

Original Articles

Seroconversion following hepatitis B vaccination in childhood steroid sensitive nephrotic syndrome

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Sri Lanka Journal of Child Health, 2017; 46(4): 312-316

Abstract

Background: The commonest factor associated with frequent relapse in minimal change nephrotic syndrome is infection, either bacterial sepsis or viral infection. Among the viral infections, hepatitis B virus (HBV) has a prominent role. Steroid sensitive nephrotic syndrome (SSNS) patients are immunocompromised because of the disease itself as well its treatment with a steroid. Thus, their seroprotection will not be enough with conventional dose as that of a healthy person.

Objective: To evaluate the seroresponse among SSNS with hepatitis B (HB) vaccination when they were in remission, to compare the antibody titre between single and double dose and to find out whether there were any complications following HB vaccination.

Method: A prospective study was conducted among thirty SSNS children from July 2012 to June 2013; children were randomly assigned to be given either 10µg (Group-A) or 20µg (Group-B) of HBV vaccine. The vaccine was administered intramuscularly according to 0, 1, 2 months protocol. After one month of the last dose of vaccine, seroprotection rate was measured.

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(Received on 23 December 2016: Accepted after revision on 20 February 2017)

The authors declare that there are no conflicts of interest

Personal funding was used for the project.

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Results: Mean vaccine titres of Group-A and Group-B were 25.60 ± 19.97 mIU/ml and 617.47 ± 292.11 mIU/ml respectively. Mean vaccine titre difference between the 2 groups was statistically significant.

Conclusion: Seroconversion was better observed by double dose (1ml) of HB vaccine in comparison to the single dose (0.5 ml) in children with SSNS during the remission period. There were no complications following HB vaccine during the study period.

DOI: <http://dx.doi.org/10.4038/sljch.v46i4.8376>

(Key words: Immune deficiency, paediatric nephrology, nephrotic syndrome, SSNS, seroconversion)

Introduction

Nephrotic syndrome (NS) is characterized by massive proteinuria, hypoalbuminaemia, oedema and hyperlipidaemia¹. The most common factor associated with frequent relapse in minimal change nephrotic syndrome (MCNS) is infection, either bacterial sepsis or viral infection. In developing countries, 50-70% relapses of childhood NS follow infection². Among viral infections, hepatitis B virus (HBV) has a prominent role³. Many authors suggest that hepatitis B (HB) vaccine is the most effective tool to control the disease^{3,4}.

The prevalence of HBV surface antigenaemia is significantly higher in nephrotic patients compared to the general population⁵. True prevalence of HB in Bangladesh is yet to be ascertained through a reliable study. Different studies show that total HBV-infected subjects in Bangladesh are about 30-50 million. Among them, 6-8 million are chronically infected with HB infection⁶. HB vaccine is one of the safest, most immunogenic and effective vaccines. Its efficacy is greatest when it is part of the infant immunization schedule⁷. In comparison to plasma-derived vaccine, recombinant HB vaccines have been very safe⁷. Nephrotic children have lower seroconversion to vaccines because of immune dysregulation, prolonged immunosuppressive therapy and recurrent prolonged albuminuria⁸. In comparison to developed countries, steroid sensitive NS (SSNS) patients in Bangladesh are more immunocompromised. Their immune response is

lower due to the disease process, steroid overuse and chronic malnutrition. Studies on seroconversion titre after giving HB vaccine are limited in children with NS.

Objectives

To evaluate the seroresponse among SSNS with HB vaccination when they were in remission, to compare the antibody titre between single and double dose and to find out whether there were any complications following HB vaccination.

Method

This prospective study was done at the Bangladesh Institute of Child Health from July 2012 to June 2013. Children with NS (infrequently relapsing, steroid dependent and frequently relapsing) who visited the nephrology follow-up clinic or who were admitted to the nephrology ward, comprised the study population. Thirty patients, having all the features of minimal change NS according to the International Study for Kidney Diseases for Children, and who were on oral prednisolone every other day and were hepatitis B surface antigen (HBsAg) negative were included in the study. Patients with non-minimal change NS or who were HBsAg positive or who had severe malnutrition (i.e. weight for age less than -3SD) or who were receiving cyclophosphamide or other disease modifying agents were excluded from the study.

Patients fulfilling the inclusion criteria were randomly assigned to Group-A or Group-B. After excluding HBV infection, the HB vaccine was administered intramuscularly according to 0, 1, 2 months protocol in a standard dose in Group-A (0.5 ml or 10µg) and a double dose (1 ml or 20µg) in Group-B. Other baseline parameters were similar in both groups. After one month of the last dose of vaccine, the seroprotection rate was measured. Follow up was done by a questionnaire containing relevant information such as age, sex, weight and height (in Z score), the number of relapses, the dose of prednisolone required for relapse, signs of other infections and investigations and side effects of vaccine during the study period.

Children were regarded as weak responders if the antibody titre after vaccination was less than 10 mIU/ml, moderate responders if the antibody titre after vaccination was 10-100 mIU/ml and strong protective responders if the antibody titre after vaccination was above 100 mIU/ml. First follow up was arranged just after the first dose of the vaccine and patients were advised to follow the vaccine schedule (0, 1, and 2 months) and one month after the last dose of vaccine, the antibody titre was recorded. Children with low antibody titres (less than 10 mIU/ml) were advised to get a booster dose. Patients were advised to visit anytime if relapse

occur or if any complication arose following vaccination.

Informed written consent was obtained from parents prior to the study and parents were given the choice to withdraw at any time from the study. The study was approved by the scientific and ethical committee of the hospital. All data were collected using a structured questionnaire and were analysed using Windows version SPSS 16.0. Results were expressed as frequency distribution, percentage and mean ± SD. For statistical analysis Student’s t-test, Chi square test and the correlation between independent and dependent parameters were used. A ‘p’ value <0.05 was considered statistically significant.

Results

The age distribution of the study patients is shown in Figure 1.

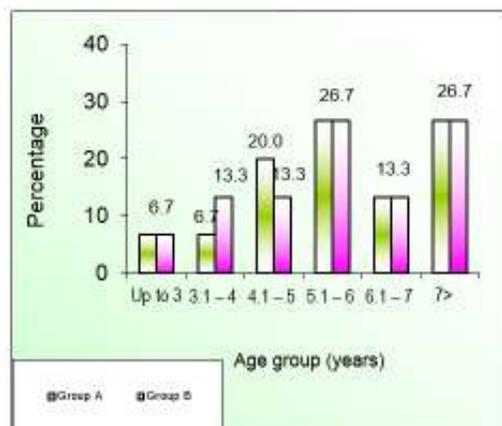


Figure 1: Bar diagram showing age distribution of study patients Group-A: Paediatric dose (0.5 ml), Group-B: Adult dose (1.0 ml)

Mean age of Group-A was 5.81 ± 1.73 years (range 2 years 7 months to 9 years 2 months). Mean age of Group-B was 5.65 ± 1.68 years (range 2 years 10 months to 8 years 6 months). This was not statistically significant (Figure-1). Among Group-A patients 09 (60%) were male and 06 (40%) were female. Among Group-B patients 08 (53.3%) were male and 07 (46.7%) were female. The difference was not statistically significant (p>0.05). Out of the 30 patients with NS, 8 were infrequently relapsing, 9 were steroid dependent and 13 were frequently relapsing. The mean dose of steroid of Group-A was 20.21 ± 5.58 mg/m²/day, and in Group-B 20.11 ± 5.51 mg/m²/day. The difference in mean dose of steroid of Group-A and Group-B was not statistically significant (p>0.05).

Comparison of mean vaccine titres between Group-A and Group-B using the Student’s t-test is shown in Table 1. The difference was statistically significant (p<0.01).

Table I: Comparison of mean vaccine titres between Group-A and Group-B

Vaccine titre (mIU/ml)	Group-A		Group-B		P value
	Number	%	Number	%	
<10	06	40.0	0	0.0	
10 – 100	09	60.0	0	0.0	
101 – 800	0	0.0	10	66.7	
> 800	0	0.0	05	33.3	
Total	15	100	15	100	
Mean ± SD	25.60 ± 19.97		617.47 ± 292.11		0.001

Group-A: Paediatric dose (0.5 ml), Group-B: Adult dose (1.0 ml)

There was a significant negative relationship (Pearson’s correlation coefficient =0.9112; p<0.001) between the dose of steroid and vaccine titre in Group A (Figure 2)

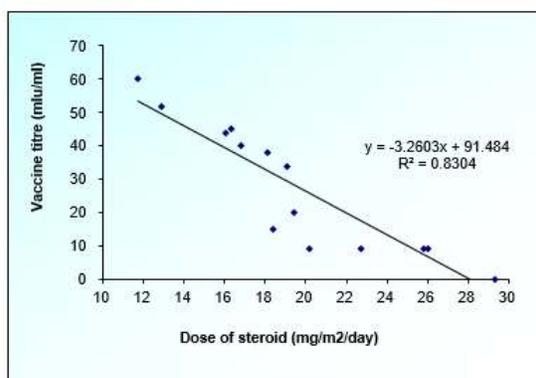


Figure 2: The scatter diagram shows significant negative relationship ($r=0.9112$) between dose of steroid and vaccine titre in Group-A

There was a significant negative relationship (Pearson’s correlation coefficient = -0.9583; p<0.001) between the dose of steroid and vaccine titre in Group B (Figure-3).

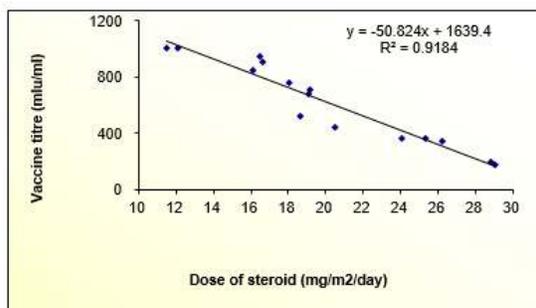


Figure 3: The scatter diagram shows significant negative relationship ($r=-0.9583$) between dose of steroid and vaccine titer in Group-B.

Discussion

Whilst the recommended dose of HB vaccine is 10µg in children, 20µg has been recommended in children with chronic kidney disease, children being haemodialysed and/or receiving chemotherapy, human immunodeficiency virus-positive children and children on other immunosuppressive drugs⁹.

A study by Mitwali A, *et al* showed that the immunogenicity and efficiency of HB vaccine was enhanced in immunocompromised patients by doubling the dosing schedule in 42 patients¹⁰. Similar results were found in a study by Mantan M, *et al* who observed more anti-HBS titre with double dose (20µg) of vaccine than with normal dose (10µg) of vaccine in SSNS¹¹. In our study, the mean HB vaccine titre was significantly higher in children receiving 20µg HB vaccine compared to those receiving 10µg. Whilst 60% of children receiving 10µg HB vaccine were moderate responders (vaccine titres 10-100 mIU/ml), 40% were weak responders (vaccine titres less than 10 mIU/ml). All children receiving 20µg HB vaccine were strong protective responders (vaccine titres more than 100 mIU/ml).

In the study by Mantan M, *et al*, only 37% children with NS on non-steroid immunosuppression had seroprotective titres after HB vaccine in comparison with 76% only on steroids¹¹. A four-dose schedule (0, 1, 2, 12 months) or double the normal dose at the routine intervals can overcome this^{11,12}. Steroid treatment inhibits CD4 cell activity and helps to reduce antibody titres^{13,14}. NS itself is associated with T and B lymphocyte dysfunction¹⁵. Further, total serum IgG levels have been demonstrated to be low in NS⁸. In this study, 6 patients (40%) in group A out of total 15 patients showed vaccine titres below 10. Of the 6 patients 5 (83.3%) were taking high doses of steroid (>20 mg/m²/day).

The present study showed a significant strong negative correlation between the dose of steroid and vaccine titre in both groups A and B. La Manna A, *et al.* showed that the response to vaccination with HBV is lower in children with SSNS (63–67 % seroconversion after 3 doses) than in healthy children, especially in children on 2 mg/kg/day of prednisolone, even if the vaccine is administered in remission¹⁶.

Study done by Chang MH *et al.* showed no relationship between HB vaccine and hepatocellular carcinoma following vaccination but two cases of MCNS developed following recombinant HB

vaccination¹⁷. The development of MCNS after vaccination strongly favours an immune mediated side effect of vaccination. Abeyagunawardena et al showed the infrequency of HB vaccine related relapses in children with NS¹⁸. Esposito S et al. showed that acquiring HBV infection at an early age is associated with a higher risk of chronicity, liver failure, and hepatocellular carcinoma¹⁹. During the present study period, none of the patients developed any complications and none of the patients relapsed following vaccination.

Limitations of the study include the small sample size, single centre study and the limited follow up. A long term, longitudinal and multicentre study on seroconversion following HB vaccine in nephrotic children is recommended to obtain more definite results.

Conclusions

Seroconversion was better observed by double dose (1ml) of HB vaccine in comparison to single dose (0.5 ml) in children with SSNS during remission period. There were no complications following HB vaccine during the study period.

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