

## Intradermal Hepatitis B Vaccine in Hemodialysis Patients Previously Non-responsive to Intramuscular Hepatitis B Vaccine route

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**Abstract:** *The aim of this study:- Is to determine the response to intradermal hepatitis B virus (HBV) vaccination in individuals on hemodialysis (HD) whom were previously non responders to two or more courses of intramuscular hepatitis B virus (HBV) vaccination.*

**Methods:** *This prospective study included 15 patients (5 males and 10 females) patients on regular HD who previously received at least two courses of intramuscular hepatitis B vaccination and were non responsive. The study, started on May 2011 by intradermal injection of 10 µg Engerix hepatitis B vaccine above deltoid muscle weekly for eight weeks and after two months from last dose, the level of hepatitis B surface antibodies was checked two and six months later. According the result patients will be divided into two groups responder group (> 10 IU/L) and non- responders group (<10 IU/L). The study look at the factors which may affect the responsiveness to hepatitis B vaccination like gender, age, the number of HBV vaccine courses, the duration (years) since starting dialysis until starting the study, presence or absence of hepatitis c virus (HCV) infection, dialysis adequacy (evaluated by Kt/v), the length of hemodialysis session, hemoglobin level, albumin level, parathormone hormone level (pth), serum calcium, serum phosphorus levels and the original renal diseases.*

**Results:** *12 patients were responder ( 80.0% of the total patients number), the non-responders group include 3female patients (20.0% of the patients). The mean age in both the responder and the non-responder group were (56.25±13.71) and (71.33±5.03) years respectively (P value =0.09), HCV status has no effect on responsiveness HCV-ve patients total number eleven (responder 9 and nonresponder 2 ), HCV +ve patients total number four (responder 3 and nonresponder 1) the (P value=0.63), the mean number of HBV vaccine courses previously taken in responders and non responders group were (2.67± 0.98 and 2.67±0.58) respectively (P value=0.69). The mean of HD duration (years) in responders and non responders group were ( 4±1.65 vs 3.33± 1.52) respectively with (P value =0.55), the mean hemodialysis session length (hours) in responders and non responders group were (3.29± 0.26 vs 3.17± 0.29) respectively with ( P value = 0.54), the effect of nutritional status, (serum albumin as indicator) has no significance as the mean in responders and non responders group were ( 35.67± 4.7 vs 33.48±2.16 gm/dl) respectively (P value=0.27). The efficiency of dialysis on responsiveness using kt/v as indicator, the result in non responders higher than responders but without significant importance as shown in the mean and p value of both groups (1.55± 0.13 vs1.37±0.21) respectively ( P value=0.22).The hemoglobin, parathormone hormone, calcium and phosphorus were comparable in both group. More patients were responders compared to female patients with (P value =0.001).*

**Conclusion:** *We report a high response rate (80%) for intradermal HBV vaccination in non responder to intramuscular route of vaccination. We also found the female gender is the only factor, which decrease the response to intradermal HBV vaccine in Saudi HD patient.*

**Keywords:** *HBV vaccination, hemodialysis, intradermal, non-responder, Saudi.*

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### 1. INTRODUCTION

Patients on HD have a well documented impaired immune response to hepatitis B vaccination. These patients have lower seroconversion rates and faster declining titers of hepatitis B virus (HBV) antibodies than individuals who do not have end-stage renal disease; these patients might be at risk of viral and non viral infections due to immune compromised state<sup>1</sup>. The implementation of infection control strategies, the screening of blood donors for hepatitis B virus surface antigen (HBsAg) and antibodies against hepatitis B virus core antigen (anti-HBc) and the use of erythropoietin with the resultant decrease in blood transfusion requirements have resulted in a decreased incidence of hepatitis B virus infection in the HD population from 3% in 1976 to a stable incidence of 0.2% between 1987 and 1991<sup>2</sup>. Low or nonresponse to hepatitis B vaccination is seen in only a small

proportion of people vaccinated with an adequate schedule and has a strong genetic basis<sup>3</sup>. The rate of low or nonresponse to hepatitis B vaccine is much higher in patients with uremia, also if co-infection with hepatitis C seems to further lower the response rate in such patients<sup>4</sup>. Approximately 90-95% of healthy people and 45-50% of dialysis patients properly respond to vaccination.<sup>5</sup> 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<sup>6</sup>. To enhance the development of anti-HBs in HD patients by the intradermal (id) administration of HBV vaccine was reported to result in 100% antibody production in previously nonimmunized patients<sup>7</sup>. The rationale for using the intradermal route of vaccine administration is that a higher concentration of resident and recruited antigen-presenting cells is present within skin – associated lymphoid tissue than in striated muscle; this high concentration facilitates rapid trafficking of these activated cells and subsequent T-cell activation, which in turn, induces adaptive immune response<sup>8</sup>. Small studies and meta-analysis have suggested that intradermal vaccination for HBV is safe and effective in patients on hemodialysis<sup>9</sup>. This prompted us to evaluate the effectiveness of intradermal recombinant HBV vaccine in selected chronic HD Saudi patients previously non-responsive to intramuscular vaccination.

## 2. PATIENTS AND METHODS

This prospective study was conducted in prince salman center for kidney diseases (PCKD), Riyadh, KSA over a period of one year from May 2011 until May 2012. This study include 15 patients (5 male and 10 females), their age ranged from 26-82 year, all the subjects were negative for all serological markers of HBV infection, including HBsAg and anti-HBc antibodies also all negative for anti-HBs. We evaluated levels of HBs antibody (anti-HBs) titer two months after eight doses of intradermal vaccination; Engerix B, 10µg administered by intradermal injection over the deltoid muscle every two weeks. The range of dialysis session duration was from 3 to 4 hour, three times weekly dialysis schedule, with a blood flow rate range from 250 to 400 ml/min, the dialysate flow rate range from 500 to 800 ml/min and bicarbonate dialysis prescription was performed for all patients. Dialysis adequacy was assessed monthly calculation of by monthly calculation Single pool Kt/v (spKt/V), was assessed using the Daugirdas second-generation formula. Parathyroid hormone level (PTH), anemia by measuring the hemoglobin (Hb), calcium and phosphorus, nutritional state of the patients as determined by serum albumin. The previous numbers of intramuscular HBV vaccine courses, the original disease of chronic renal failure and the duration of hemodialysis per years were calculated. The factors which can affect the response to vaccine.

### Statistics:

The results were summarized as the mean  $\pm$  standard deviation (SD). Unpaired student's t test for testing the significance of differences of values measured between responders and non responders was used, P value < 0.05 was taken as statistically significant. All analysis were performed using the SPSS version 16. The mann-Whitney rank-sum test was used as appropriate.

## 3. RESULTS

A total of 15 patients were included in this study who were non responder to HBV vaccine after at least two courses of intramuscular HBV vaccine with titer level less than 10IU/L. They were vaccinated by 10ug Engerix HBV vaccine weekly for 8 weeks by intradermal route. HBsAg was measured two and six months after the last dose.

### Response to ID vaccination

Twelve out of fifteen patients (80%) were responder (HBsAb titre > 10IU/L), five of them have titer > 100IU. This number increased to seven patients by repeated measurement 6 months later.

### Demographic (see table1)

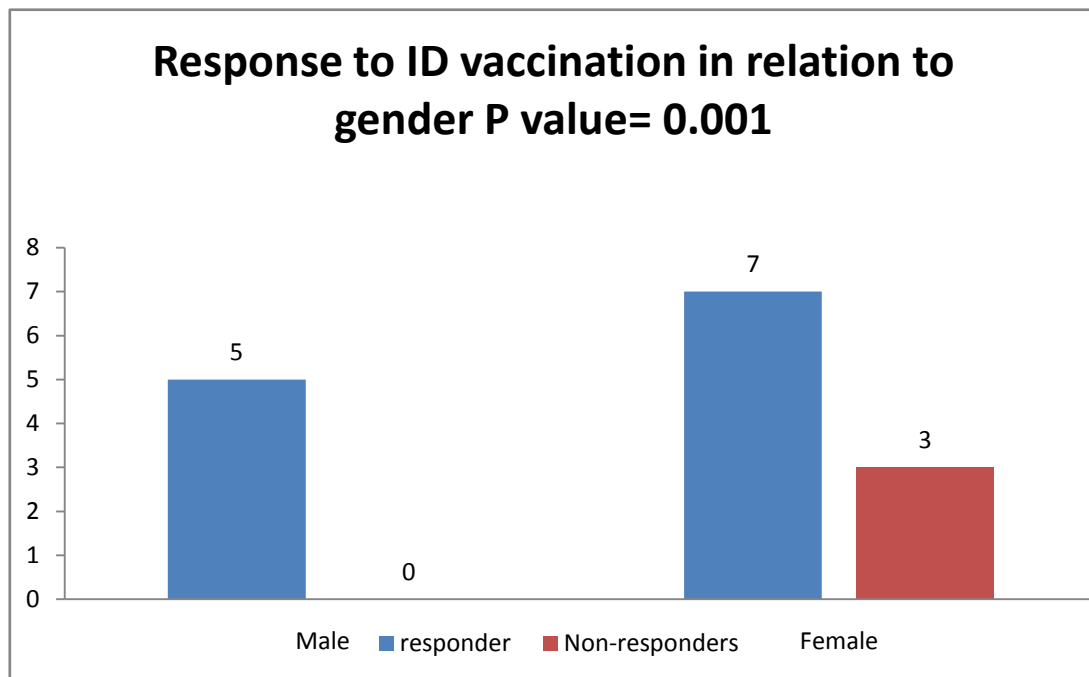
A total of 15 chronic HD patients non-responder to two courses of intramuscular HBV vaccine at PCKD were enrolled in our study (5 males and 10 females). The mean age was 59.26 $\pm$ 13.08 years (range 26–82 y). The mean age was lower in the responder compared to the non-responder group (56.25 $\pm$ 13.718 vs 71.33 $\pm$ 5.03 years respectively, P value=0.26). The etiology of end-stage renal failure were diabetes mellitus in 4 cases (26.6%), hypertension in 6 cases (40.0%), glomerulonephritis one case (6.7%), congenital cause one case (6.7%) and unknown causes in 3 cases (20%).

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Seven females out of ten while all males were responders (p value=0.001), see table 1 and figer1.No statistically significant difference was found between responder and non responder regarding the number of IM courses ( $2.67 \pm 0.98$  vs  $2.67 \pm 0.58$  p value= 1.0).

**Table1.** Demographic and Laboratory Criteria

Parameter	The mean	Responder	Non-responder	P value
Age years	59.26±13.08	56.25±13.718	71.33±5.03	0.258
HepatitisB vaccine courses	2.66±0.98	2.67±0.98	2.67± 0.58	1.0
Hb g/dl	11.32± 0.86	11.2 ± 0.93	11.77 ± 0.07	0.062
Duration of HD session hours	3.266 ±0.258	3.29 ± 0.26	3.17 ± 0.29	0.075
HD duration years	3.87 ± 1.59	4.0±1.65	3.33±1.53	0.55
Serum Albumin g/l	35.23±4.35	35.67±4.71	33.48±2.17	0.45
Serum Calcium mmol/l	2.22±0.14	2.21±0.15	2.26±0.04	0.61
Serum phosphorus mmol/l	1.58±0.41	1.62±0.46	1.45±0.07	0.13
KT/V	1.58 ± 0.41	1.62 ± 0.46	1.45 ± 0.07	0.13
HCV +ve cases numbers	4 cases	3 cases	1 case	0.637
The gender	The total number	12 case	3 case	0.001
	15	5 males 7females	0 males 3 females	
PTH pmol	52.81±18.19	The range		0.84
		1.62- 300.2 pmol		



**Figier1.** Effect of gender on response to intradermal HBV vaccine

### Laboratory Criteria

Again no statistically significant difference was observed regarding dialysis duration between responder and non responder groups ( $3.29 \pm 0.26$  vs  $3.17 \pm 0.29$  p value= 0.07), dialysis adequacy ( kt/v) ( $1.62 \pm 0.46$  vs  $1.45 \pm 0.07$  p value= 0.13 , years on HD( $4.0 \pm 1.65$  vs  $3.33 \pm 1.53$  p value= 0.55),) for all patients were within the target without any difference between responder and non responder groups,

Regarding nutritional state no significant difference between responder and non responder groups (serum albumin) ( $35.67 \pm 4.71$  vs  $33.48 \pm 2.17$  with p value= 0.45).

Regarding bone profile parathormone hormone (the mean  $52.81 \pm 18.19$  p value=0.84), serum calcium ( $2.21 \pm 0.15$  vs  $2.26 \pm 0.04$  p value=0.61), serum phosphorus ( $1.62 \pm 0.46$  vs  $1.45 \pm 0.07$  p value=0.13), without significant difference between responder and non responder groups.

No statistically significant difference was found between responder and nonresponder regarding hemoglobin as indicator of anemia ( $11.20 \pm 0.93$  vs  $11.77 \pm 0.07$  with p value= 0.32).

#### **Hepatitis C infection see table 1:**

There was no significant difference between hepatitis C negative and positive patients regarding to responsiveness to ID HBV vaccine with (p value=0.64).

#### **4. DISCUSSION**

The present study is undertaken with the aim of evaluating the efficacy of intradermal hepatitis B vaccine in nonresponder patients to IM route<sup>10</sup>. There are two reasons for choosing the ID route of administration, firstly, it is less expensive and secondly, the skin is known to have a large numbers of antigen presenting cells, which enhance the immune response to vaccine<sup>11</sup>. This study result is in agreement with Barraclough et al<sup>12</sup>, and Chanchairujira et al<sup>13</sup>. they were found revaccination by ID route, in stable HD patients previously not responder to IM vaccination had higher conversion rate, also rapid induction of protective level of antibodies. But the conflicted result were prescribed by Met et al<sup>9</sup>, and Sorkhi et al<sup>14</sup>. found that less seroconversion in patients vaccinated by ID and subcutaneous (SC) versus IM route.

Fabrezi et al.<sup>15</sup> Found no relation between age and seroconversion rate, this result in agreement with this study; which conflict with Chin<sup>16</sup> and Nancy M et al.<sup>17</sup> In their study found that the older age was being associated with a decrease responsiveness to HB vaccine.

Peces et al.<sup>18</sup>; and Navarrow et al<sup>19</sup>. Did not report any difference in response rate regard to duration of hemodialysis, this result in agree with our study result. This conflict the result of Steketee, R et al.<sup>20</sup> whom were observed that antibody response rates increases with increasing length of time on dialysis prior to receipt of vaccine but duration of dialysis has no association. Kovacic et al<sup>21</sup>. and Salwa I. et al.<sup>26</sup> Show that HBV vaccination response is weaker in hemodialysis patients with inefficient dialysis; this conflict our study and Nancy M et al.<sup>17</sup> Regina H. et al<sup>22</sup>. Low hemoglobin levels had no effect on response to HBV vaccine response, this result in agreement with this study and conflict with the result of McMaster KR et al<sup>23</sup> and Vlassopoulos D.<sup>5</sup> Found low hemoglobin levels may have weaker immunologic response to vaccines. Peces et al<sup>18</sup> and Navarro et al<sup>19</sup>. not report any difference in the response rate with regard to serum albumin, this result in agreement with the result of our study, in contrast Fernandez et al.<sup>24</sup> had shown that malnutrition negatively influences the response to the HBV vaccine in hemodialysis patients; patients with serum albumin levels between 3-3.5g/dl were nonresponders in higher percentage than those with serum albumin levels between 4.5-5g/dl. Nancy M. et al<sup>17</sup> found that primary origin of the ESRD had no statistically significant effect on response to HBV vaccine, this in agreement with our study result, conflicting the study result of Fabrizi F. et al<sup>27</sup> who found that diabetes mellitus (DM), an important cause of unresponsiveness to HBV vaccine.

Regarding to HCV positive patients, we not found any effect on responsiveness to HBV vaccine, this result in agreement with result of Urbanowicz W.<sup>25</sup> and Salwa I. et al<sup>26</sup>, but conflict the result of Navarro et al<sup>4</sup>. He reported a low response to HBV vaccination in HCV-infected hemodialysis patients.

Salwa I. et al.<sup>26</sup> and DaRoza G. et al.<sup>28</sup> found parathyroid hormone level did not significantly influence antibody response to hepatitis B immunization, their result in agreement with our study result.

Nahar et al.<sup>29</sup> and Sezer et al<sup>30</sup>. found antibody response rate was higher in female than male subjects and it was highly statistically significant, this conflict the result in our present study where the male response is highly significant than female. Peces et al<sup>18</sup>. and Marangi et al.<sup>31</sup> studies have observed that the subject's gender did not influence the response rate to hepatitis B vaccine in hemodialysis patients.

#### **5. CONCLUSION**

We reported a higher response rate to intradermal hepatitis-B vaccination in previously non responder to at least two courses of intramuscular vaccination. The gender was the only factor affect the

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response to hepatitis B vaccine, other factors such as age, efficiency of dialysis, the cause of ESRD, anemia, HCV +ve antibodies status, the number of HBV vaccine courses, the duration of dialysis, the length of hemodialysis session and parathormone hormone level, calcium and phosphorus had no association with response to ID HBV vaccination route.

We suggest the administration of low –dose intradermal inoculation in order to re-vaccinate dialysis individuals showing unresponsiveness to HB vaccine.

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