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Clinical study on the efficacy of hepatitis B vaccination in hepatitis C virus related chronic liver diseases in Egypt

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ABSTRACT

Background: Chronic hepatitis B (HBV) and C virus (HCV) infections represent significant public health issues internationally. HBV vaccination has high sero-conversion rates in patients with mild to moderate chronic liver disease but has reduced efficacy in advanced stages.
Aim: to evaluate the efficacy of hepatitis B vaccination in HCV-related chronic liver disease and identify possible factors that may contribute to hypo-responsiveness in those patients.
Methods: Our study was a retrospective observational clinical study carried out at the tropical medicine department. It was conducted on 500 individuals (400 chronic HCV patients and 100 healthy controls). Individuals were divided into 5 groups: A (control group), B (cirrhotic patient not receiving treatment), C (chronic hepatitis patients receiving treatment), D (cirrhotic patients receiving treatment), and E (HCC patients receiving treatment). All individuals were subjected for comprehensive history taking, clinical examination, laboratory investigations, and assessment of anti-HBs titer.
Results: There is an inverse relationship between the level of anti-HBs Abs and the duration of vaccine. Diabetes and presence of cirrhosis have statistically significant relationship with serum anti-HBs Abs titer ($P = 0.007$). Oral DAAs therapy is associated with reduced response to HBV vaccine (only 31.75% of the patients were protected).
Conclusion: HCV infection and its complications significantly impair HBV vaccine response. Levels of anti-HBs Abs decline progressively with increasing duration from the last dose in immunization schedule of HBV vaccine. Diabetes and presence of cirrhosis being the main risk factors for vaccine hypo-responsiveness, also oral DAAs therapy is associated with reduced response to HBV vaccine.

1. Introduction

Chronic hepatitis B and C virus infections represent significant public health issues internationally. Chronic HBV infection affects over 350 million peoples; the progress to liver cirrhosis is a vital stage of chronic hepatitis B (CHB) (Konstantinou and Deutsch, 2015). Likewise, Globally, an estimated 58 million people have chronic hepatitis C virus infection, with about 1.5 million new infections occurring per year (World Health Organization 2020) and a marked geographic variation exists, with infection rates about 15% in Egypt (Karoney and Siika, 2013). Recent research demonstrated about 15–40% of CHB patients would progress to cirrhosis, liver failure, or hepatocellular carcinoma (Zoulim and Mason, 2012; Wei, 2019). Strong epidemiological evidence suggests an increased occurrence of fulminant liver failure, cirrhosis and hepatocellular carcinoma in patients with HBV, and HCV co-infection. Co-infected patients represent a diverse group with various patterns of viral replication and great variations of immune profiles (Benvegnù, 1994).

Patients with chronic HBV who developed acute HCV infection presented a suppression of the HBV replication (Liaw, 2004). Likewise, inhibition of HCV replication has been noted in patients with chronic

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HCV superinfected with HBV infection (Sagnelli, 2002). Finally HBV reactivation was observed in some co-infected patients after successful clearance of HCV with pegylated interferon-α (peg-IFN-α) and ribavirin (RBV) (Potthoff, 2008).

Vaccine efficacy (defined as anti-HBs concentration of ≥10 mIU/ml) is greatest in infants, children and young adults—with protective antibody levels achieved in ~95% of those vaccinated (Aspinall, 2011). HBV vaccination has high sero-conversion rates in patients with mild to moderate CLD but has reduced efficacy in advanced liver disease and after liver transplantation (Arslan, 2001). To minimize the occurrence of HBV infection in chronic liver disease (CLD), a variety of organizations have recommended HBV vaccination for these patients (Roni, 2013). Other factors associated with a reduced response to vaccination include immunosuppression, liver disease, renal failure, smoking and obesity (Shouval, 2003).

We aimed to evaluate the efficacy of hepatitis B vaccination in HCV-related chronic liver disease and identify possible factors that may contribute to hypo-responsiveness in those patients.

2. Patients and methods

Our study was a retrospective observational clinical study evaluating the efficacy of hepatitis B vaccination in patients with HCV related chronic liver diseases such as chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) compared to healthy population. The present study was carried out at the Endemic medicine department, Minia University Hospital, Minia, Egypt, through the period from May 2020 to November 2021. It was conducted on 500 individuals (400 chronic HCV patients and 100 healthy controls) after ethical committee approval and a written consent was obtained from each individual. Patients were admitted at Endemic medicine department, Liver and Digestive system center, Minia University hospital.

2.1. Patient population

-Inclusion criteria: Chronic HCV patient, adult individuals (18–65) years, history of receiving the three doses of HBV vaccine and patients with normal renal functions.

-Exclusion criteria: HCV & HBV co-infected patient, acute liver disease, HIV- positive patients and pregnant or lactating women.

2.1.1. Individuals were divided into 5 groups:

-Group A (control group): included 100 healthy volunteers working in a public organization in the Minia city.

-Group B**:** included 100 patients with HCV-related liver cirrhosis, who have not received any treatment for HCV previously. Diagnosis of liver cirrhosis was done through: Liver function tests and abdominal examination and ultrasonography.

-Group C: involved 100 chronic hepatitis patients who have received HCV treatment previously (Oral sofosbuvir (400 mg) + oral daclatasvir (60 mg) +/- oral ribavirin).

-Group D: involved 95 patients with HCV-related liver cirrhosis, who have received HCV-therapy previously (Oral sofosbuvir (400 mg) + oral daclatasvir (60 mg) +/- oral ribavirin). Diagnosis of liver cirrhosis was done by liver function tests and abdominal ultrasonography.

-Group E: included 105 patients with HCV-related hepatocellular carcinoma, who have received HCV-therapy previously (Oral sofosbuvir (400 mg) + oral daclatasvir (60 mg) +/- oral ribavirin), diagnosis of HCC was done by multiphasic CT and abdominal ultrasonography.

2.1.2. Each individual in the studied groups was subjected for:

-Comprehensive history taking: stressing upon: personal data including name, age, gender and residence, special habits like smoking, history of chronic liver disease as chronic hepatitis C, liver cirrhosis and HCC, history of metabolic diseases as diabetes mellitus, history of receiving HBV vaccine and duration of vaccination and history of any drug use.

-Clinical examination: General and local examination of abdomen was done.

-Laboratory Investigations: CBC, INR, complete liver and renal function tests.

Assessment of anti-HBs titer: Anti-HBs titer assay was done by HBsAb ELISA Kit, supplied by Prechek Bio, Inc, (920 E.Orangethorpe Ave., #D Anaheim, CA 92,801, USA). Assay was done using HumaReader HS, Wiesbaden Germany.

Statistical analysis: The collected data were inserted, tabulated, and statistically anatomized using Statistical Package for Social Sciences program (SPSS) software version 25. Quantitative data were expressed as frequency (%) and as mean + standard deviation (SD). Data were analyzed by Chi square test and results were compared with either Kruskal Wallis test followed by Bonferroni post hoc test, Analysis of Variance (ANOVA), or Linear Regression test. For correlation studies Spearman correlations were used. For all analyses, statistical significance was defined as p-values less than 0.05.

3. Results

Table 1 shows the demographic data for all studied individuals. The age range was (22 - 65) years old. The study included 300 males (60%) and 200 females (40%). Smokers were (45%) of the studied individuals. Diabetics patients were (43%) of the studied individuals. Table 2 shows laboratory parameters for all the studied individuals including ALT, AST, total bilirubin, direct bilirubin, albumin, serum creatinine, blood urea, platelets' count, total leucocytes count, hemoglobin level and INR. All values are expressed as mean± S.D. Fig. 1 shows percentage of protected individuals (serum anti-HBs Abs titer>=10 IU/L) vs. non-protected individuals (serum anti-HBs Abs titer<10 IU/L) in each studied group (response rate of 85% in chronic hepatitis group, 80% in cirrhotic group), oral DAAs therapy in cirrhotic patients is associated with reduced response to HBV vaccine (only 31.75% of the patients were protected). Fig. 2 shows the relation between serum anti-HBs Abs titer versus the duration of HBV vaccination (years) for all studied individuals. There is an inverse relationship between the level of anti-HBs Abs and the duration of vaccine. Table 3 shows serum anti-HBs Abs titer in each studied group and in all studied individuals as whole. All values are expressed as mean± S.D. Tables 4 and 5 show linear regression test for the effect of the studied factors on the serum anti-HBs Abs titer. Age, gender and smoking have statistically non-significant effect on serum anti-HBs Abs titer while diabetes and liver disease severity have statistically significant effect on serum anti-HBs Abs titer. Diabetes and liver disease severity are independently associated with serum anti-HBs Abs titer.

Table 1
Demographic data for all studied individuals.

	All studied individuals $N = 500$
Age:	
Range (years)	(22–65) years
$M \pm SD$	41.08 ± 14.16
Gender:	
Male:	300(60%)
Female:	200(40%)
Smoking:	
No.	275 (55%)
Yes.	225 (45%)
Residence:	
rural	330 (66%)
urban	170 (34%)
Diabetes:	
Diabetics	215 (43%)
Non-diabetics	285(57%)

Table 2
Laboratory parameters for all the studied individuals.

	All studied individuals $N = 500$
ALT(U/l)	28.49 ± 17.17
AST (U/l)	44.86±50.5
Bilirubin total (mg/dl)	1.02± 0.93
Bilirubin direct (mg/dl)	0.39± 0.41
Albumin (g/dl)	3.89±0.71
Creatinine (mg/dl)	1.13±0.21
Urea (mg/dl)	47.32±17.19
Platelets count (*10^3/ul)	187.4 ± 54.29
Total leucocytes count (*10^3/ul)	6.92±3.28
Hemoglobin (g/dl)	10.78±1.89
INR	1.19±0.14

4. Discussion

The goal of active HBV immunization is to enhance the host's immunity, resulting in the loss of HBV surface antigen (HBsAg) and ongoing HBV replication control. Traditional HBsAg vaccines, human anti-HBV surface antibody (anti-HBs), T cell vaccines, DNA vaccines, apoptotic cells producing HBV antigens, and viral vectors expressing HBV proteins are all options for HBV vaccination (Das et al., 2019).

This study was conducted to determine the efficacy of hepatitis B vaccination in patients with hepatitis C virus and in its related chronic liver diseases.

In the present study, there is significant difference in the level of serum anti-HBs Abs titer across the studied groups. HCV infection and its complications significantly impair HBV vaccine response (response rate of 85% in chronic hepatitis group, 80% in cirrhotic group). Diabetes and presence of cirrhosis are being the main risk factors for vaccine hyporesponsiveness. Oral DAAs therapy in cirrhotic patients is associated with reduced response to HBV vaccine (only 31.75% of the patients were protected). In Ashhab et al. (2020) study, 1506 patients with chronic HCV infection were evaluated, of which 525 received appropriate HBV vaccination and were assessed for response. They found a significantly lower response to HBV vaccination in HCV-infected individuals, with an overall response rate of 79%. Notably when assessing for the presence of cirrhosis, the rate of non-responders with cirrhosis was higher than that in the responders' group, but the difference was not statistically significant. However, on multivariate analyses that included age, gender, cirrhosis, alcohol abuse, and Diabetes Mellitus (DM), only patients with liver cirrhosis were less likely to be reactive.

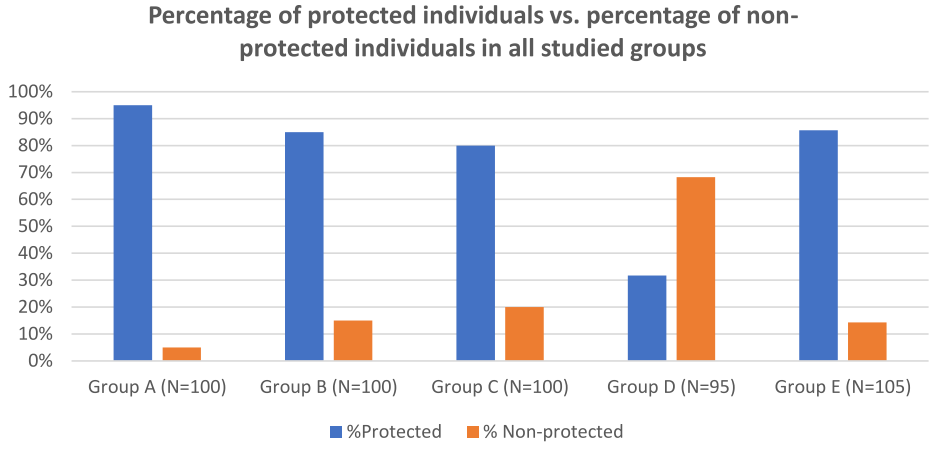

Fig. 1. Percentage of protected individuals vs. non-protected individuals in each studied group.

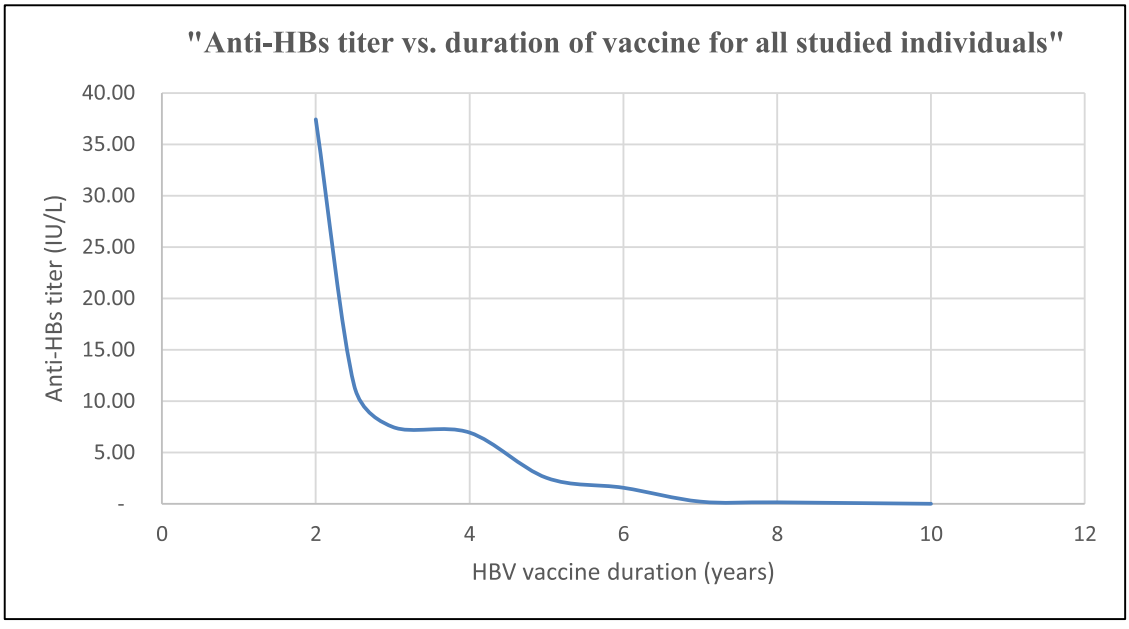

Fig. 2. Relation between serum anti-HBs Abs titer vs. the duration of HBV vaccination for all studied individuals.

Table 3
Anti-HBs Abs titer in each studied group.

	Group A $N = 20$	Group B $N = 20$	Group C $N = 20$	Group D $N = 19$	Group E $N = 21$	All individuals $N = 100$
Anti-HBs titer (IU/L) $M \pm$ SD	20.39 ±23.23	9.16 ±4.29	4.49 ±3.9	0.61 ±0.72	3.33 ±2.34	7.62±12.65

Group A: healthy volunteers, group B: cirrhotic patients who did not received HCV treatment, group C: chronic HCV patients who received oral DAAs therapy, group D: cirrhotic patients who received oral DAAs therapy, group E: HCC patients.

Table 4
Relation between serum anti-HBs Abs titer and liver disease severity, gender, age, smoking, diabetes in all studied individuals ($N = 500$) by Spearman's rho tests.

Test	Studied factor	Correlation Coefficient	Significance (P value)
Spearman's rho	**Liver disease severity**	−0.61	0.00
	Gender	0.115	0.256
	Age	−0.146	0.148
	Smoking	0.151	0.135
	Diabetes	0.269	0.007

Table 5
Linear Regression test for the effect of the studied factors in this study on the serum anti-HBs Abs titer.

Model	Unstandardized Coefficient β value	Significance (P value)	
	(Constant)	19.38	0.013
	Liver disease severity	−2.897	0.024
	Diabetes	2.149	0.040
	Smoking	1.53	0.548
	Gender	−1.086	0.673
	Age	−0.147	0.286

After vaccination schedule in Asan et al. (2017) study, 264 (83.5%) patients had antibody response to HBV vaccine and 52 (16.5%) had no response. Hepatitis B vaccine unresponsiveness is more common in the patients with hepatitis C positivity.

In this study, a significant inverse relationship was observed between serum anti-HBs Abs titer and presence of diabetes for all studied individuals; moreover, similar positive significant relationship was observed in each group. However, other factors such as age, gender and smoking had non-significant relationship with anti-HBs Abs titer. Our finding regarding the effect of diabetes on serum anti-HBs Abs titer agreed with Nashibi et al. (2015) study results which revealed that DM was in association with non-response to HB vaccine. In addition, aggregation of Leonardi et al. (2012) study results showed a significant decrease in response rates among the diabetic versus the non-diabetic patients.

Thomas et al. (2015) found no significant difference in sero-protection rate between gender ($P = 0.088$). Similarly, in Asan et al. (2017) study showed that there was no statistically significant difference between genders.

In a disagreement with this study results, Varshochi and Mahmodian (2011) study showed that there was a significant reverse linear relation between age and antibody titer in the studied staff and antibody titer decreased significantly as age increased ($p = 0.003$, $R = -0.162$); however, no significant difference was observed in the response between genders ($p = 0.127$).

The conflicting results between different studies about the relation between DM and response to vaccination may be related to different factors such as type of population studied, control of DM, type of treatment and ethnicity.

In the current study, there is an inverse relationship between the level of serum anti-HBs and the duration of HBV vaccination (years) in all studied groups. These findings are analogous to those obtained by Ren et al. (2020) study results which showed that the anti-HBs levels declined progressively with time after a primary hepatitis B immunization schedule. Yoshioka et al. (2017) preliminary data suggested that it may be useful to differentiate HB vaccine responders based on their primary response durations to maintain protective levels of anti-HBs efficiently. On comparing the association of year of vaccination with titer in Madhavan et al. (2021) study, it was seen that out of the 71 participants with (titer <10 mIU/ml), 31 (43.7%) had last vaccination more than 10 years ago ($P < 0.001$). There was a weak negative correlation ($R - 0.259$, $P < 0.001$) with antibody titer and increasing years of vaccination. An antibody titer of (350 mIU/ml) was seen in a participant who had taken the vaccine 25 years back.

To identify factors independently associated with an anti-HBs titer (<10 IU/L) in Coppola et al. (2015) study, a logistic regression analysis was performed with gender; age at vaccination, type of school attended, and years elapsed from vaccination as the variables. The analysis identified age at vaccination as the only independent predictor of low anti-HBs titer.

Abd El-Wahab et al. (2021) reported that cirrhosis in non-responders was more common than that in responders (57.1% vs. 49.2%); however, the difference was not statistically significant. Anti-HBs seroconversion rates after vaccination in Herta CDE et al. (2019) study was lower than expected for patients with end-stage liver diseases.

This study has some limitations. Because all patients got three vaccination doses, we were unable to determine the duration it took for seroconversion and, as a result, any potential variance in response rates.

5. Conclusion

In conclusion, we found that HCV infection and its complications significantly impair HBV vaccine response, with diabetes and severity of liver disease being the main risk factors for vaccine hyporesponsiveness. Levels of anti-HBs Abs decline progressively with increasing duration from the last dose in immunization schedule of HBV vaccine. Oral DAAs therapy is associated with reduced response to HBV vaccine.

Declarations

Ethical Approval and Consent to participate: Informed and written consent was obtained from all individual participants included in the study, and also, for publication of the work. Institutional Review Board "IRB", Faculty of Medicine, Minia University, Egypt reviewed and approved the research protocol and consent forms; Approval No. 9:3/2021. All procedures performed in the study were in accordance with the ethical standards of the national research committee and with the 1975 Helsinki declaration.

CRediT author contribution statement

MS and AH were concerned with the design of the study; YM, EA and HS were responsible about statistical analysis; ZZ performed the laboratory parameters; ME, SA, and AE analyzed the data and drafted the manuscript. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

Declaration of Competing Interests

All authors declare no Conflict of interest

Consent for publication

Informed and written consent was obtained from all individual participants included in the study, and also, for publication of the work.

Availability of data and materials

This published article contains all the knowledge produced or analyzed during this research

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