

Cardiovascular and Renal Protection in Type 2 Diabetic Hypertensive Patients. The Role of Calcium Channel Blockers

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ABSTRACT

Objective: To study the effects of Calcium Channel Blocker (Amlodipine) as monotherapy in diagnosed hypertensive, non-insulin dependent diabetes mellitus (NIDDM) patients.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at Jinnah post graduate medical centre (JPMC) Karachi, in collaboration with the department of medicine JPMC, Karachi from July 2010 to January 2011.

Materials and Methods: This study is to examine the effects of Amlodipine in type 2 diabetic hypertensive patients with base line proteinuria. 20 normal subjects were also selected as a control group.

Results: with CCB (Amlodipine) baseline to final change for SBP as well as DBP was significantly reduced i.e. 24.70 % ($p < 0.001$) and 16.20% ($p < 0.001$) respectively. CCB showed 44% ($p < 0.001$) reduction in FBS, creatinine clearance reduced by 8.10% ($p < 0.5$), serum potassium reduced by 4.50%, non significant increase in serum urea i.e. 3.70% and serum creatinine i.e. 3.8% was observed.

Conclusion: Aim of treating hypertension is to control or limit its cardiovascular complications; CCBs are the drug of choice in controlling blood pressure and to prevent the progress of cardiovascular events in patients without diabetic nephropathy as well as reserves for add-on therapy in hypertensive patients complicated with diabetic nephropathy.

Key Words: Cardiovascular, Renal Protection, Diabetic Hypertension, Calcium Channel Blockers

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INTRODUCTION

In an estimate by world health organization currently 170 million people are affected by diabetes mellitus that will grow up to 370 million by the year 2030. Renal function is declining in half of these affected patients¹. Most commonly occurring comorbid conditions are hypertension and diabetes mellitus. The prognosis of a combination of diabetes and hypertension is particularly very poor². It is recommended in the 7th report of Joint National Committee and European society of hypertension guideline that patients having systolic blood pressure more than 20 mmHg and diastolic 10 mmHg above the treatment goals should be considered for treatment with combination therapy. It is also advised for patients with cardiovascular and other risk factors^{3,4}. The most promising combination that is highly effective and easily tolerated by the patients is

calcium channel blocker and angiotensin receptor blockers.

Morbidity and death related to hypertension can be reduced to a large extent with antihypertensive therapy. For the prevention of cardiovascular diseases in high risk individuals and to control blood pressure amlodipine is the most suitable agent from the class of calcium channel blockers. It is documented that angiotensin converting enzyme inhibitors and CCBs are helpful in reducing cardiovascular complications in hypertensive patients; however, the best choice to start therapy is still uncertain⁵. Amlodipine can control blood pressure in young adults and elderly patients that is proven in many research trials⁶. It also provides vasculoprotection independent of its blood pressure lowering effect⁷. Calcium channel blockers are more suitable agents to treat hypertension in patients of kidney transplant due to their vasodilation property at preglomerular level⁸.

It is also established in previous studies that glucose tolerance and low levels of insulin are improved with amlodipine⁹. CCBs improve insulin sensitivity and secretion in tissues sensitive to insulin by causing

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vasodilation without activating sympathetic nervous system^{10, 11}. Metabolic effects of amlodipine are exerted by its antioxidant effects. Inhibition of glucose transporters and glycogen synthase by calcium is also prevented by calcium channel blockers^{12, 13}. Multiple hemodynamic beneficial effects of CCBs make them valuable to treat high blood pressure and related cardiovascular disorders.¹³

MATERIALS AND METHODS

The study was conducted in Jinnah post graduate medical centre (JPMC) Karachi, in collaboration with the department of medicine JPMC, Karachi from July 2010 to January 2011.

Minimum forty patients with NIDDM were selected from medical OPD and diabetic clinics of JPMC, Karachi. All had mild to moderate hypertension which was not previously been treated and were suitable for first line antihypertensive therapy. 20 normal control subjects apparently healthy and not taking medication were included after excluding any medical illness.

Inclusion criteria were defined as follows, newly diagnosed and untreated patients with mild to moderate hypertension between 30-65 years of ages, duration of diabetes more than 10 years with FBS > 140mg/dl and persistent proteinuria. Patients with history of malignant hypertension, myocardial infarction, coronary artery bypass surgery, unstable angina, cardiac failure, insulin dependent diabetes (IDDM) with renal failure or impaired hepatic function, pregnancy or having allergy to the medications involved in the study were excluded from the study. Two patients dropped out from the study while the remaining completed the study successfully.

All patients underwent an initial 12 weeks dietary titration period before starting antihypertensive therapy (controlled period). They were then assigned to receive the study medication i.e. tablet Amlodipine 10 mg once a day for a period of 12 weeks. Blood sugar level was controlled by Glibenclamide 5 mg, the dose of which was adjusted according to the glycemic control. 24 hour urinary proteins, serum urea, serum creatinine, serum potassium and creatinine clearance were measured 6 weekly while systolic and diastolic blood pressure and FBS was measured fortnightly. Throughout the study period the patients were advised to take a diabetic diet. Blood pressure was measured in sitting position in the morning OPD every fortnight according to recommendations of the 7th JNC published in 2003³.

RESULTS

38 diagnosed hypertensive type 2 diabetic patients with albuminuria were studied and 20 normal subjects were also selected for the control group. No concomitant antihypertensive or diuretic therapy was given throughout the study. Table 1 shows the baseline characteristics of the patients enrolled in the study.

Table No.1: Base line characteristics of the patients

Characteristic	Amlodipine Group (N=38)	Control Group (N=20)
Age (years)	52±7	50±5
Male	24(63.15%)	12(65.5%)
Female	14(36.8%)	8(34.5%)
BMI	31±6	30±8
Urinary proteins (mg/24hrs)	329.79±261	22±5
Systolic Blood Pressure (mmHg)	151±9	113±11
Diastolic Blood Pressure (mmHg)	96±6	73±8
FBS (mg/dl)	159±53	86±15
Serum urea (mg/dl)	34±9	24±5
Serum creatinine (mg/dl)	0.87±0.13	0.86±0.13
Creatinine clearance (ml/min)	102±27	92.7±8.8
Serum potassium (mmol/l)	4±0.57	3.56±0.31

Table No.2: Changes in the various parameters from day 0 to day 90 of the treatment with tablet Amlodipine 10mg / day

Parameters	Day-0	Day-45	Day-90	Change %
Urinary proteins (mg/24hrs)	329.79 ±261	325.90 ±258	316 ±194	4.20 (NS)
Systolic Blood Pressure (mmHg)	151±9	120 ±8	113.9 ±7.9	24.7 (p<0.001)
Diastolic Blood Pressure (mmHg)	96±53	80±7	80±9	16.2 (p<0.001)
FBS (mg/dl)	159±53	99±12.8	89±13.8	44 (p<0.001)
S.urea (mg/dl)	34±9	34.8 ±4.7	35±3.8	3.70 (NS)
S.creatinine (mg/dl)	0.87±0.13	0.88 ±0.10	0.90 ±0.12	3.8 (NS)
Creatinine clearance (ml/min)	102±27	94 ±8.7	94 ±4	8.10 (p<0.05)
S.potassium (mmol/l)	4±0.57	4 ±0.55	4 ±0.52	4.50 (NS)

Table 2 shows the effects of CCB (amlodipine) monotherapy on various laboratory parameters (see figure # 1). There is significant reduction in systolic blood pressure (SBP) from baseline by 24.70% i.e. from 151mmHg to 113mmHg (p<0.001%). Diastolic blood pressure (DBP) also declined by 16.20% i.e. from 96mmHg to 80mmHg (p0.001%) on day 90th of the treatment. Creatinine clearance reduced by 8.10% i.e. from 102.3±27.3 on day 0 of the treatment to 94.03±14.6 ml/min on day 90 of the treatment. A significant reduction (44%) of fasting blood glucose was also observed on day 90th of the treatment i.e. declining from 159mg/dl to 89mg/dl (p0.001%). A

significant increase of 3.70% i.e. from 34.32 ± 9.26 to 35.59 ± 3.89 was observed in serum urea. Also a non significant increase was observed in serum creatinine of 3.8mg/dl during the study. Non significant decrease of 4.50% in serum potassium level was observed on completion of study.

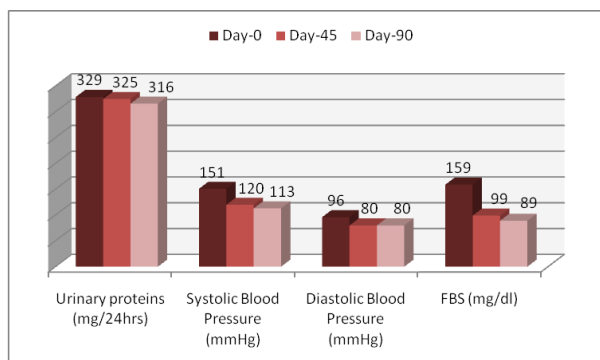


Figure No.1: Changes in various parameters from Day0, 45 & 90 of the treatment with Amlodipine

DISCUSSION

This study is the clinical trial of CCB (Amlodipine) in hypertensive diabetic patients for a period of three months. In this study 20 subjects were kept in control (group N), their mean urinary protein was 22.63 ± 5.28 mg/24hrs, which is less than the recommended range of 300mg/24hrs. In current study, we found significant reduction in Systolic and diastolic blood pressure i.e. 24% and 16% respectively which coincides with the results found by lino that is 11% reduction in SBP and 15% reduction in DBP¹⁵. Several studies have reported that calcium antagonists improve target organ damages and the clinical outcome in patients with hypertension¹⁶. Study conducted by agodoa concluded an increase in proteinuria by 58% in patients treated with amlodipine, disfavours our study showing a reduction of 4.20% in proteinuria, while other parameters are consistent with our findings¹⁷. Another study by kuriyama showed an increase in proteinuria by 11% and unchanged serum potassium with CCB compared with our study where a decrease of 4.2% proteinuria and 4.5% reduction in serum potassium was observed¹⁸. It is proven in previous studies that there is increased prevalence of insulin resistance amongst patients with essential hypertension. Standard antihypertensive agents can be used but there are particular problems in their use especially in NIDDM patients, like thiazide diuretics inhibit the secretion of insulin and beta blockers impair insulin sensitivity, whereas CCBs (amlodipine) decrease insulin resistance¹⁹. Role of calcium channel blocker was also evaluated in diabetic hypertensive patients and found that amlodipine apart from decreasing blood pressure also decreases blood glucose levels²⁰. In our study there is significant reduction in serum blood glucose levels i.e. 44% supported by the study conducted by Erosy

this may explain a decrease in insulin resistance with amlodipine¹⁹.

At the end of the discussion we concluded that selecting specific antihypertensive therapy, is the most important decision made in the treatment process. In older days beta blockers were the drug of choice for initial therapy, but they are replaced by newer antihypertensive drugs because of their failure to protect against coronary artery disease. Long acting CCBs, particularly amlodipine, in hypertensive patients for protection of cardiovascular events are as effective as other antihypertensive agents. Amlodipine can be safely combined with other antihypertensive drugs including diuretics to provide early and effective blood pressure control in high risk patients²¹. CCBs in combination with ARBs have potentially useful antiproteinuric effect in patients with type 2 diabetic nephropathy, even when their renal function is reduced²². CCBs provide sustained antihypertensive activity over 24 hrs, among them amlodipine seems to be the drug of choice in controlling blood pressure and prevents the progress of cardiovascular events in patients without diabetic nephropathy because of its low side effect profile. CCBs also reserved for add-on therapy to achieve effective blood pressure control in hypertensive patients complicated with diabetic nephropathy.

CONCLUSION

Aim of treating hypertension is to control or limit its cardiovascular complications; CCBs are the drug of choice in controlling blood pressure and to prevent the progress of cardiovascular events in patients without diabetic nephropathy as well as reserves for add-on therapy in hypertensive patients complicated with diabetic nephropathy.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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