PREVALENCE OF HYPERGLYCAEMIA IN ACUTE LYMPHOBLASTIC LEUKAEMIA AND ITS IMPACT ON THERAPY DURING INDUCTION AT JNIMS - A PRELIMINARY DATA

Anil Singh Irom[1], Lokeshwar Singh Khumukcham[2], Ginzaniang T[3], Kameshore Singh Nandeibam[4], Banashree Devi R. K[5], Vedanti Devi Pukhrambam[6], Mustaque Mohammed[7], Peepa Khoinaijam[8]

[1]Assistant Professor, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[2]Associate Professor, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[3]Associate Professor, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[4]Associate Professor, Department of Paediatrics, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[5]Associate Professor, Department of Pathology, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[6]Assistant Professor, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[7]Senior Resident, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.
[8]Postgraduate Trainee, Department of General Medicine, Jawaharlal Nehru Institute of Medical Sciences, Porompat, Manipur.

ABSTRACT

BACKGROUND

Glucocorticoids and L-asparaginase form essential components of induction therapy in Acute Lymphoblastic Leukaemia (ALL). These drugs produce hyperglycaemia in about 10-16% in children and 10-56% among adults. Hyperglycaemia has been associated with shorter duration of remission, decreased survival periods, increased infections and mortality rate. We wanted to study the prevalence of hyperglycaemia in patients suffering from ALL and the impact of hyperglycaemia during induction therapy.

MATERIALS AND METHODS

ALL patients admitted in the medicine ward and paediatric ward (Haematology) from July 2017-October 2018 were included in the study. Known cases of diabetes were excluded. Random blood glucose levels >200 mg/dL or fasting blood glucose >126 mg/dL in two occasions were defined as hyperglycaemia. All hyperglycaemic patients were treated with insulin (Basal and Sliding Scale).

RESULTS

The incidence of hyperglycaemia in the study was 23%. All of the hyperglycaemic patients were above 30 years of age. The prevalence of infections including bacterial and fungal infection was more in the hyperglycaemic group. The complete remission (CR) was achieved in 76.08% patients. There were 11 deaths during induction and 4 deaths after CR.

CONCLUSION

Bacterial sepsis and fungal infections are more common in hyperglycaemic patients. Hyperglycaemia associated with increased mortality rate and causing decreased CR.

KEYWORDS

Hyperglycaemia, Steroids, L-Asparaginase, Acute Lymphocytic Leukaemia (ALL); Complete Remission.

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BACKGROUND

Glucocorticoids and L-asparaginase form an essential component acute lymphoblastic leukaemia (ALL) management. These drugs are known to produce hyperglycaemia in about 10-16% of patients during induction therapy in children.[1] Hyperglycaemia may be detected during the induction of acute leukaemia in adults in a range of 10-80%.[2,3] Hyperglycaemia is also produced during any acute illness due to release of stress hormones (e.g. epinephrine and cortisol) or release of inflammatory cytokines due to sepsis. The increase in blood glucose can produce increased hospital mortality, increase the duration of hospitalization, infection, and admission to the intensive care units in non-critical patients.[1] Hyperglycaemia can cause proliferation of leukemic cell due to increasing glucose uptake with increased glucose utilization for nucleic acid synthesis and decrease glucose oxidation.[4] High blood glucose is known to produce shorter remission, shorter median survival, increased risk of sepsis in adults.[2] Thus, hyperglycaemia can arise from various reasons in ALL including drugs, infections and the disease itself being a

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Corresponding Author:
Dr. Khumukcham Lokeshwar Singh,
Department of General Medicine,
Jawaharlal Nehru Institute of Medical Sciences,
Porompat- 795005, Manipur.
E-mail: lokeshwarsingh57@gmail.com
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stressful condition. It remains a formidable challenge for the clinicians managing the ALL when there is hyperglycaemia in the induction therapy. So far various authors have tried to study the effects of hyperglycaemia in non-critical illness, but lesser studies were done in haematological malignancies. The majority of the studies done so far on acute leukaemia were from other parts of the world. So, the study is being conducted to understand hyperglycaemia in ALL therapy in the Indian scenarios.

Aims and Objective

1. To study the prevalence of hyperglycaemia in patients suffering from acute lymphoblastic leukaemia.
2. To study the impact of hyperglycaemia on therapy during induction.

MATERIALS AND METHODS

The study was conducted at the Department of Medicine and Paediatrics, Jawaharlal Institute of Medical Sciences, Imphal. The preliminary data were collected from patients July 2017 to November 2018. The study was an observational study. Inclusion criteria was all newly diagnosed Acute lymphoblastic leukaemia (ALL) and exclusion criteria included Acute myeloid leukaemia (AML), relapsed ALL, known diabetes and severe active infections rendering patients unfit for the chemotherapy. Diagnosis of ALL was made by morphology and flowcytometry of bone marrow. Cytogenetic study was done for all the patients. Reverse transcription polymerase chain reaction for BCR ABL1 done for B-ALL patients. The patients were stratified as standard risk or high risk per the NCI (National cancer institute) risk. The patients with standard risk were treated with standard BFM protocol and high risk was treated with augmented BFM protocol. Patients up to 30 years of age were treated with augmented BFM protocol and age older than 30 years were treated with adult ALL protocol. The induction therapy was same in both the standard and augmented BFM protocol. Prednisolone was given at 60 mg/m^2 per day orally from 1-28 days then taper over 10 days. The patients in the adult ALL protocol received one week of steroid pre-induction therapy. Dexamethasone at 5 mg/m^2 IV for two days followed by oral prednisolone at 60 mg/m^2 for 5 days. After the completion of steroid pre-induction phase patients were given prednisolone at 60 mg/m^2 orally from 1-22 days then taper over 10 days. Vincristine was given at 1.5 mg/m2 (max, 2 mg) IV and daunorubicin at 25 mg/m2 IV on day 1, 8, 15 and 22 in standard and augmented protocols. While in adult protocol vincristine was given at 1.5 mg/m2 (max, 2 mg) IV and daunorubicin at 40 mg/m2 IV on day 1, 8, 15 and 22. L-Asparaginase - 6000 U/m^2 IV/IM on day 3, 5, 7, 10, 12, 14, 17, 19 and 21 in the standard or augmented BFM while in the adult protocol it was added on the 23rd day and given for 9 days consecutively. Intrathecal chemotherapy was given in all at baseline. All the patients were provided supportive therapy as per standard care.

Serum electrolytes, KFT and LFT were done on alternate days during the induction. Blood glucose levels were checked before the patients were put on therapy to know baseline glucose levels. Fasting blood glucose ≥126 mg/dl or random blood glucose ≥200 mg/dl on more than two occasions were recorded as hyperglycaemia. Blood glucose was routinely checked three times a day before meals during induction. Patients having hyperglycaemia were started on insulin sliding scale as per standard protocol. The patients with high glucose level with sliding insulin were given basal-bolus insulin regimen after consulting the Endocrinology Dept. Infection were classified as uncomplicated (including upper respiratory infection, urinary tract infection, PICC line infection or fever of unknown origin) or complicated (sepsis or a documented infection involving a major organ system including the lungs, kidneys, heart, soft tissue, central nervous system, or gastrointestinal tract (MODS)and fungal infection as either possible, probable and proven). Complete remission (CR) was assessed by doing bone marrow examination after the haematological parameters were recovered.

All statistical tests were performed using STATA 13.0 software. The statistical analysis included two sample tests of proportions; chi 2, Fisher's exact where applicable. P-value of less than 0.05 was significant.

RESULTS

The total number acute leukaemia during the study period was 68. Of them 40 patients were suffering from AML and they were excluded from the study. There were 28 ALL patients. Baseline characteristics of the patients are shown in table no. 1.

Characteristics	(n=28) (%)
Age (yrs.)	
1-10	12 (42%)
11-20	3 (11%)
21-30	4 (14%)
>30	9 (35%)
Male	15 (53%)
Female	13(47%)
BALL	21 (75%)
TALL	7(25%)
BCR-ABL+ve	
<10 years	1 (3.5%)
>10 years	3 (10.7%)
Baseline infection +ve	1 (3.5%)

Table 1. Baseline Characteristics of Patients

In the study, hyperglycaemia was not present in patients below 30 years of age. Hyperglycaemia was present in 8 (28.5%) in patients with age above 30 years. It was found that uncomplicated infection was seen in 75% hyperglycaemic patients vs. 45% non-hyperglycaemic (p-value=0.15). The incidence of complicated infection in hyperglycaemic patients was 50% while there was none in non-hyperglycaemic (p-value=0.006). The majority of fungal infection was probable fungal infection comprising and seen only in the hyperglycaemic group 50% (p-value 0.006).

	Hyperglycaemia		p-value
	Yes (n =8) (%)	No (n=20) (%)	
Uncomplicated Infection	6(75%)	9(45%)	0.15
Complicated infection	4 (50%)	0	0.006
Fungal infection	4(50%)	0	0.006

Table 2. Infection During Induction

In the study, normoglycaemic patients achieved complete remission (CR) rate of 100% while hyperglycaemic patients had CR rate of 87.5% (p-value=0.13). There were 2(25%) deaths in the hyperglycaemic group during the study period. Of which 1 patient died during induction and the second one died after CR was achieved due to defaulting the treatment.

	Hyperglycaemia		P-value
	Yes (n =8) (%)	No (n=20) (%)	
CR	7(87.5%)	20(100%)	0.13
Death	2(25%)	0	0.002

Table 3. Induction Outcome

DISCUSSION

Several studies by various authors have reported the incidence of hyperglycaemia among paediatric ALL about 10-16%.[1,5,6] In our study, the hyperglycaemia was not detected in paediatric ALL patients less than 10 years of age. Our finding may be due to small study sample. In the older age groups, the various authors have reported incidence in the range of 10-80%. Weiser et al had reported an incidence of 37% hyperglycaemia in adult ALL patients treated with Hyper CVAD regimen.[4] While Matias et al in their study of adult acute leukaemia treatment had reported hyperglycaemia in 63.3% and found that 80% patients above 30 years had hyperglycaemia.[3] In our study, the incidence of hyperglycaemia in patients above 30 years of age was 28.5% which is comparable to that of Weiser et al. The patients above 30 years of age were all hyperglycaemic.

Various authors have reported increase bacteraemia or fungemia in the hyperglycaemic group. Sonabend et al had reported that out of 43 patients with bacteraemia or fungemia, 36 (83.7%) patients were hyperglycaemic. They had reported that hyperglycaemic patients were more likely to have documented infection 2.2 times more than the normal glycemic patients.[6] In another study by Robertson et al, they had reported that the mean number of infection per patient who experienced hyperglycaemia was 1.4 versus 1.2 in those who did not experience hyperglycaemia (p=0.34).[7] While another study by Julianne et al had shown that the suspected or proven infection was common in mild and overt hyperglycaemia group.[8] Weiser et al also reported that the rate of infection was more in the hyperglycaemic group (71.8% vs. 56%; p=0.009). The chance of getting complicated infection was also more in the hyperglycaemic group (38.8% vs. 25.1%; p=0.013).[4] The rate of complicated infection among the hyperglycaemic patients in the work of Sonabend et al, Weiser et al, and Caroline et al had reported 29.25%, 38.8% and 29.3% respectively. In our study the uncomplicated infections were seen in 75% hyperglycaemic patients vs 45% in non-hyperglycaemic (p=0.15). Whereas the incidence of complicated infection was 50% in hyperglycaemic and none in non-hyperglycaemic group (p-value=0.006). In our study the incidence of infections was much higher than that of previous authors. The small sample size as well as lack of proper isolation might compound to increase incidence.

Stary et al had studied 5197 childhood ALL patients in the ALL IC-BFM 2002 trial and have reported a complete remission rate as high as 97%.[9] Study of 307 paediatric patients treated with BFM protocol in India by Bajel et al had reported CR of 91%.[10] The CR was different among different age group; 94% for <30 years, 85% for 30-59 and 39% for more than 60 years. In our study, out of the 28 patients analysed, 27 patients went into CR. So, the overall CR rate in our study was only 96%. The CR rate is comparable to previous reports.

Zhang et al had reported that the ALL patients with hyperglycaemia achieved CR lesser than the euglycemic group (86.8% vs. 95%; p-value= 0.134) though not significant.[11] Roberson et al in their study of childhood ALL during remission induction had found that patients with hyperglycaemia during induction were less likely to achieve CR by the end of induction (p-value=0.03).[7] In our study the CR rate was lower in hyperglycaemic group vs. non hyperglycaemic group (87.5% vs 100%; p-value=0.13). So our study also recorded similar results.

Weiser et al had shown that the presence of hyperglycaemia was a risk factor for higher mortality and recurrence. In another research by Matias et al, the odd ratio of death among the hyperglycaemic patient was 3.5 more than the non-hyperglycaemic patients.[3] In our study, the mortality rate was found to be significantly higher in the hyperglycaemic group when compared to the non-hyperglycaemic group (25% vs 0%; p-value=0.02).

CONCLUSION

The incidence of hyperglycaemia is similar to that of previous researchers among the patients above 30 years of age. There were significant complicated and fungal infections in hyperglycaemic group. But the overall results in term of CR are very promising. One of the major drawbacks of our study was small sample size and limited time. So, we would be coming up with a larger study population with longer follow up period.

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Kh. Jitenkumar Singh, Ph.D. Scientist-D (NIMS), (ICMR), Dept. of Health Research, Ministry of Health & Family Welfare, Govt. of India.

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