ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 08 | August - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

A PROSPECTIVE OBSERVATIONAL STUDY OF THE ADVERSE DRUG REACTIONS OF L-ASPARAGINASE IN NEWLY DIAGNOSED CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Paediatrics

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ABSTRACT

Aim & Background: L-asparaginase is associated with clinically significant toxicity notwithstanding its high therapeutic efficacy. The present study aimed to evaluate the prevalence, type and severity of these adverse drug reactions amongst children aged 1 to 12 years. **Materials and methods:** A prospective observational study was conducted in the Pediatric Haematology-Oncology division of a tertiary care centre, after Institutional Ethics Committee clearance. 30 patients with newly diagnosed Acute Lymphoblastic Leukemia (ALL), without any coexisting comorbidities, were included, and monitored for clinical and biochemical evidence of toxicity. Baseline and weekly monitoring of liver and renal function, random blood sugar, serum triglycerides, cholesterol, and coagulation profile was performed. Data was analysed using Stata Version 23. Analysis of Variance (ANOVA) and Kruskal-Wallis equality-of-population rank test were used for parametric data and non-parametric data, respectively. **Results:** The mean age of the study population was 7.60 ± 3.38 years with a male preponderance. The majority of the patients (80%) were of the precursor B-cell type. While 73.34 % of patients did not show any clinical manifestations of L-asparaginase toxicity, 10% complained of pain in abdomen, and 6.67 % complained of pain at the local site. One patient each developed acute pancreatitis (requiring discontinuation of future L-asparaginase therapy), thrombosis and myalgia. Across the period of induction, serum albumin showed a statistically significant decline (p=0.01), whereas serum bilirubin trend demonstrated a statistically significant elevation (p=0.04). Serum triglyceride (p=0.048) and cholesterol (p=0.038) demonstrated a statistically significant elevation. L-asparaginase therapy did not significantly affect other biochemical parameters in this study. **Conclusion:** We conclude that though L-asparaginase was associated with some toxicity, it did not lead to the necessity to withhold it, except in one child. However, regular monitoring of patients on L-asparaginase for clinical and biochemical adverse effects is crucial.

KEYWORDS

L-asparaginase, Acute Lymphoblastic Leukemia (ALL), Adverse Drug Reaction (ADR)

INTRODUCTION:

Acute Lymphoblastic Leukemia (ALL) accounts for about 80% cases of childhood cancer (1). In a study by D'çosta et al, in India, the incidence of childhood leukemia was reported as 26.45% (2). Presently, the treatment for ALL comprises the use of drugs such as L-asparaginase, vincristine, anthracyclines, methotrexate, 6-mercaptopurine and steroids. L – Asparaginase, an essential component of multi-agent chemotherapy in ALL, is an enzyme isolated from the bacterium Escherichia coli or the bacterium Erwinia chrysanthemi. The enzyme hydrolyzes L-asparagine to L-aspartic acid and ammonia in leukemic cells, resulting in the depletion of asparagine, inhibition of protein synthesis, cell cycle arrest in the G1 phase, and apoptosis in susceptible leukemic cell populations (3).

L-asparaginase shows high therapeutic efficacy but is also associated with clinically relevant toxicity, which may sometimes warrant interruption of therapy. Varied adverse reactions, including myelosuppression, acute pancreatitis, hypersensitivity reactions, hyperglycaemia, transaminitis, etc, are reported (4). L-asparaginase significantly improves survival rates in children with ALL. Literature shows that interruption of therapy with L-asparaginase due to its toxicity is associated with unfavourable outcomes (5,6). Hence, it becomes imperative, especially in the pediatric population, to be pharmacovigilant about L-asparaginase. Indian studies in this context are scarce. The present study aimed to study the prevalence of adverse events due to L-asparaginase during the induction phase of chemotherapy in children with ALL.

MATERIALS AND METHODS:

AIM & OBJECTIVES:

1) To study the prevalence of adverse reactions due to L-asparaginase in newly diagnosed children (aged 1 to 12 years) with ALL
2) To study the type of adverse reaction and its severity

INCLUSION CRITERIA:

- All consecutive newly diagnosed children with ALL (aged 1 to 12 years) at the centre during the study period (1 year)

EXCLUSION CRITERIA:

- Children with coexisting morbidities like HIV, Hepatitis B or C infection
- Children with deranged liver function or deranged coagulation profile at the onset of the study
- Children who received partial treatment with chemotherapeutic agents/steroids elsewhere

The study was a prospective observational study at the Paediatric Haematology-Oncology Division of a tertiary care institute. Institutional Ethics Committee approval was obtained. 30 newly diagnosed patients with acute leukemia, fulfilling all inclusion and exclusion criteria, were included in the study. A written informed consent/ assent (where applicable) was obtained. For all patients' demographic details, history and examination findings were noted in a predesigned case record form. Patients were stratified into high, intermediate and standard risk according to the NCI (National Cancer Institute) criteria (7). The chemotherapy protocol was planned as per the institutional policy. Native E. coli L-asparaginase was used for all patients.

Patients were monitored carefully through 4 weeks of induction for the development of any adverse effects. Symptoms like nausea, vomiting, pain in abdomen, rash, local reactions, fever, chills, myalgias, altered behaviour, depression, etc, if any were noted in detail and appropriate investigations were done wherever indicated.

Baseline followed by weekly monitoring of following parameters were done for 4 weeks and entered in the proforma: Complete Blood

Count, Liver function tests (Total proteins, albumin, bilirubin, AST, ALT and alkaline phosphatase), Renal function tests (Serum creatinine and BUN), Coagulation profile (PT/ aPTT/ Serum Fibrinogen), Random blood sugar and Serum cholesterol and triglyceride levels. Age and gender-matched specific values were used to define abnormal values for these parameters (8). Additional investigations, including serum amylase, lipase, ultrasonography, and computed tomography, were performed whenever clinically indicated. Adverse reactions and their severity were defined using version 5.0 of the Common Toxicity Criteria for Adverse Events (CTCAE) (9). Consequence of the adverse drug reaction (ADR) was noted with respect to the following: Patient continued the drug, dose had to be reduced, drug had to be stopped or withdrawn, and any need for surgical intervention.

Data were entered in Microsoft Excel and analysed using Stata Version 23. We calculated the means, standard deviations, medians and interquartile ranges for the linear variables. We estimated the proportions for categorical variables. We used Analysis of Variance (ANOVA) and Kruskal-Wallis equality-of-population rank test for parametric data and non-parametric data, respectively. The proportions were compared using the Chi-square test or Fisher's exact test (for low expected cell counts). A p-value of less than 0.05 was considered to be statistically significant.

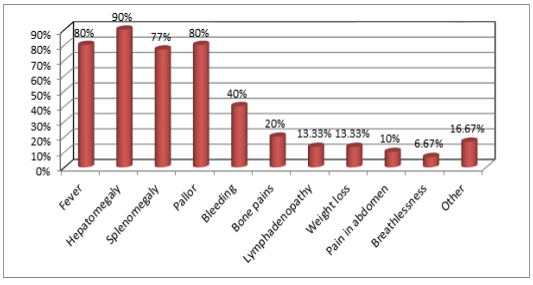
RESULTS:

30 newly diagnosed ALL patients (aged 1 to 12 years) were included in the study. The majority of patients (43.33 %) belonged to the age group of > 9 years. The mean age was 7.60 ± 3.38 years. There was a male preponderance among the cases, with a male-to-female ratio of 1.14.

Table 1: Clinico-Demographic Profile of the Study Population (n=30)

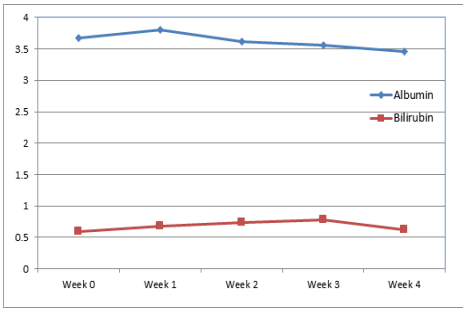
Parameter		Number
Age Distribution	1 to 5 years	10 (33.33%)
	5 to 9 years	07 (23.33%)
	>9 years	13 (43.34%)
Gender Distribution	Males	16 (53.33%)
	Females	14 (46.67%)
Nutritional status (< 5 years of age) n=10	Normal	04 (40.00%)
	Moderate Acute Malnutrition	04 (40.00%)
	Severe Acute Malnutrition	02 (20.00%)
Nutritional status (> 5 years of age) n=20	Normal	11 (55.00%)
	Thin	05 (25.00%)
	Severely Thin	03 (15.00%)
	Overweight	01 (5.00%)
Significant Family History	Diabetes	08 (26.67%)
	Dyslipidemia	03 (10.00%)
	Allergies	02 (6.67%)
Diagnosis	B ALL	25 (83.33%)
	T ALL	05 (16.67%)
Risk Stratification	High Risk	22 (73.33%)
	Intermediate Risk	06 (20.00%)
	Standard Risk	02 (6.67%)

Chart 1: Clinical presentation at diagnosis (n=30)



73.34 % patients did not show any clinically apparent adverse drug reactions. Pain in abdomen (10%) was the most common clinical ADR noted. The other adverse events described were pain at the local site (6.67%), acute pancreatitis (3.33%), thrombosis (3.33%) and myalgia (3.33%). The mean hemoglobin in the study population was 8.34 ± 1.98 g/dl. The median total leukocyte count was 5350 /mm3, and the median platelet count was 54500 /mm3.

Chart 2: Mean albumin and bilirubin at weekly intervals in the study population (n=30)



There was a decline in the mean albumin values from the baseline value of 3.67 g/dl to 3.46 g/dl in week 4 of induction (Chart 2). This decline was statistically significant (p=0.01). An increase in the mean bilirubin values was noted. From the baseline value of 0.59 mg/dl, it reached a peak of 0.78 mg/dl during week 3. This elevation was statistically significant (p=0.04).

Table 2: Trend of laboratory abnormalities in study population (n=30)

Parameter		Week 0	Week 1	Week 2	Week 3	Week 4	p value
BUN	Normal	29 (96.67 %)	29 (96.67 %)	28 (93.33 %)	27 (90.00 %)	26 (86.66 %)	0.54
	Abnormal	1 (3.33 %)	1 (3.33%)	2 (6.67 %)	3 (10.00 %)	4 (13.34 %)	
Serum Creatinine	Normal	29 (96.67 %)	27 (90.00 %)	27 (90.00 %)	30 (100 %)	29 (96.67 %)	0.31
	Abnormal	1 (3.33 %)	3 (10.00 %)	3 (10.00 %)	0 (0.0%)	1 (3.33%)	
Serum Alkaline phosphatase	Normal	13 (43.33 %)	13 (43.33 %)	12 (40.00 %)	14 (46.67 %)	14 (46.67 %)	0.82
	Abnormal	17 (56.67 %)	17 (56.67 %)	18 (60.00 %)	16 (53.33 %)	16 (53.33 %)	
Serum Triglycerides	Normal	29 (96.67 %)	25 (100%)	26 (100%)	22 (88.00 %)	24 (100%)	0.048
	Abnormal	1 (3.33 %)	0 (0.0%)	0 (0.0%)	3 (12.00 %)	0 (0.0%)	
Serum Cholesterol	Normal	29 (96.67 %)	22 (88.00 %)	20 (76.92 %)	19 (76.00 %)	18 (75.00 %)	0.038
	Abnormal	1 (3.33 %)	3 (12.00 %)	6 (23.08 %)	6 (24.00 %)	6 (25.00 %)	
Blood sugar level	Normal	30 (100 %)	26 (96.30 %)	29 (96.67 %)	25 (96.15 %)	23 (95.83 %)	0.91
	Abnormal	0 (0.0%)	1 (3.70 %)	1 (3.33%)	1 (3.85%)	1 (4.17%)	
Prothrombin Time	Normal	30 (100 %)	24 (100 %)	22 (88.00 %)	23 (92.00 %)	17 (89.47 %)	0.11
	Abnormal	0 (0.0%)	0 (0.0%)	3 (12.00 %)	2 (8.00 %)	2 (10.53 %)	
aPTT	Normal	29 (96.67 %)	23 (100%)	25 (100%)	22 (88.00 %)	24 (100%)	0.10
	Abnormal	1 (3.33 %)	0 (0.0%)	0 (0.0%)	3 (12.00 %)	0 (0.0%)	

A significant proportion of patients showed elevation in serum triglycerides (p=0.048) and serum cholesterol (p=0.038) during 4 weeks of induction therapy. A decline in the mean fibrinogen levels over 3 weeks was noted, with the nadir noted in Week 3 when the mean fibrinogen levels dropped to 218.7 mg/dl. However, this decline was not statistically significant (p=0.066).

DISCUSSION:

L-asparaginase has been studied extensively and is associated with a wide variety of adverse effects. However, Indian studies on the adverse effects of L-asparaginase, particularly in young children, are scarce. Our study evaluated the adverse effects of L-asparaginase in newly diagnosed children with Acute Lymphoblastic Leukemia.

The mean age in our study was 7.60 ± 3.38 years. Ortiz et al, in their study, noted a mean age of 8.1 (± 3.4 years) (10). The male-to-female ratio in our study was 1.14:1. Nesheli et al, also observed a male preponderance in their study (11).

Majority of patients (83.33%) had precursor B-cell ALL on immunophenotyping. Other Indian studies also describe the preponderance of Pre- B ALL. Siddaiahgari et al in their article have cited the immunophenotypic distribution of ALL as Pre B cell ALL in 82.44% and Pre T and T cell ALL in 15.46% children (12).

Pain in abdomen, not related to pancreatitis (10%) was the most common clinical ADR noted. These children were managed with symptomatic measures. L-asparaginase was continued in them as the adverse event was not classified as severe. When reviewing literature, though, abdominal pain is a commonly cited side effect of L-asparaginase, it has been more often due to other reasons during induction therapy. It may be due to other drugs like vincristine and steroids used during this phase (10).

1 patient developed acute pancreatitis during induction therapy, confirmed on biochemical and radiographic investigations. L-asparaginase was withdrawn from all further treatment phases in this child. In a study by Schmidt et al, 3% patients on L-asparaginase therapy developed pancreatitis (13). Both Vincristine and L-asparaginase are known to cause pancreatitis, and hence, when used in combination, it is impossible to incriminate one or the other. However, there is literature to suggest that the combination of vinca alkaloids and L-asparaginase therapy has been linked to pancreatitis in humans (14).

Though literature cites hypersensitivity as the most common adverse effect of L-asparaginase, none of the patients in our study developed hypersensitivity. Our observations were in agreement with the suggestions by Larson et al (15), who observed that, when L-asparaginase is given early in the treatment program, the incidence of hypersensitivity reactions may be less. This is because the patients could be profoundly immunosuppressed both by their disease and by the corticosteroid-containing chemotherapy regimen used during induction. As our study subjects comprised patients undergoing induction therapy, this could be the reason for the absence of clinical hypersensitivity. The risk of antibody formation for patients increases with repeated exposure to asparaginase; consolidation and reinduction phases of treatment show the greatest incidence of hypersensitivity reactions and antibody formation (16).

While clinical adverse events may be obvious to the observer, L-asparaginase may also cause biochemical adverse effects that manifest only with careful monitoring. We observed a progressive decline in mean serum albumin values across induction (Chart 2), which was statistically significant (p=0.01). Other studies in literature also corroborate the relationship between hypoalbuminemia and therapy with L-asparaginase. In an Iranian study by Bani-Hashem et al (17), significant differences were noted in serum albumin levels between patients who received L-asparaginase therapy as compared to those patients who did not. While the hepatotoxic effect of L-asparaginase is a major cause for the development of hypoalbuminemia, it may also be potentiated by inadequate intake in children with acute leukemia undergoing chemotherapy.

The present study revealed abnormalities not only in the synthetic functions but also in other aspects of liver function. We observed significant elevation of serum bilirubin levels over the period of 4 weeks of induction (Chart 2) (p=0.04). Raetz et al, who studied the tolerability and efficacy of L-asparaginase therapy in pediatric ALL, demonstrated similar findings as our study (5). We observed a significant increase in both serum triglyceride (p=0.04) and cholesterol levels (p=0.03). In another study, Yeang et al (18) observed that 3.6% patients developed hypertriglyceridemia attributable to the native E. coli asparaginase. The role of steroids in contributing to hyperlipidemia cannot be undermined. Parsons et al, who studied L-asparaginase-associated lipid abnormalities in children, showed that combined treatment with asparaginase and corticosteroids leads to hypertriglyceridemia in up to 67% of patients receiving asparaginase treatment for ALL (19). Hassan et al (11) suggest monitoring serum triglyceride and cholesterol levels every 3-4 days during induction.

We observed hyperglycaemia in only one patient, who was overweight for age. Regular monitoring of blood sugar levels showed a persistent elevation, which was controlled with insulin and oral hypoglycaemic agents. Iyer et al, in their study observed that obesity was a predisposing factor for hyperglycemia in children receiving therapy with L-asparaginase (20). In an Indian study by Panigrahi et al (21), 21% patients showed an abnormal glucose level. Both hypoglycemia and hyperglycemia were observed in that study. Literature mentions that parallel use of glucocorticoids may mask the hypoglycemic effect of L-asparaginase and may accentuate the occurrence of hyperglycaemia (21).

We did not observe a significant derangement of the coagulation profile in our study. No patients developed thrombotic or bleeding events. Ramsay et al (22) evaluated 26 patients during induction with L-Asparaginase, vincristine and prednisolone. They reported prolongation of the PT, aPTT and reduced fibrinogen levels, and these parameters returned to normal within 2 weeks of completion of L-Asparaginase. Another study by Pui involving 13 patients during induction reported a similar pattern of results (23).

Though we observed a wide variety of adverse events with the use of L-asparaginase therapy, of the 30 patients included in the study, only 1 patient required discontinuation of L-asparaginase from further phases of treatment. The rest continued to receive L-asparaginase, and only transient adverse effects were noted, which responded to standard therapy.

Study Limitations: The small sample size and single-centre design may limit the generalizability of the findings. Additionally, the concurrent administration of other chemotherapeutic and supportive agents may have confounded the attribution of specific toxicities to L-asparaginase alone.

CONCLUSION:

Our study emphasises the importance of regular monitoring of patients on L-asparaginase for clinical and biochemical adverse effects. It is imperative to be vigilant about the adverse effects, to identify them and institute corrective measures at an appropriate time.

ACKNOWLEDGEMENTS: The authors would like to express their gratitude to Division of Pediatric Haematology-Oncology, Department of Pediatrics and Dean (LTMMC and LTMGH, Sion) for permission to conduct the study and for providing necessary facilities to carry out the work. We would like to sincerely thank Dr. Radha Ghildiyal, Professor & Head, Department of Pediatrics, LTMMC & GH, for her support and guidance. The authors would also like to thank the parents, children, nurses and staff members who made the study possible.

Declarations:

Ethics Clearance: Ethical clearance was obtained from the Institutional Ethics Committee.

Conflict of interest: There is no conflict of interest in the above-mentioned article, and all the authors have equally contributed to data collection as well as in writing the manuscript. The authors have no competing interests to declare that are relevant to the content of this article.

Funding: No funds, grants, or other support were received.

Consent: Written informed consent was taken from all the participants.

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