RESPONSE OF BOOSTER DOSE OF CUBAN RECOMBINANT HEPATITIS-B VACCINE IN NONRESPONDER AND HYPORESPONDER CHILDREN

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ABSTRACT

Background: Acute hepatitis B infection can debilitate a patient for weeks and occasionally has a fatal outcome, while chronic infection is a major threat to the individual.

Objective: To assess response of nonresponder and hyporesponder children to booster dose of Cuban recombinant hepatitis B vaccine.

Subjects and Methods: An interventional, descriptive study has been conducted on children who had been immunized with Cuban recombinant Hepatitis B vaccine and their antibody titers were ≤10mIU/ml (nonresponder) and 10-100mIU/ml (hyporesponder) administered booster dose of the same vaccine in their Deltoid muscles.

Results: The response of 141 children with the mean age of 1.9 years to booster dose of vaccine were 94.3% and 100% vaccinees with the first and second booster dose of vaccination respectively. The anti-HBs titer in nonresponders and hyporesponders were 468±346 and 783± 346mIU/ml respectively with significant differences between two groups (P=0.001).

Conclusion: This study demonstrate moderately increase antibody production in the majority of vaccinees with single supplementary vaccine.

KEY WORDS: Hepatitis B virus, Vaccination, Cuban vaccine, Hyporesponders, Nonresponders.

Abbreviations used

anti = Antibody HBsV = Hepatitis B surface antigen virus HBc = Hepatitis B core antigen
HLA= Human Leukocyte antigens miU/ml = Milli international units per milliliter

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INTRODUCTION

Immunization against hepatitis B virus infection is practiced in many countries. The American Academy of pediatrics in 1992 recommended immunization after birth and infancy.[1] In most studies on non-Cuban HBV vaccines (Engerix-B) in immunocompetent subject, approximatyely 5% to 10% apparently healthy individuals fail to respond to vaccination but remain susceptible to infection.[2-5] On the basis of classification of international group,[6] Dahifar, H in a recent study have demonstrated that Iranian children who received three doses of Cuban Hepatitis B vaccine, 15.6% and 27.7% were nonresponders and hyporesponders respectively.[7] The reasons for these failures are multifactorial and genetically related.[2-5] Therefore, the response of these children to reimmunization is of interest. This study will evaluate the response of revaccination with Cuban recombinant HBV vaccine in nonresponders and hyporesponders who received three primary series of vaccine.

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SUBJECTS AND METHODS

An interventional, descriptive and prospective study has been conducted on children who were available and had received three doses of Cuban recombinant HBV vaccine at 0, 1.5, 9 months of age in accordance with the Iranian national vaccination scheme were included in the study on account of their HBs antibody titers, hyporesponder (10-100mIU/ml) and nonresponder (<10mIU/ml). All children who were nonresponders or hyporesponders were selected randomly from outpatients centers of Shaheed Beheshti Medical University during 2000-2003. The parents signed the informed consent for booster dose and serological follow-up; however it was difficult to persuade the parents for further booster vaccination in children with non or hyporesponse.

All children in both groups were injected with one dose (10µg per 0.5ml) of Cuban recombinant HBV vaccine into the deltoid muscle. The recombinant vaccine used in this study was yeast-derived vaccine (Herberbiovac HB, Herber Biotec, S.A.A partade postal 1662, Habana, Cuban), containing 20µg per ml of HBsAg. Blood samples were obtained from children 4-6 weeks after the booster dose. Measurment of anti-HBs and anti-HBc level were performed by Enzyme linked immunsorbent assay (ELISA), using commercial kits (RADIM, Roma, Italy). Anti-HBs was quantitatively measured in accordance with manufacturer's instructions by testing a dilution series of a positive sample with known concentration of anti-HBs expressed as mIU/ml in accordance with the order of international group.[6] Anti-HBc was qualitatively measured and expressed as positive or negative. Differences in variables were analyzed by chi-square test, while *t* test was done for differences in the mean titer of anit-HBs.

The study was approved by the Pediatric Research and Ethic Committee of Shaheed Beheshti University of Medical Sciences and Health Services.

RESULTS

One hundred–forty one children with the mean (±SD) age of 1.9 (±0.4) years with no significant differences among females and males were included the study, of these 60 were nonresponders, 26 females, 34 males and 81 hyporesponders, 45 femals, 36 males. The mean (±SD) interval time between booster dose and last dose of first vaccination series were 6 (±1.3) months. The total responders to the first booster dose were 133 (94.3%) of 141 children and 100% with the second dose vaccine. Eight boys (5.6%) of 141 children, 4 of each group did not increase their antibody titers by the first booster dose and required the second dose. Anti-HBc in all children were negative. The mean±SD anti-HBs titers with no regard to sex in nonresponder and hyporesponder children were 468±383mIU/ml (range 249-1250mIU/ml) and 783±346mIU/ml (range 183-1511mIU/ml) respectively. There were significant differences in antibody production among hyporesponders and nonresponders (P = 0.001) Table-I.

DISCUSSION

In most previous studies it has been shown that protective serum titers of anti-HBs developed in >95-99% of healthy infants, children and young adults who received a series of three intramuscular doses of non-Cuban hepatitis B vaccine.[8-10] In a recent study, the results of concentration of serum anti-HBs Cuban vaccine in 538 children who had received three doses of the same vaccine were 15.6% nonresponder, (<10mIU/ml), 27.7% hyporesponder, (10-100mIU/ml) and 56.7% good responder (>100mIU/ml).[7] The rate of unresponsiveness to non-Cuban HBV vaccine has been variable

Table-I: Anti HBsAg titers in two groups before and after booster dose.

Group	*Total no*	*Anti-HBsAg titers mlu/ml**	
		befor (range)	*after (range)*
Nonresponders	60	undetectable	468±138 (249-1250)
Hyporespanders	81	48±35 (13-91)	783±346(183-1511)

* Titers shown as Mean±SD

in different studies.[11] Furthermore, the international group recommends a booster dose of vaccine immediately for non-responders and one year later for hypo-responders.[6] The reason why some healthy children may be hypo or non responder to vaccination are not well understood. The proposed reasons are improper storage, administrating the vaccine into the buttock rather than the deltoil muscle, improper recommended vaccination schedule, temperature stability of vaccine and diminished immunogenicity in aged or obese vaccinees.[2,5]

A role for genetic modulation of immune response to HBV vaccine and a number of environmental factors have been attributed. The most important ones being the haplotype of HLA antigen and immunological tolerance.[12] A variety of HLA classes I and II antigen have been reported in different ethnic population.[13] The present study demonstrates good response in all vaccinees to Cuban HBV vaccine with the booster dose. In a study with recombinant HBV vaccine (Engerix-B) only 52% responded to 4th intramuscular vaccine dose (anti-HBs level ≥10mIU/ml).[14] The concentration of antibody and rate of responder of this study is lower than our study.

Shokri, et al conducted a study on nonresponder of Iranian children who received three series doses of non-Cuban HBV vaccine (Engerix-B), a supplementary dose of the same vaccine was administered, the response was observed in 90% of infants and the mean titer of anti-HBs was significantly higher than our study and in 100% of children with the second supplementary dose (mean±SD 7131±3384mIU/ml)[15] that is similar to our study and it seems that it can not be related to the genetic or haplotype of HLA antigen and immunological tolerance of Iranian children.

Cheng, et al, reported 53.1%, 87.5%, 100% after first, second, and third doses of supplementary vaccine respectively in children who failed to respond to a primary series of vaccination and concentration of anti-HBs titer>1000 mIU/ml were noted in 50% of the vaccinees after three doses of vaccine and 46.9%<10mIU/ml, 37.5% 10-100mIU/ml, and 15.6% 100-1000mIU/ml after the first dose of the supplementary vaccination.[16] The rate of responders after the first dose of supplementary vaccination in comparison with our study is low and rate of nonresponders are high. It seems that Cuban HBV vaccine induces higher responders and concentration after the first dose of supplementary vaccination. Unfortunately, the present study had some limitations: A- In obtaining the informed consent from parents for further supplementary dose and samplings, so this study can not establish the mean concentration of anti-HBs>1000 mIU/ml after further revaccination. B- This study could not compare immunogenicity of the Cuban vaccine with the non-Cuban vaccine because of unavailability of non-Cuban vaccine and we had to use the other investigator's studies.

UK guideline recommended that non-responders should be given a repeat course of vaccine and hyporesponders a single booster dose, others should be boosted at 3-5 years[17] and Tilzey, et al believe all vaccinees with initial anti-HB_s titers between 10mIU/ml to 500mIU/ml, should be given an immediate booster dose and those with titers between 500mIU/ml to 4000mIU/ml should be boosted at about five years and the rest need not be boosted for at least 10 years.[18] Therefore, as we have also explained before, we must choose especial method with further investigations by other investigators in different areas of Iran.

CONCLUSION

This study demonstrated high response rate after the fist dose of supplementary vaccination and low titer antibody production.

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