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Original Article

Comparison of minimal inhibitory and bactericidal capacity of oral penicillin V with benzathine penicillin G to *Streptococcus beta-hemolyticus* group A in children with rheumatic heart disease

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Abstract

Background Injection of benzatine penicillin G (BPG) every 28 days is still the drug of choice for secondary prevention of rheumatic heart disease (RHD). BPG sometimes poses problems due to pain at the injection site, possible anaphylaxis, and is not always available. Some centers choose oral penicillin over BPG.

Objectives To compare minimal inhibitory capacity (MIC) and minimal bactericidal capacity (MBC) of oral penicillin V serum with those of BPG among SGA infected RHD.

Methods This was a clinical trial with crossover design study to compare MIC of penicillin V and BPG. Outcome measures were MIC and MBC. Statistical analysis was performed using paired t-test and wilcoxon test.

Result There were 32 subjects consisted of 17 males and 15 females. The mean value of MIC and MBC serum of penicillin V were 0.031 and 0.125. The mean value of MIC and MBC serum of BPG3 were 0.094 and 0.031. Respectively the MIC of penicillin V was similar to that of BPG_3. The mean value of MIC and MBC of BPG4 were 0.125 and 0.250. Respectively the MIC of penicillin V was significantly higher than that of BPG_4. The MBC of penicillin V was significantly higher than that of BPG_4. The MIC of BPG_3 was similar to that of BPG_4. The MBC of BPG_3 was similar to that of BPG_4.

Conclusions The MIC of penicillin V was similar to that of BPG_3, the MBC of oral penicillin V was higher than that of BPG_3. The MIC and MBC of penicillin V was higher than those of BPG_4. **[Paediatr Indones 2008;48:152-5]**.

Keywords: *bactericidal, oral penicillin V and benzathine penicillin G, Streptococcus beta-hemolyticus group A*

In developing countries rheumatic fever and rheumatic heart disease are common health problems.[1] The peak occurrence is between 5-15 years.[2] The prevalence of rheumatic heart disease among school children aged 5-14 years varies from 1.36 to 6.4/1000.[3] It is estimated that the prevalence of rheumatic heart disease in Indonesia is around 0.3-0.8 per 1000 school-age children aged between 5-15 years.[4,5] Data from Department of Child Health, Medical School, University of Indonesia/Cipto Mangunkusumo Hospital showed that there is no significant decreased prevalence of rheumatic fever and rheumatic heart disease within 10 years (1983-1992).[4,5] For secondary prophylaxis to prevent Group A Streptococcus hemolyticus,

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injection of benzathine penicillin G 1,200,000 units intramuscularly every 4 weeks is still effective, but WHO recommends a 3-weekly injection schedule to prevent recurrences of the disease.[6] The reason for using benzathine penicillin G (BPG) for treatment or prophylaxis is because this preparation is inexpensive and produces low but sustained concentration for three to four weeks after intramuscular injection.

However, BPG injections sometimes pose problems due to pain at the injection site, that lead patients and their parents to worry. Moreover, this drug is not always available outside Java Island, especially in the eastern and central parts of Indonesia. the possibility of anaphylaxis reaction also makes some physician reluctant to give BPG injection. Due to the above consideration some centers choose oral penicillin over injection.The aim of this study was to compare minimal inhibitory capacity (MIC) and minimal bactericidal capacity (MBC) of oral penicillin V with those BPG in rheumatic heart disease.

Methods

A clinical trial with crossover design was conducted to compare MIC and MBC of oral penicillin V with those of BPG among rheumatic heart disease cases caused by Group A beta-hemolyticus Streptococcus (GABHS in out-patients setting of Cardiology Division, Department of Child Health, Cipto Mangunkusumo Hospital, Jakarta from October 2007 to January 2008. The inclusion criteria was rheumatic heart disease. Patients with allergy to penicillin, heart failure complication and with upper respiratory infection who needed antibiotics were excluded. Written informed consent was obtained from parents.

Thirty-two subjects were enrolled and randomized to either receive oral penicillin V twice daily (group A) or intramuscular BPG monthly (group B). Demographic and clinical data were obtained before intervention. After one month treatment we made crossover patients who initially received oral penicillin V to BPG and vice versa. Blood sampling was taken on the third and fourth week, on the first and second month of treatment to determine MIC and MBC. Blood speciemns were collected in vaccine carrier and brought to Microbiology Department, Medical School, University of Indonesia, Jakarta.[7] All data were processed by SPSS version 13.0 for Windows@. We used paired t-test and Wilcoxon test to compare MIC and MBC of oral penicillin V with BPG.[8] Difference were considered significant if $P<0.05$. The study was approved by the Ethics Committee of Medical School, University of Indonesia, Jakarta.

Results

There were 32 subjects consisted of 17 males and 15 females. The mean age of patients who got oral penicillin V (16 subjects) and BPG groups were 13 and 15 years respectively. Meanwhile mean value of body weight of those who recieved oral penicillin V and those who received BPG were 43,969 and 39,531 kilograms respectively.

The MIC mean value of oral penicilline V and weekly BPG_3 were 0.031 and 0.094 respectively. the MIC of oral penicillin V was similar with to that of BPG_3 and did not show statistically significant difference with $P=0.098$. Meanwhile the MBC mean value of oral penicillin V and BPG_3 were 0.031 and 0.125 respectively. MBC of oral penicillin V was significantly higher than that of BPG_3 with $P=0.002$ (**Table 1**).

The MIC mean value of oral penicillin V was 0.031 and of BPG_4 was 0.125. MIC of oral penicilline V was significantly higher than that of BPG_4 with $P=0.003$. The MBC mean value of oral penicillin V was 0.031, while BPG_4 was 0.250. The MBC of oral penicillin V was higher than BPG_4 and showed significant statistical differences with $P< 0.001$ (**Table 2**).

The MIC mean value of BPG_3 and BPG_4 were 0.094 and 0.125, respectively. The differences were not statistically significant with $P=0.262$. The MBC mean value of BPG_3 and BPG_4 were 0.125 and 0.250 respectively. The differences were not statistically significant with $P= 0.123$ (**Table 3**).

Tabel 1. Comparison of MIC and MBC of oral penicillin V with those of BPG_3

No	Variabel	Oral penicillin V		BPG3		Hipotesis test
		Mean	SD	Mean	SD	
1	MIC	0.031	0.002-0.500	0.094	0.008-0.500	P = 0.098*
2	MBC	0.031	0.001-0.500	0.125	0.008-0.500	P = 0.002**

SD = Standard deviation; ICM= Inhibitory capacity minimal (penicillin V oral n=27,BPG_3 n=14); BCM= Bactericidal capacity minimal (penicillin V oral n=32,BPG_3 n=32); *paired t-test; ** Wilcoxon-test

MBC distribution of all subjects showed that oral penicillin V, BPG_3 and BPG_4 still existed in tube V; in tube VII only oral penicillin V and BPG_3, while in tube VIII to X only oral penicillin V (**Figure 1**) alone remain exists. However in our research we found additional data that there were different MBC mean value of oral penicillin V before and after crossover in 16 cases. The MBC mean value of oral penicillin V after crossover were higher than before (**Figure 2a. 2b**).

Tabel 2. Comparison of MIC and MBC of oral penicillin V with those of BPG_4

No	Variabel	Oral penicillin V		BPG4		Hipotesis test
		Mean	SD	Mean	SD	
1	MIC	0.031	0.008-0.500	0.125	0.031-0.500	P= 0,003*
2	MBC	0.031	0.001-0.500	0.250	0.062-0.500	P< 0,001**

SD = Standard deviation; MIC= Minimal inhibitory capacity (penicillin V oral n=27, BPG_3 n=25); MBC= Minimal bactericidal capacity (penicillin V oral n=32, BPG_3 n=32); *paired t-test; ** Wilcoxon-test

Tabel 3. Comparison of MIC and MBC of BPG3 with those of BPG_4

No	Variabel	Groups				Hipotesis test
		BPG3		BPG4		
		Mean	SD	Mean	SD	
1	MIC	0.094	0.008-0.500	0.125	0.031-0.500	P= 0.262*
2	MBC	0.125	0.008-0.500	0.250	0.062-0.500	P= 0.123**

SD = Standard deviation; ICM= Inhibitory capacity minimal (BPG_3 n=14,BPG_4 n=25); BCM= Bactericidal capacity minimal (penicillin V oral n=32,BPG_3 n=32);*paired t-test; ** Wilcoxon-test

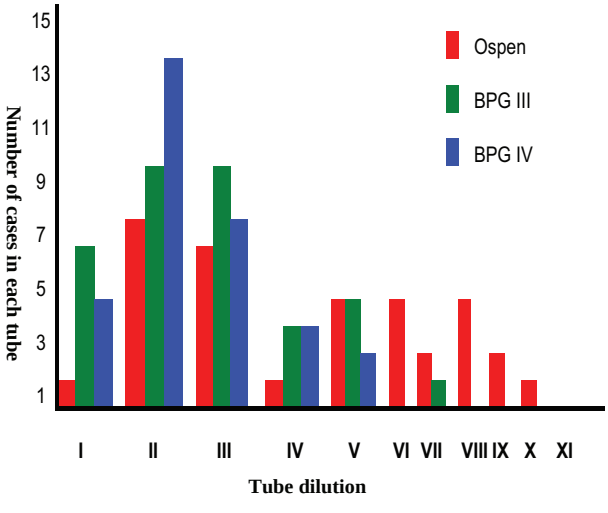

Figure 1. Diagram of MBC distribution in 32 subjects

Discussion

Rheumatic heart disease is commonly found in children age 5-15 years old.[2,9,10] Our subjects were rheumatic heart disease patients who met the criteria.The age range of patients who got BPG was 9.5-20.5 years with mean of age of 15 years. Meanwhile the intervals age range of those who got oral penicillin V was 9.3-16.5 years with mean age of 13 years (Statisitically insignificant with P=0.222).

The age range of all subjects was 6-24 years with mean age of 14 years. This was similar with that found by Madiyono *et al*[11] i.e, 10-23 years with mean age of 15.5 years. Lue *et al*[6] reported that the age range of his

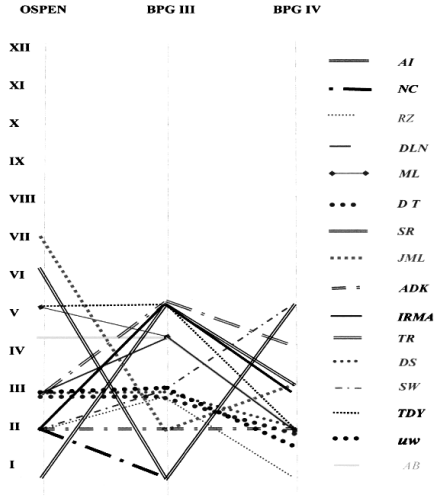

Figure 2a. MBCditribution in penicillin V group

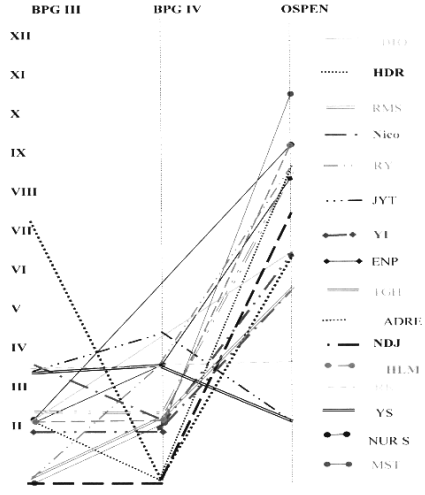

Figure 2b. MBC distribution in BPG group

patients was 5-19 years with mean age of 12.1 years.

The mean MIC value of oral penicillin V and that of BPG_3 were 0.031 and 0.094 respectively. The difference was not significant statistically. This findings may be influenced by the data that were not completed because of difficulties in interpreting the results. On the contrary there were significant differences between BCM cases who got oral penicillin V with those who got BPG_3 with P=0.002. This findings may be associated with the concentration of oral penicillin V which was higher and more stable in serum than that of BPG_3 due to daily oral consumption of oral penicillin V.

The mean MIC value of oral penicillin V and BPG_4 were 0.031 and 0.125 respectively, which was statistically significant different with P=0.003. The mean BCM value of the oral penicillin V and BPG_4 were 0.031 and 0.250 respectively, also significantly different (P < 0,001). This also related to higher concentration of oral penicillin V. Lue *et al*[6] reported that the concentration of penicillin in serum after intramuscular BPG with interval of four weeks was under 0.02 μg /ml and this was not adequate to inhibit *Streptococcus beta-hemolyticus* grup A.

The mean MIC value of BPG_3 and BPG_4 were 0.094 and 0.125 respectively which was not statisticalely significant different (P=0.262). The differences between BPG_3 and BPG_4 BCM (0.125 and 0.250) were not statistically significant different with P=0.123. This finding was similar with that of the previous studies by Madiyono *et al*.[12] This could be associated with prolong renal clearance of the pasients so that the penicillin level in serum was sustained and stable for a long time. This explain that BPG is still effective until four weeks after intramuscular injection. Our finding was different from that of Lue *et al*[6], Padmavati *et al*[4] and Kaplan *et al*[12].

In our research we also got additional information that there were different value of MBC between patients who got oral penicillin V before and after crossover and this were differences statistically significant with P=0.002.

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