

Double-Dose Hepatitis B Vaccination in Cirrhotic Patients on a Liver Transplant Waiting List

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Development of immunity to hepatitis B virus in cirrhotic patients waiting for liver transplantation is highly desirable. Though a double-dose regimen is available, little is known about its effectiveness. We examined the efficacy of double-dose hepatitis B virus vaccination in cirrhotic patients waiting for liver transplantation. We studied 43 patients who were waiting for liver transplantation. They were vaccinated with three doses of 40 µg hepatitis B vaccine at 0, 1 and 6 months; the normal dose is 20 µg. Efficacy was measured based on seroconversion of anti-HBs. Global response to the primary vaccination scheme was 67.5% (29 patients). Forty-one per cent of responders had anti-HBs titers above 1,000 IU/mL. No factors were associated with response, based on multivariate analysis. The vaccination scheme of 40 µg at 0, 1 and 6 months was superior to conventional vaccination doses (20 µg) for cirrhotic patients on a waiting list for liver transplantation.

Key-Words: Vaccine, cirrhotic, hepatitis B, liver transplant.

Hepatitis B virus (HBV) is transmitted through sexual and parenteral routes, including blood transfusion and organ donation [1,2]. Cirrhotic patients and those submitted to transplant procedures are potentially exposed to these risk factors [3], and infection may lead to hepatic decompensation [4-6] or shorter graft survival [2]. In order to reduce this risk, it is desirable to induce immunity to HBV in this type of patient.

The conventional vaccination scheme consists of three doses of recombinant vaccine against HBV (20 µg), applied at 0, 1 and 6 months, which gives immunity in 95% of the general population [1,5]. However, these high rates are not seen in HIV-infected patients [7], in patients undergoing dialysis [6,8,9], or in cirrhotic patients [2,4,6]. A double-dose regimen (40 µg) has been used in HIV-infected patients and hemodialysis patients, giving an improved response [6,7]. This higher dose was subsequently tested on other groups of immunocompromised patients [10]; we adopted the double-dose regimen for cirrhotic patients on a waiting list for liver transplantation.

We examined the efficacy of double-dose hepatitis B vaccination in cirrhotic patients waiting for liver transplantation and evaluated factors associated with seroconversion.

Material and Methods

Two hundred and eight patients waiting for liver transplantation at the Clinical Hospital of the University of São Paulo Medical School were retrospectively evaluated. The following inclusion criteria were required: cirrhotic patient more than 18 years old; the HBV vaccine was given from January 2003 to August 2004; the vaccination scheme had

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been completed and a anti-HBs level measurement was made between one and two months after vaccination. The exclusion criteria were: HIV patients, dialysis patients and patients with any serological marker of previous hepatitis B infection.

The HBV vaccine consisted of three 40 µg doses, applied into the deltoid muscle, at 0, 1 and 6 months. Efficacy was measured by the seroconversion of anti-HBs (negative to positive). Anti-HBs levels were analyzed by ELISA one to two months after the last vaccine dose. The titers above 10IU/mL were considered positive.

The following factors were analyzed as variables for vaccine response: age, gender, Child-Turcotte-Pugh classification [11], MELD (Model for End Stage Liver Disease) classification [12] and etiology of hepatic disease at first vaccination dose. The data was analyzed using the EpiInfo 3.3.2 computer program. Univariate analysis was made by χ^2 test or Fischer's exact test. Multivariate analysis was made by stepwise logistic regression. Independent variables were introduced, depending on p values. The significance level adopted was 0.05.

Results

Forty-eight patients were selected based on the inclusion and exclusion criteria. Five of them had incomplete information and were excluded afterwards. Among these 43 patients, 24 were female (56%). Age varied between 22 and 63 years (mean of 44.2 years). Predominant etiologies were hepatitis C virus (35%), alcohol use (12%) and autoimmune hepatitis (19%). Child-Turcotte-Pugh score varied from A5 to C11; most were classified as Child B (58%).

Global response to the primary vaccination scheme was 67.5% (29 patients, Table 1). Forty-one per cent of responders had anti-HBs titers above 1000 IU/mL, 35% between 100 and 1,000 IU/mL and 24% between 10 and 100 IU/mL. Three of 14 non-responders were submitted to a new vaccination scheme of three more double doses of 40 µg (0, 1 and 6 months); anti-HBs levels rose to above 10 IU/mL one month after the sixth dose.

Table 1. Double-dose hepatitis B virus vaccine in 43 cirrhotic patients – factors associated with vaccine response.

	Responders 29 patients (67.5%)	Non-responders 14 patients (32.5%)	p
Gender			
Male	12 (63%)	7 (37%)	0.83
Female	17 (71%)	7 (29%)	
Age			
18-40 years-old	12 (75%)	4 (25%)	0.63
> 40 years-old	17 (63%)	10 (37%)	
Etiology			
Hepatitis C	9 (60%)	6 (40%)	0.67
Alcohol	3 (60%)	2 (40%)	1
Auto immune hepatitis	7 (87.5%)	1 (12.5%)	0.23
Others	10 (67%)	5 (33%)	1
Child-Turcotte-Pugh			
A	3 (37.5%)	5 (62.5%)	0.02*
B	17 (68%)	8 (32%)	
C	9 (90%)	1 (10%)	
Meld			
< 15	13 (68%)	6 (32%)	0.63*
15-20	10 (59%)	7 (41%)	
> 20	6 (86%)	1 (14%)	

*Chi-square for trend.

Based on univariate analysis, Child-Turcotte-Pugh C patients had better seroconversion rates ($p=0.03$; $CI=1.2$ to 185 , Table 1). When we used multivariate analysis, no significant differences were identified.

Discussion

Recombinant vaccine against HBV is responsible for a reduction in rates of chronic hepatic disease and hepatocellular carcinoma secondary to HBV [1]. The conventional dose regimen recommended for immunocompetent adults is $20 \mu\text{g}$ at 0, 1 and 6 months, resulting in approximately 95% of seroconversion rates [1,5]. Factors such as male gender, tobacco use, age (more than 40 years old), place of vaccine application and obesity are associated with lower vaccine response rates [2,4,8]. Low response rates are also found in immunocompromised patients. Improved seroconversion rates were obtained when double-doses ($40 \mu\text{g}$) were administered to patients under hemodialysis [6] and to HIV-infected patients with T-CD4 lymphocyte counts above 350 cells/mm^3 [7], using the same application intervals of 0, 1 and 6 months.

Cirrhotic patients waiting for liver transplants are particularly exposed to contamination risk [2]. Vaccine efficacy in this population is not as high as in immunocompetent individuals. Some studies show rates of seroconversion varying from 16% [13] to 70% [14]; in the face of these results, we examined the efficacy of vaccination with higher doses (Table 2).

A controlled randomized trial was conducted using a double-dose regimen of vaccine ($40 \mu\text{g}$) at 0, 1 and 6 months in a group of alcohol-abuse patients, some of whom had hepatic

disease; improved results were obtained with this higher dose. However, no consistent conclusion was obtained due to the reduced number of cirrhotic patients in this study [10]. There have been few studies comparing doses of 20 and $40 \mu\text{g}$ in cirrhotic patients. Engler et al. compared 20 and $40 \mu\text{g}$, but used application intervals of 0, 7 and 21 days; they found no difference between the treatment groups [2]. Accelerated vaccination schemes, reducing the application interval to 0, 7 and 21 days or 0, 1 and 2 months have been used in countries where the waiting time for an organ is less than six months. However, seroconversion was not satisfactory [2,4,6,15,16].

Using doses of $40 \mu\text{g}$ at 0, 1 and 6 months, we obtained 67.5% seroconversion, which is above what is generally observed in studies with this type of patient. Mattos et al. [14] obtained 70% response with a conventional scheme, but they only included patients with Child-Turcotte-Pugh A classification. Our elevated response rates could be explained by the dose and scheme utilized; however, ours was a young cohort, which is associated with improved responses, and there were few cases of alcohol etiology, which otherwise negatively affects response [2,8,10].

Based on univariate analysis, we found better response to vaccine in Child-Turcotte-Pugh C patients, different from published reports [4,8]. However, this conclusion was not confirmed by multivariate analysis.

Our study had some limitations, including a retrospective design, a relatively small number of patients and absence of a control group. However, the high seroconversion rates lead us to suggest that a prospective evaluation would be worthwhile, including testing of shorter schemes.

Table 2. Evaluation of hepatitis B virus vaccine efficacy: studies including cirrhotic patients.

Type of study	CLD (number)	Cirrhotic (number)	Controls (number)	Etiology	CTP	Dose (µg)	Scheme	SC* CLD (%)	SC* Cirrhotics (%)	SC* Controls (%)	P
Prospective (2)	-	34	39	Miscellaneous	B/C	20 (14 pts)	0,7,21 days	-	31	100	ND
					x	x			x		
Retrospective (3)	-	140	-	Miscellaneous	A/B/C	40 (20 pts)		-	26	-	ND
Prospective (4)	138	86	26	Miscellaneous	A/B/C	40	0,2,4 months	-	37	-	ND
Retrospective (5)	-	23	-	HCV, alcohol, Cypogenis	B/C	40→80	0,1,2→3 months	74	42	92	<0001
Prospective (6)	-	86	26	Miscellaneous	-	40	0,1,2 months	-	42	92.3	<0001
Prospective (10)	-	10	-	Alcohol	-	20x40	0,1,6 months	-	-	-	ND
Retrospective (13)	-	57	-	Miscellaneous	-	20	0,1,6 months	-	16	-	ND
Prospective (14)	65	20	46	HCV	A	20	0,1,6 months	50.8	70	97.8	<0001
Prospective (15)	-	20	53	HCV, PSC, PBC, alcohol	B/C	20	0,7,21 days	-	36	95	<0001
Prospective (16)	102	50	26	HCV	A	40→80**	0,1,2→3 months	80.4→100	54→55	92.3	<0001
Prospective (17)	-	50 (15)	-	Miscellaneous	B/C	40	0,1,2→0,1,2 months***	-	44→62	-	ND
Prospective (18)	-	24	-	Miscellaneous	-	40	0,1,2 months	-	87	-	ND
Retrospective****	-	43	-	Miscellaneous	A/B/C	40	0,1,6 months	-	67.5	-	ND

CLD=chronic liver disease; CTP=Child-Turcotte-Pugh classification; Pts=patients; ND=not done; HCV=hepatitis C virus; PSC=primary sclerosing cholangitis; PBC=primary biliary cirrhosis. *Seroconversion if anti-Hbs=10IU/mL. **Booster in patients with no seroconversion. ***New cycle of vaccination in 15 patients who were non-responders to a primary scheme. ****Data of this study.

We conclude that the a double dose of 40 µg HBV vaccine at 0, 1 and 6 months is superior to a conventional 20 µg dose at the same intervals, for cirrhotic patients on waiting lists for liver transplants; however, controlled and comparative studies using 20 *versus* 40 µg are needed before such a treatment scheme can be recommended.

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References

1. Poland G.A., Jacobson R.M. Prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* **2004**;351:2832-8.
2. Engler S.H., Sauer P.W., Golling M., et al. Immunogenicity of two accelerated hepatitis B vaccination protocols in liver transplant candidates. *Eur J Hepato* **2001**;13:363-7.
3. Horlander J.C., Boyle N., Manam R., et al. Vaccination against hepatitis B in patients with chronic liver disease awaiting liver transplantation. *Am J Med Sci* **1999**;318:304-7.
4. De Maria, Idilman, Calantoni, Van Thiel. Increased effective immunogenicity to high-dose and short-interval hepatitis B virus vaccination in individuals with chronic hepatitis without cirrhosis. *Journal of Viral Hepatitis* **2001**;8:372-6.
5. Arguedas M.R., McGuire B.M., Fallon M.B. Implementation of vaccination in patients with cirrhosis. *Dig Dis Sci* **2002**;47:384-7.
6. Idilman R, Colantoni A, De Maria N et al. Impaired antibody response rates after high dose short interval hepatitis B virus vaccination of immunosuppressed individuals. *Hepatogastroenterol* **2003**;50:217-21.
7. Fonseca M.O., Pang L.W., de Paula Cavalheiro N., et al. Randomized trial of recombinant hepatitis B vaccine in HIV infected adult patients comparing a standard dose to a double dose. *Vaccine* **2005**;23:2902-8.
8. Castells L., Esteban R. Hepatitis B vaccination in liver transplant candidates. *Eur J Hepato* **2001**;13:359-61.
9. Leroy V., Bourliere M., Durand M., et al. The antibody response to hepatitis B virus vaccination is negatively influenced by the hepatitis C virus viral load in patients with chronic hepatitis C: a case-control study. *Eur J Gastroenterol Hepatol* **2002**;14:485-9.
10. Rosman A.S., Basu P., Galvin K., Lieber C.S. Efficacy of a high and accelerated dose of hepatitis B vaccine in alcoholic patients: a randomized clinical trial. *Am J Med* **1997**;103:217-22.
11. Pugh R.N.H., Murray-Lyon I.M., Dawson J.L., et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* **1973**;60:646-9.
12. Kamath O.S., Wiesner R.H., Malinchoc M., et al. A model predict survival in patients with end-stage liver disease. *Hepatology* **2001**;33:464-70.
13. Chalasani N., Smallwood G., Halcomb H.J., et al. Is vaccination against hepatitis B infection indicated in patients waiting for or after orthotopic liver transplantation? *Liver Transplant Surg* **1998**;4:128-32.
14. Mattos A.A., Gomes E.B., Tovo C.V., et al. Hepatitis B vaccine efficacy in patients with chronic liver disease by hepatitis C virus. *Gastroenterol* **2004**;41:180-4.
15. Kallinowski B., Benz C., Buchholz L., Stremmel W. Accelerated schedule of hepatitis B vaccination in liver transplant candidates. *Transplant Proc* **1998**;30:797-9.
16. Idilman R., De Maria N., Colantoni A., et al. The effect of high dose and short interval HBV vaccination in individuals with chronic hepatitis C. *Am J Gastroenterol* **2002**;97:435-9.
17. Domínguez M., Bárcena R., García M., et al. Vaccination against hepatitis B virus in cirrhotic patients on liver transplant waiting list. *Liver Transpl* **2000**;6:440-2.
18. Macedo G., Maia J.C., Gomes A., et al. Efficacy of a reinforced protocol of HBV vaccination in cirrhotic patients waiting for orthotopic liver transplantation. *Transplant Proc* **2000**;32:2641.