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Effect of nebivolol beneficial on lipid profile and glycemic control in comparison with Atenolol in patients with type 2 DM with concomitant hypertension

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Abstract: Blood pressure control in hypertensive patients with metabolic abnormalities is challenging because many antihypertensive drugs adversely affect metabolism. Nebivolol a 3rd generation vasodilatory β-blocker offer neutral or beneficial effects on insulin sensitivity and lipid metabolism. The purpose of this study was to evaluate the effect of nebivolol and atenolol on glycemic control and lipid profile in type 2 diabetes patients with concomitant hypertension. We conducted a 12 weeks double blind randomized clinical trial at Sheik Zayed Hospital Rahim Yar Khan. Patients were randomly divided in to two groups. Patients in group were given tablet nebivolol 5-10mg while patients in group B were given tablet Atenolol 25-50mg/daily for a period of 12 weeks. Pre and post data were analyzed by SPSS 20. After 12 weeks, Both drugs lowered blood pressure significantly i.e. nebivolol (SBP from152±12 to130±14 with p=0.004, DBP from 95±12 to78±8.5 with p=0.002) Atenolol (SBP from148±16.5 to 128±15.5 with p=0.006, DBP from 90±10.5 to 82±12 with p=0.003).Similarly both Nebivolol and Atenolol did not any significant effect on glycemic control and lipid profile at 12 week with in groups. However when comparison was done between two groups, Nebivolol significantly reduced blood sugar (p=0.001), HbA1c (p=0.0032), total Cholesterol (p=0.002), triglycerides (p=0.012), LDL-Cholesterol (p=0.007) and HDL-Cholesterol (p=0.001) as compared to atenolol. In comparison with atenolol, Nebivolol has a beneficial effect on glycemic control and serum lipid profile.

Keywords: Nebivolol, hypertension, atenolol, blood sugar, lipid profile.

INTRODUCTION

Diabetes mellitus is one of the most prevalent metabolic disorders and a health change all across the world. Approximately one out of eleven people have diabetes with predominantly (90%) type 2 DM. Genetics, a sedentary life style, urbanization and environment factor plays a vital role in its pathogenesis (Zheng *et al.*, 2018). Current prediction reveals that number of diabetic cases worldwide is expected to rise from 460 million to 700 million in last two decades. Pakistan stands at 4th position in world diabetes ranking and had 19.4 million people with diabetes in 2019. The number of diabetic cases is projected to reach 26.2 million in 2030 if aggressive steps are not undertaken (Saeedi *et al.*, 2019).

Hypertension is common comorbid condition in diabetes and vice versa. There is approximately 40% to 60% co existence of diabetes and hypertension in patients with type 2 DM. Moreover hypertensive patients often exhibits insulin resistance and may precede the onset of diabetes (Tsimihodimos *et al.*, 2018). Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 DM which is aggravated by hypertension The cause of strong association between type 2 DM and hypertension is due to existence of similar risk factors such as obesity, dyslipidemia, vascular inflammation, endothelial dysfunction and atherosclerosis (Petrie *et al.*, 2018).

Nebivolol is a 3rd generation cardioselective beta-adrenoreceptor antagonist (BAA). In comparison with 1st and 2nd generation BAA, Nebivolol offer a better hemodynamic profile due to its vasodilating properties (do Vale *et al.*, 2019). Nebivolol exercises its vasodilatory effect through the production of nitric oxide derived from the endothelium by stimulating the Nitric Oxide Synthase (NOS) mediated by β3 receptor agonism Nebivolol also exerts neutral or beneficial effects on insulin sensitivity and lipid metabolism. It could be a very good option for hypertensive patients with impaired glucose and lipid metabolism (Arazi and Gonzalez, 2017). Erectile dysfunction is quite common in diabetic and hypertensive patients. Nebivolol has strong potential to improve erectile dysfunction due to nitrous oxide potentiation. Nebivolol improves endothelial dysfunction and central hemodynamics as compared to others BAA. It has also anti platelets, anti inflammatory, anti proliferative and antioxidant properties (Olawi *et al.*, 2019).

The main purpose of this study was to compare the effect of nebivolol and atenolol on serum lipid profile and glycemic control in T2DM patients with mild to moderate hypertension.

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MATERIALS AND METHODS

This double blind randomized clinical trial was conducted at Sheik Zayed Medical College/Hospital Rahim Yar Khan from January to March 2020. Consent was obtained or waived by all participants in this study. Institutional Review Board, Sheikh Zayed Medical College and Hospital issued approval 24/IRB/SZMC/SZH. The study perspectives were clearly explained to all patients and confidentiality maintained throughout the study period. Initially 560 type 2 patients were screened at a diabetic clinic and cardiology outdoor over a period of 03 months on the basis of presenting complaints such as generalized body aches & pains, headache, dizziness, dyspnea, restlessness, anxiety and loss of sleep. Out of which 190 patients were enrolled in the study on the basis of inclusion and exclusion criteria. The inclusion criteria were type 2 diabetic patients aged 35-56 years, HbA1c <8, grade 1 hypertension according to international society of hypertension criteria (Unge *et al.*, 2020). Borderline serum lipid profiles according to ATP III guideline criteria. The exclusion criteria were bradycardia (<60 beats/min), severe hypertension according to WHO criteria, poorly controlled diabetes (HbA1c >8) and high serum lipid profile according to ATP 111 guidelines criteria. Patients with history of smoking, ischemic heart diseases, stroke, heart failure and depression were excluded from the study. In addition detailed history was taken about secondary causes of dyslipidemia such as hypothyroidism, pregnancy, alcoholism, chronic kidney diseases, chronic hepatic diseases, NAFLD, cholestatis, rheumatoid arthritis, SLE, anabolic steroids, oral contraceptives, second generation anti psychotics, corticosteroids, immunosuppressive.

Patients were randomly divided in to two groups. Patients in group A were allocated even number while patients in group B were allocated odd numbers respectively through computed generated software. Patients in both study groups were blinded to treatment plan. Patients in group A were given tablet nebivolol 5-10mg while patients in group B were given tablet Atenolol 25-50mg/daily for a period of 12 weeks. The dose of each tablet was titrated with respect to blood pressure. The targeted blood pressure was below 140/90. If targeted blood pressure was not achieved within two weeks of anti hypertensive drug therapy then patients were dropped out from the study.

Blood pressure was measured twice in right arm at an interval of 10 minutes through brachial artery by standard sphygmomanometer apparatus. Body mass index (BMI) was estimated by known formula weight in kg/height in $m^{2.}$ A 5ml overnight fasting blood sample was collected from median cubital vein through aseptic technique using 5cc disposable syringe. This sample was used to analyze serum sugar and lipid profile though semi automated chemistry analyzer.

STATISTICAL ANALYSIS

A statistical package for social sciences (SPSS 20) was used to analyze numeric data which was presented as mean±standard deviation and percentages. A Kolomogorov-Smirnov test was used to analyze continuous variables for normal distribution. To see the baseline difference between two groups, t-test was applied. To compare the difference after 12 weeks of treatment paired t-test was used within groups while Mann-Whitney U-test and t-test were used between groups. A p-value <0.05 were seemed to be statistically significant.

RESULTS

A total of 560 patients were screened, out of which 140 patients were enrolled in the study. The tolerability and safety profile of both drugs were quite good. There were no major adverse effects noted in nebivolol group. However three patients in the atenolol group developed severe bradycardia and five patients complaint fatigue were dropped out from the study. Blood pressure of four patients was not responded to nebivolol in spite of maximum dose titration. Six patients in nebivolol group and four patients in the atenolol group could not complete the study because of loss in follow up. A total 118 patients completed the study 60 in group A and 58 in group B. These have shown in fig. 1.

There was no significant statistical difference in baseline demographic and clinical characteristics between two study groups at the start of study (table 1).

However at 12 weeks, Both drugs lowered blood pressure significantly i.e. nebivolol (SBP from152±12 to130±14 with p=0.004, DBP from 95±12 to78±8.5 with p=0.002) Atenolol (SBP from148±16.5 to 128±15.5 with p=0.006, DBP from 90±10.5 to 82±12 with p =0.003).Similarly both Nebivolol and Atenolol did not any significant effect on glycemic control and lipid profile at 12 week with in groups. However in comparison with Atenolol, Nebivolol significantly reduced blood sugar (p=0.001), HbA1c (p=0.0032), total Cholesterol (p=0.002), triglycerides (p=0.012), LDL-Cholesterol (p=0.007) and HDL-Cholesterol (p=0.001) table 2.

DISCUSSION

There is quite variation in determining the effect of nebivolol on glycemic control and serum lipid profile in type 2 diabetic patients in various clinical studies. Some studies revealed that nebivolol exerts beneficial effects, while others studies found neutral or no significant effects on dyslipidemia and insulin sensitivity (Walczak-Gałęzewska *et al.*, 2018; Kwon *et al.*, 2018; Marketou *et al.*, 2017).

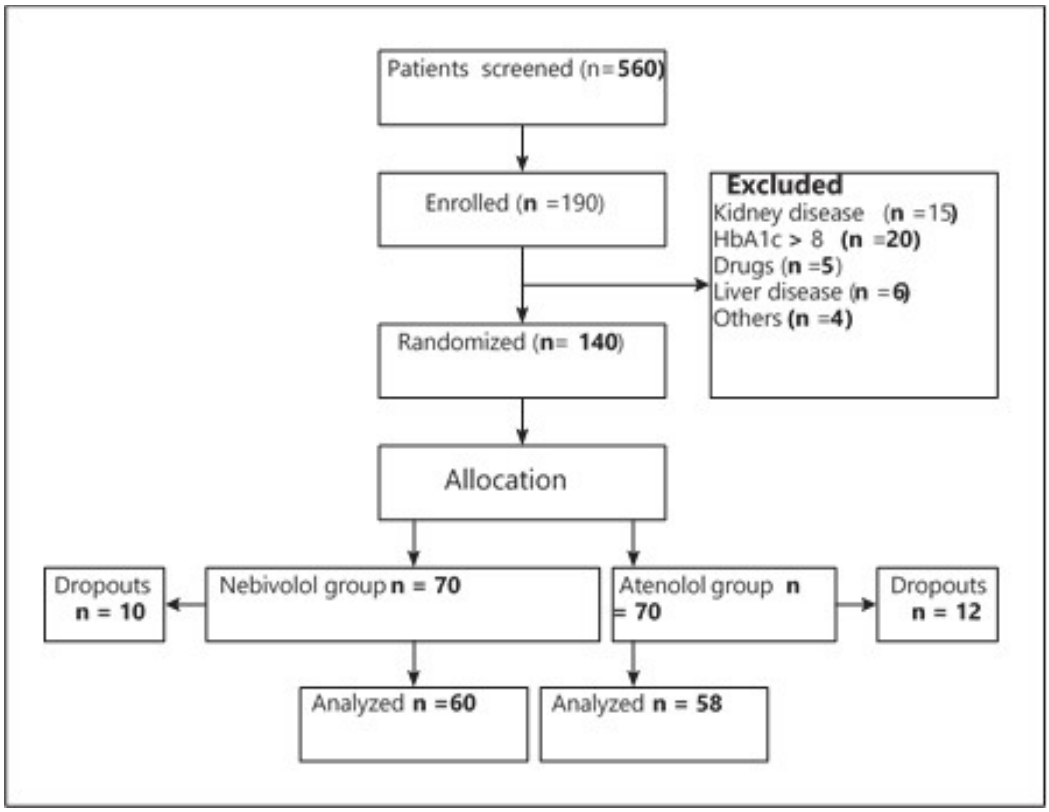

Fig. 1: Study Flow chart

Table 1: Baseline characteristics and clinical parameters of patients (N=118)

Baseline parameters	Nebivolol (n=60)	Atenolol (n=58)	P-value
Age(years)	32±11	36±15	0.36
Gender (M/F)	34/20	36/19	0.86
Body weight(kg)	92±12.5	84 ±15	0.07
BMI (Body Mass index kg/m^2)	32±2.5	29 ±5.5	0.04
Blood pressure Systolic (mmhg)	152±12	148±16.5	0.42
Blood pressure Diastolic (mmhg)	95±12	90±10.5	0.07
Blood sugar fasting(mg/dl)	100±16	95±22.5	0.031
HbA1c	7.8±4.2	8.6±2.8	0.92

T-test between two groups

Table 2: Comparison of the changes at baseline and end point within and between two groups

Study Parameters	Nebivolol(60)		P value*	Atenolol(58)		P value*	P value^{+}
	Baseline	End Point		Baseline	End Point		
SBP	152±12	130±14	0.004*	148±16.5	128±15.5	0.006*	0.72
DBP	95±12	78±8.5	0.002*	90±10.5	82±12	0.003*	0.87
Blood Sugar	100±16	90±14.8	0.71	95±22.5	115± 18	0.65	0.001^{+}
HbA1C	7.8±4.2	7.4±3.8	0.83	8.6±2.8	9.2±3.4	0.97	0.0032^{+}
Total Cholesterol	200±22	192±18	0.32	186±32	220±28	0.88	0.002^{+}
Triglycerides	180±35	174±28	0.84	170±26	182±22	0.21	0.012^{+}
LDL-Cholesterol	156±19	150±16	0.67	148±28	158±32	0.46	0.007^{+}
HDL-Cholesterol	38±4.5	42±5.2	0.22	40±3.6	37±4.5	0.32	0.001^{+}

* Significantly ($p<0.05$) comparison within groups
$^{+}$ Significantly ($p<0.05$) comparison of changes of each variable between the two groups.

The purpose of present study was to determine the effect of nebivolol on glycemic control and serum lipid profile in type 2 diabetic patients with mild to moderate hypertension in comparison with atenolol. The results of our study showed that both drugs significantly reduced blood pressure. However in comparison with atenolol, nebivolol significantly improved glycemic control and serum lipid profile.

The results of our study were in consistent with Badar *et al.*, 2011 who revealed that although both nebivolol and atenolol had significantly reduced blood pressure but nebivolol has significantly improved deranged serum lipid profile and blood sugar as compared to atenolol over a period of 6 months. Similarly Ozyıldız *et al.*, 2017 showed that vasodilating beta blockers carvedilol and nebivolol significantly improved serum glucose, serum insulin, HOMA-IR, total cholesterol, HDL-Cholesterol, LDL-cholesterol and apolipoprotein B in patients with essential hypertension.

In comparison with our study Van Bortel LM, 2010 pointed out that nebivolol significantly reduced total cholesterol, LDL-Cholesterol and LDL/HDL cholesterol ratio. However no significant effects were recorded on serum triglycerides and HDL- cholesterol in hypertensive patients with concomitant diabetes. On the other hand nebivolol significantly improved all lipid profile parameters in our study. A study conducted on more than 2500 hypertensive patients with concomitant type 2 diabetes concluded that nebivolol at a dose of 5mg/day significantly reduced blood pressure. This blood pressure reduction was accompanied by improvement in lipid level, HbA1c and microalbuminuria over a period of 3 months. Our study showed similar results but we did not analyzed microalbuminuria (Schmidt *et al.*, 2007).

Eight randomized clinical trials and three observational studies of 4 weeks to 6 months duration summarized that nebivolol displayed neutral or beneficial effects on insulin sensitivity and lipid metabolism in hypertensive patients. These studies concluded that nebivolol could be a good therapeutic option in obese, metabolic syndrome and diabetic patients with concomitant hypertension (Marketou *et al.*, 2017). Similarly in another randomized controlled trial tolerability and safety profile of nebivolol is better than atenolol in patients of essential hypertension (Bhosale *et al.*, 2014).

A meta analysis of eight randomized controlled trial demonstrated that in comparison with 2nd generation β-blockers, nebivolol was significantly better tolerability profile with lower risk of adverse effects (Liu *et al.*, 2020). A nationwide multicentre cohort study pointed that vasodilating β-blockers resulted in better clinical outcome then conventional β-blockers in patients with acute myocardial infarction after percutaneous coronary intervention (Chung *et al.*, 2017). Microalbuminuria is an early predictor of renal and cardiovascular events in hypertensive and diabetic patients. In a small sample study nebivolol significantly reduced microalbuminuria in hypertensive patients with or without diabetes (Merugu and Bingi, 2020). Endothelial dysfunction is quite common in diabetics and hypertensive patients. Nebivolol has a strong potential to improve endothelial dysfunction due its antioxidant and anti inflammatory properties. Seeing these pleiotropic effects of nebivolol it can be safely used in diabetic patients with cardiovascular disease and other comorbidities.

CONCLUSION

In comparison with atenolol, Nebivolol has a beneficial effect on glycemic control and serum lipid profile. It can be safely used in hypertensive patients with concomitant diabetes.

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