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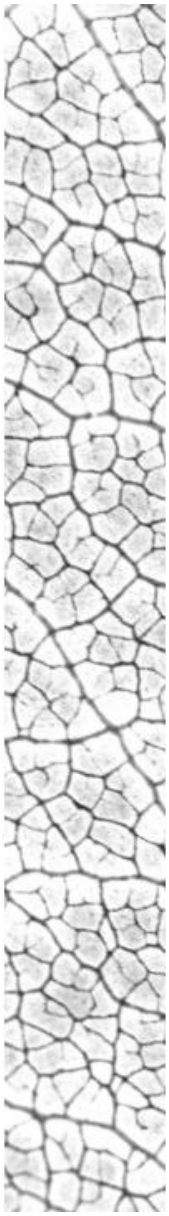

Comparison of the effects of giving captopril and valsartan in cases of heart failure for people with congenital heart disease

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Abstract

Background: Congenital Heart Disease (CHD) has a prevalence ranging from 6 to 10 per 1000 live births, with an average of 8 out of 1000 live births. One of the pathological consequences of CHD is heart failure. Therapy for heart failure in CHD is still unsatisfactory. **Purpose:** Comparing the effect of captropyl and valsartan on clinical improvement, echocardiography, electrocardiography, and chest radiograph in cases of heart failure with congenital heart disease left to right. **Method:** The study design was Randomized Control Trial (RCT) by giving Double Blind Study treatment. There are 2 treatment groups, namely X1 by giving captopril and X2 by giving valsartan. Data were analyzed by Paired T-Test, T-Test, Mann-Whitney Test, and 5% significance. **Result:** The results of statistical analysis showed a significant change in the PHFS score, but it was not significant when compared between the two treatment groups. Increased LVEDV and LV dimension less after giving captopril than valsartan. There was an increase in LVEF after captopril administration although it was not significant when compared to the valsartan group. The reduction in CTR in the valsartan group was significant and the mean reduction in CTR in the valsartan group was greater than in the captopril group. **Conclusion:** Clinical, echocardiographic, electrocardiographic, and chest radiograph improvement after adding captopril and valsartan, but better improvements were obtained in valsartan administration than captopril.

Keywords: congenital heart disease, heart failure, captopril, valsartan, pediatric

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INTRODUCTION

Congenital heart disease (CHD) is a congenital disease with abnormal structural and / or circulatory function of the heart that is seen at birth or after birth (Friedman, 1992).The prevalence of CHD ranges from 6 to 10 per 1000 live births, with an average of 8 out of 1000 live births. About one third of them give symptoms that vary from mild to severe that may cause emergencies in the early first week of life (Bernstein, 2007; Buleshov et al., 2019; Delongchamp et al., 2019; Tione, et al, 2018). If not detected early and not treated properly, 50% of deaths can occur in the first month of life.

One of the pathological consequences of CHD is heart failure. Types of CHD that generally can cause heart failure are the type of Left to Right Shunt, among others, Ventricular Septum Defect (VSD), Atrial Septal Defect (ASD), and Persistent Arteriosus Duct (PDA) (Bernstein, 2007).Heart failure is a condition of the heart as a blood pumping meet adequately the body's metabolic needs. This situation can be caused by primary disorders of the heart muscle or excessive cardiac burden or a combination of both (Rusgo, 2019).

Therapy for heart failure in CHD is still unsatisfactory. Many new drug studies to treat heart failure have been conducted (Beggs, et al. 2009). Angiotensin Converting Enzyme Inhibitor (ACEI) has been at the forefront of heart failure therapy for about a decade. ACEIs that are frequently used are Kaptopril and Enalapril. Angiotensin-Receptor Blocker (ARB) is said to be as effective as ACEI in the treatment of hypertension, congestive heart failure, and chronic kidney failure (McMurray, 2003).Valsartan is an ARB that works to block Renin Angiotensin Aldosteron System (RAAS) more perfectly at receptor level without receptors. Inhibits kininase (Flynn, et al. 2008).Valsartan is an antihypertensive drug that selectively inhibits angiotensin type II receptors. In general, valsartan is available as a film-coated tablet

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Table 1. Changes in clinical features, echocardiography, electrocardiography, and chest radiograph

	VARIABLE	GROUP I (CAPTOPRIL)		PRICE P	IK95%	GROUP II (VALSARTAN)		PRICE P	IK95%
		Pre	Post			Pre	Post		
1	Score PHFS	7,06±2,04	4,75±2,43	<0,0001	-2,98 - -1,65	6,81±2,25	3.94±1,98	<0,0001	-3,76 - -1,98
2	ECHO								
	LVEDV	44,58±20,05	46,12±23,63	0,689	-6,48-9,56	58,74±29,77	61,32±35,11	0,721	-12,51 - 17,67
	LVEF	74,54±3,84	75,55±4,66	0,423	-1,60 - 3,62	74,26±3,86	73,28±4,10	0,494	-3,97 - 2,00
	%FS	41,31±2,80	42,21±5,17	0,562	-2,35 - 4,17	41,53±4,29	41,11±3,48	0,761	-3,24 - 2,42
	LV dimension	3,29±0,58	3,30±0,71	0,961	-0,23 -0,24	3,64±0,72	3,65±0,78	0,919	-0,28 - 0,31
3	EKG								
	Heartbeat frequency	117,75±14,67	109,63±17,59	0,039	-15,78 - -0,46	117,1±21,86	108,6±20,66	0,006	-14,17 - -2,83
	AmplitudeR in *lead* V1	7,06±6,69	7,13±5,16	0,962	-2,73 - 2,83	9,13±4,96	7,69±2,91	0,169	-3,56 - 0,68
	Amplitude R in *lead* V6	15,5±6,02	13,63±7,66	0,373	-6,23 - 2,48	16,6±6,62	14,38±5,87	0,125	-5,19 - 0,69
	Amplitude S in *lead* V1	6,38±5,12	6,56±6,14	0,885	-2,52 - 2,89	10,06±6,78	7,31±5,99	0,009	-4,69 - -0,81
	Amplitude S in *lead* V6	5,03±7,15	3,59±4,88	0,095	-3,16 - 0,28	3,81±3,06	3,53±2,70	0,660	-1,61 - 1,05
4	CTR	60,92±5,64	59,61±5,16	0,062	-2,70 - 0,07	59,74±4,72	57,19±5,14	<0,001	-3,87 - -1,23

(Febry, et al. 2015).Most ARB studies on heart failure have been conducted in the adult population and so far researchers have not found similar studies in children with left-to-right CHD who experience heart failure in Indonesia.

From the description above, it is necessary to do research on children with left-to-right CHD with heart failure by comparing clinical, echocardiographic, electrocardiographic, and chest radiograph changes in patients with left-to-right CHD who have heart failure before and after captopril administration before and after valsartan administration. Echocardiography is produced from sound waves at a certain intensity (Aziz, et al. 2018).Electrocardiography is known to be accurate in measuring cardiac output in infants and children suffering from CHD. Variations in the anatomical position of the thoracic vessels in congenital heart disease also do not affect the accuracy of measurements (Kusumastuti, & Osaki, 2015).

METHOD

The design of this study was the Randomized Control Trial (RCT) by giving a Double Blind Study treatment. This research was conducted in the children's care room and outpatient unit of the Children's Cardiology Division of Dr. Soetomo Regional General Hospital Indonesia for 4 months.

PJB shunt left to right accompanied by heart failure divided into 2 groups, namely group X1 with captopril administration and group X2 with valsartan administration. In group X1 (before captopril administration) clinical, echocardiographic, ECG, and chest radiograph measurements were then measured and the changes from group X1 (pre-captopril) to group Y1 (post-captopril) and the changes were analyzed (δ1). In group X2 (before valsartan administration) clinical, echocardiographic, ECG and chest radiograph measurements were then measured and changes were made from group X2 (pre-valsartan) to group Y2 (post-valsartan) after valsartan administration and the changes were analyzed (δ2). So in this study the aim is to compare δ1 and δ2.

Population and sample

All patients with congenital left-to-right shunt heart disease who met the inclusion criteria and were willing to take part in the study were randomly selected as many as 32 children to be grouped into the group receiving valsartan and the group receiving captopril with the corresponding sample count.

Data analysis

Research data were analyzed by Paired T-Test for interval data before and after drug administration in one group; T-test and Mann-Whitney test to compare differences in data before and after drug administration between groups; computer program assistance for statistical calculations; and the significance level used is 5%.

RESULTS

Changes in clinical features can be seen from the results of the PHFS score. Changes in echocardiographic features can be seen from the results of LVEDV, LVEF,% FS, and LV dimensions. Changes in electrocardiographic features were seen based on the results of the heart rate frequency, amplitude R in lead V1, amplitude R in lead V6, amplitude S in lead V1 and amplitude S in lead V6. Changes in chest radiograph obtained based on the results of the CTR measurements. All data is shown in **Table 1** and **Table 2**.

Changes in the clinical picture seen from the PHFS score obtained a significant decrease in PHFS scores between before and after administration of Valsartan captopril (**Table 1**). The mean decrease in clinical scores was greater in the valsartan group than in the captopril group (**Table 2**).

Changes in echocardiographic features seen from the results of LVEDV examination showed an increase in LVEDV after administration of captopril and valsartan (**Table 1**). This increase in LVEDV in the administration of captopril and valsartan was not statistically significant. (**Table 2**). The results of LVEF examination showed an increase in LVEF after captopril administration (**Table**

Table 2. Differences in clinical features, echocardiography, electrocardiography, and chest X-ray between captopril and valsartan

	VARIABLE	Group I (Captopril)	Group II (Valsartan)	Price P
1	Skor PHFS:	-2,31±1,25	-2,87±1,66	0,289
2	ECHO			
	LVEDV	1,53±15,06	2,57±28,33	0,898
	LVEF	1,01±4,90	-0,983±5,61	0,293
	%FS	0,907±6,12	-0,412±5,31	0,520
	LV dimension	0,005±0,45	0,010±0,49	0,961
3	EI Electrocardiography:			
	Heart rate	-8,12±14,37	-8,50±10,63	0,934
	Ampllitude R in *lead* V1	0,0625±5,20	-1,43±3,98	0,367
	Amplitude R in *lead* V6	-1,875±8,17	-2,25±5,53	0,880
	Amplitude S in *lead* V1	0,187±5,08	-2,75±3,64	0,070
	Amplitude S in *lead* V6	-1,43±3,22	-0,281±2,50	0,267
4	CTR	-1,31±2,60	-2,55±2,47	0,178

1), but the increase in LVEF was not statistically significant (**Table 2**). In valsartan administration, there was a decrease in LVEF after valsartan administration, but the decrease in LVEF was not statistically significant (**Table 2**). The results of examination of% FS on captopril (**Table 1**) found an increase in% FS after administration of captopril, but the increase in% FS was not statistically significant (**Table 2**). In valsartan (**Table 1**), there was a decrease in% FS after valsartan administration, but the decrease in% FS was not statistically significant (**Table 2**). The results of LV dimension examination on captopril (**Table 1**) showed an increase in LV dimension after the administration of captopril, but the increase in LV dimension was not statistically significant (**Table 2**). In valsartan (**Table 1**), there was an increase in LV dimension after giving valsartan, but the increase in LV dimension was not statistically significant (**Table 2**).

Changes in electrocardiographic features on heart rate were found to be a statistically and clinically significant decrease in heart rate in both groups, but the mean decrease in heart rate in the valsartan group was greater than in the captopril group. The mean values of amplitude R in lead V1, amplitude R in lead V6 and amplitude S in lead V6 did not differ significantly between the two groups before and after drug administration ($p < 0.05$). The mean decrease in amplitude R in leads V1, amplitude R in leads V6, and S amplitude in lead V6 in the valsartan group were greater than in the captopril group.

Changes in the chest X-ray picture from the results of the CTR measurements showed a decrease in CTR after captopril administration (**Table 1**), but the decrease was neither statistically nor clinically significant (**Table 2**). In valsartan, there was a significant decrease in CTR after valsartan administration (**Table 1**). The mean CTR reduction in the valsartan group was greater than the captopril group (**Table 2**).

DISCUSSION

In this study, the results of statistical analysis showed a significant change in the PHFS score ($p < 0.0001$), but it was not statistically significant when compared between the two treatment groups. These results are the same as the results of the Val-HeFT and RESOLVD studies which stated that there were no significant differences after the administration of ACEI and ARB on clinical scores (Anand, et al. 2003). However, in this study, the mean decrease in PHFS scores appeared to be greater in the valsartan group than in the captopril group so It can be seen that the clinical improvement that occurs seems better after valsartan administration.

In this study, there was an increase in LVEDV and LV dimension less after giving captopril than valsartan. This is not in accordance with research conducted by Funabiki et al (Funabiki, et al. 2004) in a preliminary study of heart muscle fibrosis and LV stiffnes in experimental dogs with heart failure mentioned a significant decrease in LVEDV after administration of captopril and valsartan for 4 weeks [11].

Moreover, there was an increase in LVEF after captopril administration although the results of statistical analysis were not significant compared to the valsartan group. These results are similar to the results of a study conducted by (Pfeffer, et al. 2003) who examined the effects of captopril on mortality and morbidity of patients with left ventricular dysfunction after myocardial infarction with the conclusion that there was an improvement in LVEF after captopril administration (Marc, et al. 2003).

Furthermore, the% FS increase was greater after captopril administration than the valsartan group even though the results of statistical analysis were not significant. However, an increase in% FS in the captopril group shows that captopril is better than valsartan in this case. Fraction shortening (fractional shortening) is one indicator that is measured to see cardiac remodeling by measuring the function of ventricular contractility. The greater the value of% FS, the better the contractility function of the ventricles (Breathett, et al. 2016)

The absence of changes in echocardiographic features in the valsartan group could be due to the fact that research time is not long enough to see the effect of drugs on the process of heart remodeling, but it can also be assumed that it does not mean that valsartan has no effect on the remodeling process, but in this case it slows

the process of remodeling and progression of heart failure.

Electrocardiographic features in left-to-right CHD depend on the magnitude of the defect and type of CHD. Amplitudes of waves R and S describe the thickness of the ventricular wall. The amplitudes of the R and S waves in leads V1 and V6 are the most important criteria for determining whether there is left or right ventricular hypertrophy (Driscoll, 2006).

The electrocardiographic features evaluated were heart rate frequency and R and S wave amplitude parameters. In this study, a statistically significant decrease in heart rate was found in both groups but the mean decrease in heart rate in the valsartan group was greater than in the captopril group. In this study the results of the amplitude measurements are in accordance with the study conducted by Segal et al (2000) who compared their research on the effects of losartan and valsartan on LVH and LV function in patients with essential hypertension and concluded that there was a more significant LVH regression after valsartan administration for 6 months 15.

Measurement and monitoring of left ventricular remodeling include one of them the size and shape of the heart that can be assessed from a chest radiograph that is a CTR 16 size.. The results of statistical analysis showed a decrease in CTR in the valsartan group was significant and the mean decrease in CTR in the valsartan group was greater than in the captopril group.

CONCLUSION

Clinical, echocardiographic, electrocardiographic, and thoracic improvements were obtained after captopril and valsartan administration, but better improvements were obtained with valsartan administration than captopril.

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