

Immune Response against Hepatitis B Vaccine in Transfusion-dependent Thalassaemic Children Vaccinated in Early Infancy

Fatema Hossain^{1,2}, Ayesha Khatun², Md. Ashadul Islam², Sonia Shormin Miah², Subarna Saha², Nusrat Noor Tanni³

¹Department of Transfusion Medicine, National Institute of Diseases of the Chest and Hospital, ²Department of Transfusion Medicine, Bangabandhu Sheikh Mujib Medical University, ³Department of Microbiology, Dhaka Medical College, Dhaka, Bangladesh

ABSTRACT

Background and Objectives: Children with thalassemia are much more vulnerable to being infected by hepatitis B virus (HBV) through transfusion of blood and blood products. Although active immunization against HBV in early infancy is being conducted in Bangladesh by the inclusion of the hepatitis B vaccine (HepB) in the expanded programme on immunization schedule, these children might have altered immune response against HepB due to inevitable iron overload resulting from the disease thalassemia itself as well as repeated transfusion therapy and also from exposure to different allogeneic antigens. The present study was designed to determine the immune response of HepB among transfusion-dependent thalassemic children. **Patients and Methods:** This cross-sectional study was conducted at a university hospital in Bangladesh. A total of 45 transfusion-dependent thalassemic children were included according to inclusion and exclusion criteria. Data collection was conducted through a structured questionnaire after taking written informed consent from each participant's guardian. Each patient underwent a detailed history taking and antibody to hepatitis B surface antigen (anti-HBs) titer was estimated to see the immune response against HepB. **Results:** Collected data were analyzed using SPSS version 23. The mean age of the studied children was 9.03 ± 3.78 standard deviation with slight female predominance (51.1% female and 48.9% male). According to the level of anti-HBs titer, the majority (44.4%) had moderate protection, whereas others had no (28.9%) or strong (26.7%) protection. No significant association between the total number of transfusions (approximate), different age groups, and postvaccination interval with anti-HBs titer was observed ($P > 0.05$). **Conclusion:** The present study observed an overall poor immune response against HepB as approximately only one-fourth of the study participants got strong protection against HBV. Assessment of anti-HBs titer followed by booster dose or revaccination if necessary is needed to be considered in transfusion-dependent thalassemic children vaccinated in early infancy.

KEYWORDS: Antibody to hepatitis B surface antigen titer, hepatitis B vaccine, hepatitis B virus, thalassemia, transfusion-dependent thalassemia

Submitted: 31-Jul-2022.

Accepted: 02-Sep-2022.

Published: 05-Nov-2022.

INTRODUCTION

Thalassemic children require repeated transfusion of blood products and are at a greater risk of acquiring infections transmitted through transfusion, most commonly hepatitis B virus (HBV) infection.^[1]

Infants or young children affected by HBV are more likely to develop chronic infection and its complications such as cirrhosis, hepatocellular carcinoma, and end-stage liver disease rather than acute hepatitis, and they can act as a reservoir

of continued HBV transmission.^[2] Vaccination against HBV before exposure is the most effective way to prevent this infection.^[2,3] Introduction of the hepatitis B vaccine (HepB) in an expanded programme on immunization (EPI) schedule

Address for correspondence: Dr. Fatema Hossain,
E-mail: fatemarubahossain@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Hossain F, Khatun A, Islam MA, Miah SS, Saha S, Tanni NN. Immune response against Hepatitis B vaccine in transfusion-dependent thalassemic children vaccinated in early infancy. Glob J Transfus Med 2022;7:134-8.

Access this article online

Quick Response Code:



Website: www.gjtmonline.com

DOI: 10.4103/gjtm.gjtm_59_22

of Bangladesh was done in a phased manner from 2003 to 2005. Now, it is provided as a combined pentavalent vaccine (diphtheria, pertussis, tetanus, *Haemophilus influenza* type B, and HepBs) at the age of 6, 10, and 14 weeks.^[4]

Hepatitis B infection is one of the significant risks of transfusion-transmitted viral infection, although there is continuous advancement in the procedures of blood donation screening^[5] due to the window period, a low titer of HBV, and the variety of virus types.^[6] In Bangladesh, previous studies showed that the prevalence of hepatitis B surface antigen (HBsAg) among transfusion-dependent thalassemia patients was 7%^[7] and 3%.^[7,8] According to the newer study, the decreasing trend of HBV infection in multitransfused patients may be explained by the increasing rate of vaccination which is 77% of patients in the previous study where the vaccination rate was only 15.84% of patients, due to inclusion of HepB in the national EPI schedule.^[7,8]

A positive immune response against the vaccine is defined as the development of antibody to HBsAg (anti-HBs).^[9] Serum anti-HBs titer of ≥ 10 mIU/ml is considered protective immunity following HBV vaccination.^[2,10,11] The chance of breakthrough infection is increased when the anti-HBs titer is lower than the level of 10 mIU/ml^[12,13] and cases of clinical hepatitis B and, rarely of chronic HBV infection were observed in persons who developed anti-HBs responses below this level.^[2] Based on the serum levels of anti-HBs titer, participants can be categorized as nonresponders/no protection (<10 mIU/ml), low responder/moderate protection (10–100 mIU/ml), and good responder/strong protection (>100 mIU/ml).^[3,14,15]

Although routine postvaccination serology is not recommended in a healthy individual, it should be considered for persons who are immunocompromised.^[11] In the case of thalassemic children, the requirement of regular packed red blood cell transfusion for maintenance of optimal hemoglobin levels makes them more susceptible to HBV infection.^[14] On the other hand, iron overload due to the disease itself and long-term frequent blood transfusion in the thalassemic patient might affect the immune system directly and lead to impaired immune response toward foreign antigens.^[16] Therefore, it is very much essential to determine the immune response against HepB in the children of transfusion-dependent thalassemia as they might have been immune deficient.^[14,17]

Aims and objectives

This study was designed to observe the immune response against HepB in transfusion-dependent thalassemic children by determining the level of anti-HBs titer who were vaccinated as per the national EPI schedule of Bangladesh.

METHODOLOGY

Study design

This cross-sectional observational study was conducted in transfusion-dependent thalassemic children attending the “Day Care Transfusion Unit” of the department of transfusion medicine from January 2021 to August 2021.

Study participants

A total of 45 thalassemic children confirmed by hemoglobin (Hb)-electrophoresis finding, aged ≥ 2 years of both sex, dependent on transfusion therapy and already had received ≥ 10 transfusions and who received HepB in early infancy as per the national EPI schedule of Bangladesh only, were included in this study. Thalassemic children who underwent splenectomy or had any proven conditions that can affect an individual's immune response, such as corticosteroid therapy, immunosuppressive drugs, autoimmune diseases, malignancy, and other chronic diseases, were excluded from the study.

Ethics

Before study enrolment, all individual guardians were informed of the voluntary nature of participation and confidentiality as well as the use of their data for research purposes only. Confidentiality of the participant's data was ensured as there was no personal identifying information. The study participant's guardians gave informed written consent before entering the study. The data collection procedure was initiated by the researcher and information was taken through a face-to-face interview.

A structured questionnaire was used to collect sociodemographic information as well as disease information and measurement. The questionnaire was filled up with comprehensive history, medical records, clinical assessment, and available previous laboratory reports. The immunization history of the participants was taken with inspection of the EPI vaccination card to ensure vaccination of HepB was done as per the national EPI schedule. In the case of illiterate guardians, data were collected from past medical records. After the final selection of participants, a blood sample (3 ml venous blood) was collected with all available aseptic precautions from each participant and sent to the department of virology, for anti-HBs assay which was done by chemiluminescent immunoassay technology for the quantitative determination of anti-HBs titer in human serum. Then necessary data were collected from anti-HBs titer reports of participants and registered in the appropriate questionnaire. All necessary information was recorded in a separate case sheet.

Statistics

After collection, collected data were checked for errors and analyzed using the statistical software SPSS version 23, developed by IBM, Chicago, Illinois, USA.

RESULTS

A slight female predominance (51.1% female and 48.9% male) was noted among the study participants and the mean (\pm standard deviation [SD]) age was 108.6 ± 44.7 months or 9.03 ± 3.78 years [Table 1].

Table 1: Distribution of participants by age (n=45)

Age groups (months)	Frequency, n (%)
24-60	7 (15.6)
61-120	19 (42.2)
121-192	19 (42.2)

The majority (68.9%) were diagnosed with cases of Hb E β -thalassemia, whereas 31.1% were β -thalassemia major and among all the participants 40 (88.9%) were receiving a regular transfusion. The majority 18 (40.0%) received a total of 51–100 units of transfusion, followed by 14 (31.1%) and 13 (28.9%) receiving >100 and 10–50 units, respectively.

Based on anti-HBs titers, only 26.7% of the participants were found to have strong protection [Table 2]. However, there was no significant association between the total number of transfusions (approximate), different age groups, and postvaccination interval with anti-HBs titer category ($P > 0.05$) [Tables 3–5].

DISCUSSION

In this study, the majority of the participants were female (51.1%) and 48.9% were male. However, other studies have shown a male predominance. A study done by Soliman *et al.* in Egypt among 125 thalassemic patients, 59.2% were male and 40.8% were female^[18] and another by Eman G. Helal *et al.* done in Egypt showed that 54% were male and 46% were female among thalassemia patients.^[19] Regarding age, the majority of the children belonged to two

age groups 61–120 months and 121–192 months (42.2% in each) and the mean (\pm SD) age of the study children was 9.03 ± 3.78 years. A study done by Ahmed *et al.* in a tertiary health-care center in Bangladesh revealed that the mean age of β -thalassemic and Hb E β thalassemic children was 6.8 ± 2.84 and 8.78 ± 2.99 years, respectively,^[20] which is slightly lower than that seen in our study, whereas another study done in Jammu by Singh and Singh in 2016 found that the mean age was 11.85 ± 6.3 years in thalassemic patients^[21] which was higher than this study.

Most of the study children (68.9%) were diagnosed with Hb E β -thalassemia and 31.1% were β -thalassemia major by Hb electrophoresis. Rahman and Jamal found Hb E β -thalassemia in 67% of total cases in a study done in Dhaka, Bangladesh which strongly supports this study.^[22] However, findings by Ahmed *et al.* disagree with this study as there were 68 (71.6%) β -thalassemic, whereas 27 (28.4%) were Hb E β -thalassemic among 95 thalassemic children.^[20]

Forty children (88.9%) were receiving a regular transfusion and only 05 (11.1%) were receiving an irregular transfusion. According to Ahmed *et al.*'s study, most of the patients were on regular transfusions which supports this study.^[20] The majority (40%) of the children received 51–100 units of transfusion, whereas 31.1% of children received >100 units and 28.9% received 10–50 units. According to Singh and Singh, the majority of the patients (60%) received more than 100 transfusions which disagree with the present study and it might be due to the higher age range of that sample population.^[21]

Regarding immune response against HepB, 13 children (28.9%) got no protection, 20 (44.4%) got moderate protection, and

Table 2: Categorization of the study children by hepatitis B surface antigen titer level ($n=45$)

Anti-HBs titer (mIU/ml)	Frequency, n (%)
No protection: <10	13 (28.9)
Moderate protection: 10–100	20 (44.4)
Strong protection: >100	12 (26.7)
Total	45 (100.0)

Anti-HBs: Hepatitis B surface antigen

Table 3: Association between the total number of transfusions (approximate) and hepatitis B surface antigen titer category ($n=45$)

Total number of transfusion (approximate)	No protection ($n=13$), n (%)	Moderate protection ($n=20$), n (%)	Strong protection ($n=12$), n (%)	Total ($n=45$), n (%)	P^*
10–50 units ($n=13$)	5 (38.5)	6 (46.1)	2 (15.4)	13 (100.0)	0.474
51–100 units ($n=18$)	6 (33.3)	6 (33.3)	6 (33.3)	18 (100.0)	
>100 units ($n=14$)	2 (14.3)	8 (57.1)	4 (28.6)	14 (100.0)	

* P -value was determined by the Chi-square test

Table 4: Association between different age groups and hepatitis B surface antigen titer category ($n=45$)

Age group	No protection ($n=13$), n (%)	Moderate protection ($n=20$), n (%)	Strong protection ($n=12$), n (%)	Total ($n=45$), n (%)	P^*
24–60 months ($n=7$)	0	5 (71.4)	2 (28.6)	7 (100.0)	0.104
61–120 months ($n=19$)	9 (47.4)	7 (36.8)	3 (15.8)	19 (100.0)	
121–192 months ($n=19$)	4 (21.1)	8 (42.1)	7 (36.8)	19 (100.0)	

* P -value was determined by the Chi-square test

Table 5: Association between postvaccination interval and hepatitis B surface antigen titer category ($n=45$)

Postvaccination interval	No protection ($n=13$), n (%)	Moderate protection ($n=20$), n (%)	Strong protection ($n=12$), n (%)	Total ($n=45$), n (%)	P^*
≤ 5 years ($n=7$)	0	5 (71.4)	2 (28.6)	7 (100.0)	0.152
>5 years ($n=38$)	13 (32.3)	15 (38.7)	10 (29.1)	38 (100.0)	

* P value was determined by the Chi-square test

12 (26.7%) got strong protection based on the levels of anti-HBs titer. A study done by Singh *et al.* in Lucknow, India concluded that out of 70 children with thalassemia, 17 (24.3%) patients were nonresponders (<10 IU/L) which agrees with this study's finding.^[23] According to a study done among healthy children in Brahmanbaria district of Bangladesh by Hossain *et al.* revealed a minority (17.6%) got strong protection (anti-HBs titer: >100 mIU/ml) which is also inconsistent with the present study.^[3] On contrary, a study conducted by Adb-Elgawad, *et al.* in Egyptian polytransfused thalassemic children who were vaccinated against HBV in early infancy revealed that 77% had no protection and none had strong protection, which is not in agreement with this study.^[9]

Among the children receiving 10–50 and >100 units of transfusion, the majority were in the moderate protection category (46.1% and 57.1%, respectively), whereas for those receiving 51–100 units of transfusion, there was 33.3% in each category of protection. No significant association was observed between the total number of transfusions and anti-HBs titer protection category. According to Soliman *et al.*, anti-HBs response was not associated with the number of transfused units which is similar to the present study findings.^[18] On the other hand, another study showed dissimilarity where there was a significant negative correlation between the number of blood transfusions in thalassemic children and the mean level of anti-HBs titer.^[9]

Among the age group of 24–60 months, out of seven children, none were in no protection category, although there was no significant association observed between different age groups and the category of anti-HBs titer ($P > 0.05$). Soliman *et al.*'s findings of association of age with anti-HBs response were similar to this study, although they mentioned that protective anti-HBs titer was reduced after the age of 3 years,^[18] whereas our study found that all the nonprotected children were over the age of 60 months (5 years). A study conducted by Sharifi, Milani, and Shooshtari (2010) in Tehran, Iran also found no meaningful association of age with anti-HBs response.^[15] On contrary, Adb-Elgawad, *et al.* found that the anti-HBs titer differences between different age groups were statistically significant which is not similar to this study.^[9]

Although there was no significant association of postvaccination interval with anti-HBs titer category ($P > 0.05$), all the nonprotected children belonged to >5 years postvaccination interval in this study. A study conducted by Azarkar and Sharifzadeh among patients with thalassemia major in Iran revealed that of 38 children 42.1% were nonresponder where there was no significant difference between anti-HBs titer and postvaccination interval groups (≤ 5 and > 5 years).^[14] Whereas Adb-Elgawad, *et al.* found a significant negative correlation between postvaccination intervals and the mean level of anti-HBs titer in thalassemic children.^[9]

Thalassemic children might have dysfunctional cell-mediated immunity due to iron overload resulting from repeated transfusion therapy, whereas some might have active humoral immunity due to repeated antigenic stimulus and this might explain our current study findings.^[24]

Routine serologic examinations of anti-HBs antibody levels or universal administration of booster doses are not recommended by the WHO after hepatitis B vaccination. However, it can be considered in the case of health-care providers, chronic hemodialysis patients, HIV-infected patients, and other immunocompromised individuals.^[25] Although long-term seroprotection following hepatitis B vaccination is variable, multiple studies suggested monitoring anti-HBs titers after primary vaccination in transfusion-dependent thalassemic children and recommend a booster dose or revaccination if indicated after determination of need on a case-to-case basis depending on the risk and vulnerability.^[9,14,24]

CONCLUSION

In this study, based on anti-HBs titer, approximately one-fourth (26.7%) of the transfusion-dependent thalassemic children had strong protection against HBV. No significant association between the total number of transfusions (approximate), different age groups, and the postvaccination interval was observed with anti-HBs titer category. But all the nonprotected children were above the age of 60 months (5 years) or with a postvaccination interval of more than 5 years. As these children are vulnerable to blood-borne infections like hepatitis B, the present study finding is a matter of concern. Repeat HepB vaccination may be considered on a case-to-case basis.

Acknowledgment

The author would grateful to the Department of Transfusion Medicine, Department of Virology, and Department of Public Health and Informatics of BSMMU.

Financial support and sponsorship

The partial financial grant from Bangabandhu Sheikh Mujib Medical University.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Vahidi AA, Varesvazirian M, Shamsadini A, Shamsadini S. Determination of hepatitis B surface antibody titer in Vaccinated children with major thalassemia in Kerman-Iran. Iran J Immunol 2006;3:30.
- Mahoney FJ. Update on diagnosis, management, and prevention of hepatitis B virus infection. Clin Microbiol Rev 1999;12:351-66.
- Hossain MM, Alam AN, Siddiqua M, Siddika A, Nessa A. Immune response among the children to hepatitis B vaccination: A community-based study in Bangladesh. Bangladesh Med Res Counc Bull 2018;44:103-8.
- Childs L, Roesel S, Tohme RA. Status and progress of hepatitis B control through vaccination in the South-East Asia Region, 1992-2015. Vaccine 2018;36:6-14.
- Candotti D, Allain JP. Transfusion-transmitted hepatitis B virus infection. J Hepatol 2009;51:798-809.
- Azarkeivan A, Karimi G, Shaiegan M, Maghsudlu M, Tabbaroki A. Antibody titration and immune response of Iranian β -thalassemic patients to hepatitis B virus vaccine (Booster effect). Pediatr Hematol Oncol 2009;26:195-201.
- Jamal CY, Rahman SA, Kawser CA. Prevalence of HBV markers in multi-transfused thalassaemic patients. Bangladesh J Child Health 1997;21:38-42.
- Karimi M, Ghavanini AA. Seroprevalence of hepatitis B, hepatitis C and human immunodeficiency virus antibodies among multitransfused thalassaemic children in Shiraz, Iran. J Paediatr Child Health 2001;37:564-6.
- Adb-Elgawad MM, Asem HM, Elbordiny MM. Evaluation of hepatitis B vaccine seroprotection in healthy and polytransfused Egyptian children with β -thalassemia major. Egypt Liver J 2015;5:1-5.
- Zanetti AR, Mariano A, Romanò L, D'Amelio R, Chironna M, Coppola RC,

- et al.* Long-term immunogenicity of hepatitis B vaccination and policy for booster: An Italian multicentre study. *Lancet* 2005;366:1379-84.
11. Hamborsky J, Kroger A, Wolfe C, editors. *Epidemiology and Prevention of Vaccine-Preventable Diseases: The Pink Book: Course Textbook*. Washington, D.C: Public Health Foundation; 2015.
 12. Rendi-Wagner P, Kundi M, Stemberger H, Wiedermann G, Holzmann H, Hofer M, *et al.* Antibody-response to three recombinant hepatitis B vaccines: Comparative evaluation of multicenter travel-clinic based experience. *Vaccine* 2001;19:2055-60.
 13. Lu CY, Ni YH, Chiang BL, Chen PJ, Chang MH, Chang LY, *et al.* Humoral and cellular immune responses to a hepatitis B vaccine booster 15–18 years after neonatal immunization. *J Infect Dis* 2008;197:1419-26.
 14. Azarkar Z, Sharifzadeh GH. Efficacy of HBV vaccination in children with thalassemia major, South Khorasan, Iran. *IRCMJ* 2009;11:318-20.
 15. Sharifi Z, Milani S, Shoostari MM. Study on efficacy of hepatitis B immunization in vaccinated beta-thalassemia children in Tehran. *Iran J Pediatr* 2010;20:211-5.
 16. Farmakis D, Giakoumis A, Polymeropoulos E, Aessopos A. Pathogenetic aspects of immune deficiency associated with beta-thalassemia. *Med Sci Monit* 2003;9:A19-22.
 17. Al-Hilaly HA, Al-Zamili AH, Al-Hamzawi SF. Immunological status of hepatitis vaccine among B-thalassemia major patients in Diwaniya. *Al-Qadisiyah Med J* 2015;11:54-8.
 18. Soliman HH, Kabbash I, El-Shanshory MR, Nagy HM, Abdou SH. Evaluation of immune status against hepatitis B in children with thalassemia major in Egypt: A single center study. *J Microbiol Infect Dis* 2012;2:44-9.
 19. Helal EG, Abu-Ouf N, El-Sayed AF, Mohamed NG, Ahmed MA. Hematological and immunological studies on the effect of hepatitis B virus vaccination in hepatitis and non-hepatitis, iron chelating dependent or independent Egyptian thalassemia patients. *Egypt J Hosp Med* 2013;53:1049-63.
 20. Ahmed FS, Joarder MS, Islam MN, Akter M, Kamal IM. Transfusion transmitted hepatitis B virus among multitrans fused thalassaemic children in a tertiary health care Centre in Bangladesh. *J Enam Med Coll* 2012;2:56-61.
 21. Singh S, Singh R, Kaul KK, Kour M. Study of serological parameters in thalassemic patients of GMC Jammu. *IOSR J Dent Med Sci* 2016;15:35-52.
 22. Rahman SA, Jamal CY. Congenital hemolytic anemia in Bangladesh: Types and clinical manifestations. *Indian Pediatr* 2002;39:574-7.
 23. Singh H, Pradhan M, Singh RL, Phadke S, Naik SR, Aggarwal R, *et al.* High frequency of hepatitis B virus infection in patients with beta-thalassemia receiving multiple transfusions. *Vox Sang* 2003;84:292-9.
 24. Gomber S, Yadav R, Dewan P, Ramachandran VG, Puri AS. Requirement of a booster dose of hepatitis B vaccine in children with thalassemia after 5 years of primary vaccination: A prospective study. *Indian Pediatr* 2021;58:237-40.
 25. Leuridan E, Van Damme P. Hepatitis B and the need for a booster dose. *Clin Infect Dis* 2011;53:68-75.