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Research Report

Comparison of Neutralizing Antibody Response to Type 1 Polio Virus on Healthy Infants Receiving either Oral Monovalen Polio Vaccine Type 1 or Oral Trivalen Polio Vaccine Given with Basic DTP/Hb Immunization

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ABSTRACT

In March 2005, there was outbreak of Polio-1 and expanded throughout Java and Sumatera island. Oral monovalent polio vaccine type 1 (mOPV1) had succeeded in evereeming polio outbreak in Indonesia in 2005. This study aimed to compare neutralizing antibody response to type 1 polio virus in healthy infants receiving either mOPV1 or oral trivalent Polio Vaccine (tOPV), given with other basic vaccination (DTP/HB). Randomized controlled singel blind clinical trial on healthy infants range age 42 to 80 days who had received first oral polio vaccine before 1 month of age. Trial group received mOPV1 and control group tOPV, each had 3 times of vaccination. Blood samples were taken three times (pre vaccination, post second and third vaccination) for measurement of neutralizing antibody to polio virus. Thirty subjects from mOPV1 group and 29 from tOPV group were analyzed. Post second vaccination, mOPV1 group (456) had more increase in geometric mean titer of neutralizing antibody than tOPV group (317) but not significant (p=0.514). Post third vaccination the level of neutralizing antibody titer was almost equal in both groups. Proportion of seroconversion to type 1 polio virus in mOPV1 group 53.9%, 57.7% and tOPV group 25.9%, 41.7% (on second and third evaluation respectively), both were statistically insignificant. Antibody response measured by neutralizing antibody titer and proportion of seroconversion on antibody to type 1 polio virus in healthy infants receiving mOPV1 vaccination was similar to they receiving tOPV.

Key words: *healthy infants, mOPV1, tOPV, neutralizing antibody, polio*

INTRODUCTION

In March 2005, there was an outbreak of Polio-1 virus infection expanded throughout Java and Sumatera island, caused by an importation of type 1 wild poliovirus/WPV. Prior to this outbreak Indonesia had been polio free since 1995. The National Polio Laboratory in Bandung reported 305 wild poliovirus isolates from 1500 cases of acute flaccid paralysis (AFP) in population aged < 15 years. Sub-National Immunization Day (SNID) and National Immunization Days with and monovalent oral polio vaccine type 1 (mOPV1) had succeeded in overcoming polio outbreak in Indonesia in 2005.[1]

There were several factors contributing for polio outbreak. The presence of source of infection and fecal transmission may enhance transmission in communities with poor sanitation. Other factors include seasonal duration of tropical condition and inadeguately vaccinated population. OPV immunization status of wild polio cases in Indonesia revealed about 37% was not immunized, 52% had 1 to 3 doses of polio vaccination and 11 % received at least 4 doses of OPV. Data from the 2005, national polio vaccination coverage was less than 80% (77.6%), although during fifteen years before the coverage was more than 80%.[1-3]

There is strong scientific evidence that the efficacy of mOPV1 is much greater than tOPV in inducing immunity against WPV1 (as much as 3 times higher per dose). This is because, with tOPV, there is competition among the three virus types to elicit immune response; the virus-attenuated vaccine particles attach themselves to the gut and tend to bring down the overall efficacy against a single virus type. This confirms that mOPV is a patent weapon against transmision, and the mOPV1 is as safe as tOPV.[4,5]

Halsey and Galazka (1985) describe several ways af assesing immunity against poliomyelitis : 1) measurement of serum neutralizing antibodies; 2) measurement of secretory antibodies in feces, duodenal secretions, nasopharyngeal secretions, or breast milk; 3) examination of previously immunized persons for the absence of poliovirus in the stool or throat following natural challenge with type virus or following challenge with a dose of attenuated oral polio vaccine and; 4) measurement of protective efficacy, e.g. prevention of paralytic disease in immunized persons as compared to unimmunized persons in exponsed populations, using epidemiologic methods.[6]

This study aimed to compare neutralizing antibody response to polio-1 virus in healthy infants receiving either mOPV1 or oral trivalent Polio Vaccine (tOPV), given with other basic vaccination (DTP/HB).

METHODS

This research was a randomized single blind controlled trial which was compares pre and post intervebtion, with comparison group as a control. Subject was healty baby 42-80 days old that has vaccinated with mOPV1 while control has vaccinated with tOPV. Each vaccination has given three times with 28-36 days interval. It given coincided with basic immunization combo DTP/HB to both groups. Blood sample was taken three times, which was at the same moment before the first and third vaccination and 28–36 days after third immunization. Neutralization antibody titre measured from blood serum by micro neutralization assay based on WHO standard. The value of neutralization antibody titre determined according to cytopathogenic effect at dilution dose of antibody that was mixed. [7] This research was approached at Primary Health Care in Surabaya at 2007–2008.

Inclusion criteria included healthy baby without any congenital or severe diseases which need special treatment, born spontaneously or by elective caesarean section without any emergency signs, gestational pregnancy age 37-<42 weeks, birth weight ≥ 2500 grams, and has gotten their first tOPV drop immunization at <1 month old. Subject excluded from trial if there is a severe reaction after vaccination (such as fever > 40º C, severe crying more than 3 hours, convulsion, and encephalopathy), can not finish basic immunization and their existence undetectable before the research finish.

Neutralization antibody stated in Geometric Mean Titre (GMT) of neutralization antibody and antibody seroconversion proportion. Seroconversion was difined as a fourfold rise in neutralizing antibody titer or a change from seronegative to seropositive. Seropositive was defined as a titer of 1:8 or higher.

Data analysis used was Chi-Square test, independent-samples t-test, and Mann-Whitney U test. Ethical proper reference of this research stated by Lembaga Penelitian dan Pengabdian kepada Masyarakat, University of Airlangga, Surabaya.

RESULTS

There was 30 subjects of approach group and 29 subject of control group. Total blood serum sample which respectable to measure was 169. Consist of mOPV1: S1 (pre vaccination) = 29; S2 (after second vaccination) = 29 and S3 (after third vaccination) = 29. In the tOPV group: S1= 29; S2= 28; and S3 = 25. Eight blood samples could not be measured because it was too little (4 samples) and lysis (4 samples). Subject characteristic mentioned in Table 1.

Table 1. Characteristic of Research's subject

	mOPV1 group (n=30)	tOPV group (n=29)	*P*
A. Range of Subject Characteristic			
- Sex			
Male	57%	45%	
Female	43%	55%	
- History of Labour			
Spontaneously	93%	93%	
Elective SC	7%	7%	
- Mean of weight birth [gram]	3213	3225	
B. Basic data of early research			
- Mean of Age [days]	56	57	0,733*
- Mean of body weight [gram]	5003	4941	0,753*
- Nutritional status Good	100%	100%	-
- GMT antibod			
Polio-1	69	105	0,37*
Polio-2	152	140	1*
Polio-3	43	75	0,277*

Exp. GMT (Geometric Mean Titre). * independent-samples t-test. ** Mann-Whitney U test

After four months research process, nutritional status and frequency of illness were disturbance factors that could influence the result of the research. Calculation of nutritional status based on Z score (age/weight) during 4 times attendance, showed good nutritional status to both groups. Total of incident of illness and days of illness in inpatient has no significant difference in both groups (p>0.05).

After second vaccination GMT Polio-1 antibody, mOPV1 group over tOPV group but not significant (p=0.514), and after third vaccination the value of GMT antibody was similar. The value of GMT Polio-2 antibody (after second vaccination) and Polio-3 (after second and

Table 2. GMT of Neutralization antibody of polio virus pre and post vaccination

Polio Virus	mOPV1 group			tOPV group		
	S1 n=29	S2 n=29	S3 n=29	S1 n=29	S2 n=28	S3 n=25
Polio-1	69	456	514	105	317	529
Polio-2	152	257	274	140	403	539
Polio-3	43	53	64	75	359	436

Exp.n= amount of subject; GMT = Geometric Mean Titre; S1(before approaching), S2 (after second vaccination), S3 (after third vaccination)

Table 3. Percentage of seropositive subject pre and post vaccination

% Seropositive	mOPV1 group			tOPV group		
	S1 n=29	S2 n=29	S3 n=29	S1 n=29	S2 n=28	S3 n=25
Polio-1	93,1	100	100	96,6	100	100
Polio-2	100	100	100	86,2	100	100
Polio-3	75,9	86,2	86,2	79,3	100	100

Exp. Seropositive (neutralization antibody titre >8 NT); S1 (before approaching), S2 (after second vaccination), S3 (after third vaccination)

Table 4. Proportion of seroconversion of Polio-1 neutralization antibody

Seroconversion	mOPV1 group n/N	tOPV group n/N	*P*
A. change from seronegative to seropositive	2/2 (100%)	1/1 (100%)	-
B. Fourfold rise of seropositive antibody titre			
- after second vaccination	14/26 (53.9%)	7/27 (25.9%)	0,072
- after third vaccination	15/26 (57.7%)	10/24 (41.7%)	0,396

Exp.n/N = total seroconversion/total of sample; *p* the result of comparison analysis with *Chi-Square* test

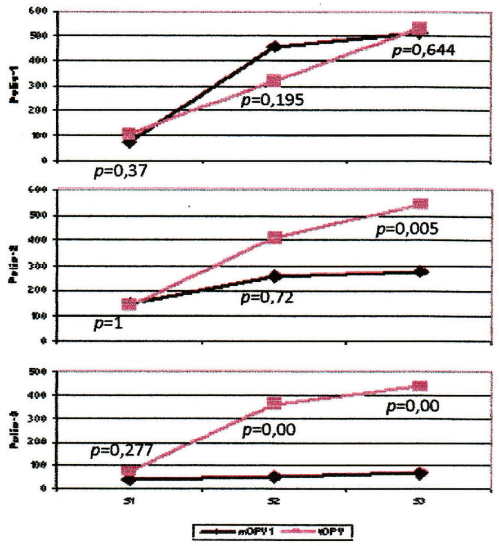

Figure 1. Graphic of Geometric Mean Titre neutralization antibody of polio virus
P value of analysis comparison results GMT in both groups using Mann-Whitney U test (S1 polio-1,2,3; S2 polio-2,3; S3 polio-1,2) and independent t-test (S2 polio-1; S3 polio-3)

third vaccination) of tOPV group was higher than mOPV1 with p>0.05 (Table 2 and Picture 1).

Both groups has high seropositive percentage (>75%), before approaching. Percentage of Polio-3 was the lowest compared to polio-1 and polio-2. Polio-3 of mOPV1 group even can not reach 100% until after third vaccination (Table 3).

Proportion of the change from seronegative to seropositive has no difference between the two groups. To proportion of seroconversion fourfold rise in neutralizing antibody titre, the result seroconversion proportion of mOPV1 group 54.9% (after second vaccination) over tOPV 25.9%, but it was not statistically significant (p=0.072). (Table 4)

DISCUSSION

There is no difference value of GMT polio-1 antibody between mOPV1 and tOPV group, after second or third vaccination. Superiority of monovalen vaccine shows more to sero-negative subject. It stated that a given of one dose monovalen polio vaccine will arouse viral replication in gastro-intestinal tract and seroconversion at 80-10%

seronegative subject. But if seronegative subject given a dose of tOPV vaccine then viral replication and antibody emerge to each type is lower.[8] While in this research, the result of antibody titre pre vaccination is almost seropositive already (Table 3). It deduced as the induction result of a dose of tOPV which has given when the subject age less than a month that was the inclusion criteria of this research.

After the third vaccination, graphic of mOPV1 group and tOPV group were in the tight place and the value of GMT polio-1 antibody similar to both groups. In 1985, Expanded Programme on Immunization Global Advisory Group recommended 4 times polio immunization schedule which are once at birth, 6 weeks of age, 10 weeks of age, and 14 weeks of age. [6,9] That schedule applied in most developing countries such as Indonesia, and it give good protection from Polio disease. At the researches in Brazil (1992), Ghana (1988), Pakistan (1988), and Togo (1990), the given of 3 times tOPV plus 1 dose at birth, response of neutralization antibody between; 89-100% at polio-1, 92-100% at polio-2, and 80-96% at polio-3. [6]

In mOPV1 group, vaccination given is polio-1 only but antibody to polio-2 increasing bit and has no influence to polio-3. A bit increase may be caused by exposure risk to vaccine viral from surround environment or cross reaction among three types of virus. [8]

Proportion of seroconversion of both groups has no significant difference. Research approached in Mexico in 1959, showed occurrence seroconversion of polio-1, mOPV1 94% and 50-70% to tOPV group. [9] John TJ et al research in 1976, showed seroconversion of polio-1, mOPV1 81% and 41% to tOPV group. [10] But those researches are not comparable because the research of Mexico and John TJ were evaluated after a given of single dose and given to subject that never been vaccinated before.

After all, percentage of seroconversion after third immunization can not reach 100%. But it doesn't mean that it has no seroprotection. Researches approached in 32 countries after 3 doses tOPV given showed sero-conversion value, 36-99% at polio-1, 71-100% at polio-2, and 51-100% at polio-3. [9] A vary sero-conversion among three types of virus affected by many factors, such as : 1) vaccine factor including formula of vaccine, the way of vaccine, vaccine stability, schedule of giving, amount of giving, and vaccine dose volume, 2) environment factor that is wild polio virus or vaccine polio virus exposure, or infection of another enterovirus, and 3) individual factor including presence of maternal antibody, breast feeding (ASI), age, nutritional status, condition of immune suppression, and genetic factor. [6,9]

Seroprotection is a serum that contain neutralization antibody which protects individual from polio disease. The value of antibody protection could determined laboratorial, how much antibody titre could endured cell cultured from injured caused by antigen that mixed it. While epidemiologically, the value of neutralization antibody in serum that able to prevent clinical signs of polio disease could not determine yet. At the research on monkey as trial animal that given antibody passively, at the antibody titre $\geq$ 20, it stated that it could prevent paralysis as clinical sign of polio disease. [12] Gelfand HM et all (1959) in Lousiana approaced a research to 237 individual with antibody titre $\leq$ 40, it showed that 98% reinfections occurred during eoidemic season of wild polio in 1953-1957. Those reinfections signed by 4 times fold increasing of neutralizationantibody titre in serum. While there were only 33% of 36 individual with antibody titre $\geq$ 80% who experienced reinfection. Furthermore, it deduced that individual who has low antibody titre in their serum no showing clinical signs of polio disease, but those reinfection could be a contagious source to another individual surround them who has not vaccinated yet. [6] Research approached by Nishio O dkk (1984) stated that reinfections occur to antibody titre that decline $\leq$ 1 : 8. Furthermore, it stated that a given tOPV booster dose is quick to response to antibody boost. [13]

OPV monovalen vaccine made for outbreak response not for routine vaccine. Epidemic seasons means that people dose not have enough neutralization antibody titre that could protected from polio disease, and also supported by the presence of contagious sources.

Immunity to infection of polio virus could measured by examine neutralization antibody in serum, measure secretory antibody in feaces, viral examination in feaces, and measurement of vaccine effectivity to prevent paralysis. Research approached by us was one of the parameter of examination to that imunity. Conclusion of this research is that there is no difference of neutralization antibody titre or proportion of seroconversion in healthy baby who has given mOPV1 and tOPV vaccination. Limitations of this research is this research approached out of epidemic season and a dose of tOPV given when the baby was < 1 month, according to the government programme, as an inclusion criteria.

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