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Hepatitis B Vaccination in Responsive and Non-Responsive Patients with End-Stage Kidney Disease undergoing Hemodialysis

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Abstract

Background Hepatitis B virus (HBV) vaccination is known as the best way to prevent the spread of the Hepatitis B virus in hemodialysis centers.

Objective To study the effectiveness of the Euvax B vaccine in end-stage kidney disease (ESKD) Iraqi patients on hemodialysis already not responded to a series of doses of HBV vaccination before, using a different route of administration.

Methods Forty-six ESKD patients on hemodialysis who did not respond to previous intramuscular HBV vaccination (defined as patients who had a series of intramuscular HBV vaccination doses and anti-hepatitis B virus surface antibody <10 IU/ml) were chosen. All 46 patients started on a new regimen of 4 doses of intramuscular recombinant HBV vaccination (Euvax B) 40 µg (double the regular dose for the non-dialysis population) at 0, 1, 2, and 6 months' interval. The immune response has been studied after 2 and 4 doses. Patients who did not respond to all four doses had started intradermal vaccination of a 5 µg weekly dose for 8 weeks.

Results Twenty-seven ESKD patients had responded to 2 doses of intramuscular doses (59%), while (70%) developed a response after completing 4 doses (P 0.001). Intramuscular injections are more effective with patients on hemodialysis for less than two years (P 0.02). Fourteen patients (who did not respond to Intramuscular doses) started on Intradermal administration of Euvax B, and nine patients (64%) responded to it.

Conclusion Starting four doses of intramuscular HBV vaccination is effective and gives better outcomes if it is done in the early years of hemodialysis. Moreover, the intradermal route of administration of Euvax B is also effective for those who have not responded to intramuscular vaccination cycles.

Keywords Hepatitis B vaccination, ESKD, Euvax B, hemodialysis, non-responders, intradermal route

List of abbreviations: ELISA = Enzyme linked immunosorbent assay, ESKD = End-stage kidney disease, HBV = Hepatitis B virus, ID = Intradermal injection, IM = Intramuscular injection

Introduction

Patients end-stage kidney disease (ESKD) on hemodialysis have an impaired immune response to hepatitis B virus (HBV) vaccination. In fact, even with higher vaccine doses, only 50-85% of dialysis patients achieve a protective titer (>10 IU/L) after hepatitis B vaccination [(1)]. The anti-hepatitis B surface antibody (anti HBs antibody) titer of ≥10 IU/L is generally regarded as a sign of protective immunity, such as a level dose not necessarily imply full protection against HBV infection, especially in poor responders and immunocompromised patients with

breakthrough infection possible [2,3]. Individuals who develop an anti-HBs titer <10 IU/L after 3 doses of vaccine are defined as "non-responders". Many factors could cause a non-response to the HBV vaccination, such as administration of the vaccine in the buttocks, impaired vaccine storage conditions, drug abuse, smoking, infections and obesity [4].

The important role of genetic factors in predisposing to hepatitis B vaccine unresponsiveness. These factors are represented by specific human leukocyte antigen (HLA) haplotypes and by single-nucleotide polymorphisms in genes encoding cytokines, cytokine receptors, and toll-like receptors [5,6]. Many vaccines are administered by the intramuscular (IM) route, although the muscle is a poorly immunogenic organ [7,8]. On the other hand, the skin is a more immunogenic site for vaccination due to the presence in the dermis of dendritic cells, capable of presenting antigens and stimulating innate and adaptive immune responses. In fact, skin protects the body from microbial infection using both its physical barrier and its immunological function performed by dendritic cells [9].

For ESKD patients who do not respond to six doses of vaccine, there is no evidence about the use of further IM doses. Different strategies have been suggested in order to increase the vaccine-induced seroconversion rate in patients with advanced CKD. In particular, the intradermal (ID) route vaccination was studied either alone or in combination with the conventional IM route [10].

The study aimed to determine the efficacy of the recombinant hepatitis B vaccine (Euvax B) in chronic hemodialysis patients who did not respond to standard IM HBV vaccination, and to evaluate whether alternative vaccination strategies, specifically repeated high-dose IM administration followed by ID vaccination, can enhance the serological response (anti-HBs ≥10 IU/L).

Methods

Patients

A cross-sectional study included 46 selected patients from the list of patients with anti-HBs <10 IU/L. Patients are on hemodialysis in Al-Kadhimein Medical City in Baghdad, Iraq. Patients had 3 or 4 doses of HBV vaccination last year, but they did not show a response. All 46 patients were put on IM doses of 40 µg at 0, 1st, 2nd, and 6th month starting from January 2016. Afterwards, those who would not respond to IM doses would be put on ID injection 5 µg doses for 8 weeks.

Data collection

Consent has been taken from all patients. The nurse has been trained to give vaccinations in a safe and correct way. Patients started on 0,1,2,6 regimes with 40 µg of Euvax B, at the deltoid muscle after sterilization of the area with alcohol and gauze. Deep IM injection delivered, and sterile cotton with pressure and plaster dressing applied. After two IM doses (one month apart) and just before the third dose (at 28 days from the second dose), a blood sample was tested for anti-HBV surface antibody by enzyme linked immunosorbent assay (ELISA). Similarly, after 28 days from the fourth IM dose (last dose), another blood sample was taken from the patients.

Of the 46 patients who had finished 4 doses of IM Euvax B, 14 patients showed anti-HBs <10 IU/L.. Those had been put on ID vaccination regimes. The nurse had been informed the correct way to administer 5 µg weekly ID after sterilizing the skin on the arm of the patient. This lasts for 8 weeks for the 14 patients, followed by a blood sample after 28 days from the last ID dose. Blood sample tested for anti-HBV surface antibody by ELISA.

Statistical analysis

All data has been collected and entered into a computer using the statistical package for social sciences (SPSS) software, version 25. The relation between different variables (age, sex, hemodialysis access, adequacy and duration of

hemodialysis, nutritional and inflammatory markers) and the response to vaccination has been studied. Chi-square test has been used to compare between variables, with a P value less than 0.05 considered significant.

Results

IM HBV vaccination

A total of 46 people in the study were on hemodialysis; there were 28 men (61%) and 18 women (39%) among the patients. Twenty males (44%) and twelve females (26%) of the immunized patients developed a protective immune response. On the other hand, 8 men (17%) and 6 women (13%) did not get vaccinated after the vaccination. There was no significant link between sex and vaccine response (P = 0.7) (Table 1).

Table 1. Comparison of response to four doses intramuscular hepatitis B vaccination according to sex of patients

Patients	Male N (%)	Female N (%)	P value
Immunized	20 (44.0)	12 (26.0)	0.7
Non-immunized	8 (17.0)	6 (13.0)	
Total	28 (61.0)	18 (39.0)	

In regard to age, 29 patients (63%) were under 65 years old, and 17 patients (37%) were 65 years old or older. Of the immunized patients, 21 (46%) were under 65 years old, and 10 (21%) were 65 years old or older. There were 8 non-immunized patients (17%) who were under 65 years old and 7 patients (16%) who were 65 years old or older. The average age of the people in the study was 48.8 years, plus or minus 17.2 years. Statistical analysis showed that there was no significant link between age group and vaccine response (P = 0.5) (Table 2).

Table 2. Comparison of response to four doses intramuscular hepatitis B vaccination according to age of patients

Patients	<65 years old N (%)	≥65 years old N (%)	Mean±SD	P value
Immunized	21 (46.0)	10 (21.0)	48.8±17.2	0.5
Non-immunized	8 (17.0)	7 (16.0)		
Total	29 (63.0)	17 (37.0)		

Fifty-nine percent of patients (27 patients) showed a response to two doses of IM injections. The percentage had increased to 70% after completing the four vaccination strategies. This is significant (P value = 0.001) (Table 3).

Table 3. Comparison of response to intramuscular hepatitis B vaccination according to number of vaccination doses

Intramuscular hepatitis B vaccination	Immunized N (%)	Non-immunized N (%)	Total N (%)	P value
2 doses	27 (59.0)	19 (41.0)	46 (100)	0.001
4 doses	32 (70.0)	14 (30.0)	46 (100)	

In regard to how long they had been on hemodialysis, 31 patients (67%) had been on it for less than two years, and 15 patients (33%) had been on it for two years or more. Of the immunized patients, 25 (54%) had been on hemodialysis for less than two years, while 7 (15%) had been on dialysis for two years or more. On the other hand, 6 of the non-immunized patients (13%) had been on dialysis for less than two years, and 8 of the non-immunized patients (17%) had been on dialysis for two years or more. Statistical analysis revealed a significant correlation between the duration of hemodialysis and vaccine response (P = 0.02), indicating that patients with a shorter duration of dialysis were more inclined to develop a protective immune response to HBV vaccination (Table 4).

Table 4. Comparison of response to intramuscular hepatitis B vaccination according to years on hemodialysis

Patients	<2 years N (%)	≥2 years N (%)	P value
Immunized	25 (54.0)	7 (15.0)	0.02
Non-immunized	6 (13.0)	8 (17.0)	
Total	31 (67.0)	15 (32.0)	

ID Hepatitis B Vaccination

Fourteen patients started on ID vaccination. Nine of them showed a response (64%), while five of them did not show a response to vaccination (36%).

There was no statistically significant difference between intradermal vaccination response and any of the variables taken (sex and age).

Discussion

The current study assessed the immunogenic response to the recombinant hepatitis B vaccine Euvax B in patients undergoing maintenance hemodialysis who had previously not responded to standard vaccination protocols. In this study, IM HBV vaccination shows 59% response from two doses one month apart. In comparison, Chancharoenthana et al. [11] showed 48% response in non-responder hemodialysis patients in 2025.

In present study, sex did not have a significant impact on the immune response to vaccination. While males represented the predominant segment of the study population (61%), the response rates were similar between males and females. This finding indicates that sex-related immunologic differences may not significantly influence hepatitis B vaccine responsiveness in hemodialysis patients, aligning with a previous report that suggest factors associated with immune dysfunction in renal failure are more critical determinants of vaccine response than sex [12].

After finishing the four doses of IM HBV vaccination for 46 patients, 70% of the patients are immunized. Puri et al. [12] showed only 34.5% response to 26 patients treated with 40 µg by IM route at 0, 1, 2 and 6 months. On the other hand, a recent study from Brazil vaccinated 42 dialysis patients with 40 µg Euvax B in a similar way (at 0, 1, 2 and 6 months). The study showed 89% response to four doses of IM vaccination.

The study showed a significant statistical difference in the response to IM vaccination based on the duration of hemodialysis; patients who spent less on hemodialysis showed a better response to vaccination. This finding is logical and accepted with another study, since patients spending more time on hemodialysis are liable for more inflammations and infections and a weak immune system [14].

Regarding ID HBV vaccination, for 14 patients who did take 5 µg per dose for 8 weeks, shows 64% response. In comparison, Girndt et al.[15] vaccinated 25 patients with the same dose but for 16 weeks and showed 100% response. Puri et al. [12] used a different approach by using a double dose of 10 µg, seven doses every 2 weeks. In this study, 92% responded at seven months. Puri et al. [13]. Again, a double dose (10 µg) weekly for 8 weeks on 30 patients, 79 % shows response.

Comparing IM versus ID HBV vaccination, Vlassopoulos et al. [16] conducted a meta-analysis on 12 controlled trials in 640 CKD patients. The results showed the ID route had a better outcome.

In conclusion, hemodialysis patients have a weak immune response to vaccination. Patients who did not respond to the first cycles of IM HBV vaccination may have a good chance of responding to the second cycle. Four doses of 40 µg IM Euvax B injection at the deltoid muscle at 0, 1, 2 and 6 months' show promising results. For forty-six non-responder hemodialysis patients, 70% of them were immunized. Moreover, vaccination in the early years of hemodialysis showed a better response. Hence, it will be wise to vaccinate as soon as patients start hemodialysis to limit the spread of Hepatitis B in dialysis centers. Again, for patients who did not respond to two cycles of the IM route, the ID route offers a good chance at about 64%.

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Author contribution

Al-Joher and Dr. Talib contributed to the implementation of the research project, writing the manuscript, contributed to the suggestion of the project idea, interpretation of analytical data, proofreading of research and writing and producing the research in its final form. Dr. Al-Delemi took the clinical history and follow-up from each adult patient.

Conflict of interest

The authors declare most explicitly and transparently that there is no conflict of interest.

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