

Original Research Article

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Hepatitis B in children with leukemia: the role of primary immunization

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ABSTRACT

Background: Children with cancer have a greatly enhanced risk of contracting hepatitis B infection due to immunosuppression secondary to chemotherapy and radiotherapy, frequent blood transfusions, bone and peripheral vein punctures, tissue damage and mucositis. During the past 3 decades, multimodality therapy for childhood leukemia has resulted in markedly improved survival. Inspite of screening and immuno prophylaxis, hepatitis B infection rates in children with leukemia are high. In view of this, we decided to study the prevalence of hepatitis B among children with leukemia in our institution, and the possible risk factors.

Methods: This was a cross sectional study carried out at a tertiary pediatric care center in North Kerala among 104 children between 1 and 12 years of age on treatment for leukemia.

Results: Among the 104 children, only 17 (16.3%) had received primary immunization against hepatitis B. Of the 87 children who had not received primary immunization, 44.8% (n=39) developed hepatitis B, compared to 11.8% (n=2) in the vaccinated group ($p=0.01$).

Conclusions: This study highlights the importance of primary immunization against hepatitis B in children with leukemia, and the need for universal coverage.

Keywords: Hepatitis B, Leukemia, Primary immunization

INTRODUCTION

Hepatitis B is one of the scourges of mankind, affecting and killing millions of children all over the world, especially in developing countries. It is a global challenge, with 400 million carriers of the hepatitis B virus, out of which 75% are in Asia. There are 40 million carriers in India alone. Depending upon the carrier state, WHO has placed India in the intermediate zone of prevalence of hepatitis B (2-7%).¹ Children with chronic illnesses are at a higher risk of acquiring hepatitis B infection due to increased exposure to blood products and invasive treatment strategies.

Children with cancer are unique since they include a large population at risk for hepatitis B due to immunosuppression secondary to chemotherapy, radiotherapy, frequent blood transfusions and bone and peripheral vein punctures, tissue damage and mucositis, which are associated with direct parenteral inoculations of the virus.²

During the past three decades, multimodality therapy for childhood cancer has resulted in markedly improved survival. Hepatitis B may indirectly contribute to the occurrence of relapse in these patients, due to change, modification or delay of chemotherapy.³

The hepatitis B carrier state among cancer survivors will lead to physical, psychological and social problems in these children, as well as their families. Hepatitis B virus causes a spectrum of liver diseases, including acute self-limited hepatitis, acute fulminant hepatitis, and chronic hepatitis B infection. Potential sequelae of chronic infection include cirrhosis, hepatocellular carcinoma and death.⁴ Hepatitis B infections in children with malignancy are characterized by a high rate of chronicity because of intensive anticancer treatment, damage of tissues, frequent blood product infusions and contact within a highly endemic environment.

Our institution caters to a majority of children with leukemia in North Kerala. In spite of screening of blood products and immune prophylaxis, HBsAg positivity in these children is high. Hence, we decided to study the prevalence and possible risk factors for hepatitis B among these children.

METHODS

This was a cross sectional study conducted at the Institute of Maternal and Child Health, Govt Medical College, Kozhikode, a tertiary pediatric care center in North Kerala. Approval from the institutional ethics committee was obtained and the study was conducted from March 2010 to September 2011.

Inclusion criteria

Children between 1 year and 12 years of age who were undergoing treatment for leukemia were included in the

study. In addition, data of those children who had completed treatment in the last two years were also analyzed.

Exclusion criteria

Children with leukemia afflicted with other chronic liver diseases were excluded from the study.

As part of hospital policy, authors administered double the pediatric dose (20 units) of recombinant hepatitis B vaccine in a schedule of 0, 1, 6 months, along with a single dose of HBIG (40 IU/kg) at the beginning of the chemotherapy

Those children undergoing chemotherapy for leukemia were screened for HBsAg status. From among children who were positive for HBsAg, history regarding hepatitis B vaccination and source of infection were taken. Those children who were negative after initial screening were kept under follow up and repeated screening was performed every six months. The total follow-up period was one and half years. Children who had completed treatment for leukemia were screened for HBsAg. A detailed history was taken, and treatment records were evaluated.

RESULTS

A total of 104 children with leukemia were screened for hepatitis B and 39.4% children were found to be HBsAg positive.

Table 1: Background characteristics of the study participants.

Characteristics	Hep B status		P value
	Negative (N=63)	Positive (n=41)	
Age group	1-4 yr	29 (58%)	P=0.65
	5-9 yr	24 (60%)	
	10-12 yr	10 (71.4%)	
Sex	Male	39 (63.9%)	P=0.4
	Female	24 (55.8%)	
Type of leukemia	ALL	54 (61.4%)	P=0.70
	AML	9 (56.3%)	
Primary hep B vaccination	Yes	15 (88.2%)	P=0.01
	No	48 (55.2%)	
Hep B vaccination during treatment	Yes	15 (88.2%)	P=0.75
	No	48 (55.2%)	
Hep B immunoglobulin (HBIG)	Yes	57 (64%)	P=0.07
	No	6 (40%)	

Among the 104 children with leukemia, 50 (48%) were in the age group of 0-4 years. Mean age of onset of leukemia was 5.4 years, 61 (58%) children were boys.

Acute lymphoblastic leukemia was diagnosed in 88 (84.6%) out of 104 children with leukemia while 16 children (15.4%) had acute myeloid leukemia (AML). It

was observed that 43.8% (7) of children with AML developed hepatitis B, compared to 38.6% (34) of those with ALL.

Of the 104 leukemic children, only 17 (16.3%) had received primary immunization against hepatitis B, while the remaining 87 (83.7%) had not received it.

Out of the 87 children who had not received primary immunization against hepatitis B, 44.8% (n=39) developed hepatitis B compared to 11.8% (n=2) of hepatitis B in vaccinated group ($p=0.01$). In the study group majority (98.1%) took, double dose active immunization against hepatitis B in the schedule of (0, 1, 6).

Among children who failed to get single dose hepatitis immunoglobulin at the induction phase of chemotherapy 60% (n=9) developed hepatitis B compared to 36% (n=32) of children received single dose of immunoglobulin ($p=0.07$) (Table 1).

DISCUSSION

Cure rate of childhood leukemia is high compared to other childhood malignancies due to advances in definitive and supportive care. At the same time, it is imperative to prevent other potential chronic diseases like hepatitis B among the survivors. The prevalence of hepatitis B in children with leukemia in the present study was 39.4%. There are several studies from India showing the prevalence of hepatitis B in children with leukemia ranging from 43-48%.^{6,7} A study from Aligarh found that the prevalence of hepatitis B in the general pediatric population of Aligarh was 4.35%.⁵ All the studies emphasize the importance of measures to decrease the burden of hepatitis B in children with leukemia.

In present study, only 16.3% of children who received primary doses of hepatitis B vaccine became HBsAg positive as against 44.8% of children who were not given primary vaccination. This difference in prevalence is statistically significant ($P=0.019$).

This points towards the importance of primary immunization against hepatitis B in children with leukemia.

Boytan B et al, from Turkey conducted a study in 2006, to evaluate the efficacy of primary HB immunization in children with ALL.⁸ It also emphasizes the role of primary immunization in bringing down the incidence of hepatitis B infection in children with leukemia.

In normal individuals seroconversion following hepatitis B vaccination is almost 96% and protective level of antibody titer was attained in 93% of vaccinated children. In contrast, the seroconversion of hepatitis B vaccine during chemotherapy is only 34. 29%.⁹

In the present study, 98.1% of children received active immunization during the induction phase of chemotherapy, irrespective of the vaccination status. We administered double the pediatric dose (20 units) of recombinant hepatitis B vaccine at 0, 1 and 6 months.

Even after administering active immunization with double dose of hepatitis B vaccine the prevalence of hepatitis B in children with leukemia was 39%. A similar study about seroconversion after hepatitis B vaccination in children receiving cancer chemotherapy by Ramesh M et al, from PGI Chandigarh, showed that only 28.6% of subjects mounted an antibody response reaching protective level after 4 double doses of recombinant hepatitis B vaccination.¹⁰ In Entachet, s study, only 32% of the subjects attained a protective level of immune response while on chemotherapy.¹¹

Thus, available data show that active immunization during the induction phase of chemotherapy is not very effective to protect children with leukemia from hepatitis B infection.

A combination of passive immunization and active immunization has been shown to be more effective in attaining protective level of antibody titer against hepatitis B.

In the present study we have given a single dose of HBIG during induction phase of chemotherapy to 89 children (86%). Among children who received HBIG, only 36% developed hepatitis B compared to 60% in those who did not ($p=0.07$). Though there are studies which show the importance of HBIG in the prevention of hepatitis B infection, present study shows only marginal benefit. So, authors need more studies before making a routine recommendation.^{12,13}

Incidence of transfusion associated hepatitis in India is 15-17 cases per 1000 units of blood transfused and, 20% of these cases were hepatitis B.¹⁴

In present study group, all the patients received blood transfusions ranging from 2-16 in number and there was no statistically significant correlation between HBsAg positivity and the number of blood transfusions. This points towards the importance of looking for other possible sources of hepatitis B virus infection, apart from blood transfusion.

Horizontal transmission is a possible route of transmission. A study from Taiwan highlights the importance of horizontal transmission of hepatitis B among children.¹⁵

In the present study, 36.1% of males are HBsAg positive against 44.2% among females. Present data showed no statistically significant gender difference in prevalence of HBsAg.

Authors also found no statistically significant difference in the incidence of hepatitis B among children with ALL and AML.

CONCLUSION

The low prevalence of HBsAg among children with leukemia, who had received primary immunization against hepatitis B gives a hope of reduction in the incidence of hepatitis B in future, since the government has already introduced hepatitis B vaccine in the national immunization schedule. However, there is a need to ensure universal coverage among all targeted beneficiaries.

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

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