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Original Article

Poor Adherence to Secondary Prophylaxis is Associated with More Severe Rheumatic Valve in Pediatric Patients: A Cross-Sectional Study

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ABSTRACT

Background : Rheumatic heart disease (RHD) contributed to a large number of proportion amoung cardiovascular problems in developing county, especially Indonesia. Secondary prophylaxis method using intramuscular injection of Benzathin Penicillin-G (BPG) has been known as the most effective strategy in the prevention of RHD. However, whether this prevention method also resulting in prevention of disease severity in Indonesian patients remained to be examined.
Objectives : This study aimed to assess the difference of rheumatic valve severity in Indonesian pediatric patients between adequate and poor adherence to secondary prophylaxis by using intramuscular BPG injection.
Methods : This cross-sectional study was conducted at Pediatric Cardiology Department of Saiful Anwar General Hospital from November 2018 to June 2019. Patients with documented history of RHD were included. Frequency of intramuscular BPG injection during the last one year was recorded. Adherence was measured using the proportion of days covered (PDC) and adequate adherence was defined as PDC ≥0.90. The severity of RHD was assessed based on the severity of the mitral and / or aortic valve using echocardiography. Bivariate analysis and multivariate logistic regression analysis was used to identify characteristics associated with rheumatic valve severity.
Results : A significant difference of rheumatic mitral and/or aortic valve severity was observed between adequate adherence compared to poor adherence group ($p = 0.016$). Rheumatic mitral and/or aortic valve were found to be more severe in patients who has one or more episode of ARF recurrence ($p = 0.003$). Multivariate logistic regression analysis demonstrated that adherence to secondary prophylaxis within the last 1 year has the strongest influence on the severity of rheumatic mitral and/or aortic valve ($p = 0.049$; OR 7.20).
Conclusion : The adherence to secondary prophylaxis has the strongest related the rheumatic valve severity compared to other factors.

1. Introduction

Rheumatic heart disease (RHD) is one of the most leading cause of morbidity and mortality of cardiovascular disease in the world.[1] RHD occurs as a complication of acute rheumatic fever (ARF), 35% of patients diagnosed with ARF developed RHD after 1 year and the rate increased to 51% after 10 years. The incidence of ARF in children aged 5-14 years ranges from 300,000-350,000 per year. Therefore, the the risk of RHD raised when the incidence of ARF also high in the population.[2-4]

Secondary prophylaxis using intramuscular BPG injection has been known as an effective treatment to prevent recurrence of ARF and to prevent the development of RHD for more than six decades.[1,5] There are still limited references and studies in RHD patients receiving secondary prophylaxis therapy.[6] It remains unclear whether secondary

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prophylaxis adherence using intramuscular BPG injection would contribute to significant difference of outcome especially in terms of rheumatic valve severity in Indonesia.

2. Methods

This was an observational analytic study with cross-sectional echocardiographic as end point. Data was also obtained from outpatient medical record at Pediatric Cardiology Clinic. History taking regarding the compliance to BPG injection recorded via phone or direct interview.

The severity of valve abnormalities was assessed using echocardiography. Echocardiography was performed by cardiology residents under supervision of pediatric cardiologist who were experienced in RHD cases. We evaluated valve severity based on quantitative and semi-quantitative methods according to the recommendations of the European Association of Echocardiography for the assessment of valvular regurgitation (2010) and European Association of Echocardiography / American Society of Echocardiography assessment of valve stenosis (2009).[7,8] We divided the valve severity of RHD into 3 groups i.e mild, moderate, and severe. This classification was made based on rheumatic mitral and/or aortic valve severity according to the Australian Guideline for Prevention, Diagnosis and Management of Acute Rheumatic Fever and Rheumatic Heart Disease (2012).[9]

Adherence was measured using the proportion of days covered (PDC) by intramuscular BPG injection. Adequate adherence was defined as PDC ≥0.90.[10] We divided into 2 groups which were adequate adherence and poor adherence groups, based on the adherence to secondary prophylaxis. Every day of delays from scheduled injection could illustrate the risk of ARF recurrence and the risk of elaborating rheumatic heart valve abnormalities.

The study protocols were conducted in accordance with the Declaration of Helsinki and were approved by the Institutional Review Board, Faculty of Medicine, Universitas Brawijaya, Malang, Indonesia. The aims, risks, and benefits of the study were explained to each participant, and they were asked to sign an informed consent form prior to enrollment. Participants were also informed that they could quit at any time during the interview session. Participations in this study were voluntary and no incentive was given.

3. Results

3.1. Patients selection

During November 2018 to June 2019, there were 47 out of 69 pediatric patients diagnosed with RHD who met the inclusion and exclusion study criteria. Twenty-two patients were excluded due to incomplete data, the use of oral secondary prophylaxis, or showing no mitral or aortic valve abnormalities during echocardiography. Other exclusion criteria were congenital heart disease, infective endocarditis, history of valve surgery, and hemodynamic changes due to volume depletion or overload.

3.2. Baseline characteristics

There was no predominance in sex proportion between samples (51.1% male vs. 48.9% female). The mean age of samples were 11.74 years in mild RHD group, 12.43 years in moderate RHD group and 12.5 years in severe RHD group. The first detection of RHD was diagnosed within approximately 9 years old among all groups. The mild RHD group was shown the highest mean body weight (approximately 36 kgs). The nutritional status of patients was mostly normal (55.3%), while the remaining sample were underweight (27.7%) and overweight (17%) Patients who received ACE inhibitors were 25.5% of total sample. The duration of secondary prophylaxis treatment ranged from 12 months to 90 months (mean 33 months) in all RHD groups. There was a total 21.3% of ARF recurrence, and the highest Wilkins score were found in severe RHD group, only 2.1% of sample suffered from severe remodeling according to wilkins score category, as shown in table 1.

Table 1. Baseline characteristics of patients included in our study

Patient characteristic	**Total (n=47)**
Sex	
Man	24 (51,1%)
Woman	23 (48,9%)
Age (years) (mean ± sd)	
Mild RHD	11,74 ± 3,44
Moderate RHD	12,43 ± 2,10
Severe RHD	12,50 ± 1,72
Age at RHD diagnostic (years) (mean ± sd)	
Mild RHD	9,04 ± 3,80
Moderate RHD	9,71 ± 2,19
Severe RHD	9,40 ± 2,46
Weight (mean ± sd)	
Mild RHD	36,17 ± 11,75
Moderate RHD	33,38 ± 17,94
Severe RHD	32,70 ± 7,60
Treatment duration (mean ± sd)	
Mild RHD	33,56 ± 19,56
Moderate RHD	33,21 ± 16,28
Severe RHD	34,90 ± 21,75

3.3. Main findings

Patients with adequate adherence to secondary prophylaxis in the last 1-year were found to experience mild RHD (66.7%), compared to patients with poor adherence who found to be moderate (45%) and severe RHD (30%). There is a significant difference between adequate compared to poor adherence group in terms of rheumatic valve severity ($p = 0.016$), see table 2.

Bivariate analysis showed that valve severity was statistically different when ARF re-occurred and the Wilkins score was higher ($p = 0.003$; $p = 0.000$, respectively), see table 3. No significant in valve severity in term of age, sex, nutritional status or treatment duration.

Multivariate analysis between adherence to secondary prophylaxis, total ARF recurrence, and Wilkins scores showed that the adherence to secondary prophylaxis variable has the strongest related to the severity of RHD ($p = 0.049$; OR 7.20) compared to others as shown in table 4.

Table 2. The effect of adding G. mangostana L. extract on lipid and glycemic profiles after 90 days of treatment

Adherence	RHD severity			Total	P value
	Mild	Moderate	Severe		
Good Adherence	18 (66,7%)	5 (18,5%)	4 (14,8%)	27 (100%)	0,016*
Poor Adherence	5 (25%)	9 (45%)	6 (30%)	20 (100%)	

Table 3. Bivariate Analysis

Adherence		RHD severity			Total	P value
		Mild	Moderate	Severe		
Sex	Woman	11 (45,8%)	6 (25%)	7 (29,2%)	24 (100%)	0,336
	Man	12 (52,2%)	8 (34,8%)	3 (13%)	23 (100%)	
ARF recurrence in 1 year	Never	22 (51,2%)	12 (27,9%)	9 (20,9%)	43 (100%)	0,419
	1x	1 (25%)	2 (50%)	1 (25%)	4 (100%)	
Total ARF recurrence	Never	22 (59,5%)	10 (27%)	5 (13,5%)	37 (100%)	0,003**
	1x	1 (10%)	4 (30%)	5 (50%)	10 (100%)	
Nutritional status	Underweight	3 (23,1%)	7 (53,8%)	3 (23,1%)	13 (100%)	0,176
	Normal	15 (57,7%)	4 (15,4%)	7 (26,9%)	26 (100%)	
	Overweight	5 (62,5%)	3 (37,5%)	0 (0%)	8 (100%)	
Wilkins score		0 ± 0	1,07 ± 1,21	3,1 ± 1,20		0,000**
Wilkins score categorical	Mild Remodeling	23 (50%)	14 (30,4%)	9 (19,6%)	46 (100%)	0,157
	Severe Remodeling	0 (0%)	0 (0%)	1 (100%)	1 (100%)	
Ace Inhibitor	No	20 (57,1%)	8 (22,9%)	7 (20%)	35 (100%)	0,121
	Yes	3 (25%)	6 (50%)	3 (25%)	12 (100%)	
Treatment duration		33,56±19,5	33,21±16,2	34,90±21,7		0,985
Age		9,04 ± 3,80	9,71 ± 2,19	9,40 ± 2,46		0,818

Table 4. Logistic Regression
Variables in the equation

		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	Adherence90(1)	1.910	1.067	3.202	1	.074	6.750	.834	54.663
	TotalRecurrence(1)	.288	1.607	.032	1	.858	1.333	.057	31.121
	WilkinScore	19.840	4006.255	.000	1	.996	413289521.710	.000	
	Constant	-2.197	.745	8.690	1	.003	.111		
Step 2[a]	Adherence90(1)	1.974	1.003	3.875	1	.049	7.200	1.009	51.392
	WilkinScore	19.961		.000	1	.996	466789367.757	.000	
	Constant	-2.197	.745	8.690	1	.003	.111		

Note; a. Variable(s) entered on step 1: Adherence 90, Total ARF recurrence, Wilkins Score.

4. Discussion

4.1. Adherence to Secondary Prophylaxis and the Severity of RHD

Twenty-seven patients (57.4%) demonstrated adequate adherence to secondary prophylaxis treatment (PDC ≥0.90), whilst 20 patients (42.6%) showed poor adherence (PDC rate was <0.90). Rates of secondary prophylactic treatment adherence varied greatly in various studies, previous study using a cut-off point of ≥0.90 in Brazil showed a total adequate adherence in 71.9% of patients.[10] Gasse et al. obtained a total adequate adherence in 54% patients by using cut-off of adherence ≥0.80.12 However, Culliford-Semmens et al. reported adequate adherence of 68.4% patients in New Zealand using the same cut-off.[5] Rahmawaty et al. has suggested a total adequate adherence in 58.7% patients, but the cut-off rate used did not clearly state.[13] According to previous data it was suggested that our result was concurrence to other. We did not explore further related factors affecting poor compliance in this study.

In contrast to several previous studies which showed a significant difference in valve severity by using an adherence cut-off ≥ 0.80, this study provides higher adherence (≥0.90) in order to achieve more significant value between mild, moderate, and severe RHD. Based on our data that used a 0.90 adherence cut-off point, the result showed that patients with adequate adherence to secondary prophylactic treatment in the last 1-year experienced milder RHD (66.7%), while patients with poor adherence had more moderate RHD (45%) and even more severe RHD (30%). Further study is warranted to explore the need of higher cut off adherence in Indonesian children correlate to genetic susceptibility or high prevalence in crowded population with poor individual hygine or other factors.

The Bivariate analysis using chi-square test demonstrated a significant relationship between the level of adherence to secondary prophylaxis with the severity of RHD valve abnormalities ($p = 0.016$). This result emphasized the need to increase adherence to secondary prophylaxis for RHD patients in Indonesia to prevent more severe valve disease. Concurrence to our study, Stewart et al. have mentioned a trend towards higher adherence was seen among children, more frequent clinic attendees, and patients with less severe disease. No trend was seen between adherence rates in men and women.[15] Remond et al. also suggested the importance of register / recall systems, dedicated health teams for delivery of secondary antibiotic prophylaxis, education about ARF and RHD, linkages with the community, and strong staff–patient relationships to improve compliance.[14] Rheumatic fever registries have gained considerable popularity as a means of improving treatment adherence. The World Health Organization has promoted the use of ARF registers in developing countries to attempt to coordinate patient management and improve adherence to secondary prophylaxis.[15,16]

This study result was consistent with many studies which stated that routine secondary prophylaxis followed by adherence to treatment is closely related to the low degree of valve severity. Sanyal et al. in India mentioned that 33% of children with ARF and carditis have shown resolution of heart murmur after 5 years of BPG secondary prophylaxis.[17] Atatoa-Carr et al. also mentioned that the administration of secondary prophylaxis could reduce the severity of RHD and was associated with regression of heart valve abnormalities in about 50-70% of patients with adequate adherence for a decade.[18] There were similarities between our study and other previous studies that poor adherence to secondary prophylaxis was associated with more severe valve abnormalities. Unfortunately, because our study only evaluated echocardiography once in a row, it was unable to assess regression or progression of valve abnormalities.

4.2. ARF Recurrence and RHD Severity

Bivariate analysis between the ARF recurrence in the last 1-year (without secondary prophylaxis) and the severity of RHD showed no significant relationship ($p = 0.419$). However, further bivariate analysis between the total ARF recurrence (after the administration of secondary prophylaxis treatment) and the severity of RHD found a significant relationship ($p = 0.003$). This can be explained by a very low recurrence rate of ARF in the last 1-year which only found in 4 patients (8.5%) before the treatment of secondary prophylaxis. However, after the administration of secondary prohylaxis, the total ARF recurrence rate was found in 10 patients (21.3%). Although not a big count, but it was statistically significant after using Fisher exact test, suggesting that this phenomenon was caused by a small size of sample. Further bigger sample might confirm the correlation between recurrence of RF with RHD valve severity.

4.3. Wilkins score and RHD severity

Bivariate analysis between the Wilkins scores and the severity of RHD demonstrated a significant relationship ($p = 0.000$). The Wilkins score was calculated numerically based on the total score of four parameters (leaflet mobility, valvular thickening, leaflet calcification, and subvalvular thickening).[19] Further analysis was attempted using the categorical Wilkins score, which divided into two category: a Wilkins score of ≥5 (severe remodeling / inflammation) and a Wilkins score <5 (minor remodeling / inflammation).[20] There was no significant relationship ($p = 0.157$) between this categorical Wilkins score and the RHD severity. This was due to the number of patients in the severe remodelling / inflammation group is only 1 patient, thus it is difficult to be statistically proven.

Aloui et al. reported that the severity of valve thickening and calcification assessed by echocardiography using the Wilkins score were associated with high levels of Matrix metalloproteinase-3 (MMP-3). High levels of MMP-3, which is a marker of remodeling, are also positively correlated with the severity of the inflammatory process.[15] With a fairly high number of mitral valve abnormalities, there should be a significant relationship between Wilkins score and rheumatic valve severity. This was evident in the Wilkins bivariate test using numerical Wilkins score on the severity of RHD. The non significant relationship in Wilkins bivariate testing using categorical 2 groups was due to the low number of patients classified as severe remodeling / inflammation. This was not surprising because the subject of this study was taken from all pediatric thus the process of chronic inflammation and remodeling of the heart valves has not been seen as clear and severe as in adult RHD patients.

There were high number of patients with mitral valve regurgitation in our study, those involving only the mitral valve (70.2%) and those that coincided with the aortic valve (27.7%). Previous study by Mehta et al. (2013) found that mitral valve regurgitation abnormalities were the most common valve abnormalities (48.7%) in RHD.[21] Carapetis et al. also mentioned that valve thickening, thickening of the chorda tendinae, and tethering in one or both valves could occur, even in mild valve abnormalities. The mechanism most often was caused by mitral regurgitation in RHD cases.[9]

The multivariate logistic regression analysis between the adherence to secondary prophylaxis, total ARF recurrence, and Wilkins scores demonstrated that adherence to secondary prophylaxis variable has the strongest relation to the severity of RHD ($p = 0.049$; OR 7.20). The magnitude of OR obtained is 7.20 which means that the likelihood of patients experiencing a degree of worsened RHD is 7.2 times higher in poor adherent compared to those adequate adherent patients.

5. Conclusion

Our study revealed that poor adherence to secondary prophylaxis is significantly associated with more severe rheumatic valve severity in pediatric patients. In addition, higher Wilkins score and higher rate of total ARF recurrence were significantly associated with rheumatic valve severity. The adherence to secondary prophylaxis has the strongest relation to the rheumatic valve severity compared to other factors. Therefore, higher level of adherence is required to prevent and reduce rheumatic mitral and/or aortic valve severity in pediatric patients in Indonesia.

6. Declarations

6.1. Ethics Approval and Consent to participate
This study was approved by local Institutional Review Board, and all participants have provided written informed consent prior to involve in the study.

6.2. Consent for publication
Not applicable.

6.3. Availability of data and materials
Data used in our study were presented in the main text.

6.4. Competing interests
Not applicable.

6.5. Funding source
Not applicable.

6.6. Authors contributions
Idea/concept: TRM. Design: TRM. Control/supervision: MSR, DS, RS, SW, HM. Data collection/processing: TRM, FWN, AH, BK, CT, RK. Extraction/Analysis/interpretation: TRM, MSR, DS, RS, SW, HM. Literature review: TRM, FWN, AH, BK, CT, RK, MSR, DS, RS, SW, HM. Writing the article: TRM. Critical review: MSR, DS, RS, SW, HM. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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