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Comparison of valsartan and captopril administration in clinical feature and echocardiogram of Congenital Heart Defect with heart failure complications.

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Abstract— **Background**: Delayed in congenital heart disease (CHD) treatment is the main reason that lead to heart failure. The diagnosis of heart failure in children does not have standard guidelines, also the current treatment of heart failure in children has not shown satisfactory results, so further research in treatment is needed to guidelines. **Objective**: To determine the differences in the improvement of clinical parameters of CHD patients with heart failure based on PHFS Scores and Echocardiogrambetween captopril compared to valsartan. **Methods**: This pre-posttest study was conducted on 29 CHD children with heart failure who were diagnosed for the first time and had not received prior therapy. All study subjects were randomly divided into 2 groups, the valsartan group as treatment and the captopril group as control. The medication was given for 3 months in each group. Treatment evaluation was carried out by examining PHFS, LVEF, LVEDV, LV Dimension, LV Mass and Fraction Shortening (FS) in the initial and final phases of the study. **Results**: The clinical assessment result of PHFS in the valsartan ($p = 0.070$) and captopril ($p = 0.180$) groups were discovered. The results of the echocardiographic examination in a row were: LVEF ($p = 0.720$), LVEDV ($p = 0.538$), FS ($p = 0.455$), LVIDd ($p = 0.826$), LVIDs ($p = 0.912$), LVM ($p = 0.065$). **Conclusion**: Valsartan and captopril administration did not show any difference in PHFS scores, LVEF, LVEDV, FS, LVIDd, LVIDs, nor LVMass.

Keywords: Valsartan, Captopril, Heart Failure, PHFS Scores, Echocardiogram

1. Introduction

Congenital Heart Disease (CHD) is the most common congenital anomaly with the prevalence 6-10/1000 live birth, and average 8/1000 live birth [1]. Definitive treatment of CHD is operative procedure or transcutaneous catheterization. Delayed in congenital heart disease (CHD) treatment is the main reason that lead to heart failure (HF). Although the proportion of CHD patients with HF is lower than the proportion with rhythm disturbances or cardiomyopathy, CHD is a much more common disease and therefore contributes a greater number of cases to the overall HF count. Nearly 60% of HF cases in pediatric patients occurred within the first year of life, but in these studies the overall mortality was lower in the CHD population than in patients with HF from other causes [2]. Left to right shunt CHD i.e. VSD and PDA that lead to volume overload is the main cause of HF [3].

Diagnosis of heart failure in children is still very far behind compared to adult patients because there are no universal standard criteria. The currently accepted clinical criteria for heart failure in children are Ross's Pediatric Heart Failure Score (PHFS), which is comparable to the NYHA criteria used in adults [4]. In addition to clinical criteria, the other ways that are also very important for diagnosing HF is echocardiography, however there are not many studies on the use of echocardiography in CHD. Some studies have conducted echocardiographic examinations on adult CHD, so further research is needed on CHD with failure heart [5,6]. Angiotensin Converting Enzyme Inhibitor (ACE-I) with Captopril as most common drug, has been at the forefront of heart failure therapy for decades, although there has been an improvement in prognosis, mortality is still high in children with heart failure [7]. Angiotensin-Receptor Blockers (ARBs) such as Valsartan, are said to be as effective as ACEI in the treatment of hypertension, congestive heart failure, and chronic renal failure, but the use of ARBs is only recommended in children with hypertension [8], while in children with heart failure is still not recommended due to a lack of clinical trials.Further investigations to evaluate clinical and echocardiography improvement of HF related to CHD

withValsartan compares to Captopril are needed.

2. Method, Population, and Analysis

2.1 Method

This pre-posttest study was conducted on 29 CHD children with heart failure who were diagnosed for the first time and had not received prior therapy. All study subjects were randomly divided into 2 groups, group X1 with captopril administration and group Y1 with valsartan administration. In group X1 (before captopril administration) clinical, echocardiographic, measurements were collected, and compared to group X2(post-captopril) results then analyzed(δ1). In group Y1 (before valsartan administration) clinical, echocardiographic were collected, then compare the change all of these criterions to group Y2 (post-valsartan) then analyzed (δ2). The medication was given for 3 months in each group. Treatment evaluation was carried out by examining PHFS, LVEF, LVEDV, LV Dimension, LV Mass and Fraction Shortening (FS) in the initial and final phases of the study.The aim of the study is to compare δ1 andδ2.

2.2 Population andsample

All patients with left-to-right shunt CHD who met the inclusion criteria and willing totakepartinthestudywererandomlyselected, andasmany as 29 children participated.

2.3 Data analysis

Categoric data between the two groups were evaluated with the *chi-square* statistical test.The data distribution normality test was tested with the Saphyro-Wilks test. The mean difference for numerical data between before and after treatment in one group will be tested by statistical paired t-test if thedata is normally distributed and Wilcoxon Summed rank or Mann-Whitney U test if the data did notnormally distributed. All tests were performed at an error rate (α) of 5%.Data analysis was performed on the computer program SPPS version 25 for mac.

3.Result and Discussion

3.1 Result

A total of 29 subjects were randomly divided into 2 groups, the control group who received standard therapy for heart failure, captopril (n = 13) with diagnosed PDA are 3 subjects and VSD 10 subjects. In valsartan group, there were 16 subjects, with diagnosed PDA were 9 patients and 7 VSD (Table 1). Six children in captopril's group experienced cough as a side effects without any history of infection and allergy. The age range of the subject is 2 years to 14 years, which is divided into 3 age groups, with the largest age distribution being 5-10 years (44.8%). Girls are more common with 16 children (55.2%).

The clinical features of patients based on the PHFS score are shown in Table 2. With the most common HF grade is mild heart failure. After receiving captopril therapy, there was an improvement in the results where there were no children with severe heart failure, and there was an increase in the number of children with mild heart failure (n = 9), and moderate heart failure (n = 4), but it was not statistically significant **(p = 0.180)**. In the treatment group (n = 16), after given valsartan, the result also improves for all the subjects, but this was not statistically significant **(p = 0.070).**Echocardiography examination also performed **(Table 3.)**, with the LV end-diastolic volume (LVEDV) average points in the control group before and after drug administration was 69.19±29.12 and 58.66±35.74 **(p=0.165).** Whereas in the treatment group, the mean LVEDV before and after drug administration was 58.35±33.37 and 70.33±49.67 **(p=0.735).** Comparison between the means of post treatment in two groups not statistically significant **(p=0,538)**. Other examinations of the LV structure shown in Table 3 did not evidence statistically significant differences.

Table 1. Subject characterized

Characterized	Criterions	CHD + HF		Total
		Valsartan	Captopril	
Diagnose	DAP	9 (56,3%)	3 (23,1%)	12 (41,4%)
	DSV	7 (43,8%)	10 (76,9%)	17 (58,6%)
Age	$\bar{x}$ ± SD	6,25 ± 3,47	9,35 ± 3,72	7,64 ± 3,85

	(Min-Max)	(2-11)	(3-14)	(2-14)
	<5 year old	7 (43,8%)	2 (15,4%)	9 (31,0%)
	5-10 year old	8 (50,0%)	5 (38,5%)	13 (44,8%)
	>10 year old	1 (6,3%)	6 (46,2%)	7 (24,1%)
Sex	Boys	7 (43,8%)	6 (46,2%)	13 (44,8%)
	Girls	9 (56,3%)	7 (53,8%)	16 (55,2%)

Table 2. Clinical assessment with PHFS score

Variable	Category	Valsartan		Captopril	
		Pre	Post	Pre	Post
PHFS scores by Ross	Mild CHF	8 (50,0%)	13 (81,3%)	8 (61,5%)	9 (69,2%)
	Moderate CHF	5 (31,1%)	3 (18,8%)	3 (23,1%)	4 (30,8%)
	Severe CHF	3 (18,8%)	0 (0,0%)	2 (15,4%)	0 (0,0%)
	p	**0,070[1]**		**0,180[1]**	

Table 3. Echocardiogram of LV structure result (Highlighted number exhibit post treatment between two groups)

Variable	Groups	Examination onset		***p***
		Pre	Post	
LVEDV ($\bar{x}$ ± SD)	Valsartan	58,35 ± 33,37	70,33 ± 49,67	0,735[1]
	Captopril	69,19 ± 29,12	58,66 ± 35,74	0,165[2]
	p	0,355[4]	**0,538[3]**	
EF ($\bar{x}$ ± SD)	Valsartan	70,83 ± 9,73	74,23 ± 10,64	0,174[2]
	Captopril	74,70 ± 8,31	72,99 ± 6,81	0,165[2]
	p	0,266[4]	**0,720[4]**	
FS ($\bar{x}$ ± SD)	Valsartan	39,79 ± 7,98	43,88 ± 8,99	0,060[2]
	Captopril	44,55 ± 8,00	42,69 ± 7,25	0,157[1]
	p	0,124[3]	**0,455[3]**	
LVIDd ($\bar{x}$ ± SD)	Valsartan	33,68 ± 12,19	34,20 ± 13,45	0,564[2]
	Captopril	32,25 ± 15,82	31,82 ± 16,17	0,157[1]
	p	0,758[3]	**0,826[3]**	
LVIDs ($\bar{x}$ ± SD)	Valsartan	24,96 ± 22,66	20,15 ± 8,78	0,866[1]
	Captopril	20,48 ± 6,42	20,48 ± 6,42	0,165[2]
	p	0,965[3]	**0,912[4]**	
LVMass ($\bar{x}$ ± SD)	Valsartan	109,61 ± 39,63	85,10 ± 53,54	0,075[2]
	Captopril	163,23 ± 81,87	152,46 ± 90,90	0,157[1]
	p	0,045[4]	**0,065[3]**	
LVMIndex ($\bar{x}$ ± SD)	Valsartan	131,65 ± 77,40	119,29 ± 60,40	0,333[2]
	Captopril	131,51 ± 77,55	145,54 ± 63,75	0,165[2]
	p	0,996[4]	**0,266[4]**	

Note: [1] Wilcoxon Summed Ranks test, [2] Paired t-test, [3] Wilcoxon – Mann Whitney test, [4] Independent t-test

3.2 Discussion

In our study, the average age at first discovered was 7.64±3.85 with ages ranging from 2-14 years, and most of them were in the 5-10 years age group. All of the samples taken are those that have never been detected before and have no history of previous heart failure treatment, this indicates that the screening system for CHD at an early age is not working well, or lack of knowledge and awareness from their parents. In some other developing countries, there is also a delay in the diagnosis of CHD, where the age of the first found is

at age 4 years (range 0-79 months), only 282 (52.8%) patients were diagnosed under the age of two years, and complications were present in 155 (29.0%) at time of diagnosis [9]. Other report from Pakistan also shown age ranging from 1 to 176 months (median 24 months), 301 (85.1%) had delayed diagnosis of CHD (mainly acyanotic 65.3%), with median delay (8 months). Main factors for delay were delayed first consultation to a doctor (37.2%) and delayed diagnosis by a health professional (22.5%). Other factors included delayed referral to a tertiary care hospital (13.3%), social taboos (13.0%), and financial constraints (12.3%). Most children were delivered outside hospital settings (88.7%). Children with siblings less than two (40%) were less delayed than those having two or more siblings (60%, $P < 0.001$) [10].Diagnosis of congenital heart defect was delayed in majority of patients. Multiple factors such as lack of adequately trained health system and socioeconomic constraints were responsible for the delay [10].

Our study showed that the PHFS scores outcome of heart failure between two groups has not different (**p=0.070** in valsartan group vs **p=0.180** in captopril group). Similar study in children subject are less than adult, but ACE inhibitor or ARB still considered as the best prescription for HF in children with good clinical improvement outcomes [11-13]. Multicenter study conducted on adult patients, Valsartan Heart Failure Trial Investigators (Val-HeFT and RESOLVD), conclude that giving ACEI and ARB to clinical scores did not show a significant difference [14], and also a combination of captopril and valsartan for 6 months in patients with congestive heart failure improved symptoms of heart failure as measured by changes in the NYHA class which was better than giving captopril alone [15].

Echocardiographic examination results obtained in this study did not shown difference between the valsartan and captopril groups at the end of the observation. Echocardiography is a very useful and accurate non-invasive examination of HF, which can provide an objective view of the structure and function of the heart. The use of LVEF with M-mode as an important modality in assessing heart failure has been applied globally, however, this is highly dependent on operator experience and the accuracy of the echocardiography trackball device [16]. The difficulty in visually assessing LVEF can occur when there is an irregular heart rhythm, the size of the left ventricle is very large or small, or when there is an extreme heart rate abnormality [16]. LVEF less than 40% is said to have a poor prognosis and is the cause of failure to treat HF [17]. ACE-I and ARB studies with improvement of LVEF parameters in children are rare, but are very much found in adult subject, both in heart failure and cardiomyopathy. ACE-I is given as an initial treatment for heart failure, and administration of ARB preparations if the patient has intolerance to ACE-I, shows an improvement in the mean LVEF [18]. Simultaneous administration of captopril and valsartan in AMI also provides improvement in LVEF [19-21]. Valsartan addition in patients with heart failure who received standard therapy for an average of 23 months significantly improved the NYHA functional class, left ventricular remodeling, LVEF, and symptoms and signs of HF [14]. Combination of captopril and valsartan can reduce mortality and morbidity, as well as improve cardiomyopathy with the mean improvement of LVEF and the reduced size of LVIDd after 4 months of observation and reaching the peak point of remodeling after 1 year [14,22,23]. ARB and captopril as a combination giving satisfactory result to repair LVEF [24]. ARB also showed significant improvements in the evaluation of LVEF, LVEDV, FS, LVIDd and heart rate of patients with CHD with heart failure compared to captopril administration [25]. ACE-I and ARB are still the main choice in international treatment guidelines for chronic HF due to CHD, both in children and adults [26]. Other LV function assessments that can be used in the evaluation of heart failure are LV Mass (LVM) and LVMI, wherein a large LVM size is associated with sudden death in people with heart failure [27]. The enlarged LVM and LVMI sizes generally indicate a left ventricular hypertrophy associated with the incidence of HF in infants, children, and adolescents [28]. The mean LVMI results in this study, both before and after treatment, showed a very large size compared to the standard LVMI for children based on previous studies [28,29].

4. Conclusion

There was no difference between valsartan and captopril administration in the degree of HF using PHFS

criteria and examinations of LVEDV, LVEF, LV Mass, LV dimension, and FS in CHD children with HF. Valsartan has same benefits effect for HF treatment and also less side effects compare to captopril.

5. References

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