

Research Article

J Ped. Nephrology 2017;5(2)
<http://journals.sbmu.ac.ir/jpn>

Are Boys at Risk of Low Immune Response to Recombinant Hepatitis B Virus Vaccine in Steroid Sensitive Nephrotic Syndrome?

How to Cite This Article: Jesmin T, Anjum F, Al Mamun A, et al. Are Boys at Risk of Low Immune Response to Recombinant Hepatitis B Virus Vaccine in Steroid Sensitive Nephrotic Syndrome? J Ped. Nephrology 2017;5(2)

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Received: June-2017

Revised: Aug-2017

Accepted: Aug-2017

Introduction

The immune system develops and matures over time and both sex and gender affect the immune response.

Introduction: This study was conducted to evaluate the immune response following vaccination with different doses and to compare the antigen specific antibody response to Hepatitis B Vaccine (HBVac) in Steroid Sensitive Nephrotic Syndrome (SSNS) patients between boys and girls.

Materials and Methods: This prospective study was conducted in 30 SSNS children at Bangladesh Institute of Child Health, Dhaka, Bangladesh from July 2012 to June 2013. Thirty patients who had all features of Minimal Change Nephrotic Syndrome (MCNS) according to International Study for Kidney Diseases for Children (ISKDC) and received oral prednisolone every alternate day and were HBsAg negative were enrolled in the study. The patients were randomly assigned to one of the two treatment group to receive either 0.5 ml (10 μ g) or double dose 1ml (20 μ g) of HB vaccine in a 0-1-2month schedule. After excluding hepatitis B virus infection, the vaccine was administered at a standard dose in group-A (0.5 ml or 10 microgram) and at a double dose (1 ml or 20 microgram) in group-B. After one month of the last dose, the seroprotection rate was measured and compared among sexes.

Results: The mean age of the participants in group-A was 5.81 ± 1.73 years with a boy to girl ratio of 9:6 and the mean age of the subjects in group-B was 5.65 ± 1.68 years with a boy to girl ratio of 8:7. The mean vaccine titer was 25.60 ± 19.97 mIU/ml in group-A and 617.47 ± 292.11 mIU/ml in group-B, with a significant difference ($p < 0.05$) between the two groups. Irrespective of the dose, the mean vaccine titer was higher in girls (37.33 ± 19.45 mIU/ml) compared to boys (16.22 ± 14.81 mIU/ml) and the difference was statistically significant in group-A. It was also observed that the mean vaccine titer was significantly higher in girls (743.00 ± 252.34 mIU/ml) compared to boys (394.88 ± 246.63 mIU/ml) in group-B ($p < 0.05$, t-test).

Conclusions: The results of our study showed a reduced response to HB Vaccine boys with SSNS in comparison to girls. As the study size was small, single center study and time limited follow-up, we cannot draw any valid conclusions.

Keywords: Immune deficiency; Sex differences; Steroid Sensitive Nephrotic Syndrome; Seroconversion.

Running Title: Immune Response to Hepatitis B Virus Vaccine in Nephrotic Syndrome

In different immunological studies, sex is considered a biological variable that contributes to the differences in response to viral vaccines that are consistently at least

twice as strong in women than men. Generally, women develop higher innate, humoral, and cellular immune responses to viral infections and vaccines [1,2]. Marked differences are also seen between males and females in various diseases. Men show an almost twofold higher risk of death from malignant cancers than women. Vaccination for hepatitis B virus infection has been highly successful [3]. In infants and children, the efficiency of recombinant HBVac assessed based on post vaccination anti-HBs antibody concentrations above 10mIU/ml is estimated at 85% to 100% [4,5]. The immune responses to multi-dose HBV vaccines differ from individual to individual. At least 5% to 20% of the healthy population fails to produce protective levels of antibodies (Ab) to recombinant HBV surface antigen (HBsAg) following standard vaccination protocols [6]. Several explanations have been proposed for hypo/non responsiveness including defects in the function of T and B cells, antigen processing and presentation, and immunological tolerance [7]. Nephrotic syndrome (NS) is a common renal disease in children. The affected children are at an increased risk of acquiring hepatitis B infection as they are immunocompromised. Therefore, the rate of chronic HBV infection is high in steroid sensitive NS (SSNS), especially in endemic regions [8]. Children with nephrotic syndrome have been shown to have lower seroconversion to various vaccines (both live and inactivated) due to immune dysregulation and prolonged immunosuppressive treatment. Therefore, recent studies have used double doses of HBVac [9]. In developing countries like Bangladesh, SSNS patients are more immune-compromised. The efficacy and the different immune responses of HBVac are not well studied in SSNS patients. The aim of this study was to evaluate the immune response and to compare the antigen specific antibody response to HBVac in boys and girls with SSNS.

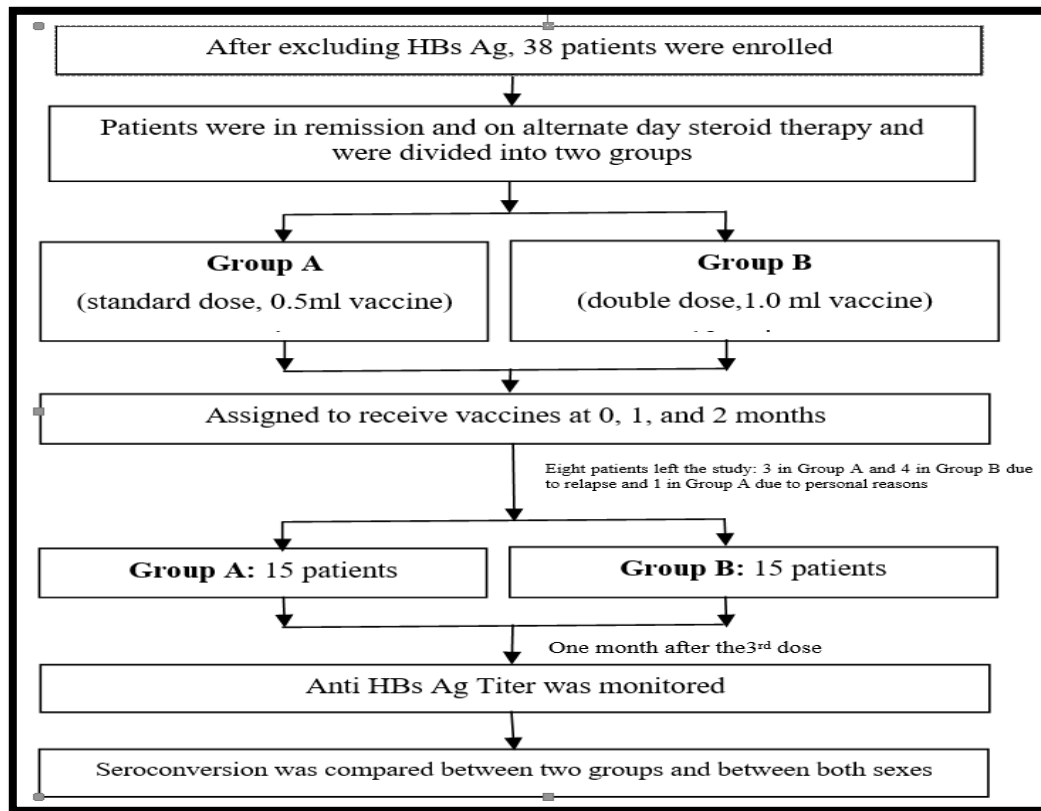
Materials and Methods

This prospective observational study was carried out at Bangladesh Institute of Child Health (BICH) Dhaka, Bangladesh from July 2012 to June 2013. Thirty-eight patients (age ranging from 2 to 10 years, 56.7% male and 43.3% female) who had all features of Minimal Change Nephrotic Syndrome (MCNS) according to the International Study for kidney Diseases for Children (ISKDC) and received oral prednisolone every alternate day were enrolled in the study.

All the children were sero-negative for HBV markers and none of them had a history of a prior course of HBVac or recent administration of blood, plasma, or immunoglobulin. Patients with non-minimal change nephrotic syndrome, HBsAg positivity, or severe malnutrition (i.e. weight for age < -3SD), and subjects who received cyclophosphamide or other disease modifying agents were excluded from the study.

Written informed consent was taken from the parents after explaining the procedure and prior to enrollment. This study was approved by BICH. Patients meeting the inclusion criteria were randomly assigned to receive either a standard dose of 0.5 ml (10µg, named as group A) or a double dose of 1ml (20µg, named as group B) of HB vaccine at 0,1, and 2 months. Other standard baseline parameters were similar in both groups. After one month of the last dose, the antibody titer was measured and compared between boys and girls. Follow-up was done by a structured questionnaire and the first follow-up was arranged after the first dose of the vaccine. Children with a low antibody titer (less than 10mIU/ml) were advised to receive a booster dose. Patients were advised to follow the vaccine schedule and to visit anytime if relapse or any complication occurred following vaccination.

During the study period, 8 patients refused to complete the study (3 in group A and 4 in group B due to relapse and 1 in group A due to personal reasons). The cause of relapse for seven patients was infection (urinary



infection in 3, enteric fever in 1, and bronchial asthma in 3).

Children were regarded as weak responders if the antibody titer after vaccination was above 10mU/ml but below 100mU/ml and strong protective responders if the titer was above 100mU/ml.

Results

The study was initially started with 38 children and ended with 30 subjects. The population was evenly divided into two groups. The mean age of children in group A was 5.81 ± 1.73 years with a boy to girl ratio of 9:6. The mean age of subjects in group B was 5.65 ± 1.68 years with a boy to girl ratio of 8:7.

The mean dose of steroid was 20.21 ± 5.58 mg/m²/day in Group A and 20.11 ± 5.51 mg/m²/day in Group B (Table 1). T-test showed no significant difference in the mean dose of steroid between Group A and Group B ($p > 0.05$).

Table 1. Comparison of dose of steroid (mg/m²/day) between Group A and Group B

Dose of steroid (mg/m ² /day)	Group-A		Group-B		P value
	n	%	n	%	
11 – 15	2	13.3	2	13.3	0.961
16 – 20	8	53.4	8	53.4	
>20	5	33.3	5	33.3	
Total	15	100	15	100	
Mean $\pm$ SD	20.21 $\pm$ 5.58		20.11 $\pm$ 5.51		0.961

Group-A: Pediatric dose (0.5 ml); Group-B: Adult dose (1.0 ml)

The mean vaccine titer was 25.60 ± 19.97 mIU/ml in Group A and 617.47 ± 292.11 mIU/ml in Group B (Table 2). T-test showed a significant difference in the mean vaccine titer (mIU/ml) between the two groups ($p < 0.05$). Irrespective of the dose i.e. the pediatric dose (Group A) or adult dose (Group B), the mean vaccine titer was

significantly higher in girls compared to boys in both the groups ($p < 0.05$, t-test).

Table 2. Comparison of vaccine titer (mIU/ml) between Group A and Group B.

Vaccine titer (mIU/ml)	Group-A		Group-B		P Value
	n	%	n	%	
<10	6	40.0	0	0.0	
10 – 100	9	60.0	0	0.0	
101 – 800	0	0.0	10	66.7	
> 800	0	0.0	5	33.3	
Total	15	100	15	100	
Mean $\pm$ SD	25.60 $\pm$ 19.97		617.47 $\pm$ 292.11		0.001

According to Table 3, the mean vaccine titer was significantly higher in girls (37.33 $\pm$ 19.45 mIU/ml) than boys (16.22 $\pm$ 14.81 mIU/ml) in Group A ($p < 0.05$, t-test).

Table 3. Comparison of vaccine titer (mIU/ml) between boys and girls in Group A

Vaccine titer (mIU/ml)	Boy		Girl		P Value
	n	%	N	%	
<10	5	55.6	1	16.7	
10 – 100	4	44.4	5	83.3	
101 – 800	0	0.0	0	0.0	
> 800	0	0.0	0	0.0	
Total	9	100.0	6	100.0	
Mean $\pm$ SD	16.22 $\pm$ 14.81		37.33 $\pm$ 19.45		0.026

As Table 4 shows, the mean vaccine titer was significantly higher in girls (743.00 $\pm$ 252.34 mIU/ml) than boys (394.88 $\pm$ 246.63 mIU/ml) in Group B ($p < 0.05$, t-test).

Table 4. Comparison of vaccine titer (mIU/ml) between boys and girls in Group B

Vaccine titer (mIU/ml)	Boy		Girl		P Value
	n	%	n	%	
<10	0	0.0	0	0.0	
10 – 100	0	0.0	0	0.0	
101 – 800	7	87.5	3	42.9	
> 800	1	12.5	4	57.1	
Total	8	100.0	7	100.0	
Mean $\pm$ SD	394.88 $\pm$ 246.63		743.00 $\pm$ 252.34		0.018

Discussion

The present study was carried out in 30 patients with MCNS on alternate day steroid therapy to assess the immune response, compare the antibody titer, and evaluate the complications in boys and girls following hepatitis B vaccination.

The usual recommended dose of hepatitis B vaccine is 10 μ g in healthy children, but studies have recommended a double dose in patients with chronic kidney disease, patients on hemodialysis and/or chemotherapy, HIV positive subjects, and those receiving other immunosuppressive agents [10].

In the present study, 15 patients were vaccinated with 10 μ g HBVac (Group A) and 15 patients received 20 μ g of HBVac (Group B) at 0, 1, and 2 months. One month after the vaccination. The antibody titer was measured. The mean vaccine titer was 25.60 $\pm$ 19.97 mIU/ml in Group A and 617.47 $\pm$ 292.11 mIU/ml in Group B and the difference was statistically significant ($p < 0.05$) between the two groups. In Group A, the vaccine titer was <10 mIU/ml in 40.0% of the patients and 60.0% showed titers between 10 to 100 mIU/ml.

In Group B, the antibody titer was 101-800 mIU/ml in 66.7% and above 800 mIU/ml in 33.3% of the patients. Similar results were found in a study by Mantan et al [11] who observed higher anti-HBs titers with a double dose (20 μ g) of the vaccine than the normal dose (10 μ g) in SSNS patients. Therefore, a double dose (20 μ g) of hepatitis B vaccine is strongly suggested for SSNS patients because of better seroresponse.

In both children and adults, responses to both inactivated vaccines (such as vaccines against brucellosis, diphtheria, hepatitis A, hepatitis B, influenza, meningococcal meningitis, pneumococcal disease (using pneumococcal polysaccharide), rabies and tetanus) and live vaccines (such as those against measles, rubella, smallpox, Venezuelan equine encephalitis, and yellow fever) has been reported to differ between males and females [12-14]. Sex is a variable that affects the immune response, resulting in

sex-specific outcomes in infectious and autoimmune diseases [1].

In the present study, comparison of the vaccine titer (mlu/ml) between boys and girls (in Group A) showed the mean vaccine titer was 16.22 ± 14.81 mIU/ml in boys and 37.33 ± 19.45 mIU/ml in girls. The mean vaccine titer was significantly higher in girls than boys ($p < 0.05$, t-test). Comparison of the vaccine titer between boys and girls in Group B showed the mean vaccine titer was 394.88 ± 246.63 mIU/ml in boys and 743.00 ± 252.34 mIU/ml in girls. The mean vaccine titer was significantly higher in girls compared to boys ($p < 0.05$) in Group B. Similarly, La Manna A showed reduced response to hepatitis B vaccine in boys with SSNS who were on alternate day steroid therapy in comparison to girls. Study results showed that the percentage of patients who responded to vaccine was significantly lower in boy and girl and the seroconversion rate was higher in female versus male patients [15].

A study done by Leroux Roels G also showed that females had a better immune response to vaccination than males. Genetic defects of antigen presentation to T lymphocytes and an acquired defect in the cellular immune response were found to be responsible for the lower antibody titer [16].

There are reports of alterations in the immune regulation in SSNS patients [17]. These alterations express a genetic defect in immune responsiveness [18]. Alperet al. [19] reported that homozygous persons (extended haplotype HLA-B8, SC01, DR3), if vaccinated with HBsAg, would not make a normal antibody response, whereas heterozygotes would have a normal antibody response. Specific Major Histocompatibility Complex (MHC) haplotypes are associated with a poor response to HBV vaccine as well as a significant increase in its frequency in children with SSNS [20]. This finding supports that MHC is responsible for inherited predisposition to SSNS, poor responsiveness to HBV vaccine, and abnormal immune response to infection or vaccination.

It is well known that boys are more susceptible to SSNS than girls and are more susceptible to be chronic carriers of HBV [21-23]. The effective vaccine dose may be lower in girls than for boys. In dose response studies using the inactivated influenza vaccine, girls vaccinated with a half dose of the influenza vaccine achieved similar antibody titers to boys vaccinated with a full dose vaccine [24,25].

In the present study, none of patients developed complications or showed relapse following vaccination. During the study period, 8 patients left the study, 7 patients due to relapse and 1 patient for personal reasons. The cause of relapse was infection in 7 patients (urinary infections in 3, enteric fever in 1, and bronchial asthma in 3 patients). Abeyagunawardena et al [26] showed that vaccine related relapses were not common in children with nephrotic syndrome, and the protection offered by vaccines greatly outweighed this minimal risk.

Conclusions

The present study showed a reduced response to HBVac in boys with SSNS as compared to girls. Due to the small sample size, single center study, and short follow-up period, we cannot draw any valid conclusions about the response of SSNS boys to HBV vaccination. Long-term, longitudinal, multicentric studies are required to evaluate seroconversion following HB vaccine in nephrotic children to obtain more definite results.

Conflict of Interest

None declared

Financial Support

None declared

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