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• BRIEF REPORTS •

Can HB vaccine yield a booster effect on individuals with positive serum anti-HBs and anti-HBc markers?

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Abstract

AIM: To evaluate if HB vaccination can yield a booster effect on the anti-HBs level of those naturally acquired HBV positive markers.

METHODS: Sera were collected from 1399 newly enrolled university students aged between 18-20 years at the entrance medical examination in 2001. Forty-four students (28 males and 16 females) with positive serum anti-HBs and anti-HBc markers served as an observation group and another 44 students (24 males and 20 females) without any HBV markers as the control. HB vaccination was given to all the students without positive serum HBsAg according to 0, 1, 6 month regimen and the peripheral venous blood was sampled from those of both observation and control groups for anti-HBs detection one month after the second and third doses. Anti-HBs levels were measured by ELISA.

RESULTS: The seroconversion rate of anti-HBs in the control group was 100% after the second dose, but the geometric mean titers (GMTs) were low. The tendency of serum anti-HBs changes after the 3rd dose was completely different between the two groups. Although more than half of those with positive anti-HBs and anti-HBc showed a mild increase of anti-HBs levels after the 2nd boosting dose (mean anti-HBs level was 320:198 mIU), but the increase of serum anti-HBs titer was much smaller than that in the control group. The averages of their initial serum anti-HBs levels and the levels after the 2nd and 3rd doses were 198, 320 and 275 mIU respectively. All the subjects from the control group had an obvious increase in their serum anti-HBs levels which was nearly 4 times the baseline level (302:78 mIU).

CONCLUSION: HB vaccination can not enhance anti-HBs levels in those with positive serum anti-HBs and anti-HBc markers.

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INTRODUCTION

HB vaccination program has been well developed for neonates and younger adults in China. Nowadays, according to Chinese regulation all the newly enrolled university students are required to have their blood detected for HBsAg and those with negative HBsAg are eligible to receive HB vaccination. Since it has been well demonstrated that an additional dose can induce a booster effect on vaccinees' serum anti-HBs titers, it is natural for most people to get the idea that the more doses they get, the more benefits they will gain. Our previous survey in a group of university students showed that HBsAg carrier rate in those of the 18-20 age group was about 4-6% and when gained entrance to the university more than 50% students with positive serum anti-HBs or anti-HBc or both were vaccinated each year. Is it necessary to vaccinate the people with positive anti-HBc and anti-HBs markers? To answer this question, we followed up the newly enrolled students from a university to observe the changes of their serum anti-HBs titers after HB vaccination, especially those with positive serum anti-HBs and anti-HBc markers before. The changes of serum anti-HBs titers in students without any HBV markers before the vaccination were observed after HB vaccination as the experimental control. The results might be helpful for the establishment of a scientific, reasonable and economic vaccination program against HBV infection in the adult population.

MATERIALS AND METHODS

Reagents

Ten *μg* of yeast recombinant HB vaccine (Lot No: 2990104-1) was produced in Kangtai Biological Pharmaceutical Company, China. ELISA kits of HBV markers were from Sino-American Biotechnology Company, Luoyang, China. ELISA kit of Measles antibody was provided by Institute of Virus, Chinese Center of Disease Control and Prevention, Beijing, China.

Subjects and vaccination methods

Forty-four students with positive serum anti-HBs and anti-HBc and 44 without any HB markers who experienced a regular medical examination in one college were selected to be investigated after vaccinated with HB vaccine according to 0, 1, 6 month scheme, in which the vaccine was intramuscularly injected into the deltoid muscle. All the subjects were also injected measles vaccine one week before the first dose of HB vaccination. An informed consent was given by each participant before the beginning of observation.

Determination of serum anti-HBs antibody

Serum anti-HBs antibody was measured respectively at one

month after the 2nd and 3rd doses of HB vaccine. The sera were randomly chosen from 35 subjects with positive anti-HBs and anti-HBc to measure the antibodies (IgG) to both measles and HBsAg according to the manufacturer's instructions. The resulting value was determined according to Holliger formula: mIU=418×[EXP×0.9(S-N)/(P-N)-1] in the light of OD values. mIU of anti-HBs titers greater than 10 was considered as positive anti-HBs. *t* test was used to compare GMTs between groups and the difference was considered significant when $P<0.05$.

Table 1 Comparison of booster effect on anti-HBs levels between two groups

	Anti-HBs (anti-HBc pos.)			Anti-HBs (anti-HBc neg.)		
No.	Before	After 2nd dose	After 3rd dose	No.	After 2nd dose	After 3rd dose
23338	161	578	362	22404	48	471
23306	266	293	163	13236	25	268
23310	406	295	293	13240	45	598
23304	168	417	337	24332	48	324
23116	44	86	76	24327	63	144
23140	30	37	43	24311	186	314
23139	372	456	344	24105	344	656
23129	309	459	225	17239	135	83
23105	145	451	461	17238	58	253
23119	162	269	252	17226	83	598
27138	592	387	533	17214	53	384
27128	406	494	449	23240	63	268
27130	341	272	199	23201	40	370
27103	182	148	145	23141	201	340
27137	53	328	211	23108	26	512
27001	326	424	269	17129	22	970
27109	99	122	116	17125	178	318
27133	573	373	316	17122	45	22
27120	151	420	207	17118	78	466
22222	115	438	588	17108	236	414
22225	442	417	338	17106	88	350
22214	283	293	466	17102	197	264
22206	176	282	208	13139	186	291
22205	547	275	377	13129	17	158
22201	183	193	158	13126	73	264
24120	128	558	393	13125	93	191
24107	239	356	257	13118	17	176
24140	35	426	409	13114	53	263
24141	212	275	231	13108	216	280
22138	392	534	659	13107	35	338
22130	660	643	504	13102	130	252
13214	247	331	244	13101	113	216
13223	491	315	176	14130	320	520
23235	106	232	199	14131	65	407
24137	108	472	280	14129	320	365
22202	61	205	253	18302	30	63
18238	244	302	303	18310	73	336
23322	422	463	503	16119	53	395
18223	333	314	389	16112	30	370
25122	355	315	286	16122	200	375
25139	206	361	337	16104	45	420
25129	116	391	303	16108	30	365
25121	38	119	204	16107	441	476
18220	65	507	506	16110	107	499
Total GMT	198	320	275	GMT	78	302

RESULTS

Anti-HBs titers before and after HB vaccination in those with positive anti-HBs and anti-HBc

The tendency of serum anti-HBs changes after the 3rd dose was completely different between the two groups. Although more than half of those with positive anti-HBs and anti-HBc markers showed a mild increase of serum anti-HBs titer after the 2nd booster dose, the increase of serum anti-HBs titer (mean anti-HBs level was 198∶320 mIU) was much smaller than that in the control group, in which 100% subjects had an obvious increase in their serum anti-HBs levels which was nearly 4 times their baseline (302∶78 mIU).

It was interesting to note that the serum anti-HBs levels did not change in most of the subjects with positive anti-HBs and anti-HBc markers after the 3rd dose. The mean serum anti-HBs level of the baseline, after the 2nd and 3rd doses was 198, 320 and 275 mIU (Table 1) respectively.

Effect of a boost dose on antibody titers of HBsAb and measles Ab

In order to confirm that all the subjects in this study had a normal immune competence, the serum antibodies to measles were detected in 35 subjects and an increased antibody level was observed in 91.4% (32/35) subjects after a booster dose. A comparison of antibody levels before and after a booster dose was made and the difference was statistically significant ($P<0.05$, Table 2).

Table 2 Effect of a boost on antibody titers of HBsAb and measles Ab

Boost	A-HBsAb		B-HBsAb		C-HBsAb		MealsesAb	
	No.	GMT	No.	GMT	No.	GMT	No.	GMT
Before	44	198	44	198	44	78	35	322
After	44	320	44	275	44	302	35	1 207

Comparison of anti-HBs induced by HB vaccination before and after a boost in HBV negative group, $P<0.05$.

DISCUSSION

Hepatitis B vaccination has been implemented for 20 years, however, the disease remains a global problem[1-4]. Although the safety and efficacy of HB vaccine have been well demonstrated[5-16], few papers regarding the immune response of those with positive anti-HBs and anti-HBc to HB vaccination are available. In this study, we observed if a booster effect and a better protection against HBV infection could be obtained after HB vaccination in those with positive serum anti-HBs and anti-HBc markers.

It has been well demonstrated that the HB vaccine-induced antibody might gradually decline or was even undetectable some years after primary immunization[17-20]. It is not clear if such persons could be protected against HB infection following exposure to HBV[21]. Although some studies have proved that memory cells to HBsAg might exist in vaccinees for a long time even the serum anti-HBs was undetectable[19,22,23]. Whether additional booster doses should be used has been under discussion[17-20,23-25]. Considering the available data on measles vaccine, which showed that loss of detectable antibody following vaccination was correlated with the waning of immunity[26], a booster HB vaccination might be necessary.

Our data revealed that the serum anti-HBs levels in the subjects with positive serum anti-HBs and anti-HBc markers did not significantly increase one month after the 2nd dose of HB vaccination. Although a mild increase was seen in some cases, the elevation of serum anti-HBs levels in the observatory

group was much less than that in the control in which 100% subjects had an obvious increase of serum anti-HBs levels that was nearly 4 times their baseline. After the 3rd dose, anti-HBs levels remained unchanged in most of the subjects with positive serum anti-HBs and anti-HBc markers compared with that in the control, in which a sharp increase of serum anti-HBs levels was observed after the 3rd dose. The phenomenon might be related to the following possibilities. First, the subjects with positive serum anti-HBs and anti-HBc markers before the vaccination might not be in a normal condition of immune competence during the observation period. In the present study, their increased response to measles after the booster dose was observed in 91.4% (32/35) subjects. Because measles vaccination has been well practiced in China and normally all the subjects have to be vaccinated in their early age, the increased immunological response could prove that the subjects had the normal immune competence. Second, the immune response to viruses can damage the host via the formation of immune complexes, or directly damage the infected cells. Thus, the poor response to the HB vaccine might probably relate to the damage caused by HBV before the vaccination.

HB vaccination program is implemented in children and adults in China. But the problem is that our current vaccination regimen is not completely suitable for adult vaccination. An appropriate vaccination program for the adult population has to be established to prevent the prevalence of HBV. Our results indicate that it is not necessary to vaccinate those with positive serum anti-HBs and anti-HBc because no significant increase of anti-HBs titers was observed after a standard HB vaccination. It suggests that the vaccine-induced anti-HBs can not be elevated in those infected with HBV naturally before the HB vaccination.

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