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Communication:

Immunological effects of a 10-μg dose of domestic hepatitis B vaccine in adults*

Jing-jing REN[1], Xue-wei DAI[2], Zheng-gang JIANG[3], Ling-zhi SHEN[3], Yong-di CHEN[3], Qian LI[3], Wen REN[4], Ying LIU[4], Jun YAO[†‡2], Lan-juan LI[†‡1]

([1]*State Key Laboratory for Diagnosis and Treatment of Infectious Disease, Key Laboratory of Infectious Diseases, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

([2]*Department of Epidemiology and Statistics, School of Medicine, Ningbo University, Ningbo 315000, China*)

([3]*Zhejiang Center for Disease Control and Prevention, Hangzhou 310003, China*)

([4]*Department of Family Medicine, the First Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou 310003, China*)

[†]E-mail: jyao@CDC.zj.cn; Ljli@zju.edu.cn

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Objective: To evaluate the immunological effects of three types of domestic 10-μg/dose hepatitis B vaccines in adults compared with a foreign vaccine, and to provide scientific evidence in support of adult hepatitis B vaccination. Methods: Adults from five counties (Deqing, Changxing, Nanxun, Wuxing, Anji) in Huzhou City, Shaoxing County and Tongxiang County, Zhejiang Province, China were selected. Blood samples were taken to assess serum HBsAg, anti-HBs, and anti-HBc using a chemiluminescence immunoassay. Adults, aged 16 to 49 years and who were anti-HBs negative at baseline, received hepatitis B immunizations at 0, 1, and 6 months. Anti-HBs levels were assessed one month after the third and final vaccination. Results: A total of 1872 adults were immunized and the average positive rate was 89.5%. Four types of hepatitis B vaccine were used, including three from Chinese companies (Shenzhen Kangtai, Dalian High-Tech, and North China Pharmaceutical) and one from a UK company (GlaxoSmithKline). Their seroconversion rates were 81.67%, 95.05%, 89.64%, and 86.81%, respectively. There was a significant difference between the anti-HBs positive conversion rates of the four types (P<0.005) but the seroconversion rates among the different vaccines were not significantly different (χ^2=2.123, P=0.145). The average anti-HBs geometric mean titers (GMTs) of non-immune adults immunized with each of the four vaccines were 177.28, 473.23, 246.13, and 332.20 mIU/ml, respectively. There were no statistically significant differences in the GMTs between the three types of domestic vaccine and the foreign vaccine (t=−1.575, P=0.116). Conclusions: Domestic recombinant hepatitis B vaccines can achieve immunization effects comparable to those of a foreign vaccine.

Key words: Hepatitis B, Vaccines, Immunization, Geometric mean titer

1 Introduction

Hepatitis B virus (HBV) infection is a current global public health concern (Ganem and Prince, 2004). It is estimated that more than 2 billion people have been infected with HBV, including 360 million chronic carriers of the virus. HBV is responsible for about 600 000 to 1 200 000 deaths annually worldwide (WHO, 2000; Lavanchy, 2004; Goldstein *et al.*, 2005; Ganczak *et al.*, 2009). HBV infection is especially severe in China; according to a national seroepidemiological survey conducted in 2006, the rate of HBsAg carriers in the general population within the age range of 1 to 59 years is 7.18% (Liang *et al.*, 2009a; 2009b). Thus, more than 93 million people are chronically infected with HBV in China (Lu and Zhuang, 2009). As there is currently no satisfactory treatment for chronic hepatitis B infection and related diseases, hepatitis B vaccination is regarded as the most economical and effective method to prevent and control hepatitis B infection (Chang *et al.*, 2004;

‡ Corresponding authors
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Ganem and Prince, 2004; Weinbaum *et al.*, 2008; Shen and Yao, 2011).

Hepatitis B control has been administered through immunization planning management in China since 1992. There have been improvements in hepatitis B prevention and control in China within the past 20 years through mass vaccination with the hepatitis B vaccine. According to the 2006 survey, the HBV infection rate among Chinese children under the age of 15 has declined from 10% in 1992 to 2.08% today (Liang *et al.*, 2009a; 2009b). With these advances in hepatitis B prevention and control, more attention is now being devoted to adult hepatitis B immunization in China. To protect the privacy of patients with hepatitis B, the Ministry of Public Health prohibits testing for HBV infection markers in medical examinations, so adult hepatitis B vaccine immunization is especially important. There is a lack of immunological performance data for hepatitis B vaccines in adults as adult hepatitis B vaccination has not been systematically carried out in many places. To assist the advancement of the hepatitis B control process and to further reduce the adverse effects of contracting HBV, we studied the effects of Chinese hepatitis B vaccines compared with a foreign vaccine in adults. Selected adults between the ages of 16 and 49 years were given a 10-μg dose of one hepatitis B vaccine at 0, 1, and 6 month intervals. The immune effects of different types of hepatitis B vaccines were then evaluated.

2 Materials and methods

2.1 Subjects

Subjects from five counties (Deqing, Changxing, Nanxun, Wuxing, Anji) in Huzhou City and from Shaoxing County, Zhejiang Province, China were selected as experimental groups in this study. Subjects underwent serological screening and only those negative for HBsAg, anti-HBs, and anti-HBc could be deemed eligible and included in the study. About 700 subjects from each county were selected and each was given one vaccine. Subjects from Tongxiang County, as the compared group, were given the vaccine from GlaxoSmithKline, UK. All the counties had a similar economic status. The study was approved by the Institutional Ethics Committee of the Zhejiang Center for Disease Control and Prevention, China.

The inclusion criteria (Yao *et al.*, 2011) included: (1) between the ages of 16 to 49 years and willing to participate in the study and provide informed consent; (2) willing to participate in the follow-up study and to provide blood samples after vaccination.

The exclusion criteria included: (1) reluctant to participate in this study; (2) history of allergies or severe reaction to vaccination; (3) known or anticipated immune dysfunction; (4) had previously received immune suppressive therapy (intravenous or oral cortisone or chemotherapy); (5) had previously received immunostimulation therapy; (6) high risk of becoming immunologically compromised; (7) history of hepatitis B vaccination; (8) history of any kind of vaccination within the previous four weeks; (9) had received any kind of observational or experimental drugs during the past four weeks; (10) acute illness within the past seven days; (11) infection that required treatment with antibacterial or antiviral therapy within the past seven days; (12) fever within the past three days (armpit temperature ≥38 °C); (13) HBsAg positive and/or anti-HBs positive.

2.2 Vaccines and vaccination

Subjects were assigned to one of four groups depending on the vaccine they were to receive: (1) Group I: hepatitis B vaccine (lot No. 20090521; dosage: 10 μg; produced by the Shenzhen Kangtai Biological Products Co., Ltd., China); (2) Group II: hepatitis B vaccine (lot Nos. 2009030906 and 2010010106; dosage: 10 μg; produced by the Dalian High-Tech Biopharmaceutical Co., Ltd., China); (3) Group III: hepatitis B vaccine (lot No. 200904A3101; dosage: 10 μg; produced by the North China Pharmaceutical Company, GeneTech Biotechnology Pharmaceutical Co., Ltd.) (Chinese Hamster Ovary (CHO)); (4) Group IV, the compared group, was given the foreign hepatitis B vaccine (lot No. XHBVB554AA; dosage: 10 μg; produced by the GlaxoSmithKline Company, UK).

We then administered hepatitis B vaccination by intramuscular injection in the upper deltoid muscle, according to the recommended immunization procedure at 0, 1, and 6 months.

2.3 Methods

Subjects were interviewed using the pre-designed questionnaire "Research Questionnaire on Adult Immunization Strategy of Hepatitis B", which included information such as each patient's date of birth, age, and gender. We collected 3 ml blood samples from each eligible HBsAg, anti-HBs, and anti-HBc negative subject prior to vaccination. Eligible subjects received three hepatitis B vaccinations. One month after the third vaccination, we collected 3 ml blood samples from each subject and preserved them for anti-HBs quantification.

2.4 Specimen collection and testing

We collected 3 ml blood samples from each subject and then froze the serum from the samples at −20 °C. The samples were sent to ADICON Clinical Laboratories Inc. in Hangzhou for HBsAg, anti-HBs and anti-HBc quantification by chemiluminescence immunoassay (CLIA). If the HBsAg and anti-HBs results did not match, samples were re-tested. Samples with an anti-HBs titer level greater than 15000 mIU/ml were excluded from further dilution testing. An Architect-i2000 (Abbott, US) analyzer was used to perform the CLIA. The HBsAg test reagent lot number was 86040LF00, and a signal-to-noise ratio (S/N) ≥0.05 was considered to be positive. The anti-HBs test reagent lot number was 82521M100; an anti-HBs antibody level greater than or equal to 10 mIU/ml was considered to be positive and was defined as having protective effects against HBV infection. The anti-HBc test reagent lot number was 85276M500, and an anti-HBc antibody level greater than or equal to 1 mIU/ml was defined as positive.

2.5 Data collation and analysis

A database using EpiData3.2 (EpiData; Norway and Denmark) was established, and double data entry performed. Statistical analysis was performed using SPSS 13.0. A chi-square test or Fisher chi-square test was used for enumeration data, a U test was used for data that followed a normal distribution before or after logarithmic transformation, and a rank-sum test was used for data that did not follow a normal distribution. We used a two-tailed probability in statistical tests, with a P value of 0.05 considered to be significant.

3 Results

3.1 General information

Of the 2600 subjects analyzed, 1872 adults completed the immunization schedule and their blood serum was tested after completing the three vaccinations. Among these subjects, 771 were males whose average age was 32.59 years (95% confidence interval (CI): 32.01–33.17) and whose median age was 32.33 years. There were 1101 female subjects whose average age was 32.42 years (95% CI: 31.94–32.91) and whose median age was 31.96 years. There were no statistically significant differences in age or gender among the four groups (Table 1; χ^2=1.555, P=0.670).

Table 1 Subject characteristics

Group	Number	Age (year)	Male (%)
Group I	593	32.45±0.66	40.81
Group II	465	33.69±0.70	39.14
Group III	579	31.71±0.69	42.49
Compared group	235	32.20±1.07	42.98
Total	1872	32.49±0.74	41.19
Parameter		F=2.45	χ^2=1.56
P value		P<0.01	P=0.67

3.2 Comparison of the anti-HBs positive seroconversion rate and the geometric mean titer (GMT) in different vaccines

The seroconversion rates of the three types of domestic vaccine were not significantly different from that of the foreign vaccine (χ^2=2.123, P=0.145). The anti-HBs-positive seroconversion rate was variable after the third dose of the different vaccines (χ^2=24.13, P<0.001). There were no statistically significant differences in the seroconversion rates between Group I and Group III (χ^2=3.30, P=0.069), Group I and the compared group (χ^2=0.06, P=0.81), or Group III and the compared group (χ^2=1.35, P=0.25). The Group II seroconversion rate was significantly higher than those of Group I (χ^2=23.00, P<0.001), Group III (χ^2=10.34, P=0.001), and the compared group (Table 2; χ^2=14.91, P<0.001).

There were no statistically significant differences in the GMTs between the three types of domestic vaccine and the foreign vaccine (t=−1.575, P=0.116). The GMTs of all groups were significantly different from each other (F=25.48, P<0.001).

Table 2 Anti-HBs positive seroconversion rate and GMT after the third dose of hepatitis B vaccine

Group	n_1	n_2	PSR (%)	GMT	95% CI
Group I	593	511	81.67	177.28	152.64–205.53
Group II	465	442	95.05	473.23	400.39–558.85
Group III	579	519	89.64	246.13	211.56–285.98
Compared group	235	204	86.81	332.20	332.20–434.67
Total	1872	1676	89.53	271.93	249.38–296.42

n_1: number of observations; n_2: number of anti-HBs positive seroconversions; PSR: positive seroconversion rate; GMT: geometric mean titer

3.3 Comparison of the anti-HBs positive seroconversion rate in different age groups after vaccination

Table 3 shows that there were no significant differences among the different age groups (χ^2=8.576, P=0.073). In the three domestic vaccine groups, there were no significant differences in the positive seroconversion rate among the different age groups (χ^2=5.850, P=0.211), but there was a significant difference when these groups were compared with the foreign vaccine group (χ^2=11.546, P=0.021). The chi-square trend test also showed a significant decrease in the anti-HBs positive rate with increasing age (χ^2=4.940, P=0.026).

3.4 Comparison of the anti-HBs GMT in different age groups after vaccination

A total of 1670 subjects were anti-HBs positive after vaccination, with a GMT of 271.95 mIU/ml. There was no significant difference in the anti-HBs GMT among the three domestic vaccines but the results for these vaccines were significantly different from those for the compared foreign vaccine (Table 4; F=5.139, P=0.001).

4 Discussion

Currently, hepatitis B vaccine is widely used to prevent HBV infection in China and abroad. The Advisory Committee on Immunization Practices (ACIP) proposed that non-immune adults should be encouraged to be immunized with the hepatitis B vaccine (Goldstein *et al.*, 2005). An American report in 2007 showed that the highest proportion of new hepatitis B infections occurs in the 25 to 44 years old age group (Daniels *et al.*, 2009). Vaccination for high-risk adults had already begun in USA in 1998 (Mast *et al.*, 1998), and in 2006, adult hepatitis B vaccination was brought into the system of community primary health care and rehabilitation clinics (Mast *et al.*, 2006). There were also immunization programs for high-risk adults in Britain and Italy (Bonanni, 1995; Zuckerman and Langer, 2005). The usual adult hepatitis B vaccine dose in China is 10 μg. There are three main types of hepatitis B vaccine in China: one is made by recombinant deoxyribonucleic acid (DNA) techniques in *Hansenula polymorpha* yeast, one is made by recombinant DNA techniques in CHO cells, and one is a recombinant hepatitis B vaccine (*Saccharomyces cerevisiae*). We chose all three for our research, as together they account for

Table 3 Anti-HBs positive seroconversion rate in different age groups after vaccination

Age (year)	Group I			Group II			Group III			Compared group			Total		
	n_1	n_2	PSR (%)	n_1	n_2	PSR (%)	n_1	n_2	PSR (%)	n_1	n_2	PSR (%)	n_1	n_2	PSR (%)
16–24	117	98	83.76	67	63	94.03	147	138	93.88	55	48	87.27	386	347	89.90
25–29	122	106	86.89	69	68	98.55	135	125	92.59	44	42	95.45	370	341	92.16
30–34	112	97	86.61	101	96	95.05	85	77	90.59	37	35	94.59	335	305	91.04
35–39	127	113	88.98	111	106	95.50	98	85	86.73	47	35	74.47	383	339	88.51
40–49	115	97	84.35	113	105	92.92	113	93	82.30	51	43	84.31	392	338	86.22
χ^2 value		1.800						11.616			11.327			8.576	
P value		0.772			0.539*			0.020			0.023			0.073	

n_1: number of subjects; n_2: number of anti-HBs positive seroconversion (the age data of six persons lost, so the total n_2 was 1670); PSR: positive seroconversion rate. * Lack of χ^2 value, using exact statistical method

Table 4 Anti-HBs GMT distribution in different age groups

Age (year)	Group I		Group II		Group III		Compared Group		Total	
	n	GMT (95% CI)	*n*	GMT (95% CI)	*n*	GMT (95% CI)	*n*	GMT (95%CI)	*n*	GMT (95%CI)
16–24	98	171.75 (121.31–240.86)	63	546.00 (343.08–863.89)	138	422.10 (319.56–556.06)	48	479.00 (270.78–838.94)	347	343.92 (284.60–415.03)
25–29	106	218.03 (155.43–303.63)	68	415.70 (275.15–624.34)	125	304.07 (222.21–414.19)	42	541.39 (279.24–1037.10)	341	310.01 (255.72–375.20)
30–34	97	158.72 (112.18–222.28)	96	365.64 (262.34–507.41)	77	268.70 (177.29–403.58)	35	685.39 (357.99–1300.18)	305	275.74 (225.67–336.19)
35–39	113	176.04 (129.72–237.18)	106	457.16 (314.41–661.75)	85	179.93 (122.01–262.32)	35	174.92 (91.43–323.92)	339	234.40 (192.81–284.36)
40–49	97	167.31 (115.42–239.85)	105	616.60 (437.22–867.14)	93	105.40 (75.74–144.76)	43	161.90 (89.61–403.58)	338	218.40 (178.25–264.29)
Total	511	177.91 (153.18–206.27)	438	473.91 (400.73–559.96)	518	244.32 (209.90–284.02)	203	341.47 (177.29–284.15)	1670	271.95 (249.38–296.42)
χ^2 value	2.385		6.269		36.695		19.144		16.013	
P value	0.665		0.180		0.000		0.001		0.003	

n: number of anti-HBs positive seroconversions (the age data of six persons lost, so the total *n* was 1 670)

more than 90% of adult vaccinations. The results of this study indicated that high anti-HBs seroconversion rates and GMT were observed in adults who received the 10 μg immunization dose. It was also shown that good protective effects can be obtained using the 10 μg dose of the hepatitis B vaccine in China (Gong and Zhong, 2009; Yao and Chen, 2009).

The seroconversion rates of the different hepatitis B vaccine types indicated that the average anti-HBs seroconversion rate was 89.92% after vaccination with the three types of domestic 10 μg hepatitis B vaccines. This was not significantly different from that of the compared group whose anti-HBs seroconversion rate was 86.81%, which indicates that the immune effects of the different types of hepatitis B vaccines were consistent. These results are similar to those of Gong and Zhong (2009), Zhang *et al*. (2010), and others (Bryan *et al.*, 1995; Rendi-Wagner *et al.*, 2001). Gong and Zhong (2009) used 10 μg of hepatitis B vaccine made by recombinant DNA techniques in *Saccharomyces cerevisiae* yeast by the Beijing Tiantan Company. The seroconversion rate was 90.69%. They selected 873 HBsAg negative subjects.

Another study of 321 subjects, using 10 μg hepatitis B vaccine produced by the North China Pharmaceutical GeneTech Biotechnology Pharmaceutical Co., Ltd.) (CHO), had an 88.8% seroconversion rate. Factors such as smoking, drinking, and obesity were reportedly associated with immune failure, in addition to a strenuous job, stressful lifestyle, and mental pressure, which may overload the body and lead to a decline in immune function and thereby affect the seroconversion rate. The immune effect of the Dalian High-Tech 10 μg Hansenula hepatitis B vaccine was the best of the four types. Its seroconversion rate reached 95.05%, a rate significantly higher than those of the other three groups. This seroconversion rate was also similar to that of the 20 μg hepatitis B vaccine reported by Young *et al.* (2001). This similarity might be caused by the high purity of the Hansenula hepatitis B vaccine, which uses a chemosynthesis complete medium only, and not a selective medium, peptone or yeast powder. The seroconversion rates of the 10 μg hepatitis B vaccine produced by the North China Pharmaceutical Company and GlaxoSmithKline were slightly higher than that of the 10 μg hepatitis B vaccine previously reported by Young *et al.* (2001). Regarding the anti-HBs GMT, the immune effects for all the vaccines were good, except those of the Shenzhen Kangtai vaccine. These results suggest that the immune effects of the four hepatitis B vaccine types were good, and that they could provide good protection for the population. Considering the high anti-HBs seroconversion rate and GMT produced by the Dalian High-Tech vaccine, and considering that the persistence of immune protection would be extended as a result of the high GMT peak value (Jilg *et al.*, 1988; Trivello *et al.*, 1995; Yuan *et al.*, 2003), we recommend the Dalian High-Tech vaccine.

An analysis of the hepatitis B vaccine immune effects in adults of different age groups was conducted. After dividing the subjects into five age groups, the relationship between the positive hepatitis B vaccine seroconversion rates and the subjects' ages was analyzed. The results showed that there was no significant difference in the positive seroconversion rate for 10 μg hepatitis B vaccines among different adult age groups (χ^2=8.576, P=0.073). The chi-square trend test also showed a significant decrease in the anti-HBs positive rate with increasing age (χ^2=4.940, P=0.026). The positive anti-HBs seroconversion rates were different between the 10 μg hepatitis B vaccine produced by the North China Pharmaceutical Company and that produced by GlaxoSmithKline in the different vaccination age groups. There was a negative correlation (using the chi-square trend test) between the 10 μg hepatitis B vaccine produced by the North China Pharmaceutical Company and the subject's age. These results indicate that the anti-HBs level attained after vaccination with hepatitis B vaccine was related to age, which was consistent with previous studies (Coates *et al.*, 2001; Gilbert *et al.*, 2011). There were no significant differences in the anti-HBs GMT among the three domestic vaccines but compared with the foreign vaccine, a significant difference was found (F=5.139, P=0.001). Overall, the study shows that vaccination of adults of different ages can result in good immune effects. The results of these studies provide good data in support of expanding immunization programs to adults.

After a long development, domestic hepatitis B vaccines have achieved some advantages, including a lower price compared to other hepatitis B vaccines. In our study, we selected three kinds of domestic vaccine and one foreign vaccine, and evaluated the immune effects of the four vaccines at the same time in a large-scale population. The results of this study confirm that there is little difference in the immune effects between the domestic hepatitis B vaccines (10 μg/dose) and the hepatitis B vaccine (10 μg) produced by GlaxoSmithKline. The immune effect of the hepatitis B vaccine produced by Dalian High-Tech was better than that of the hepatitis B vaccine produced by GlaxoSmithKline. Thus, the evidence supports the widespread use of domestic hepatitis B vaccine (Dong *et al.*, 2009). The subjects involved in this study will be followed up closely, after one, three, and even five years. We believe this will provide useful scientific data of significance to China's hepatitis B prevention and control programs.

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