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Extra-high dose hepatitis B vaccination for peritoneal dialysis patients: a randomised controlled trial

Key Messages

1. The response rate to recombinant hepatitis B vaccine was suboptimal (70.1%) in the peritoneal dialysis population.
2. We investigated whether a three-dose regimen of extra-high dose (80 μg) of Engerix-B would achieve a higher rate of primary seroconversion and more persistent seroprotection in peritoneal dialysis patients, compared with the conventional 40-μg dose.
3. The rates of seroconversion (hepatitis B surface antibody level of ≥10 IU/L 3 months after treatment) were not significantly different between the two regimens.
4. The normalised protein nitrogen appearance was the only predictor for the development of primary seroconversion and persistent seroprotection.
5. Although the extra-high-dose regimen had no significant clinical benefit, improved protein intake may improve the immune response to hepatitis B vaccine in peritoneal dialysis patients.

Hong Kong Med J 2012;18(Suppl 6):S41-3

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RFCID project number: 06060072

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Introduction

Viral hepatitis B infection is a major health hazard to end-stage renal disease patients on dialysis. The direct costs of hepatitis B infection and its long-term impact on morbidity and mortality are substantial in such patients. In patients on dialysis, the traditional intramuscular recombinant vaccine (40 μg Engerix-B at months 0, 1, and 6) attains a seroconversion rate of 44 to 76%.

To improve the immunogenicity (seroconversion and seroprotection rates of hepatitis antibody levels) of intramuscular Engerix-B recombinant hepatitis B virus vaccine, various dosages of the vaccine have been compared,[1] but the response rates did not differ significantly. Using a three-dose regimen of 80 μg Engerix-B, there was an absolute risk reduction of 18% for losing the antibody response. Compared with historical controls, this extra-high dose would lead to one extra end-stage renal disease subject with persistent seroprotection (antibody to hepatitis B surface [anti-HBs] level of ≥10 IU/L at one year) for every 5.6 (95% confidence interval [CI], 5.4-5.8) patients treated.[1] The extra-high dose also showed similar benefits in chronic liver disease patients without adverse events.[2] We therefore compared the conventional dose (40 μg) with extra-high dose (80 μg) Engerix-B vaccine in peritoneal dialysis patients in terms of primary seroconversion and long-term seroprotection.

Patients and methods

This multi-centre, randomised, non-blinded clinical trial was conducted from May 2005 to May 2009 at three dialysis units. Written informed consent was obtained from each patient. A total of 109 end-stage renal disease patients (mean age, 60 years) on peritoneal dialysis who were serologically negative for hepatitis B surface antigen and antibody to hepatitis core antigen without previous hepatitis B vaccination were included. Those with active malignancy, alcoholic liver disease, chronic hepatitis C and/or human immunodeficiency virus infection were excluded, as were those expected to survive <6 months, refusing vaccination, or in receipt of immunosuppressive medications.

Patients were randomly assigned to receive the conventional dose (40 μg) or extra-high dose (80 μg) Engerix-B administered intramuscularly into the deltoid muscle at 0, 1, and 6 months. A single booster dose (40 μg) was given to patients who had a negative antibody response 3 months after treatment.

Medications were recorded at the start of the vaccination. The modified Charlson's Comorbidity Index, which was validated in continuous ambulatory peritoneal dialysis patients, was used. Adequacy of peritoneal dialysis was determined by measuring Kt/V using the standard method. Serum albumin was measured using the bromocresol purple method, and normalised protein nitrogen appearance (nPNA) was calculated using the modified Bergstrom formula and normalised to ideal body weight. The residual glomerular filtration rate was calculated as a mean of the 24-hour urinary urea and creatinine clearance using standard methods.

Blood samples were collected 3, 6, and 12 months after completion of vaccination to measure anti-HBs using a commercial kit with enzyme immunoassay (Cobras Core Anti-HBs Quant EIA II; Roche Diagnostics GmbH, Mannheim). All laboratory personnel were blinded to the group assignment of the sera.

Seroconversion and seroprotection were defined as anti-HBs levels of ≥10 IU/L 3 and 12 months after completion of vaccination, respectively. Comparisons were made between patients with an anti-HBs level of ≥10 IU/L or <10 IU/L with regard to the diabetes mellitus rate, Charlson's Comorbidity Index, age, dialysis adequacy, nutritional status, and residual renal function after hepatitis B vaccination.

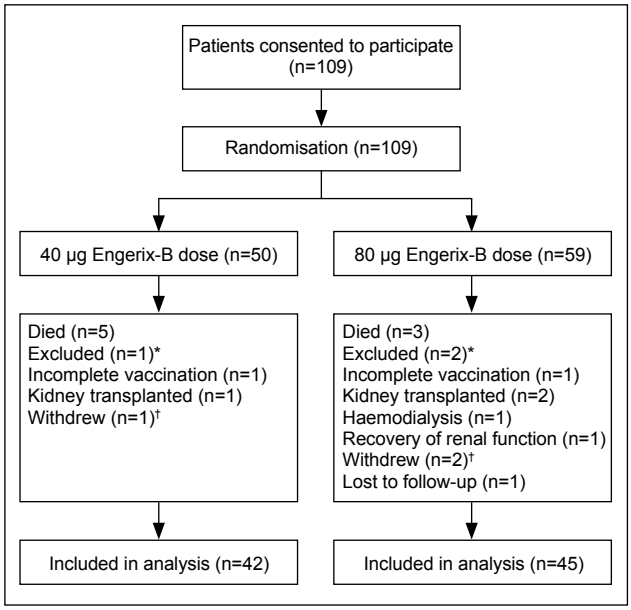

Fig. Enrolment, randomisation, and follow-up of participants
* Missing antibody to hepatitis B surface titres data
† Protocol violation because of occult hepatitis B

Results

Of the 109 patients, 87 completed the vaccination (Fig). Dropouts were related to the physical condition of the patients (death, renal recovery, transplantation, or switch to haemodialysis), protocol violation, or loss to follow-up. None of the dropouts was vaccine- or procedure-related.

Of the 87 patients, 41% were female, and 52% had diabetes mellitus. Forty-two patients received the conventional dose (40 µg) and 45 received the extra-high dose (80 µg) Engerix-B. Baseline characteristics of the two groups did not differ significantly, except for a higher percentage of human recombinant erythropoietin use in the extra-high-dose group.

The immune response was assessed by anti-HBs titre at 3 and 12 months after treatment. Overall, 70.1% of the patients achieved seroconversion; seroprotection rates decreased over time in both groups. At 3 months after treatment, 78.6% of the patients receiving the conventional dose and 62.2% of the patients receiving the extra-high dose achieved seroconversion (P=0.11). At 12 months after treatment, persistence of protective anti-HBs did not differ significantly in the two groups (45.2% vs 51.1%, respectively, P=0.67).

The geometric mean antibody titres were estimated longitudinally. The anti-HBs geometric mean titres elicited 3, 6, and 12 months after treatment did not differ significantly in the two groups (P>0.50 at all time points). For example at 12 months, the anti-HBs geometric mean titres in the respective groups were 18.1 (95% CI, 15.1-21.2) and 18.2 (95% CI, 15.2-21.1) IU/L (P=1.00). Repeated measures analysis of variance confirmed no significant difference in antibody titres between the groups throughout the study period.

Table. Univariate comparison of patients with antibody to hepatitis B surface (anti-HBs) levels of ≥10 IU/L or <10 IU/L 3 and 12 months after completion of vaccination

Parameter	3 months after completion of vaccination			12 months after completion of vaccination		
	Patients with anti-HBs levels of ≥10 IU/L	Patients with anti-HBs levels of <10 IU/L	P value	Patients with anti-HBs levels of ≥10 IU/L	Patients with anti-HBs levels of <10 IU/L	P value
No. of subjects	61	26	-	42	45	-
No. of males:females	33:28	18:8	0.24	21:21	30:15	0.13
Mean±SD patient age (years)	59.1±9.5	60.6±13.4	0.61	58.3±10.8	60.6±10.7	0.32
Median (range) duration of dialysis (years)	0.46 (0.11-1.74)	0.32 (0.09-1.75)	0.65	0.36 (0.11-1.59)	0.36 (0.11-2.08)	0.92
Mean±SD body mass index (kg/m^2)	25.4±6.3	25.7±4.1	0.80	25.5±4.1	25.5±6.2	0.99
% of patients with diabetes mellitus	47.5	61.5	0.25	47.6	55.6	0.52
Mean±SD serum albumin at baseline (g/L)	35.8±5.2	34.0±6.3	0.16	35.7±4.8	34.9±6.2	0.50
Mean±SD Charlson's Comorbdity Index	4.9±1.9	5.7±2.0	0.07	4.9±2.0	5.4±1.9	0.22
% of patients receiving human recombinant erythropoietin	16.4	15.4	1.00	21.4%	11.1%	0.25
Mean±SD haemoglobin level at baseline (g/dL)	9.0±1.4	8.9±1.8	0.82	8.9±1.5	9.0±1.5	0.71
Mean±SD residual glomerular filtration rate (mL/min/1.73 m^2)	3.02±2.37	4.17±3.46	0.28	3.23±2.50	3.38±2.95	0.84
Mean±SD total Kt/V	2.2±0.5	2.1±0.8	0.79	2.3±0.5	2.1±0.6	0.12
Mean±SD normalised protein nitrogen appearance (g/kg/day)	1.16±0.25	0.96±0.23	0.001	1.18±0.24	1.03±0.25	0.007
Mean (95% CI) anti-HBs geometric mean titres 3 months after treatment (IU/L)	-	-	-	357 (356-359)	9 (7-11)	<0.00001

Patients with higher baseline nPNA were more likely to achieve an anti-HBs level of ≥10 IU/L 3 months after treatment (Table). The mean nPNA was significantly higher in patients with seroconversion than in those without seroconversion (1.16±0.25 vs 0.96±0.23 g/kg/day, P=0.001). Patients with an nPNA at least 1 g/kg/day were four times more likely to develop seroconversion (odds ratio, 4.01; 95% CI, 1.48-11.00; P=0.006). Higher total Kt/V and residual renal function did not improve the chance of developing a seroprotective anti-HBs titre. The primary seroconversion rate did not correlate with patient age. Patients with primary seroconversion tended to have a slightly lower Charlson's Comorbidity Index (4.9±1.9 vs 5.7±2.0, P=0.07).

At 12 months after treatment, the baseline nPNA was also significantly higher in patients with a persistent seroprotective anti-HBs level of ≥10 IU/L than in those with the level <10 IU/L (1.18±0.24 vs 1.03±0.25 g/kg/day, P=0.007). Patients with and without diabetes did not differ significantly with respect to persistent seroprotective anti-HBs levels. Baseline serum albumin concentration, haemoglobin level, Charlson's Comorbidity Index, total Kt/V, and residual renal function did not influence the persistence of anti-HBs seroprotection. The geometric mean titres of anti-HBs 3 months after treatment differed significantly in patients with and without persistent seroprotection 12 months after treatment (357 vs 9 IU/L, P<0.00001, Table).

Discussion

Although beneficial effects of extra-high dose recombinant hepatitis B vaccination has been reported,[1] this study did not confirm such finding. Primary seroconversion and persistent seroprotective anti-HBs antibody titres were similar in patients receiving conventional or extra-high dose hepatitis B vaccination. By contrast, the amount of dietary protein intake, as measured by nPNA, was predictive of the response.

Increased nPNA was associated with a higher rate of primary seroconversion and maintenance of a seroprotective anti-HBs titre. Reasons for the impaired immunological response in those with protein-energy malnutrition include lower granulocyte-macrophage colony stimulating factor (GM-CSF), among other relevant cytokine responses. Data from animal and human studies indicate that protein-energy malnutrition leads to deficiency or impaired response of GM-CSF.[3] Administration of GM-CSF to end-stage renal disease patients significantly improves the hepatitis B vaccine response rate and achieves an earlier seroconversion following vaccination.[4]

One limitation of our trial related to patient selection. The mean patient age was 60 years, which was much older than the cohort in our previous study (mean age, 43 years).[1] In patients on dialysis, poor response to hepatitis B vaccine correlates with old age.[1] This is further supported by a meta-analysis of end-stage renal disease patients.[5] Therefore, the primary seroconversion rate was lower (70.1%) and long-term immunogenicity was less impressive (48.3% at one year) in this study than in the previous study. Nonetheless, our subjects were representative of the 'real-world' scenario. Recognising the benefits of vaccination at an earlier stage of chronic kidney disease, more younger patients had received hepatitis B vaccination before the start of dialysis therapy.

In conclusion, we found no evidence to support routine extra-high dose intramuscular hepatitis B vaccination, but this needs to be balanced against the fact that our study was underpowered.

Acknowledgements

This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#06060072). We thank Ms Shirley Sun Kiu Tsang for the clerical support. Results of this study have been published in: Chow KM, Lo SH, Szeto CC, et al. Extra-high-dose hepatitis B vaccination does not confer longer serological protection in peritoneal dialysis patients: a randomized controlled trial. *Nephrol Dial Transplant* 2010;25:2303-9.

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