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Research Article

A COMPARATIVE CLINICAL STUDY OF BETA BLOCKERS VERSUS CALCIUM CHANNEL BLOCKERS AS ADDITIONAL ANTIHYPERTENSIVE AGENTS IN DIABETIC PATIENTS

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Key words:

BB:Betablockers, CCB: calcium channel blockers, FBS: fasting blood sugar, FPI: fasting plasma insulin, TC: total cholesterol, TG: triglycerides, LDL: low density lipoproteins, HDL: high density lipoproteins, HBA1c : glycated hemoglobin

A B S T R A C T

Background: Hypertension (HTN) is one of the important risk factors for cardiovascular morbidity and mortality in diabetic subjects. Tight control of HTN prevents or retards both micro vascular and macro vascular complications.
Aim &objective: To compare safety and efficacy of beta blockers in diabetic patients to those on calcium channel blockers as additional antihypertensive agents.
Material & Method: After institutional ethics committee approval and obtaining written informed consent patients' were divided into two groups. Group A BB (n=30) and Group B CCB (n=40). The present study was designed to compare clinical and biochemical parameters of BBs versus CCBs as additional antihypertensive agents in diabetic patients. It was designed as an open – label parallel group comparative clinical study.
Results: Both BB and CCB reduced the systolic and diastolic blood pressures. But the reductions in systolic and diastolic BP were not significantly different for the two drug groups. However, CCB caused a significantly greater reduction in BMI when compared to BB. Fasting plasma insulin levels were raised by adding BB to type 2 DM patients whereas the levels were reduced by CCBs .However this was not statistically significant. BB raised the levels of FBS & TC and reduced HDL cholesterol levels which were opposite in effect to that seen with CCBs and were statistically significant. HBA1clevels were raised by BBs and lowered by CCBs, which was statistically highly significant.
Conclusion: Except in co-morbid conditions of ischemic heart diseases, especially following acute MI, CCBs rather than BBs, appear to be better agents to be combined with ACEIs/ ARBs for effective control of blood pressure in diabetics.

INTRODUCTION

Diabetes mellitus (DM) is a common disorder world wide. At least 171 million people world wide have DM & is likely to double by 2030, in which the most affected age group will be 35-64 yrs (1). Hypertension (HTN) is one of the important risk factors for cardiovascular morbidity and mortality in diabeticsubjects. Tight control of HTN prevents or retards both microvascular and macrovascular complications. Nearly 70% of deaths in diabetic patients occur due to macrovascular complications, and these risks can be prevented by tight control of HTN, along with optimal control of hyperglycemia(2).Diuretics, Beta blockers (BBs), Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptor Blockers (ARBs) and Calcium Channel Blockers (CCBs) have all been used often in combination, in the treatment of hypertension in diabetic patients (3). Beta blockers have been shown to possess certain unfavorable metabolic and other properties which may hamper their effective treatment especially in patients of type 2 diabetes mellitus. In particular, their properties of aggravating hyperglycemia, hyperinsulinemia, dyslipidemia, easy fatigability and depression (4), may lead to poor outcomes in diabetic patients. Compared with Beta Blockers, Calcium Antagonists, Diuretics and ACEIs were found to have more favourable effects on indices of arterial stiffness in several studies (5).

The present study was planned to confirm the risks associated with the use of BBs vis a vis CCBs as additional antihypertensive agents in patients of diabetes mellitus.

MATERIAL AND METHODS

The present study was designed to compare health related quality of life (HRQOL) index, clinical and biochemical parameters of beta blockers (BBs) versus calcium channel blockers (CCBs) as additional antihypertensive agents in diabetic patients. It was designed as an open – label parallel group comparative clinical study in medical outpatient department (OPD) of the tertiary care hospital from November 2017 to January 2019.Type 2 DM patients who visited the

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medical OPD for their ailments and those who required additional anti hypertensives over and above ACEIs/ARBs were screened and enrolled in the present study. Patients of either sex, aged 40 to 69 years and diagnosed with type 2 Diabetes mellitus and hypertension with poor control of blood pressure by drugs suppressing Renin Angiotensin System were included. Recording of BP was done after 10 min of rest in sitting posture with the right arm well supported. Diabetic patients with BP >130/80 mm of Hg without Proteinuria (6) and BP >125/75 mm of Hg with micro or macro albuminuria was defined as poor BP control (7). Patients suffering from any malignancies, psychiatry disorders, HIV or any life threatening condition were excluded from the study. Patients enrolled were assigned to BB group or CCB group at random. Anthropometric measurements like Height, Weight, Body mass index (BMI) were recorded. Overnight fasting of 12 hrs blood samples were collected which was used for estimation of the Fasting plasma insulin, Fasting plasma glucose, Lipid profile and HBA_{1c}.Estimation of insulin was done by ELISA method using UBI MAGIWEL^{TM}. ***Statistical Analysis:*** Data recorded were summarized as mean ± SD for continuous variables and percentages for categorical variables. The tests of statistical significance included students paired t test for testing the difference in means within groups and students unpaired t test for testing the difference in means between groups. Chi square test of significance was used to study the difference in proportions between the groups. The threshold was set at p value < 0.05 for statistical significance and p value < 0.001 for highly significant levels.

RESULTS

The demographic profile of patients in both groups is comparable in all the respects. (Table1).There was no significant difference in weight, pulse, and Body mass index before and after 35 weeks of treatment between the groups. The average increase in body weight in beta blocker group was less than 0.7 kg and the pulse rate fell by almost one beat per minute but both were not significant. However there was significant reduction in both systolic and diastolic blood pressures (p value < 0.001) caused by beta blockers. (Table 2)

Table 1 Comparison of demographic profile

Profile	Type 2 DM with BB as additional antihypertensive (mean ± SD)	Type 2 DM with CCB as additional antihypertensive (mean ± SD)	P value and significance*
Age (years)	51.83± 8.80	54.50± 7.11	0.18 (NS)
Sex (number males: females enrolled)	17:13	25:15	0.953(NS)
Duration of type 2 DM (years)	5.27±1.89	4.46±1.95	0.087(NS)
Smokers :Non smokers(number)	4:26	4:36	0.339(NS)

BB=Beta blockers, CCB =calcium channel blockers, SD=standard deviation, NS=not significant when P >0.05, S=significant when P<0.05, HS =highly significant when P<0.001

Table 2 Comparison of clinical parameters within BB group

Clinical parameters	Baseline data (mean ± SD)	Data after 35 weeks (mean ± SD)	P value and significance*
Weight(kg)	68.00± 8.80	68.67± 9.72	0.223 (NS)
Pulse (beats per minute)	79.80± 5.16	78.87± 5.11	0.318 (NS)
Systolic blood pressure (mm of Hg)	133.47± 7.96	126.27± 4.45	< 0.001(HS)
Diastolic blood pressure (mm of Hg)	86.33± 4.99	82.53 ± 3.06	< 0.001(HS)
BMI (kg/m^2)	28.02± 3.28	28.09± 3.65	0.773(NS)

BB=Beta blockers, SD=standard deviation, NS=not significant >0.05, S=significant <0.05, HS =highly significant <0.001 *Student's paired t -test was used for testing the difference in means between the groups.

Table 3 Comparison of biochemical parameters with in BB group

Biochemical parameters	Baseline data (mean ± SD)	Data after 35 weeks (mean ± SD)	P value and significance*
FBS(mg/dl)	118.93±16.55	127.23±18.15	0.02(S)
FPI(µU/ml)	11.23± 7.28	12.33± 6.04	0.417(NS)
TC(mg/dl)	210.27± 24.32	211.70± 19.63	0.589(NS)
TG(mg/dl)	155.07± 58.79	167.77± 59.57	0.001(S)
LDL(mg/dl)	85.97± 30.48	92.83± 29.45	< 0.001(HS)
HDL(mg/dl)	57.37± 17.97	55.43± 17.72	0.302(NS)
HBA_{1c}(%)	5.18± 1.23	6.30± 1.06	0.078(NS)

BB=Beta blockers, n=BB=30, SD=standard deviation, NS=not significant >0.05, S=significant <0.05, HS =highly significant <0.001. Legend of FBS=fasting blood sugar, FPI=fasting plasma insulin, TC=total cholesterol, TG=triglycerides, LDL=low density lipoproteins, HDL=high density lipoproteins, HBA_{1c} =glycated haemoglobin.*

Beta blockers added as additional antihypertensives to type 2 DM patients did not significantly alter the biochemical parameters of FPI, HBA_{1c} and the total and high density cholesterol levels. But there were significant increase in the levels of blood sugar and triglycerides. The increase in LDL cholesterol level was highly significant. An increase in fasting plasma insulin of more than 1 µU /ml could be clinically significant even if not significant statistically (Table 3).

Table 4 Comparison of clinical parameter within calcium channel blocker group

Clinical parameters	Baseline data (mean ± SD)	Data after 35 weeks (mean ± SD)	P value and significance*
Weight (kg)	69.19± 9.13	68.03± 9.37	<0.001(HS)
Pulse (beats per minute)	80.58± 5.65	80.50± 4.72	0.928 (NS)
Systolic blood pressure (mm of hg)	137.65± 9.28	128.70± 4.63	<0.001(HS)
Diastolic blood pressure (mm of hg)	88.05± 4.70	84.78± 3.77	<0.001(HS)
BMI(kg/m^2)	28.46± 3.29	27.86± 3.42	<0.001(HS)

CCB =calcium channel blockers, n=CCB=40, SD=standard deviation, NS=not significant > 0.05, S=significant < 0.05, HS =highly significant < 0.001

*Student's paired t -test was used for testing the significance .The threshold of statistical significance was set at p value < 0.05.

The clinical parameters of patients of type 2 diabetes mellitus enrolled in the calcium channel blockers arm as additional antihypertensive did not differ significantly in pulse rate before and after completion of 35 weeks of treatment. However there were significant reduction in both systolic and diastolic blood pressures along with significant reduction in both weight and BMI with p value (< 0.001)(table 4)

Table 5 Comparison of biochemical parameters within calcium channel blocker group.

Biochemical parameters	Baseline data (mean ±SD)	Data after 35 weeks (mean ±SD)	P value and significance*
FBS (mg/dl)	122.23±37.34	110.28±17.04	0.01(S)
FPI (µU/ml)	20.66±17.53	18.37±17.59	0.241(NS)
TC(mg/dl)	168.08±36.51	159.28±38.49	<0.001(HS)
TG(mg/dl)	122.95±40.13	117.95±36.82	0.001(S)
LDL(mg/dl)	93.60±34.49	87.18±30.35	0.001(S)
HDL(mg/dl)	47.82±14.19	50.97±12.21	<0.001(HS)
HBA_{1c} (%)	4.45±1.04	4.28±0.78	0.147(NS)

CCB =calcium channel blockers, SD=standard deviation, NS = notsiginificant p>0.05, S=significant p<0.05, HS = highly significant p<0.001 *Student's paired t -test was used for testing the difference within the group. The threshold of statistical significance was set at p value <0.05

Amongst the biochemical parameters of patients of type 2 DM patients enrolled in the CCB arm as additional antihypertensive, there were no significant difference in the levels of FPI and HBA_{1c} before and after 35 weeks of treatment, though they were reduced. However there was a significant decrease in FBS, TG and LDL levels and highly significant decrease in TC level with p values <0.05 and <0.001 respectively. The increase in HDL level before and after 35 weeks of treatment is also highly significant with p value <0.001(Table 5).

Table 6 Comparison of difference in mean values of clinical parameters between those enrolled with CCBs and BBs for 35 weeks of treatment

Clinical parameters (data after 35 weeks of treatment -baseline data)	BB group (mean ± SD) n=30]	CCB group (mean ± SD) [n=40]	P value and significance*
Systolic blood pressure (difference in mm of hg)	-7.20± 6.14	-8.95± 6.61	0.258 (NS)
Diastolic blood pressure(difference in mm of hg)	-3.80± 3.87	-3.28± 4.38	0.598 (NS)
BMI(difference in kg/m^2)	0.07± 1.35	-0.60± 0.94	0.023 (S)

BB=Beta blockers, CCB =calcium channel blockers, SD=standard deviation, NS=not significant >0.05, S=significant <0.05, HS =highly significant <0.001

*Student's unpaired t -test was used for testing the difference between the means. The threshold of statistical significance was set at p value < 0.05

Both beta blockers and calcium channel blockers reduced the systolic and diastolic blood pressures when used as additional antihypertensive in type 2 DM patients. But the reductions in systolic and diastolic BP were not significantly different for the two drug groups. However, calcium channel blockers caused a significantly greater reduction in BMI when compared to beta blockers (Table 6).

Table 7 Comparison of difference in mean values of biochemical parameters between those enrolled with CCB's and BB's for 35 weeks of treatment

Biochemical parameters (data after 35 weeks of treatment - baseline data)	BB group (mean ± SD) [n=30]	CCB group(mean ± SD) [n=40]	P value and significance*
Diff_FBS (mg/dl)	8.30± 18.43	-11.95± 28.09	0.001(S)
Diff_FPI(μU/ml)	1.10± 7.32	-2.30± 12.21	0.153(NS)
Diff_TC(mg/dl)	1.43± 14.36	-8.80± 12.60	0.003(S)
Diff_HDL(mg/dl)	-1.93± 10.07	3.13± 5.04	0.016(S)
Diff_ HBA_{1c} (%)	1.12± 1.21	-0.18± 0.75	< 0.001(HS)

BB=Beta blockers, CCB =calcium channel blockers, SD=standard deviation, NS=not significant > 0.05, S=significant < 0.05, HS =highly significant < 0.01 *Student's unpaired t -test was used for testing the difference between the means. The threshold of statistical significance was set at p value < 0.05

Fasting plasma insulin levels were raised by adding beta blockers to type 2 DM patients where as the levels were reduced by CCBs .However this was not statistically significant. Beta blockers raised the levels of FBS & TC and reduced HDL cholesterol levels which were opposite in effect to that seen with CCBs and were statistically significant. HBA_{1c}levels were raised by beta blockers and lowered by calcium channel blockers, which was statistically highly significant (Table 7).

DISCUSSION

In the present study, we have attempted to compare beta blockers versus calcium channel blockers in respect control of blood pressure and effect of these drugs on biochemical parameters when used as add on antihypertensive agents in diabetic patients. The baseline demographic profiles of patients in both the arms were comparable in respect to age, duration of DM, and sex ratio. Patients enrolled in this study had type 2 DM of more than four years duration. Males and nonsmokers were predominant in the study group of both the arms.

In the Fosinopril versus Amlodipine Cardiovascular Events Trial (FACET), patients on the combination of amlodipine and Fosinopril had a lower cardiovascular event rate than those treated with either ACEIs or DHP-CCBs (8). In RENAAL trial also, there is no reduction in renal/ cardiovascular protection with losartan when CCBs were added (9). It appears that combination of DHP-CCBs with ACEIs / ARBs are effective since blood pressure is lowered synergistically (10).

Since 1960s, the metabolic side effects of beta-blockers have been widely studied (11). Non-vasodilating beta-blockers such as atenolol and metoprolol have been reported to worsen insulin sensitivity, alter lipid metabolism and cause weight gain (12). Other potential mechanisms through which these conventional beta-blockers impair glucose metabolism include decreased exercise, decreased skeletal muscle blood flow, decreased islet cell insulin secretion and the antagonistic effects of blockade of the beta-2 receptor on insulin metabolic signaling (12). In the present study, fasting blood sugar was significantly reduced by CCBs administered as additional anti hypertensive possibly due to better patient adherence and monitoring as CCBs are known to be glucose neutral. Beta blockers were found to significantly aggravate FBS level as is well established.

In the present study, adding beta blockers to diabetics did not aggravate hperinsulinemia and the effect on FPI were comparable in both the groups of CCBs and BBs, though there was a trend to increase the levels by BB drugs and reduction of levels by CCBs. The variation in values of plasma insulin levels was very high within both the groups, and so insulin levels are not measured routinely in diabetics.

CONCLUSION

Based on existing information and results from the present study, it can be concluded that except in co-morbid conditions of ischemic heart diseases, especially following acute MI, CCBs rather than BBs, appear to be better agents to be combined with ACEIs/ ARBs for effective control of blood pressure in diabetics.

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