The improvement chest x-ray after carvedilol theraphy in heart failure due to left to right shunt congenital heart disease

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RESEARCH ARTICLE

THE IMPROVEMENT CHEST X-RAY AFTER CARVEDILOL THERAPHY IN HEART FAILURE DUE TO LEFT TO RIGHT SHUNT. CONGENITAL HEART DISEASE.

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Abstract

Background: Heart failure due to left to right shunt congenital heart defect will increase pulmonary blood flow and cause volume overload. This condition activated the sympathetic nervous system and the renin-angiotensin-aldosteron system. Conventional therapy has not blocked the sympathetic system yet. Carvedilol, a novel non selective β-blocker, reduced mortality and hospitalization in adults with heart failure. Limited information was available about its use in children.

Objective: To evaluate the effect of carvedilol on chest x-ray in children with heart failure due to left to right shunt congenital heart defect.

Methods: A randomized, double-blind, placebo-controlled study was done. In addition to conventional therapy, patients were assigned to receive placebo or carvedilol. Carvedilol was initiated at a dose of 0.05 mg/kg/day, with a target dose of 0.2 mg/kg/day. Chest x-ray was done before-after treatment and evaluated for cardio-thoracic ratio and pulmonary vascularity. The data was analyzed using independent sample t-test and Chi-square test, with confidence interval 95%.

Results: Of 30 patients, 15 in each group. The mean age was 57.6(SD 43.57) months, 19(63.3%) were boys. There were 21(70%) children with VSD and 9(30%) children with PDA. Compared to control group, children in the carvedilol group had a significant decrease of cardio-thoracic ratio(-2.94±2.34% versus -0.48±3.19%, p=0.023, CI 95%:-4.556 to-0.360). However, there was no significant change of pulmonary vascularity(p=0.153).

Conclusion: Carvedilol decreased the cardio-thoracic ratio on chest x-ray, but did not improve the pulmonary vascularity in children with heart failure due to left to right shunt Congenital heart defect.

Introduction:-

Left to right shunt congenital heart defect (CHD) is the most frequent structural abnormality in baby and children. One of the complications that often occur on the left to right shunt CHD is heart failure. Up to 25% children with CHD suffered from heart failure(Beggs, *et al*., 2009; Madriago and Silberbach, 2010).

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Heart failure due to left to right shunt congenital heart defect (CHD) will increase pulmonary blood flow and cause volume overload. This condition activated the sympathetic nervous system and the renin-angiotensin-aldosteron system(Giardini, *et al*., 2003, Madriago and Silberbach, 2010). Chronic adrenergic stimulation leads to worsening heart failure by inducing ventricle and vascularity remodelling(Cohn, *et al*., 2000; Marin, 2000; Roig, 2006; Adatia, *et al*., 2010).

Conventional therapy has not blocked the sympathetic system yet(Atmosudigdo, 2007; Hsu and Pearson, 2009). Carvedilol, a novel non selective β-blocker, reduces mortality and hospitalization in adults with heart failure(Packer, *et al*., 1996, 2002). This may due to its dual mechanism of action: nonselective beta blockade and vasodilatation due to α-1 blockade (Shaddy, *et al*., 2007). Limited published information was available about the efficacy of carvedilol in children with heart failure, especially due to left to right shunt CHD (Nishiyama, *et al*., 2009).

The present study investigated the efficacy of carvedilol in children with heart failure due to left to right shunt CHD based on chest x-ray.

Subjects and Methods:-

A randomized, double-blind, placebo-controlled study of Pediatric-Cardiologic Outpatient Clinic of dr. Soetomo Hospital during November, 2011 to April, 2012 was done. Subjects that were eligible to criteria were enrolled in the study. The inclusion and exclusion criteria were based on previous study by Shaddy, *et al*. 2007. There were 15 subjects in each group.

In addition to conventional therapy, patients were assigned to receive placebo or carvedilol. Carvedilol was initiated at a dose of 0.05 mg/kg/day, which was increased by 0.05 mg/kg/day each week with a target dose of 0.2 mg/kg/day for 3 months.

Chest x-ray was done before-after treatment and evaluating for cardio-thoracic ratio (CTR) and pulmonary vascularity. Cardio-thoracic ratio was obtained by relating the largest transverse diameter of the heart to the widest internal diameter of the chest. Increased pulmonary vascularity was present when the right and left PAs appear enlarged and extend into the lateral third of the lung field.

The data was analyzed using independent sample t-test and Chi-square test, with 95% confidence interval.

Results:-

There were 32 pediatric patients that met inclusion and exclusion criteria. Unfortunatelly, there were 2 subjects who did not continue the research, 1 subject in the control group discontinued the treatment and one subject experienced worsening heart failure. Fifteen subjects in each group, which consists of two groups: a treatment group with standard therapy given (ACE inhibitors and diuretics) and carvedilol, and a control group with standard therapy and placebo. Chest x-ray was performed before and after the research for 3 months. Table 1 describes the basic characteristics of the subjects. Based on the statistical analysis, it was found that the subject characteristic was homogeneous.

Changes in CTR:-

The mean CTR in the treatment group before carvedilol administration was 57.84 ± 5.86%, while in the control group was 56.03 ± 6.52%.There was a decrease of CTR after carvedilol administration in both groups. There was a significant difference in treatment group ($p<0.0001$), while there was no significant difference in control group (-2.94 ± 2.34% vs -0.48 ± 3.19%) (table 2).There was a significant difference in CTR decrease between two groups after carvedilol therapy($p=0.023$) (Figure 1).

Changes inpulmonary vascularity:-

There were 17 subjects with increasing pulmonary vascularity before carvedilol therapy, 8 subject in control group and 9 subjects in treatment group. After carvedilol therapy, 3 subjects (37.50%) in control group, pulmonary vascularity became normal, while 7 subjects (77.80%) in treatment group (Figure 2). There was no significant difference in pulmonary vascularity between two groups after carvedilol therapy with independent t test $p=0.153$.

Discussion:-

Carvedilol, a nonselective inhibitor of adrenoreceptor β-1 and β-2 and adrenoreceptor α-1, has antioxidant activity which improve ventricular and vascular function (Doughty. *et al*., 1997; Rusconi. *et al*., 2004; Maurer. *et al*., 2009). In previous large-scale studies on the use of carvedilol for heart failure in adults (such as the U.S. Carvedilol HF Study (1996), COPERNICUS (2001), and CAPRICORN (2001), efficacy was demonstrated and has been considered useful (Packer, *et al*., 1996, 2002). Use of carvedilol in children has been reported by Bruns *et al*., Laer *et al*., Williams *et al*., Giardini *et al*., Toyono *et al*., Rusconi *et al*., and Azeka *et al*. However, the number of patients in each report was small and only include dilated cardiomyopathy population.

In this study, carvedilol administered group has a significant decrease in CTR compared to placebo group. Study by CARMEN (*Carvedilol ACE-Inhibitor Remodelling in Mild Heart Failure Evaluation*) showed that combination of carvedilol and ACE-inhibitor enalapril improved ventricle remodeliling better than enalapril alone (Komajda.et al., 2004). There have been several trials in children that shown decrease in CTR (Li *et al*.,2008, Nishiyama *et al*., 2009, Ishibashi *et al*., 2011). Study by Colucci *et al*. (1996) in adult with mild heart failure for 12 months, RCT, *double blind* showed that carvedilol did not decrease CTR. This difference was due to different population with recent study.

Cardio-thoracic ratio on chest x-ray has significant corelation with LVEDV by echocardiography (Satou. *et al*., 2001). Study by Clark and Coats (2000) reported that CTR has a strong relationship with LVEF and *shortening fraction*. Carvedilol decreased LVEDV and improved LVEF and LVSF, as previously demonstrated by Gachara *et al,* 2001; Gairdini *et al*., 2003; Rusconi *et al*., 2004; Bruns *et al*., 2001; Laer *et al*., 2002; Williams *et al*., 2002; Blume *et al*.,2006; Azeka *et al*., 2002.

Recently, preliminary results suggested that carvedilol does not significantly improve outcome of patients younger than 18 years with chronic symptomatic heart failure due to systemic ventricular systolic dysfunction (Shaddy *et al*., 2007). However, this study showed that carvedilol improved heart failure in children with CHD. The difference in these outcomes may be attributable to different etiology of the heart failure. Study by Shaddy, subjects with dilated cardiomyopathy can improve naturally.

Mechanisms that might be responsible for the improvement of ventricle function were first, adrenergic blocking of carvedilol. Carvedilol inhibited coronary vasoconstriction and peripheral vascular by α1-receptor, so that oxygen demand and afterload decreased. Carvedilol decreased heart rate by β1, β2 receptor blockade. The decrease of heart rate would improve the cardiac filling, hence the stroke volume increased. The increase of stroke volume later on would improve LVEF and decrease LVEDV-LVESV. Taken together, these mechanisms will reverse ventricle remodeling (Doughty *et al*., 1997; Rusconi *et al*., 2004; Maurer *et al*., 2009).

The second mechanism could be due to carvedilol as an antioxidant. A direct interaction with free radical, such as superoxide and hydroxyl would neutralize those dangerous radical scavanger, as previously study by Kukin *et al*., 1999; Dandona *et al*., 2000; and Nakamura *et al*. 2002.

In this study, carvedilol has no significant difference in improving pulmonary vascularity. This was due to different degree of pulmonary hypertension in each subjects, depend on naturally history of pulmonary hypertension. The finding in this study was similar to previous report by Ishibashi *et al*., 2011.But there was one report by Horenstein. *et al*. (2002), in 4 year old subject with dilated cardiomyopathy, there was decrease in mean pulmonary arterial pressure after carvedilol therapy, moreover there was also decrease in LVEDD.

Pulmonary hypertension frequently aroused in patients with congenital heart disease. Initially in majority patients, with congenital cardiac shunts, manifest as left-to-right (i.e. systemic-to-pulmonary) shunts that caused volume overload. This condition was called as hyperkinetic pulmonary hypertension, a high flow normo resistance hemodynamic characteristic. In this stage, there was ongoing increase in pulmonary vascularity. The natural history of disease progression involved vascular remodeling and dysfunction that lead to increased pulmonary vascular resistance and, finally, development of Eisenmenger's syndrome, a low/normo flow high resistance hemodynamic characteristic. In this stage, due to increased resistance in pulmonary arterial bed, usually at the arteriolar level, characterized radiographically by enlargement of the pulmonary trunk and right and left main pulmonary arteries with disproportionately small peripheral vessels, this has been referred to as "pruning" of the pulmonary arteries on the chest x-ray(Burrows and Robinovitch. 1985; Landzberg.2007).

There were no specific criteria for interpreting pulmonary vascularity. Study by Tumkosit *et al*. (2012) demonstrated an accuracy of pulmonary vascularity chest x-ray interpretation compared to cardiac catheterization. They reported that chest x-ray had high sensitivity to diagnose increased pulmonary vascularity.

Carvedilol improved pulmonary vascularity by decreasing heart rate. Lower heart rate would improve diastolic function, so that decreasing the pulmonary arterial pressure (Horenstein *et al*., 2002). The other mechanism was the inhibition of smooth muscle proliferation in patient with pulmonary hypertension (Fujio *et al*., 2006).

Conclusion:-

Carvedilol decreased the CTR on chest x-ray, but did not improve the pulmonary vascularity in children with heart failure due to left to right shunt CHD.

Table 1:- Baseline characteristics of the subjects

Characteristics	Carvedilol	Control	p
Age (Month) (Mean±SD)	49.80±41.20	65.40±45.88	0.33
Age			
≤ 24 month	6(40.00)	3(20.00)	0.18
25-83 month	7(46.70)	7(46.70)	
84-131 month	0(0.00)	3(20.00)	
≥ 132 month	2.00(13.3)	2(13.30)	
Sex			
Male	7.00(46.70)	12.00(80.00)	0.13
Female	8.00(53.30)	3.00(20.00)	
Weight (kg) (Mean±SD)	11.93±4.98	15.43±6.94	0.12
Nutrition Status			
Goodnutrition	9.00(60.00)	9.00(60.00)	0.88
Moderate malnutrition	5.00(33.30)	4.00(26.70)	
Severe malnutrition	1.00(6.70)	2.00(13.30)	
Defect type			
DAP	6.00(40.00)	3.00(20.00)	0.42
DSV	9.00(60.00)	12.00(80.00)	
Defect size			
Large	4.00(26.70)	3.00(20.00)	0.96
Medium	11.00(73.30)	9.00(60.00)	
Small	1.00(6.70)	2.00(13.30)	
PHFS Score			
Score 3	11.00(73.30)	13.00(86.70)	0.65
Score 4	4.00(26.70)	2.00(13.30)	

Table 2:- Changes in Cardio-Thoracic Ratio (CTR)

Parameter	Pre	Post	Changes	p
CTR (%)				
Control group	56.03 ± 6.52	55.55 ±6.71	-0.48 ±3.19	0.572
Treatment group	57.84 ± 5.86	54.90 ± 5.02	-2.94 ± 2.34	<0.0001 *

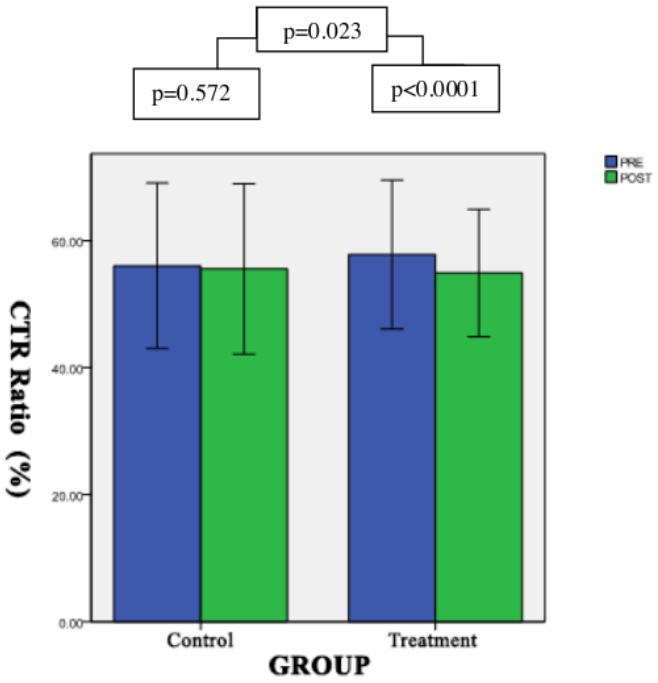

Fig. 1:- Changes of Cardio-Thoracic Ratio (CTR) before and after carvedilol therapy. Mean value of CTR in the treatment group before carvedilol administration was 57.84 ± 5.86%, while in the control group was 56.03 ± 6.52%. There was a decrease of CTR after carvedilol administration in both groups. There was a significant difference in treatment group (p<0.0001).There was a significant difference in CTR decrease between two groups after carvedilol therapy (p=0.023).

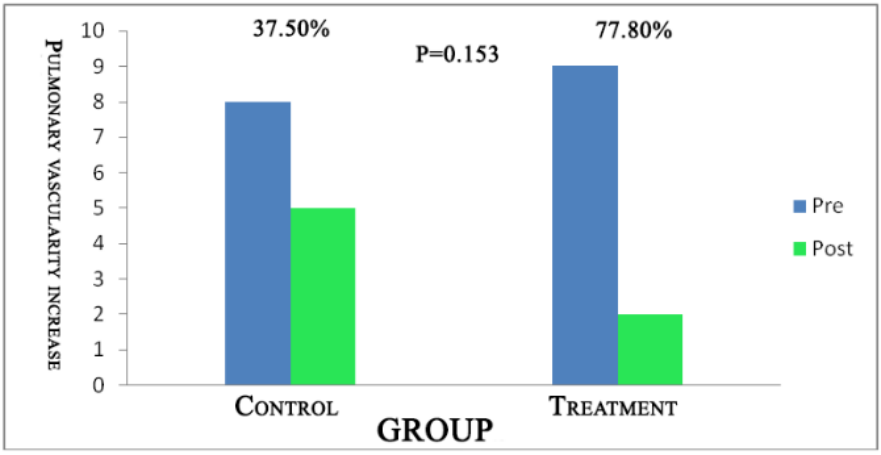

Fig. 2:- Changes of pulmonary vascularity before and after carvedilol therapy. After carvedilol therapy, 3 subjects (37.50%) in control group, pulmonary vascularity became normal, while 7 subjects (77.80%) in treatment group. There was no significant difference in pulmonary vascularity between two groups after carvedilol therapy with independent t test p=0.153.

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Conflict Of Interest And Funding Disclosure:-

Authors declare no conflict of interest and financial support.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

PAGE 5

PAGE 6

PAGE 7