

ANTI-HBs IN IMMUNIZED CHILDREN WITH CUBAN HEPATITIS B VACCINE AND IMPACT OF BOOSTER DOSE AFTER FIVE YEARS

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ABSTRACT

Objectives: Hepatitis B virus infection and associated diseases are a major public health problem. This study was planned to find out the persistence of antibody against hepatitis B surface antigen in Iranian vaccinated children after five years.

Methodology: Anti-HBs titers in a group of healthy good - responder children who were vaccinated with Cuban hepatitis B vaccine in infancy were measured after five years. Children with antibody titers <100mIU/ml were revaccinated and retested after four weeks.

Results: Mean anti-HBs titers in 68 children (29 females, 39 males) were 482.1mIU/mL at six months after the third dose of primary vaccination and 153mIU/mL at five years later. Total mean anti-HBs titers in 36 (52.9%) children out of 68 (17 females, 19 males) were 38.3mIU/ml and 4(5.8%) of 68 children (two of each sexes) had no detectable antibody after five years. Total mean anti-HBs titers in these hypo- responder and non- responder were 774.3mIU/mL and 625.5mIU/mL respectively after booster dose.

Conclusion: In a group of children, who were immunized with Cuban hepatitis B vaccine from birth, anti-HBs titers fell at 6.5 years of age and almost half of children became hypo responder or no responder and their anti-HBs titers developed secondary rise after booster vaccination. All children showed immunologic memory to a booster dose.

KEY WORDS: Hepatitis B virus, Anti-HBs, Vaccine.

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INTRODUCTION

The aim of universal vaccination of infants against hepatitis B (HB) infection is to reduce and ultimately eliminate hepatitis B virus (HBV) infection and associated disease. Current guidelines for vaccination is 3-doses of hepatitis B vaccine to be initiated on the first day or at the latest by two months of age and at least 96% of vaccinated infants develop an anti- hepatitis B surface (anti-HBs) level of at least 10mIU/ml. Efficacy trials are associated with protection against acute HB disease or chronic HBV infection in the US.^{1,2} Most HBV infection in the US result from sexual transmission or exposure to contaminated blood

during adolescence or adulthood; therefore immunity induced by infant vaccination either must extend into adulthood or booster vaccination will be needed during childhood or early adolescence. The duration of hepatitis B vaccine protection has not been firmly established. Long term protection of 10-12 years appears to occur in those infants who are at high risk or whose mothers were positive for hepatitis B surface antigen (HBsAg) and Hepatitis B antigen.³⁻⁵ However, the duration of protection in low risk infants whose mothers are negative for HBsAg and who receive hepatitis B vaccine from birth is unknown. In these populations, the risk of HBV infection increases during adolescent and early adulthood primarily because of the risk of sexual transmission.⁶

Whether booster doses might eventually be necessary to extend protection through adulthood has not been established. An international group⁷ classified anti-HBs titer in to three groups, non-responder (<10mIU/mL), hypo-responder (10-100mIU/mL) and good-responder (>100mIU/mL). We have previously demonstrated that Iranian children who were vaccinated with Cuban recombinant hepatitis B vaccine, were non responders, hypo responders and good-responders 15.6%, 27.7% and 56.7% respectively.⁸

The aim of this study was to investigate the persistence of anti-HBs level after five years in a group of healthy children whose mothers are negative for HBs Ag and who had been initially vaccinated against HB infection with Cuban recombinant hepatitis B vaccine starting at birth, 1.5 and 9 months of age and their anti-HBs levels were >100mIU/ml (good-responder). We also assessed the titer and status of immunologic memory for HBV in children through a booster dose of a hepatitis B vaccine in those children whose serum anti-HBs had fallen below 100mIU/mL (hypo-responder).

This study is approved by research and ethic committee of Shaheed Beheshti University of Medical Sciences.

METHODOLOGY

This study was performed in 2002 in Tehran, Iran. Here, in 1994, a universal vaccination programme was initiated that included all newborn babies. All the babies completed the vaccination in the first year of life with following vaccination schedules: Three pediatric doses (10µg) Cuban recombinant HB vaccine (Heberbiovac HB, Heber Biotec, Havana, Cuba) at birth, 1.5 and 9 months of age.

These healthy children were originally part of a long term follow-up study of children who had received hepatitis B vaccine from birth and their sera tested for anti-HBs after completion of the initial vaccination series. Only children who responded with anti-HBs titer of 100mIU/mL (good – responder) approximately six months after the initial vaccine series of Cuban recombinant HB vaccine according to the above schedules and had never received a booster dose of vaccine were eligible for inclusion in this study. All children had been received their vaccine in the external thigh.

At the beginning of this study the parents of children were informed and after obtaining their consents, 3ml blood sample was obtained from each child and tested for anti-HBs and anti-HBc. Finally, all children who were found to have anti – HBs titers of ≤ 100 mIU/ml at 6.5 years of age received a single booster dose of Cuban recombinant HB vaccine (Heberbiovac HB) and retested for anti – HBs titer and anti-HBc four weeks after the booster dose. Those children whose anti-HBs titers were ≥ 100 mIU/ml were excluded from the study.

Anti-HBs and anti-HBc titers were measured by using Enzyme-linked immunosorbent assay (ELISA) method, using commercial kits (RADIM, Roma, Italy). The anti-HBs titer was quantitatively measured according to recommendation of manufacture's instructions and international group⁷ and expressed as milli-international Units (mIU) per ml and anti-HBc was qualitatively measured and expressed as positive or negative to ensure that no child was infected with HBV.

RESULTS

This study enrolled 68 children (29 females, 39 males) with mean age of 6.5 years who met the eligibility requirements. Of the 68 children who had received three doses of a Cuban recombinant hepatitis B vaccine in infancy, 28(41.1%) had anti HBS titers $\geq 100\text{mIU/mL}$, good-responders, 36 (52.9%) 10 - 100mIU/mL were hypo responders (19 females and 17 males) and 4 (5.8%) were non-responders (two females and two males) after five years. All were negative for anti-HBC and all (100%) hypo responders and non responders responded with single dose of booster vaccine after about four weeks. Mean anti-HBs titers in 17 females and 19 males were 41.5 and 35.1mIU/mL respectively at 6.5 years before booster dose. There were no significant difference in antibody titers among females and males at 6.5 years of age but significant at 15 months of age $P < 0.05$.

Children with highest titers of anti-HBs after primary vaccination were most likely good-responder at 6.5 years of age, but overall nearly 40(58.7%) of the children became hyporesponders or nonresponders at 6.5 years of age and there were no relation to primary anti-HBS titers among them (range 111 to 715mIU/ml). Booster vaccination induced large increases in the titers of anti-HBs nearly more than 10-fold rise before booster vaccination. The mean anti-HBs titers in four children with no detectable antibody at 6.5 years of age were 236.5mIU/mL at 15 months of age and rose to 625.5mIU/mL after booster dose. There were no significant differences among their

antibody titers with other children after booster dose at 6.5 years of age see Table-I.

DISCUSSION

This study provides important information on the long-term efficacy of the Cuban recombinant hepatitis B vaccine now available in Iran. Such data may be critical in devising appropriate strategies for booster dose in persons who have received the primary vaccine series. Our data showed that antibody titers in good-responder recipients of the hepatitis B vaccine decline substantially after five years vaccination and that loss of antibody is related to the maximal antibody response of the vaccinated persons that is similar to other studies.^{9,10} The recommendation of international group⁷ in western industrialised countries in individuals with anti-HBS $< 10\text{mIU/ml}$ (non responders) after completion of vaccination is that probably these children lacks protection against HBV infection and need booster dose and individuals with anti-HBS levels of 10-100mIU/ml (hypo responders) need booster dose within one year. Thus, all individuals in our study whose anti-HBs in titers declined to $< 100\text{mIU/ml}$ needed booster dose and should be retested after the booster dose. However, there is no unanimity on this point. On the other hand, UK¹¹ investigators classified vaccines into four groups, non-responder $< 10\text{mIU/ml}$, poor-responder 10-500mIU/ml, moderate responder $> 500-4000\text{mIU/ml}$, good responder $> 4000\text{mIU/ml}$. They recommend that non – responders should receive a repeat course of vaccine, poor responders should receive an immediate booster dose, Moderate responders

Table-I: Persistence of mean anti-HB_s titer among children ages 15 months and 5 years later with prebooster and post booster dose

Group	At 15months		After 5 years		Anti-HBs of hyporesponders after 5 years		Anti-HBs of Non responders after 5 years				
	n	%	Anti-HB _s titers	n	%	Pre booster	Post booster	n	%	Postbooster	
Females	29	(42.6)	504.4	169.6	17	(58.6)	41.5	820.8	2	(2.9)	432
Males	39	(57.3)	464.5	196.1	19	(48.7)	35.1	766.3	2	(2.9)	819
Total	68	(100)	484.4	182.8	36	(52.9)	38.3	793.5	4	(5.8)	626.5

Anti-HB_s expressed as mean mIU/mL

should be boosted at about five years and the rest do not need booster dose for at least 10 years. We have previously demonstrated that mean anti-HBs titers in Iranian good responder children were <500mIU/ml. Therefore according to the UK recommendation, they are poor responders and all Iranian children with anti-HBs titers less than 500mIU/ml should receive booster dose. European consensus group¹² recommended that protective level of anti-HBs in vaccinated individuals is >10mIU/ml and anamnestic antibody response to antigen lasts for at least 12 to 15 years in immunocompetent individuals. We should not forget that all studies in the world were by Engerix-B or Recombivax-HB vaccines. These vaccines induce at least >10mIU/ml anti-HBs in 96% of vaccinated infants whereas Cuban HB vaccine is used in Iran developed anti-HBS levels >10mIU/ml in approximately 84% of vaccinated children. Not only that the duration of use and study by non-Cuban HB vaccines in the world is more than 20 years whereas in Iran the duration of use of Cuban HB vaccine is approximated 10 years and there are not many studies about this vaccine. In addition, we do not know how many vaccinated children by Cuban vaccine has manifested or will manifest hepatitis B infection symptoms or have asymptomatic infection. This aspect need to be investigated further.

CONCLUSION

This study specifically found that a group of children immunized with Cuban Hepatitis B vaccine within the nine months of age become hypo responders or non responders at 6.5 years of age and all of them show secondary rise of more than 10-folds in anti-HBS titer after a booster dose of vaccine.

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