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THE COMPARISON OF SHORT TERM MONOTHERAPY AND COMBINATION THERAPY OF RAMIPRIL AND METOPROLOL IN THE MANAGEMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

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ABSTRACT

Objective: To compare the short term monotherapy and combination therapy of Ramipril and Metoprolol in the management of left ventricular systolic dysfunction (LVSD). **Methods:** This prospective observational study entitled "Comparison of short term monotherapy and combination therapy with Ramipril and Metoprolol in the management of LVSD" included patients with LVSD with ejection fraction (EF <50%). We identified all patients with LVSD and advised ECHO, from which baseline data were obtained. Selected patients were randomly divided into 3 groups. Group A received Ramipril (2.5-5mg), Group B received Metoprolol (25-50mg), Group C received combination of both (2.5 mg Ramipril+25 mg Metoprolol). After 2months changes in ejection fraction was recorded by echocardiography screening and the effect was determined based on the improvement in EF. **Results:** Results showed that Diabetes Mellitus (DM) (74%), Coronary Artery Disease (CAD) (56%), Hypertension (HTN) (54%) were probably dominant factors in the progression of LVSD. Baseline EF of Ramipril (33.31%) increased to 34.75% at second review with mean difference of 1.4%. For Metoprolol, baseline EF was 29% and it increased to 30.73% at second review with mean difference of 1.7%. At the same time, EF of combination of both increased from 33.25% to 35.36% with a mean difference of 2.1%. **Conclusion:** The most common risk factors associated with LVSD were DM, CAD, and HTN. Combination therapy with Ramipril and

Metoprolol increased the ejection fraction more effectively than monotherapy with Ramipril or Metoprolol in this short term study.

KEYWORDS: Left Ventricular Systolic Dysfunction, Heart Failure, Ramipril, Metoprolol, Ejection Fraction.

INTRODUCTION

LVSD is defined as a left ventricular ejection fraction less than 50%.[1] The patients with heart disease are classified according to normal or abnormal LV systolic function.[1] Angiotensin converting enzyme inhibitors(ACEi) and β-blockers have been found to improve exercise tolerance and symptoms (usually assessed by the NYHA functional class) in patients with heart failure due to LVSD as well as to significantly prolong survival and reduce hospitalization rates.[2,3]

Echocardiogram and ECG are the most useful tests in patients with suspected HF which provide information on chamber volumes, ventricular systolic and diastolic function, wall thickness, and valve function.[4] EF is calculated as stroke volume (which is the end-diastolic volume minus the end-systolic volume) divided by the end-diastolic volume.[5] More severe the systolic dysfunction, more the EF is reduced from normal and greater the end-diastolic and end-systolic volumes.[5] It is recognized that heart failure can arise in the presence of normal or near-normal EF: called heart failure with preserved ejection fraction.[6,7]

Pharmacotherapy of left ventricular systolic function comprise β-blockers, ACEi, statins, and digoxin as well as other drugs such as mineralocorticoid antagonist, ivabradine.[8] The combined use of β blockers and ACEi cause a significantly greater reduction in cardiovascular mortality and morbidity.[9,26,27] Conversely, ACEi, which reduce the production of angiotensin II that mediates an increased risk of cardiovascular disease events, reduce the risk of cardiovascular diseases in patients with LVSD.[10] The beneficial protective effects of Ramipril were more likely due to effects in preventing ventricular remodeling and in reduction of myocardial ischemic events.[11,12] Treatment with Ramipril decreased the rates of death, myocardial infarction, stroke, coronary revascularization, heart failure(HF) and the risk of DM and its complications.[13]

Use of β-blockers as secondary prevention is of proven value in the population of post infarction patients.[14,30] β- blockers are safe and effective in improving survival rate and

reducing the incidence of sudden death and reinfarction.[15] Furthermorethese agents confer an additional benefit to the patient with asymptomatic LVSD who is already taking an ACEi.[16] Metoprolol have been shown to reduce mortality and morbidity in patients with HF resulting from LVSD.[17,28,29]

DM was found to be an independent risk factor for the development of HF.[18] Chronic HF and DM increases the likelihood of developing the other, and the risk of morbidity and mortality increases when these occur together in the same patient.[20]

MATERIALS AND METHODS

Study Design

This prospective observational study was conducted in the cardiology department of a 650 bedded tertiary care teaching hospital for a duration of 6 months. 105 patients with EF< 50%, who were on Ramipril/ Metoprolol/ Ramipril+Metoprololwere randomly selected and advised echocardiography from which baseline data were obtained. These patients were categorized into 3 groups. Group A (n=35) received Ramipril (5-10 mg), Group B(n=35) received Metoprolol (25-50 mg), Group C (n=35) received combination of both (5-25 mg). The data were obtained through patient interview and patient's case records for demographics, medical and medication history, laboratory investigation reports and prescribed drugs. After 2 months changes in EF was recorded by ECHO screening.

STATISTICAL ANALYSIS

Improvement in EF (difference of mean±SD, median, between baseline to follow-up) by Ramipril, Metoprolol and its combination before and after treatment was analyzed by ANOVA, univariate analysis. Absolute LVEF change of 2.5% (P-value <0.05, 95% confidence intervals) was considered significant and clinically relevant. All calculations were performed using SPSS statistics 17 version,a commercially available program.

STUDY CRITERIA

Subjects (>18 years) with LVSD (EF<50 %), prescribed with Ramipril (dose), Metoprolol or combination of both, DM for at least 6 months and who signed the informed consent, were enrolled in the study. Pregnant women, lactating mothers, psychiatric patients, patients prescribed with other drugs that affect EF(digoxin), those who died and those who failed to follow up during the period of study were excluded.

Obtained ethical approval (IEC No: NCP/IEC 2017/No.074) from institution ethics review board before recruiting patients.

RESULTS

From November 2017 to May 2018, a total of 250 patients were assessed for eligibility. Of those, 105 eligible patients consented to participate in the study, remaining 145 were not included for the following reasons: failure to follow-up (n=87), concern about possible side effects (n=8), treatment costs(n=27), and preference for treatment in a different hospital(n=14) and 9 patients did not give a reason for declining to participate. Threepatients died after giving informed consent and two patients were withdrawn from the treatment due to Ramipril-induced dry cough. Number of dropouts did not differ significantly between treatment groups.

Effectiveness of these drugs was observed by improvement in ejection fraction. No substantial imbalances in baseline characteristics were observed between treatment groups.

Demographic details and risk factors in groups treated with drugs are shown below (table: 1).

Table 1: Categorization of Age, Gender, Alcoholic Consumption, BMI and Risk Factors in Groups Treated with Ramipril and Metoprolol and their combination.

		Ramipril	Metoprolol	Combination
Gender	Males	29	22	26
	Females	6	13	9
Age group	<40	1	0	2
	40-59	12	6	10
	60-79	23	26	21
	>80	1	2	1
Smoking	Non- smoker	12	24	27
	Ex- smoker	11	5	4
	Smoker	11	6	5
Alcohol consumption	Alcoholic	8	4	10
	Non- alcoholic	25	29	24
	Ex- alcoholic	2	2	1
BMI	<18.5	0	2	2
	18.5-24.99	27	25	25
	≥25	8	8	8
Risk factors	HTN	19	19	21
	DM	26	23	29
	VHD	6	5	3
	CAD	18	19	22
	CKD	5	5	1
	DLP	6	6	14
	Unknown	1	0	0

VHD: Valvular Heart Disease, CKD: Chronic Kidney Disease, DLP: Dyslipidemia.

Study revealedminor differences between the effect of Ramipril and Metoprolol on left ventricular function in patients with HF and reduced LVEF. The EF for Ramipril improved from 33.31%, (baseline) to 33.82% at first review and 34.75% at second review.

Similarly, for Metoprolol, EF increased from 29.00% (baseline) to 29.62% at first review and to 30.73% on second review. Improvement in EF for combination was found to be from 33.25% (baseline), to33.60% (first review), to 35.36% (second review).

Mean difference in EF was found to be 1.4%, 1.7%, 2.1%, for Ramipril, Metoprolol and combination respectively. (Fig :1).

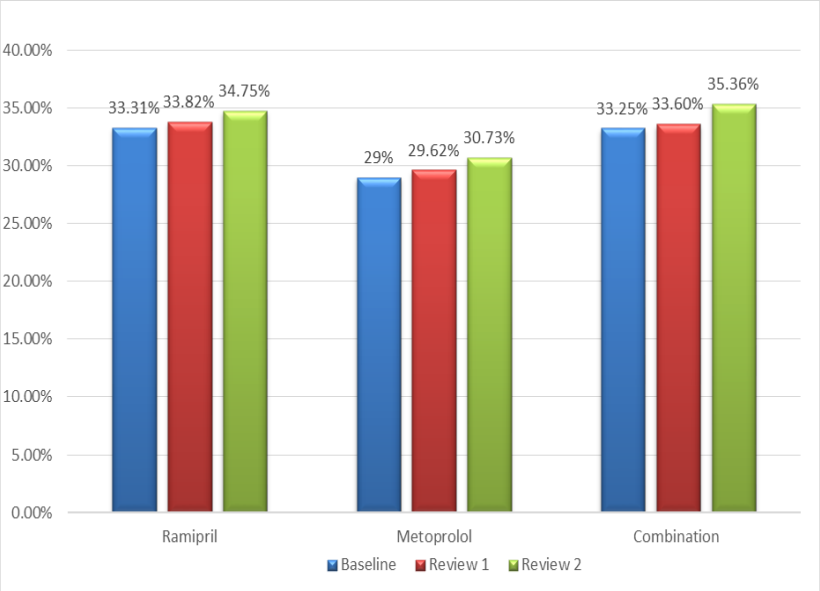

Fig 1: Mean EF of Ramipril, Metoprolol and Combination.

DISCUSSION

Present study showed that incidence of heart failure was inversely related to age. In connection witha study conducted by Wei Ting Chang et al., in 2014 at National Cheng Kung University Hospital, Taiwan, entitled "Characterization of Aging- Associated Cardiac Diastolic Dysfunction" (n=919) has stated that myocardium gets stiffer in aging hearts with high intra ventricular pressure, which in turn increases the incidence of heart failure.[21]

In 2014, a study in Poland (n= 8890)found that heart failure is the most common cardiovascular complication of diabetes mellitus.[23] Among all the risk factors of LVSD, DM

(74%), CAD (56%), HTN (54%) were found to be dominant and DLP (24%), VHD (11%), CKD (10%) were found to be predominant. It indicates DM, CAD, HTN and DLP as causative factors in the progression of LVSD. Our results were compatible with the above study.

In our study, after the administration of Ramipril, minor improvement in EF was found, which is comparable to the study (n=9297) reported by Sleight Yusuf et al., from Hamilton in 2000, who showed that ACEi showed improvement in ejection fraction among patients with left ventricular dysfunction, whether or not they have heart failure.[11]

Figueiredo Neto J etal., (n=50), in 2002 observed an improvement in survival rate in symptomatic stable chronic heart failure(CHF) who were on Metoprolol.[24] This is consistent with our study which showed a marked reduction in the morbidity and mortality.

Combination of Ramipril and Metoprolol showed a statistically significant improvement in EF. Similar to a study conducted by Heinz P. Theres etal., at Clinic for Internal Medicine, Germany in 2000 has stated that there was an improvement in cardiac function and mortality due to a combination of ACE inhibition and Beta Blockade after myocardial infarction.[25]

CONCLUSION

In patients with chronic heart failure (CHF) and reduced left ventricular ejection fraction (LVEF), Ramipril, Metoprolol, reduce mortality and improve LVEF. However, long-term survival and quality of life remain markedly impaired, especially in patients with diabetes. From the collected data it has been observed that the most common risk factors associated with heart failure are DM followed by CAD and HTN respectively. Even though the administration of Ramipril and Metoprolol separately was affected with an increase of the baseline values of ejection fraction, it showed more effectiveness when the combination of both (Metoprolol and Ramipril) was administered.

Limitation of The Study

The study requires long follow up periods, to get accurate results. On the other hand, treatment with an angiotensin-converting enzyme inhibitor, or a beta-blocker induces cardiac remodeling after approximately 3months. Lack of interest of the patients. As the data collection was based on patient interviewing, chances of high bias. Since heart failure is a life

threatening condition, the accessibility of subjects throughout the study period may not be possible.

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