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Original Articles

Value of Serum Lactate Dehydrogenase Level in the Detection of Hemato-oncological Malignancies and its Response to Induction in Childhood Acute Lymphoblastic Leukemia

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Abstract

Serum lactate dehydrogenase (LDH) level was estimated in 77 childhood (age range 1-15 years) hemato-oncological malignancies: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's disease (HD) and Non- Hodgkin's lymphoma (NHL) on admission. Serum LDH level was also measured in ALL on day 14 and day 29 of induction. Another 25 children without hemato-oncological malignancies were included as control. On admission, the level of serum LDH was significantly raised in all hemato-oncological malignancies but the levels was highly significant in ALL than control ($p<0.001$). Total WBC count was significantly decreased along with serum LDH level on day 14 and day 29 of induction ($p<0.001$). A significant rise of platelet count was observed on day 29 of induction in relation to significant decrease of serum LDH level ($p<0.001$). Significant decrease of peripheral and bone marrow blast cell percentages were also observed on day 29 of induction along with significant decrease level of serum LDH ($p<0.001$). It is observed in this study that serum LDH level was significantly elevated in all hemato-oncological malignancies on admission but the levels were highly significant in ALL patients. Following induction of remission in ALL, level of serum LDH was decreased along with the return of hematological parameters towards normal. So, the measurement of serum LDH level can be accepted as a predictor in diagnosis of hemato-oncological malignancies and prognosis of childhood ALL.

Key wards: *Serum lactate dehydrogenase (LDH), Hemato-oncological malignancies, Induction, Acute lymphoblastic leukemia (ALL).*

Introduction

Lactate dehydrogenase (LDH) is a hydrogen transfer enzyme that catalyzes the oxidation of L-lactate to pyruvate with the mediation of NAD^+ as hydrogen acceptor. Tissue level of LDH are about 500 times greater than that of normally found in serum[1]. Leukemia is characterized by persistent and enormous production of immature white blood cell. The incidence of leukemia in various paediatric centers in India varies from 0.3 to 1.2%[2].

Serum LDH level increases in many patients with hemato-oncological malignancies: acute lymphblastic leukemia (ALL), acute myeloid leukemia (AML), Hodgkin's disease (HD), Non-Hodgkin's lymphoma (NHL), sarcomas and disseminated carcinoma. A good correlation is found between serum LDH level, the course of neoplasia and the degree of dissemination of the neoplastic process. The patients with neoplasia, level of serum LDH correlate with the response to therapy[3]. ALL in children are a highly curable disease. Now a days, the cure rate in western countries lie between 70-80%[4]. In Bangladesh, though exact incidence is unknown, there appears to be an increase in the cases of childhood malignancies. Yet it we take

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the cognizance of the incidence of other countries of this region we can presume that 5 to 6 thousands new cases should diagnosed each year[5].

There is a good relationship between neoplasia and increased serum LDH level. The LDH level is moderately elevated in many cases of acute leukemia, irrespective of their cell type. Markedly elevated level of LDH is recorded in the majority of patients with ALL and is suggestive of increase cell proliferation and turnover[6]. It is thought that the determination of serum LDH activity has received attention in several medical centers both as an investigative tool and as clinical laboratory procedures because of the promise that it has shown in the diagnosis and prognosis of childhood ALL[7]. Quantitative biochemical estimation of serum LDH provides a simpler and more objective measurement of tumor volume. Such measurement should be included in the evaluation of patient with ALL[8].

Higher serum LDH level is associated with higher leukocytes counts, lower blast cell DNA indices, lower platelet count and a larger spleen size. Patients with highest LDH level (greater than 1000 U/L) are most likely to be non-responsive to treatments, whereas those with lowest level (less than 300 U/L) have the minimum risk of failure of treatment. The measurement of serum LDH level is useful in risk assessment or stratification of ALL patients. Early measurement of serum LDH can be used in identifying a group of standard risk ALL patients with a high relapse hazard[9]. Serum LDH is almost certainly produced by the tumor cell. Its concentration rises during tumor growth. Level of serum LDH has significant correlation with total tumor burden[10]. A good relationship is found between initial serum LDH level and the extent of the tumor. Estimation of serum LDH level may be helpful in evaluating the response to therapy[11].

Serum LDH which may reflect the mass of tumor present and it is lowest in patients with localished disease. Level of serum LDH not only serves as an enzymatic indicator or mass of tumor but also has prognostic significance for prolonged disease free survival[12]. A definite and consistent shift in the pattern of molecular form of LDH has been found in a large series of malignant human neoplasm as compared with benign tumors and normal controls[13]. Serum LDH activity approximate to normality when tumour regression is near completion so that its reliability as an indicator is evident. LDH activity of serum increases promptly after tumour transplantation and decreases with tumour regression[14].

Till now, in Bangladesh there is no such study of serum LDH level estimation in children to detect hemato-oncological malignancies on admission and its response to induction of remission in childhood ALL. But it is proposed that the level of serum LDH is elevated in hemato-oncological malignancies at presentation and its measurement is a dependable tool for the detection and to observe the response to induction in children with ALL. As the estimation of serum LDH is easy, readily available and economic, therefore, this study is conducted to evaluate the serum LDH level estimation in children with hemato-oncological malignancies at presentation and to observe the response to induction of remission in childhood ALL.

Materials and Methods

This hospital based cross sectional comparative study was carried out in 102 subjects: hemato-oncological malignancies (77) and control (25) of both sexes, age ranged from 01 to 15 years in the Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, between the period from March 2006 to February 2007. The study subjects were stratified into diagnosed case of hemato-oncological malignancies (ALL-44, AML-16, HD-9, NHL-8) who did not have any sign of hemolysis, were not severely sick, did not receive any previous chemotherapy, in ALL who completed the induction of remission and control who did not suffer from any kind of illness.

The diagnosis of every patient of hemato-oncological malignancy on admission was established on the history, clinical manifestation, complete blood count, peripheral blood film, biochemical investigations (serum LDH) and the findings of bone marrow aspirate. All hematological and biochemical investigations were done in the laboratory, Pediatric Hematology and Oncology. Other relevant investigations were obtained from respective department. Serum LDH level was estimated by using the kits based on photometric system by microflow cell photometer, RA-50 chemistry system. The peripheral blood films and bone marrow aspirate for morphological study were stained with Geimsa; for cytochemistry of bone marrow aspirate were stained with periodic Acid Schiff (PAS) and viewed under high power lenses primarily on the basis of light microscope and in more difficult cases immunophenotyping were performed.

Estimation of serum LDH level and complete blood count were performed in control when they attended in the out patient department for health check up and found healthy. Informed written coercion free consent was taken after describing clearly about the nature, purpose and importance of this study to the parents or guardian of the patients. Then, following proper hydration with 3 litre/m^2 day of intravenous fluid and alkalization in ALL patients, protocol based (UKALL-X) induction was given with vincristine 1.5 mg/m^2 intravenously weekly 4 weeks, intrathecal (methotrexate 12.5mg + hydrocortisone 25mg) weekly 4 weeks, donomycin 45 mg/m^2 D_1 and D_2 intravenously, L-asparaginase 6000 IU/m^2 deep intramuscularly every alternateday from third day 12 doses, prednisolone 40mg/m^2 first 4 weeks of induction orally, allopurinol 100 mg/m^2 first 2 weeks of induction orally, sodium bicarbonate 100mg/m^2 first 2 weeks of induction orally. The hematological values were done every alternate day in the whole induction period but the biochemical investigations were performed weekly before chemotherapy.

The values of serum LDH level in ALL patients were assessed by measuring it along with the hematological parameters, the bone marrow aspirate and its morphological examination again on day 14 and day 29 of induction. Serum LDH level of all hemato-oncological malignancies on admission was correlated with serum LDH level in control. Serum LDH level was also correlated with the hematological parameters, peripheral and bone marrow blast cell percentages on admission, day 14 and day 29 of induction in ALL.

Collected raw data were organized into a statistical format and appropriate statistical analysis was done. All continuous data were expressed as mean ± SD and the categorical data in percentage. The values were analyzed statistically with paired "t" test, correlation co-efficient "r" test. "p" value of <0.05 was taken as minimum level of significance.

Results

Among 102 subjects, hemato-oncological malignancies were 77 (ALL-44, AML-16, HD-9 and NHL-8) and control 25 (Fig-1).

The mean ± SD of serum LDH level in hemato-oncological malignancies on admission were (2091.98±1073.20) U/L in ALL, (507.50±171.53) U/L in AML, (495.89±156.92) U/L in HD (633.50±296.52) U/L in NHL and in control it was (362.32±89.69) U/L. It was about six times the control value in ALL (Table-I).

On admission serum LDH level was significantly raised in AML, HD, NHL but the value was highly significant in ALL (p<0.001) (Table-II).

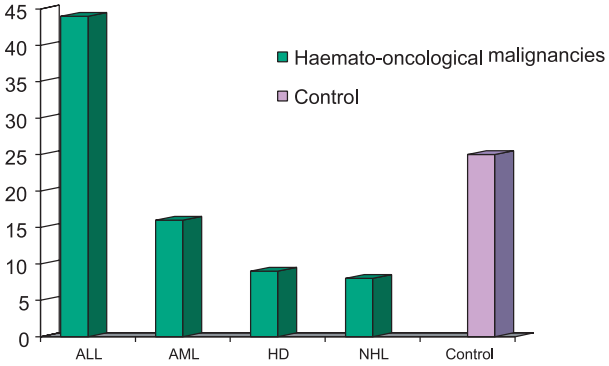

Fig.-1: *Grouping of the subjects (n=102)*

Table-I

Serum LDH level in study subject on admission (n=102)

Groups		Serum LDH (U/L) Mean± SD
Haemato-oncological malignancies	ALL	2091.98±1073.20
	AML	507.50±171.53
	HD	495.89±156.92
	NHL	633.50±296.52
Control		362.32±89.69

Table-II

Comparison of serum LDH level between hemato-oncological malignancies and control on admission (n=102)

Parameter	Hemato-oncological malignancies		Control	"p"
Serum LDH (U/L) Mean ±SD	ALL	2091.98±1073.20	362.32±89.69	*<0.001
	AML	507.50±171.53	362.32±89.69	<0.01
	HD	495.89±156.92	362.32±89.69	<0.05
	HNL	633.50±296.52	362.32±89.69	<0.05

*Highly significant

Mean ± SD of total WBC count and serum LDH level in ALL on admission, day 14 and day 29 of induction were 121306.82±141005.02,15002.27±14208.08 and 8047.73±7372.21/mm^3 and 2091.98 ± 1073.20, 561.43 ± 266.24 and 701.70 ± 420.17 U/L respectively. Total WBC count was very high on admission and significantly decreased along with significant decrease of serum LDH level on day 14, day 29 of induction from admission (p<0.001) (Fig-2).

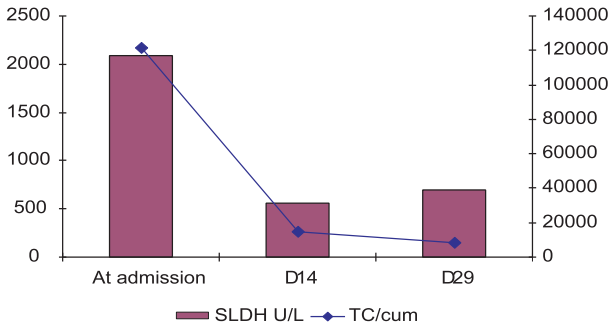

Fig.-2: *Correlation between serum LDH level and total WBC count on admission, day 14 and day 29 of induction in ALL (n=44)*

On admission, day 14 and day 29 of induction mean ±SD of platelet count were 72272.72±57176.33, 67795.45±39949.14 and 84136.36±47897.94/ mm^3 respectively. There was high platelet count observed on day 29 of induction from admission in relation to significant decrease level of serum LDH (p<001) (Fig-3).

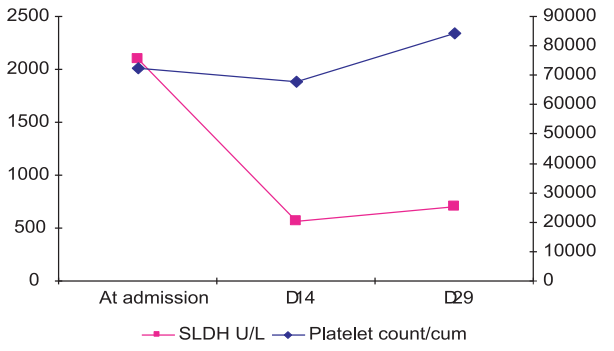

Fig.-3: *Correlation between serum LDH level and platelet count on admission, day 14 and day 29 of induction in ALL (n=44)*

In ALL patients mean ± SD of peripheral blood and bone marrow blast cell on admission, day 14 and day 29 of induction 62.27±26.80, 4.02±5.27 and 1.36±2.65% respectively and 45.95±17.08, 18.34±8.47 and 9.98±11.53% respectively. Level of serum LDH were significantly decreased along with significant decrease of peripheral blood and bone marrow blast cells percentages on day 29 of induction of remission from admission (p<0.001) (Fig-4 and Fig-5).

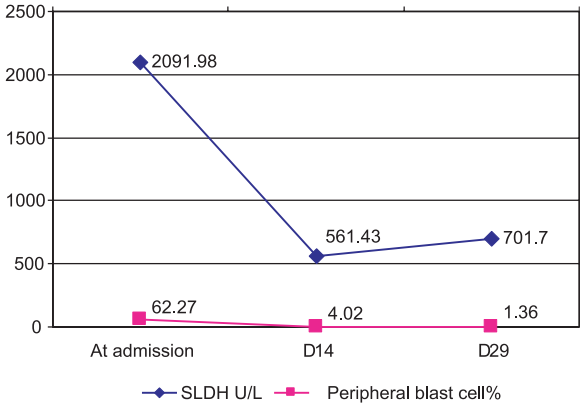

Fig.-4: Correlation between serum LDH level and peripheral blast cell percentage on admission, day 14 and day 29 of in induction in ALL (n-44).

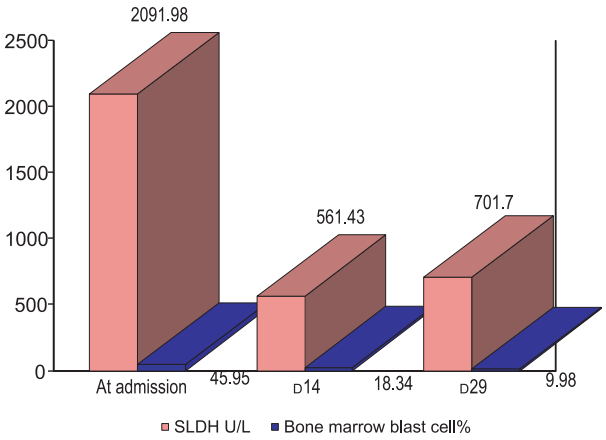

Fig.-5: *Correlation between serum LDH level and bone marrow blast cell percentage on admission, day 14 and day 29 of induction in ALL (n=44).*

Discussion

The observation in this study is that the level of serum LDH on admission was significantly raised in AML, HD and NHL but the values were found highly significant in ALL and it was about six times more than control (p<0.001). These findings are consistent with the observations of Kornberg and Polliack[6], when they showed that marked elevations of serum LDH

level are highly suggestive of acute leukemia of lymphoblastic type. Increased cellular LDH activity reflects a shift towards anerobic metabolism and increased glycolysis in the cytoplasm of malignant cells accompanied by high cellular turnover rate, two separate study performed by Stuart et al[15] and Field et al[16].

Our results are similar to those obtained by Stuart et al[15], Sector et al[17], and Bierman et al[18], when they found increased serum LDH activity in isolated lymphoblasts and in the serum of patients with ALL and in animals with transplantable lymphatic leukemia. In contrast to the above data and the findings of this study, Bierman et al, reported the elevated level of LDH in 47 of 54 patients with lymphatic leukemia and in all patients with the myeloid leukemia and 86% of patients with malignant lymphoma.

Though serum LDH level was significantly decreased on day 14 and day 29 of induction from admission but on day 29 of induction the level was somewhat higher than that of day 14, this may be due to 6 (13%) patients with ALL who did not responded to usual doses of chemotherapy. With increasing genetic instability due to decreasing cell cycle control mechanism, the malignant cell may acquire additional characteristics of invasiveness and decrease sensitivity. Basing on a better understanding of the cancer cells new therapeutic approaches can now be tested reported by Wagner, 2001[19], but the rest 38 (87%) patients with ALL undergone complete remission. This observation had similarities with the findings of Erickson and Morales, where they showed that with exacerbations in patients under treatment for leukemia the level of serum LDH raises again[7].

Though there was no significant rise of platelet count observed on day 14 of induction, significant raised level of platelet on day 29 from admission in relation to significant decrease level of serum LDH ($p<0.001$). These findings are consistent with the observation of West et al, when they found that following treatment with chemotherapeutic agents serum LDH levels were decreased[20]. These observations also had similarities with the study of Erickson and Morales, when they proved that estimation of serum LDH level has prognostic value during induction of remission[21].

On admission and day 14 of induction, there was no significant correlation found between the peripheral and bone marrow blasts cell percentages with serum LDH level but a significant decrease value of both peripheral and bone marrow blast cell percentages were observed along with the significant decrease level of serum LDH on day 29 of induction from admission ($p<0.001$). These findings were consistent with the observations of Kornberg and Polliack, where they found where the elevated serum LDH levels might relate more to the total leukemic cell mass than to the number of circulating blasts[6]. However, in individual patient with ALL, a good correlation was found during cytotoxic treatment, remission and relapse[6].

Conclusion

It can be presumed from this study that marked elevation of serum LDH level is very common in childhood ALL than other hemato-oncological malignancies and the level decreases along with the return of hematological parameters towards normal during induction of remission.

So, it is recommended that serum LDH level estimation can be accepted as a good and reliable enzymatic predictor for diagnosis of the hemato-oncological malignancies and prognosis of children with ALL. Further multicenter prospective study with large sample size may be helpful to justify this statement.

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