Original Research Article

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Low response rates to hepatitis B vaccine in patients with chronic hepatitis C

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ABSTRACT

Background: Hepatitis B is an infectious disease with converging routes of transmission with hepatitis C, making vaccination important in hepatitis C infected people. The objective was to evaluate the vaccine response against hepatitis B virus (HBV) in patients with chronic hepatitis C virus (HCV).

Methods: Retrospective observational study was conducted between November 2018 and April 2020. Subjects with anti-HBs levels ≥10 mUI/ml were considered protected against HBV and those with chronic HCV who did not receive at least one dose of the vaccine schedule or with anti-HBc reagent or even with anti-HBs positive prior to the first dose documented in the HBV vaccine record were excluded. The immune response rates to VHB vaccine in patients with HCV was obtained and different variables were analysed.

Results: The study group was compound of 370 subjects. The majority (55.7%) were male, with a median age of 55.6 ± 11 years. Regarding present or past smoking, 56.9% of patients reported that were active or past tobacco users. HCV genotype 1 corresponded to 59.7% of the cases, followed by genotype 3 (36.88%). One hundred and fourteen (30.9%) of the patients had liver cirrhosis. The immune response to complete HBV vaccine was 62.3%, whereas the response to a single dose was 57.1% (p=1). Only the age of the patient at first dose (p=0.030), smoking status (p=0.017) and the presence of cirrhosis (p=0.046) influenced the immune response to HBV vaccine.

Conclusions: The rate of immune response to standard schedule of HBV vaccination in patients with HCV was low (62.3%).

Keywords: Hepatitis B, Chronic hepatitis C, HBV vaccine

INTRODUCTION

Hepatitis B is a viral infectious disease caused by HBV, which is estimated that one-third of the world's population has already been exposed. Thirty-five percent of the infected adults will undergo an acute episode of the disease whereas 65% will have a subclinical and asymptomatic form of infection. However, both scenarios can lead to chronic hepatitis B.² Among those that had the acute form, 5% of the adults and more than 90% of the

children will develop a chronic stage which affects 240 million people worldwide.¹

Nearly 15% to 40% of the cases of chronic infection evolve to cirrhosis, which can lead to hepatic failure and hepatocellular carcinoma.³ These conditions raise the morbimortality rate of the disease, which is the cause of 780,000 deaths per year in the world.^{4,5} Concerning these alarming epidemiologic data, since 1989 Brazil has progressively used measures in regards to prevention and immunization in its public healthcare system (unified

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health system, SUS). In spite of these efforts, around 17,000 new cases were detected and reported annually in the country.6 Vaccination campaigns for hepatitis B emerged in the late 1980s, initially for the population of an endemic region in Amazon. In 2004, through ordinance 597 from the health ministry, vaccination schemes for various infections were formalized including HBV, which began to be performed in a three-dose scheme for both adults and children (with intervals of 0-1 6 months between doses). In 2012, the National immunization programme had changed, becoming available the pentavalent vaccine, adding 4 doses of the hepatitis B vaccine for children.⁸ The first dose must be made within the first 12 hours of birth; the second one. after two months: the third, at four months and the fourth one at the sixth month of birth 8.

It was estimated that the seroconversion rate for healthy adults was roughly 90%. However, this data can become questionable when the high number of notified cases per year in Brazil was analysed. It's difficult to measure the impact that the vaccine had on the number of cases since it was only in 1996 that hepatitis B became a compulsory notification disease. Nevertheless, the vaccine was considered a necessary preventive measure to avoid infection. 9

The immunogenicity and safety of hepatitis B vaccination in patients with HCV were both studied, with data regarding the seroconversion for hepatitis B surface antigen (anti-HBs) varying from 56 to 91%. Whether HCV infection decreases the response to hepatitis B vaccine was still a controversy.¹¹

The cases of coinfection from HBV and HCV may occur in different moments and even at the same time of contact since both infections have the same transmission methods: unprotected sexual intercourse (especially in men who have sex with men), blood transfusions and/or blood products transfusions, use of injectable illicit drugs, accidents with needlestick and sharp injuries. ¹² In patients with positive HBV antigen (HBsAg), the expected prevalence of coinfection with HCV ranges from 5 to 20%, while in patients with chronic hepatitis C, the prevalence of coinfection ranges from 2 to 10%. ¹³

Patients who were infected by both viruses have a faster progression to cirrhosis and a greater risk to develop hepatocellular carcinoma 14 and fulminant hepatitis. 15,16 The mortality rate in this group of patients may be above 10%. 14 Therefore, it became clear the need for further study in the vaccine response to hepatitis B in HCV-infected patients.

This study aimed to evaluate the seroconversion rate for anti-HBs (>10 mIU/ml) and the influence of epidemiological and clinical factors on the seroconversion rates after vaccination for hepatitis B in patients with chronic hepatitis C in a Southern city of Brazil.

METHODS

In this retrospective observational study, we analysed data from electronic patient charts who were treated in the orientation and counselling center (COA) in Curitiba. The study had been conducted between November 2018 and April 2020 and it was carried out in accordance with the ethical principles of the declaration of Helsinki and was approved by the local ethics committee on human research.

Subjects with age 18 or over with chronic hepatitis C in clinical follow up were included in this study. The exclusion criteria were total anti-HBc positive, anti-HBs positive before the first HBV vaccination dose and patients who have never received a single dose of the HBV vaccine. Seven hundred ninety-two electronic charts from HCV-infected patients were analysed, independently of the presence of cirrhosis.

Data with the number of doses of the HBV vaccine and the seroconversion rate (anti-HBs titles) were obtained. The demographic and clinical aspects analysed were sex, age, body mass index (BMI), HIV serum-positivity, past or present smoking, treatment for HCV, treatment of hepatitis C with interferon, sustained virological response to HCV, viral genotype, degree of hepatic fibrosis, presence of cirrhosis and model end-stage liver disease (MELD).

Patients who presented with hepatic fibrosis of degree 4 in the metavir score via biopsy or equivalent through transient elastography examination were considered to have cirrhosis. The same consideration was made in patients with radiological findings suggestive of cirrhosis or who had esophageal varices. The laboratory aspects analysed were the presence of total anti-HBc, anti-HAV, post-vaccinal anti-HBs and, if negative, anti-HBs after the booster dose.

The data retrieved were arranged in a Microsoft excel® spreadsheet and analysed with the computational program Stata/SE v.14.1. StataCorpLP, USA. The results were expressed in medians, minimal values, maximal values and standard deviations (quantitative variables) or frequencies and percentages (categorical variables). The evaluation of the association between two categorical variables was performed using Fisher's exact test or Chi squared test. For the univariate and multivariate analysis of the association between demographic and clinical factors and the vaccination response, logistic regression models were adjusted and the values of the odds ratio estimated, with respective confidence intervals of 95%. Wald's test was used to evaluate the significance of each variable. Values of p lower than 0.05 were considered of significance.

RESULTS

In the period ranging from March 2012 to April 2020, 792 patients were referenced to COA for evaluation of hepatitis C, a reference center in Curitiba. From that initial group, 503 of them maintained clinical follow up with medical consultations and complimentary examination. One hundred and thirty-three subjects presenting the following isolated exclusion criteria, 111 (22.1%) positive total anti-HBc, 13 (2.58%) with anti-HBs positive before vaccination, 8 (1.6%) did not receive any vaccine dose and 1 (0.19%) patient with positive HBsAg as only serological information.

The analysed group was compound of 370 subjects. The majority of the patients (55.7%) were male, with a

median age of 55.6±11 years. According to the BMI classification, 34.4% were overweight and 16% obese. Thirty-two individuals (8.6%) were HIV positive. Regarding present or past smoking, 56.9% of patients reported that were active or past tobacco users. In the follow up period, 278 (75.13%) of the patients with chronic hepatitis C received medical treatment and 30.51% of them were treated with interferon. The sustained virological response rate was 92.8% in the whole group. HCV genotype 1 corresponded to 59.7% of the cases, followed by genotype 3 (36.88%). One hundred and fourteen (30.9%) of the patients had liver cirrhosis. Only 51.62% of the analysed population of this study had been tested for HAV serology and 89.5% had reactive total anti-HAV. The data regarding the population of the study can be found in Table 1.

Table 1: Demographic data of the studied group (n=370).

**	C1 16 1	Studied group	
Variables	Classification	N (%)	
Candan	Male	206 (55.7)	
Gender	Female	164 (44.3)	
Age (years)		55.6±11.0	
		349	
BMI (kg/m²)	Underweight	9 (2.6)	
	Normal or healthy weight	164 (47.0)	
	Overweight	120 (34.4)	
	Obese	56 (16.0)	
		370	
HIV	Positive	32 (8.6)	
	Negative	338 (91.4)	
		311	
Smoker	Yes	107 (34.4)	
Smoker	No	134 (43.1)	
	Ex-smoker	70 (22.5)	
		278	
SVR	Yes	258 (92.8)	
	No	20 (7.2)	
		355	
	1	9 (2.5)	
	1a	126 (35.5)	
	1b	77 (21.7)	
HCV genotype	2	9 (2.5)	
	3	130 (36.6)	
	3a	1 (0.28)	
	4	2 (0.56)	
	Indeterminate	1 (0.28)	
		369	
Cirrhosis	Yes	114 (30.9)	
	No	255 (69.1)	
		236	
	0	28 (11.9)	
Fibrogia	1	17 (7.2)	
Fibrosis	2	58 (24.6)	
	3	48 (20.3)	
	4	85 (36.0)	
		191	
Total anti-HAV	Positive	171 (89.5)	

BMI: body mass index (kg/m²); HIV: human immunodeficiency virus; HCV: hepatitis C virus; SVR: sustained virological response; HAV: hepatitis A virus.

Table 2: Vaccine response of patients with chronic hepatitis C with positive isolated total anti-HBc, according to the number of received doses of HBV vaccine (n=33).

Number of doses		Anti-HBs >10 mUI/ml N (%)
1 (n=4)	Positive	3 (75)
	Negative	1 (25)
2 (n=5)	Positive	3 (60)
	Negative	2 (40)
3 (n=19)	Positive	14 (73.7)
	Negative	5 (26.3)
4 (5)	Positive	2 (40)
4 (n=5)	Negative	3 (60)

Table 3: Vaccine response of patients with chronic hepatitis C, according to the number of doses of vaccine against the HBV (n=238).

Number of doses		Anti-HBs >10 mUI/ml N (%)
1 (n=7)	Positive	4 (57.1)
	Negative	3 (42.9)
2 (n=19)	Positive	12 (63.2)
	Negative	7 (36.8)
3 (n=212)	Positive	132 (62.3)
	Negative	80 (37.7)

Table 4: Correlation between clinical and demographic variables and response to hepatitis B vaccination.

Variables	Classification	N	Anti-HBS		_ P*	OD (CL 050()
		IN	Positive	Negative	P	OR (CI 95%)
Age at 1st dose of the vaccine			46.5±1.7	50.5±12.5	0.007	1.03 (1.01-1.05)
Body mass index (kg/m ²)	Body mass index (kg/m²)		26.0±4.3	26.1±5.2	0.884	1.00 (0.96-1.06)
MELD score			9.0 ± 2.7	9.4 ± 3.2	0.603	1.04 (0.90-1.20)
BMI (kg/m²)	<25	136	68 (50.0)	68 (50.0)		
	25 to 29.9	98	60 (61.2)	38 (38.8)	0.090	0.63 (0.37-1.07)
	≥ 30	47	25 (53.2)	22 (46.8)	0.706	0.88 (0.45-1.71)
Gender	Female	131	72 (55)	59 (45)		
	Male	164	87 (53.1)	77 (47)	0.743	1.08 (0.68-1.71)
HIV	Positive	269	145 (53.9)	124 (46.1)		
	Negative	26	14 (53.9)	12 (46.2)	0.996	1.00 (0.45-2.25)
	No	102	70 (68.6)	32 (31.4)		
Smoker	Ex-smoker	60	33 (55.0)	27 (45.0)	0.083	1.79 (0.93-3.46)
	Yes	85	37 (43.5)	48 (56.5)	0.001	2.84 (1.56-5.17)
Treatment for HCV	No	36	15 (41.7)	21 (58.3)		
	Yes	259	144 (55.6)	115 (44.4)	0.119	0.57 (0.28-1.16)
Treatment with IFN	No	205	121 (59.0)	84 (41.0)		
Treatment with IFN	Yes	90	38 (42.2)	52 (57.8)	0.008	1.97 (1.19-3.26)
SVR	No	12	6 (50.0)	6 (50.0)		
	Yes	228	126 (55.3)	102 (44.7)	0.721	0.81 (0.25-2.59)
Genotype 1	No	122	63 (51.6)	59 (48.4)		
	Yes	166	94 (56.6)	72 (43.4)	0.401	0.82 (0.51-1.31)
Cirrhosis	No	200	119 (59.5)	81 (40.5)		
	Yes	94	39 (41.5)	55 (58.5)	0.004	2.07 (1.26-3.41)
Number of doses	1	7	4 (57.1)	3 (42.9)	0.784	1.24 (0.27-5.670
	2	19	12 (63.2)	7 (36.8)	0.939	0.96 (0.36-2.55)
	3	212	132 (62.3)	80 (37.7)		

OR: odds ratio; CI 95%: confidence interval 95%; BMI: body mass index (kg/m²); HIV: human immunodeficiency virus; HCV: hepatitis C virus; IFN: interferon; SVR: sustained virological response.

Table 5: Multivariate analysis of the association between the variables and vaccine response.

Variables	Classification	P*	OR (CI 95%)
Age at 1st dose of the vaccine		0.030	1.03 (1.003-1.05)
	No		
Smoker	Ex-smoker	0.478	1.31 (0.62-2.74)
	Yes	0.017	2.25 (1.16-4.39)
Treatment with IFN	No	0.798	0.91 (0.45-1.85)
Treatment with IFIN	Yes	0.798	
Cirrhosis	No	0.046	1.88 (1.01-3.48)
CITTIOSIS	Yes	0.046	

IFN: interferon.

Among the 111 patients with positive anti-HBc, 52 developed immunity against HBV. A total of 95 patients of this group performed HBsAg study and 3 (3.2%) were also HBV infected. Forty one participants of this study with isolated reactive total anti-HBc underwent one or more applications of the HBV vaccine but only 33 of them performed a post-vaccinal anti-HBs study (Table 2). It was possible to obtain anti-HBs levels >10 mIU/ml in 73.7% of patients who presented themselves with isolated reactive total anti-HBc after three doses of the HBV vaccine. In these individuals, between the 4 patients who had received only one dose, 3 (75%) had seroconversion. However, this difference was not significant (p=1).

From the total of 370 patients in follow up for chronic hepatitis C in the study group, 11 (3%) received only one dose against HBV, 36 (9.7%) received 2 doses, 256 (69.2%) received the full scheme and 67 (18.1%) received a booster dose in addition to the 3 doses. Despite having received at least one dose of the HBV vaccine, 75 (20.3%) individuals did not perform anti-HBs study post-vaccination. The response to the complete vaccination scheme was 62.3%, whereas the response to a single dose was 57.1%. This difference between the number of doses was not significant (p=1). The vaccinal response of these patients can be found in Table 3. The overall seroconversion of patients who received at least one dose was 53.9%.

In the group of patients who did not present seroconversion after the complete vaccination scheme, 37 received a booster dose and were later tested for anti-HBs positivity. Eighteen (48.65%) of them presented a response to the booster dose.

Table 4 contains the evaluation of the association between the analysed variables and the vaccination response, in which statistical significance was found in the following factors: age of the patient when receiving the first dose (p=0.007), smoking (p=0.001), use of interferon for HCV treatment at any given time (p=0.008) and hepatic cirrhosis (p=0.004). However, in the multivariate analysis, only the age of the patient at first

dose, smoking and the presence of cirrhosis influenced the immune response to the vaccine (Table 5).

DISCUSSION

Our study was the biggest study in Brazil to analyse the vaccine response of the HBV in patients with chronic hepatitis C and found a seroconversion rate (with a complete 3 doses schedule) of 62.3%. This number was lower than the ones found in healthy adults, which was more than 90% and greater than the number between patients with Down syndrome. 9,17,18 But regarding HCVinfected individuals, the data in the literature was variable. Some studies have shown similar numbers to our result and other had a better vaccinal response. 19-22 One meta-analysis that included 11 studies compared the seroconversion rate of the hepatitis B vaccine among 704 HCV patients and a control group of 812 people. Liu et al concluded that chronic HCV infection can reduce the immune response to the standard HBV vaccination schedule.11

The HBV vaccine was a recombinant hepatitis B surface antigen, an aluminium hydroxide adjuvant and a virus-like particle. The aluminium hydroxide adjuvant induced humoral immunity by promoting the production of the HBV envelope-specific antibody by the stimulation of the auxiliary T cells (Th2) and the production of IL-4.²³

The minor response to hepatitis B vaccine in HCV patients was multifactorial. Studies evaluated the relation between the vaccinal response, the HCV chronic infection and PD-1 (programmed cell death receptor 1). PD-1 is a negative receptor on activated T and B cells that induces an inhibition by the B cells receptor signalling pathways. Patients who did not respond to HBV vaccination that were infected by HCV had greater levels of PD-1, which attenuated the stimulation of T cells and induced their depletion. Another mechanism that suppressed the vaccinal response was the KLRG1 (killer cell lectin-like receptor subfamily G member 1) which was positively regulated by NK (natural killers) cells and T lymphocytes in people infected by HCV and suppressed the proliferation of T cells and secretion of IL2 (interleukin

2). Moreover, the HCV stimulates the activated B lymphocytes to create immunoglobulins unable to recognize and destroy the HBV by the TALL-1 (tumour necrosis factor- and - Apo-L-related leukocyte-expressed ligand-1) stimulation and by SOSCS-1 (suppressor of cytokine signalling-1) inhibition.²³

Among the epidemiological and clinical factors studied that could interfere in the vaccinal response, the significant ones were patient age at first vaccine dose, smoking and cirrhosis. Studies showed that cirrhosis was related to a minor HBV vaccinal response due to a dysfunction in lymphocytes B and T and consequently, a minor seroconversion rate. 25-27 Smoking was also an important factor in the non-vaccinal response in our study. Another study did not find the same association. However, one meta-analysis studied the factors that influenced the HBV vaccine response among healthy patients and concluded that smoking and age over 40 years were factors that decrease the HBV vaccine seroconversion rate. 28

The hepatitis B vaccination for isolated anti-HBc patients was important to distinguish patients with hidden infection by HBV and patients with a lack of immune memory do HBV, which was defined by a positive vaccinal response with the production of anti-HBs.²⁹ Our study found a vaccinal response in this population of 73.3% after 3 vaccine doses, which was smaller than other literature data in patients without HCV, group in which the seroconversion rate was 91.67%.³⁰ Our data also showed that, for these patients, only one vaccine dose was enough to produce satisfactory levels of anti-HBs; possibly, in this situation, the 3-doses schedule was not necessary.

Studies have shown that the HCV genotype can interfere in the process of the HBV vaccine seroconversion rate, considering that genotype 1 of HCV had the worse rates. ^{19,20} Our study did not find the impact of the genotype in the seroconversion rate of the HBV vaccine.

Studies suggested a modification in the HBV vaccine regimen in patients with HCV.31,32 Our study carried out an additional dose in patients who did not respond to the current 3-doses regimen, obtaining a seroconversion value of 48.65%. Minakari et al reported that a doubledose regimen of HBV vaccine (40 µg/ml) at intervals of 0, 1 and 6 months in patients with HCV induced a similar rate of HBV vaccine seroconversion to one of the healthy patients.31 Another study suggested that patients with HCV vaccinated with a double dose regime (40 µg/ml) and intervals of 0, 1 and 2 months, may have a better seroconversion rate in non-cirrhotic patients, but not in cirrhotic patients.³² Therefore, the implementation of a vaccination schedule with a double dose regime for all HCV patients could be interesting since the response to the usual regime was low.

Our study had some limitations. First, it was a retrospective study of data collected via electronic medical records. Besides, some patients did not complete the three-doses vaccination schedule and others did not perform the post-vaccination anti-HBs level. It was interesting to note that although HCV patients follow a public referral service for viral hepatitis and can receive the vaccine immediately after consultation, not all of them did it. Another relevant point was that the HBV vaccine response after treatment with the new DAA (direct-acting antivirals) was not evaluated.

CONCLUSION

In conclusion, our data show an HBV vaccine seroconversion rate in patients with chronic HCV of 62.3%, with statistical significance for age when the first vaccine dose was applied, smoking and liver cirrhosis. Further studies are needed to evaluate the ideal scheme for HBV vaccination in patients with chronic HCV, especially after treatment with new DAAs.

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