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Antihepatitis B response to hepatitis B vaccine administered simultaneously with tetanus toxoid in nonresponder individuals

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Abstract

In this prospective study, our aim was to test the effect of simultaneous administration of preS2 and S containing recombinant hepatitis B vaccine (S2SRHB) with tetanus toxoid (TT) to the individuals who did not respond after three doses of hepatitis B vaccine previously.

There were three groups (healthy individuals, pregnant women, hemodialysis patients), each was divided into two subgroups as groups A and B. Group A received S2SRHB + TT and group B received only S2SRHB.

We found that in groups receiving both vaccines, both seroconversion rate and antibody titer level were significantly higher ($P < 0.05$).

In conclusion, simultaneous administration of S2SRHB + TT is more effective than administration of S2SRHB alone.

Keywords: Hepatitis B vaccine; Tetanus toxoid; Nonresponder

1. Introduction

Some healthy individuals, hemodialysis patients or hepatitis B carrier mothers' neonates may not respond to S2SRHB vaccine [1–4]. The mechanism causing nonresponsiveness to hepatitis B vaccines in humans still remains unexplained. However, peripheric blood mononuclear cells (PBMC) from nonresponders did not proliferate to HBsAg in vitro, but they vigorously proliferated upon stimulation with tetanus toxoid (TT) [5]. It was found that in vitro response of PBMC to stimulation with HBsAg was correlated with serum anti-HBs titer and the deletion of CD8 + T-cells. Nonresponders have a lower cytokine response to the vaccine than responders [6]. Patients with uremia up to 30% fail to respond to the usual vaccination schedules. Coinfection with hepatitis C of uremia patients may lower the response rate [7]. Genetic determinants are also present in uremic patients [8]. Repeated IM booster injections is recommended for such patients. If this does not achieve the goal, revaccination with regular IM or ID injection at short intervals is thought to be appropriate until satisfactory response has been achieved [3,9,10].

In this study, we compared the antibody responses to S2SRHB + TT and S2SRHB alone in different nonresponder groups to S2SRHB vaccine previously.

2. Materials and methods

Seventy-six subjects (age range 18–60 years, mean age 30.67 ± 6.97 years) were included in the study. All of them were negative for all HBV markers (by ELISA, ORGANON) and all received at least three shots of S2SRHB vaccine (recombinant DNA vaccine, Genhevac, Pasteur) but still remained negative for anti-HBs antibody (anti-HBs <10 IU/l) which are named as nonresponders. All subjects were scanned for the liver function tests (ALT and AST) and rheumatoid factor. The individuals with normal ALT and AST levels and negative rheumatoid factor were included in the study.

There were three different groups of subjects (group I, otherwise healthy individuals, $n = 40$, mean age 29.01±5.2 years; group II, pregnant women, $n = 12$, mean age 28.05± 7.0 years; group III, hemodialysis patients, $n = 24$, mean age ±8.72 years). They were divided into two subgroups as A and B. Group IA ($n = 25$, 13 males and 12 females), group IIA ($n = 7$, 7 females) and group IIIA ($n = 13$, 9 males and 4 females) received S2SRHB vaccine (recombinant DNA

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vaccine, Genhevac, Pasteur) intramuscularly in the left deltoid muscle as 20 μg with 1 month intervals for three times simultaneously with tetanus toxoid (adsorbede tetanus vaccine: Te Anatoxel, Berna) intramuscularly in the right arm as 1 ml (80 IU).

Blood samples were taken 1 month after the first and second shots and 2 months after the third shot. Anti-HBs titers exceeding 10 IU/l generally were accepted as protective titer.

Group IB ($n = 15$, 9 males and 6 females), group IIB ($n = 5$, 5 females), group IIIB ($n = 11$, 6 males and 5 females) received only additional three injections of S2SRHB and blood samples were taken as mentioned earlier.

The χ^2-test was used for statistical analysis.

3. Results

In group IA, after first S2SRHB + TT vaccination, 6 of 25 (24%) responded, 8 individuals responded after the second shots and 1 more responded after the last shot reaching a total response rate of 60% (15/25). In group IB, after the first additional S2SRHB dose, 1 of 15 (6.6%), after the second 2 and after the third dose 1 more responded. Total response rate for this group was 26.6% (4/15). The statistical difference was significant between these groups ($P < 0.05$, Table 1).

In group IIA, none of the pregnant women responded after the first shots. Two responded after the second dose and 1 after the third dose. Totally 43% (3/7) of them responded. In group IIB, no response was obtained after the first and third shots, only one pregnant women responded after the second shots (1/5, 20%). The statistical difference was significant between these groups ($P < 0.05$, Table 1).

In group IIIA, one after the first and one after the second shots responded, one more response was obtained after the third shots. Totally 3 out of 13 (23%) responded in hemodialysis patients after simultaneous injections of both vaccines. In group IIIB, only one patient responded after the second shot with response rate of 9% (1/11). The statistical difference was significant between these groups ($P < 0.05$, Table 1).

Table 2
Anti-HBS titers at 4 months in groups

Group	*n*	<10 IU (%)	10–50 IU (%)	≥50 IU (%)
IA	25	10	10	5
IB	15	11	3	1
IIA	7	4	2	1
IIB	5	4	1	–
IIIA	13	10	2	1
IIIB	11	10	1	–
Total	76	49 (64)	19 (25)	8 (11)

Table 3
Comparison of S2SRHB + TT and additional S2SRHB vaccine in nonresponders at 4 months

Vaccine type	*n*	Anti-HBS titer >10 IU/l (%)	*P*
S2SRHB + TT	45	21 (47)	<0.005
Additional S2SRHB	31	6 (19)	

Table 4
Comparison of groups for S2SRHB + TT vaccine at 4 months

Group	*n*	Anti-HBS titer (>10 IU/l) (%)	*P*
Healthy	25	15 (60)	<0.05
Pregnancy	7	3 (43)	
Hemodialysis patients	13	3 (23)	

Both seroconversion rate and antibody titer level of anti-HBs were significantly higher in group A than group B ($P < 0.05$, Tables 1 and 2).

The number of cases yielding anti-HBs titer over 10 IU/l at 4 months of the vaccination programme was 15 in group IA, 4 in group IB, 3 in group IIA, 1 in group IIB, 3 in group IIIA, 1 in group IIIB. As shown on Table 3, 47% response rate was achieved by S2SRHB + TT protocol whereas S2SRHB only protocol yielded 19% response rate at 4 months.

Also, in the fourth month of vaccination, the number of individuals in group A who had antibody titer greater than 50 was more than group B ($P < 0.05$, Table 2). In group IA, response rate was greater than all the other groups ($P < 0.05$, Table 4).

Table 1
Anti-HBS responses in the groups

Group	*n*	Anti-HBS (IU/l)							
		1 month		2 months		4 months		Total	
		<10	>10	<10	>10	<10	>10	<10 (%)	>10 (%)
IA	25	19	6	11	8	10	1	10 (40)	15 (60)
IB	15	14	1	13	2	11	1	11 (73)	4 (27)
IIA	7	7	0	5	2	4	1	4 (57)	3 (43)
IIB	5	5	0	4	1	4	0	4 (80)	1 (20)
IIIA	13	12	1	11	1	10	1	10 (77)	3 (23)
IIIB	11	11	0	10	1	10	0	10 (91)	1 (9)

4. Discussion

In previous studies, S2SRHB vaccine was shown to be highly immunogenic in adults. It induced antibodies against to HBsAg at a protective level in more than 90% of the subjects [11]. But some persons did not respond to S2SRHB vaccine [12–14].

In a preliminary study, about efficiency of TT to immune response of S2SRHB in nonresponders and simultaneous administration of S2SRHB + TT was more effective in nonresponders than additional S2SRHB doses given by the same route as the initial vaccination [14].

We found total response rate of 47% (21/45) to simultaneous administration of S2SRHB + TT in the nonresponders. And we found total response rate of 19% (6/31) S2SRHB vaccine with additional doses. There was statistically significant difference between two different vaccination protocol groups ($P < 0.05$, Table 3).

Sönmez et al. [14], Strue et al. [3], and Hemmerling et al. [15] found seroconversion after additional recombinant HB vaccine doses as 16.6, 61, and 76.2%, respectively. We found rate of 19% S2SRHB vaccine with additional doses in nonresponders. These different results may depend on different group characteristics different vaccine dose and route.

Sönmez et al. [14] found response rate of 50 % to simultaneous administration of S2SRHB + TT in the nonresponders. Again in this study; we found response rate of 47% to simultaneous administration of S2SRHB + TT in the nonresponders.

Lower vaccine responses have been reported in haemodialysis patients when compared with healthy subjects [13]. In this study, it was reported that when 40 μg of Euvax-B vaccine (recombinant hepatitis B vaccine) was administered at 0, 1, 2 and 6 months route, the response rate was 89.5%. Hemodialysis patients had been vaccinated in random according to different vaccination schedules as 5, 10, 20, and 40 μg and variations in the number of injections as well as the dose and type of vaccine did not result in clinically important enhancement of the anti-HBS responses [12,16]. We found a total response rate of 23% (3/13) to S2SRHB + TT vaccine protocol in nonresponder hemodialysis patients (group IIIA). This was effective than additional S2SRHB vaccine route ($P < 0.05$, Tables 1 and 2). In hemodialysis patients, the responses were lower than healthy nonresponder groups ($P < 0.05$, Table 4).

Routine antenatal screening for hepatitis B carriage was more cost-effective and should be considered a standard of care in maternity practice [17]. In developing countries, tetanus vaccine is administered in the third trimester. In seronegative pregnant women, tetanus and hepatitis B vaccine can be administered simultaneously. In neonates, hepatitis B vaccine has been shown to be successful when applied simultaneously with the other vaccines. Successful results were obtained in several studies in which hepatitis B vaccine was administered simultaneously with pertussis-, diphtheria- and tetanus vaccine, oral or inactive polio vaccine or Haemophilus influenzae type b [18–20]. In our study, total response rate of S2SRHB + TT vaccine was found as 43% (3/7) in nonresponder pregnant women (group IIA). This result was different significantly than additional S2SRHB vaccine protocol ($P < 0.05$, Tables 1 and 2).

In the fourth month of vaccination, the number of individuals in group A who had antibody titer greater than 50 was more than group B ($P < 0.05$, Table 2). In group IA, response rate was greater than all the other groups ($P < 0.05$, Table 4).

In conclusion, simultaneous S2SRHB + TT vaccination is remarkably effective in inducing antibodies in nonresponders and this protocol is more effective than additional S2SRHB vaccine.

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