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Original Article

Response to Hepatitis B Vaccination in Children on Hemodialysis

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ABSTRACT

Background: Following hepatitis B vaccination, dialysis patients show lower production and more rapid decline of protective antibodies compared to healthy individuals. Higher doses of vaccine are therefore recommended for adults with end stage renal disease. The issue has been less well studied in children.

Objective: To assess the efficacy of hepatitis B vaccine in Egyptian children on regular hemodialysis for end stage renal disease (ESRD).

Methods: Three intramuscular doses of hepatitis B vaccine; 20 μg hepatitis B surface antigen each, was investigated in 30 Egyptian children (age 5-13 years) on regular hemodialysis for end stage renal disease (ESRD). Antibody response was assessed after the third dose and antibodies to hepatitis B surface antigen (HBsAB) levels were measured one and three years thereafter.

Results: Initial response with positive HBsAB occurred in 26 patients (87%). Protective antibodies (≥ 10 mIU/mL) were present in 83% of cases after one year and 65% after three years. Antibody response was maintained for three years in all patients who had HBsAB levels of 100 mIU/mL or higher at one year. There was no significant relation between the response to the vaccine and either gender, age, weight, serum albumin, hemoglobin or hepatitis C infection.

Conclusion: A series of three 20 μg doses of hepatitis B vaccine is effective in inducing an appropriate antibody response in most children with ESRD on hemodialysis.

INTRODUCTION

The development of hepatitis B vaccine is considered one of the major achievements of modern medicine[1]. Despite advances in antiviral therapy, only a minority of patients with chronic hepatitis B will have a sustained therapeutic response. Therefore, primary prevention through vaccination is the main method for controlling hepatitis B[2]. Patients treated with chronic hemodialysis represent a well recognized high risk group for hepatitis B infection. Despite the increasing adoption of infection control precautions, new cases of hepatitis B are being encountered in hemodialysis units[3] Vaccination of susceptible hemodialysis patients has thus become a routine practice. It has been widely applied in Egypt from year 1999 as a result of the promulgation of the Ministry of Health & Population[4]. The safety of hepatitis B vaccine has been well established[5,6].

Nevertheless, patients with chronic renal failure (CRF) have impaired immune response, leading to diminished antibody production in response to the usual doses of hepatitis B vaccine indicated for healthy subjects. This has led to a greater dosage recommendation (40 μg of HB surface antigen [HBsAg]) for adults with chronic

renal failure (CRF), but an appropriate dosage for children with CRF has not been established[6].

Based on studies in adults, dialysis patients are more likely to have declining antibody levels following initial response[3]. Although Van Damme P and Van Herck K recently concluded that there is no support for the use of booster doses of hepatitis B vaccine when a complete primary vaccination course is offered to immunocompetent individuals[7], the issue is different in the dialysis population. High risk of exposure, together with declining antibody levels has led many centers to regularly test for hepatitis B surface antibody (HBsAB) in vaccinated individuals.

AIM OF THE WORK

The present study aims to evaluate the efficacy of three intramuscular doses of recombinant hepatitis B vaccine (20 μg HBsAg each), given at 0, 1 and 6 months, in Egyptian children with chronic renal failure undergoing hemodialysis. This includes assessment of the initial antibody response following completion of the series, as well as the antibody levels up to three years following vaccination.

SUBJECTS AND METHODS

This is a prospective study of 30 patients enrolled from Cairo University Center of Pediatric Nephrology and Transplantation (CPNT). Eligible patients were five to 15 years old with end-stage renal disease on regular hemodialysis. Patients were tested for HBsAg before inclusion and those with hepatitis B infection; defined as positive HBsAg at the time of enrollment or at any time before, were excluded from the study.

Patients were subjected to history taking and clinical examination. Routine laboratory studies included assessment of dialysis adequacy using single pool KT/V (urea) by the natural logarithm formula[8], hemoglobin, serum albumin, calcium, phosphorous, alkaline phosphatase and antibodies to hepatitis C virus (HCV) and human immunodeficiency virus (HIV).

Included patients were administered three doses of hepatitis B vaccine. The second and third doses were given one and six months respectively after the first dose. The pediatric formulation of Engerix B, a non-infectious recombinant DNA based vaccine developed by GlaxoSmithKline Biologicals was used. Each dose consisted of one mL of vaccine containing 20 μg purified HBsAg, given intramuscularly (IM) into the deltoid.

Patients were qualitatively tested for antibodies to hepatitis B surface antigen (HBsAg) one month after the third dose using commercially available Enzyme Immunoassay (ELISA) based kits. HBsAB levels were measured one and three years after completing the immunization series. HBsAg, HCV and HIV antibodies were checked every six months.

Data analysis:

Patients who failed to respond by HBsAB seroconversion after the third dose were analyzed as initial non-responders. They were given additional doses of vaccine but were not analyzed further. Patients who were not available for antibody testing after the third dose were excluded; however, those who dropped out later were analyzed

for the available follow up period (initial response with or without one year response). An HBsAB level of 10 mIU/mL or higher was considered positive and a level ≥ 100 mIU/mL or higher indicative of good response[4].

Nominal data were expressed as frequency and percentage and were compared using Chi square test. Quantitative data were expressed as mean and standard deviation and were compared using t test. Pearson's correlations were used to check for association between quantitative data. p values less than 0.05 were considered significant. Predictive roles were assessed using sensitivity, specificity, positive and negative predictive values. Data analysis was assisted with Statistical Package for Social Science (SPSS) version 11 and Microsoft Excel 2003.

RESULTS

Thirty-six patients were evaluated. Four patients were excluded because of documented HBsAg positivity prior to vaccination and two did not complete the vaccination series (one died and another continued dialysis at a local center). Thirty patients were thus eligible for evaluating their antibody responses. They included 19 males (63.3%) and 11 females. Their ages ranged between 5 and 13 years (mean ± SD = 8.4 ± 2.18), with body weights ranging between 10 and 38 Kgs (mean ± SD = 20.8 ± 5.81). The etiology of chronic renal failure is shown in table 1. Major associated morbidity included convulsions (8 cases), cardiomyopathy (3 cases) and mental retardation (2 cases).

Figure 1 shows that 26 patients (86.7%) became seropositive for HBsAB upon completing the three doses of vaccine. One year after completing vaccination, one of them was lost to follow up and another became seronegative (HBsAB < 10 mIU/mL).. Three years after vaccination, 23 patients were available for antibody testing, of whom 15 (65.2%) were still positive. Table 2 shows the antibody levels one and three years after completing vaccination. Levels at three years were significantly lower and there was a highly significant correlation between one- and three-year levels (Fig. 2). Maintenance of a good antibody response (≥ 100 mIU/mL) after one year is a powerful predictor of seropositivity at three years (Table 3). Three of four children with antibody levels between 10 and 100 mIU/mL at one year became negative by three years (Fig. 3).

Nine patients (30%) were positive for HCV antibody at the time of enrollment. The mean HBsAB level after three years was lower in HCV positive cases (112.8 ± 257.8 mIU/mL compared to 171.6 ± 266.7 mIU/mL); however, the difference was not significant ($p > 0.10$). Over the duration of the study, seven cases (35%) developed HCV antibody seropositivity. No patient developed HBsAg positivity; apart from three children showing transient post vaccination antigenemia. All three developed HBsAB seroconversion and rapid disappearance of HBsAg.

Table 4 shows that there was no relation between gender, age, weight, serum albumin, hemoglobin or hepatitis C infection and the initial response to the vaccine. Although not reaching statistical significance, responders tend to have higher

KT/V indicating higher efficiency of dialysis. Results were similar regarding responses one and three years after vaccination. There was no significant correlation between HBsAB levels at one year and either age ($r = -0.372$, $p = 0.07$), weight ($r = -0.246$, $p > 0.10$), serum albumin ($r = 0.019$, $p > 0.10$), hemoglobin ($r = 0.107$, $p > 0.10$) or KT/V ($r = 0.383$, $p = 0.07$).

Table 1: Etiology of renal failure in the study group.

Cause	**No.**	**%**
Urinary Tract Disorders*	11	36.7
Glomerulopathies	4	13.3
Cystinosis	3	10
Interstitial Nephritis	1	3.3
PKD	1	3.3
Undefined	10	33.3
Total	**30**	**100**

* Vesico-ureteric reflux and obstructive uropathies PKD = Polycystic kidney disease

Table 2: Hepatitis B surface antibody levels one and three years following vaccination.

	1 yr *(no. = 29)*		**3 yrs** *(no. = 23)*	
	No.	**%**	**No.**	**%**
Negative (< 10 mIU/mL)	**5**	**17.2**	**8**	**34.8**
Positive	**24**	**82.8**	**15**	**65.2**
10 - < 100 mIU/mL	4	13.8	9	39.1
Good response (≥ 100 mIU/mL)	20	69	6	26.1
AB titre (mIU/mL)* *[mean ± SD (range)]*	377.8 ± 366.8 (-ve - >1000)		148.6 ± 258.9 (-ve - 797)	

* $p = 0.01$

Table 3: Prediction of hepatitis B surface antibody status three years after vaccination from early response.

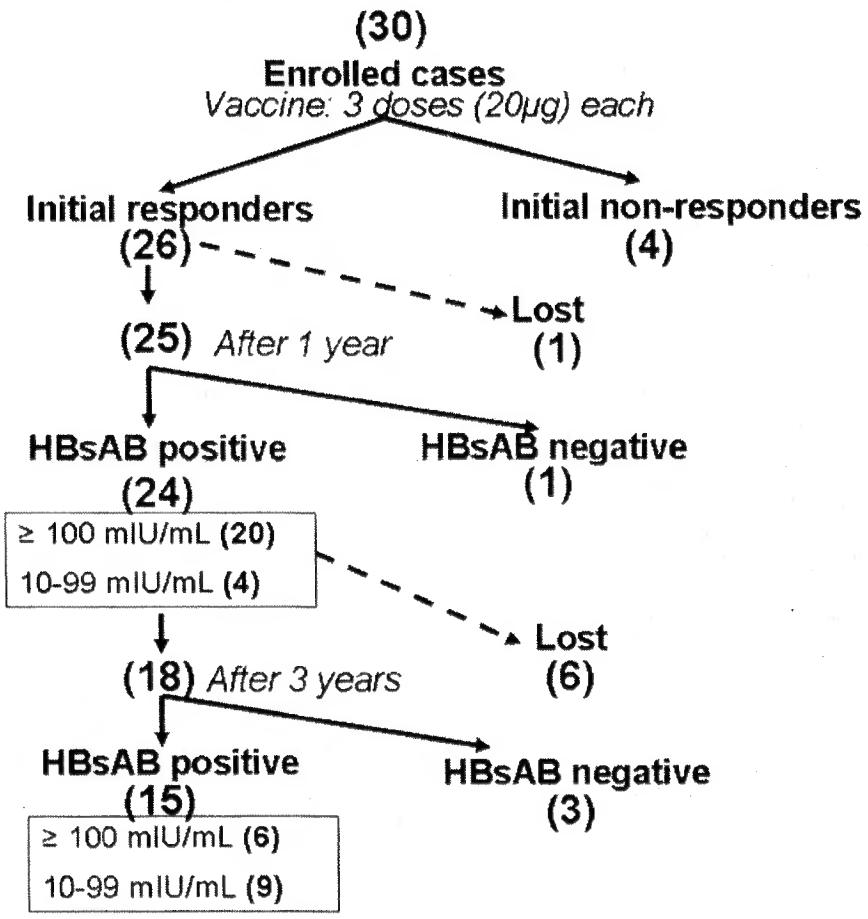
Potential predictor	3 year status	Sensitivity	Specificity	PPV	NPV	accuracy	p value
Initial response	Positive [a]	100	50	78.9	100	82.6	0.003
	Good response [b]	100	23.5	31.6	100	43.4	> 0.10
Good response at 1 year [b]	Positive [a]	93.3	100	100	88.9	95.7	0.0001
	Good response [b]	100	52.9	42.9	100	65.2	0.02

PPV = positive predictive value, NPV = negative predictive value
(a) Positive: HBsAB ≥ 10 mIU/mL (b) Good response: HBsAB 100 mIU/mL or higher
Initial response and good antibody response after one year could predict seropositivity after three years.

Table 4: Potential factors affecting response* to hepatitis B vaccine.

	Responders *(no. = 26)*	**Non-responders** *(no. = 4)*	**Comparison**
Male	16 (61.5 %)	3 (75 %)	p > 0.10
Female	10 (38.5 %)	1 (25 %)	
HCV infection	8 (30.8 %)	1 (25 %)	p > 0.10
Age (yr)†	8.3 ± 2.29	9.3 ± 0.96	p > 0.10
Weight (Kg) †	20.8 ± 6.25	21 ± 1	p > 0.10
KT/V †	1.27 ± 0.22	1.075 ± 0.17	p = 0.06
Albumin (g/dL) †	3.31 ± 0.52	3.4 ± 0.43	p > 0.10
Hemoglobin (g/dL) †	10.03 ± 1.43	9.8 ± 1.03	p > 0.10

* Development of HBsAB positivity after three doses of vaccine
† Mean ± SD



Figures in brackets indicate numbers of patients

Fig. 1: Progression of HBsAB following vaccination.

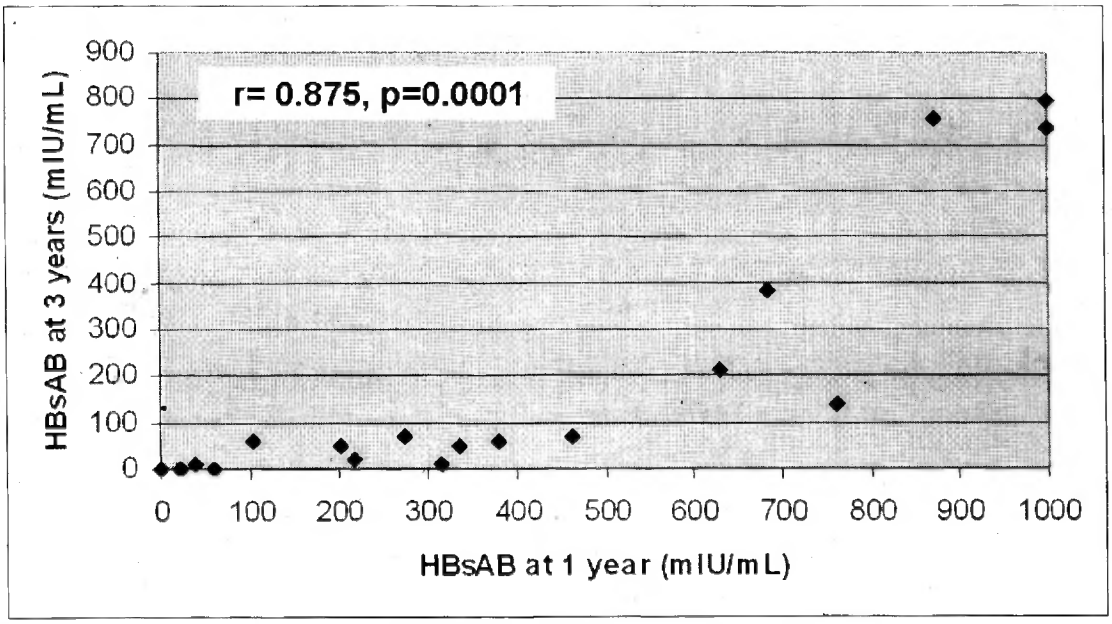


Fig. 2: Correlation between HBsAB levels one and three years after completion of vaccination.

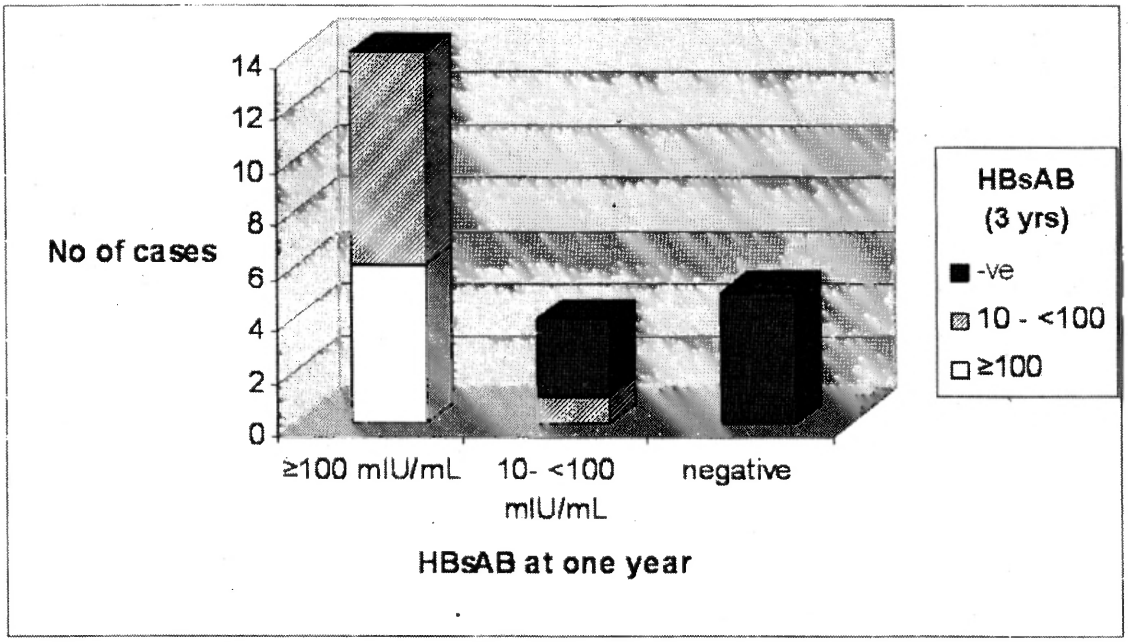


Fig. 3: Relation between HBsAB levels one and three years after vaccination.

All patients who maintained good response (≥ 100 mIU/mL) after one year were positive after three years; while only one of four patients with levels between 10 and 100 mIU/mL at one year remained positive after three years.

DISCUSSION

Prevention of hepatitis B infection in patients with chronic renal failure on hemodialysis requires appropriate immunization[2]. Compared to healthy individuals, these patients show lower production and more rapid decline of protective HBsAB following vaccination. Whereas healthy adults require 20 µg HBsAg per dose of vaccine, a dose of 40 µg is generally used for adults with CRF; albeit with some failures[3,9]. There is no well established dosing regimen for children on hemodialysis. Based on the recommendation of 10 µg for healthy children and adolescents up to 19 years of age[9] and the work of Watkins and colleagues in children with CRF[6], a dose of 20 µg was selected for evaluation in this study. Antibody response to three IM doses of recombinant hepatitis B vaccine (Engerix) was assessed upon completion of the series, one and three years later in thirty children aged 5-13 years on regular hemodialysis.

After the three doses, 87% of patients developed antibodies to HBsAg. One year later, 83% retained HBsAB positivity while 69% of children remained positive after three years. This is comparable to the results reported by Watkins et al. in children with CRF following a similar vaccination protocol[6]. They reported an initial seroconversion rate of 91% decreasing to 88% after a year. Both results indicate that the vast majority of initial responders retained HBsAB positivity after one year. To our knowledge, antibody status after three years was not previously reported in children.

Concerning adult studies, 93% seroconversion was reported in a study from Egypt

using four 40 µg doses[10], while other studies quoted rates around 80%[3,11]. Much lower rates were reported after one year (67% by Kara et al.[3] and 40% by Bel'eed et al.[12]).

Although HBsAB positive individuals with levels between 10 and 100 mIU/mL are sometimes referred to as weak responders[10], an antibody level of 10 mIU/mL is generally considered adequately protective[13]. However, most weak responders became negative by three years after vaccination. All patients who maintained good antibody response (HBsAB ≥ 100 mIU/mL) one year after vaccination retained protective levels at three years (sensitivity 93%, specificity 100%, p = 0.0001). Of all initial responders, 79% were still positive after three years; in accordance with antibody decline by time.

Hepatitis B is one of the compulsory vaccines received by Egyptian children during infancy. Children under the age of five would be expected to have protective HBsAB levels and were not included in this study. In older children, vaccination previously received during infancy might be expected to result in better response to the subsequent series used in the current study. Despite this, four patients failed to respond; in accordance with the immunocompromised state of patients with CRF.

Hepatitis C infection has been reported to be associated with a poor response to hepatitis B vaccination[3,4]. This association was not found in the present study, although HCV positive children had lower HBsAB levels three years after vaccination, with the difference not reaching significance. Over a period of three years, 35% of HCV negative patients developed HCV infection. This agrees with Shatat et al. who reported a HCV seroprevalence of 78.5% in adults on hemodialysis[4]. This; together with HIV and other infectious hazards, emphasizes the fact that vaccination is an essential adjunct but not a replacement for infection control measures.

Several adult studies attempted to identify factors affecting the response to vaccination. Ibrahim et al.[10] found that dialysis efficiency (measured by KT/V) tends to be higher in responders than non responders. The same tendency (albeit not significant) was observed in this study. Treatment with erythropoietin (EPO) was found to augment vaccine response due to reduction in transfusion requirement and concomitant immunosuppression[14]. Because all children in the current study were started on EPO, this association could not be tested. Even if the benefit in terms of vaccine responsiveness is doubtful, adequate dialysis and EPO therapy remain reasonable recommendations. We did not find the previously reported better response in females[4] and in patients with normal serum albumin[3]. Genetic factors have been linked to vaccine responsiveness[1,15] and further studies are needed to address this issue.

Vaccine dose was reported to be the single most important determinant of response. The use of 80 µg in adults improved one year success (Number Needed to Treat = 5.6; compared to 40 µg)[11]. Conversely, the use of 10 µg was associated with an initial response as low as 65%[4]. Hence, a higher dose of 40 µg might improve the response in children. The use of up to three

additional doses has been recommended in healthy non-responders[16] and booster doses were reported to be effective for those who lost protective titers[12]. One or more additional doses of 20 or 40 μg may therefore be considered for non-responders and when protective antibodies are lost. The observation of Watkins et al. that children with CRF who were vaccinated before starting dialysis had better response (with 100% seroconversion after the second dose)[6] makes it reasonable to recommend early vaccination of children with CRF before dialysis becomes needed.

Other potential strategies used in adults for enhancing immunogenicity include intradermal administration of 10% of the IM dose (resulting in lower costs and higher initial response but more rapid antibody decline)[17,18] and the use of levamisole[19].

In conclusion, three IM doses of hepatitis B vaccine (20 μg HBsAg each) administered at 0, 1 and 6 months are effective in 87% of children (5-13 years of age) on hemodialysis. One year after completing the series, very few initial responders (< 5%) will become HBsAB negative and the rest will maintain protective antibodies. Those with HBsAB levels ≥ 100 mIU/mL represent the majority and will not need further evaluation before three years following vaccination. The additional value and cost-effectiveness of using a four-dose series and/or a higher dose (40 μg) warrant further study. Subsequent research may address the best management of non-responders, the long-term management of those with declining antibody levels and whether children below five years who received three doses during infancy need further management.

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