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Characteristic of immune response of hepatitis B immunization on infants with two different schedules

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ABSTRACT Hepatitis B immunization gives protection to hepatitis B disease. The purpose of this study was to assess the immune response of hepatitis B immunization on infants with 0,2,9 and 3,4,9 months of age schedule. The study was performed cross sectionally at the Child Health clinic of Social Pediatric sub division H. Adam Malik Hospital from November 1st 1998 until February 28th 1999. The anti HBs responses were examined in blood by ELISA method one month after the third immunization at the Clinical Pathology Division FK-USU/H. Adam Malik Hospital. Protective immune response defined if the anti HBs level ³ 10 mIU/ml. Nutritional status of infants were grouped according to the NCHS classification. The result obtained were statistically tested by Fisher exact test and t-test, on the level of significance $p < 0.05$. Twenty six (86.7%) of the infants had protective immune response and there were no significant difference on the level of immune response among these two groups. Gender and nutritional status seems to have no influence on the anti HBs level. In Conclusion, hepatitis B immunization either with 0,2,9 or 3,4,9 months of age schedule obtained the same immune response. **[Paediatr Indones 2001; 41:197-201]**

Keywords: *Hepatitis B, immune response, immunization*

HEPATITIS B VIRUS (HBV) INFECTION AND DISEASE are major public health problems with an estimated 350 million carriers of virus worldwide whereas 78% of them were found in Asia and over a million of deaths attributable annually.[1-3] Indonesia is classified as an area with moderate to high endemicity of HBV. In this setting, the dominant mode of transmission is a transmission from infected mothers to their infants and young children.[2-9] Management of hepatitis B patient especially in children is still become a problem until now. There is no effective drug that can be used. So, in area with high endemicity, World Health Organisation (WHO) recommended immunization to break the chain of infection, reduce the pool of virus carriers and ultimately reduce the burden of serious liver disease.[9] Effectiveness of immunization depends on some conditions, such as age of recipient, sex, genetic, infection disease, immunity sistem of the body, type of vaccine, dosage, schedule, location and frequency of injection.[2] There are some schedules recommended by WHO, AAP or ACIP but all of them suggest to integrate the hepatitis B immunization schedule into the current schedule for extended program on immunization (EPI).[9] In Indonesia, hepatitis B mass immunization program begun in 1996/1997 and the Indonesian Health and Social Department suggest two schedules, a 0, 2, 9 month of age for infants born in hospital and a 3, 4, 9 months of age for infants born outside the hospital or children coming further to hospital and posyandu.[11]

The objective of this study was to assess the level of immune response of hepatitis B immunization on infants with these two different schedules.

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Methods

The study was carried out cross sectionally at the Child Health Clinic of Social Pediatric Sub Division from November 1st 1998 to February 28th 1999. The inclusion criteria were healthy male and female infants, age < 10 months, and fullterm babies borned spontaneously without asphyxia given HB basic immunization of 3 times (with the schedules 0, 2, 9 or 3, 4, 9 months of age). They were excluded if premature infants and mother or infants suffered from icteric or hepatitis. We used HB plasma vaccine from Biofarma , each injection was 0.5 cc, given intramuscularly on anterolateral thigh. Sample size was calculated by using formula : $n = \frac{(Z\alpha)^2 PQ}{(d)^2}$. The total subjects needed for each schedule were 15 infants. Response immune (anti HBs) level in blood was examined by ELISA one month following the third immunization at the Clinical Pathology Division H. Adam Malik Hospital. Protective immune response defined as anti HBs level not less than 10 mIU/ml. These result was further classified into : non response if there were no anti HBs found, low response if anti HBs < 10 mIU/ml, moderate response if anti HBs between 10-100 mIU/ml, high response if anti HBs level > 100 mIU/ml. Nutritional status was determined based on body weight to age as classified according to NCHS standard as: well nourished if the body weight to age was more than –1 SD, mild malnutrition if the body weight to age was -2 SD or less and less than -1 SD, moderate malnutrition if the body weight to age was -3 SD or less and less than -2 SD and severe malnutrition if the body weight to age was more than -3 SD. Body weight measured by using baby scale (Kubota) with 100 mg precision. Data were analyzed by Fisher exact test and t-test using SPSS computer program, 95% confident interval were supplied and level of significance was $p < 0.05$.

Results

Eighteen (60%) infants were males and 12 (40%) were females. There were 14 (46.7%) infants with mild malnutrition but no infants with severe malnutrition. More details of the subjects characteristic were presented on table 1.

Most of the infants seemed to be in good response to the hepatitis B immunization. Twenty nine (96.7%) of the infants had positive immune response consisted of 16 (100%) infants using the 3, 4, 9 months of age schedule and 13 (93%) infants using the 0, 2, 9 months of age schedule. There was no difference on immune response of this two groups statistically. (Table 2)

Protective immune response was found on 26 (86.7%) of the infants where 15 (93.7%) of them on the 3, 4, 9 month of age group and 11 (78.6%) from the 0, 2, 9 month of age group schedule. But this difference not statistically significant ($p > 0.05$). (Table 3)

High immune response were found in almost all of the two groups of immunization and the non response case was only one of the 0, 2, 9 months of age schedule group as shown on table 4.

The GMT of 0, 2, 9 months of age schedule were 184.3 mIU/ml higher than GMT from 3, 4, 9 months of age schedule were 130.8 mIU/ml, although this difference was not statistically different. (Table 5)

According to the distribution frequency of the GMT, the most frequent GMT found was 217.7 mIU/ml. (Table 6) There was no influence of gender on immune response found in this study, whereas 16 (88.9%) of males produced protective immune response compared to 10 (83.3%) of females. (Table 7)

Mild malnutrition produced the highest percentage of protective immune response while the non protective immune response happened in two infants of the well-nourished group and one of the mild and moderate malnutrition. (Table 8)

Discussion

Hepatitis B vaccine is known as an effective, safe and highly immunogenic vaccine especially when used to infant, young children and adolescent.[12,13] From the 30 infants, 29 (96,7%) of them produced positive seroconversion. Previous study by Moyes et al[2] found seroconversion rate 86% - 98%. Alisjahbana et al[14] in Bandung reported a seconversion rate of 96%.

TABLE 1. CHARACTERISTIC OF THE SUBJECTS

Characteristic	n	%
Gender		
Male	18	60
Female	12	40
Nutritional status		
Well-nourished	10	33
Mild malnutrition	14	47
Moderate malnutrition	6	20
Severe malnutrition -	-	
Immunization schedule of		
0, 2, 9 month	14	47
3, 4 ,9 month	16	53

TABLE 2. ASSOCIATION BETWEEN IMMUNE RESPONSE AND IMMUNIZATION SCHEDULE

Immunization schedule (mo)	Immune response (+)	(-)	Total
0, 2, 9	13	1	14
3, 4, 9	16	0	0
Total	29	1	30

Fisher exact test x^2=0.467 df = 1 p>0.05

TABLE 3. ASSOCIATION BETWEEN PROTECTIVE IMMUNE RESPONSE AND IMMUNIZATION SCHEDULE

Immunization schedule	Protective immune response (+)	(-)	Total
0, 2, 9	11	3	14
3, 4, 9	15	1	16
Total	26	4	30

Fisher exact test x^2=0.315 df = 1 p>0.05

Note: Positive protective immune response if anti HBs ³ 10 mIU/ml
Negative protective immune response if anti HBs < 10 mIU/ml

Hepatitis B immunization produce protection to hepatitis B disease if the anti HBs level ³ 10 mIU/ml. This study found that most of the infants, 26 (86,7%) had protective immune response. Hepatitis B immunization assumed to be an effective program of immunization if the seroconversion rate between 70-

TABLE 4. COMPARISON OF THE LEVEL OF IMMUNE RESPONSE ACCORDING TO IMMUNIZATION SCHEDULE

Immunization schedule (mo)	Immune response High	Mod	Low	NR	Total
0, 2, 9	9	2	2	1	14
3, 4, 9	11	4	1	0	16
Total	20	6	3	1	30

Mod = moderate; NR = non-response
Non response : anti HBs (-), Low : anti HBs< 10 mIU/ml,
Moderate : anti HBs 10-100 mIU/ml, High : anti HBs > 100 mIU/ml

TABLE 5. COMPARISON OF GMT AND RANGE OF IMMUNE RESPONSE ACCORDING TO IMMUNIZATION SCHEDULE

Immunization schedule (mo)	GMT	Range of immune response Lowest (mIU/ml)	Highest (mIU/ml)	Total
0, 2, 9	184.3	7.1	1018	14
3, 4, 9	130.8	9.9	239	16

t = 0.783 df=28 p= 0.448

TABLE 6. DISTRIBUTION FREQUENCY OF THE GMT

HbsAb titre (mIU/ml)	GMT (mIU/ml)	SD	n	Total
(-)	0	0		1
< 10	8.3	1.4		3
10 – 100	48.3	31.9		6
> 100	217.7	199.8		20

TABLE 7. RELATIONSHIP BETWEEN PROTECTIVE AND NON PROTECTIVE IMMUNE RESPONSE WITH GENDER

Gender	Protective immune response (+)	(-)	Total n
Boy	16	2	18
Girl	10	2	12
Total	26	4	30

Fisher exact test x^2=1 df = 1 p>0.05

TABLE 8. RELATIONSHIP BETWEEN PROTECTIVE AND NON PROTECTIVE IMMUNE RESPONSE WITH NUTRITIONAL STATUS

Nutritional status	Protective immune response (+)	(-)	Total n
Well -nourished	8	2	10
Mild malnutrition	13	1	14
Moderate malnutrition	5	1	6
Severe malnutrition	-	-	-
Total	26	4	30

90%. Former study by Chirico[15] shown that seroconversion rate of 98% and other study by West et al[10] reportedseroconvertion rate of 94 -100%. Higher immune response found if there was the longer interval between second and third immunization.

Everybody had different level of response to hepatitis B immunization, where it could become a non response, low response, moderate response and high response. The non response group of infants was estimated between 2-5%.[7] From all subjects of this study, 20 (66.7%) of them produced high response and the low response found in 3 (10%) subjects. A previous study by Jilg et al[16] found that the number of low response was 7.8%, moderate response 25.9%, high response 39.7% and very high response 24.7%. Wiharta et al[8] reported the non response case was 3.5% and the low response was 13.8%.

According to the relationship between GMT and the immunization schedule, we found that GMT on the 0, 2, 9 months of age was 184.3 mIU/ml and on the 3, 4, 9 months of age was 130.8 mIU/ml. Previous study by Poovorawan et al[17] found that GMT on 0,1,6 months of age was 317 mIU/ml and on 0, 2, 9 months of age was 165 mIU/ml. West et al[10] reported that GMT is higher if the interval between the second and third immunization longer. Alisjahbana et al[14] in Bandung got GMT 69 mIU/ml.

This study used plasma vaccine. Alisjahbana et al[14] reported that safety, immunogenecity and efficacy of plasma vaccine was the same with recombinant vaccine. Chirico et al[15] found that there was no difference in efficacy between plasma and recombinant vaccine.

This study found that gender was not influence the immune response ($p > 0.05$). Former study by Chirico et al[15] found that there was no influence of birth weight, gender and way of feeding in immune response. Wiryo[4] and Kayserling[18] found that girls produce better immune response than boys.

Most of the infants, 14 (46.7%) had moderate malnutrition and no infant with severe malnutrition. Protective immune response found mostly on the moderate malnutrition group. Non protective immune response got two cases on well-nourished and one on the mild and moderate malnutrition.

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