Does infection by the hepatitis C virus decrease the response of immunization against the hepatitis B virus in individuals undergoing dialysis?

Infecção pelo virus da hepatite C diminui a resposta vacinal para o vírus da hepatite B em uma população em diálise?

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Abstract

Introduction: Vaccination is the most effective tool in preventing transmission of Hepatitis B Virus (HBV). The patient with chronic kidney disease (CKD) on dialysis appear to be at greater risk of becoming infected with this virus and does not show the same vaccine response when compared to patients without uremia. **Objectives:** To evaluate the results related to the HBV vaccine and identify factors associated with the response in patients with CKD on hemodialysis. **Methods:** Individuals with HBsAG and negative anti-HBC, under hemodialysis were assessed in two units of São Luis, Maranhão and were undergone full vaccination schedule for HBV. They were divided in groups: anti-HBs10 mUI/mL and compared as to age, gender, presence of *diabetes mellitus* (DM), time on dialysis and anti-HCV status. Logistic regression analysis was performed to identify factors independently associated with the vaccine response. p10mUI/Ml (or = 5.239 IC: 1.279-21.459, p = 0.021). **Conclusion:** The rate of vaccine response to HBV in patients with CKD on dialysis was 70% and the lack of anti-HCV infection was associated with seroconversion of anti-HBs suggesting that infection by the hepatitis C virus may be a factor that decreases the response of the HBV vaccine in dialysis CKD patients.

Keywords: hepatites B vacines; hepatites B vírus; hepatitis C; renal insufficiency, chronic; vaccination.

Resumo

Introdução: A vacinação é a medida mais efetiva na prevenção da transmissão do vírus da hepatite B (HBV). O portador de doença renal crônica (DRC) em diálise apresenta maior risco de se contaminar com este vírus e não tem a mesma resposta vacinal quando comparada com indivíduos sem uremia. **Objetivos:** Avaliar os resultados da vacina para o HBV e identificar fatores associados à resposta, em portadores de DRC em hemodiálise. **Metodologia:** Foram avaliados indivíduos com HBsAg e anti-HBc negativos, que estavam sob hemodiálise em duas unidades de São Luís, Maranhão e que haviam sido submetidos ao esquema completo de vacinação para o HBV. Foram distribuídos em dois grupos: anti-HBs < 10mUI/mL e anti-HBs ≥ 10mUI/mL e comparados quanto à idade, gênero, presença de *diabetes mellitus* (DM), tempo em diálise e status do anti-HCV. Análise de regressão logística foi realizada para identificar fatores independentemente associados à resposta vacinal. Anti-HBs ≥ 10mUI/mL(OR = 5.239 IC:1.279-21.459, p = 0.021) **Conclusões:** A taxa de resposta vacinal ao HBV em portadores de DRC em diálise foi de 70% e a ausência do anti-HCV foi associada à soroconversão do anti-HBs, sugerindo que a infecção pelo vírus da hepatite C pode ser um fator que diminui a resposta da vacina para o HBV em indivíduos portadores de DRC em diálise.

Palavras-chave: hepatite C; insuficiência renal crônica; vacinação; vacinas contra hepatite B; vírus da hepatite B.

Introduction

An estimated 240 million people live with chronic hepatitis B in the world, making it the most common chronic infection of all.[1] In 2010, the *Global Burden of Disease study* ranked it among the top priorities in human health, as 786,000 deaths per year are connected to the disease's acute and chronic manifestations.[2]

According to a recent review, the global prevalence of infection by the hepatitis B virus (HBV) among individuals on dialysis

ranges from 1.2% to 6%.[3] Individuals with chronic kidney disease (CKD) are at risk of contracting HBV infection mainly when dialysis units fail to comply with the standards for the prevention of transmission of bloodborne pathogens.[4] Immunization against the virus stands as one of the main means to prevent infection by HBV.[5,6]

Seroconversion rates after vaccination against HBV in individuals with CKD range between 50% and 80%.[7] The impaired response to immunization seen in patients treated for CKD vis-à-vis individuals with normal renal function has been attributed to disordered immune function in areas such as antigen processing, antibody formation, and cell-mediated immunity associated with renal impairment and uremia.[6] Other factors have been associated with suboptimal response to vaccination for HBV in individuals with CKD, such as age of 60+ years, inefficient dialysis, malnutrition, *diabetes mellitus* (DM), stage of CKD, time on dialysis, and co-infection by the hepatitis C virus (HCV).[8-12]

The Brazilian Reference Center for Special Immunobiologicals (*Centro de Referência para Imunobiológicos Especiais* - CRIE) recommends that individuals with CKD be immunized with four doses (time zero then on months one, two, and six) of the HBV vaccine, using twice the dosage recommended for the patient's age.[13]

This study aimed to assess the response of patients with CKD undergoing hemodialysis in two renal replacement therapy (RRT) centers in São Luís, Brazil, to immunization against HBV and identify associated factors.

Methods

This analytical cross-sectional study used the database from study "Occult hepatitis B virus infection in patients with chronic kidney disease undergoing hemodialysis," approved by the institution's Ethics Committee and granted permit no. 004913/2009-40 (Annex 1), whose results were published recently.[14]

The aforementioned study was carried out from 2010 to 2013 in the two largest dialysis centers in São Luís, the capital of the State of Maranhão, Brazil. The two units combined responded for more than two thirds of the patients on dialysis in São Luís.

All HBsAg-negative patients on hemodialysis for at least six months seen in the two RRT centers were interviewed. Three hundred and two of the 342 individuals meeting the enrollment criteria provided written consent to join the study.

The selected patients had blood samples taken and tested for HBsAg, total anti-HBc, anti-HBs, and anti-HCV. The enrolled patients were immunized against HBV infection as per the recommendations of the CRIE.[13] The following data were taken from the patients' charts: age, gender, marital status, etiology of renal disease, and time on RRT.

Serological tests were run using enzyme-linked immunosorbent assay (ELISA) kits (SIEMENS, ADVIA CENTAUR).

Confirmatory tests were run to validate the HBsAg-negative status of every patient. The study included anti-HBc-negative individuals grouped based on anti-HBs levels: < 10 mIU/mL or ≥ 10 mIU/m. The differences between groups were analyzed in terms of age, time on dialysis, gender, diagnosis of *diabetes mellitus* (DM) and positive anti-HCV tests.

Software package IBM SPSS *Statistic*s version 22.0 was used in data analysis. Numerical variables were presented in the form of mean values ± standard deviation (SD); frequencies were presented in the form of percent values. The differences between numerical variables were calculated using Student's *t*-test, while nominal variables had their differences analyzed through the chi-square or Fisher's exact test, when appropriate.

Multivariate logistic regression analysis was performed to identify the factors independently associated with anti-HBs levels ≥ 10 mIU/m. Statistical significance was attributed to differences with p values ≤ 0.05.

Results

The study sample included 188 patients (HBsAg- and anti-HBc-negative). Most (54.8%) were males, and their mean age was 46.1 years (11 to 83 years of age). The mean time on dialysis was 40.9 months. Fifty patients (26.6%) were diagnosed with DM and ten (5.3%) were anti-HCV-positive. See Table 1 for a summary of patient information.

One hundred and thirty-two patients (70.2%) had anti-HBs ≥ 10 IU/mL and 56 (29.8%) had anti-HBs < 10 IU/mL. The mean age (45 ± 15.6 and 48.7 ± 14.4) and time on dialysis in months (40.4 ± 30.1 and 41.9 ± 32.7) of the individuals in the two groups were similar (p = 0.13 and p = 0.76, respectively).

Table 1 Clinical and demographic characteristics of the patients immunized against hepatitis B on hemodialysis in São Luís, Maranhão, Brazil, 2010-2013 (N = 188)

		n (%)
Age (years) mean ± SD	46.1 ± 15.4	
Gender	Female	85 (45.2)
	Male	103 (54.8)
Marital status	Single	55 (29.3)
	Married	112 (59.6)
	Divorced/separated	1 (0.5)
	Widow(er)	5 (2.7)
	State-registered domestic partnership	15 (8)
Hemodialysis (months) mean ± SD	40.9 ± 30.9	
Cause of chronic kidney disease	Hypertension	50 (26.6)
	Diabetes mellitus	50 (26.6)
	Urinary tract infection	5 (2.7)
	Autoimmune disease	17 (9)
	Inherited kidney disease	7 (3.7)
	Urinary tract obstruction	10 (5.3)
	Unknown	49 (26.1)
Anti-HCV	Positive	11(3)
	Negative	178(97)

Table 2 Comparison of immune response to vaccination against hepatitis B of patients on hemodialysis in São Luís, Maranhão, Brazil - 2010-2013 (N =188)

Características	Anti-HBs < 10UI/MI (n = 56)	Anti-HBs > 10mI U/mL (n = 132)	*p* value
Male	28 (50%)	75 (56.8%)	0.39
Age (years)	48.7 ± 14.4	45 ± 15.6	0.13
Time on hemodialysis (months)	41.9 ± 32.7	40.4 ± 30.1	0.76
Diabetes Mellitus	13 (23.2%)	37 (28%)	0.49
Anti-HCV(+)	07(12.5%)	03 (2%)	0.008

Table 3 Factors associated to anti-HBS (≥ 10 mIU/mL) seroconversion in patients with chronic kidney disease on hemodialysis immunized against hepatitis B virus (HBV) infection in São Luis, Maranhão, Brazil - 2010-2013 (N = 188)

Variables	OR	95% CI	*p* value
Age (years)	0.984	0.962-1.006	0.15
Tempo em diálise (em meses)	0.999	0.988-1.009	0.82
Sexo masculino	0.662	0.343-1.279	0.22
Diabetes Mellitus	0.729	0,337-1.577	0.42
Anti-HCV negativo	5.239	1.729-21.459	0.021

The groups were not statistically different in terms of gender or diagnosis of DM. Only anti-HCV-positive test results were statistically associated with low anti-HBs titers (p = 0.008) (Table 2). Logistic regression analysis, including all variables from univariate analysis, revealed that only anti-HCV-negative test results were independently associated with anti-HBs levels ≥ 10 mIU/mL (OR = 5.239 CI:1.279-21.459, p = 0.021) (Table 3).

Discussion

Dialysis patients with CKD are more susceptible to parenterally transmitted diseases such as HBV infection. Compliance to universal pathogen transmission prevention measures in dialysis units has decreased the global prevalence of HBV infection.[15] One of the main preventive measures is immunization against HBV.[16]

This study found that 70% of the immunized individuals susceptible to HBV had levels above 10 mIU/ml and were deemed protected against infection. This finding has also been reported in other studies, with seroconversion rates ranging between 50% and 80%[3,6-10].

The pathogenesis of this trait was recently reviewed by Sit *et al.*[17] and has been attributed to a series of variables such as genetic characteristics, nutritional factors, vaccine dosages and route of administration, stage of CKD, diagnosis of *diabetes mellitus*, time on dialysis, dialysis adequacy, co-infection by HIV or HCV, and others.

Of the factors analyzed in this study through multivariate analysis, only positive anti-HCV

test results were negatively related to anti-HBs seroconversion. Anti-HCV-negative individuals had a five-fold chance of having protective anti-HBs levels than HCV-positive patients.

The association between infection by HCV and impaired response to immunization in the population on dialysis is controversial. A recently published meta-analysis including eight studies (and 520 patients altogether) was unable to show a negative effect of infection by HCV on anti-HBs seroconversion.[18] However, the authors recognized that the quality of the included studies and the number of patients may have biased and potentially reduced the accuracy of the reported results.

One of the studies included in this meta-analysis was a randomized trial carried out in the Brazilian State of Rio Grande do Sul, in which infection by HCV (OR = 8.69 CI:1.26-58.8 p = 0.028) and old age (OR = 1.2 CI:1.02-1.30 p = 0.022) were reported as the only independent factors associated with non-seroconversion of anti-HBs.[9]

Another possible explanation for the lack of response to vaccination against HBV is the presence of occult hepatitis B virus infection (chronic infection by HBV with negative HBsAg), since HCV may inhibit HBV replication and produce non-positive HBsAg test results, while infection is present.[19,20] Occult hepatitis B virus infection (OBI) has been frequently observed in CKD patients with HCV infection.[21,22] In fact, our study involved 302 HBsAg-negative individuals (188 of whom were studied) and identified infection by HCV as the only factor associated with OBI.[14]

Another possible explanation for the non-seroconversion of anti-HBs in these individuals is the presence of liver disease, since changes in liver function may cause significant immune impairment, thus limiting the response to vaccination.[23,24] Unfortunately, this fact could not be confirmed since the study was based on a database in which there was no information on the level of liver involvement of the patients infected by HCV.

Conclusion

This study found that the response rate to HBV immunization was within the range expected for patients with CKD on dialysis, and that anti-HCV-negative individuals had higher chances of responding to vaccination. Studies with a greater number of patients, including the assessment of their levels of liver involvement, may shed light on whether infection by HCV hinders the response to HBV immunization in individuals on hemodialysis.

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APPENDIX A - FREE INFORMED CONSENT FORM

TITLE: Occult hepatitis b virus infection in patients with chronic kidney disease underogoing hemodialysis

Dear Patient,

This study will look into the status of occult hepatitis B virus infection affecting individuals with chronic kidney disease (CKD) undergoing hemodialysis in the city of São Luís. This important will provide you with important information on serology parameters. Blood samples will be taken - the same way it is done every month in the clinic you go to. We would like to invite you to join our study.

In the first part of the study you will be invited to answer a questionnaire on facts such as your age, marital status, level of education, and social status. Then, a series of questions concerning your disease will be asked and a sample of your blood will be taken.

This study is entirely separated from your treatment. Your refusal to join the study will not affect your condition as a patient at all. Nonetheless, you might benefit from joining the study, as you will be required to reflect on your health and have some time to discuss whatever questions you may have. If you agree to join the study, the information gathered in the study may be passed on to your health care team and help them understand your case.

The researchers responsible for this study will treat the information you give them with the utmost confidentiality. Your data will be grouped and presented together with the answers given by other participants without identifying anyone involved.

I hereby voluntarily agree to join this study.

São Luís,____ _____ _____

Patient signature_____

Signature or fingerprint_____

Interviewer_____

CONTACT INFORMATION

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APPENDIX B - SOCIO-ECONOMIC/MEDICAL QUESTIONNAIRE

I. Identification	COD
Registration:	
Initials:	
Address:	
Phone:	
Date of interview:	
Interviewer:	
1. Gender: (1) Male (2) Female	SEX
2. Birth date: / / Age (years):	ID (years)
1. 20 to 30	
2. 31 to 40	
3. 41 to 50	
4. 51 to 60	
5. 61 to 70	
6. 70+	
3. City of residence	SL/INT
4. Marital status 1-married 2-widow(er) 3-single 4-SRDP 5-divorced/separated	
5. Level of education	
6. Occupation	
7. How long have you been on dialysis?	
8. How many session of hemodialysis do you go to on a week?	
9. How did you lose your renal function?	
10. Do you have other diseases in addition to renal disease?	
11. Did you get the hepatitis shot? How many times?	
12. Have you been submitted to transplantation?	
13. Have you ever been given a blood bag? 1- one 2-more than 2 3-more than 5 4- mais more than 10	
14. Are you on erythropoietin (Hemax)? How many times a week?	