Original Article

DOI: 10.7860/JCDR/2018/33890.11899

Vaccine Therapy in Chronic Hepatitis B Carriers: A Randomised Double-Blind Controlled Trial

Microbiology Section

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ABSTRACT

Introduction: Chronic carriers of Hepatitis B Virus (HBV) are persistent sources of the virus and may transmit HBV to healthy individuals.

Aim: This study was conducted to assess therapeutic effects of HBV vaccine on Chronic HBV Carriers (CHC).

Methods and Materials: This clinical trial was conducted on CHCs aged 20-65 years, randomly allocated into four groups. Group 1 (control) did not receive vaccine. Group 2, 3 and 4 (vaccine groups) received different doses of HBV vaccine. HBV viral load (IU/mL) was assessed at baseline and two months after the last dose of HBV vaccine. Reduction or elimination of HBV viral load was considered as positive response.

Absolute Response Rates (ARR) was calculated for each group. Subgroup analysis was done on subjects with baseline viral load of <100,000 and negative HBeAb. Relative Response Rates (RRR) was defined as ARR in vaccine group divided by that of control. RRRs were calculated for total participants (overall RRR) and the above-mentioned subgroup of subjects (subgroup RRR).

Results: In total, 97 CHCs were recruited. No adverse reaction was reported. There was no significant difference in ARRs between study groups (p-value=0.09). An overall RRR of 0.78 and a subgroup RRR of 1.18 has been reported. A 50% increase was found in the RRR in subgroups of subjects with baseline viral load of <100,000 and negative HBeAb compared to the overall RRR.

Conclusion: It may be worth future studies to assess the therapeutic effects of HBV vaccine.

Keywords: Chronic carrier state, Hepadnaviridae, Treatment, Vaccination, Viral load

INTRODUCTION

Hepatitis B Virus (HBV) infection is considered as the most common infectious disease in modern societies. The chronic form of the disease is becoming a major global health problem. Generally, if the surface antigen of HBV is positive for more than 6 months, the person is considered as a carrier of chronic HBV. More than 350 million people or 5% of the world population are carriers of chronic HBV infection [1]. Chronic carriers of HBV infection may be asymptomatic. However, in some cases, the symptoms of hepatitis may appear over time and leads to cirrhosis and hepatocellular carcinoma [2]. About 600000 hepatitis B-related deaths occur annually in the world [3]. About 93% of cases of liver cirrhosis and hepatocellular carcinoma are due to this virus [3]. HBV infection was suggested as a very common cause of chronic liver diseases in Iran [4]. Chronic carriers of HBV are permanent sources of HBV virus and may transmit the infection to healthy subjects. Therefore, HBV chronic carrier state is considered as one of the most important public health problem [5], especially in high-risk area. Golestan province, located in Northern Iran has been known as a high risk-area for HBV with a prevalence of about 10% [6].

The aim of treatment in chronic HBV carriers include complete disposal of HBV from the host body, loss of HBV e-Antigen (HBeAg) and appearance of HBV e-Antibody (HBeAb) (Seroconversion), loss of HBV s-Antigen (HBsAg) and appearance of HBV s-Antibody (HBsAb) and prevention of complications such as cirrhosis and liver cancer [7]. Antiviral drugs such as lamivudine, adefovir, entecavir and pegylated interferon are therapeutic options for patients with chronic hepatitis B, but the effect of these drugs remains limited and not always stable.

Several studies have also shown that these drugs can not absolutely provide one of above mentioned goals of therapy [8]. Due to the need for long-term treatment, the use of these medications is not enough. Starting the treatment is indicated if HBV DNA <2,000 IU/ml, ALT elevated, and/or histological evidences of fibrosis or advanced cirrhosis reported [9]. Safe and effective preventive vaccines against HBV infection are available for more than 20 years [8]. Some studies have shown that high doses of HBV vaccine may control the disease or reduce the virus concentration in serum [10-14]. In other words, it was proposed that HBV vaccine might have therapeutic effects (in addition to preventive effects) in subjects with chronic HBV infection. Pol S et al., for the first time, reported that prophylactic administration of hepatitis B vaccine to chronic HBV carriers is effective in treating them [15,16]. This study was designed to assess the therapeutic effects of various doses of hepatitis B vaccine in chronic HBV carriers from a high-risk area in Northern Iran.

MATERIALS AND METHODS

This randomised double blind controlled trial (IRCT ID: IRCT20120 2259124N1) started February 2014 and continued until the sample size completion Study population included chronic HBV carriers aged 20 to 65-year-old who referred to infectious diseases clinic of our academic hospital in Gorgan, Golestan province, Iran. After obtaining informed consent, subjects were enrolled into the study.

In total, 120 patients in chronic carrier state of HBV were invited to participate.

Inclusion Criteria

Age between 20 and 65 years, absence of clinical manifestations of hepatitis B infection.

Exclusion Criteria

Patients with clinical manifestations of HBV infection as well as those with ALT levels of higher than 40 IU/L, those with positive HBeAg (ELISA method), patients with severe co-morbidities such as renal failure or any other underlying disease, and those who were under treatment for HBV were excluded.

Randomisation

The participants were randomly classified into four groups according to the time of referring through simple randomization method. Group 1 (control group) was observed without administering HBV vaccine. Group 2 was treated with a single dose of HBV surface antigen vaccine (0.5 cc, Euvax B, Korea) at months 0, one and six of the study. Group 3 was administered two doses (1 cc) of HBV vaccine at once in months 0, one and six. Group 4 was treated with two doses (1 cc) of HBV vaccine at once in months 0, one, two and six. Both physicians and patients were blinded to this classification.

HBV viral load was assessed at baseline and two months after the last dose of HBV vaccine (post-treatment) using real-time PCR method, artus HBV TM PCR Kit, ABI Prism 2300, Sequence Detection System (Applied). QIAamp MinElute Virus Spin kit (Qiagen company) has been used for extracting HBV DNA

The following changes in HBV viral load were considered as positive response: 1- post-treatment viral load of less than 100000 IU/mL in subjects with baseline viral load of higher than 100000 IU/mL; or 2- post-treatment viral load of less than 10000 IU/mL in subjects with baseline viral load of 10000-100000 IU/mL; or 3- negative viral load at post-treatment in cases with baseline viral load of less than 10000 IU/mL.

The effects of different doses of vaccine on HBV viral load were assessed. The ARR for each of the study groups were defined as the number of subjects with positive response divided by the total subjects of that group.

Regarding differences between study groups in some of baseline characteristics (proportion of subjects with positive HBeAb and viral load of higher than 100,000 IU/mL), subjects with baseline viral load of lower than 100,000 IU/mL and negative HBeAb, were entered into subgroup analysis. For this reason, Group 2, 3 and 4 were merged into a single group, called vaccine group. The RRR for total participants (overall RRR) and the above-mentioned subgroups (subgroups RRR) were defined as ARR in vaccine group divided by those of control group.

Ethics

This study was approved by the ethical committee of Golestan University of Medical Sciences (1455863249). An informed consent has been obtained from all participants after all questions have been answered by the main principal investigator. Entering into the study was voluntary and had no effect on the regular treatment course of included or excluded cases.

STATISTICAL ANALYSIS

ARR were calculated for each group. Subgroup analysis was done on subjects with baseline viral load of <100000 and negative HBeAb. RRR was defined as ARR in vaccine group divided by that of control. RRRs were calculated for total participants (overall RRR) and the above-mentioned subgroup of subjects (subgroup RRR). A p-value of less than 0.05 was considered as significant.

RESULTS

In total, 97 (81%) of 120 invited subjects accepted to participate in our study. Forty-four of subjects were male and 53 were female. The mean (SD) of participants' age was 33.6 (8.6) years. [Table/Fig-1] shows baseline characteristics of participants.

Variables	DCP	Group 1 (n=23)	Group 2 (n=26)	Group 3 (n=26)	Group 4 (n=22)	p-value
Age	Mean (SD)	35.96 (11.62)	32.62 (5.56)	32.31 (8.26)	33.64 (5.26)	0.45
Gender	Male (%)	52.2	50.0	30.8	50.0	0.38
	Female (%)	47.8	50.0	69.2	50.0	
Place of residence	Urban (%)	69.6	53.8	61.5	68.2	0.65
	Rural (%)	30.4	46.2	38.5	31.8	
HBe-Antibody	Positive (%)	60.9	50.0	7.7	0.0	<0.001
	Negative (%)	39.1	50.0	92.3	100.0	
HBV Viral load (IU/mL)	<10000 (%)	26.1	42.3	38.5	40.9	0.08
	10000-100000 (%)	0.0	23.1	19.2	22.7	
	>100000 (%)	73.9	34.6	42.3	36.4	

[Table/Fig-1]: Baseline characteristics of chronic HBV carriers.
Group 1: Received no HBV vaccine (control)
Group 2: Received one dose of HBV vaccine at months 0, 1 and 6
Group 3: Received two doses of HBV vaccine at months 0, 1 and 6.
Group 4: Received two doses of HBV vaccine months 0, 1, 2 and 6.

The ARR were 73.1%, 46.2%, 62.1% and 41.7% in Group 1, 2, 3 and 4, respectively (p-value=0.09). There was no significant difference in response rate between control and vaccine groups (p-value=0.19). [Table/Fig-2] shows the results of subgroup analysis. The overall RRR was 0.78, suggesting higher absolute response rate in control than vaccine groups. But, subgroup analysis on subjects with negative baseline HBeAb showed an increase in RRR. When subjects with baseline viral load of less than 100000 IU/mL or those with both of these criteria were entered into subgroup analysis, the RRR showed 50% increase and reached to 1.18, suggesting higher ARR in vaccine group than controls.

Participants	Response to treatment	Absolute response rate			Relative response rate
		Control group, n (%)	Vaccine group, n (%)	p-value	
Total participants (Overall)	Positive	16 (69.6)	40 (54.1)	0.78	0.19
	Negative	7 (30.4)	34 (45.9)		
Subgroup 1	Positive	6 (66.7)	34 (57.6)	0.86	0.61
	Negative	3 (33.3)	25 (42.4)		
Subgroup 2	Positive	2 (33.3)	16 (38.1)	1.14	0.82
	Negative	4 (66.7)	26 (61.4)		
Subgroup 3	Positive	1 (33.3)	13 (39.4)	1.18	0.84
	Negative	2 (66.7)	20 (60.6)		

[Table/Fig-2]: Therapeutic responses to HBV vaccine in total participants and specific subgroups of subjects with chronic HBV carriers.
Subgroup 1. Subjects with negative HBeAb at baseline
Subgroup 2. Subjects with baseline viral load of less than 100000 IU/mL
Subgroup 3. Subjects with baseline viral load of less than 100000 IU/mL and negative HBeAb

DISCUSSION

Chronic HBV carriers are important health issues in high-risk areas. They are permanent sources of HBV infection and transmit HBV to uninfected healthy individuals. There is no effective therapeutic option for these subjects. Recently, HBV vaccines were suggested to have possible therapeutic effects on these patients. We aimed to assess the effects of this safe and inexpensive intervention on virological activity of HBV in chronic carriers from a high-risk area in Northern Iran.

Results showed no significant difference in response rate between vaccine and control groups. Results of previous studies showed controversies in therapeutic effects of HBV vaccine. Results of some

previous studies suggested therapeutic effects for prophylactic administration of hepatitis B vaccine in chronic HBV carriers [16,17]. HBV vaccine reported to cause a decrease in viral load and even a sustained clearance in subjects with chronic HBV [17] and has been suggested as the cheapest and potentially most beneficial treatment in chronic HBV patients [18].

On the other hand, there are studies that showed no differences in the clearance of HBV DNA in children with chronic HCV infection or in chronic carriers [19,20]. These controversies may be due to differences in study design, study population, type of vaccine and dose and duration of intervention. HBV vaccination is a safe and inexpensive intervention and is available and acceptable to all population, even those in low resources countries. Regarding the importance of chronic HBV carrier state, especially in high-risk areas, further studies with different study design may be warranted to determine the best strategy for using HBV vaccine, especially newly developed ones in treatment of HBV carriers [21].

Baseline characteristics of our subjects showed higher proportion of subjects with viral load of higher than 100000 IU/mL in control group than in vaccine groups. The baseline results also showed significant higher proportion of subjects with positive HBeAb in controls when compared to vaccine treated groups. To adjust the effects of these variables on the response rates to vaccine therapy, we performed subgroup analysis on subjects with baseline viral load of less than 100,000 IU/mL and those with negative HBeAb. The results showed that the RRR was improved in subgroup analysis. This may partly be explained by the effects of HBeAb positivity. In other words, subjects with positive HBeAb may have full immune response to HBV and additive therapeutic effects of HBV may not be expected in these subjects. But, in HBeAb negative subjects, it seems that the anti-HBV activity of immune system has not yet been completed and it might be expected that vaccine therapy induced the immune system to produce antibody and consequently reduce the HBV activity and viral load.

LIMITATION

Although small sample size in subgroup analysis made the present study unpowered to detect significant differences, but, it seems to be worth considering these variables for conducting future studies to assess the therapeutic effects of HBV vaccine in chronic HBV carriers.

CONCLUSION

To conclude, no significant difference has been found in this study regards to the response to HBV vaccine between control and intervention groups. Subgroup analysis on subjects with baseline viral load of less than 100000 and/or those with negative HBeAb showed an increase in RRR. It is recommended to consider these variables for conducting future studies on assessing the therapeutic effects of HBV vaccine.

ACKNOWLEDGEMENTS

Authors acknowledge Research Deputy of Golestan University of Medical Sciences for the financial support in this project.

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FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Oct 09, 2017**
Date of Peer Review: **Feb 07, 2018**
Date of Acceptance: **May 26, 2018**
Date of Publishing: **Aug 01, 2018**