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Antihypertensive Efficacy of Carvedilol and its Influence on Blood Glucose and Lipid Profile in Patients of Stage 1 Hypertension as Seen in a Teaching Hospital of India

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Abstract

Objective: To investigate Antihypertensive efficacy of Carvedilol and its influence on blood glucose and lipid profile in patients of stage 1 hypertension. *Materials and Methods:* Total of 60 patients were enrolled in the study, randomly allocated into two groups, group A and group B with 30 patients, group A received Metoprolol 25mg twice daily and group B received Carvedilol 12.5mg twice daily, reduction in blood pressure compared at 12 and 24weeks, effect on fasting blood glucose and lipid profile compared at 24th week, Statistical analysis was done using paired and unpaired t test and data is presented as mean±SD. *Results*: Mean SBP reduction with Carvedilol is 23±6.16 mmHg with no significant difference ($p>0.05$) compared to Metoprolol group (20.13±5.73), Mean DBP reduction with Carvedilol is 9.93±1.349 with no significant difference ($p>0.05$) compared to Metoprolol group (8.87±2.148) at 24th week of the study. Metoprolol showed a significant ($p<0.05$) elevation on Fasting blood sugar, Serum total cholesterol,LDL,VLDL and serum triglycerides, when compared with Carvedilol at the end of the study. *Conclusion:* Result of the study shows that Carvedilol and Metoprolol are equally effective in reduction of blood pressure and Carvedilol has added advantage in less elevation of fasting blood glucose, serum total cholesterol, LDL, VLDL and serum triglycerides and which is an advantage to the hypertensive patients with lipid disorder and impaired glucose tolerance.

Keywords: Carvedilol; Metoprolol; Lipid Profile; Hypertension; Fasting Blood Glucose.

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Introduction

Pharmacological treatment of hypertension can, cause clinically significant alterations in lipid metabolism and glucose homeostasis [1].

Betablockers have been shown to reduce cardiovascular risk in patients with hypertension, however some components of metabolic syndrome are worsened [2], It is important to use antihypertensive drugs that not only reduce cardiovascular risk but also help to stabilize components of metabolic syndrome [3]. GEMINI trial is first randomized trial to compare effects of two different betablockers on glycaemic control as well as other cardiovascular risk factors [4].

Carvedilol is a drug used in hypertension, angina and congestive heart failure. It is β1, β2 antagonist (onset in 1 hour), α1 antagonist (onset in 30 minutes) and on oral administration it is rapidly absorbed and reaches peak plasma concentration within one to 2 hours.

At higher doses, it has calcium channel blocking property of moderate potency (blocks L-type voltage gated channels) [5,6] but the effect of this blockade on blood glucose levels is a scantily explored domain [7,8].

Some studies reported beta blocking induced hyperglycaemia contradicting the ideas of its vasodilating property inducing hypoglycaemia by improving insulin sensitivit [9,10,11].

Several head-to-head studies have convincingly shown that non-selective agents, such as atenolol and metoprolol, have a negative effect on myocardial contractility, vascular resistance and carbohydrate and lipid metabolism [12] while newer agents with vasodilating properties, such as carvedilol, have a hemodynamic and metabolic profile that is much better than that of older compounds [13].

Study Drugs

Carvedilol [14]

Nonselective β-adrenergic blocking agent with antihypertensive α1-blocking activity. It is (±)-1-(Carbazol-4-yloxy)-3-[[2-(o-methoxyphenoxy) ethyl] amino]-2-propanol.

Mechanism

Racemic mixture in which nonselective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α1-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency, no intrinsic sympathomimetic activity [15].

Carvedilol has been tested in numerous double-blind, randomized studies including the following: U.S. Carvedilol Heart Failure Trials Program, Carvedilol or Metoprolol European Trial (COMET) [16], Carvedilol Prospective Randomised Cumulative Survival (COPERNICUS) trial, and the Carvedilol Post Infarct Survival Control in LV Dysfunction (CAPRICORN) trial [17].

Metoprolol [18,19]

$Beta_1$-selective receptor antagonist that is devoid of intrinsic sympathomimetic activity and membrane-stabilizing activity, it is almost completely absorbed after oral administration, but bioavailability is relatively low (about 40%) because of first-pass metabolism. Plasma concentrations of the drug vary widely, perhaps because of genetically determined differences in the rate of metabolism.

It is extensively metabolized in the liver, with CYP2D6 the major enzyme involved, and only 10% of the administered drug is recovered unchanged in the urine. The half-life of metoprolol is 3 to 4 hours, but can increase to 7 to 8 hours in CYP2D6 poor metabolizers [20].

Carvedilol combined with RAS blocker therapy in diabetic patients with hypertension results in better glycemic control and less insulin resistance than combination therapy that includes metoprolol [21].

Objective

To investigate antihypertensive efficacy of Carvedilol and its influence on blood glucose and lipid profile in patients with stage 1 hypertension

Materials & Methods

Patients between 20 - 65 years of age with stage I essential hypertension attending medical outpatient department in a tertiary care hospital, were selected for the study.

Prior permission was taken from the institutional Ethics committee to conduct the study.

Study Design

Prospective randomized double blind comparative study

Sample Size

Sample size was 60 patients. They were randomly allocated to two groups with 30 patients each.

(Group-A (n=30) were received Metoprolol 25mg twice daily.

(Group-B (n=30) were received Carvedilol 12.5mg twice daily.

Inclusion Criteria

Patients aged 20-65 years with newly diagnosed and untreated hypertension or those who had discontinued antihypertensive medication voluntarily for more than 4 weeks.

Patients with Stage 1(140-159 /90-99 mmHg) essential hypertension according to JNC 7 classification are selected by taking the average of three readings of blood pressure taken in sitting, standing and supine positions.

Exclusion Criteria

Patients on other antihypertensive therapy, history of sensitivity or severe adverse reactions to Betablockers, patients of secondary hypertension or malignant hypertension(retinal haemorrhages, exudates or papillary oedema), patients with history of Diabetes mellitus, patients with impaired liver function defined as SGOT or SGPT >2 times the normal limit and with impaired kidney function defined as serum creatinine>2mg/

dl,patients with history of Bronchial Asthma, Chronic obstructive pulmonary disease, Sinus bradycardia, Sicksinus syndrome, Prinzmetal's angina, heartblock and Chronic heart failure and Pregnant & Lactating women.

After fulfilling the inclusion and exclusion criteria, the patients were enrolled into the study and informed written consent was obtained from all patients after a detailed explanation prior to enrollment

Drugs used in the study

Tab Metoprolol25mg twice daily is given to one study group.

Tab Carvedilol 12.5 mg twice daily is given to other study group.

The Drugs used were identical in appearance & taste.

Laboratory Investigations: Fasting Blood Sugar, Serum Cholesterol, Serum VLDL (Very Low Density Lipoproteins), Serum LDL (Low Density Lipoproteins), Serum Triglycerides and Serum HDL (High Density Lipoproteins)

Recording of Blood Pressure: The blood pressure was measured in sitting position.

Equipment: Mercury Sphygmomanometer, Cuff size : 12 - 13 cm x 35 cm, Cuff is applied firmly so as to cover 75% to 80% circumference of the arm & 2/3 of length of the bare arm.

Method of measuring the blood pressure: Cuff is tired to the arm firmly. The Cuff is inflated till the radial pulse is not palpable. The Cuff is re inflated to 30 mm Hg higher than the pressure at which the redial pulse is not felt. The diaphragm of stethoscope is placed over the brachial artery, Cuff is placed at the level of heart, Korotkoff Sounds phase-I (appearance of sounds) was regarded as systolic pressure and phase-V (disappearance of sounds) was regarded as diastolic pressure.

Estimation of Metabolic Parameters: Blood sample were drawn by taking all precautions in fasting state. Base line fasting Blood Sugar, S. Cholesterol, S. Triglycerides, S.VLDL, S.LDL, S.HDL were done. Estimation of fasting blood sugar, & Serum lipids were done by using calibrated semiautoanalyzer,by using glucose oxidased peroxidase method for the estimation of fasting blood sugar, cholesteroloxidase peroxidase method for serum cholesterol, precipitation method for HDL, glycerol phosphate oxidase method for TG, Friedewald's formula for calculation of VLDL & LDL.

Duration of treatment; patients were randomly allocated in to two groups to be treated for 24 weeks.

Follow-Up: Patients were followed for every 4 weeks for recording blood pressure and for measuring Fasting blood sugar throughout the study period (6 months or 24 weeks).

Compliance of the patient regarding medication consumption was assessed by the "Pill Count Method".

Assessing Efficacy: Blood pressure was recorded every 4^{th} week and readings noted, after 12^{th} week and 24^{th} week of the study, the reduction in blood pressures (SBP, DBP) with the both drugs were compared, after 24^{th} week of the study the effect of both the drugs on S.TC, S.TG, S.LDL, S.HDL, S.VLDL, FBS was compared.

Stastistical Analysis

Data is presented as mean±SD, effect on blood pressure reduction within the group is compared by paired "t" test and the effect on reduction of blood pressure between two study groups compared by unpaired "t" test

Observation and Results

Table 1: Reduction in systolic blood pressure

Weeks	Metoprolol (mean ± SD)	Carvedilol (mean ± SD)	t - value	p - value
0 Weeks	148.93 ± 7.09	149.93 ± 6.65	-	-
12 Weeks	134.066 ± 7.172	131 ± 7.08	1.666	>0.05 (Not significant))
24 Weeks	128.8 ± 5.737	126.93 ± 6.164	1.864	>0.05 (Not significant)

Table 2: Reduction in diastolic blood pressure

Weeks	Metoprolol (Mean ± SD)	Carvedilol (Mean ± SD)	T - value	P - value
0 Weeks	89.80 ± 5.182	90.73 ± 5.343	-	-
12 Weeks	83 ± 3.394	82.33 ± 2.734	0.837	>0.05 (Not significant)
24 Weeks	80.93 ± 2.148	80.80 ± 1.349	0.0287	>0.05 (Not significant)

Table 3: Metabolic parameters at 0 weeks & 24 weeks in metoprolol group

Metabolic Parameters	0 Weeks	24 Weeks
Serum Total cholesterol	154.53 ± 3.40	162.2 ± 6.89
Serum Triglycerides	74.73 ± 14.966	87.2 ± 8.507
Serum LDL	75.2 ± 9.38	83.76 ± 8.08
Serum VLDL	14.94 ± 2.993	17.44 ± 1.701
Serum HDL	43.83 ± 8.275	43.93 ± 11.58
Fasting blood sugar	87.4 ± 5.360	85.6 ± 4.359

Table 4: Metabolic parameters at 0 weeks & 24 weeks in carvedilol group

Metabolic Parameters	0 Weeks	24 Weeks
Serum total cholesterol	153.7 ± 2.680	152.13 ± 2.145
Serum triglycerides	81.8 ± 10.172	87.2 ± 8.507
Serum LDL	79.1 ± 8.96	78.43 ± 14.462
Serum VLDL	16.36 ± 2.034	15.68 ± 2.892
Serum HDL	44.13 ± 11.078	44.9 ± 11.576
Fasting blood sugar	88.7 ± 4.647	82.53 ± 4.606

Table 5: Evaluation of metabolic parameters at 24th week

Metabolic Parameters	Metoprolol (Mean ± SD)	Carvedilol (Mean ± SD)	T - Value	P – Value
Serum total cholesterol	162.2 ± 6.89	152.13 ± 2.145	7.942	<0.05 (S)
Serum triglycerides	87.2 ± 8.507	78.43 ± 14.462	2.861	<0.05 (S)
Serum LDL	83.76 ± 8.08	80.03 ± 8.364	1.75	>0.05 (NS)
Serum VLDL	17.44 ± 1.701	15.68 ± 2.892	1.78	>0.05 (NS)
Serum HDL	43.93 ± 11.58	44.9 ± 11.576	0.323	>0.05 (NS)
Fasting blood sugar	85.6 ± 4.359	82.53 ± 4.606	2.648	<0.05 (S)

Discussion

Hypertension is a major cardiovascular risk factor but most patients remain asymptomatic for many years, successful therapy not only needs to be effective, it also needs to be well tolerated, Lowering BP to normal levels without quality of life deterioration is the most important means of reducing cardiovascular risk, Beta-blockers are well established as effective antihypertensive agents, third generation beta-blockers such as carvedilol with their favourable therapeutic profiles constitute a new spectrum in the treatment of hypertension as opposed to old fashioned drugs such as atenolol Carvedilol possesses both [beta]- and [alpha]1-blocking activity, [alpha]1-blocking properties of this drug help to produce a desirable hemodynamic profile and facilitate appropriate blood pressure and heart rate response. Principal aim is to investigate Antihypertensive efficacy of carvedilol and its influence on blood glucose, lipid profile in patients of stage 1 hypertension Present study is a double blind randomized study comparing Carvedilol and Metoprolol in patients with stage-1 hypertension,total 60 patients were included in this study, Mean SBP reduction with Carvedilol is 23±6.16 mmHg with no significant difference (p>0.05) compared to Metoprolol group (20.13±5.73), Mean DBP reduction with Carvedilol is 9.93±1.349 with no significant difference (p>0.05) compared to Metoprololgroup (8.87±2.148) at 24th week of the study.

Metoprolol shows a significant (p<0.05) elevation on Fasting blood sugar, Serum total cholesterol, LDL,VLDL and serum triglycerides, when compared with Carvedilol at the end of the study.

Conclusion

Result of the study shows that Carvedilol and Metoprolol are equally effective in reduction of blood pressure and Carvedilol has added advantage in less elevation of fasting blood glucose, serum total cholesterol, LDL,VLDL and serum triglycerides and which is an advantage to the hypertensive patients with lipid disorder and impaired glucose tolerance.

Conflict of Interest

Nil

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