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Comparing The Response Rates between High-Dose and Standard Dose Hepatitis B Vaccine in Thai Cirrhotic Patients

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ABSTRACT

Background: HBV vaccination is recommended to prevent superimposed acute or chronic HBV infection in chronic liver disease patients. The immune response in patients with liver cirrhosis is rather low with the standard dose. We conducted a randomized study comparing a high-dose schedule of hepatitis B vaccine (Engerix B®; 40 mg at 0, 1, 2, and 6 months) and the standard-dose schedule (20 mg at 0, 1, and 6 months) in cirrhotic patients.

Patients and methods: A total of 40 patients were randomized to receive either the standard dose or the high-dose regimen. The anti-HBs titer was measured at the 7th month after administration of the first vaccine dose. Responders were defined as those with an anti-HBs titer ≥ 10 mIU/mL.

Results: 38 subjects completed the study. Sixteen of 18 (88.9%) patients administered with the high-dose regimen seroconverted, compared with 16 of 20 (80%) in the standard-dose group (p=0.663). The mean anti-HBs titer in the high-dose group was significantly greater than of the standard-dose group (754.93 vs. 363.67 mIU/mL, p=0.01). No other factors including adverse drug reactions showed significant differences between the two study groups ($p > 0.05$).

Conclusion: There was no significant difference in the response rates between the high-dose and the standard-dose vaccine schedule in cirrhotic patients, although the high-dose regimen was associated with a better response rate.

Key words : High dose, Hepatitis B vaccine, Cirrhosis, Thai

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INTRODUCTION

Globally, chronic HBV infection affects over 350 million people, and up to 40% of these cases may progress to cirrhosis, liver failure, or hepatocellular carcinoma[1]. Chronic liver disease (CLD) contributes to approximately 400,000 hospitalizations and nearly 30,000 deaths annually worldwide[2,3]. When compared with patients without liver disease, patients with CLD are more likely to have severe complications and also severe fatality rate due to superimposed acute or chronic HBV infection. Both acute and chronic coinfections with HBV can be prevented by HBV vaccination[4,5]. Strong epidemiological evidence suggests an increased occurrence of fulminant liver failure, cirrhosis and hepatocellular carcinoma in patients with HBV, and HCV coinfection[6,7].

HBV vaccination is safe and well tolerated with high seroconversion rates in patients with mild to moderate CLD, but with reduced efficacy in advanced liver disease and after liver transplantation[8-17]. To minimize the occurrence of HBV infection in CLD, several of organizations have recommended HBV vaccination for these patients[18,19]. The immune response to HBV vaccines among patients with cirrhosis varies from 16% to 70%[20,21]. Increasing the dose[22,23] or frequency[22,24] of vaccine injections may improve the response in cirrhotic and immune compromised patients. Thus, a high- and accelerated-dose schedule (subsequently to be referred to as the high-dose schedule) of the available recombinant hepatitis B vaccine has been recommended for immunocompromised subjects[25].

We conducted a randomized study comparing a high-dose schedule of hepatitis B vaccine (Engerix-B®; 40 mg at 0, 1, 2, and 6 months) and the standard-dose schedule (20 mg at 0, 1, and 6 months) in cirrhotic patients.

METHODS

Patients

Eligible cirrhotic patients were seronegative for hepatitis B viral infection (HBsAg, anti-HBs, and anti-HBc). The diagnosis of cirrhosis was based on history, physical examination and laboratory findings.

Exclusion criteria were pregnancy, contraindications to intramuscular injections (e.g., severe coagulopathy or thrombocytopenia), acute and chronic renal failure (GFR <30 mL/min), Child-C cirrhosis, cancers, HIV, use of immunosuppressive drugs, and inability to comply with the protocol. An informed consent was obtained from each subject. The study was approved by the Bhumibol Adulyadej Hosipital Ethics Committee for Human Research.

Study design

Patients were randomized by block-of-four into two groups, the standard-dose group (20 mg Engerix-B® at 0, 1, and 6 months) or the high-dose group (40 mg Engerix-B® at 0, 1, 2, and 6 months). Engerix-B® was provided by GlaxoSmithKline). The 40-mg dose was administered as two 20-mg injections as recommended by the manufacturer[25]. All injections were administered intramuscularly at the deltoid site.

We chose to use the anti-HBs titers obtained at the 7th month after administration of the first vaccine dose as a measure of immunity[23,26]. Anti-HBs quantification was performed using an enzyme immunoassay method (Abbott Laboratories). The highest measurable titer was > 1000 mIU/mL. Good responders were defined as those having the anti-HBs titer were ≥ 100 mIU/mL, partial responders having anti- HBs titer between 10 and < 100 mIU/mL, and non-responders having anti-HBs titer <10 mIU/mL. The secondary objective was to assess the safety of HBV vaccination in CLD. Patient-reported adverse events, infusion site reactions and routine laboratory parameters were considered safety markers of the study.

Statistical analysis

Data was entered into excel spreadsheet 2007 and analyzed by using the SPSS programs. All the continuous data will be expressed as mean ± SD. Categorical data was expressed as numbers and percentages. Chi-square test (or Fisher's exact) and student's t-test was used to compare differences between the groups for categorical and continuous variables, respectively. A two-tailed *p*- value < 0.05 was considered statistically significant.

RESULTS

Forty patients (mean age ± SD, 56.24 ± 15.37 years) were randomized to receive either the standard-dose (n = 21) or the high-dose (n = 19) vaccine. Two patients died from unrelated causes during the study

(intracerebral hemorrhage 1, pneumonia 1). Of those who completed the study, 20 were assigned to the standard-dose group and 18 to the high-dose group. There were no significant differences ($p > 0.05$) in the baseline characteristics between the two groups (Table 1).

Seroconversion after vaccination and side effects

A quantitative anti-HBs titer was measured 4 weeks after administration of the last vaccine dose. A titer of ≥ 10 mIU/mL was considered adequate for im-

Table 1. Demographic Characteristics.

	Standard dose (n=20)	High dose (n=18)	*p*-value
Sex			
- Male	11 (55%)	6 (33.3%)	0.209
- Female	9 (45%)	12 (66.7%)	
Age (mean±SD) yrs.	55.4 ± 14.04	57.17 ± 17.1	0.720
- < 50 years	6 (30%)	7 (38.9%)	0.734
- ≥ 50 years	14 (70%)	11 (61.1%)	
BMI (mean±SD) kg/m^2	25.91 ± 4.44	25.36 ± 4.06	0.684
- < 23	5 (25%)	6 (33.3%)	0.724
- 23-29.9	11 (55%)	10 (55.6%)	
- ≥ 30	4 (20%)	2 (11.1%)	
Smoking			
- Never	13 (65%)	11 (61.1%)	1.000
- Used	5 (25%)	5 (27.8%)	
- smoking	2 (10%)	2 (11.1%)	
Etiology			
- Hepatitis C	8 (40%)	8 (44.4%)	1.000
- Alcohol	5 (25%)	3 (16.7%)	
- NASH	6 (30%)	6 (33.3%)	
- Others	1 (5%)	1 (5.6%)	
CTP			
- class A	18 (90%)	17 (94.4%)	1.000
- class B	2 (10%)	1 (5.6%)	

Table 2. Response rates and adverse drug reactions.

	Standard dose (n=20)	High dose (n=18)	*p*-value
Anti HBs (mean±SD) IU/mL	363.67 ± 438.41	754.93 ± 384.88	0.010*
Response			
- no response	4 (20%)	2 (11.1%)	0.663
- response	16 (80%)	16 (88.9%)	
Level of response			
- partial response	5 (25%)	1 (5.6%)	0.183
- good response	11 (55%)	15 (83.3%)	
Adverse drug reactions			
- none	19 (95%)	18 (100%)	1.000
- minor	1 (5%)	0 (0%)	

munity against hepatitis B. The mean anti-HBs titer was significantly greater in the high-dose group as compared with the standard-dose group (754.93 vs. 363.67 mIU/mL, $p < 0.05$). The seroconversion rate was not significantly greater in the high-dose group compared with the standard-dose (88.9 % vs. 80.0 %, p=0.663) (Figure 1).

Other than transient focal soreness on the arm, other vaccination side effects were infrequent.

Effects of other factors on seroconversion

Other relevant factors were not statistically significant with regard to the vaccine response rates in the two groups (Table 3).

DISCUSSION

Vaccination with HBV vaccine is very safe both in the general population and in patients with chronic

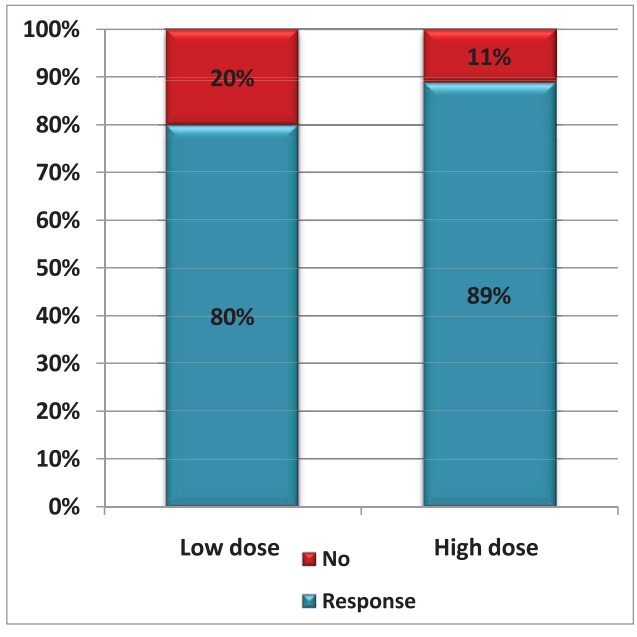

Figure 1. Response rate between high and standard dose hepatitis B vaccine.

Table 3. Factor associated with the response rates.

	Low dose (n=20)			High dose (n=18)		
	No response (n=4)	Response (n=16)	*p*-value	No response (n=2)	Response (n=16)	*p*-value
Sex						
- Male	3 (75%)	8 (50%)	0.591	1 (50%)	5 (31.3%)	1.000
- Female	1 (25%)	8 (50%)		1 (50%)	11 (68.8%)	
Age						
- < 50 years	1 (25%)	5 (31.3%)	1.000	0 (0%)	7 (43.8%)	0.496
- ≥ 50 years	3 (75%)	11 (68.8%)		2 (100%)	9 (56.3%)	
BMI (Kg/m^2)						
- < 23	1 (25%)	4 (25%)	1.000	1 (50%)	5 (31.3%)	1.000
- 23-29.9	2 (50%)	9 (56.3%)		0 (0%)	10 (62.5%)	
- ≥ 30	1 (25%)	3 (18.8%)		1 (50%)	1 (6.3%)	
Smoking						
- None	3 (75%)	10 (62.5%)	1.000	1 (50%)	10 (62.5%)	1.000
- Used	1 (25%)	4 (25%)		1 (50%)	4 (25%)	
- Smoking	0 (0%)	2 (12.5%)		0 (0%)	2 (12.5%)	
Etiology						
- Hepatitis C	2 (50%)	6 (37.5%)	1.000	0 (0%)	8 (50%)	0.477
- Alcohol	0 (0%)	5 (31.3%)		0 (0%)	3 (18.8%)	
- NASH	2 (50%)	4 (25%)		2 (100%)	4 (25%)	
- Other	0 (0%)	1 (6.3%)		0 (0%)	1 (6.3%)	
CTP						
- class A	4 (100%)	14 (87.5%)	1.000	2 (100%)	15 (93.8%)	1.000
- class B	0 (0%)	2 (12.5%)		0 (0%)	1 (6.3%)	

liver disease. The immunogenicity rates of vaccination in the general population are > 90%, whereas in CLD the rate varies from 16% to 100%[27]. We conducted a randomized trial in cirrhotic patients comparing the high-dose versus the standard-dose schedule.

In our study, the high-dose vaccine resulted in no significantly greater seroconversion rate than the standard dose (88.9% vs. 80%, p=0.663). However, higher anti-HBs titers were observed in the high-dose group as compared with the standard-dose group (754.93 vs. 363.67 mIU/mL, p = 0.01). The comparison level of good seroconversion response rates was also significant in the high dose group (88.3% vs. 55%, p= 0.086) but did not reach statistical significance.

In the standard-dose group, the magnitude of seroconversion response rates in our study was similar to that in a previous study[28]. The "none", "partial" and "good" response were 20%, 25%, 55% respectively. Higher anti-HBs titers and good seroconversion response were observed only in the high dose group, however, which was similar to that in another previous study[11].

The present study had limitations. First, the number of patients was rather small. Second, we evaluated only CTP-A and CTP-B cirrhotic patients, CTP-C subjects not included.

Conclusion

We found no significant differences in the response rates between the high-dose and the standard-dose vaccine schedules in cirrhosis patients, although the high-dose regimen was associated with a better response rate.

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