ORIGINAL ARTICLE

# RESPONSE TO INTRADERMAL ROUTE OF HEPATITIS B VACCINATION IN CHILDREN ON MAINTENANCE HEMODIALYSIS: A SINGLE CENTER EXPERIENCE

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## ABSTRACT

**Background:** To determine the response of intradermal route of hepatitis B vaccine (HBV) in pediatric dialysis patients.

**Material and Methods:** Prospective, observational study carried out in the Hemodialysis Unit, Sindh Institute of Urology and Transplantation (SIUT), Karachi, from October 2021 to September 2022. Patients younger than 18 years, Hepatitis B surface antigen negative irrespective of primary vaccination status, were tested for anti-Hepatitis B antibody titers. Those with levels less than 10IU/L were recruited for intradermal vaccination at 0,1 and 6 months and titers rechecked in the 2nd and 7th month of study.

**Results:** Of the 168 children screened, 81 (48%) patients were eligible for vaccination, however, 52 agreed to participate. Males were 27 (52%). Mean age was 12.18± 2.61 years. End-stage kidney disease due to unknown etiology was the most common cause in 27 (52%) patients with mean dialysis duration being 1.43±1 years. Most, 48 (92%) patients were hypertensive and majority, 47 (90%) patients tested negative for hepatitis C. Final analysis was done on 38 patients. Thirty-four (89.4%) patients responded; 25 (65.8%) being good and excellent responders. Mean antibody titers before intradermal vaccination of 2.87±3 IU/L improved to 383±397 IU/L. Ages 11-15 years showed a statistically significant association with the development of anti-Hepatitis B antibody titers (p value: 0.02) while gender, dialysis duration, pre-vaccination HBs titers, hepatitis C status, hypertension and cause of end-stage kidney disease did not have any effect.

**Conclusion:** ID route of HBV is efficacious in producing seroprotective anti-HBs titers in pediatric ESKD patients. Children 11-15 years had more robust response.

**Keywords:** Children, Hemodialysis, Hepatitis B, Intradermal, Vaccination

## BACKGROUND

Exposure to blood borne viral infections like hepatitis B (Hep B) remains an accompaniment risk to the life-saving treatment modality of hemodialysis, for end stage kidney disease patients (ESKD) including children. The highly infectious Hep B virus can be acquired via the percutaneous or mucosal route by contact with central dialysis lines, contaminated blood products and potentially infected instruments or surfaces. Chronically infected patients and health care workers, and an impaired immunity in ESKD patients also form an important part of the equation.[1] Resultantly, the reported prevalence of Hep B ranges from 6%- 15% in the various pediatric hemodialysis populations studied. Shah SR *et al* documented the prevalence of Hep B to be 2.5% in pediatric hemodialysis patients in Pakistan.[1] Long- term carriers have an increased risk of progressive chronic liver disease, cirrhosis, and hepatocellular carcinoma.[3,4] Immunization and robust infection control practices are the two strategies to contain Hep B. The Centre for Disease Control recommends double the dose of hepatitis B vaccine (HBV) in adults via intramuscular (IM) route to account for the low seroconversion rates in ESKD patients.[1,5] In patients younger than 20 years of age, higher doses might be more immunogenic, but no specific recommendations have been made. The Southwest Pediatric Nephrology group found seroprotection rate of 91% in pediatric dialysis patients with an augmented intramuscular vaccine dose.[6] However, titers reported by Sonia JF *et al* after secondary IM HBV vaccination were lower in ESKD patients even after 100% seroconversion.[7] Measures including intradermal (ID) route, use of third

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generation vaccines with newer adjuvants or immunostimulants have reported better response rates.[8] Administration of ID HBV in healthy children[9] and in those with conditions like celiac disease[10] has shown comparable seroprotection rates of more than 90% similar to that of the primary Hep B vaccination. While, multiple studies in adults[11] have shown better efficacy of ID HBV route in non-responders to the IM route; no study to the best of our knowledge has been conducted in pediatric hemodialysis patients. Hence, the aim of this study was to determine the seroprotection rate of the ID route of HBV in previously vaccinated pediatric hemodialysis patients with inadequate hepatitis B virus surface antibody (anti-HBs) titers. Secondly, it also aimed to determine if any of the clinical features correlated with the response to the ID vaccine.

## MATERIAL AND METHODS

This prospective interventional study was conducted at the hemodialysis unit of Sindh Institute of Urology and Transplantation (SIUT), Karachi, over 12 months from October 2021 to September 2022, after approval from the ethical and scientific committee (SIUT-ERC-2021/ A-329).

Considering the approximate number of pediatric patients on hemodialysis in 6 months to be 200, with a margin of error of 10%, a confidence interval of 95%, and a reported response rate of 75.8%[12] to ID HBV, a sample size of at least 53 patients was calculated using the Epi Info[13] sample size calculator. A consecutive, non-probability sampling technique was used.

Written and informed consent was taken from parents/guardians, and assent was obtained from children more than 12 years of age. Demographic and clinical details were recorded. Patients younger than 18 years and on maintenance hemodialysis for at least 1 month were screened for Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV) using the Micro-Particle Enzyme Immunoassay (MEIA) ARCHITECT SYSTEM. Patients with negative HBsAg and HCV were subsequently tested for anti-HBs titers using the same immunoassay and those with titers <10 IU/L were recruited in the study. Patients who tested HCV positive but were not on anti-retroviral therapy were included in the study. Patients with a history of hepatitis B infection, localized skin infection, and human immunodeficiency virus (HIV) positive patients were excluded from the study.

Participants were vaccinated with low dose (2µg) ID recombinant HBV (AMVAX 10µg/0.5ml, AMSON VACCINES AND PHARMA (PVT) Islamabad) at 0,1, and 6 months[9] by the principal investigator using a 1ml tuberculin syringe and "wheal" formation was documented as evidence of the ID injection.

Side effects at the injection site were noted at the time of vaccination and, at home by parents. They were recorded on the subsequent dialysis session. They included pain at the time of injection till a maximum of 5 minutes, dark pigmentation, skin nodules, itching and fever.

Blood samples for anti-HBs titers were collected in the 2$^{nd}$ and 7$^{th}$ month of the study. Patients with titers <10 IU/L were considered non-responders, and those with titers >10 IU/L were considered responders. The responders were further categorized on the basis of their Anti-HBs titers as very poor: 10 to 50 IU/L, poor: 50 to 100 IU/L, good: 100 to 1000 IU/L, and excellent > 1000 IU/L.[15]

Statistical analysis was performed using SPSS version 20. Categorical variables were expressed as frequency and percentages, while continuous variables were represented by mean and standard deviation. Fisher exact test was used to determine the association between the categorical variables. A p-value of <0.05 was considered statistically significant

## RESULTS

Among the 168 screened patients as shown in Figure-I, 81(48%) patients were eligible for vaccination, of which, only 52 (31%) agreed to participate in the study. Fourteen (27%) patients were further excluded from the final analysis as 3 (6%) died from disease-related complications, 6 (11.5%) transferred to other facilities, 1 (2%) patient received a live-related kidney transplant and 4 (7. 6%) more patients withdrew from the study.

Of the 52 enrolled participants, 27 (52%) were males with a mean age of 12.18 ± 2.61 years. Table-I shows the demographic and clinical characteristics of the participants. Most patients had end-stage kidney disease (ESKD) due to unknown etiology and had been on dialysis for a mean time period of 1.43±1 years. Majority i.e., 48 (92%) were hypertensive and most patients, 47 (90%) tested negative for hepatitis C.

Overall, 34 (89.4%) out of 38 patients who completed the study showed response to ID vaccination, of which, 25 (65.8%) patients were good and excellent responders. The mean anti-HBs titers before ID vaccination were 2.87±3 IU/L while after vaccination they improved to 152.31±249.24 IU/L after the second dose and to 383±397 IU/L at the end of the study as shown in Table-II. Of the clinical variables studied, patients of the age group 11-15 years showed a statistically significant association with the development of anti-HBs titers (p value 0.02) as shown in Table-III. None of the other variables including gender (p= 0.53), duration of dialysis (p= 0.56), pre-vaccination HBs titers (p= 0.20), hepatitis C status (p= 0.45), hypertension (p= 0.46) or cause of ESKD (p= 0.24) had any statistically significant effect on the development of seroprotection.

**Table-I: Demographic and Clinical characteristics of study participants (n=52*)**

| Variable | n (%) |
|---|---|
| **Gender** | |
| Male | 27 (52) |
| Female | 25 (48) |
| **Age (years) *median (IQR)*** | 12 (10-14) |
| **Age Categories (years)** | |
| 5-10 | 11 (21.2) |
| 10-15 | 36 (69.2) |
| >15 | 5 (9.6) |
| **Duration of hemodialysis (years) *mean±SD*** | 1.43±1 |
| **Cause of ESKD** | |
| Glomerular Disease | 7(13.5) |
| CAKUT | 13 (25) |
| Renal Stones | 5 (10) |
| Unknown | 27 (52) |
| **Hypertension** | |
| Yes | 48 (92%) |
| No | 4 (8) |
| **Anti HCV Status** | |
| Negative | 47 (90) |
| Positive | 5 (10) |
| **Side Effects** | |
| None | 6 (11) |
| Pain at injection site and anxiety | 28 (54) |
| Skin pigmentation | 16 (31) |
| Fever | 1 (2) |

*14 children were excluded from final analysis. Details in text
ESKD: end stage kidney disease, CAKUT: congenital abnormality of kidney and urinary tract

**Table-II: Hepatitis B surface antibody (Anti-HBs) Titers (n=38)**

| Variable | n (%) |
|---|---|
| Pre-vaccination titres (IU/L) *mean±SD* | 2.87±3 |
| Response | |
| Responder | 34 (89.4) |
| Non-Responders | 4 (11) |
| Post-vaccination titres (IU/L) at 2 months *mean ± SD* | 152.31 ± 249.24 |
| Post vaccination titers at 2 months | |
| *Non-Responder* | |
| <10 IU/L | 9 (24) |
| *Responder* | |
| Very Poor (10-50 IU/L) | 13 (34) |
| Poor (50-100 IU/L) | 5 (13) |
| Good (100-1000 IU/L) | 9 (24) |
| Excellent (>1000 IU/L) | 2 (5) |
| Post vaccination titers at 7 months | |
| *Non-Responder* | |

| | |
|---|---|
| <10 IU/L | 4 (10.5) |
| *Responder* | |
| Very Poor (10-50 IU/L) | 4 (10.5) |
| Poor (50-100 IU/L) | 5 (13.2) |
| Good (100-1000 IU/L) | 18 (47.4) |
| Excellent (>1000 IU/L) | 7 (18.4) |
| Post-vaccination titres (IU/L) at 7 months *mean±SD* | 383±397 |

**Table-III: Association of clinical and demographic features with response to Hepatitis B vaccine.**

| Variable | Responder | Non-responder | P value |
|---|---|---|---|
| **Age in years** | | | |
| 5-10 yrs | 9 | 0 | |
| 11-15 yrs | 23 | 2 | 0.02 |
| >15 yrs | 2 | 2 | |
| **Gender** | | | |
| Male | 20 | 3 | 0.53 |
| Female | 14 | 1 | |
| **Pre-vaccination titers** | | | |
| 0-5 IU/L | 24 | 4 | 0.20 |
| 6-9.9 IU/L | 10 | 0 | |
| **Duration on Dialysis** | | | |
| <1yr | 17 | 1 | |
| 2-5 yrs | 16 | 3 | 0.56 |
| >5 yrs | 1 | 9 | |
| **Anti HCV Status** | | | |
| Negative | 30 | 3 | 0.45 |
| Positive | 4 | 1 | |
| **Hypertension** | | | |
| Yes | 30 | 4 | 0.46 |
| No | 4 | 0 | |
| **Cause of ESKD** | | | |
| Glomerular diseases | 6 | 0 | |
| CAKUT | 9 | 3 | 0.24 |
| Renal Stones | 4 | 0 | |
| Unknown Etiology | 15 | 1 | |

## DISCUSSION

In this prospective, interventional study, the ID route of HBV was found to be efficacious in inducing seroprotection in the majority of our dialysis dependent children who were previously vaccinated but had anti-HBs titers less than 10 IU/L.

Our study found a seroprotection rate of 90% after 3 doses of ID vaccine. In contrast, Kamath *et al* found seroprotection of only 72% after 3 doses of IM vaccine in chronic kidney disease (CKD) children who had previously received primary immunization.[15] In fact, Drachman *et al* observed a response rate of 86% after giving 5 injections of augmented dose of 40 micrograms IM HBV in dialysis- dependent children.[16] Better seroprotection via ID route is likely due to the abundance of antigen presenting Langerhans cells in the dermis that elicit an enhanced immune response in the otherwise low immunity state of ESKD.[12] A German study demonstrated vaccine-reactive T cells in previously vaccinated Hep B patients but having inadequate anti-HBs antibody titers. These T cells can possibly be induced to produce seroprotection via the ID route of vaccination.[17] While, Barraclough KA *et al* from Australia found the ID route of vaccination to be the only factor predictive of seroprotection in ESKD patients.[3]

Response rate of 76% was seen at 8 weeks in our study after the second ID dose and that of 90% after the third dose at 28 weeks. In comparison, the adult hemodialysis population at our institute reported a seroprotection of 76% after 18 weeks of the ID dose as reported by Hanif F *et al*.[12] It appears that children mount a better antibody response as compared to adults. Age less than 30 years appears to be a non-modifiable factor against HBV vaccine response.[18]

In this regard, Chanchairujira T *et al* found 92% patients to have good and excellent response and titers greater than 100 IU/L with ID vaccination as compared to 69% patients developing good seroprotection with the IM route.[19] A slightly lesser percentage (69%) of our patients developed anti-HBs titers more than 100IU/L. A possible explanation is that in the aforementioned cohort of Chanchairujira T

*et al*, 7 doses of ID vaccine were given compared to 3 doses in our study.

The age group of 11-15 years was found to have the most response rate to ID vaccine. An African study group similarly showed maximal seroprotective rates after primary HBV in children less than 15 years of age.[20] Children younger than 10 years made up a smaller proportion of patients needing revaccination in our cohort. This could likely be because of residual titers from the effect of primary immunization series.

No gender predilection was seen in our study. Conversely, the pediatric study from Bangladesh showed better seroconversion rates in girls.[7] However, a predominance of males is usually noted in ESKD patients as reported by Preka *et al*.[21] This could perhaps be because of greater prevalence of congenital abnormalities of the urinary tract in boys.

Hepatitis C infection has been proposed to impair dendritic cell antigen presentation. Co-infection with hepatitis C in 10% of our studied patients did not hamper vaccine response. This finding has been supported by other studies too.[22] However, in a duo of studies conducted by Navarro *et al*, induction of seroprotection by HBV was low in hemodialysis patients with HCV co-infection.[23]

Hypertension has also been implicated in decreased response rates as it appears to cause mechanical and oxidative injury of vessels which leads to modification of the immune system.[24] While most of our patients were hypertensive, possibly because measurements were taken just before a dialysis session, it did not appear to affect antibody formation.

Injection site pain and anxiety were the most common side effects in 54% of our patients. Bunapuradah *et al*, however, reported pain in only 7.7% of their patients.[25] On the contrary, Egemen A *et al* documented skin pigmentation in 26% of the infants and 35% of the preschoolers as the most observed side effects in their study.[26]

In conclusion, our study has documented a robust seroprotective response of ID route of HBV in ESKD patients with low anti-HBs titers. The limitations of our study include a single-center analysis of a small cohort of patients with a short-term follow up. Our drop-out rate was also high due to several reasons, including switching of dialysis facility to a center closer to patients' area of residence. Large scale studies comparing augmented IM dose with ID dose and with longer follow up to determine the duration of persistence of adequate anti-HBs titers are needed.[14]

## CONCLUSION

The ID route of HBV can be used as an alternative vaccination method in pediatric ESKD patients who have low anti-HBs titers. It appears to induce good protective antibody levels against Hep B in the uremia-associated immune suppressed and high-risk pediatric dialysis population who were previously vaccinated but have low seroprotection.

## CONFLICT OF INTEREST

Authors declare no conflict of interest

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## AUTHOR CONTRIBUTION

**Kalimullah Khan:** Conception, the acquisition, analysis, interpretation of data and manuscript writing

**Aasia Zubair:** Conception, the acquisition, analysis, interpretation of data and manuscript writing

**Madiha Aziz:** Conception, analysis, interpretation of data and manuscript writing

**Sanaullah Agha, Pawan Kumar:** Data collection and analysis

**Seema Hashmi:** Revised critically for important intellectual content

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