e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2022; 14(9); 441-445

Original Research Article

An Observational Assessment of the Requirement of a Booster Dose of Hepatitis B Vaccine in Children with Thalassemia 5 Years after Primary Vaccination

Amit Kumar[1], Bankey Bihari Singh[2], Ravindra Kumar[3]

[1]Senior Resident, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

[2]Associate Professor, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

[3]Associate Professor, Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India.

Received: 08-07-2022 / Revised: 27-07-2022 / Accepted: 19-08-2022
Corresponding author: Dr. Amit Kumar
Conflict of interest: Nil

Abstract

Background: Due to the frequent blood transfusions, thalassemia patients are more vulnerable to hepatitis than the general population.

Aim: To determine anti-HBs antibody levels in multi-transfused children with beta thalassemia major who had received primary hepatitis B vaccination ≥5 years ago, and to document their antibody response to a booster dose of hepatitis B vaccine.

Material & Methods: This study was conducted in the Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India, over a period of one year. A total of 60 children with beta-thalassemia major and 60 age-matched healthy controls who had documentary evidence of completion of primary hepatitis B vaccination schedule with three doses given more than five years ago, and without subsequent booster were recruited. Depending on how long it had been following the primary vaccination, participants were split into three groups. Group 1: 60–120 months, Group 2: 121–180 months, and Group 3: 181–240 months.

Results: A total of 63 children with beta-thalassemia major aged 5- 20 years were assessed for eligibility in the study; of which 60 (31 males) were included in the study; three subjects were excluded as two were HBsAg positive and one was anti-HBc positive. 60 age matched controls (38 males) were also recruited. Among the 14 seronegative children with beta thalassemia major, CD4 counts were normal in all except 1 children, IL-2 was detectable in only 2 children and IFN-γ was undetectable in all children. Even following antigenic stimulus (HBV booster), only 11 children had detectable IL-2 and five had detectable IFN-γ levels.

Conclusion: A single booster dose of hepatitis B vaccine after 5 years of primary immunization is adequate to provide seroprotection to multi-transfused children with beta-thalassemia major.

Keywords: Seroprotection, Infection, Immunity, Multi-transfused thalassemia.

Introduction

Thalassemia syndromes are the most common single gene disorder worldwide; about 3% of world population carries β - thalassemia genes. [1] Beta thalassemia major (β-TM) is an inherited hemoglobin disorder characterized by failure of production of beta hemoglobin chains; resulting in severe chronic hemolytic anemia requiring regular lifelong blood transfusions and daily iron chelation therapy, or stem cell transplantation to survive. [2]

A few studies have shown these children to have immune dysfunction, especially cell mediated immunity, possibly due to iron overload [3-6]. Contrarily, a few studies have also shown that this group has a particularly active humoral immune response due to repeated antigenic stimulation [5-7]. The long term seroprotection following hepatitis B vaccination has been reported as to vary from 13-80% [8-11] in different studies and the need for booster doses remains controversial.

Thus, we aim to determine anti-HBs antibody levels in multi-transfused children with beta thalassemia major who had received primary hepatitis B vaccination ≥5 years ago, and to document their antibody response to a booster dose of hepatitis B vaccine.

Material & Methods:

This study was conducted in the Department of Pediatrics, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar, India ,over a period of one year.

A total of 60 beta-thalassemia major children and 60 age-matched healthy controls who had documentation proving they had completed the primary hepatitis B vaccination schedule with three doses administered more than five years ago and without further booster were selected. The study excluded children who had hepatitis B infection or known immunodeficiency conditions like HIV infection. The beta-thalassemia major children's healthy siblings or the healthy individuals seeking outpatient care for non-life-threatening illnesses made up the control group.

A written informed consent was taken from the parents/guardians of all participants prior to recruitment in our study. An informed written assent was also obtained for all participants aged more than 12 years. Ethical clearance was obtained from the institutional ethics committee.

Depending on how long it had been following the primary vaccination, participants were split into three groups: Group 1: 60–120 months, Group 2: 121–180 months, and Group 3: 181 –240 months.

For baseline tests (anti-HBc IgG, HBs Ag, anti-HBs, and anti-HCV) on each subject, a 2 mL venous blood sample was taken. Using ELISA-based kits, HBs Ag, anti-HCV, and anti-HBc levels were measured (Biored, France). ELISA-based kits were used to measure the anti-HBs titers (DIAPRO). Anti-HBs 10 mIU/mL was used to define seroprotection.

Before receiving a single booster dose of the recombinant hepatitis B vaccination intramuscularly in a dose of 10 μg for individuals younger than 20 years or 20 μg for patients aged 20 years or older, all seronegative children with beta-thalassemia major underwent immunological testing. Immunological processes as determined by the Mantoux test, cytokine assays (IL-2, IFN- γ), and absolute CD4 count (intradermal test following 5TU). Children with beta thalassemia major had their IL-2, IFN-γ, and anti-HBs titers checked before and 4-6 weeks after receiving the booster dose of the hepatitis B vaccine.

To measure the CD4+ cells using flow cytometry, 2 mL of fresh whole blood was collected in heparinized tubes (BD FACS

Count). Using ELISA-based kits, cytokines (IL 2, IFN-γ) in serum were analyzed (Diaclone).

Statistical analyses: Chi-square test was used for comparing the proportion of seroprotection between children with beta thalassemia major and those without thalassemia. Unpaired student t test was used for comparing the anti-HBs titers between groups and also the serum ferritin levels between the seroprotected and seronegative children with beta-thalassemia major. SPSS software version 25 was used for analysis.

Results:

A total of 63 children with beta-thalassemia major aged 5- 20 years were assessed for eligibility in the study; of which 60 (31 males) were included in the study; three subjects were excluded as two were HBsAg positive and one was anti-HBc positive. 60 age matched controls (38 males) were also recruited.

A total of 14 children with beta-thalassemia major were found to lack seroprotective titers following primary hepatitis B vaccination. Their mean (SD) age was 11.31 (4.3) years with a mean (SD) time lag between completion of primary hepatitis B vaccination and estimation of anti- HBs titers as 11 (3.5) years. All of them were administered a booster dose of hepatitis B vaccine. Anti-HBs titers estimated after 4.1 (0.83) weeks were >10 mIU/mL for all children. The median (IQR) of anti-HBs titers before and after booster dose of hepatitis B vaccine was 5.3 (1.5-8.6) mIU/mL and 271.46 ((174.8-356.8)) mIU/mL, respectively; 10 children had anti-HBs titers >100 mIU/mL.

Among the 14 seronegative children with beta thalassemia major, CD4 counts were normal in all except 1 children, IL-2 was detectable in only 2 children and IFN-γ was undetectable in all children. Even following antigenic stimulus (HBV booster), only 11 children had detectable IL-2 and five had detectable IFN-γ levels.

Table I Response to a Single Booster Dose of Recombinant Hepatitis B Vaccine in Children with Thalassemia Having Anti-HBs Titre <10 IU/ML after Primary Hepatitis B Vaccination (n=14)

Parameter	Before booster dose	After booster dose
Anti-HBs titers (mIU/mL)	5.3	271.46
	(1.5-8.6)	(174.8-356.8)
Interleukin 2 levels (pg/mL)	0	0 (0-1583)
CD4 count (cells/mm^3)	877 (692-1192)	-

Discussion:

Several studies with controversial results regarding the immunity level and duration of acquired immunity from hepatitis B vaccination have been performed in different countries.

Azarkar Z et al in their study found Serum levels of anti HBS-Ab, subjects were categorized as: Good responder (anti HBS> 100 IU/lit) (34.2%) Low responder (anti-HBS 10-100 IU/lit) (23.7%) Non responder (anti-HBS < 10 IU/lit) (42.1 %).

In the present study all children had Serum levels of anti HBS-Ab >10 IU/lit so all were either low or good responder ([9]

A study in Iran on 215 thalassemic children age ranged between 1-4.5 years. Based on the time lapsed since last vaccine injection, the subjects were divided into three groups; 0-15 months, 15-30 months and 30-45 months, respectively The mean range of anti-HBs level in the above mentioned groups were 205.34, 128.8 and

54.25 IU/lit, respectively. 75 (35%) were good responders, 65(30%) low responders and 75 (35%) non-responder. [10]

In another study on 98 patients with thalassemia major, 78% of the cases were low or good responders, 6 years after vaccination. [12]

In Spain, serum anti-HBS level was evaluated 6.5 years after vaccination. In this study, 85% of the immunized patients had complete immunity after 6.5 years; therefore, administration of booster dose was not advised. [13].

In Taiwan, 15 years after vaccinating the neonates, 75% were anti-HBS positive, but the level was not detected. [14] In another study in Spain on a pre-pubertal group, 50% of those vaccinated had serum protective anti-HBS level after 7.5-10 years. It was suggested to have a booster dose, 10 years after the primary vaccination to acquire complete immunity. [15]

An Egyptian study performed in Ismailia governorate found the percent of good responders (Anti-HBs titer>100 IU) to decline from 75.3% one month after vaccination to 28% after one year follow up of the same patients. The protective titer (>10 IU) in that study was reported in 93.7% after one month versus 82% after one year follow up. [16]

A few studies have suggested that a possible reason for having higher protection rate is due to passive transport of anti-HBs antibodies through the donor blood [17-19].

Conclusion:

A single booster dose of hepatitis B vaccine after 5 years of primary immunization is adequate to provide seroprotection to multi-transfused children with beta-thalassemia major.

References:

1. Sexana A, Phadke SR. Feasibility of thalassemia control by extended family screening in Indian context. J Health Popul Nutr 2002; 20:31-35.
2. Rund D, Rachmilewitz E. ß-Thalassemia. N Engl J Med 2005; 353: 1135-1146.
3. Gharagozloo M, Karimi M, Amirghofran Z. Double-faced cell-mediated immunity in beta-thalassemia major: Stimulated phenotype versus suppressed activity. Ann Hematol. 200 9;88:21-7.
4. Dwyer J, Wood C, McNamara J, et al. Abnormalities in the immune system of children with beta-thalassaemia major. Clin Exp Immunol. 1987;68:621-9.
5. Pardalos G, Kanakoudi-Tsakalidis F, Malaka-Zafiriu M, et al. Iron-related disturbances of cell-mediated immunity in multitrans fused children with thalassemia major. Clin Exp Immunol. 1987;68:138-45.
6. Bao W, Zhong H, Li X, et al. Immune regulation in chronically transfused allo-antibody responder and nonresponder patients with sickle cell disease and beta-thalassemia major. Am J Hematol. 2011;86:1001-6.
7. Amin A, Jalali S, Amin R, Aale-yasin S, Jamalian N, Karimi M. Evaluation of the serum levels of immunoglobulin and complements factors in Beta thalassemia major patients in southern Iran. Iran J Immunol. 2005;2:220-5.
8. Soliman HH, Kabbash IA, 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. Accessed June 3, 2019. Available from: https://dergipark.org.tr/download/articlefile/104992.
9. Azarkar Z, Sharifzadeh G. Efficacy of HBV vaccination in children with thalassemia major, South Khorasan, Iran. Iran Red Crescent Med J. 2009; 1:318.
10. 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;3:30-4.
11. Dentico P, Buongiorno R, Volpe A, Zavoianni A, De Mattia D, Sabato V. Long-term persistence of anti-HBs after hepatitis B immunization in thalassaemic patients. Infection. 1992;20:276-8.
12. Hepatitis Group. An Essay on durability of hepatitis B antibody in health services staff and the thalassemic patients, six years after vaccination in Sari. J Mazandaran Univ Med Sci 2001;32:60-5.
13. Ayerbe MC, Pérez-Rivilla A; ICOVAHB group. Assessment of long term efficacy of hepatitis B vaccine. Eur J Epidemiol 2001;17:150-6.
14. Ni YH, Chang MH, Huang LM, Chen HL, Hsu HY, Chiu TY, Tsai KS, Chen DS. Hepatitis B virus infection in children and adolescents in a hyperendemic area: 15 years after mass hepatitis B vaccination. Ann Intern Med 2001;135:796-800.
15. Simo Minana J, Gaztambide Ganuza M, Fernandez Millan P, Pena Fernandez M. Hepatitis B vaccine immunoresponsiveness in adolescents: a revaccination proposal after primary vaccination. Vaccine 1996; 14:103-6.
16. El Ghandour S, El Sayed H, Abdel Hamid A, Gad S. Effectiveness of Hepatitis B Vaccination in Egyptian infants in Ismailia Governorate. Suez Canal University Med J 1998; 1:123-130.
17. Gulati S, Marwaha RK, Dilawari JB, Midha U, Walia BN. Serological responses to hepatitis B virus infection in multitrans fused thalassemic children. Indian Pediatrics. 1992; 29:7 3-7.
18. Ramrakhyani K, Dilawari JB, Verma S, et al. Hepatitis B viral markers and liver disease in haemophiliacs: A study in an Indian population. J Gastroenterol Hepatol. 1988;3:4379.
19. Madjiténgar Rataïngar, Baba Diallo, Fidèle Binam, Alexandre Nkoum, Samson Nkoumou, Aboubacar S.T. Kane, Oumar Sangho, & Aissata Koné dite Néné Tjini. Treatment of strokes in the emergency department of N'Djamena general hospital: study of delays, care and clinical course of patients in the first hours. Journal of Medical Research and Health Sciences, 2021;4(9): 1451–1455.