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EFFECTS OF *PERINDOPRIL* ON MICROALBUMINURIA AND ENDOTHELIAL DYSFUNCTION IN HYPERTENSIVE *TYPE II DIABETES MELLITUS* PATIENTS

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ABSTRACT
We studied the effects of perindopril, an angiotensin converting enzyme (ACE) inhibitor in Improving Endothelial function, administered during 24weeks, in diabetic subjects with mild to moderate hypertension. 50 patients and 10 healthy were included based upon their blood pressure and urinary albumin excretion rate. Patients were given Perindopril 2 mg orally once daily and were followed during a total active treatment period. We assessed diameter of Brachial artery by Flow Mediated Dilatation (FMD) method and Microalbuminuria. No major side effects were observed. We conclude that Perindopril normalizes blood pressure in a large majority of hypertensive diabetic patients without affecting the quality of diabetes control. It also reduced microalbumin excretion rate on long term therapy in hypertensive Type 2 Diabetes Mellitus patients.

KEYWORDS : *Perindopril, microalbuminuria, hypertension, endothelial dysfunction, Type 2 diabetes mellitus.*

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INTRODUCTION

The progression of insulin resistance to type 2 diabetes parallels the progression of endothelial dysfunction to atherosclerosis[1]. More recently, other plasma biomarkers produced by adipose tissue, including Tumour Necrosis Factor and resistin, have been shown to have elevated levels during obesity and to mediate insulin resistance. Brachial artery responses were found to be abnormal to both endogenous and exogenous Nitrous Oxide donors, suggesting that there was increased inactivation of NO, possibly caused by enhanced metabolism of NO or abnormal vascular smooth muscle cell responses to NO because of alterations in signal transduction in the guanylate cyclase pathway[2]. Under physiological conditions, there is a balanced release of endothelial-derived relaxing and contracting factors, but this delicate balance is altered in diabetes and atherosclerosis,

thereby contributing to further progression of vascular and end-organ damage[3].

Endothelial dysfunction

An impaired function or structure of the vascular endothelium results in a disturbed balance between vasoconstriction and vasodilation and triggers a number of processes (increased endothelial permeability, leukocyte adhesion, platelet aggregation, synthesis and release of cytokines) which play crucial roles in development, progression, and exacerbation of atherosclerotic vascular disease[4].

Endothelial dysfunction: uncoupling of endothelial nitrous oxides

Endothelial dysfunction reflects an imbalance between release of vasodilator and vasoconstrictor endothelium-derived factors. A decrease in the bioavailability of NO involves either a decrease in NO synthesis or inactivation of NO due to increased endothelial production of reactive oxygen species[5].

Endothelial dysfunction in type 2 diabetes mellitus

Endothelial dysfunction has been demonstrated in T2DM, in both the resistance and conduit vessels of the peripheral circulation as well as in the coronary circulation[6].

Risk factors for endothelial dysfunction

Occupying an anatomic position that is both strategic and vulnerable, the endothelium is a target organ for the damaging effects of hypertension, diabetes, and hyperlipidemia, as well as for vascular injuries and mechanical injuries[7].

Flow mediated dilatation

Flow mediated dilatation of large arteries has been demonstrated in many vessels *in vitro* and *in vivo* in animals and in humans, and it appears to be an endothelium-dependent phenomenon. Increasing blood flow through a superficial conduit artery would induce flow-dependent dilatation that could be measured non-invasively using high-resolution ultrasound, the degree of dilatation indicating the functional integrity of the endothelium. Blood flow was increased in the brachial artery by releasing a forearm cuff that had been inflated for five minutes. Sublingual glyceryl trinitrate was used as a control endothelium-independent stimulus. Brachial artery diameter may be measured during diastole by 'onscreen' callipers applied to a B-mode (2 dimensional imaging) ultrasound image. This requires high-resolution ultrasound and a transducer frequency of 7–10 MHz. Ultrasonic callipers have a 0.1 mm resolution and multiple measurements improve accuracy. Blood velocity is measured using continuous wave Doppler. Brachial blood flow is increased by releasing a cuff that has been inflated to suprasystolic pressure for up to five minutes around the forearm, wrist or upper arm. The brachial artery diameter is measured every 30 seconds for up to three minutes after cuff release. Blood velocity is recorded for the first 30 seconds. Endothelium-independent dilatation is measured as the diameter change caused by sub-lingual glyceryl trinitrate (400 µg)[8]. Studies using pulse wave analysis to measure the augmentation index have demonstrated the endothelial dysfunction that occurs in the course of diseases such as diabetes mellitus, hypertension and end-stage renal disease[9]. Treating endothelial dysfunction in type 2 diabetes Strategies for treating ED in T2DM will necessarily target the pathophysiological factors that underlie endotheliopathy, such as hyperglycaemia, insulin resistance, dyslipidaemia, increased oxidative stress, inflammation and hypertension[10]. A randomised, crossover study of combined aerobic and resistance exercise training for eight weeks demonstrated increases in brachial artery Flow Mediated Dilatation and acetylcholine stimulated forearm blood flow (FABF) in T2DM subjects[11]. Although glycaemic control also improved, reductions in HbA1C and fasting glucose were not correlated with changes in endothelial function[12].

MATERIALS AND METHODS

Study design

This is a 24-week, randomized, active controlled, parallel-group study conducted at a single centre. Each patient attended one screening visit during which inclusion/exclusion criteria were assessed. Eligible patients, at visit 2, were given Perindopril 2mg daily. Efficacy and tolerability were assessed

during two additional visits at 12th week and 24th week of treatment.

Study population

A total of 53 patients were selected based on the inclusion and exclusion criteria. Out of 53 patients, 50 patients continued the study due to non-compliance. Also 10 healthy individuals were enrolled. Patients received Perindopril 2mg OD along with regular diabetic treatment. Patients between the ages of 40 and 75 years with type 2 diabetes, hypertension defined as supine systolic BP (SBP) ≥140 mm Hg ≤180 mm Hg and supine diastolic BP (DBP) ≥110 mm Hg. Patients with HbA1c ≥9% within the 3 months before the study, with presumed nondiabetic kidney disease, serum creatinine ≥140mol/L, known contraindications to ACE inhibitor therapy, or other severe disease were excluded. Non study antihypertensive drugs were not permitted.

Ethics

The study was performed in accordance with the Declaration of Helsinki, Ethics committee approval was obtained for the study center, and written informed consent was obtained from all patients.

Baseline demographic and clinical characteristics

A total of 53 subjects were screened for enrolment in the study. 50 subjects were enrolled to perindopril therapy and 10 healthy volunteers were included. All were evaluated for safety and efficacy and all the 60 completed the study. Reasons for not completing the study patient choice, protocol violations, lack of follow-up, treatment failure, and no microalbuminuria measurement. The mean age was 49.3 years in treatment group and 24.5 in healthy volunteers and approximately of the subjects in group included 36% female. The treatment groups generally were well matched with respect to the remaining baseline characteristics.

Study method

Endothelial dysfunction was assessed by Flow Mediated dilatation method and microalbuminuria was assessed by conventional laboratory method.

Study dose

The final dose for Perindopril was 2mg/day along with the treatment for diabetes.

Statistical analysis

All data are means ± SEM. Paired comparisons between the treatment groups were made using a two-way Student's *t* test for paired samples. $P < 0.05$ was considered to be statistically significant. Where, * represents highly significant at $P<0.01$; ** represents very significant *at* $P<0.001$; *** represents extremely significant at $P<0.0001$.The analysis was carried out using Graph pad Instat 3.0 software.

RESULT

Over the duration of the study, BP (systolic/diastolic) was reduced by Perindopril treatment resulted in a statistically higher fall in BP (16.96± 1.8; $P<0.0002$) for SBP mean difference is 11.52% and (6.0±1.0 for DBP $P< 0.0207$) and mean difference is 6.37%. Microalbuminuria was reduced by Perindopril by a mean of (17.64±1.6; $P<0.0005$) and mean difference is 45.63%. Flow mediated dilatation of the artery during the systole was found to be (3.92±0.75; $P<0.5608$) and mean difference is 3.25%. During the diastole was found to be (4.46±0.7; $P<0.7396$) and mean difference is1.88%.

Table 2, 4 and 5 summarizes the effects of perindopril treatment. Where, * represents highly significant at $P<0.01$; ** represents very significant *at* $P<0.001$; *** represents extremely significant at $P<0.0001(n=50)$.

No deaths occurred during the study. No clinically significant differences were observed in vital signs and laboratory parameters throughout the study from baseline to end point within each group or between treatment groups.

Table 1: Parameters evaluated in Healthy volunteers

Microalbuminuria	13.98±0.628
Systolic blood pressure	117±4.454
Diastolic blood pressure	78±2.00

Table 2: Effects of drug treatment in patients

Parameters	Before treatment	After treatment	
		12^{th} week	24^{th} week
Microalbuminuria	32.456±8.058	20.56±3.077**	17.64±1.635***
Systolic blood pressure	147.12±3.802	140.24±2.667*	130.16±1.847**
Diastolic blood pressure	89.36±2.268	86.4±1.637*	83.36±1.847**

Table 3: Assessment of endothelial dysfunction using Brachial artery method in Healthy Volunteers

Flow mediated dilatation- before inflation of BP cuff	Systolic blood pressure	3.64±0.1631
	Diastolic blood pressure	4.62±0.2177
Flow mediated dilatation- after inflating BP cuff for 5 minutes	Systolic blood pressure	4.14±0.2874
	Diastolic blood pressure	5.08±0.1619

Table 4: Assessment of Flow mediated dilatation in patients- before inflation of BP cuff in patients:

Parameters	Before treatment	After treatment	
		12^{th} week	24^{th} week
Systolic blood pressure	3.424±0.1424	140.24±2.667*	130.16±1.847**
Diastolic blood pressure	3.98±0.1421	4.044±0.1414*	4.072±0.1437**

Table 5: Assessment of Flow mediated dilatation in patients- after inflating BP cuff for 5 minutes

Parameters	Before treatment	After treatment	
		12^{th} week	24^{th} week
Systolic blood pressure	3.8±0.1587	3.89±0.1546*	3.928±0.1502**
Diastolic blood pressure	4.38±0.1619	4.44±0.1542*	4.46±0.1596**

Where, * represents highly significant at *P<0.01*; ** represents very significant *at P<0.001*; *** represents extremely significant at *P<0.0001(n=50)*

DISCUSSION

This trial in patients with type 2 diabetes, hypertension, and albuminuria demonstrates the benefits of first-line therapy with a combination of a low dose of 2 mg perindopril, in the reduction of both Systolic and Diastolic blood pressure. It also induced a marked and sustained reduction of microalbuminuria in patients at risk of developing diabetic nephropathy. A clinically and statistically significant decrease in BP reduction was observed in this study. Patients required dose adjustments, with only approximately a few of patients requiring the highest doses.

CONCLUSION

The results of this study indicate that Perindopril is safe and effective for use over 24 weeks with decrease in Blood pressure. Long-term studies that include additional assessments, such as testing of creatinine clearance and cardiovascular events are needed to better establish the safety and efficacy profile. Further

studies are warranted to determine the optimal combination of diet, exercise, and oral antihyperglycaemic therapy to improve short- and long-term outcomes in subjects with hypertension and type 2 diabetes mellitus.

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