Haematology and Oncology, BSMMU, Dhaka during the study period.

Sample size

It is calculated using the following formula

Calculated sample size n=z2 pqe2

Inclusion criteria

Age 1 to 17.9 years, newly diagnosed case of ALL, Admitted cases.

Exclusion criteria

Age less than 1 year. Age 18 Years or more. Old or relapse case of all. Patient developed pancreatitis prior to receiving asparaginase.

Sampling technique

Consecutive sampling will be done.

Data collection instrument

Structured questionnaire.

Pre-testing

Pre-testing of data collection instrument will be done on 3 cases, which will be eliminated from study cases.

Study procedure

Newly diagnosed children with ALL aged 1 year to 17.9 years who were admitted into the Department of Pediatric

Hematology and Oncology, BSMMU for induction therapy were enrolled in this study. Informed written consent from the parent or guardian was obtained at the time of study enrollment. Data were collected using a preformed data collection sheet (questionnaire).

Demographic data regarding age, sex, socio–economic status, family history of malignancy had been collected from guardian or parents. Clinical information about pallor, temperature, pulse, blood pressure, respiratory rate and other general and systemic clinical parameters had been taken. All acute lymphoblastic leukemia patients received chemotherapy based on the UK ALL 2003 protocol, stratified by risk.

Standard-risk patients (regimen A) received oral dexamethasone, vincristine and L-asparaginase during the 35-day induction phase, along with intrathecal methotrexate, hydrocortisone and/or cytosine-arabinoside. High-risk patients (regimen B) additionally received daunorubicin. General supportive measures were administered to all, including hydration, alkalinization, and symptom management.

During induction phase, patients were monitored for pancreatitis symptoms and underwent physical exams. Baseline CBC, serum amylase and lipase were obtained prior to chemotherapy. Periodic assessments followed specified doses, with ultrasonography conducted for suspected pancreatitis. Intramuscular native *E. coli* L-asparaginase was administered after hypersensitivity testing. Serum enzyme levels were analyzed using an auto analyzer at BSMMU's biochemistry department.

Data analysis

The following steps were used to analyze the collected data, The data were collected and edited manually. The entered data were checked, verified and analyzed by appropriate computer software. The data were presented in tabular or diagrammatical form. Appropriate statistical tests were applied for data analysis. All data were recorded systematically in preformed data collection form. Statistical analysis will be performed by using appropriate statistical formula. P value<0.05 was considered statistically significant.

Ethical implication

Prior to the commencement of this study, the thesis protocol will be approved by the Institutional Review Board of BSMMU, Dhaka. The thesis protocol will be explained to parents or legal guardians before taking their consent.

Then a written consent will be taken from each patient's legal guardians to be included in the study. Every precaution will be taken so that study will not cause any harm or delay for treatment of cases. No incentive will be given to the participants. Guardians will have the liberty to exclude their children from the study at any time. Anonymity of patients will be maintained by coding of results.

RESULTS

This single centered, prospective observational study was conducted for a period of one year from March 2018 to February 2019 in the department of pediatric hematology and oncology, Bangabandhu Sheikh Mujib Medical University.

All patients aged 1 to 17.9 years of both sexes, diagnosed newly as acute lymphoblastic leukemia admitted in the department of Pediatric Haematology and Oncology were the study population. Total 80 children with ALL were included in this study. Among them 16 patients died in different stages of induction chemotherapy and 4 patients were lost from the follow up.

Table 1 demonstrates age distribution of 80 children with ALL in this study. Among them, 68 (85%) were in age group of <10 years, 12 (15%) patients were in age group of >10 years. Mean age was 5.72+-3.35 years, median age was 5 years and range was between 1.25 to 15.0 years. Table shows sex distribution of 80 children with ALL included in this study.

Among 80 patients 52 (65%) were male and 28 (35%) were female patients. Male children are predominant in number male: female ratio was 1.9:1. Table shows distribution of WBC count at diagnosis of 80 patients of ALL included in this study. At diagnosis WBC count <50,000/cumm was found in 57 (71.2%) patients, on the other hand, at diagnosis WBC count >50,000/cumm was found in 23 (28.8%) patients.

Table 2 shows distribution of total 80 children with ALL by their CNS status obtained by CSF study. Among 80 patients, 78 (97.5%) were CNS negative and 2(12.5%) patients were CNS positive.

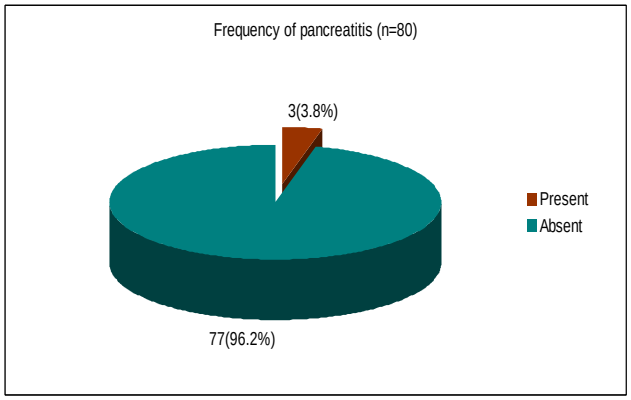

Figure 1: The frequency of pancreatitis among the children with ALL during induction chemotherapy.

Figure 1 demonstrates frequency of pancreatitis among the 80 children with ALL included in this study. Out of 80 patients, pancreatitis was encountered in 3 (3.8%) patients. Rest of the 77 (96.2%) patients did not develop pancreatitis during induction period of chemotherapy.

Table 3 shows association of pancreatitis with age, sex, at diagnosis WBC count, type of ALL, type of treatment regimen and CNS status of total 80 patients. In this study, age, sex, at diagnosis WBC count, lineage of ALL, treatment regimen and CNS status cannot be considered as risk factor, because those factors had no statistical significance with pancreatitis.

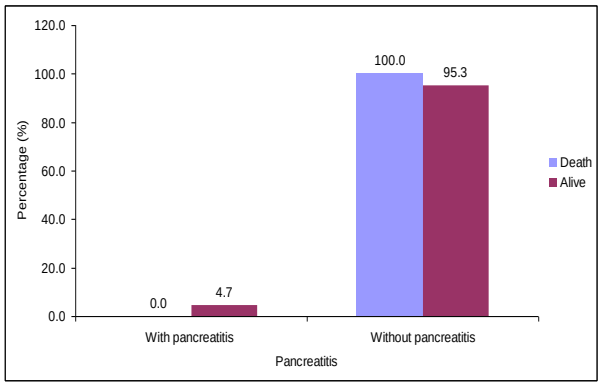

Figure 2: The association of mortality with pancreatitis.

Figure 2 shows association of mortality with pancreatitis. Out of total 80 patients, 16 patients died in various stages of induction therapy. Among those 16 patients, no one died due to pancreatitis. On the other hand, out of 64 survived patients 3(4.7%) patients had pancreatitis. Fisher Exact test revealed no significant association of mortality with pancreatitis.

Table 4 shows the association of pancreatitis with clinical presentations at various level of induction chemotherapy. The children with ALL who were suffering from abdominal pain and tenderness after 3rd and 6th dose of L-asparaginase had statistically significant relation with pancreatitis. But other manifestation like nausea, vomiting or fever had no statistically significance with pancreatitis presented at various stage of induction.

Table 5 shows the demographic characteristics and chemotherapeutic drugs profile of 3 patients developed pancreatitis. All 3 patients were below three years of age. Among the 3 patients, 2 female and 1 male.

All 3 patients got same dose of L-asparaginase that was 6000 IU/m^2. 1st patient developed pancreatitis after getting 3rd dose of L-asparaginase at induction remission day 9 and total cumulative dose was 8640 IU. 2nd patient developed pancreatitis after getting 7th dose of L-asparaginase at induction remission day 18 and total cumulative dose was 22680 IU. 3rd patient developed pancreatitis after getting 2nd dose of L-asparaginase at induction remission day 7 and total cumulative dose was 6000 IU.

1st and 3rd patient got standard risk chemotherapeutic regimen and received vincristine and dexamethasone along with L-asparaginase. 2nd patient got high risk chemotherapeutic regimen and received vincristine, dexamethasone and daunorubicine along with L-asparaginase.

Table 1: Distribution of the study patients by age, sex, initial WBC count (n=80).

	Frequency	Percentage
Age group (in years)		
>1 to <10	68	85.0
≥10	12	15.0
Total	80	100.0
Mean±SD	5.72±3.35	
Median	5.0	
Range	(1.25 – 15.0) years	
Sex		
Male	52	65.0
Female	28	35.0
Total	80	100.0
Male: Female ratio	1.9:1	
Initial WBC count		
≤50,000	57	71.2
>50,000	23	28.8
Total	80	100.0
Mean±SD	60925.4±96202.3	
Median	15850	
Range	(1000.0-370840.0)	

Table 2: Distribution of the study patients by CNS status (n=80).

CNS status	Frequency	Percentage
CNS positive	2	2.5
CNS negative	78	97.5
Total	80	100.0

Table 3: Association of pancreatitis with risk factors in children with ALL (n=80).

Risk factors	Frequency	With pancreatitis no (%)	Without pancreatitis no (%)	P value
Age (in years)				
>1 to <10	68	3 (4.4)	65 (95.6)	0.458^{ns}
≥10	12	0 (0.0)	12 (100.0)	
Total	80	3 (2.8)	78 (96.3)	
Sex				
Male	52	1 (1.9)	51 (98.1)	0.241^{ns}
Female	28	2 (7.1)	26 (92.9)	
Initial WBC				
<50,000	57	2 (3.5)	55 (96.5)	0.858^{ns}
>50,000	23	1 (4.3)	22 (95.7)	
Phenotype of ALL				
B cell	68	3 (4.4)	65 (95.6)	0.458^{ns}
T cell	12	0 (0.0)	12 (100.0)	
Regimen				
A	51	2 (3.9)	49 (96.1)	0.915^{ns}
B	29	1 (3.4)	28 (96.6)	
CNS status				
CNS 1	78	3 (3.8)	75 (96.2)	0.777^{ns}
CNS 2	2	0 (0.0)	2 (100.0)	

Fisher Exact test was done to see the association, ns=not significant

Table 4: Association of pancreatitis with clinical characteristics (n=80).

Clinical features	Frequency	With pancreatitis no. (%)	Without pancreatitis no. (%)	P value
Abdominal pain				
Baseline	5	0 (0.0)	5 (100.0)	-
After 3rd L-aspa	7	2 (28.6)	5 (71.4)	0.001^{s}
After 6th L-aspa	11	1 (9.1)	10 (90.9)	0.027^{s}
After 9th L-aspa	9	0 (0.0)	9 (100.0)	-
At end of induction	7	0 (0.0)	7(100.0)	-
Abdominal tenderness				
Baseline	5	0 (0.0)	5 (100.0)	0.642^{ns}
After 3rd L-aspa	9	2 (22.2)	7(77.8)	0.003^{s}
After 6th L-aspa	14	1 (7.1)	13 (92.9)	0.048^{s}
After 9th L-aspa	12	0 (0.0)	12 (100.0)	-
At end of induction	10	0 (0.0)	10 (100.0)	-
Nausea/vomiting				
Baseline	-	0 (0.0)	0 (0.0)	-
After 3rd L-aspa	16	2 (12.5)	14 (87.5)	0.062 ^{ns}
After 6th L-aspa	23	1 (4.3)	22 (95.7)	0.184^{ns}
After 9th L-aspa	16	0 (0.0)	16 (100.0)	-
At end of induction	4	0 (0.0)	4 (100.0)	-
Fever				
Baseline	51	2 (3.9%)	49 (96.1)	0.915^{ns}
After 3rd L-aspa	11	1 (9.1%)	10 (90.9)	0.366^{ns}
After 6th L-aspa	24	0 (0.0%)	24 (100.0)	0.452^{ns}

Continued.

Clinical features	Frequency	With pancreatitis no. (%)	Without pancreatitis no. (%)	P value
After 9th L-aspa	28	0 (0.0%)	28 (100.0)	-
At end of induction	9	0 (0.0%)	9 (100.0)	-

Fisher Exact test was done to see the association, ns=not significant

Table 5: Demographic characteristics and chemotherapeutic drugs history of patients developed pancreatitis (n=3).

Id. No.	Age (yrs.)	Sex	BSA	Dose of L-aspa	Total cumulative dose of L-aspa	No of L-aspa prior AP	Interval from last L-aspa & onset of AP	Onset of AP (days)	Concurrent drugs at onset of AP
22	2.90	Female	0.48 m^2	6000/m^2	8640 IU	3rd dose	During therapy	Day 9	VCR Dexa
24	2.50	Female	0.54 m^2	6000/m^2	22680 IU	7th dose	During therapy	Day18	VCR, Dauno Dexa
43	3.00	Male	0.50 m^2	6000/m^2	6000 IU	2nd dose	During therapy	Day 7	VCR Dexa

Table 6: Clinical features of patients developed pancreatitis (n=3).

Id. no	Abdominal and pain tenderness	Nausea/vomiting	Fever	Jaundice	Dehydration
22	Yes	Yes	Yes	No	No
24	Yes	Yes	No	No	No
43	Yes	Yes	No	No	No

Table 7: Biochemistry and radiological findings of patients developed pancreatitis (n=3).

Id No	Highest S. amylase (U/l)	Highest S. lipase (U/l)	USG of whole abdomen	Hematocrit	RBS mmol/l	S. Calcium mg/dl
22	367	1065	Pancreas appears ill defined, swollen & heterogeneous in echotexure	40.1%	4.4	10.2
24	1280	6840	Pancreas is swollen with heterogeneous in parenchyma	40.0%	5.7	9.4
43	237	4056	Pancreas appears swollen & heterogeneous	39.2%	4.6	9.5

Table 6 shows the clinical features of 3 patients developed pancreatitis. Abdominal pain, tenderness, nausea and vomiting were the common clinical feature of all 3 patients developed pancreatitis. 1st patient had associated fever also. No patients were suffering from jaundice or dehydration.

Table 7 shows the biochemical parameters and radiological findings of the children developed pancreatitis.1st patient had elevated level of both amylase and lipase 3 times from upper normal limit. She also had sonographic findings consistent with pancreatitis but normal Hematocrit, RBS and S. calcium level.

2nd patient had high level of both amylase and lipase level along with positive sonographic findings consistent with pancreatitis. She also had normal Hematocrit, RBS and S. calcium level. It is notable that 3rd patient had very high serum lipase level but not serum amylase level 3 times of upper normal limit. He had sonographic confirmation of pancreatitis and normal Hematocrit, RBS and S. calcium level.

DISCUSSION

Asparaginase associated pancreatitis is an important cause of morbidity in children with ALL. The exact mechanism that leads to pancreatic toxicity is unknown. In this study, there was a male predominance with a male: female ratio of 1.9:1. Male predominance in acute lymphoblastic leukemia was also found in previously reported studies. In a study showed Sixty percent male in his study as well as another study reported male to female ratio was 3.33:116.[17] We did not find any clinical parameters associated with the risk of developing AAP in this study. Age, sex, initial WBC count, type of ALL, treatment regimen and CNS status cannot be considered as risk factor in this study, because those factors had no

statistically significant relation with pancreatitis. Also, another study show attempted to explore the potential predisposing factors and by Analyzing of the presenting characteristics, they did not reveal any other risk factors for the development of asparaginase-associated pancreatitis.[12]

In a study reported that older children and adolescents were at higher risk for developing APP. Another study observed similar age demography.[10,12] But this finding is not consistent with our study findings. In this study, all 3 patients who developed pancreatitis were under 3 years of age. Though it is not statistically significant, female patients seems to develop more pancreatitis in this study. But a study found no difference between the incidence in females and males for developing AAP. In this study, regimen B (which incorporates Daunorubicin) had no significant association with pancreatitis.[10]

Among the 29 patients who received regimen B, only one patient developed pancreatitis. This finding is also compatible with the finding.[18] All patients had elevated level of serum amylase and/or serum lipase. Notable that, one patient had amylase levels below three times of the upper normal limit, but lipase levels was three times above the upper normal limit. Thus, measuring both serum lipase and serum amylase is important. It is noteworthy that all three children with clinical and chemical pancreatitis had ultrasonographic abnormalities. However, reported that 39% of children with pancreatitis did not have abnormalities detected by ultrasound.[12]

Therefore, he suggested that the diagnosis should not be dependent on radiographic confirmation. In some previous studies, the association of L-asp treatment with other therapeutic agents especially corticosteroids have been reported to induce toxicities. In our study, all patients received L-asparaginase concomitant with dexamethasone. Although, corticosteroids are capable of inducing pancreatitis, it is difficult to know whether this could contribute to the severity of these cases. A very important observation was that all three patients with pancreatitis were re-treated with dexamethasone after resolution of the acute episode. They completed induction phase without recurrence of pancreatitis. Thus, steroid was not thought to be the major contributor to pancreatic toxicity.

There was a high occurrence of severe complications to AAP. The time to onset of pancreatic toxicity was notable. Previous studies have shown that pancreatitis can occur within days to weeks following a dose of asparaginase. In this study, all patients developed pancreatitis within a few days following first exposure to L-asparaginase. So we agree with this observation of pancreatitis tends to develop after the first few doses of asparaginase suggests that asparaginase-associated pancreatitis may occur as a result of an underlying predisposition rather than as a cumulative drug effect.[12]

Extensive ongoing research investigating the pharmacogenomics of chemotherapy-induced toxicities may help to identify patients at high risk of developing this complication. They reported that daunorubicin had no association with drug induced pancreatitis. Although high risk regimen had no significant association with pancreatitis in this study, in a study identified high risk chemotherapy regimen as a risk factor for developing APP.[13] Higher doses of L-asparaginase in the regimen would be a major risk factor for AAP. An important observation in this study was that mortality had no relation with pancreatitis.

Total 16 patients with ALL died at different stage of induction phase due to complications not related to the pancreatic episode or its complications, mostly due to septicemia. Out of 16, 10 patients died within 14 days of induction remission. But the patients who developed pancreatitis were survived. It may be due to early detection of toxicity and improved supportive care measures. However, pancreatitis related mortality was reported to occur in up to 2-5% in some previous studies.[14,19] The diagnosis of asparaginase-induced pancreatitis was straightforward. Clinically, 100% of patients presented with abdominal pain along with nausea vomiting and one also experienced fever. None of them experienced shock in contrast to what other studies on severe cases report.

In this study, no patient was re-challenged with asparaginase. Although pancreatitis following administration of asparaginase has been reported for over 30 years, it remains difficult to predict who will experience such toxicity. We agree with a study where suggested that individuals with drug-induced pancreatitis likely have an unknown predisposition. Further research is needed to understand the mechanism of this toxicity and to increase our ability to predict, and ultimately prevent, pancreatitis following asparaginase.[20]

CONCLUSION

Asparaginase associated pancreatitis is one of the most serious complications of ALL therapy. In this study no definite risk factor for pancreatitis has been identified in children with acute lymphoblastic leukemia during induction remission chemotherapy. So, it remains difficult to predict who will experience such complication.

The limitations of the studies were small sample size of the study population. The drugs (L- asparaginase) used by the study population were not from the same batch number of manufacturer.

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

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