

Research Article

Efficacy of Hepatitis B Virus Vaccination on Iranian Patients with Hemophilia and Thalassemia

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ABSTRACT

This study was designed to investigate the efficacy of HBV vaccination and also determine factors affecting on its response among Iranian patients with hemophilia and thalassemia. Hepatitis B virus (HBV) is still proposed as a major public health problem which can lead to cirrhosis, hepatocellular carcinoma, and death. Recipients of blood and blood products such as patients with hemophilia and thalassemia can be at risk of HBV infection.

In this cross-sectional study, 73 patients with hemophilia and 84 with thalassemia who attended in Tehran hepatitis centre, were randomly selected. Demographic data, time of last HBV vaccination, test results of HBsAb, HBsAg and HBcAb levels from patients' files were extracted. Effect of different factors like demographic data and elapsed time from last vaccination on its effectiveness was evaluated using SPSS software.

Sixty-five (89%) of hemophilia and 45 (53.6%) of thalassemia patients were male. Mean age (standard deviation) was 28.05 (9.41) and 26.25 (5.06) years for hemophilia and thalassemia patients respectively. In hemophilia group 59 (80.8%), and in thalassemia group 74 (88.1%), had an effective response (HBsAb \geq 10mIU/Lit) to HBV Vaccination. Among all of the evaluated factors, only elapsed time from last vaccination was significantly effective in the response to HBV vaccination in both hemophilia (more than 4 years) and thalassemia (more than 7 years) patients (P=0.02).

Based on our data, checking HBsAb titer, booster doses, and revaccination are recommended every four and seven years in the hemophilia and thalassemia patients respectively.

Keywords: Hepatitis B, Vaccination, Hemophilia, Thalassemia

INTRODUCTION

Hepatitis B virus (HBV) is still proposed as a major public health problem. It is the most common cause of hepatocellular carcinoma worldwide which accounts as the third most common cause of death due to cancer (1). Only in 2013, about 686000 deaths has been estimated to be related to this infection which put HBV in the top 20 reasons of human mortality (2). It is

estimated that in 2010, Nearly 250 million people were living with chronic HBV infection. HBV prevalence varied from 0.01% in United Kingdom and Norway to more than 20% in countries such as Sudan and Kiribati (3). Iran has HBV prevalence rate of about 2.2% in the general population. However, considering studies after 2010, a prevalence rate of 1.3% has been reported

for HBV infection which indicates a decrease in the related prevalence and places Iran in low endemicity areas (4).

Blood transfusion is categorized as the main risk factor for acquiring viral hepatitis, especially in patients with hematological disorders and transfusion-transmitting infections (TTI) are still an important problem in many regions. Recipients of blood and blood products such as patients with hemophilia and thalassemia are at risk of HBV infection (5). It is reported that in Iran about 1.5% of thalassemia patients have HBV infection (6). Also, various rates of HBV prevalence (1.4% to 2.7%) in some provinces of Iran have been reported among hemophilia patients (7,8).

HBV vaccination can provide effective protection against this infection (9). There are different factors can be considered for reducing response rate of HBV vaccination including irregular vaccination, liver and kidney diseases, genetics, obesity and immune deficiency (10-13). Furthermore, response rate and related immunological aspects need to be more investigated among some group of patients like multi-transfused patients (14).

This study was designed to investigate the efficacy of HBV vaccination and also determine factors affecting on its response among Iranian patients with hemophilia and thalassemia. It also tries to determine the time required for revaccination or booster doses among these group of patients.

MATERIAL & METHODS

Population and Setting

In this cross-sectional study, data of 834 Iranian patients with hemophilia and thalassemia who attended Tehran hepatitis center between January 2007 and January 2014 were investigated and according to the eligibility criteria of our project and using simple random sampling method, we enrolled 73 hemophilia and 84 thalassemia patients.

Eligibility Criteria

We included patients which have received three cycles of three doses of HBV vaccination in

periods of 0, 1 and 6 months. Therefore we did not include those who had the incomplete vaccination, missed information about the last time of vaccination and have passed over 10 years or less than one year from their last vaccination. Furthermore, we excluded patients with positive results of HBsAg test, diabetes, HIV infection, advanced cirrhosis or with a history of dialysis.

Data Collection and Measurements

The study protocol was in accordance with the Declaration of Helsinki. All participants had written informed consent before enrolment and their data will be kept confidential. Demographic data including age, gender, body mass index (BMI), date of HBV vaccination, history of Phlebotomy, smoking, and alcohol consumption were extracted from patients' files. We also collected data related to the profile of hemophilia and thalassemia diseases, such as severity of the bleeding disorder in hemophilia patients and splenectomy in thalassemia patients. Furthermore, we extracted data on presence or absence of HBcAb and HBsAg from the patients' files.

Patients were divided into two groups of having an effective or non-effective response to HBV vaccination according to their HBsAb titer. Seroprotection for HBsAb titer was defined as having ≥ 10 mIU/Lit. HBsAb titers less than 10 mIU/Lit and greater or equal than 10 mIU/Lit were considered as a non-effective and effective response to HBV vaccination respectively. The HBsAb titers had been determined by ELISA method and entered into the files of patients.

Statistical Analysis

We analyzed data using SPSS version 18 (SPSS Inc., Chicago, IL, USA). We presented quantitative and qualitative variables in mean \pm standard deviation (SD) and in frequency (percentage) respectively. The relationship between serum viral markers with any of the quantitative and qualitative variables was determined by using independent t-test and chi-square or Fisher's exact tests respectively. P value less than 0.05 was considered as statistically significant.

RESULTS

The mean age of hemophilia and thalassemia patients was 28.05 (9.41) and 26.25 (5.06) year respectively. Fifty-nine (80.8%) of hemophilia patients and 74 (88.1%) of thalassemia patients

had an effective response to HBV vaccination. Demographic data and patients' classification according to HBsAb titer are presented in table 1.

Table 1- Gender, Age Groups, BMI and HBsAb Titer of Hemophilia and Thalassemia Patients.

Variables	Hemophilia (n= 73)	Thalassemia (n= 84)
Male Gender	65 (89%)	45 (53.6%)
Age groups	11-20	17 (23.3%)
	21-30	33 (45.2%)
	31-40	15 (20.5%)
	41-50	5 (6.8%)
	51-60	3 (4.1%)
BMI	Less than 18.5 (Underweight)	13 (17.8%)
	Between 18.5 - 25 (Normal weight)	34 (46.6%)
	Between 25 - 30 (Extra weight)	24 (32.9%)
	More than 30 (Obese)	2 (2.7%)
	HBsAb Positive (>10 mIU/Lit)	59 (80.8%)

Abbreviation: BMI, Body Mass Index; HBsAb, hepatitis B surface antibody

Based on the level of coagulation factor (<1%, severe; between 1% and 5%, moderate and >5%, mild), we have 44 (60.3%) of severe, 18 (24.7%) of moderate and 11 (15.1%) of mild hemophilia cases. HBsAb, HBsAg and HBcAb were seen in 59 (80.8%), 1 (1.4%) and 22 (30.1%) of hemophilia patients and in 74 (88.1%), 0 (0%) and 12 (14.3%) of thalassemia patients, respectively.

In both groups of the study, there was no significant relationship between a history of alcohol consumption, smoking, phlebotomy, Cirrhosis, Gender, and BMI with patients' classification according to HBsAb titer. Among 59 hemophilia patients with effective response to HBV vaccination and 14 without effectively related response, 89.4% and 10.6% were in the group of fewer than 4 years from the last dose of vaccination respectively. Additionally, among 74 and 10 thalassemic patients with and without an effective response to HBV vaccination, 91.8%, and 8.2% were in the group of fewer than 7 years from the last dose of vaccination respectively. Therefore, among all of the evaluated factors, only elapsed time from last vaccination dose was significantly effective in the response to HBV vaccination in both hemophilia (more than 4 years) and thalassemia (more than 7 years) patients (P=0.02). (Tables 2 and 3).

Table 2- Characteristics of Hemophilia Patients According to the Response to the Hepatitis B Virus Vaccination.

Variables	Effective Response (n= 59)	Non-Effective Response (n= 14)	Odds Ratio (P Value)
Alcohol Consumption	6 (100%)	0 (0%)	0.791 (0.58)
Smoking	10 (66.7%)	5 (33.3%)	0.367 (0.14)
Phlebotomy	3 (75%)	1 (25%)	0.696 (1)
Cirrhosis	2 (100%)	0 (0%)	0.889 (1)
BMI (≤ 25)	44 (83%)	9 (17%)	0.614 (0.50)

Age Group (≤ 30 years)	43 (86%)	7 (14%)	0.372 (0.11)
Male Gender	51 (78.5%)	14 (21.5%)	0.785 (0.34)
Elapsed Time From Vaccination (≤ 4 years)	42 (89.4%)	5 (10.6%)	0.225 (0.02)

Abbreviation: BMI, Body Mass Index. Data are presented as frequency and percent of related positive cases to each variables

Table 3- Characteristics of Thalassemia Patients According to the Response to the Hepatitis B Virus Vaccination

Variables	Effective Response (n= 74)	Non-Effective Response (n= 10)	Odds Ratio (P Value)
Alcohol Consumption	2 (66.7%)	1 (33.3%)	0.250 (0.32)
Smoking	4 (80%)	1 (20%)	0.514 (0.47)
Phlebotomy	2 (100%)	0 (0%)	0.878 (1)
Cirrhosis	27 (84.4%)	5 (15.6%)	0.600 (0.69)
Splenectomy	51 (85%)	9 (15%)	0.246 (0.26)
BMI (≤ 25)	68 (87.2%)	10 (12.8%)	0.872 (1)
Age Group (≤ 30 years)	61 (85.9%)	10 (14.1%)	0.859 (0.34)
Male Gender	39 (86.7%)	6 (13.3%)	1.346 (0.74)
Elapsed Time From Vaccination (≤ 7 years)	67 (91.8%)	6 (8.2%)	0.157 (0.02)

Abbreviation: BMI, Body Mass Index. Data are presented as frequency and percent of related positive cases to each variables

DISCUSSION

In this project, we showed that 80.8% of hemophilia and 88.1% of thalassemia patients had an effective response to HBV vaccination. We also demonstrated that elapsed time from the last dose of Vaccination is the important factor that significantly influences the effectiveness of HBV vaccination among these groups of patients. This indicates a time decreasing response for HBV vaccination and proposes a need for booster doses. A meta-analysis in 2014 with the inclusion of 52 studies reported HBV vaccination efficacy rate of 82.82%, 87.87% and 86.37% among children, adult and the general population of Iran. This study reported a lower efficacy of HBV vaccination (59.62%) among special groups of patients including patients with thalassemia, hemodialysis and HIV infection (15). However, authors of this study did not report related response in thalassemia patients specifically. Accelerated schedule of HBV vaccination among hemophilia patients may help for increasing the

rate of immune subjects. Furthermore, Booster doses can provide higher titers of HBsAb and also more persistent immunity among this group of patients (16). To the best of our knowledge, we could not find a study which evaluates time decreasing response to the normal schedule of HBV vaccination among hemophilia patients. Here, although in a cross-sectional study, we reported this issue for the first time.

Consistent with our findings, Azarkar et al. reported that gender and age cannot significantly affect the efficacy of HBV vaccination among thalassemia patients (17). Although we did not observe a significant relationship between a history of Phlebotomy and HBsAb titers, Kabir et al reported that it can significantly reduce the response to HBV vaccination (18). Furthermore, like our study, it has been proved that splenectomy has not significant effect on the efficacy of HBV vaccination in thalassemia patients (19).

In a study in Mazandaran province and with evaluation of 98 thalassemic patients, it has been reported that after six years of vaccination, 78% of patients had the effective related response which means that HBsAb level of 22% of patients has been reduced to less than 10 mIU/Lit after six years (20). It should be noted that T Cell memory to HBsAg can be remained many years after HBV vaccination even in the persons with HBsAb <10 mIU/Lit and therefore sometimes a booster dose may not be necessary at least in healthy subjects with this characteristic (21). In line with our results, Daryani et al. investigated 100 children with and without thalassemia regarding the efficacy of response to HBV vaccination after 7 years. They concluded that children with thalassemia have a lower response to HBV vaccination compared to those without thalassemia. Also, they reported that in thalassemic group, the efficacy of HBV vaccination reduced significantly after 7 years and recommended revaccination for this patients after mentioned period of time (22). On the other hand, Azarkar et al. suggested that thalassemia patients should be checked for HBsAb titer after seven years of vaccination and if necessary revaccination should be considered (17).

Our major limitation in this project was related to the type of study which was a cross-sectional one. Unfortunately, we had to use patients' files in this study and some of them had missing data affecting our sample size. We also believe that cohort studies can give us more reliable and exact results for evaluation of the effect of the time on the efficacy of HBV vaccination in special population groups such as thalassemia and hemophilia. Hence we recommend cohort studies with appropriate sample size especially for hemophilia patients.

It seems that time decreasing response to the HBV vaccination is an important issue among hemophilia and thalassemia patients. We recommend an appropriate and regular program for checking HBsAb titer in these patients. According to the results of our project, they can be checked every four and seven years for hemophilia and thalassemia patients respectively

and if necessary, booster doses and revaccination for HBV should be taken into account for these group of patients.

CONFLICT OF INTEREST

Authors declare that there is no conflict of interest.

REFERENCES

- 1- Nguyen, V.T., Law, M.G., Dore, G.J. (2009). Hepatitis B-related hepatocellular carcinoma: epidemiological characteristics and disease burden. *J Viral Hepat.* 16(7): 453-463.
- 2- Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M. (2015). GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *The Lancet.* 385(9963): 117-171.
- 3- Schweitzer, A., Horn, J., Mikolajczyk, R.T., Krause, G., Ott, J.J. (2015). Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet.* 386(10003): 1546-1555.
- 4- Salehi-Vaziri, M., Sadeghi, F., Almasi Hashiani, A., Gholami Fesharaki, M., Alavian, S.M. (2016). Hepatitis B Virus Infection in the General Population of Iran: An Updated Systematic Review and Meta-Analysis. *Hepat Mon.* 16(4): e35577.
- 5- El-Faramawy, A.A., El-Rashidy, O.F., Tawfik, P.H., Hussein, G.H. (2012). Transfusion transmitted hepatitis: where do we stand now? A one center study in upper egypt. *Hepat Mon.* 12(4): 286-291.
- 6- Mirmomen, S., Alavian, S.M., Hajarizadeh, B., Kafaee, J., Yektaparast, B., Zahedi, M.J., et al. (2006). Epidemiology of hepatitis B, hepatitis C, and human immunodeficiency virus infections in patients with beta-thalassemia in Iran: a multicenter study. *Arch Iran Med.* 9(4): 319-323.

- 7- Torabi S.A., Abed-Ashtiani K., Dehkada R., Moghadam A.N., Bahram M.Kh., Dolatkhah R., et al. (2006). Prevalence of hepatitis B, C and HIV in hemophiliac patients of East Azarbaijan in 2004. *Sci J Iran Blood Transfus Organ.* 2(7): 291-299.
- 8- Javadzadeh Shahshahani, H., Atar, M., Yavari, M.T., Savabieh, S. (2006). Study of the prevalence of hepatitis B, C and HIV infection in hemophilia and thalassemia population of Yazd. *Sci J Iran Blood Transfus Organ.* 2(7): 315-322.
- 9- Rezaee-Zavareh, M.S., Einollahi, B. (2014). Hepatitis B vaccination: needs a revision. *Hepat Mon.* 14(3): e17461.
- 10- Havlichek, D., Jr., Rosenman, K., Simms, M., Guss, P. (1997). Age-related hepatitis B seroconversion rates in health care workers. *Am J Infect Control.* 25(5): 418-420.
- 11- Mandell, G.L., Bennett, J.E., Dolin, R. (2005). Principles and practice of infectious diseases. In: *Hepatitis B virus and Hepatitis D virus.* 6 ed. Churchill Livingstone. USA. 1864-1890.
- 12- Asgharian, A., Afzali, M. (2010). Evaluation of anti-hepatitis B antibody among nurse's aid conservatory students of IRIAF Be'sat Hospital. *EBNESINA- Journal of Medical.* 12(4): 21-24.
- 13- Afrasiabian, S.H., Hajibageri, K., Yousefinejad, V., Esmail Nasab, N., Sayfi, S. (2007). Response to Hepatitis B Vaccine in HIV-Infected Patients. *Armaghane Danesh J.* 12(2): 11-18.
- 14- Alavian, S.M., Tabatabaei, S.V. (2010). Immunological response to hepatitis B vaccine in polytransfused thalassemic patients. *Pediatr Hematol Oncol.* 27(4): 324-325.
- 15- Tazhibi, M., Hajivandi, A., Tafti, A.D., Fallahzadeh, H. (2014). The efficacy of hepatitis B vaccine in Iranian population: A systematic review and meta-analysis. *J Educ Health Promot.* 3: 53.
- 16- Santagostino, E., Mannucci, P.M., Gringeri, A., Rumi, M.G., Rafanelli, D., Rocino, A., et al. (1993). Accelerated schedule of hepatitis B vaccination in patients with hemophilia. *J Med Virol.* 41(2): 95-98.
- 17- Azarkar, Z., Sharifzadeh, G., Chahkandi, T., Mahmoudi Rad, A., Sandoughi, M., Rezaiee, N. (2009). Survey of HBV and HCV markers in haemodialysis and thalassemia, South Khorasan, Birjand 2007. *Sci J Iran Blood Transfus Organ.* 6(3): 233-237.
- 18- Kabir, A., Keshvari, M., Alavian, S. (2007). Effect of Vaccination Against Hepatitis B in Cases with Isolated Anti-HBc. *GOVARESH.* 12(2): 86-91.
- 19- Azarkeivan, A., Karimi, G., Shaiegan, M., Maghsudlu, M., Tabbaroki, A. (2009). Antibody titration and immune response of Iranian beta-thalassemic patients to hepatitis B virus vaccine (booster effect). *Pediatr Hematol Oncol.* 26(4): 195-201.
- 20- Saffar, M., Nikkhah, M., Anvari, M. (2001). An assay on durability of Hepatitis B antibody in health services staff and the Thalassemic patients, six years after vaccination in Sari, 1999. *J Mazandaran Univ Med Sci.* 32(11): 60-65.
- 21- Saffar, H., Saffar, M.J., Ajami, A., Khalilian, A.R., Shams-Esfandabad, K., Mirabi, A.M. (2014). Long-Term T-Cell-Mediated Immunologic Memory to Hepatitis B Vaccine in Young Adults Following Neonatal Vaccination. *Hepat Mon.* 14(9): e22223.
- 22- Daryani, F., Sharifi, M., Vahid Shahi, K. (2003). Surveying the association between HBS-Ab and time elapsed following vaccination in patients with Thalassemia Major of Boali Hospital 2001. *Pejouhandeh Quarterly Res J.* 33(8): 203-205.