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EFFECT OF CALCIUM CHANNEL BLOCKERS AND BETA BLOCKERS AS ADDITIONAL ANTI-HYPERTENSIVE AGENTS ON QUALITY OF LIFE IN T2DM PATIENTS

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ABSTRACT

Current recommendations exist to control BP < 140/90 mm of Hg for all ages with diabetes. RAS blockers are the anti-hypertensive agents of choice in diabetics with albuminuria. Calcium channel blockers (CCBs) and beta blockers are established anti-hypertensive agents used in T2DM patients. The present study was conducted to compare health related quality of life (HRQoL) index between CCB versus beta blockers as add-on anti-hypertensive agents in T2DM patients. An open-label prospective study was conducted on 100 T2DM patients with poor BP control while on RAS blockers. HRQoL index was measured using EQ-5D VAS scores and its five domains. After 35 weeks, EQ-5D VAS score improved in CCB group while it worsened in beta blocker group and this was highly significant statistically. Beta blocker group also had a higher and significant proportion of patients with pain and anxiety/depression self-rating. The quality of life index by self-assessment was in favour of CCBs compared to beta blockers in T2DM patients. It is suggested therefore that RAS blockers in combination with CCBs maybe a better choice of dual anti-hypertensive therapy in T2DM patients.

KEYWORDS: T2DM patients, RAS blockers, Calcium channel blockers, Beta blockers, HRQoL index EQ-5D.

INTRODUCTION

It is unfortunate that Indians are highly vulnerable to develop diabetes mellitus and coronary artery disease among ethnic groups.[1] The number of diabetics in India has doubled between the years 1995 and 2005 and by 2025, it is estimated to reach around 70 million patients.[2] Uncontrolled hyperglycemia in diabetes leads to early and higher risks of complications. Microvascular complications namely, retinopathy, neuropathy, and nephropathy are more commonly seen in diabetics with poor control of plasma glucose. Coronary artery disease, peripheral arterial disease and cerebrovascular disease are the macrovascular complications of diabetes. It is therefore very important to maintain plasma glucose under control in diabetes with lifestyle modification and drugs. It has been often found that quality of life (QoL) is poor in diabetics, which gets worsened with disease progression and complications.[3]

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 microvascular and macrovascular complications. It is recommended that BP should be maintained at < 140/90 mm Hg for all ages with diabetes.[4,5,6] American Diabetes Association in 2017 recommends Renin Angiotensin System (RAS) blockers as the anti-hypertensive agents of choice in diabetics with albuminuria.[6] Presently, evidence exists that single drug therapy with any of the first line classes of thiazide diuretics, calcium channel blockers (CCBs) or RAS blockers have similar efficacy in reducing cardiovascular events in diabetics.[6,7] However, in most clinical settings, anti-hypertensives are required in combination for optimal BP control. Diabetic patients with dyslipidemia are best managed by combining RAS blockers with CCBs while those after MI or in heart failure are managed by combining RAS blockers with beta blockers.[8]

Beta blockers are known to aggravate hyperglycemia, hyperinsulinemia, dyslipidemia, easy fatigability, COPD and depression. But they continue to be highly efficacious and reasonably well tolerated by most diabetic patients with ischaemic heart diseases or hypertension. CCBs are metabolically neutral and lead to lower incidence of stroke or peripheral arterial disease.[9]

Surprisingly, beta blockers had no material impact on the health related quality of life (HRQoL) of patients with peripheral arterial disease in a cohort of COPD patients.[10] Further, beta blockers had a lower 1- year mortality for both types 1 and 2 DM and also non-diabetics, with no increased rates of hospital readmission

for diabetic complications.[11] The issue of which drug provides better patient compliance was made more complex by a study on hypertensive patients in UAE. It was observed in the study that those using CCBs had the lowest self- reported health assessment.[12]

Despite established efficacy and a reasonable safety profile of beta blockers, they continue to be used in diabetic patients with scepticism about acceptability by the patient. Further, drug adherence is an important factor to achieve target BP in hypertensive patients. A drug regime which has high HRQoL index is expected to ensure high adherence. Hence, the present study was designed to compare the HRQoL index between CCBs in combination with RAS blockers versus beta blockers in combination with RAS blockers when used in T2DM patients.

MATERIAL AND METHODS

An open – label prospective, parallel group clinical study was conducted on diabetic patients with hypertension attending medical OPD of a tertiary care hospital in western India, after the approval from Institutional Ethics Committee.

A total of one hundred T2DM patients of either sex, aged 40 to 69 years with poor control of BP despite using RAS blockers were included in the study after obtaining written informed consent. Patients suffering from any malignancy, psychiatry disorder, HIV or any life threatening condition were excluded from the study. Enrolled patients were assigned to beta blocker (BB) group or CCB group by the treating physician as per the existing clinical protocol of managing diabetics with co-morbidities. The assignment of patients to BB or CCB group was done keeping in mind, the safety profile of the additional anti-hypertensive agent.

The demographic profile in terms of age, sex, BMI, duration of diabetes, and smoking/ non-smoking habits were recorded for all patients in either group. HRQoL index using EQ-5D –VAS[13] was carried out on all diabetic patients enrolled in the study. It was based on the patients response to the questionnaire translated in the regional language as understood by them. Patients were interviewed using a standardized questionnaire and self- rated health status was recorded using visual analogue scale (VAS), which consist of a linear scale divided into intervals with fixed limit points (0-100). VAS value of 100 denotes best imaginable health status and 0 denotes worst. The EQ-5D form included domains of mobility, self care, usual activities, pain, anxiety/ depression. Patients were asked to tick whether they had no problem, some problems or severe problems in all these domains. The questionnaire forms were repeated for response by the enrolled patients after 35 weeks of additional antihypertensive agent added (before and after response).

Statistical analysis

Students unpaired t test, was used to test the difference in means between the groups BB and CCB, for continuous variables at the start of the study. Mean values of EQ-5D-VAS were also tested between the groups at the start and after 35 weeks of drug combinations using unpaired t test. Chi square test of significance was used to test the difference in proportions between the groups. The EQ-5D domains of mobility, pain and anxiety/ depression were tested between the groups at 35 weeks of dual anti-hypertensive therapy using chi square test, since response was categorical in all, having either no problem or some problems. The threshold was set at p value < 0.05 for statistical significance and p value < 0.001 for highly significant levels.

RESULTS

The first 100 T2DM patients who required an additional agent over and above RAS blockers to control their BP were included in the study.

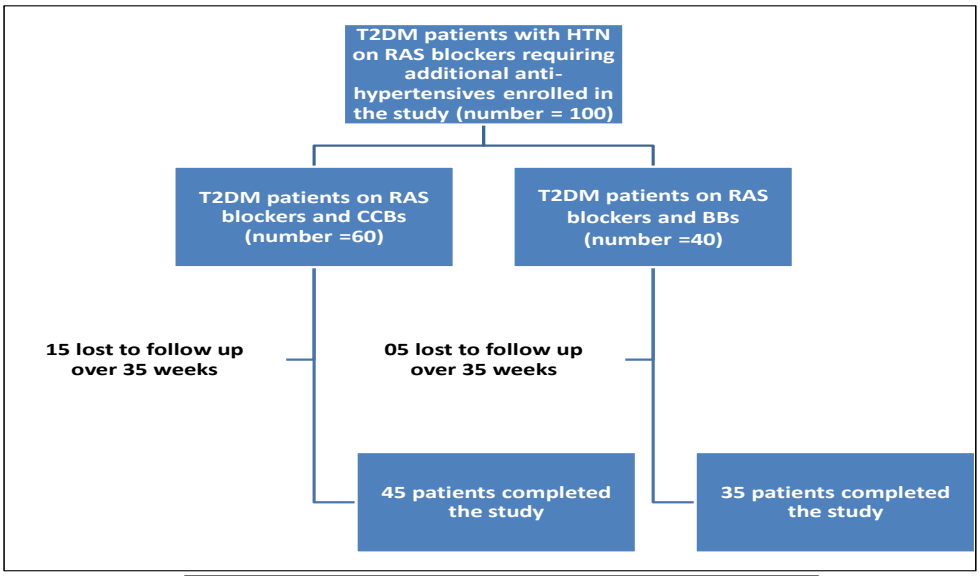

Figure 1: Flow chart of patients enrolled in the study.

The demographic profile and baseline clinical parameters of the two groups were as depicted in Table 1. EQ-5D VAS scores at the start and after 35 weeks of dual anti-hypertensive therapy are depicted in Table 2.

Table 1 - Comparison of demographic profile of T2DM patients between those enrolled in CCB group (n=45) versus BB group (n=35) at the start of the study.

Profile	Group CCB (mean ± SD)	Group BB (mean ± SD)
Age (years)	54.50 ± 7.11	51.83 ± 8.80
Sex (number males : females enrolled)	28 : 17	20 : 15
Duration of T2DM (years)	4.46 ± 1.95	5.27 ± 1.89
Smokers : Non smokers	5 : 40	5 : 30
BMI (Kg/ sq. metres)	28.46 ± 3.29	28.02 ± 3.28
Systolic BP (mm Hg)	137.65 ± 9.28	133.47 ± 7.96*
Diastolic BP (mm Hg)	88.05 ± 4.70	86.33 ± 4.99

(*SD = standard deviation, * denotes p<0.05*)

Table 2: Comparison of EQ-5D VAS scores of T2DM patients between those enrolled in the CCB group (n=45) versus BB group (n=35) at the start of the study and after 35 weeks of follow up.

VAS score (maximum = 100)	Group CCB (mean ± SD)	Group BB (mean ± SD)
Before adding additional drug	69.75 ± 8.32	68.17 ± 5.49
After 35 weeks of follow up	72.50 ± 5.43	63.67 ± 5.86***

(*SD = standard deviation, *** denotes p<0.001*)

Addition of CCBs to RAS blockers improved the EQ-5D- VAS scores while there was worsening of the score on adding beta blockers to RAS blockers in T2DM patients. On follow up of 35 weeks, and on comparison of before and after score differences between the groups CCB versus BB, the difference was highly significant as depicted in figure 2.

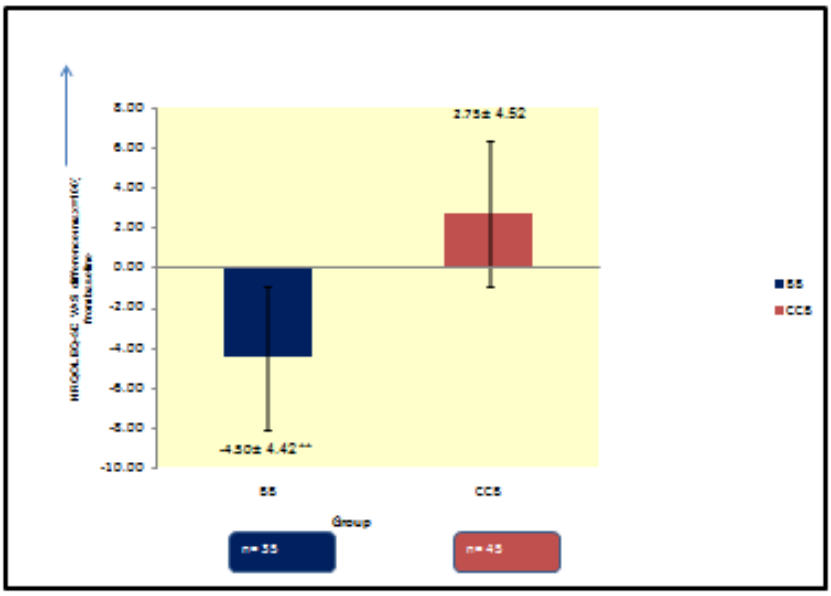

Figure 2: Comparison of difference in EQ-5D VAS scores between the groups RAS blockers and CCB versus RAS blockers and BB after 35 weeks of treatment

After 35 weeks of treatment with RAS blockers in combination with CCBs or beta blockers respectively, the comparison of three domains of EQ-5D on T2DM patients were as depicted in table 3. There were no significant differences between the combination drug groups in the domains of mobility. But perceptions of pain and anxiety/ depression as assessed by the patients at 35 weeks of dual anti-hypertensive therapy, were both much higher in the BB group.

Table 3 - Comparison of three domains of EQ-5D of T2DM patients treated for 35 weeks with RAS blockers and CCB (n=45) versus RAS blockers and BB (n=35).

EQ-5D Domain	Group CCB		Group BB	
	Present (%)	Absent (%)	Present (%)	Absent (%)
Mobility	24 (53.33)	21 (46.67)	24 (68.57)	11 (31.43)
Pain	5 (11.11)	40 (88.89)	28 (80)***	7 (20)
Anxiety/ Depression	1 (2.22)	44 (97.78)	8 (22.86)**	27 (77.14)

(*SD = standard deviation, ** denotes p<0.01, *** denotes p<0.001*)

DISCUSSION

India has emerged as the diabetic capital of the world with 41 million people having diabetes.[14] Incidence of hypertension is two – fold higher in patients with T2DM than those without the disease after matching for age.[15, 16] A study by Tharkar et al showed prevalence of hypertension in T2DM patients to be 39%, with a range from 36.8% in rural India to 63.2% in urban areas. [17]

As per JNC 8, thiazide – type diuretics, CCBs, ACEIs or ARBs are the initial agents recommended to treat hypertension, including those with diabetics in the general non-black population.[4] Beta blockers have also been recommended as the initial drug treatment option in general non- elderly adults with hypertension by ESH/ ESC and CHEP.[5,18]

In a study on prescribing pattern of anti- hypertensive agents in T2DM patients, 29 % of patients were prescribed with CCBs while 14 % were prescribed with beta blockers.[19] A prospective observational cohort study on acute coronary syndrome patients reported that beta blockers were prescribed to 66.7 % of patients with diabetes and to 67 % of those without diabetes.[20] Beta blockers (especially in coronary arterial disease) and CCBs are established add-on anti-hypertensive agents to RAS blockers in the management of hypertension in diabetics.[21] Adverse effects of beta blockers include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia, dyslipdemia and masking of hypoglycemic symptoms in diabetics.

In the present study, we have attempted to compare CCBs to beta blockers in respect of HRQoL index among T2DM patients, when used in combination with RAS blockers. The baseline demographic profiles of patients in both the arms were comparable in respect to age, sex, smokers and duration of diabetes. All patients enrolled had T2DM of more than four years duration. Males and non- smokers were predominant in the study group of both the arms. As shown in Table 1, clinical parameters at the baseline were comparable in both the arms of study except that the mean value of systolic BP happened to be slightly higher in the group started with CCBs as additional anti- hypertensive agent. This was unavoidable as the study was designed as per protocol of management of diabetic patients, without stratification due to ethical reasons.

A few patients were lost to follow up due to poor compliance, change of treating physician or change of place. Those requiring hospital admissions due to complications or unrelated diseases were treated accordingly without intervening in the disease management. In the ASCOT-BPLA trial, amlodipine was shown to reduce the relative risk of cardiovascular events by more than 15% in all ages in comparison to atenolol,[22] proving better outcomes with CCBs. The reduction in BP among INVEST patients were similar for both CCB and beta blocker groups but while depression and quality of life scores improved significantly from baseline to 1 year in the CCB group, it remained unchanged in the beta – blocker group.[23] Our study too, has demonstrated that overall quality of life index in T2DM patients was better with CCBs than beta blockers. Further, perceptions of pain and anxiety/ depression were much higher in the group added beta blockers. Depression is an established adverse effect seen with beta blockers and many patients complain of cold extremities on long term usage. Hence, poor mood response and pain as observed in our study is in conformity with the established pharmacological properties of beta blockers.

CONCLUSION

In the present study, the negative effects of beta blockers are obvious when compared with the VAS scores of EQ-5D of CCBs, both these agents used in combination with RAS blockers on T2DM patients. Problems perceived due to pain and anxiety/ depression were significantly higher in T2DM patients with add-on beta blockers. Hence, in our study the quality of life index was in favour of CCBs than beta blockers. The pharmacological basis of the above observation is well known. These observations also suggest that CCBs may be a better choice than beta blockers in T2DM patients.

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