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Seroprotection of Hepatitis B in Children with Steroid Sensitive Nephrotic Syndrome

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Abstract

Introduction: *Children with Steroid sensitive nephrotic syndrome is associated with lower seroconversion of hepatitis B vaccine due to prolonged period of proteinuria, prolonged period of steroid therapy* ***Objective:*** *The primary aims of this study was to assess the seroconversion rate in children with steroid sensitive nephrotic syndrome (SSNS) who were previously vaccinated against hepatitis B and to compare with the titre of vaccinated healthy children. The secondary aims was to study the association of antiHBs titre in different clinical types of diseases and comparison of persistant antibody titre after prolong post vaccinal duration in both nephritic syndrome and control group.* ***Materials and Methods:*** *This cross sectional study was carried out in the department of Paediatric Nephrology, Bangabandhu Sheikh Mujib Medical University, Dhaka from July 2014 to June 2015. A total of 75 vaccinated Children against hepatitis B aged 1 to 12 years of both sex suffering from steroid sensitive nephrotic syndrome were included in this study. Seventy five healthy children against hepatitis B were taken to compare the immunogenecity of hepatitis B vaccine as comparison group.* ***Result:*** *Out of seventy five children with steroid sensitive nephrotic syndrome (SSNS) 51(68%) were male and 24 (32%) were female. Most of the patients belonged to 2-4 year group (39.6%) and of them 42% had 1st attack. In comparison group most of the healthy children belonged to 2-4 year age group 22(28.2%). In nephrotic syndrome group, majority(57.3%) of the patients with nephrotic syndrome had antibody titre <10 miU/ml(not seroprotected). On the contrary 78.7% healthy control were seroprotected (antibody titre >10 miU/ml)and this difference was significant (p value =<0.001). In nephrotic syndrome group significant titre was present in 2-4 years post vaccinal duration which also declined after 9-10 years post vaccinal duration group . In healthy control group significant titre was present in 2-4 years post vaccinal duration group which also declined gradually after increasing post vaccinal duration.* ***Conclusion:*** *In nephrotic syndrome group significant titre was present in 2-4 years post vaccinal duration which also declined after 9-10 years post vaccinal duration group. In healthy control group significant titre was present in 2-4 years post vaccinal duration group which also declined gradually after increasing post vaccinal duration.*

Keywords: *Hepatitis B vaccine, Seroconversion, Nephrotic syndrome.*

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Introduction:

Nephrotic syndrome is a common renal disease in children.It is 15 times more common in children than adult[1]. There is epidemiological evidence of higher incidence in south Asia where incidence is 9-10 per 100,000 population[2]. A study in on Asian children in two cities of united kingdom has reported 9 and 16 per 10,0000 population respectively[3]. It is characterized by massiveproteinuria (urinary total protein >1gm/m²/24 hours), hypoalbuminemia (serum albumin < 2.5 gm/dl), edema and hypercholesterolemia (serum cholesterol >250mg/dl)). Nephrotic syndrome is typically seen in children in the age group 2-6 years[4]. The disease is uncommon in the first year of life.Eighty percent of children with nephrotic syndrome are less than six years old at presentation with median age at diagnosis being 2.5 years for minimal change nephrotic syndrome (MCNS) and 6 years for focalsegmental glomerulosclerosis[5,6] . The initial event in the pathophysiology of nephrotic syndrome is a derangment in the glomerular capillary walls resulting in increased permeability to plasma proteins resulting in massive proteinuria.This heavy proteinuria leads to depletion of albumin mainly,but also lipoproteins & globulins. The loss of immunoglobulin & low IgG levels make the child vulnerable to infections[7]. About 2 billion people are infected with hepatitis B virus all over the world. Rate of new infection acute disease are higher among adult but chronic infection is more likely to occur in person infected as infant or young children. India is an intermediate endemicity for Hepatitis B with a HBsAg positivity prevalence between 2-7% of the population studied[8]. Hepatitis B infection acquired in childhood has higher chance of chronicity and can lead to chronic hepatitis, cirrhosis & hepatocellular carcinoma[9]. These outcome are all preventable by early childhood immunization. In Bangladesh prevalence of hepatitis B is scarce and few sporadic data are available. Considering the alarming situation a pilot project of HBV vaccine started incorporated with EPI in 6 distrcts in 2005.The vaccine is safe & well tolerated.The classical schedule is 0,1,6 months. The vaccine is highly immunogenic & seroconversion rates are greater than 95% after a 3 doses schedule in healthy infants, children & adolescents[11]. Seroconversion rates are lower in elderly, immunocompromised, & those with renal failure.Four doses at 0,1,2 &12 months of double dose may be given in these patients[12]. Grzesiowski et al shows that efficacy of standard dose of vaccine versus double dose,in both group seroprotection rate is similar(standard dose 96%, double dose group 93%). However , anti HBs antibody level was significantly higher in double dose group during a three months observation period. Mantan M et al showed that children with nephrotic syndrome were less likely to seroconvert to HBV vaccination.The study shows 48% children are seroprotected (value >10mIu/ml antibody titres) and 52% in the group studied were unprotected (value <10mIu/ml antibody titres). 63.6% of children with SSNS & 35.7% of children with SRNS were found to have protective level of titres in the study. La Manna A et al compared the seroconversion rate between steroid sensitive nephrotic syndrome with the control group which showed 66% and 100% seroconversion accordingly.

Materials and Methods:

This is a Prospective observational study was conducted in the Department of Paediatric Nephrology, BSMMU, Dhaka from July 2014 to June 2015 where Seventy five children with steroid sensitive nephrotic syndrome were included in this study of both sexes between age group of 1-12 years both admitted and attended in the OPD during study period whose parents agreed to participate(by written informed consent) and who met the inclusion criteria as vaccinated with vaccine at least 6 weeks before enrollment. Healthy children vaccinated against hepatitis B were included as comparison group. For seropositivity rates of 65-73% with 95% confidence interval & precision of 10%, we need a sample size of 75 children.Children aged 1-12 years of both sexes having nephrotic syndrome of 1st episode and relapse (IFRNS, FRNS). Steroid dependent nephrotic syndrome is included in FRNS.Children with a negative test for Hepatitis B surface Antigen (HBsAg), Children with a completed course of HBV vaccination with EPI or classical schedule at least 6 months before onset of the disease were included as inclusion criteria. Children with Congenital NS (onset of nephrotic syndrome < 3 months of age), Children with steroid resistant nephrotic syndrome and children known to have other associated immunosuppressive diseases such as chronic kidney disease(CKD), chronic liver disease(CLD), congenital heart disease (CHD),Secondary nephrotic syndrome like SLE, HSP etc and those parents/patients who will refuse to participate were excluded from the study. The following variable was noted in the study group as age, gender, clinical type of nephrotc syndrome,vaccination schedule, AntiHBs antibody titre (quantitative vaccine response against hepatitis B and Clinical history noted including age of onset of 1st attack of nephrotic syndrome, duration of disease, number and type of relapse. Drug history like immunosuppressant and immunomodulating agent with dose and duration was included.Vaccination history such as EPI schedule

(0,1,2 month) or classical schedule (0,1.6 month), dose of HBV vaccination , timing of HBV vaccination was included. After providing informed written consent 6 ml of venous blood collected from each patient, the sample divided into sample of 3 ml each. One sample for determining biochemical parameter & other sample used to determine HbsAg positivity. AntiHBs assay is a chemiluiminescence immunoassay (CMIA)in fully automated analyser for quantitative determination of antibody to HBsAg. After collecting data by structured questionnaire including all the variables data were checked and edited and analysed using statistical package for social science (SPSS). The chi square test used to compare the categorical data and antibody titre between two group, in different clinical type of steroid sensitive nephritic syndrome. Analysis of variance (ANOVA) test were done for comparison of biochemical parameters. For all comparison, the 5% probability level ($p<0.05$) was considered significant. Prior to commencement of this the research protocol was approved by Instititional review board(IRB) and procedure to guardian in easily understandable local language and with written consent from patient guardians and healthy comparison.

Results:

A total of 75 children of both male and female included in this study. Most of the case (39.6%) were in 2-4 years group and of them 42% had 1st attack. In comparison group most (28.3%) healthychildren belongs to 2-4 year age group. In nephritic group M:F was 2.2:1 but in comparison group M:F=1.4:1

Table I shows there was significant statistical difference in, antiHBs between nephrotic syndrome group and comparison group.

Table I : Comparison of antiHBs titre between nephrotic syndrome group and comparison group.

Antibody titre (miu/ml)	Group: Nephrotic syndrome group(N=75)	Comparison group(N=75)	p value*
Mean±SD	74.29±193.85	161.54±295.07	0.034
Median	6.4	37.70	
Range(min-ma)	3-1000	5-1005	
Total	**75 (100.0)**	**75(100.0)**	

Mann whitney test was done to measure the level of significance.

Table II shows, in 1st attack 66.7% patient were seroprotective. The difference was statistically significant (p=0.002).

Table II : Comparison of antiHBstitre between different clinicaltypes **nephrotic syndrome group**

Antibody titre (miu/ml)	Group: 1st	IFRNS	FRNS	SDNS	p value*
<10	8 (33.3)	8(44.4)	15 (78.9)	12(85.7)	0.002
≥10	16 (66.7)	10(55.6)	4(21.1)	2(14.3)	
Total	**24 (100.0)**	**18(100)**	**19(100.0)**	**14(100)**	

*Chi-square test was done to measure the level of significance.

Table III shows, in 1st attack 66.7% patient were seroprotective, where in FRNS 21.1% patient were seroprotective.The difference was statistically significant (p=0.003).

Table III : Comparison of antiHBstitre between 1st attack of **nephrotic syndrome group and FRNS.**

Antibody titre (miu/ml)	Group: 1st attack	FRNS	p value*
<10	8 (33.3)	15 (78.9)	0.003
≥10	16 (66.7)	4(21.1)	
Total	**24 (100.0)**	**19(100.0)**	

*Chi-square test was done to measure the level of significance.

Table IV shows in nephrotic syndrome group significant titre was present in 2-4 years post vaccinal duration group which also declined after 9-10 years post vaccinal duration group.

Table IV: AntiHBs titre following post vaccination duration in nephritic syndrome

Post vaccinal duration	>10mIU/ml n(%)	<10mIU/ml n (%)	P value
2-4 years	15(46.9)	14(32.2)	0.094
5-6 years	10(31.3)	8(18.6)	
7-8 years	7(21.9)	5(11.6)	
9-10 years	0(0.0)	11(25.6)	
11-12 years	0(0.0)	5(11.6)	
Total	**32(100.0)**	**43(100.0)**	

Table V shows in healthy control group significant titre was present in 2-4 years post vaccinal duration group which also declined gradually after increasing post vaccinal duration.

Table V: AntiHBs titre following post vaccination duration in healthy group

Post vaccinal duration	>10mIU/ml n(%)	<10mIU/ml n (%)	P value
2-4 years	22(37.3)	2(12.5)	0.045
5-6 years	13(22.0)	2(12.5)	
7-8 years	14(23.7)	4(25.0)	
9-10 years	8(13.6)	5(31.3)	
11-12 years	2(3.4)	3(18.8)	
Total	**59(100.0)**	**16(100.0)**	

Figure -1

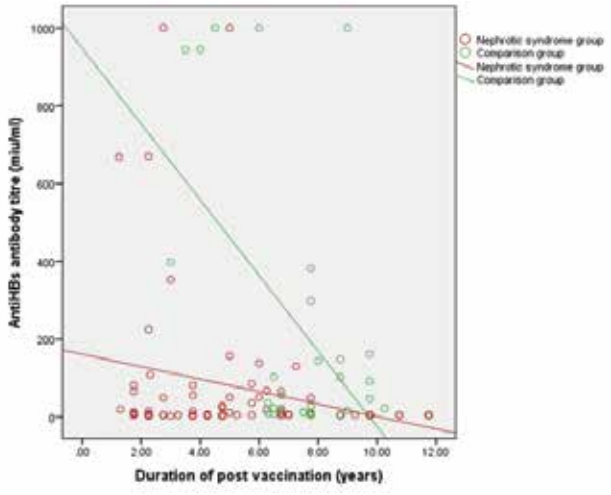

Figure 1: Correlation of AntiHBs with duration of post vaccination in Nephrotic syndrome and comparison groups.

Pearson's correlation test was done to measure the level of significance. AntiHBs reduced with the increase of duration of post vaccination.Nephrotic syndrome group: r= -0.243 and p = 0.035Comparison group: r= -0.391 and p= 0.004.

Discussion:

Though HBV infection is a significant health problem around the world, fortunately it is one of the oncoviruses that is vaccine preventable. HB vaccine induces anti-HBs response that can prevent HBV infection. Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications like liver failure and hepatocellular carcinoma[13].

Nephrotic syndrome being an immune mediated disease and its treatment with steroids and other immunosuppressant drugs have a tendency to reduce the seroprotection against HBV. Various published studies have demonstrated that seroprotection after a routine immunization in children with nephrotic syndrome is lower than that of healthy children.In this study , 75 steroid sensitive nephrotic syndrome patient was enrolled. Most of our patient received hepatitis B vaccination through EPI schedule as hepatits B included in EPI in 2005 in our country. Here we consider antiHBs titre >10 miu/ml to be seroprotective which is described in our studies. Out of the 75 vaccinated SSNS patient, 42.7% patient had seroprotective level of antiHBs titre, where as it was 83.3% in healthy vaccinated children. Similar study done by Mantan M et al showed that among 75 enrolled children, 44% was SSNS and 56% was SRNS. Total 48% patient were seroprotected where 63.6% was SSNS patient and 35.4% was SRNS patient respectively.Another study, La manna et al (1992) compared boys with SSNS (n=18) and controls (n=21) for their response to hepatitis B vaccination which shows 66% seroprotection against hepatitis B in SSNS patients compared to 100% seroprotection among the control group. In our study children with initial episodes of nephrotic syndrome had significantly increased seroprotection than relapse case (66.7% vs 36.9%) respectively.The cause of this lower seroconversion due to longer period of disease and longer exposure of immunosuppressive therapy. Steroid therapy inhibit CD4 cell activity which is necessary for optimal antibody response and contribute to lower antibody titre. Shams Shahemabadi A et al[14] showed that antiHBs antibody titre of previously hepatitis B vaccinated children who completed standard chemotherapy at least for 6 months , 80.8% patient was non seroprotective where 2.94% of healthy control was non seroprotective. Allegra V et al[15] showed that comparing between maintainance haemodialysis(MHD) patient and healthy control that seroprotection rate were lower in MHD group (52.9%) then control 98.4% after a booster dose. Maritsi D et al[16] shows markedly decreased antibody titre against hepatitis B in previously immunized children presented with juvenile immune arthritis shows 55% seroconversion compared with 92% in control group .

In this study, Pearsons correlation test showed that antiHBs antibody level reduced with the increase duration of post vaccination time in both steroid sensitive nephrotic syndrome group and comparison group. Agladioglu et al[18] showed that delaying in the first dose of Hepatitis B vaccine until 2 month after birth produce higher immune response and provide longer term protection. AntiHBs in infant compared in two different schedule 0.2.9 months

(group I) & 2.4.9 months (group II) were analysed 14 months of 3rd dose.GMT were 95.00 and 379.51 miu/ml and rate more then 100 miu/ml were 57.7 % & 94.9 % compared in two vaccination group. Karaoglu L et al[19] showed that immune response of 1-3 years child to hepatitis B vaccination during infancy, 95% shows high seroprotection rate and no difference by sex, anthropometry, time after 3rd dose and place of vaccine administered . Teoharov et al[19] show that presence of immune memory and protection 5-15 years after the initial course of newborn immunization with recombinant vaccine against hepatitis B. Gilca V[20] et al show that three dose of low dose (2.5microgram) recombinant Hep B vaccine of 8-10 years old children induce a 10 years long lasting immunity. Nese Saltoglu et al[21] show that three week hepatitis B vaccination schedule (Day 0,10,21) provide immediate and protective immunity within a short time compared to the classic schedule (months 0,1,2) Duval B et al[22] show that there is no significant diffrerence of protective antibody titre and long term immunogenecity of two recombinant hepatitis B Yildiz et al[23] demonstrated 41 children with SSNS and 30 control were vaccinated with hepatitis B and patient were divided into 3 subgroup : full dose steroid users, alternate day steroid users and steroid non user. Seroconversion rate was lower in steroid users then nonusers at 6th (p=0.005) and 12th (p=0.036) months. At the 15th month the seroconversion rate was significantly lower in the full dose steroid users compared to the controls (p=0.009). In our study children with initial episodes of nephrotic syndrome had significantly increased seroprotection than relapse case (66.7% vs 36.9%) respectively. In treatment of NS, type of therapy received significantly influenced the seroprotective titres. In nephrotic syndrome group significant titre was present in 2-4 years post vaccinal duration group which also declined after 9-10 years post vaccinal duration group and in healthy control group significant titre was present in 2-4 years post vaccinal duration group which also declined gradually after increasing post vaccinal duration,mean antibody titre was declining with the duration of post vaccination period which is not statistically significant in both nephrotic syndrome group and control group. The cause of this lower seroconversion due to longer period of disease and longer exposure of immunosuppressive therapy. Steroid therapy inhibit CD4 cell activity which is necessary for optimal antibody response and contribute to lower antibody titre.

Agakhani A et al (2011) showed that in low hepatitis B endemic area,vaccination in infant protective antibody titre which was 65% after 1 year of vaccine gradually decline in 30%, 29%, 24% in 5,10,15 years of vaccination.Hepatitis B infection has plagued human kind since the beginning of the recorded history.Though HBV infection is a significant health problem around the world, fortunately it is one of the oncoviruses that is vaccine preventable. HB vaccine induces anti-HBs response that can prevent HBV infection. Prevention of primary infection by vaccination is an important strategy to decrease the risk of chronic HBV infection and its subsequent complications. Harpaz R (2000) Studies have shown that childhood vaccination significantly reduced the rate of chronic HBV infection. Various published studies have shown that seroprotection against hepatitis B observed after a routine immunization in children with nephrotic syndrome is lower than that of healthy children.In this study 75 children enrolled , of them 4 patient is SRNS and 71 patient SSNS. Most of our patient received hepatitis B vaccination through EPI schedule as hepatits B included in EPI in 2005. Here we consider antiHBs titre >10 miu/ml to be seroprotective which is describe in our studies . Out of the 75 children enrolled in our study , 57.3% (42) patient are sero negative and 42.7%(35) patient are seroprotective.We also found that majority of patient and healthy control vaccinated according to EPI schedule.We found a significant association between different type of nephrotic syndrome and proportion of children who had seroprotective titre with the proportion of children with seroprotective titre being higher in SSNS 42.7% (66.7 vs 55.6 vs 20.7 %) with SRNS (o.oo%) respectively (p=0.001).And in comparison group 83.3% had significant antibody titre. Mantan et al.(2013) show that among 75 cohort steroid sensitive and steroid resistant are 44% and 56% respectively and 36 patient (48%) were seroprotected where 63.6 % in SSNS patient and 35.7% in SRNS subjects (Mantan et al. 2013).Another study (La manna et al 1992)compared boys with SSNS(n=18) and controls (n=21) for their response to hepatis B vaccination which shows 66% seroconversion against hepatitis B in SSNS subject compared to 100% among the control. Jafarzedah A et al (2005) shows that after 10 years of primary vaccination 47.9% had protective level of antibody with geometric mean titre 68.12 iu/ml who were vaccinated at birth, with no gender difference. Agladioglu et al 2010 show that delaying in the first dose of HB vaccine until 2 month after birth produce higher immune response and provide longer term protection showing GMT for antiHBs were 95.00 & 379.51 iu/ml and rate more then 100 iu/ml were 57.7 % & 94..9 % vaccinated compared in 0,2,9 month and 2,4,9 month group. Agakhani A et al(2011) show that in low hepatitis B endemic area ,vaccination in infant protective

antibody titre which was after 1 year of vaccine 65% of children gradually decline in 30%,29%,24% in 5,10,15 years of vaccinated. Karaoglu L et al shows immune response of 1-3 years child to hepatitis B vaccination during infancy 955 shows high seroprotected rate and no difference by age, sex, anthropometry, time after 3rd dose and place of vaccine administered. Maritsi D et al (2013) shows markedly decreased antibody titre against hepatitis B in previously immunized children presented with juvenile immune arthritis shows 55% with 92% in control group .Most person with normal immune function who respond adequately with three dose of hepatitis B vaccination probably remain protected indefinitely. Steroid therapy inhibit CD4 cell activity which is necessary for optimal antibody response and contribute to lower antibody titre. The European consensus group guidelines on hepatitis B immunity concluded that there was no need of booster dose in healthy children previously vaccinated against hepatitis B. How ever in children who were immunocompromised there is a need to ascess antibody titre every 6-12 months for antiHBs antibody level and a booster dose should be given if the titre <10miu/ml. The effect of booster dose is usually seen after 4 week of vaccination. Gilca V et al show that three dose of low dose (2.5microgram) recombinant Hep B vaccine of 8-10 years old children `induce a 10 years long lasting immunity. Duval B et al (2005) show that there is no significant diffrerence of protective antibody titre and long term immunogenecity of two recombinant hepatitis B vaccine and effect of booster dose given after five years. Before the booster dose antibody titre was detected in 94.7% in Engerix B group and 95.2% in recombivax group , after booster dose detectable antiHbs titre 97.9 and 98.5% respectively.

Conclusion:

It can be concluded from present study that children with steroid sensitive nephrotic syndrome previously vaccinated against hepatitis B had lower seroconversion rate in FRNS. In healthy control group significant seroconversion than nephrotic syndrome group. In nephrotic syndrome group significant titre was present in 2-4 years post vaccinal duration group which also declined after 9-10 years post vaccinal duration group in healthy control group significant titre was present in 2-4 years post vaccinal duration group which also declined gradually after increasing post vaccinal duration.

Conflict of Interest: None.

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