

# ESCALATED REGIMEN OF HEPATITIS B VACCINE IN CHILDHOOD HEMATOLOGICAL MALIGNANCIES WHILE ON CHEMOTHERAPY

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**Abstract.** This prospective study was conducted to find the effective vaccination schedule against hepatitis B virus (HBV) infection for children with hematological malignancies. Sixty patients ages 2-15 years old with hematological malignancies on chemotherapy, negative for hepatitis B surface antigen (HBsAg) and never vaccinated for HBV before, were vaccinated with 40 µg of vaccine at 0, 1 and 2 months. Antibody titers were measured 6 weeks after administration of last dose. Out of the 60 children enrolled, 5 died during the course of treatment and 4 dropped out before completion, leaving 51 for final analysis. More than 70% exhibited protective levels of antibodies (>10 mIU/ml) against hepatitis B virus. There were no significant effects of age or sex on the antibody response, although antibodies were higher among girls (90.9%) than boys (65%). Patients with non-Hodgkin's lymphoma were found to exhibit a better antibody response than leukemic children ( $p = 0.024$ ). Children with hematological cancers should be vaccinated with an escalated regimen of the vaccine.

**Key word:** hepatitis B virus, vaccination schedule, HBsAg, children, hematological malignancies

## INTRODUCTION

In childhood malignancies, hepatitis B infection remains a major co-morbid condition, which may affect the outcome of treatment (Indolfi *et al*, 1992). A high risk for developing hepatitis B infection may

be due to immunosuppression secondary to chemotherapy or radiotherapy, the multiple blood transfusions, intravenous medications, and repeated invasive investigations (Meral *et al*, 2000). Treatment with immunosuppressive drugs enhances the possibility of developing a chronic carrier state or reactivation of HBV infection in asymptomatic carriers (Ramesh *et al*, 2000). This plays an adverse prognostic role for disease-free survival due to delays in chemotherapy (Meral *et al*, 2000).

Considering the high risk for infection, children with cancer should be routinely vaccinated against hepatitis B. However,

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several studies have shown vaccination with a conventional regimen and doses may result in antibody titers which do not reach protective level due to impaired immune response (Indolefi *et al*, 1992; Somjee *et al*, 1999; Mannan and Ghosh, 2003). We vaccinated 131 children age 2-15 years old with cancers and 100 otherwise healthy children of the same age as controls. All children were negative for hepatitis B markers. The vaccination regimen and dosages used were 10 µg for children < 10 years old and 20 µg for age >10 years old given at 0, 1 and 6 months. The antibody levels were measured 6 weeks after the last dose; 10% of the studied group were found to have protective level (> 10 IU/l) compared to 98% of controls (Mannan and Ghosh, 2003). Several studies have shown using conventional dosages of 10 and 20 µg, for an additional 4<sup>th</sup>, 5<sup>th</sup> or even 6<sup>th</sup> dose did not help significantly to increase the antibody titer (Drachman *et al*, 1989; Yetgin *et al*, 2001; Mannan and Ghosh, 2003).

We, carried out the present study with an increased dose of 40 µg of hepatitis B vaccine (Engerix B), irrespective of age, in childhood cancer patients using a schedule of 0, 1 and 2 months. Antibody titers were measured 6 weeks after administration of the last dose, a titer >10 IU/l, was considered protective.

## MATERIALS AND METHODS

The study was conducted at Bangabondhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, from January to September 2006. Ethical clearance was obtained from the Ethical Review Committee of the University before the study was carried out. Children attending the Out-Patient and In-Patient clinics of the Pediatric Hematology and

Oncology Department at BSMMU and a private clinic of a pediatric hemato-oncology specialist in Dhaka were recruited for the study. The age range was 2 to 15 years old, with a diagnosis of either leukemia or lymphoma.

All children recruited were in the maintenance phase of chemotherapy and were not previously vaccinated against hepatitis B. Those who were HBsAg positive or anti-HBsAg positive were excluded from the study.

Sixty children were enrolled in the study. Informed written consent was obtained from the parents. Families were told they could withdraw their children from the study at any time they wanted (Helsinki Declaration for Medical Research Involving Human Subjects, 1964).

Recombinant hepatitis B vaccine was given intramuscularly at 40 µg per dose at 0, 1 and 2 months, irrespective of age. The generic product of Glaxo-Smithkline Pharmaceuticals (Engerix-B) was used for the study. Anti-HBs was measured using a kit ELISA method (Immunodiagnostic System, San Diego, AZ) 6 weeks after administration of the 3<sup>rd</sup> dose. Information regarding the child, hematological malignancy type, stage, age at diagnosis, specific treatment for malignancy and present health status, were collected from medical and laboratory records.

Vaccination date and blood test results were recorded. The data were analyzed using SPSS for Windows (version 10.2). Descriptive analysis performed included chi-square test, mean, median and standard deviation (SD). A  $p < 0.05$  was considered significant.

## RESULTS

Sixty patients were enrolled in the study, 5 died before antibody levels were

**Table 1**  
Numbers and percentages of patients  
by age (N = 51).

Age (years)	Number	%
< 5	17	33.3
5-10	28	54.9
> 10	06	11.8

Mean, 6.16 ± 3.14 years; range, 2 - 15 years.

**Table 2**  
Association between age and antibody  
response (N = 51).

Age (years)	Antibody titer (mIU/ml)		p-value
	< 10 (n = 15)	≥ 10 (n = 36)	
< 5	5 (33.3) <sup>a</sup>	12 (33.3)	0.752
5-10	1 (6.7)	5 (13.9)	
< 10	9 (60.0)	19 (52.8)	

<sup>a</sup> Figures in the parentheses denote corresponding %. Chi-square ( $\chi^2$ ) test was done to analyze the data; the level of significance was set at 0.05.

measured and 4 dropped out during follow-up. Therefore, 51 patients were included in the final analysis. The age range was 2 to 15 years old; 17 (33.3%) were below 5 years old, 28 (54.9%) were between 5 and 10 years old and the rest (6, 11.8%) were above 10 years old (Table 1). Forty patients (78%) were male.

Out of 51 patients, 29 (56.9%) were diagnosed as having leukemia and 22 (43.1%) had lymphoma. Out of the 29 with leukemia, 26 (51% of the total of 51) had acute lymphocytic leukemia (ALL) and 3 (5.9% of the total of 51) had acute myelocytic leukemia (AML). Out of 22 with lymphoma, 20 (39.2% of the total of 51) had non-Hodgkin's lymphoma, and 2 (3.9% of the total of 51) had Hodgkin's lymphoma.

**Table 3**  
Association between sex and antibody  
response (N = 51).

Sex	Antibody titer (mIU/ml)		p-value
	< 10 (n = 15)	≥ 10 (n = 36)	
Male	14 (35.0)	26 (65.0)	0.093
Female	1 (9.1)	10 (90.9)	

Figures in the parentheses denote corresponding %. Fisher's exact test was done to analyze the data; the level of significance was set at 0.05.

Over 70% of the patients 6 weeks after the 3<sup>rd</sup> dose of hepatitis B vaccine had protective antibody level. The median antibody level was 125.0 ± 17.09 mIU/ml.

Table 2 shows the association between age and antibody response. No particular age group was found to be significantly more immunogenic than any other following hepatitis B vaccination ( $p > 0.05$ ).

Table 3 demonstrates the association between sex and antibody response. The proportion of girls developing protective antibodies was higher (90.9%) than the boys (65.0%), but the difference was not significant ( $p > 0.05$ ).

Table 4 demonstrates the antibody response of patients based on diagnosis. The patients with lymphoma had a higher level of protective antibodies (81.8%) than the patients with leukemia (62.1%), although the difference was not significant ( $p > 0.05$ ).

Table 5 demonstrates 90% of patients with non-Hodgkin's lymphoma had protective antibody levels, while 61.5% of patients with ALL and 65.7% of patients with AML had protective antibody levels. The association between non-Hodgkin's disease and antibody response to hepatitis B vaccination was significant ( $p = 0.024$ ).

## DISCUSSION

Hepatitis B vaccination can induce seroconversion in 65-95% of healthy children (Jilg *et al*, 1989). The present study demonstrated more than 70% of subjects developed protective antibody titers (>10 mIU/ml) 6 weeks after administration of the 3<sup>rd</sup> dose of 40 µg of recombinant HBV vaccine. No undesirable side-effects other than pain and redness at the site of injection, were encountered by subjects. In our previous study where 10 µg of vaccine was used in children <10 years of age and 20

µg in older children at 0, 1 and 6 months, the protective antibody level in the cancer group measured 6 weeks after the last dose was 10% compared to 98% in the control group ( $p < 0.01$ ) (Mannan and Ghosh, 2003). In the 2<sup>nd</sup> phase of the same study, the vaccination program was rescheduled with the number of doses increased from 3 to 4 given at close intervals (0, 1, 2 and 6 months). The results showed an increase in protective antibody level in the cancer group from 10% to 57% (unpublished data). Three series of studies have shown an escalated hepatitis B dose regimen immune-compromised children can result in increased protective antibody levels. Meral *et al* (2000) using a higher dose at 0, 1, 2 and 12 months achieved a seroconversion rate of 75% in patients with hematological malignancies following the first three doses and 86% after completion of 4 doses, consistent with our findings.

In the present study a significantly higher proportion of lymphoma patients (90%) developed protective antibody levels than leukemia patients (61.5%). Meral's study (2000) showed that patients with lymphoma had a lower response than patients with leukemia and solid tumors ( $p = 0.0003$ ,  $p = 0.0161$ , respectively). The

Table 4  
Association between diagnosis and antibody response (N = 51).

Diagnosis	Antibody titer (mIU/ml)		p-value
	< 10 (n = 15)	≥ 10 (n = 36)	
Leukemia	11 (37.9) <sup>a</sup>	18 (62.1)	0.125
Lymphoma	4 (18.2)	18 (81.8)	

<sup>a</sup>Figures in the parentheses denote corresponding %. Fisher's exact test was done to analyze the data; the level of significance was set at 0.05.

Table 5  
Association between type of malignancy and antibody titer (N = 51).

Type of malignancy	Antibody titer (mIU/ml)		p-value
	< 10 (n = 15)	≥ 10 (n = 36)	
ALL	10 (38.5) <sup>a</sup>	16 (61.5)	0.024
AML	1 (33.3)	2 (66.7)	
Hodgkin's lymphoma	2 (100.0)	00	
Non-Hodgkin's lymphoma	2 (10.0)	18 (90.0)	

ALL, acute lymphocytic leukemia; AML, acute myelocytic leukemia

<sup>a</sup>Figures in parentheses denote corresponding %. Chi-square ( $\chi^2$ ) test was done to analyze the data; the level of significance was set at 0.05.

reason of this discrepancy may be that in our study the majority of lymphoma patients had non-Hodgkin's disease, whereas in their study the majority of children with lymphoma had Hodgkin's disease, which might play a role in the diminished response to vaccination owing to basic cellular immune disorders associated with the disease (Goyal *et al*, 1998). Moreover, in their study, children with lymphoma and solid tumors were vaccinated at diagnosis when they had the most intensive chemotherapy. This could cause more immunosuppression in them. Previous studies also demonstrated an impaired immune response to active vaccination in children with leukemia during intensive chemotherapy (Berberoglu *et al*, 1995; Hudson and Donaldson, 1997). In the Meral's study (2000), 86% of fully vaccinated children (4 doses completed) developed anti-HBs positivity. Seroconversion rates with respect to diagnosis were 90.3% in leukemia patients, 74% in lymphoma patients and 94.4% in solid tumor patients. Seropositivity increased from 48% to 74% in lymphoma and from 77% to 94% in solid tumors after the fourth dose. Berberoglu *et al* (1995) demonstrated seropositivity increased from 56% at 6 months to 70.5% at 12 months after the fourth dose.

A vaccination program was conducted by Indolfi *et al* (1992), among 80 patients age 1-15 years old, having negative serology for hepatitis B and normal liver function, using a recombinant DNA hepatitis B vaccine at a dose of 40 µg at 0, 1 and 2 months with a booster dose at one year. A fourth dose (40 µg) was given during the fourth month to patients who did not respond to three doses. Sixty-one children, 38 with a diagnosis of leukemia/lymphoma and 23 with solid tumors, completed the scheduled course. Over half (52.45%) the subjects responded with an

anti-HBs titer >10 mIU/ml, further emphasizing the importance of a higher dose on HBV vaccination in immune-compromised children.

However, there are reports of low antibody responses even after using a higher dose when the number of vaccinations is unchanged. Ramesh *et al* (2000) found only 28.6% of subjects mounted an antibody response >10 mIU/ml after four double doses of recombinant hepatitis B vaccine. Similar observations were seen in an earlier study (Hudson and Donaldson, 1997) where only 32% of pediatric cancer patients on chemotherapy mounted a protective response, with the number of responders being similar among hematological and solid malignancy patients. Rokicka-Milewska *et al* (1993) immunized children with leukemia and lymphoma. They found antibody titers were much higher in patients vaccinated after cessation of chemotherapy than those vaccinated during chemotherapy.

Goyal *et al* (1998) vaccinated leukemic children at diagnosis, but only 10.5% of them developed protective antibody titers. In their study, 48.8% of children were infected with HBV. Their data demonstrated that vaccination during chemotherapy was not effective. This may be due to immunosuppression induced by either disease or treatment with cytotoxic drugs which diminished the response to vaccination. Therefore passive immunization with hyper immunoglobulin followed by active immunization after the cessation of chemotherapy may be a better alternative in these children. Pilecki *et al* (1995) used both passive and active immunization in children with hematological proliferative diseases. They also reported the use of both active and passive immunization helped reduce the rate of HBV infection from 43.3% to 2.56%.

Studies regarding hepatitis B vaccination in children with cancer have observed the effects of age, sex, tumor and vaccine type on antibody response. The response has been reported to be better in children younger than 10 years old and in girls (Hollinger, 1989; Berberoglu *et al*, 1995). Several studies found the highest antibody responses were obtained in children with solid tumors since impaired lymphocyte function causes poor vaccine response in lymphoreticular malignancies (Hudson and Donaldson, 1997; Lehmbecher *et al*, 1997; Meral *et al*, 2000). Corapcioglu *et al* (2001) did not find any effect of age, sex, vaccine or tumor type on antibody response. In our study, we found no significant effect of age on antibody response. However, protective antibodies were demonstrated to be higher among girls (90.9%) than boys (65%), although the difference was not significant ( $p = 0.093$ ).

Patients with non-Hodgkin's lymphoma exhibited significantly higher antibody levels than leukemic children ( $p = 0.024$ ).

In conclusion, hematological cancer patients classified as "non-responders" after being vaccinated with conventional doses, appear to need higher doses to stimulate their already compromised immune systems, since most of these children responded to higher doses of the vaccine.

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