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Original Article

Comparing immune response of intradermal low dose versus intramuscular high dose of hepatitis B vaccination in hemodialysis patients

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Abstract

BACKGROUND: Hepatitis B is the most important cause of cirrhosis in developing countries. Hemodialysis patients are susceptible to infection due to repeated contact with dialysis machines and blood products. The aim of this study was to compare the efficacy of intradermal low dose with intramuscular high dose hepatitis B vaccination in hemodialysis patients.

METHODS: In a cross-sectional study on 24 hemodialysis patients that not responded to conventional method of vaccination in this center (double dose in 0, 1 and 6 months) and have antibody titer less than 10 mu/ml were enrolled to intramuscular or intradermal group, randomly. In intradermal (ID) group 10 µg (0.5 ml) recombinant vaccine, every 2 weeks to 6 months and in intramuscular (IM) group 40 µg (2 ml) at 0, 1, 2, and 6 months were prescribed and antibody titer were checked after 1 and 3 months of the end of vaccination.

RESULTS: Mean HBS antibody titer in patients was 4.4 ± 3.1 mu/ml at the beginning of study (minimum: 1.1 mu/ml and maximum: 9.2 mu/ml) and after 1 month and 3 months, mean HBS antibody were 190.4 ± 59 and 223.3 ± 83.9, respectively ($p < 0.001$). After one month, in intradermal and intramuscular groups, mean HBS antibody was 198.8 ± 75.6 mu/ml and 181.2 ± 61.8 mu/ml, respectively ($p = 0.5$) and after 3 months it was 230 ± 76 mu/ml and 216.2 ± 94.3 mu/ml, respectively ($p = 0.83$).

CONCLUSIONS: Antibody titer was high (> 50 mu/ml) in two groups after 1 and 3 months of vaccination and no significant difference was found between the 2 groups. Therefore, two methods of vaccination (high dose IM and low dose SC) are equally effective and the selection of vaccination method is based on health policy.

KEYWORDS: Hepatitis B, Hemodialysis, Vaccination, Intradermal, Intramuscular.

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Hepatitis B is the most important cause of cirrhosis in developing countries.[1] Complications of this infection are chronicity, hepatocellular carcinoma and chronic active hepatitis.[2] Blood and other secretions of patients have virus and are infective.[3,4] The most important sources of infections are blood, saliva and semen.[5] Hospital equipments such as mechanical ventilators, endoscopes, and hemodialysis machines can transmit this viral infection.[6,7] Hemodialysis patients are susceptible to infection due to repeated contact with dialysis machines and blood products.[2,8,9] Intramuscular (deltoid) vaccination in months 0, 1 and 6 is the standard method and after immunization, HBS antibody titer should be greater than 10 mu/ml.[10] Approximately 90-95% of healthy people and 45-50% of dialysis patients properly respond to vaccination.[11,12] To increase efficacy of vaccination in dialysis patients, different methods of vaccination such as high dose of intramuscular, subdermal, intradermal and adding adjuvant as erythropoietin or interleukin have been administrated.[13,14]

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Table 1. Demographic Characteristics of Patients

Variable	Intramuscular Group	Intradermal Group	P
Number of Patients	12	12	1.00
Gender Male	7	7	1.00
Female	5	5	1.00
Age (year)	55.9±16.7	54.4±21	0.85
Body Mass Index (BMI) (kg/m²)	23.9±4.4	22.7±4.1	0.39
Dialysis Duration (months)	52.5±56.8	45±22.5	0.68

Methods

In a cross-sectional study in 78 hemodialysis patients of Hajar Hospital of Shahrekord University of Medical Sciences, 24 patients that did not respond to conventional method of vaccination in this center (double dose in 0, 1 and 6 months) and had antibody titer less than 10 mu/ml, were enrolled to intramuscular or intradermal group, randomly. In intradermal (ID) group, 10 µg (0.5 ml) recombinant vaccine was prescribed every 2 weeks to 6 months and in intramuscular (IM) group, 40 µg (2 ml) at 0, 1, 2 and 6 months were prescribed and the antibody titers were checked after 1 and 3 months of the end of vaccination. Inclusion criteria were age greater than 18 years and having at least 3 months dialysis. Exclusion criteria were as follows: 1- incompliance during study, 2- vaccination with methods other than conventional 3 doses, and 3- injection of booster dose. After the end of study, data were entered to SPSS software (Statistical Package for the Social Sciences, version 13.0 SPSS Inc, Chicago, IL) and Mann-Whitney and Spearman tests were used for statistical analysis. All data and information were confidential and for vaccination, an informed consent was taken from the patients. This study was approved in ethic committee of Shahrekord University of Medical Sciences.

Results

In 24 patients studied (14 males and 10 females), mean age was 55.1 ± 18.6 years. Mean age of the patients in the two groups had no significant difference (p = 0.85). Cause of renal failure in 10 patients was diabetic nephropathy, in 8 patients was hypertensive nephrosclerosis, in 2 patients was chronic glomerulonephritis and in 4 patients was unknown.

Mean body mass index (BMI) was 23.3 ± 4.2 and there was no significant difference between the two groups (p = 0.39). Mean HBsAg specific antibody titer in patients was 4.4 ± 3.1 mu/ml at the beginning of study (minimum of 1.1 mu/ml and maximum of 9.2 mu/ml) and after 1 month and 3 months, mean HBsAg antibody titer was 190.4 ± 59 and 223.3 ± 83.9, respectively (p < 0.001). After one month, in intradermal and intramuscular groups, mean HBsAg antibody was 198.8 ± 75.6 mu/ml and 181.2 ± 61.8 mu/ml, respectively (p = 0.5) and after 3 months, was 230 ± 76 mu/ml and 216.2 ± 94.3 mu/ml, respectively (p = 0.83).

Mean duration of dialysis in patients was 48.6 ± 46.6 months (minimum of 7 and maximum of 217).

Three patients had hepatitis C. Fifty patients were 50 years or more than 50 years old and 10 patients had less than 50 years. There was no correlation between age and antibody titer (Table 1).

Duration of dialysis in 11 patients was less than 36 months and in 13 patients was equal or more than 36 months. Mean HBsAg antibody titer after one month in the above two groups was 221.5 ± 37.7 mu/ml and 158.6 ± 47.8 mu/ml, respectively (p = 0.01) and after 3 months was 251.4 ± 61.2 mu/ml and 193.9 ± 90.7 mu/ml, respectively (p = 0.17). Frequency of dialysis was 2 times per week in 5 patients and 3 times per week in 19 patients. There was no significant correlation between frequency of dialysis and HBsAg antibody titer (Table 2).

Table 2. Mean antibody titer after 1 and 3 months of the end of vaccination based on vaccination method, age and gender

Time	Vaccination method – Age– Gender	Mean antibody titer	Standard deviation	P
1 month after the end of vaccination	Intradermal	194.7	56.9	0.5
	Intramuscular	176.4	61.5	
3 months after the end of vaccination	Intradermal	225.8	75.8	0.83
	Intramuscular	211.4	93.1	
1 month after the end of vaccination	Less than 50 years	202	50	0.38
	50 years and older	175.7	63	
3 months after the end of vaccination	Less than 50 years	266.6	35	0.039
	50 years and older	188.2	91	
1 month after the end of vaccination	Male	193.9	58	0.47
	Female	175.6	60.7	
3 months after the end of vaccination	Male	217	78	0.9
	Female	221.3	93	

Discussion

The aim of our study was comparison of two methods of hepatitis B vaccination. Different methods of vaccination have been offered to increase the rate of seroconversion in hemodialysis patients. In Morais et al study, patients with antibody titer less than 10 mu/ml were recived low dose of intradermal HB vaccinne and in 82% of patients, antibody titer were greter than 10 mu/ml and age, duration of dialysis, smoking, and BMI of patients had no correlation with antibody titer.[15] In 35 dialysis patients, intradermal vaccination led to seroconvertion in 96% of patients in Mat et al study.[16] In Sorkhi et al study, low dose intradermal and subcutaneous vaccination caused less seroconversion versus intramuscular method.[17] In Fabrizi et al study, incresed dose of Engrix from 20 to 40 µg, increased the seroconversion rate.[18] Chou showed that low dose hepatitis B vaccination incresed HBS antibody titer in the first 6 months but decresed it during the next 2 years.[19] In Sombonsilip et al study, there was no difference between ID or IM vaccination and two methods were equally effective in seroconversion.[20] Beleed showed that boster dose of vaccine is effective in efficacy of vaccination and is essential each year.[21] In Choy et al study, in 24 dialysis patients that did not respond to IM method, ID vaccination with IM booster dose was effective.[22] In Fabrezi et al study, age of patients was not correlated with seroconversion rate[23]and in our study also similar result was achieved. In our study, BMI and dialysis frequency per week had no correlation with antibody titer; these results are comparable with Morais et al study results.[15] Three patients had hepatitis C and in these patients, antibody titer was not different with that in other patients but in Bock et al study, antibody titer in these patients were lower than that in other patients.[24] Discrepancy between these results may be due to difference between number of patients in two studies. In our study, antibody titer was high (> 50 ul/ml) in two groups after 1 and 3 months

of vaccination and no significant difference was observed between the 2 groups. Results of this study correlated with Sorkhi et al[17] and Choy et al[22] studies and different with Chau et al[19] study. In the review study written by Edey et al, results of different methods were illustrated; in some of them, intradermal method had higher rate of antibody titer production.[25] In patients with dialysis duration greater than 36 months, there was lower antibody titer after 1 month (may be due to suppression of immune system by renal failure and dialysis) but this effect was transient and after 3 months of vaccination, this difference disappeared. Probably, dialysis duration has an inhibitory effect on rising HBS antibody titer, transiently. Results of this study showed that two methods of vaccination (high dose IM and low dose SC) are effective and the selection of vaccination method could be based on health policy.

Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

Both authors have carried out the study, participated in the design of the study and acquisition of data performed the statistical analysis and wrote the manuscript. Both authors read and approved the final manuscript.

References

1. Raymond T, Daniel k. Cirrhosis and Its Complications. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al, Editors. Harrison's Principles of Internal Medicine. New York: McGraw-Hill; 2008. p. 1971-9.
2. Dien S, Kurtj I. Acute Viral Hepatitis. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL et al, Editors. Harrison's principles of Internal Medicine. New York: McGraw-Hill; 2008. p. 1822-3, 1932-49.
3. Robinson SW. Hepatitis B and D virus. In: Mandell GL, Bennett JE, Dolin R, Editors. Principles and Practice of Infectious Diseases. New York: Churchill Livingstone; 2004: 1406-13.
4. Dufour DR. Evaluation of liver function and injury. In: Henry JB, Davey FR, Herman CJ, McPherson RA, Pincus MR, Threatte GA, et al, Editors. Clinical Diagnosis and Management by Laboratory Methods. New York:WB. Saunders; 2001. p. 264-80.
5. Carrilho FJ, Moraes CR, Pinho JR, Mello IM, Bertolini DA, Lemos MF, et al. Hepatitis B virus infection in Haemodialysis Centres from Santa Catarina State, Southern Brazil. Predictive risk factors for infection and molecular epidemiology. BMC Public Health 2004; 4: 13.
6. Rosini N, Mousse D, Spada C, Treitinger A. Seroprevalence of HbsAg, Anti-HBc and anti-HCV in Southern Brazil, 1999-2001. Braz J Infect Dis 2003; 7(4): 262-7.
7. Horvat RT, Tegtmeier GE. Hepatities B and D viruses. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, Editors. Manual of Clinical Microbiology. Washington: American Society Microbiology, 1999: 1464-7.
8. Sali S. HBV Vaccination in chronic renal failure patients. Hepatitis Monthly 2006; 6(1): 25-9.
9. Sav T, Gursoy S, Torun E, Sav NM, Unal A, Oymak O, et al. Occult HBV infection in continuous ambulatory peritoneal dialysis and hemodialysis patients. Ren Fail 2010; 32(1): 74-7.
10. McNulty CA, Bowen JK, Williams AJ. Hepatitis B vaccination in predialysis chronic renal failure patients a comparison of two vaccination schedules. Vaccine 2005; 23(32): 4142-7.
11. Fabrizi F, Di Filippo S, Marcelli D, Guarnori I, Raffaele L, Crepaldi M, et al. Recombinant hepatitis B vaccine use in chronic hemodialysis patients. Long-term evaluation and cost-effectiveness analysis. Nephron 1996; 72(4): 536-43.
12. Vlassopoulos D. Recombinant hepatitis B vaccination in renal failure patients. Curr Pharm Biotechnol 2003; 4(2): 141-51.
13. Sennesael JJ, Van der NP, Verbeelen DL. Treatment with recombinant human erythropoietin increases antibody titers after hepatitis B vaccination in dialysis patients. Kidney Int 1991; 40(1): 121-8.
14. Kayatas M. Levamisole treatment enhances protective antibody response to hepatitis B vaccination in hemodialysis patients. Artif Organs 2002; 26(6): 492-6.
15. Morais EO, Resende MR, Oliveira AM, Sinkoc VM, Garcia MT, Angerami RN, et al. Intradermal hepatitis B

vaccination in patients with advanced chronic renal failure: immunogenicity and follow-up. Aliment Pharmacol Ther 2007; 25(7): 849-55.
16. Mat O, Mestrez F, Beauwens R, Muniz-Martinez MC, Dhaene M. Primary high-dose intradermal hepatitis B vaccination in hemodialysis: cost-effectiveness evaluation at 2 years. Hemodial Int 2006; 10(1): 49-55.
17. Sorkhi H, Dooki MR, Ebrahimnejad MS. Low-dose intradermal and subcutaneous versus intramuscular hepatitis B vaccination in primary non-responding hemodialysis patients. J Med Assoc Thai 2006; 89(10): 1648-53.
18. Fabrizi F, Dixit V, Magnini M, Elli A, Martin P. Meta-analysis: intradermal vs. intramuscular vaccination against hepatitis B virus in patients with chronic kidney disease. Aliment Pharmacol Ther 2006; 24(3): 497-506.
19. Chau KF, Cheng YL, Tsang DN, Choi KS, Wong KM, Chak WL, et al. Efficacy and side effects of intradermal hepatitis B vaccination in CAPD patients: a comparison with the intramuscular vaccination. Am J Kidney Dis 2004; 43(5): 910-7.
20. Somboonsilp W, Eiam-Ong S, Tungsanga K, Tirawatanapong T. Immune response of intradermal hepatitis B vaccination at lower dose versus intramuscular vaccination at double standard dose in predialytic chronic renal failure patients. J Med Assoc Thai 2003; 86(12): 1122-7.
21. Bel'eed K, Wright M, Eadington D, Farr M, Sellars L. Vaccination against hepatitis B infection in patients with end stage renal disease. Postgrad Med J 2002; 78(923): 538-40.
22. Choy BY, Peiris JS, Chan TM, Lo SK, Lui SL, Lai KN. Immunogenicity of intradermal hepatitis B vaccination in renal transplant recipients. Am J Transplant 2002; 2(10): 965-9.
23. Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G. Meta-analysis: the effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. Aliment Pharmacol Ther 2004; 20(10): 1053-62.
24. Bock M, Barros E, Veronese FJ. Hepatitis B vaccination in haemodialysis patients: a randomized clinical trial. Nephrology (Carlton) 2009; 14(3): 267-72.
25. Edey M, Barraclough K, Johnson DW. Review article: Hepatitis B and dialysis. Nephrology 2010: 15(2): 137-45.