

COMPARISON OF TWO DRUG REGIMENS IN TREATMENT OF RV FAILURE

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ABSTRACT

Heart failure is one of the most common heart diseases with high rates of cardiovascular mortality and morbidity. Beta blockers are considered treat these patients to reduce mortality and improve right ventricular function and symptoms. Due to the increasing prevalence of this disease in the country, this study compared to determine the effect of carvedilol was performed on drugs right ventricular function Method: This clinical trial study was performed on 60 patients with right ventricular failure. In this study, only standard therapy control group patients received the underlying disease in addition carvedilol to standard treatment group. And at the end of the second and sixth months in both groups, right ventricular failure indices were evaluated with echocardiography. And then data were compared using statistical software SPSS. Mean age 61.8 ± 9.0 years. Our results showed that administration of carvedilol reduced the second month Tr severity is significant ($p < 0.001$) and continue taking it until the sixth month in addition to reducing Tr, significant decreases are also Rvmpi. ($p < 0.001$). But compared Taps index and right ventricular dilatation in the carvedilol group differences with the placebo group showed no significant ($p > 0.05$). Based on present study findings in patients with right ventricular failure, patients prescribed carvedilol is improves symptoms of right ventricular function.

Keywords: CHF, COPD, carvedilol, right ventricular failure, right ventricular function.

INTRODUCTION

Heart failure is a syndrome in which structure and functional abnormalities of the heart is responsible for its inability to drain the blood into the tissues in accordance with their need. Clinical signs of heart failure lead to a series of complications including: Vascular congestion, shortness of breath, fatigue and weakness.

Most of the heart failure clinical manifestations are caused by excessive accumulation of fluid at the back of ventricle that have faced difficulties at the beginning of the disease, for example, hemodynamic overload imposed on the left ventricle such as aortic insufficiency or poor left ventricular function due to the loss of myocytes after Myocardial infarction causes lung congestion, resulting in shortness of breath and orthopnea (Babu *et al.*, 2005). This condition is called left heart failure.

When the underlying abnormality first affect the right ventricle such as secondary pulmonary hypertension to chronic respiratory thromboembolism, pulmonary congestive symptoms are uncommon, but edema, congestive hepatomegaly, Systemic venous distention and in other words, more right ventricle clinical

symptoms would appear.

It has shown that the three beta-blocker medications (metoprolol, Bisoprolol and carvedilol) increase survival in patients with heart failure. The first two drugs are selective and only block B1 receptors, while carvedilol block α , B2, B1 receptor and this way cause mild vasodilation. It seems that carvedilol also has antioxidant effect. During heart failure, according to the increased effect of the renin - angiotensin - aldosterone - system, failure heart is forced to maintain blood flow by increase adrenergic mechanism. Sympathetic activation which occurs due to beta receptors, increase myocardial oxygen demand and arterial vasoconstriction through alpha receptors would be harmful to the heart in long term. In addition, increased catecholamines, which continues chronically is cardio toxic and cause cardiomyocyte apoptosis. Beta-adrenergic blocking with additional adrenergic signal would help myocytes; also induced useful remodeling and cardiomyocyte mass reconstruction.

In studies up to now, cardiac remodeling improvement and systolic activity by beta-blocker therapy in CHF patients has become clear. In addition, adrenergic block effect on anti-arrhythmic and anti-ischemic properties is beneficial as well. The third generation of beta-blockers such as carvedilol, beside the above occasions, have a vasodilation, anti-

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endothelin, anti-oxidant effect which may have protective results especially in advanced heart failure. Beta-blockers with respect to the features are used increasingly in human to reduce mortality in mild and intermediate heart failure as well as severe cases and can be said that it has beneficial effect, at least in reducing sudden cardiac death.

Studies on adults with congestive heart failure have shown that the use of beta blockers can improve the clinical status and physical activity tolerance in patients, whereas peak vo_2 does not change. Progressive right ventricular failure mechanism remains unknown. According to previous studies, myocardial ischemia is the basis of right ventricular failure in patients with Systemic RV (Bellenger *et al.*, 2004; Ohlstein *et al.*, 1998). Some other studies have shown that there is a relation between the extent of ischemia and right ventricular function. Precise mechanisms that can trigger ischemia are not yet known, but most of the researchers emphasize that the difference between the amount of available oxygen and its consumption may be of importance (Hall *et al.*, 1995). Recently, lack of the right ventricle preload especially in terms of low activity, has considered as a result of RV dysfunction in patients who underwent arterial surgery (Hauser *et al.*, 2003). Neuro-hormonal activation and its predictive significance is common in heart failure, since it seems to creates additional neuro-hormonal activation by permanent reduction in cardiac function (Wilson *et al.*, 2003). It is known that neuro-hormonal activation includes several paths that are

characteristic of heart failure in patients with congenital heart failure.

About carvedilol should be said that its different pharmacodynamic mechanisms can lead to right ventricular positive remodeling and RV function improvement. RV mass to volume positive improvement results in reduction of wall pressure and may be helpful through reduction in RV demand. Carvedilol can also improve myocardial blood supply, coronary perfusion and HR, as well as cardiac output by reducing the wall pressure in diastolic phase. In addition it can block neuro-hormonal activation which typically seen in heart failure and neutralize its harmful effects to the myocardial performance (Donadona *et al.*, 2000). Other mechanisms includes: cardiomyocyte contract performance improvement (intrinsic) and inhibition of secreting embryonic forms of contractile proteins.

According to what was said, review of previous studies and also due to high frequency of right heart failure in the region (Donadona *et al.*, 2000; Ohlstein *et al.*, 1998), we decided to compare carvedilol effect in short-term on right ventricular function in a case group and a control group who received standard therapy.

MATERIALS AND METHODS

The study populations were patients with right ventricular failure who had visited Heart Clinic of Khatam Aalnbya and Ali Ibn Abi Talib Hospital in Zahedan city.

Table 1. Variables.

variable scale	variable definition	Variable type				Variable role			Name of variable
		quality		quantity		dependent	independent	background	
		ordinal	nominal	discrete	continuous				
carvedilol	Drug type		*				*		drug used in heart failure
Month / II / VI	-----			*			*		Medication time
precent	Based on standard echocardiography				*	*			right ventricular failure Index
cm	Based on standard echocardiography				*	*			right ventricle dilation

According to the available samples and previous studies, 60 patients were conducted into the study (CIBIS, 1999; The MERIT –HF, 1999); sampling was non-probability and people were randomly assigned into two groups (Table 1).

Performance procedure was to explain study protocol to patients so that they would be fully understood and in a second step, a complete history of patients were taken before administration of the study (they should meet our inclusion criteria but not the exclusion ones). The control group only received the standard treatment for the underlying condition (Bristow, 1993); but in the case group in addition to standard therapy, 6.25 mg carvedilol twice daily was added, and at the end of the second and sixth months the two groups were compared in terms of right ventricular failure indices.

Data analysis

After recording the data in the information forms, to describe the data, descriptive analysis techniques including: mean, standard deviations were used. To compare quantitative variable means in binary groups, Independent T student test were used.

RESULTS

There are 60 patients with right ventricular failure from Khatam Aalnbaya and Ali Ibn Abi Talib Hospital in Zahedan city, were studied. The patients, aged between 34 and 78 years with an average age of $61/8 \pm 9/0$ years. Among patients, (36) 60% were men and (24) 40% were women. The case group included 20 men and 10 women, while the control group included 16 men and 14 women. No statistically significant difference was observed between the two groups (Table 2).

Table 2. Distribution of patients with right ventricular failure in context of sex.

p-value	Total	control	case	Group/sex
0.215	36 (60)	16 (53.3)	20 (66.7)	Men
	24 (40)	14 (46.7)	10 (33.3)	women
	60 (100)	30 (50)	30 (50)	total

The comparison of right ventricular failure indices in the second month of standard and Carvedilol treatment

Three indices of 60 patients were examined in the current study: tricuspid anular planar systolic (TAPSE), Right ventricle myocardial performance index (RVmpi) and tricuspid regurgitation (TR severity). No significant differences was observed between the two groups in the terms of three indices ($P > 0/05$). After two months all three indices

were evaluated again, this time TR severity showed a significant difference ($p < 0/001$) (Table 3).

Table 3. Comparison of right ventricular failure indices in the second month of standard and Carvedilol treatment.

Sig	Df	T	Mean	Independent t- test
0.498	58	0.682	8.7	Taps (Case)
			8.5	Taps (Control)
0.109	58	-1.628	0.43	Rvmipi (Case)
			0.46	Rvmipi (Control)
$p < 0/001$	58	-6.233	2.6	Tr severity (Case)
			3.4	Tr severity (Control)

The comparison of right ventricular failure indices in the sixth month of standard and Carvedilol treatment

After six months all three indices were evaluated again, this time TR severity and RVmpi showed a significant decrease in the case group ($p < 0/001$) (Table 4).

Table 4. Comparison of right ventricular failure indices in the sixth month of standard and Carvedilol treatment.

Sig	Df	T	Mean	Independent t- test
0.394	58	0.859	8.7	Taps (Case)
			8.3	Taps (Control)
$p < 0/001$	58	-6.839	0.35	Rvmipi (Case)
			0.44	Rvmipi (Control)
$p < 0/001$	58	-5.137	2.4	Tr severity (Case)
			3.1	Tr severity (Control)

Comparison of dilation in the second month of standard and Carvedilol treatment

RV dilation mean on arrival in the case and control group were 4.9 and 4.7 with respect with no statistically significant difference ($P > 0/05$) (Table 5). After two months, again no statistically significant

difference was observed between the two groups ($P > 0/05$).

Table 5. Comparison of dilation in the second month of standard and Carvedilol treatment.

Sig.	Df	T	Mean	Independent t-test
0/507	58	0/670	4.9	right ventricle dilation (case)
			4.7	right ventricle dilation (control)

Comparison of dilation in the sixth month of standard and Carvedilol treatment

After six months, the two groups were compared again on the basis of the right ventricle dilation and no significant difference were observed between the two groups ($P > 0/05$) (Table 6).

Table 6. Comparison of dilation in the sixth month of standard and Carvedilol treatment.

Sig.	Df	T	Mean	Independent t-test
0/583	58	0/555	4.8	right ventricle dilation (case)
			4.7	right ventricle dilation (control)

DISCUSSION

Heart failure is a syndrome in which abnormalities in the structure and function of the heart is responsible for its inability to drain the blood into the tissues in accordance with their need. Clinical signs of heart failure led to a series of compounds including: Vascular congestion, shortness of breath, fatigue and weakness.

The role of beta-blockers in heart failure has been discussed for years, but after confirming the beneficial effects on mortality, morbidity and clinical status, started to be used in clinical practice. It appears that carvedilol can reduce mortality rather than other beta-blockers. Symptoms improvement and reduction in hospital stay duration is guaranteed by carvedilol. In addition, its functional capacity to work will not change significantly. In fact, the cardiac output increases, but heart rate decreases. Carvedilol after a mean duration of 6 months, decreases the right ventricular volume and mass and increases ejection fraction.

In this study, the effects of prescribing carvedilol on right ventricular function in patients with right ventricular failure were studied. The study evaluated

the effects of carvedilol in the second and sixth months in the terms of indices: RVmpi, TAPS and TR severity, and right ventricle dilation mean was compared with placebo group.

The results showed that administration of carvedilol in the second month leads to significant decrease in TR severity and continuing to use it up to sixth month significantly decreased RVmpi and TR severity as well. However, TAPS index and right ventricular dilation in the carvedilol group which compared to the placebo group did not show a significant difference. Quaipe *et al.* (1998) analyzed the effects of carvedilol administration on right ventricular function in patients with CHF and the findings suggest an increase in ejection fraction and right ventricular function.

Another study conducted by Tatli *et al.* (2008) 74 patients were divided into two groups and were treated for 4 months with carvedilol. The study showed that in carvedilol group ejection fraction increased while the level of TNF, IL-6 decreased.

The main effects of carvedilol include prevention and antagonism adrenergic heart injury; reduced heart rate and reduced oxygen consumption are two other antagonists. Beta-blocker consumptions was associated with an increase in ejection fraction and decrease in demand for oxygen. Down regulation of beta 1 receptors is a typical phenomenon of heart failure due to exposure to high levels of catecholamines. Experimentally it has shown that carvedilol is set to induce upregulation of beta-1 receptors. Other potential effects of carvedilol include: diastolic function return, decreased the renin-angiotensin activity and increased protein synthesis, increased anti-oxidant and anti-inflammatory effects. All of these effects are involved in ventricular function and heart capacity improvement.

Carvedilol effects and related previous investigations showed that it can lead to right ventricular positive remodeling and RV function improvement. RV mass to volume positive improvement results in reduction of wall pressure and may be helpful through reduction in RV demand (Communal *et al.*, 1998). Carvedilol can also improve myocardial blood supply, coronary perfusion and HR, as well as cardiac output by reducing the wall pressure in diastolic phase.

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