Persistence of hepatitis B vaccine immune protection and response to hepatitis B booster immunization *

LI Hui[1], LI Rong-Cheng[2], LIAO Su-Su[1], YANG Jin-Ye[2], ZENG Xian-Jia[1], WANG Shu-Sheng[2]

Subject headings hepatitis B vaccines; immune protection persistence; booster; immunization

Abstract

AIM To identify the persistence of immune protection of China-made, plasma-derived hepatitis B vaccine after infancy immunization and the time table of booster immunization.

METHODS A cross-sectional follow-up study and an experimental study on booster were used for the evaluation of the serological effect 7 years after vaccination and the antibody anamnestic response. Radioimmunoassay was used for the detection of hepatitis B virus markers.

RESULTS The protective anti-HBs positive rates of 1018 children, who were vaccinated according to the regimen of three doses of 10 μg hepatitis B vaccine in their infancy, declined from 75.0% during the first two years to 48.2% in the 7th year after the first dosage, however, the positive rates for HBsAg and anti-HBc always fluctuated at a low frequency. A total of 144 subjects aged 6 or 7 years, who were negative for both HBsAg and anti-HBc before booster, were selected from 1018 children of the follow-up study, and boosted with 1μg intradermally or 2μg hypodermically hepatitis B vaccines. Their anti-HBs GMT and anti-HBs positive rates were 190.6mIU/ml and 89.6% in the first month after booster, significantly higher than 14.7mIU/ml and 54.9% before booster ($P < 0.01$), and declined back to 25.3mIU/ml and 75.5% in the 12th month; among 65 children with the anti-HBs negative before booster, 40 had a level of anti-HBS ⩾100mIU/ml one month after booster, suggesting retention of immune memory in most of them.

CONCLUSION No need for revaccination against hepatitis B in the 7th year after the initial immunization due to better persistence of immune protection of the vaccine and retention of immune memory to hepatitis B virus in the vast majority of the vaccinees.

[1]Institute of Basic Medical Sciences, CAMS and PUMC, Beijing 100005, China
[2]Guangxi Anti-Epidemic & Hygiene Center, Nanning 530021, Guangxi Zhuang Autonomous Region, China
Professor LI Hui, M.D., M.P.H., male, born on 1943-06-20 in Jiangjin County, Sichuan Province, China, graduated from Beijing Medical University in 1970 and from Peking Union Medical College as a postgraduate in 1982, now professor of epidemiology, majoring hepatitis B control and etiology on cardiological vascular diseases, having 28 papers and 7 books published.
***Supported by the China Medical Board, New York, Inc., Grant No.93-582.**
Correspondence to: Prof. LI Hui, Director, Department of Epidemiology, institute of Basic Medical Sciences, CAMS & PUMC, 5 Dong Dan San Tiao, Beijing 100005, China
Tel. +65·296971(O), 65141591(H)
Received 1998-11-09

INTRODUCTION

Infant hepatitis B vaccine immunization integrated with EPI program has become a principal strategy for the hepatitis B control. Since the end of the 1980s, large-scale hepatitis B vaccination in infants has been implemented in the many areas of China[1]. The short-term effectiveness of hepatitis B vaccine has been confirmed in many studies[1-4]. The low-dose immunization has been recommended as a principal strategy to infancy vaccination of the rural areas[5]. However, it is necessary to answer the following questions in community-based hepatitis B prevention: what is the persistency of immune protection of China-made, plasmaderived hepatitis B vaccine, especially in the infancy should low-dose immunization be used? Is there antibody anamnestic reaction to hepatitis B surface antigen (HBsAg) in the vaccinees with vaccine-induced antibody negative-conversion When should the booster immunization be administered? In order to determine the duration of immune protection and the immune memory to HBsAg 7 years after the infancy vaccination, a follow-up study on the long-term effectiveness of hepatitis B vaccination and an experiment study of hepatitis B booster immunization were carried out in Longan County, a remote hepatitis B endemic rural area of China, from 1994 to 1995.

MATERIALS AND METHODS

Sample size and subjects

A total of 1018 children aged 1-7 years, born in the period of 1987 to 1994 in Longan County and

having the vaccination record of three doses of 10μg plasma-derived hepatitis B vaccine (produced by the National Institute for Biological Products, Beijing) according to 0, 1 and 6 month schedule, were selected in terms of cluster sampling as a sample for the observation of long-term effectiveness. Among them 144 children were recruited as subjects for the experiment of booster immunization.

Method and dosage of booster

The 144 subjects were divided into two groups. One group of 91 subjects were intradermally injected with a dose of 1μg plasma-derived hepatitis B vaccine, another group of 53 subjects were hypodermically immunized with a dose of 2μg vaccine.

Reagents

Hepatitis B radioimmunoassay (RIA) reagent kits were purchased from the National Institute of Biological Products, Beijing.

Specimens collection and lab test

Peripheral blood of 3ml-5ml was collected in all samples in April 1994, and from all subjects at 1- and 12 month after the booster, respectively. Serum specimens were kept at -20℃ for the test. RIA was used for the detection of anti-HBs, anti-HBc and HBsAg. Anti-HBs-S/N ratio ≥10.0, anti-HBc inhabitation ratio ≥75% and HBsAg S/N ratio ≥ 2.1 were defined as sera positive. Both scales, anti-HBs mIU/ml GMT and anti-HBs positive rate, were used for comparison of the differences of antibody level between before and after booster, and between different doses of booster vaccine. The following formula was used for calculating anti-HBs mIU/ml:

$$\text{mIU/ml} = 130.75\ [\ \text{EXP}\ (\ 0.66765 \times \frac{\text{CPM of sample-CPM of negative control}}{\text{CPM of positive control-CPM of negative control}}\ ) -1]$$

Data analysis

Softwares, dBase-III and SAS, were used for the data base and the statistical analysis.

RESULTS

Positive rates for anti-HBs, anti-HBc and HBsAg 1-7 years after immunization

The age distribution of positive rates for anti-HBs, anti-HBc and HBsAg of 1018 immunized children aged 1-7 years after infancy hepatitis B vaccination is shown in Table 1.

Table 1 shows that the anti-HBs positive rate significantly declined from 75.0% of age group of 1-2 years to 48.2% of 7-year age group (X^2=51.2, P<0.01), while anti-HBc and HBsAg positive rates were not found significantly increased with age (P >0.05). The results suggested that the hepatitis B vaccine induced-antibody level in infancy immunization was decreasing year by year after vaccination, however, the difference of hepatitis B virus (HBV) infectious rate between age groups was not statistically significance.

Change of anti-HBs before and after hepatitis B vaccine booster

The results of comparison of anti-HBs level change of 144 subjects before and in the first and 12th month after booster are shown in Table 2.

Anti-HBs GMT of 144 subjects one month after booster was significantly higher (by 18.3 fold) than that before booster (t = 17.4, P < 0.01). However, in the 12th month after booster, the anti-HBs GMT of 106 subjects dropped significantly, and there was no difference before and after booster (t =1.3, P> 0.05); and the anti-HBs positive rates were 89.6% in the 1st month and 75.5% in the 12th month, significantly higher than (54.9%) before booster (P<0.05). The antibody positive rates of both subgroups with low anti-HBs titer (10mIU/ml-99mIU/ml) and the subjects with negative anti-HBs (<10.0mIU/ml) in the first month after booster were significantly lower than before (P<0.01), increasingly recovering in the 12th month.

Relationship of anti-HBs level before and after booster

Anti-HBs level distribution after booster among the subjects with different antibody level before booster is shown in Table 3.

Table 1 Positive rates for anti-HBs, anti-HBc and HBsAg of 1018 children aged 1-7 years after infancy hepatitis B immunization in Longan County in 1994

Age group (yr)	No. of subjects	Anti-HBs(≥10S/N)		Anti-HBc(≥75%)		HBsAg(≥2.1S/N)	
		n	%	*n*	%	*n*	%
1-2	220	165	75.0	1	0.5	2	0.9
3-4	341	178	52.2	13	3.8	9	2.6
5-6	320	144	45.0	8	2.5	7	2.2
7	137	66	48.2	8	5.8	1	0.7
Total	1018	553	54.3	30	3.0	19	1.9

Table 2 Comparison of anti-HBs level before and after hepatitis B booster in 144 subjects immunized with hepatitis B vaccine

Time point of observation	No. of subjects	Anti-HBs (mIU / ml)								GMT	*t*	*P*
		<10		⩾10		⩾100		⩾1000				
		n	%	*n*	%	*n*	%	*n*	%			
Before booster	144	65	45.1	58	40.3	20	13.9	1	0.7	10.4		
One month after booster	144	15	10.4	16	11.1	100	69.4	13	9.0	190.6	17.4	<0.01
12 months after booster	106	26	24.5	43	40.6	33	31.1	4	3.8	25.3	1.3	>0.05

*blood specimens only collected from 106 children in the 12th month after booster.

Table 3 Distribution of anti-HBs levels one and twelve months after booster among immunized children with different anti-HBs levels before booster

Anti-HBs (mIU / ml) before booster	Anti-HBs levels (mIU / ml) one month after booster									Anti-HBs levels (mIU / ml) 12 months after booster								
	No.	<10		⩾10		⩾100		⩾1000		No.	<10		⩾10		⩾100		⩾1000	
		n	%	*n*	%	*n*	%	*n*	%		*n*	%	*n*	%	*n*	%	*n*	%
<10	65	15	23.1	10	15.4	35	53.9	5	7.7	47	22	46.8	14	29.8	9	19.1	2	4.3
⩾10	58	0	0.0	5	8.6	49	84.5	4	6.9	45	4	8.9	24	53.4	15	33.3	2	4.4
⩾100	20	0	0.0	1	5.0	15	75.0	4	20.0	13	0	0.0	5	38.5	8	61.5	0	0.0
⩾1000	1	0	0.0	0	0.0	1	100.0	0	0.0	0	0	0.0	0	0.0	1	100.0	0	0.0

One month after booster 76.9% of 65 subjects with negative anti[a2]HBs before booster, had anti-HBs ⩾10mIU/ml; 91.4% of 58 subjects with anti-HBs low titer possessed anti-HBs ⩾100mIU/ml; in 20 of 21 subjects with anti-HBS ⩾100mIU/ml antibody increased obviously and decreased in one. Fifteen of 65subjects with anti-HBs <10mIU/ml before booster, were still anti-HBs negative in the first and 12th month after booster, accounting for 23.1%, in 10 children anti-HBs level increased from 10mIU/ml to 100mIU/ml and in the remaining 40 subjects it was 100mIU/ml or over. Thirty-two individuals of the latter two groups were followed up for 12 months, 7 had antibody negative conversion.

Tables 2 and 3 indicate that most of immunized children possessed immune memory to HBsAg, and also in some individuals who had the vaccine-induced anti-HBs negative-conversion, 6 or 7 years after their infancy immunization.

Comparison of anti-HBs level between two booster dosages with different immunization routes

Anti-HBs GMTs of 91 subjects of intradermal 1μg group and 53 subjects of hypodermical 2 μg group before booster were 9.3 mIU/ml and 11.3mIU/ml, and no statistically significant difference was found between the two groups (t = 0.6, P>0.05). One month after booster, anti-HBs GMTs of both groups increased to 160.8mIU/ml and 247.2 mIU/ml. However, there was no statistical difference between both groups (t = 1.3, P > 0.05). The difference of booster-induced antibody levels between the intradermal group and the hypodermical group was not found in this study.

DISCUSSION

The observation should be conducted from two aspects to study the persistence of hepatitis B immunization: ①the trend of change of anti-HBs, anti-HBc and HBsAg after vaccination in the given immunized populations; ②to clarify whether the immunized individuals possess immune memory in the certain period after vaccination. The evidence of their immunological anamnestic reaction to HBsAg can be provided through a booster experiment.

The results of our study in Longan County showed that the anti-HBs positive rate of the immunized children was 48.2% in the 7th year, lower than 75.0% during the first two years after infancy hepatitis B immunization, suggesting that the hepatitis B vaccine-induced protective antibody level was gradually decreasing; however, the positive rates for anti-HBc and HBsAg were not significantly increased with the time after vaccination, but obviously lowered than before immunization. The following two explanations might be used for this phenomenon: ① an assumption that the opportunity exposed to HBV was obviously decreased in the immunized population. In recent years the large-scale infant hepatitis B vaccination did significantly decrease the HBsAg carrier rate among the children aged under 5 years[2-4], while, the HBsAg carrier rate in the

older-age population did not decrease, shown in our another study on the population aged 20-30 years without hepatitis B vaccination in Longan County in 1995. ② A part of immunizxed population were found to have vaccine-induced anti-HBs negative-conversion, but they might still have immune memory to HBsAg. If these children expose to HBV, they will quickly develop enough protective antibody to avoid becoming a HBsAg carrier. The second explanation has been confirmed through a hepatitis B vaccine booster experiment in our study.

The results of the booster experiment indicated that 61.5% (40/65) of 65 subjects with anti-HBs, anti-HBc and HBsAg negative marker, yielded anti-HBs level of ⩾100mIU/ml one month after a low dose of hepatitis B vaccine booster, and the post-booster antibody increase of these children was referred to immunological anamnestic reaction, according to the standard that the anamnestic reaction was defined as subjects with the anti-HBs-negative yielding anti-HBs level of ⩾100mIU/ml four weeks after booster[6]. Therefore, the reason why the HBsAg positive rate of immunized population always fluctuated at a low level of around 2% was probably attributable to the fact that they still keep immune memory 6-7 years after the initial vaccination. In 50 of 65 subjects with the anti-HBs and HBsAg-negative the antibody increased obviously after booster. It is interesting that 21.9% (7/23) of those children with anamnestic reaction had antibody negative-conversion in the 12th month after booster, and 23.1% (15/65) of subjects were anti-HBs negative at in the first and 12th month after and before booster. The outcome when these two groups of children expose to HBV should be observed in the future. Of 79 subjects with antibody level of ⩾ 10mIU/ml, 68 (86.1%) had antibody level increased by 2-fold or more one month after booster, suggesting that a low dose of hepatitis B vaccine booster can induce extremely high titer of antibody in most of these children.

The results of our research are similar to that of a study on booster 4-5 years after infancy hepatitis B vaccination by Chen Hui-Fang[7]. Both studies reveal that the majority of children immunized with China-made, plasma-derived hepatitis B vaccine, can quickly produce antibody anamnestic reaction to HBV (titer ⩾100 mIU/ml) 4-7 years after infancy.

These evidences indicate that low dose of China-made, plasma-derived hepatitis B vaccine in infancy may yield a better persistency of immunization and an ideal protective effect in immunized population. It is suggested that no need for revaccination against hepatitis B in the 7th year after the initial immunization, due to no evidences of booster obtained in our study.

REFERENCES

1 Xu ZY,Liu CB, Yan TJ, Sha QH, Sun YD, Fu TY *et al*. Evaluation of effectiveness of large-scale hepatitis B vaccination in neonates. *Chin J Virol*, 1991;7(Suppl.):48-52

2 Chotard J, Inskip HM, Hall AJ, Loik F, Mendy M, Whittle H *et al*. The Gambia Hepatitis B Intervention Study: follow-up of a cohort of children vaccinated against hepatitis B.*J Infectious Dis*, 1992;166(4):764-768

3 Tsen YJ, Chang MH, Hsu HY, Lee ChY, Sung JL, Chen DS. Seroprevalence of hepatitis B virus infection in children in Taipei, 1989: five years after a mass hepatitis B vaccination program.*J Med Virol*, 1991;34(2):96-99

4 Wainwright RB, McMahon BJ, Bulkow LR, Hall DB, Fitzgerald MA,Harpster AP *et al*. Duration of immunogenicity and efficacy of hepatitis B vaccine in a yupik Eskimo population.*JAMA*, 1989;261(16):2362-2366

5 Xu ZY, Xi LF, Liu CB, Cao HL. Strategies for hepatitis B vaccination in neonates'a costenefit analysis.*Chin J Virol*, 1991;7(Suppl.): 53-55

6 Aoki SK, Finegold D, Kuramoto IK, Douville C, Richards C, Randell R *et al*. Significance of antibody to hepatitis B core antigen in blood donors as determined by their serologic response to hepatitis B vaccine.*Transfusion*, 1993;33(5):362-367

7 Chen HF, Guo ZhY, Zhang YJ, W ZhH, Yang Jzh, Tao ZhH *et al*. Long-term efficacy of hepatitis B vaccine in newborn and revaccination study. *Chin J Epidemiol*, 1994;15(2):76-79