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Research Paper

Predicting response to HBV vaccination in people with positive anti-HBc but negative HBsAg and anti-HBs

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Key words: hepatitis B, recombinant, hepatitis B vaccine, isolated anti-HBC antibody, HBsAg

Objective: **There are 5.1–6.5% of people with positive anti-HBc in Iran. The aim of this study was to assess the predicting factors of response to hepatitis B vaccination in anti-HBc positive subjects.**

Results: **Total response rate to vaccination was 79.8% (75 cases) and 67.9% (38 cases) in cases and controls, respectively. Nineteen persons (20.2%) in cases and 18 persons (32.1%) of controls had negative anti-HBs even after three doses of HB vaccination. Factor associated with decreased response to vaccination was prior history of being HBsAg positive (OR = 1.3, p = 0.01).**

Methods: **In a quasi-experimental study, 94 people with negative HBsAg, negative anti-HBs and positive anti-HBc (cases) and 56 persons with negative HBsAg, anti-HBs and anti-HBc (controls) were vaccinated at zero, one and six months with recombinant hepatitis B vaccine. Successful immunization was defined by anti-HBs antibody titer ≥10 mIU/mL.**

Conclusion: **The rate of response to hepatitis B vaccination is nearly like other studies but somewhat different. Higher percent of married cases together with higher percent of positive HBsAg in spouses may explain the slight difference in the response to vaccination in cases in comparison with controls as a result of booster like effect that seldom happens because of recurrent contacts between the subjects and the HBsAg positive spouses spontaneously.**

Introduction

Antibodies to hepatitis B core (HBc) antigen are a marker of acute, chronic or resolved HBV infection and remain detectable for life.[1] Isolated anti-HBc serological profile may be associated with a: (1) chronic carrier state in which HBsAg is not detectable; (2) remote infection with loss of measurable anti-HBs; (3) passive transfer of anti-HBc; (4) nonspecific, cross-reacting antibody; or (5) the period when HBsAg has disappeared and anti-HBs has not yet been detected.[2,3] Anti-HBc is therefore detected in anyone who has been infected with HBV.[1,4,5]

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It has been demonstrated that some HBsAg negative individuals and those positives for anti-HBc continue to replicate HBV.[6,7] These findings suggest that so-called recovery from acute hepatitis B virus infection may not result in complete virus elimination, but rather the immune system keep the virus at a very low level. A positive correlation has been shown between anti-HBc titer and detection of HBV-DNA in serum samples of HBsAg negative individuals.[8]

Currently, a number of countries, including the United States screen all donations for anti HBc, which is not mandatory in some other countries.[9] However, detection of HBV-DNA by polymerase chain reaction (PCR) has the same significance as detection of HBsAg, and indicates current HBV infection. All blood donations in Iran are collected from volunteer donors, and tested for HBsAg as a marker of transmissible HBV. Though these measures have resulted in low rates of transmission by transfusion they have not eliminated it fully.

Despite the availability of an effective vaccine, HBV infection continues to be an important problem in Iran and nearly 8,000 to 10,000 deaths occur each year due to this sequelae. In Iran, the rate of asymptomatic hepatitis B carriers (HBsAg positive) varies between 0 and 3.9 per cent with an average of 1.7 percent.[10,11]

Iran is an area of low endemicity for hepatitis B virus (HBV) in the Middle East.[12] A recent study showed that of the 2,000 samples of healthy blood donors, 131 (6.55%) blood samples were found to be positive for anti-HBc in the south of Iran.[13] A previous study on 4,930 subjects of general population had shown that 5.13% were positive for anti-HBc alone.[14] Hepatitis B vaccination of these individuals has been largely used to understand the meaning of isolated anti-HBc.[15-17] Those who are immune will present an anamnestic anti-HBs response, after a single dose of vaccine.[18,19]

The ability to differentiate HBV chronic infection, immunity or false-positive results in donors with isolated anti-HBc pattern has obvious significance for the prognosis, treatment and well being of such individuals.[3]

In an attempt to identify the response rate to HB vaccination we have surveyed 94 healthy blood donors with positive anti-HBc and compared with controls. This study can particularly be of interest as it shows the predictors of non-response to HB vaccination as well as other prognostic factors that are related with higher non-response to HB vaccination.

Table 1 **Basic characteristics and risk factors of the cases and controls**

Variables	Cases N = 94	Controls N = 56	Sig.
Age [years, mean (95% CI)]	43.8 (41–46.6)	13.6 (9.9–17.3)	<0.001
Sex [male, No. (%)]	58 (61.7)	28 (50)	0.161
Married [No. (%)]	73 (83)	11 (19.6)	<0.001
Job [No. (%)]			<0.001
Homemaker	30 (33)	2 (12.5)	
Free	25 (27.5)	0	
Employed	11 (12.1)	0	
Retired	5 (5.5)	0	
Military	5 (5.5)	0	
Student	3 (3.3)	14 (87.5)	
Past medical history (%)			
Icter or liver disease	20.7	17.2	0.6
Prior HBsAg positivity	14.9	0	0.001
Family history of liver disease	55.9	55.4	0.947
Positive HBsAg in spouse	23.4	12.5	<0.001
Dental procedure	89.2	67.2	0.03
Surgery	44.6	25.6	0.02
Hejamat* (cupping)	23.7	5.8	0.006
Tattoo	10.8	7.8	0.231
Blood transfusion	5.4	6	0.87
Liver function test (LFT)			
AST (mean ± SE, U/L)	26 ± 1.2	21.4 ± 1.4	0.021
ALT (mean ± SE, U/L)	27.1 ± 2.2	21.6 ± 1.6	0.101
Alkaline phophatase (mean ± SE, mg/dl)	181.5 ± 9	188.2 ± 23	0.748
Total bilirubine (mean ± SE, mg/dl)	0.96 ± 0.1	0.88 ± 0.2	0.772
Direct bilirubin (mean ± SE, mg/dl)	0.18 ± 0.02	0.17 ± 0.04	0.698
PT (mean ± SE, sec)	13.1 ± 0.1	13 ± 0.2	0.912
Complete blood count			
WBC (mean ± SE, /ml)	6514 ± 240	5788 ± 402	0.412
Hemoglobin (mean ± SE, g/dl)	14.8 ± 0.3	14.7 ± 0.3	0.822
Platelet (mean ± SE, /ml)	224250 ± 11894	233422 ± 13071	0.291
Anti-HBe	48 (54.5)	0	<0.001

*A procedure in Iranian traditional medicine done by making shallow cuts on the trunk (upper back) and producing a suction effect that results in drawing blood from cuts (less than 100 cc). It is usually done by a non-physician, using non-standard instruments (done for healing or cure purposes).

Results

Cases were significantly older ($p < 0.001$), more married ($p < 0.001$), had higher AST ($p = 0.021$), prior HBsAg positivity ($p = 0.001$), positive HBsAg in spouse ($p < 0.001$), positive anti-HBe ($p < 0.001$), surgery ($p = 0.02$), dental procedure ($p = 0.03$) and history of Hejamat ($p = 0.006$). Gender, family history of liver disease, ALT, alkaline phosphatase and CBC were not statistically different between cases and controls. Basic characteristics and risk factors of the cases and controls are summarized in Table 1.

Total response rate to vaccination was 79.8% (75 cases) and 67.9% (38 cases) in cases and controls, respectively. It was not statistically different. Nineteen persons (20.2%) in cases and 18 persons (32.1%) of controls had negative anti-HBs even after three doses of HB vaccination.

In cases, There were 17 cases that had at least one abnormal variable of LFT (liver function test); although, mean of indices of LFT and CBC were normal at baseline. According to repeated measurement analysis, indices of LFT and CBC did not change significantly during and after vaccination.

All cases were followed up. HB vaccination caused immunity in 2 (2.1%), 24 (25.5%), 45 (47.8%) and 4 (4.3%) people in the 1st, 2nd, 7th and 12th month respectively. From all of the cases, 19 (20.2%) showed no response to vaccination of whom 2 (2.2%) tested HBsAg positive during follow up.

None of the cases and controls showed adverse effects against recombinant vaccine.

Responders to HB vaccine were not significantly different from non-responders in view of age, LFT, CBC, gender, marital status, job, liver disease, family history of liver disease, positive HBsAg in spouse, dental procedure, surgery, hejamat (cupping), tattoo and blood transfusion. (Table 2) Non-responders had only higher prior history of being HBsAg positive. Prior history of being HBsAg positive

Table 2 Comparison of responders and non responders

Variables	Responders N = 113	Non-responders N = 37	Sig.
Age (years, mean (95% CI))	32.8 ± 1.84	32.1 ± 3.78	0.854
Sex (male, No. (%))	68 (60.2)	18 (48.6)	0.218
Married (No. (%))	64 (59.3)	20 (58.8)	0.964
Job (No. (%))			0.727
Homemaker	26 (30.6)	6 (27.3)	
Free	19 (22.4)	6 (27.3)	
Employed	9 (10.6)	2 (9.1)	
Retired	3 (3.5)	2 (9.1)	
Military	5 (5.9)	0	
Student	13 (15.3)	4 (18.2)	
Past medical history (%)			
Prior HBsAg positivity	7 (9.2)	7 (30.4)	0.017
Family history of liver disease	62 (54.9)	21 (58.3)	0.715
Positive HBsAg in spouse	24 (36.4)	5 (26.3)	0.26
Hejamat* (cupping)	16 (14.7)	9 (25.9)	0.119
Tattoo	9 (7.7%)	1 (2.8%)	0.297
Blood transfusion	3 (4.1%)	2 (10.5%)	0.269
Liver function test (LFT)			
AST (mean ± SE, U/L)	25.2 ± 1.25	22.9 ± 1.22	0.269
ALT (mean ± SE, U/L)	25.3 ± 1.93	25.3 ± 2.87	0.987
Alkaline phophatase (mean ± SE, mg/dl)	190.8 ± 13.1	170.1 ± 13.39	0.324
Total bilirubine (mean ± SE, mg/dl)	0.95 ± 0.11	0.98 ± 0.21	0.883
Direct bilirubin (mean ± SE, mg/dl)	0.18 ± 0.02	0.1667 ± 0.02843	0.667
PT (mean ± SE, sec)	13.1 ± 0.1	13.1 ± 0.2	0.91
Complete blood count			
WBC (mean ± SE,/ml)	6376 ± 254	6850 ± 553	0.376
Hemoglobin (mean ± SE, g/dl)	14.8 ± 0.31	14.7 ± 0.56	0.803
Platelet (mean ± SE,/ml)	231393 ± 14941	207583 ± 18902	0.366
Anti-HBe (No. (%))	32 (29.9)	16 (43.2)	0.138

causes the probability of non-response to vaccination increases 1.3 times significantly. [p = 0.01, relative risk (95% CI) = 1.3 (1–1.7)].

Discussion

While none of different factors between cases and controls were not different among responders and non-responders (like age, AST and anti-HBe), these variables can not be a confounder in comparison of responders and non-responders in our study. So, results can be discussed easily.

The low rate of reproducibility and persistence of anti-HBc together with the high rate of primary anti-HBs response to hepatitis B vaccine in subjects with isolated anti-HBc raise doubts as to the reliability of anti-HBc as a single screening test for hepatitis B infection prior to vaccination and suggest that subjects with isolated anti-HBc, in particular those with low anti-HBc titers, can be included in vaccination programs.[16] Low primary response rate to vaccination in our study showed that either sensitivities of HBsAg or anti-HBs kits are unsatisfying or the immune responses of these individuals are impaired in some way to the virus.

In a recent study in Korea, the first and third vaccinations caused successful immunity in 70.6 and 70.6% in isolated anti-HBc group, and 34.4 and 81.2% in the control group, respectively. In the isolated anti-HBc and control groups, the primary, anamnestic and no responses were 0 vs. 46.9%, 55.9 vs. 6.3% and 29.4 vs. 18.8%, respectively. This study concludes that none of the subjects with isolated anti-HBc had a false positive result (primary response); therefore, they should be excluded from vaccination programs in Korea. To differentiate between immunity and occult infections, a single dose of vaccine, with a follow-up anti-HBs test, is preferable for subjects with isolated anti-HBc. An anamnestic response indicates late immunity and no response shows a suspected occult infection[20] (Table 3).

Response to four doses of HB vaccine in another similar study was the same (96% in both groups) in cases with isolated anti-HBc and controls (age- and sex-matched normal susceptible vaccinees).[21] Non-response rate was 9.7% in the other study[22] (Table 3) It was 20.2% in cases and 32.1% in controls in our study. Higher percent of married cases together with higher percent of positive HBsAg in spouses may explain slight more response to vaccination in cases in comparison with controls as a result of booster like effect. Because these cases have had recurrent contact with HBsAg and maybe are vaccinated spontaneously.

In a recent study in Turkey, the response to HB vaccination in persistent isolated anti-HBc positive subjects was 50%, 68.7% and 89.6% after first, second and third vaccination. There were no statistical differences between these cases and healthy controls.[23] (Table 3) These figures were 27.7%, 61.7% and 75.5% in our study and 48.4%, 63.6% and 90.9% in another study in Turkey, respectively[24] (Table 3). Our response rate is lower.

In similar studies, most cases with isolated anti-HBc have had a primary response to HB vaccination.[17,25] (Table 3).

Comparison of findings of similar studies with the present study has shown in Table 3. Non-response to HB vaccination in the present study can be a marker of low level HBV infection or undulating level in these cases. Non-persistence of presence of HBsAg in the two cases in our study (detected only once) is consistent with this diagnosis.

In our study, prior history of positive HBsAg increased the probability of non-response to HB vaccination. It shows that positive anti-HBc antibody is not a false positive result in these cases specifically when anti-HBc (and even all other markers of HBV) was rechecked in each follow up session. Some of these cases had a low level of HBV infection and had no response to HB vaccination.

Even though there are some differences between the response rates of HB vaccine after each injection in our study and the similar ones, the total response is nearly the same in all of them.

All of the mentioned studies show that in isolated anti-HBc subjects false positive results (primary response) or prior infection by HBV (anamnestic response) can be detected by anti-HBs response after HBV vaccination.

Nearly all of the studies about vaccination in isolated anti-HBc positive cases have focused on primary and anamnestic responses and also the implementation of new methods such as HBV DNA assay.

Although our study did not show the results of HBV DNA in persons with non-response to HB vaccination, its novelty is finding the predictor of non-response to HB vaccination with more accessible (through the patients' medical history) and cost benefit variable. Accuracy and power of such variable should be assessed in future studies. However, its RR shows that prior history of being HBsAg positive increase the probability of non-response by 1.3.

Methods

Intervention. The recombinant hepatitis B (HB) vaccine, HEBERBIOVAC HBR (HAVANA, CUBA) was administered in three doses of 10 μg in the deltoid muscle of the arm at 0, 1 and 6 months.

Study population. The efficacy of HB vaccine was evaluated in a quasi-experimental study between 2002 and 2005. Based on percent of response to vaccination in case and control group equal to 82% and 60% respectively, $\alpha = 0.05$, power = 80%, using comparing two ratios, 75 cases were calculated to be sufficient in each group. But, unfortunately, no more than 56 subjects were found in control group. So, we increased the number of cases to 94 persons.

All study subjects (cases) were selected from Hepatitis Consult Center of Tehran Blood Transfusion Organization, a referral outpatient clinic in Tehran, Iran. Ninety four cases with negative for HBsAg, anti-HBs, anti-HCV and anti-HIV but positive for anti-HBc and 56 controls with negative result for all mentioned markers were selected according to a convenience sampling.

Exclusion criteria were history of HB vaccination, immunodeficiency, organ transplantation, immunosuppressive therapy, hemophilia, hemodialysis, needle stick and any contraindication of vaccination.

Follow up. All of the cases were evaluated one month after each injection. If there was no response to vaccination, follow up was continued till 12 months. History of HBV infection, icter and liver disease in these people and their family and risk factors of HBV infection were evaluated based on a classic interview. Complete blood count (CBC), aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase, billirubine, anti-HBe antibody, HBsAg, anti-HBs antibody and anti-HBc antibody were (re)checked in every visit.

Assessment. Immunogenicity was assessed using anti hepatitis B surface antibody (anti-HBs) titers one month after each vaccine inoculation. Anti-HBs levels of 10 mIU/ml or higher are thought to be protective.

Efficacy of active immunization was evaluated by considering the percentages of HBsAg and/or anti-HBs antibody positive cases one month after injection, which implied the preventative effect of the intervention against the HBV infection.

Laboratory testing and facilities. For detection of HBV infection, HBsAg was determined using commercially available enzyme-linked immunosurbent assay (ELISA) kits (Hepanostika HBsAg Uni-Form II microelisa system, Organon Teknika, Holland). Positive samples were rechecked by ELISA method. ELISA kits were used for determining anti-HBs (ETI-AB-AUK-3, DiaSorin, Italy), total anti hepatitis B core antibody (anti-HBc) (ETI-AB-COREK-2, DiaSorin, Italy), and anti hepatitis B e antibody (anti-HBe) (ETI-AB-EBK, DiaSorin, Italy).

For HCV infection, anti-HCV antibody was detected using a third-generation ELISA kits (ETI HCV K-3, DiaSorin, Spain).

Table 3 Comparison of findings of similar studies with the present study

Study, year	Experimental group (anti-HBc$^+$, anti-HBs$^-$, HBsAg): sample size; and response rate to HB vaccination	Control group (anti-HBc$^-$, anti-HBs$^-$, HBsAg$^-$): sample size; and response rate to HB vaccination	Sig.	Reference
Kabir A, 2008	94; 79.8%	56; 67.9%	NS*	present study
McMahon BJ, 1992	80; 78.8%	No control group	-	17
Koh HJ, 2005	34; 70.6%	32; 81.2%	NS	20
Chan CY, 1995	50; 96%	25; 96%	NS	21
Coz Yataco A, 2005	31; 90.3%	No control group	-	22
Ural O, 2001	48; 89.6%	50; 94%	NS	23
Sünbül M, 2000	33; 90.9%	No control group	-	24
Silva AE, 1998	59; 86.4%	No control group	-	25
McIntyre A, 1992	17; 88.2%	17; 94.1%	NS	26

*not significant.

The serum samples were tested for anti-HIV antibody using ELISA kits (Genscreen HIV, Biso Rad, France).

Data processing and analysis. Mean ± SE (standard error), for description of quantitative variables, t-test and one way ANOVA for comparison of quantitative variables, and chi-square and fisher exact test (if necessary) for comparison of categorical variables were used in the analysis. Repeated measurement analysis was used for comparison of the same quantitative variables at different visits. Relative risk (RR) and its 95% confidence interval (95% CI) were also calculated to assess the strength of probability of response to vaccination. Differences or correlations with a $p < 0.05$ were considered statistically significant. SPSS 13 software (SPSS Inc., Chicago, Illinois, USA) was used in analysis.

Ethical consideration. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients signed an informed consent. We conducted the study with the approval of Nikan Health Researchers Institute (NHRI) ethics committee.

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