Original article

Outcome of Tumor Lysis Syndrome with Hydration and Alkalinization in Children with Acute Lymphoblastic Leukemia

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Abstract:

Objective: To observe the out come of tumor lysis syndrome (TLS) following treatment with hydration and alkalinization in children with acute lymphoblastic leukemia. ***Methodology*:** This is an observational study which included 30 diagnosed ALL children who were at high risk of developing TLS in the Department of Pediatric Hematology & Oncology, BSMMU, from January 2010 to July 2010. ***Result*:** The mean (±SD) age was found 10.2±2.9 years and maximum (46.7%) numbers were found between 11 to 15 years. Male female ratio was 2.3:1. High risk patients for developing TLS presented with huge organomegaly such as hepatomegaly, splenomegaly, and lymphadenopathy associated with fever, anemia, and bony tenderness. For diagnosis of Acute Lymphoblastic Leukemia (ALL) bone marrow study was done in all patients and immunophenotyping in 40.0% patients. Hydration, Alkalinization, Tab Allopurinol and Oral Aluminum hydroxide were used in all study patients while treatment. WBC and serum uric acid were found higher in all patients during baseline investigation. After hydration and Alkalinization serum potassium, serum phosphate, serum calcium and serum creatinine level were normal within 72 hours and serum uric acid within day five. Mortality was found 6.7% and the cause of mortality was septicemia.

Introduction:

Tumor lysis syndrome (TLS) is a potentially life threatening complication of massive cellular lysis in rapidly proliferating bulky, or highly chemo-radio sensitive cancer cells[1]. It is a group of metabolic complication that occurs after treatment of cancer, usually lymphomas and leukemia and sometimes even without treatment[2]. These complications are caused by the break-down products of dying cancer cells and include hyperkalemia, hyperphosphatemia, hyperuricemia and hypocalcaemia and consequent acute uric acid nephropathy and acute renal failure [2]. TLS is observed in patients with acute lymphoprolifeatve disorders with high proliferative rate, and high tumor sensitivity to chemotherapy. Like acute lymphoblastic leukemia, Burkitt's lymphoma[3].

Risk of TLS based on patient's characteristics is as follows[4]:

High tumor burden-(define as tumor large in size serum lactate dehydrogenase level >1500Iu/L, WBC > 25,000/mm^3)
Elevated pretreatment uric-acid level
Tumor that is highly sensitive to treatment
Dehydration
Decreased urine output
Pre-existing renal dysfunction
Acidic urine
Tumor involvement of the kidney or renal vasculature

The pathogenesis of TLS is rapid cell lysis following the administration of cytotoxic therapies. The large amount of intracellular components dumped into the extracellular compartment exceeds the catabolic and excretory capacities of the liver and kidneys. This sharp increase in the concentration of selected cellular components overwhelms the body's normal homeostatic mechanisms, resulting in impaired organ function (such as renal failure) and associated morbidity (such as cardiac dysrhythmias and tetany). The characteristic metabolic anomalies of TLS include hyperuricemia, hyperphosphatemia with associated hypocalcaemia, and hyperkalemia[5].

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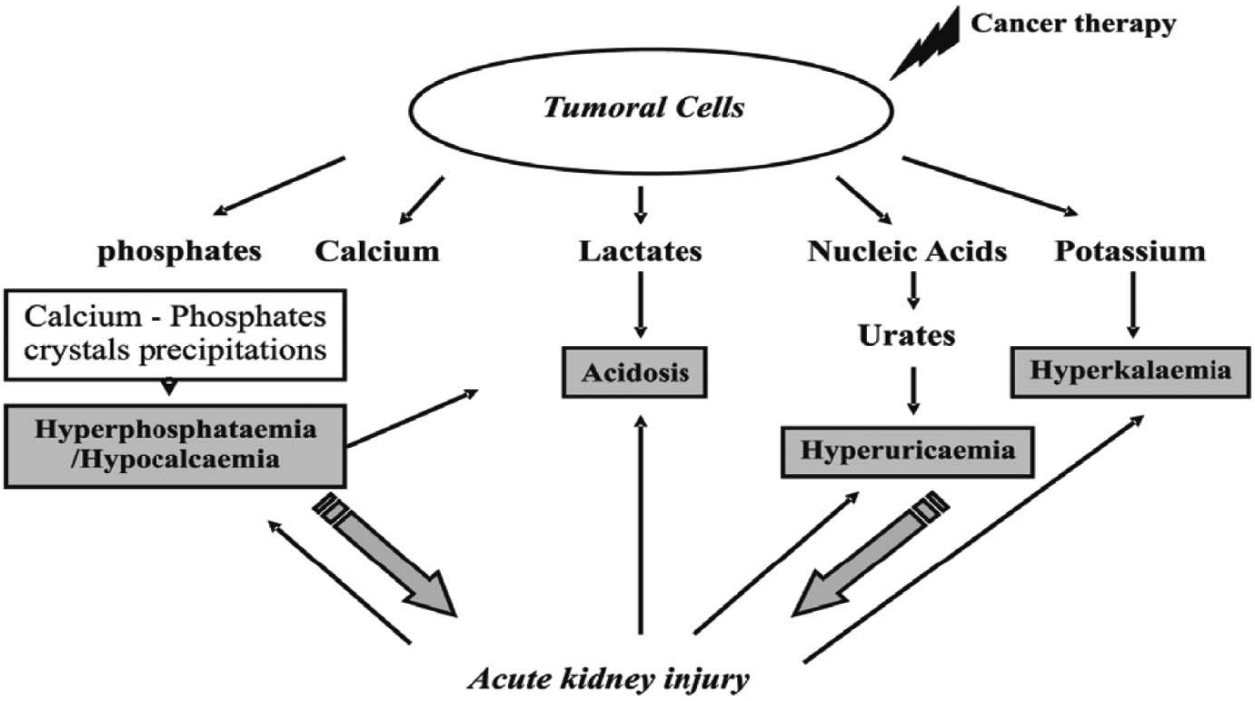

Pathophysiology of the tumor lysis syndrome

Clinical signs and symptoms associated with TLS may include nausea, vomiting, lethargy, edema, congestive heart failure, dysrhythmias, muscle cramps, tetany, paresthesias, back pain, syncope, renal failure, and seizures[4]. Although symptoms may develop upon individual patient presentation, they are more likely to manifest within 12 to 72 hours after administration of anti cancer therapy.

Hyperuricemia occurring two to three days after initiation of cytotoxic therapy is a result of the rapid release and catabolism of intracellular nucleic acids[4]. Hyperphosphatemia is frequently found in association with hypocalcaemia[6]. The most serious consequence of TLS is hyperkalemia, which usually is seen within 6 to 72 hours after cytotoxic therapy is initiated[6]. Liberation of intracellular potassium into the extracellular space can quickly overwhelm the kidneys ability to excrete potassium. High serum concentrations of potassium, which can be exacerbated by renal failure, acidosis, and hypocalcaemia, can lead to ventricular arrhythmias and sudden death. Symptomatic patients should be evaluated for dialysis, as this is the most effective method of lowering serum potassium values[6].

Aggressive hydration should be started at least 24 to 48 hours prior to chemotherapy initiation at a rate 3L/m^2/day[5]. Alkalinization of the urine assists in decreasing the incidence of uric acid nephropathy and subsequent renal failure. Methods of alkalinizing the urine include the addition of sodium bicarbonate, 50-100 mEq/L[5].

Materials and Methods:

This is an observational study which was done between January 2010 to July 2010 among 30 children aged between 1 to 15 years at Department of Pediatrics Hematology & Oncology, BSMMU, Dhaka. The inclusion Criteria of the study were as follows:

1. Children diagnosed as a case of ALL
2. Presence of two or more following serum levels

Hyperleukocytosis (WBC>50,000/mm^3)
Serum uric-acid > 6 mg/ dl.
Serum potassium > 5 mmol/l.
Serum phosphate > 4 mg/dl
Serum calcium < 8mg/dl
Serum Creatinine > 2mg/dl

Children less than 1 year of age and malignancy other than ALL were excluded from the study.

There was no ethical concern for this study. Informed consent was obtained from the parents before including their children in the study. Careful physical examination was performed. All relevant investigations were done. The patients were managed accordingly. Structured questionnaire was used for data collection.

Data was analyzed by statistical package for social-sciences (SPSS) version 14.0 programme. Statistical significance was assigned to two sided p values less than 0.05.

Results:

Total 30 children diagnosed as ALL between 1 to 15 years of age fulfilling the inclusion criteria were studied. Age, sex, mode of presentation, laboratory findings and treatment were recorded. All the relevant findings were reviewed in the following tables.

In this current study it was observed the mean (±SD) age was 10.2±2.9 years ranging from 1 to 15 years and most (46.7%) of the patients were found between 11 to 15 years (Table I). The study was similar with Alavi et al[7]. and Ozdemir et al studies [8]. Male children were predominant in this study and male female ratio was 2.3:1.

In this present series it was observed that high risk patients for developing TLS presented with huge organomegaly. Fever, anemia and hepatomegaly were present in all of the study patients. Splenomegaly was observed in 96.29%, bony tenderness in 76.7%, lymphadenopathy in 70.0%, nausea & vomiting 50.0%, bleeding in 46.7%, joint/Limb pain in 40.0%. (Table II). Similar observations regarding the clinical presentations were also made by Davidson et al. (2004)[9] and Hagino[10].

Bone marrow study was done in all patients, immunophenotyping done in 40.0% and both diagnoses were done in 40.0% study patients. The mean (±SD) HB% was observed 6.1±0.9%; platelet count 48.6±15.3, S. LDH 1989±479.3 U/L, S. ALT 104.5±37.9 U/L and S. Na 139.8±3.2 mmol/L (Table III). Alavi et al. reported that pretreatment LDH, and initial WBC count were not associated with higher incidence of TLS after chemotherapy, but a significant correlation was found between pretreatment renal involvement at imaging studies and development of TLS after chemotherapy (p = 0.027). The results indicate that despite all preventive measures, tumor lysis syndrome still occurs in children following chemotherapy.

In this current series it was observed that Hydration, Alkalinization, tab Allopurinol and oral Aluminum hydroxide were used in all study patients while treatment. oral Calcium carbonate was used in 36.7%, Inj. Mannitol in 13.3% and parenteral 10% calcium in 6.7%. Dialysis was not required while treatment (Table IV). The study was almost similar to the treatment used by Alavi et al. (2006)[7], Ozdemir et al. (2009)[8] and Hagino(2010) [10]. The study shows that, only 2 (6.7%) children died during the study period and the cause of death was septicemia (Table X).

Table I: Table showing Age group of the study patients (n=30)

Age in years	Number of patient (n= 30)	Percentage
1-5	0	0.0
5 – 10	16	53.3
11 – 15	14	46.7
Mean± SD	10.2±2.9	

The mean (±SD) age were found 10.2±2.9 years ranging from 1 to 15 years and most (46.7%) of the patients were found between 11 to 15 years.

Table II: Common clinical profile of study patients (n=30)

Clinical information	Number of patient (n=30)	Percentage
Fever	30	100.0
Anemia	30	100.0
Hepatomegaly	30	100.0
Splenomegaly	29	96.7
Bony tenderness	23	76.7
Lymphadenopathy	21	70
Bleeding manifestation	14	46
Joint/ limb pain	12	40
Convulsion	0.0	0.0

Clinical features of the study patients shows, fever, anemia and hepatomegaly present in the entire study group. Splenomegaly was observed in 29 (96.29%), bony tenderness in 23 (76.7%), lymphadenopathy in 21(70.0%), bleeding in 14(46.7%), joint/Limb pain in 12 (40.0%) and convulsion among none.

Bone marrow study was done in all patients, immunophenotyping in 12(40.0%) and both diagnosis in 12(40.0%) of the study patients. The mean (±SD) HB% was observed 6.1±0.9% ranging from 4.2 to 7.5%. Mean (±SD) platelet was 48.6±15.3 ranging from 30 to 77. Mean (±SD) S. LDH was

Table III: Laboratory findings of the study group (n=30)

Laboratory findings	Number of patient (n=30)
Bone marrow study	30 (100%)
Immunophenotyping	12 (40%)
Both Bone marrow study & immunophenotyping	12 (40%)
Hb%	
Mean±SD	6.1±0.9
Range (min-max)	(4.2-7.5)
Platelet (platelet count × 10^9/L)	
Mean ± SD	48.6±15.3
Range (min-max)	(30 – 77)
S. LDH (U/L)	
Mean±SD	1989 ± 479.3
Range (min-max)	(1245 – 3424)
S. ALT (U/L)	
Mean±SD	104.5±37.9
Range (min-max)	(27 – 179)
S. Na (mmol/l)	
Mean±SD	139.8±3.2
Range (min-max)	(130 – 148)

observed 1989±479.3 U/L ranging from 1245 to 3424 U/L. Mean (±SD) S. ALT was observed 104.5±37.9 U/L ranging from 27 to 179 U/L. Mean (±SD) S. Na was observed 139.8±3.2 mmol/L ranging from 130 to 148 mmol/L.

Table IV: Treatment given to study group of patients (n=30)

Treatment	Number of patient (n=30)	Percentage
Hydration (3 litre/m^2)	30	100.0
Alkalinization (sodium bicarbonate)	30	100.0
Tab. Allopurinol	30	100.0
Oral Aluminum hydroxide	30	100.0
Oral calcium carbonate	11	36.7
Inj. 10% calcium gluconate	2	6.7
Inj. Mannitol	4	13.3
Dialysis	0	0.0

The table shows that, Hydration, Alkalinization, Tab Allopurinol and Oral Aluminum hydroxide were used in all study patients while treatment. Oral Calcium carbonate was used in 11(36.7%), Inj. Mannitol in 4(13.3%) and 10% calcium gluconate in 2(6.7%). Dialysis was not required in any patient.

Table V: WBC count of the study sample (n=30)

Investigation	Baseline	After 24 hrs	After 72 hrs	After 5 days
WBC (total count ×10^9/L)				
Mean ± SD	140.6±48	88.9±28.6	30.3±13.12	33.9±15.3
Range (min-max)	(90-292.5)	(85–155)	(33.6–71.22)	(17.4–71.3)

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The WBC count of the study patients and the mean (±SD) WBC at baseline was 140.6±48 ranging from 90 to 292.5. Mean (±SD) WBC after 24 hours was 88.9±28.6 ranging from 85 to 155, after 72 hours was 30.3±13.12 ranging from 33.6 to 7122 and after 5 days was 33.9±15.3 ranging from 17.4 to 71.3.

Table VI: Serum uric acid level of the study sample (n=30)

Serum Uric acid mg/ dl	Baseline (n=30)		After 5 days (n=30)		p value
	n	%	n	%	
Normal	0	0	30	100	
High	30	100	0	0	0.001
Mean ±SD	7.8 ± 0.8		3.9 ± 0.5		
Range (min-max)	6.3 – 11		3.2 - 5		

The serum uric acid level of the study patients shows that, during baseline all of the study patients had high serum uric acid level but after 5 days all had normal level. The mean (±SD) serum uric acid level at baseline was 7.8±0.8 mg/dl ranging from 6.3 to 11. Mean (±SD) serum uric acid after 5 days was 3.9±0.5 ranging from 3.2 to 5. The difference was observed significant ($p<0.05$) in Chi square test.

Table VII: Serum potassium level of the study group (n=30)

Serum Potassium mmol/l	Baseline (n=30)		After 72 hrs (n=30)		p value
	n	%	n	%	
Normal	13	43.3	30	100	0.001
High	17	56.7	0	0	
Mean ± SD	6.2	6.8	3.7	0.3	
Range (min - max)	(3.5 – 5.9)		(3.5 – 4.3)		

The serum potassium level of the study patients shows that, more than half (56.7%) of the study patients had high serum potassium level, but after 72 hours all had normal values. The mean (±SD) serum potassium level at baseline was 6.2±6.8 mmol/l ranging from 3.5 to 5.9 mmol/l. Mean (±SD) serum potassium after 72 hours was 3.7±0.3 mmol/l ranging from 3.5 to 4.3 mmol/l. The difference was observed significant ($p<0.05$) in Chi square test.

Table VIII: Serum calcium level of the study group (n= 30)

Serum Calcium mmol/l	Baseline (n=30)		After 72 hrs (n=30)		p value
	n	%	n	%	
Normal	19	63.3	30	100	0.001
Low	11	36.7	0	0	
Mean ± SD	8.6 ± 1.4		9.1 ± 0.4		
Range (min - max)	(6.2– 11)		(8.5 – 10)		

Maximum 19 (63.3%) number of the study patients had normal serum calcium at baseline and all after 72 hours. The mean (±SD) serum calcium at baseline was 8.6±1.4 mg/dl ranging from 6.2 to 11 mg/dl. Mean (±SD) serum calcium after 72 hours was 9.1±0.4 mg/dl ranging from 8.5 to 10 mg/dl. The difference was observed significant ($p<0.05$) in Chi square test.

Table IX: Serum creatinine level of the study group (n= 30)

Serum Creatinine Mg / dl	Baseline (n=30)		After 72 hrs (n=30)		p value
	n	%	n	%	
Normal	23	76.7	30	100	0.001
High	7	23. 3	0	0	
Mean ± SD	1.2 ± 0.9		0.9 ± 0.1		
Range (min - max)	(0.5 – 3.3)		(0.7 – 1)		

Majority 23(76.7%) of the study patients had normal serum creatinine level at baseline and all after 72 hours. The mean (±SD) serum creatinine at baseline was 1.2±0.9 mg/dl ranging from 0.5 to 3.3 mg/dl. Mean (±SD) serum creatinine after 72 hours was 1.2±0.9 mg/dl ranging from 0.7 to 1 mg/dl. The difference was observed significant ($p<0.05$) in Chi square test.

Table X: Mortality and cause of mortality of the study patients (n=30)

	Number of patients (n=30)	Percentage
Alive	28	93.3
Died	2	6.7
Cause of mortality		
Septicemia	2	6.7

Table X shows the mortality and the cause of mortality of the study patients. 2(6.7%) children with ALL died while on treatment and the cause of death was septicemia.

Discussion

This observational study was carried out with an aim to observe the outcome of Tumor Lysis Syndrome (TLS) in children with ALL who were treated adequately with hydration and alkalinization; to improve awareness in diagnosis and management of TLS.

A total of 30 children diagnosed as a case of ALL who are developing TLS, age ranging from 1 to 15 years were enrolled in the study, in the Department of Pediatric Hematology & Oncology, BSMMU, Dhaka, during January 2010 to July 2010.

In this current study it was observed that the mean (±SD) age was 10.2±2.9 years with ranging from 1 to 15 years and most (46.7%) of the patients were found between 11 to 15 years, which was similar with Alavi et al. and Ozdemir et al. studies.

Male children were predominant among the study patients and male female ratio was 2.3:1. In this present series it was observed that, high risk patients for developing TLS presented with huge organomegaly. Fever, anemia and hepatomegaly were present in all of the study patients. However, splenomegaly was observed in 96.29%, bony tenderness in 76.7%, lymphadenopathy in 70.0%, nausea & vomiting 50.0%, bleeding in 46.7%, joint/Limb pain in 40.0%. Convulsion and tetany was not observed. Similar observations regarding the clinical presentations were also made by Davidson et al.[9] and Hagino[10].

Bone marrow study was done in all patients, immunophenotyping in 40.0% and both diagnoses were done in 40.0% study patients. The mean (±SD) HB% was observed 6.1±0.9%, platelet 48.6±15.3, S. LDH 1989±479.3 U/L, S. ALT 104.5±37.9 U/L and S. Na 139.8±3.2 mmol/L. Alavi et al. (2006) reported that pretreatment LDH, and initial WBC count were not associated with higher incidence of TLS after chemotherapy, but a significant correlation was found between pretreatment renal involvement at imaging studies and development of TLS after chemotherapy ($p = 0.027$). The results indicate that despite all preventive measures, tumor lysis syndrome still occurs in children following chemotherapy.

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The present study shows that the mean (±SD) WBC at baseline was 140.6±48 ranging from 90 to 292.5, after 24 hours 88.9±28.6 ranging from 8.5 to 155, after 72 hours 303.3±1312 ranging from 33.6 to 7122 and after 5 days was 33.9±15.3 ranging from 17.4 to 71.3. Ozdemir et al. (2009) mentioned that intravenous low-dose prednisolone continuous infusion treatment can prevent the progression to tumor lysis syndrome and it may be

used for the patients presenting with white blood cell counts between 100 and 400 x 10(9)/l in centers where leukopheresis is not readily available.

In this present series it was observed that all patients had serum uric acid level high during baseline and after 5 days it was found within normal level. Serum potassium and serum phosphate level were high in 56.7% and 16.7% respectively during baseline and after 5 days it was found within normal level. Serum calcium level was low in 36.7% during baseline and after 5 days it was found within normal level. Serum creatinine was high in 23.3% during baseline and after 5 days it was found within normal level. Abdullah et al. (2008) have shown the mean serum phosphate levels decreased after sevelamer administration, in eleven patients, from a baseline 2.2±0.4 mmol/L (95% CI, 1.7-3.1) to 1.1±0.2 mmol/L at hour 72 (95%CI, 0.6-1.5).

Finally the current study shows that 6.7% children with ALL died during the study period and the cause of death was found to be septicemia.

Conclusion

Tumor lysis syndrome is a potentially life-threatening complication of cancer treatment in patients with extensive, rapidly growing, chemo sensitive malignancies. The result is a constellation of metabolic disturbances that can cause acute kidney injury (AKI) of which, the most common mechanism is uric-acid crystal formation in the renal tubules. Another cause of AKI is calcium-phosphate deposition related to hyperphosphatemia. AKI may, in itself, cause substantial morbidity and mortality. High risk patients developing TLS presented with huge organomegaly (hepatomegaly, splenomegaly). Maximum (46.7%) numbers were found between 11 to 15 years and male children were predominant in the whole study. WBC and serum uric acid were found higher in all patients during baseline investigation. After hydration and Alkalinization, serum uric acid, serum potassium, serum phosphate, serum calcium and serum creatinine level were found within normal range.

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