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The average of HBS antibody titer in different months after hepatitis B premier vaccination.

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Abstract

Background: Vaccination is the most effective prevention in Hepatitis B, so this study aimed to compare the average of antibody titer (anti-HBs) in various age after the last given of Hepatitis B premier vaccination.

Method: Inclusion criteria including the record of hepatitis B Immunization was 4 times and parents had sign the consent form, while exclusion criteria including mother with Positive HBsAg, infants with poor nutrition, congenital disease and the last received hepatitis B vaccination was less than a month. The data were analyzed by using descriptive method and Kruskal Wallis Test.

Result: 84 infants age 5-7 months was divided into three groups based on how long it has been since the last given of hepatitis B vaccination. Group 1 consists of 25 infants, 18 infants were protected with average of anti-HBs 107.12 mIU/ml. Group 2 consisted of 22 infants, 15 were protected with average of anti-HBs 162.5 mIU/ml. Group 3 consist of 37 infants, 24 infants were protected with average of anti-HBs 85.93 mIU/ml. Kruskal Wallis Analysis result showed no significant difference among the three groups with p=0.322.

Conclusion: There was no significant difference of HBs antibody titter in 1,2, and 3 months after hepatitis B vaccination.

Keywords: Hepatitis B, Vaccination, HBs antibody titer.

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Introduction

Hepatitis B virus (HBV) has spread throughout the world and it is estimated that more than 2 billion people are infected by HBV. In low endemic areas such as United States, Northern Europe, Australia, hepatitis B carrier prevalence was <2%, while in high endemic areas such as Southeast Asia, Africa, Brazil, it was about 8%. In Indonesia, 9.4% of the population has been infected. Prenatal transmission is the most common routes of infection in developing countries. The most effective prevention to prevent prenatal transmission is by giving hepatitis B vaccination. In Indonesia, first hepatitis B immunization was done by giving a *uniject* injection (containing HBsAg 10 mcg) as early as possible within 12 h after birth. The following three doses will be given at age 2, 3 and 4 months with a combination vaccine consisting of diphtheria, pertussis, tetanus, hepatitis B and Haemophilus influenza type B [1-3].

An antibody titer against hepatitis B surface antigen (≥ 10 mIU/ml) measured 1-3 months after the last dose of vaccination Primary hepatitis B is considered a marker for short and long term protection against hepatitis B infection. The antibody titer in the body is affected by several factors such as age of first immunization, sex, child nutritional status, birth weight, distance between immunization time, vaccine type, vaccine quality and quantity, vaccine properties, injection route, injection site, immunization dose, immune status (HBsAg) Mother, host immunity status, maternal age at delivery, maternal education level, socioeconomic level of the elderly, genetic factors and endemicity of hepatitis B virus in the area [1,2,4,5].

This study aimed to compare anti-HBs titer examination at 1, 2, and 3 months after the last dose of primary hepatitis B vaccination.

Method

This study is a comparative study with cross sectional design done in outpatient clinic of RSUP Prof. Dr. RD Kandou and Puskesmas Tuminting, Manado from October to December 2016. The subjects were infants aged 5-7

months who received four doses of hepatitis B vaccination at birth, and then at 2 months, 3 months and 4 months received a combination vaccine as evidenced by the records in immunization books. Parents are given an explanation and if willing to follow the research it will sign informed consent. Exclusion criteria were mothers with positive HBsAg, infants with malnutrition, congenital aberration and recent hepatitis B vaccination less than 1 month ago. The subjects were divided into 3 groups, group 1 was screened for anti-HBs titer 1 month after the last Hepatitis B vaccination (age 5 months), group 2 at 2 months after the last Hepatitis B vaccination (age 6 months) and group 3 at 3 months after Hepatitis B vaccination (age 7 months).

A sample of 3 ml of blood was taken using a needle connected to a vacuumtainer of infants meeting the inclusion criteria. Blood samples were then sent to the laboratory for anti-HBs examination with Chemiluminescent Microparticle Immunoassay (CMIA). Anti-HBs titer <10 mIU/ml is categorized as non-responder and anti-HBs titer ≥ 10 mIU /ml is categorized as responder [6].

The minimum number of samples required for this study was 80 children. This study was approved by the ethics committee of Prof. Dr. Ir. Dr. R.D Kandou and the ethics committee of the Faculty of Medicine, University of Sam Ratulangi. Data were analyzed by descriptive analysis and Kruskal Wallis test using SPSS version 23.

Results

Out of 96 children who met the inclusion criteria, 3 samples was excluded due to parents rejection and 9 samples was lysis (parents did not allow to taking blood samples) so, there was only 84 children who met the inclusion and exclusion criteria in this study. Characteristic of the study sample can be seen in Table 1.

84 children age 5-7 months who met the criteria of the study was later divided into three groups based on how long it has been since the last given of hepatitis B vaccination. Group 1 (one month after vaccination) consist of 25 infants, only 18 infants were protected with average of anti-HBs 107.12 (17.02-245.56) mIU/ml. Group 2 consisted of 22 infants, but only 15 were protected with average of anti-HBs 162.5 (16.26-518.47) mIU/ml. Group 3 consist of 37 infants, 24 infants were protected with average of anti-HBs 85.93 (11.82-320.33) mIU/ml. Kruskal Wallis Analysis result showed no significant difference among the three groups with p=0.322.

Table 1. *Characteristic of sample*

Characteristics	Total (%), n=84
Sex	
Male	45 (53.6)
Female	39 (46.4)
Age	
5 months	25 (29.7)
6 months	22 (26.3)
7 months	37 (44.0)
Gestational Age	
≥ 37 weeks	56 (66.7)
<37 weeks	28 (33.3)

Discussion

This study was conducted on 45 male infants and 39 female infants, and there was no significant difference of seroprotection between the two groups (p=0.392). It was similar with the study by Cheang et al. [6] which found that gender did not associate with seroprotection Hepatitis B and the immune response after primary hepatitis B immunization in this study; there were infants with small gestational age and appropriate gestational age. However, advanced analysis was not done on that part. Some studies got prevalence and seroprotection value of anti-HBs titer after three months of the third hepatitis B immunization was lower in premature infants [7-9]. Meanwhile, some other studies did not found any difference of prevalence and seroprotection value of anti-HBs titer in both groups of infants [10-12].

This study took infants aged 5-7 months as the sample because of the World Health Organization (WHO) stated that a 10 mIU/ml anti-HBs titer measured 1-3 months after the last dose of hepatitis B immunization is a long-term protective marker of hepatitis B infection [13]. American Academy of Pediatrics (AAP) recommended the examination of anti-HBs titer after immunization at 1-2 months after the third dose of vaccination under certain conditions [14]. All study subjects received mandatory hepatitis B immunization at 0, 2, 3 and 4 months as recommended by the Ministry of Health of Indonesia. At the age of 0 month, infants would receive hepatitis B immunization in *uniject* packaging, while at age 2, 3 and 4 months would receive combine immunization of DTP-hepatitis B-HiB [15].

Analysis with Kruskal Wallis test showed that there was no significant difference in average of anti HBs titer between the three groups. Hepatitis B antigen (HBsAg) in hepatitis B vaccine will be presented by dendritic cells which have a function as antigen presenting cell (APC). Dendritic cells, binds to the T cell receptor on the CD8+T via the Major Histocompatibility complex (MHC) class II and CD4+Th0 through cell MHC class I CD8+T will

Table 2. *Seroprotection of anti-HBs titer*

Age	N	Median (mIU/mL) (Minimum-Maximum)	p*
5 months	18	107.12 (17.02-245.56)	p=0.322
6 months	15	162.5 (16.26-518.47)	
7 months	24	85.93 (11.82-320.33)	

* Kruskal Wallis Test

proliferate into cytotoxic T cells to stimulate the secretion of Interleukin-2 (IL-2). Interferon-St (IFN-St) stimulation will cause the proliferation of CD4+Th0 cells into Th1 cells which then become T memory cells and activate macrophages. Meanwhile, through the stimulation of IL-4, CD4+Th0 will proliferate into Th2 cells then bind to MHC class I molecules on the cell receptor B (T dependent) causing the activation and proliferation of B cells become memory cells B and plasma cells that produce antibodies -HBs. Secondary immune responses occur faster and more effectively because memory T cell and memory B cell activity and immunoglobulin (Ig) production are higher with IgG dominance [16].

Anti-HBs antibodies are T dependent. Bauer et al. [17] did research by inducing lymphocytes B with HBsAg in the absence of T lymphocytes The study found that there is no B lymphocytes that produce antibodies, this indicates that the anti-HBs production depends on the presence of T lymphocytes (T-dependent). Adequate stimulation of T lymphocytes induces proliferation and differentiation of B cells into plasma cells that produce immunoglobulins and memory cells. T cells themselves multiply and differentiate into effectors T cells and T memory cells that will be highly effective in secondary immune responses.

The study of Cheang et al. [18] in Malaysia in 572 infants (mean age 8.3 ± 2.7 months, range 6.3-48 months) received 553 infants (96.7%) had anti-HBs titer ≥ 10 mIU/ml while 14 (3.2%) of infants in this study were infected with hepatitis B. Research by Qawasmi et al [19] in 400 children in Palestine who received Hepatitis B immunization found that the anamnestic immune response was not affected by age (p=0.392). Studies by Zhang et al. [20] in infants who received full Hepatitis B immunization in China mentioned that sex, gestational age, birth weight, and age did not affect anti-HBs titers. The study also suggests that immune memory responses can last up to 5 years after primary hepatitis B immunization. Rampengan et al. [4] in his study found that first hepatitis B ≤ age 7 days and second and third hepatitis B intervals ≥ 2 months were factors affecting anti-titer-HBs. McMahon dkk17 in a study to get as much as 81% of the subjects had anti-HBs titers were protective in 60 days after immunization of Hepatitis B. Other factors that may affect the titer of anti-HBs were including the quality and quantity of vaccine (the route of administration, dosage, frequency of administration, Adjuvant use, and type of vaccine), host immune status and genetic factors [21,22].

The limitations of this study are cross sectional design so it is difficult to obtain anti-HBs titer data from time to time. In addition, no data on other factors could affect anti-HBs titers such as the quality and quantity of vaccines, gestational age, and immune status of the study subjects.

Conclusion

In conclusion there was no difference in average of anti HBs titer at 1, 2 and 3 months after primary hepatitis B vaccination.

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