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Efficacy of Double Dose Intradermal Vaccination in Chronic Hepatitis B Carriers: A Double-Blinded Randomized Clinical Trial

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Abstract

Background: Specific vaccine therapies have been proposed recently as possible alternative treatment modalities to interferon and antiviral drugs to enhance the immune response in HBV chronic carriers through induction of T cell activity which can lead to control viremia. To assess the efficacy of long term intradermal (ID) hepatitis B virus (HBV) vaccination with double standard dose as an active immunotherapy in elimination of HBV infection in chronic hepatitis B carriers.

Materials and Methods: This double-blinded randomized clinical trial was conducted on all HBsAg positive patients. Among them 80 immunotolerant patients were recruited and randomly allocated to alternate study groups (vaccination or placebo) consecutively. Eligible healthy carriers in group 1 were assigned to vaccinate with six ID injections of the Heberbiovac HB vaccine at 30-day intervals and with double standard doses (2cc) in two forearms. Controls received normal saline with the same setting as a placebo. The mean ALT levels, detectable HBV DNA and seroconversion to anti-hepatitis B e antigen (anti-HBe) and anti hepatitis B surface antigen (anti-HBsAb) compared between groups at the beginning and the 6th and 12th months.

Results: No significant difference was found in the mean ALT values, the clearance of HBV DNA, seroconversion from HBeAg to HBeAb and developing of HBsAb between vaccinated and control group at the end of the 6th and 12th months (P>0.05).

Conclusion: Intradermal administration, even with double standard dose, is not an efficient treatment in the elimination of virus in chronic carriers of HBV.

Keywords: Vaccine therapy; Hepatitis B virus; Intradermal; Vaccination

Introduction

Hepatitis B virus (HBV) infection is one of the major public health concerns. About 2 billion infected individuals globally, 350 million chronic hepatitis [1] and up to 1.2 million death annually [2,3] due to HBV infection have been made the emergency of this infection inevitable. Approximately 75% of patients with chronic hepatitis live in Asia and Africa [4] and up to 15-45% of HBV infected patients grows to cirrhosis, liver failure and hepatocellular carcinoma (HCC) [5].

More than 35% of Iranian populations have been exposed to HBV and more than 3% of the community estimated to be virus carriers [6,7]. Since 1992, national vaccination program has been applied for neonates and recent investigations implied a substantial decline in the prevalence of HBV infection from 2.5-7.2% in 1997 to 0.45% in 2003 [8,9]. Two large scaled study before and after national vaccination program showed a significant decline in seropositivity rate in the age group 2-14 years (1.3% Vs. 0.8%, P<0.05) [10]. Furthermore the percentage of covered population under vaccination has been improved from 62% in 1993 to 94% in 2005 [11]. Despite acceptable reports of prevention managements, there is no efficient treatment for the high percentage of healthy carriers in the society [12] who possess a considerable proportion of involved patients. These patients are at risk for subsequent cirrhosis and HCC and act as a substantial source for spreading the infection.

It has been illustrated that in persistently infected individuals it is not possible to eliminate HBV from all infected hepatocytes by HBV-specific immune response, but this response is strong enough to continuously destroy HBV-infected hepatocytes, and thus it may induce chronic inflammatory liver disease. The primary aim in the treatment of chronic hepatitis B is to induce sustained disease remission and prevent serious complications like liver failure and/or hepatocellular carcinoma. Consequences of nucleoside analogue monotherapy such as drug-resistant HBV mutants and post-treatment relapse emphasize that the principal goal should change to provide a successful immune response [13]. Treatments targeting stimulation and enhancement of T cell responsiveness might be helpful to obtain long-lasting viral suppression and disease remission [14]. Specific vaccine therapies have been proposed recently as possible alternative treatment modalities to interferon and antiviral drugs to enhance the immune response in HBV chronic carriers through induction of T cell activity which can lead to control viremia [15,16].

However HBV vaccine is administrated using intramuscular (IM)

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route in the national prevention program, there are several published studies in favor of intradermal (ID) administration toward IM injection for its usage as replacement route or even the first choice in primary non-responders to the vaccine or hemodialysis patients [17,18]. Intradermal vaccine requires a small inoculums than IM one and can substantially reduce the cost of HBV vaccination [19]. Several studies have demonstrated that ID administration of HBV vaccine can be as efficient as IM vaccination in producing seroconversion and long-term seropositivity [20]. These mentioned studies are about prevention usage of ID vaccination while to our knowledge there is no published study toward therapeutic intradermal vaccination in healthy carriers and all previous investigations have used conventional IM route. This study is designed to assess the efficacy of intradermal HBV vaccination with double standard dose for six doses as an active immunotherapy in elimination of HBV infection in CHB carriers in a controlled, randomized trial.

Materials and Methods

Study design, inclusion and exclusion criteria

This randomized clinical trial was conducted between March 2007 and March 2009. Target population included all healthy carriers of hepatitis B who were positive for hepatitis B surface antigen (HBsAg) with normal alanine transaminase level (ALT). Accessible population was HBsAg positive patients who were referred from hepatology and infectious diseases clinics and laboratories in all over the Guilan province, North of Iran. These patients were evaluated for Inclusion and Exclusion criteria. Inclusion Criteria were those who had age more than 18 years; no previous history of HBV vaccination; positive HBsAg in the serum for at least 6 months; absence of hepatitis B surface antibody (anti-HBs), and hepatitis B e antibody (anti-HBe); HBV DNA detectable with liquid hybridization and serum ALT values lower than 1.5 times the upper limit of normal (40 IU/L).

Those patients who had history of antiviral or immunosuppressive medications; decompensated liver disease; positive test results for antibody to hepatitis D virus, hepatitis C virus or human immunodeficiency virus; evidence of other known causes of liver disease; or had other serious medical illnesses such as hypertension, diabetes, cardiomyopathy, malnutrition, or metabolic, neurologic, autoimmune or neoplastic diseases were taken apart. The present study is in full compliance with the ethical principles of the Declaration of Helsinki and the 26 ethical principles mandated by the Iranian Ministry of Health [21]. In addition, an ethical approval was obtained from the National Committee on Medical Ethics which was registered under IRCT138706131155N3 at the Iranian Registry of Clinical Trials (www.irct.ir).

Intervention

Eighty immunotolerant patients were recruited and randomly allocated to alternate study groups (vaccination or placebo) consecutively using computerized software. The sequence of allocation and administration (vaccine or placebo) were concealed from both patients and treatment physicians who performed administration and only a third observer was aware of participants` groups.

Eligible inactive carriers in group 1 were assigned to vaccinate with six ID injections of the Heberbiovac HB vaccine (Cuba made, available vaccine in Iran) at 30-day intervals and with double standard doses (2cc) in two forearms (1 cc in each forearm). This injection was evidenced by a cutaneous bleb seen in the injection site. Controls received no vaccine but normal saline with the same setting as a placebo.

Clinical data and laboratory assays

Variables including age, sex, body mass index, smoking, past surgical history, history of high risk behaviors (tattoo, blood transfusion, intra venous drug use and leech) were collected from each participant at the beginning of the study. HBs Ag, hepatitis B e Ag (HBeAg), HBe Ab and HBV DNA were measured at 0, 6th and 12th months by the microparticle enzyme immunoassay test system (Organon Teknika BV, Boxtel, the Netherlands). HBS Ab titration equal or greater than 10 IU/L was considered as seroconversion. HBV DNA was assessed by the Digene Hybrid Capture Systems (Beltsville, MD). Serum ALT levels were measured by using an automated analyzer and the values upper than 40 IU/L were considered as abnormal.

Outcome measurement

Primary outcome was the proportion of patients with HBsAb titration of 10 IU/L or greater at the defined times of measurements. Complete response to therapy was defined as loss of HBV DNA in serum by liquid hybridization and HBeAg and HBsAg seroconversion (loss of HBeAg and HBsAg and development of anti-HBe and anti-HBs). Secondary outcomes were proportion of patients who were positive for HBV DNA and had abnormal ALT levels at defined measuring times.

Statistical analysis

Results were reported as mean ± standard deviation (SD) for quantitative variables and percentages for categorical variables. The groups were compared using the Student's t- test for continuous variables and the chi-square test (or Fisher's exact test if required) for categorical variables. P values of 0.05 or less were considered statistically significant. All the statistical analyses were performed using SPSS version 13 (SPSS Inc, Chicago, IL, USA) for Windows.

Results

In this randomized clinical trial 85 inactive HBs Ag positive that were presented to all laboratories of Guilan province, Iran were selected for the study. Two patients din not agree with study protocol and three patients were lost in follow up period. Finally 80 cases (mean age: 37.6 ± 11.3 years, range: 19-62 years) enrolled the study. Participants` demographic and clinical data are summarized in table 1.

Two groups were compared for mean levels of ALT, detectable HBV DNA and seroconversion to HBeAb and HBsAb at baseline, 6 and 12

Variables	Vaccination (n=41)	Placebo (n=39)	P value
Male gender	63.4	64.1	0.94
Age (year)			0.97
<25	9.8	7.7	
25<, 35>	34.1	33.3	
35<, 45>	26.8	30.8	
45<	29.3	28.2	
BMI (Kg/m2)			0.17
<18	51.2	30.8	
18<, 25>	26.8	35.9	
25<	22.0	28.2	
Smoking	9.8	7.7	0.74
Past surgical history	48.8	46.2	0.81
High risk behaviors *	9.8	0.5	0.17
Family history of hepatitis	56.1	46.2	0.37

* High risk behaviors include tattoo, blood transfusion, intra venous drug use and leech. All the results are expressed as percentage.

Table 1: Demographic characteristics and clinical data of the participants.

Value	Vaccinated (n=41)				Placebo (n=39)			
	Day 0	3rd mo	6th mo	12th mo	Day 0	3rd mo	6th mo	12th mo
ALT (IU/l)	26.95 ± 10.67	26.98 ± 14.25	27.79 ± 18.15	25.37 ± 13.03	28.62 ± 13.89	25.05 ± 17.79	23.85 ± 10.95	27.63 ± 17.37
Detectable HBV DNA (n%)	35 (85.4)	NE	38 (92.7)	33 (80.5)	36 (94.7)	NE	35 (89.7)	34 (89.5)
Seroconversion anti-HBe (n%)	0	NE	0	1 (2.4)	0	NE	0	0
Seroconversion to anti-HBs (n%)	0	NE	2 (4.9)	3 (7.3)	0	NE	3 (7.7)	4 (10.3)

NE= not evaluated at that time.
All of the comparisons for the same values in the same time between two groups were not statistically significant (P>0.05)

Table 2: Comparison of virologic, serologic and biochemical values at the beginning of the study, at the end of the 6th and 12th months in vaccinated and placebo groups.

months after first injection. Table 2 shows the values for mentioned markers in each group at those defined times. No significant difference was detected for these virologic, serologic and biochemical values in the same time between two groups (P>0.05). ALT levels were always in its normal range in both groups. In 2 patients in each group serum DNA clearance was detected at the 12th month which was not a significant difference (P>0.05). No vaccine-related side effect was found in the participants.

Discussion

Despite the fact that HBV is a carcinogenic agent in chronic carriers without objective evidence of liver disease and the high prevalence of HBsAg positive individual [22], no current efficient treatment have been recommended for patients in the immunotolerant phase [12]. The annual risk of growing HCC in asymptomatic hepatitis B carriers is 0.47% [22]. An efficient treatment of CHB infection can decrease this risk [23].

Chronic carriers have great role in spreading the infection and act as chief reservoirs for subsequent development of cirrhosis and HCC. Thus control of infection in this population can lead to destroying the main source of chronic HBV infection in the society. Investigations in recent decade illustrated that since applying national vaccination program for neonates in 1992, a considerable decline has been occurred in seropositivity rate in the age group 2-14 years [10] and it seems that the major proportion of carriers in the society have age more than 14 years and are from those who had not received vaccine in their childhood. So we select our patients from those presenting patients with age >18 years who had not received vaccine in their childhood for sure.

Specific vaccine therapy is the new treatment modality for virus clearance in CHB patients which has been recently assessed in several studies [24,25]. To our knowledge, there is no large scaled study about using intradermal vaccination in CHB infection and all the previous studies have used conventional IM route of administration. It has been demonstrated that ID vaccine administration rapidly induce T cell activation and initiation of an adaptive immune response and may cause trapping of antigen in the cutaneous tissue for longer time than IM administration [26,27]. Several studies postulated that ID vaccination can be as effective as IM one even with much lower required dose which can substantially be cost-effective [20].

In our study patients in vaccination group received six monthly ID administrations of 2 cc Heberbiovac HB vaccine, but a significant difference was not found between vaccinated and unvaccinated groups at the end of 6th and 12th months in the mean ALT values, detectable HBV DNA and seroconversion to HBeAb and HBsAb (P>0.05). In the same setting Dikici et al. conducted a RCT with 74 previously unvaccinated patients dividing into two groups (vaccination and control). They also could not confirm a statistically significant difference between mean ALT values and viral load of HBV DNA at the end of 6th and 12th months after the first vaccine administration [28]. They applied three standard IM injections of vaccine with 30-day intervals while we examined six ID administrations with a double dose of vaccine, but the outcome was not changed. In contrast a pilot study showed that specific vaccine therapy by standard protocol could cancel or reduce HBV replication in about 50% of chronic carrier subjects [29].

Various vaccine schedules with different doses have been used in previous studies for specific vaccination therapy. Pol et al. found that five injections of vaccine can reduce HBV DNA compared to those with no treatment (16.3% vs. 2.7% respectively) [30]. Maybe vaccination with higher doses and short interval could induce anti-HBsAb in patients with chronic liver disease [31]. In contrast to what has been believed, despite six ID injections at 30-day intervals and double standard doses, only two and three patients in vaccination group developed HBsAb at the end of 6 and 12 months follow-up which was not significantly different from placebo group (3 and 4 patients at the 6th and 12th months). Moreover, high viral load and T cell hyporesponsiveness to HBV antigens are associated with poor response to specific therapy [32]. At the beginning HBV DNA was detectable in 85.4% of the intervention group and this might explain the poor response rate observed in our study.

A significant difference has not been found for seroconversion to HBeAb and HBsAb between vaccinated and unvaccinated participants in our participants, even surprisingly seroconversion to HBsAb was seen more among placebo group; it might be due to the natural pattern of the disease and is not related to receive vaccine or placebo. In two patients in each group serum DNA clearance was detected which was not a significant difference.

We were not able to assess the association between background variables and response rate, due to the little numbers of patients who development of HBeAb and anti-HBsAb. Anemia and malnutrition assumed to be responsible for the worse response of vaccination against hepatitis B, but these variables were not investigated among our participants. Further large scaled studies with longer follow-up period are required to clarify this doubt whether specific vaccination therapy (either IM or ID administration) is helpful in the elimination of virus in chronic inactive carriers or not. The effectiveness of different vaccination schedules and their combination with antiviral therapies are other issues which required more investigations in order to choose the best treatment option.

Finally, it can be concluded that intradermal administration, even with double standard dose for six doses, is not an efficient treatment in the elimination of virus in chronic carriers. No significant difference was found in the clearance of HBV DNA, seroconversion from HBeAg to HBeAb and developing of HBsAb between vaccinated and unvaccinated carrier patients.

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