TO STUDY THE EFFECT OF ANGIOTENSIN RECEPTOR BLOCKERS ON DIABETIC RETINOPATHY

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ABSTRACT

BACKGROUND

Diabetic Retinopathy (DR) is the most common microvascular complication of Diabetes Mellitus (DM) and is the leading cause of blindness in working age adults of patients with type 1 and 2 DM. Large observational and randomised studies shown that optimal blood glucose and blood pressure control halt or regress the disease and limit the risk of progression to the proliferative stage and visual loss. Recently, evidence has also emerged that Renin-Angiotensin System (RAS) inhibitors may electively prevent or delay progression of retinopathy by acting on local RAS. Thus, metabolic and blood pressure control by RAS inhibition is to prevent or limit the onset of retinopathy and its progression towards visual-threatening stages.

The aim of the study is to categorise and analyse grading of DR who are on currently ACE and ARBs unchanged for at least 2 years.

MATERIALS AND METHODS

178 patients with type 1 and 2 DM of both genders on ARBs and ACEI unchanged for at least 2 years are divided into two groups as follows-

1. ARB group, which includes-
   a) 28 patients on losartan (50 mg).
   b) 32 patients on losartan (50 mg) + hydrochlorothiazide (12.5 mg).
   c) 28 patients on telmisartan (40 mg).
   d) 32 patients on telmisartan (40 mg) + hydrochlorothiazide (12.5 mg).
2. ACE inhibitor group includes-
   a) 30 patients on enalapril (5 mg).
   b) 28 patients on ramipril (2.5 mg) + hydrochlorothiazide (12.5 mg).

Retinopathy grading assessed by indirect ophthalmoscope and comparison of retinopathy grading between ARBs and ACEI groups have done. Two-tailed Chi-square test, GraphPad Prism Software used for statistical calculations.

RESULTS

Losartan and telmisartan (ARB group) showed significant protection from diabetic retinopathy than enalapril and ramipril (ACEI group) ($p<0.05$).

CONCLUSION

ARBs help in preventing the progression of DR and vision loss in those belonging to mild and moderate nonproliferative diabetic retinopathy patients.

KEYWORDS

Diabetic Retinopathy, ARBs, ACEI, Renin-Angiotensin System.

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BACKGROUND

Diabetic Retinopathy (DR) is a vascular disorder affecting the microvasculature of the retina occurs both in type 1 and type 2 diabetes mellitus and has been shown that nearly all type 1 and 75 percent of type 2 diabetes will develop DR after 15 years duration of diabetes.[1,2] According to the World Health Organization (WHO) report, the number of diabetic subjects in India is expected to increase to an alarming 79.4 million by the year 2030.[3] They have shown that prevalence of DR is as high as 33.9%.[4]

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Diabetic Retinopathy (DR) has become the leading cause of visual impairment especially among people of working age.[5,6,7] Hence it is appropriate that it is managed with timely intervention so that the perceived quality of life and psychosocial functioning is preserved. The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) Study sought to examine the role of an Angiotensin-Converting Enzyme (ACE) inhibitor in reducing the incidence and progression of retinopathy.[8]

AIMS AND OBJECTIVES

To analyse the observed difference of diabetic retinopathy grading between ARB treatment groups and against the ACEI treatment groups who were receiving for at least two years of treatment unchanged.

MATERIALS AND METHODS

Study Site- The study was carried out in the Sarojini Devi Tertiary Care Eye Hospital affiliated to Osmania Medical College, Hyderabad.

Study Population- Male and female patients above 18 years with either type 1 or type 2 diabetes with diabetic retinopathy and receiving either angiotensin receptor blocker or angiotensin-converting enzyme inhibitors unchanged for at least 2 years were included.

Exclusion Criteria

1. Patients with type 1 diabetes patients having disease less than 5 year's duration.
2. Patients who have undergone previous laser therapy.
3. Patients having other retinal vascular disease or who have undergone recent intraocular surgery (in the last 6 months).
4. History or presence of Clinically Significant Macular Oedema (CSME).
5. Angle closure glaucoma, which precludes pharmacological dilatation of the pupil.
6. Known patients of secondary diabetes.

Study Period- Study period for 6 months.

Ethics Committee Approval- The study protocol is approved by the Institutional Ethical Committee.

Study Design- It was a cross-sectional study.

Study Procedure- All the patients fulfilling the inclusion and exclusion criteria were assessed for the retinopathy grading by indirect ophthalmoscopy.

Data Collection- Details pertaining to age, gender, duration and type of diabetes, duration of prescribed unchanged hypertension medication, glycated haemoglobin (HbA1c) and blood pressure, retinopathy grading (Image 1) were recorded in a carefully predesigned proforma and data of the patients having diabetic retinopathy grading from the colour fundus photographs were only analysed.

Statistical Methods- The statistical analysis of the categorical data from the patients in the ARB treatment groups was analysed for the observed difference against the ACEI treatment groups using nonparametric test - two-tailed Chi-square test using GraphPad Prism Software, Version 6.05. The level of significance shall be set at 0.05. The baseline characteristics shall be expressed in mean and standard deviation.

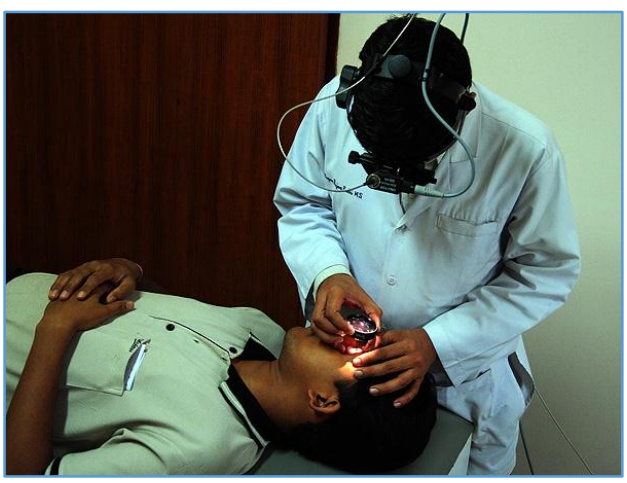

Image 1. Indirect Ophthalmoscopy

OBSERVATIONS AND RESULTS

Demographic Data- A total of 178 patients with diabetic retinopathy, 31/178 (17.41%) females and 147/178 (82.58%) males. The number of patients with type 1 diabetes mellitus are 37/178 (17.41%) and type 2 diabetes mellitus are 141/178 (82.58%). 103/178 (58%) patients are less than 60 years and 75/178 (42%) patients were more than 60 years (Table 1).

Treatment Data- 28/178 (15.73%) received losartan group (50 mg), 32/178 (17.98%) losartan (50 mg) plus (12.5 mg) hydrochlorothiazide, 28/178 (15.73%) (40 mg) telmisartan and 32/178 (17.98%) telmisartan (40 mg) plus (12.5 mg) hydrochlorothiazide, 30/178 (16.85%) (5 mg) enalapril and 28/178 (15.73%) patients in ramipril (2.5 mg) plus (12.5 mg) hydrochlorothiazide (Table 2).

Retinopathy Data- On comparison of losartan and telmisartan (ARB group) showed significant protection from diabetic retinopathy than enalapril and ramipril (ACEI group) ($p<0.05$) (Table 2).

Characteristic	L	LHCT	T	THCT	E	RHCT
Number of patients	28	32	28	32	30	28
Age (yrs.)	57.9 ± 5.0	57.4 ± 5.3	57.3 ± 5.2	56.8 ± 4.8	60.4 ± 5.6	57.2 ± 4.6
Duration type 1 DM (yrs.)	9.0 ± 1.2	8.8 ± 2.6	10.8 ± 2.0	7.9 ± 0.6	7.5 ± 1.6	8.4 ± 3.0
Duration type 2 DM (yrs.)	5.3 ± 1.6	4.4 ± 1.3	4.9 ± 2.0	4.5 ± 1.2	4.9 ± 1.9	4.6 ± 1.6
Duration HTN treatment (yrs.)	3.3±0.8	3.1 ± 0.7	3.2 ± 0.6	2.87 ± 0.5	3.4 ± 0.8	3.4 ± 0.7
HbA1c (%)	7.9 ± 0.8	7.8 ± 0.7	8.1 ± 0.8	7.6 ± 0.6	7.9 ± 0.6	7.9 ± 0.7
SBP (mmHg)	127.4 ± 8.0	127.9 ± 8.1	129.4 ± 7.4	129.3 ± 9.3	130.1 ± 7.4	128.9 ± 7.1
DBP (mmHg)	83.6 ± 5.0	84 ± 6	83.9 ± 6.3	83.6 ± 6.8	86.0 ± 4.4	84.9 ± 5.0
Losartan-L, Losartan+HCT-LHCT, Telmisartan-T, Telmisartan+HCT-THCT, Enalapril-E, Ramipril+HCT-RHCT						

Table 1. Demographic, Clinical and Treatment Profile of Patients with Diabetic Retinopathy

Drug	Mild+Mod NPDR (n=89)		Severe NPDR+PDR (n=89)		Total (n=178)		P value
Angiotensin Receptor Blockers							
Losartan	18	20.22%	10	11.24%	28	15.73%	P<0.05
Losartan+HCTZ	19	21.35%	13	14.61%	32	17.98%	
Telmisartan	13	14.61%	15	16.85%	28	15.73%	
Telmisartan+HCTZ	17	19.10%	15	16.85%	32	17.98%	
Total	**67**	**75.28%**	**53**	**59.55%**	**120**	**67.42%**	
Angiotensin-Converting Enzyme Inhibitors							
Enalapril	10	11.24%	20	22.47%	30	16.85%	
Ramipril+HCTZ	12	13.48%	16	17.98%	28	15.73%	
Total	**22**	**24.72%**	**36**	**40.45%**	**58**	**32.58%**	

Table 2. Severity of Retinopathy and Treatment Profile of Patients with Diabetes

DISCUSSION

The study included a collection of data from patients with diabetic retinopathy attending the outpatient clinic in the Department of Ophthalmology who were receiving the hypertensive treatment unchanged for at least 2 years.

Analysis and Interpretation of Retinopathy Grading between ARB Group and ACEI Group

1. Analysis- Diabetic retinopathy grading of the losartan group in comparison with enalapril group.
   In losartan group, mild and moderate NPDR patients were 18 and severe NPDR and PDR were 10, a total of 28 patients in losartan group. In enalapril group, mild and moderate NPDR patients were 10 and in severe NPDR and PDR were 20, total 30 patients. P-value is 0.0184, which is significant. Mean duration of type 1 DM in losartan group is 9.0 ± 1.2 years for enalapril 7.5 ± 1.6 years. P-value for the average duration of type 1 DM is 0.0002, which means duration of DM in losartan group is 9.0 ± 1.2 years and has beneficial effects from losartan in comparison with enalapril. Mean SBP in losartan group and enalapril group is 127.4 ± 8.0 mm of Hg and 130.1 ± 7.4 mm of Hg showing that increase in blood pressure has an association with diabetic retinopathy development.
2. Analysis diabetic retinopathy grading of the losartan+HCTZ group in comparison with enalapril group (Table 6).
   In losartan+HCTZ group mild and moderate NPDR patients were 19 and severe NPDR and PDR were 13. A total of 32 patients in losartan+HCTZ group. In enalapril group, mild and moderate NPDR patients were 10 and in severe NPDR and PDR were 20, total 30 patients. P-value from is 0.04, which is significant. The mean age for losartan+HCTZ group is 57.4 ± 5.3 years for enalapril group is 60.4 ± 5.6 years showing that development of diabetic retinopathy will progress with increasing age. Percentage of glycated haemoglobin in losartan+HCTZ group is lesser than enalapril group showing that there is an association between HbA1C levels and development of diabetic retinopathy. There is also a significant difference between SBP in two groups.

Diabetic retinopathy is primarily classified into Nonproliferative DR (NPDR) also known as simple or background retinopathy and Proliferative DR (PDR). Mild NPDR is characterised by microaneurysms (dot/blot haemorrhages). Progression to moderate NPDR is characterised by increased vascular permeability and then severe NPDR is marked by the vascular closure and an increased risk for the development of PDR distinguished by the growth of new blood vessels on the retina and posterior surface of the vitreous. PDR is characterised by neovascularisation, bleeding in the vitreous body and sometimes detachment of retina.[9]

The current study showed that duration of diabetes, glycated haemoglobin, type of hypertension medication and systolic and diastolic blood pressure have a possible association with the development of diabetic retinopathy. Correlation with duration of diabetes is also well known. The role of hyperglycaemia in the development of diabetic retinopathy is also well known and has been clearly

demonstrated in the diabetes control and complication trial. In this study, a strong association between HbA1c level and retinopathy is also observed. Patients with HbA1c levels more than 8.0%, development of severe NPDR and PDR was more when compared to patients with HbA1c levels less than 8.0%. There is a strong correlation between the type of hypertension medication and retinopathy.

Among new approaches to retinopathy prevention, there has been considerable interest in whether drugs that block the Renin-Angiotensin System (RAS) might have a preventive effect, over and above their blood pressure lowering effect. RAS blockade can slow the progression of diabetic nephropathy and there is growing evidence that the RAS may also play a major role in the pathogenesis of diabetic retinopathy.

A local RAS has been shown to operate in the eye and there is evidence from clinical and experimental models that this system is upregulated in active retinopathy. Angiotensin II has been demonstrated to increase exudation from retinal vessels as well as stimulate formation of new retinal blood vessels via upregulation of Vascular Endothelial Growth Factor (VEGF) activity and other growth factors and studies in animal models suggest that RAS blockade might be associated with protective effects on the retina.[10]

There is growing evidence that the Renin-Angiotensin System (RAS) plays a major role in the pathogenesis of diabetic retinopathy and this has led to an interest in RAS inhibitors as agents to prevent retinopathy. Several trials have suggested that ACE inhibitor therapy can inhibit progression of retinopathy. The DIabetic REtinopathy Candesartan Trials (DIRECT) Programme is currently investigating the effects of the angiotensin II receptor blocker candesartan on the incidence of retinopathy in type 1 diabetes and its progression in type 1 and type 2 diabetes. These results suggest that treatment with candesartan in type 2 diabetic patients with mild-to-moderate retinopathy could induce improvement of retinopathy. The direct study suggests that complete blockade of the renin-angiotensin system is necessary for an organ protective effect.[11,12]

The present study helps to contribute to the data that is already available and also to compare it with the current trends in prescribing to make our approach more current in the pharmacotherapeutic considerations of the management of patients with diabetic retinopathy.

Angiotensin-converting enzyme inhibitors along with ARBs continue to be studied for their effects on diabetic retinopathy. The actions of both classes of agents provide the rationale for pursuing a blockade of the Renin-Angiotensin System (RAS) as a therapeutic approach to retinopathy. Angiotensin promotes proliferation of vascular cells in the human eye and ACE inhibition reduces the retinal expression of VEGF. Furthermore, the ACE inhibitor captopril may reduce uptake of D-glucose and ACE inhibitors and the ARB losartan prevents neovascularisation in rodent models of retinopathy of prematurity.

The renin-angiotensin system has been implicated in the pathogenesis of diabetic retinopathy. Angiotensin II synthesis occurs in ocular areas susceptible to diabetic retinopathy. Vitreous levels of vascular endothelial growth factor are increased in the eyes of patients with proliferative diabetic retinopathy 40 and are correlated with the vitreous activity of ACE. Thus, the benefits of enalapril and losartan on diabetic retinopathy in the present study may represent direct effects on the eye independent of effects of systemic blood pressure.[13]

The present study is carried out for understanding the role of renin-angiotensin and RAS blockade in diabetic retinopathy. The relationship between microvascular and macrovascular morbidities and the role of RAS is well established. Many studies have shown that RAS blockade delays and prevents the progression of retinopathy.

Current measures for the prevention of diabetic retinopathy are restricted to tight blood glucose and blood pressure control, while current treatment only applies to late, progressed stages of retinopathy and consists of quite invasive approaches such as laser photocoagulation or regular intravitreal injections of VEGF inhibitors. In vitro and in vivo preclinical studies have provided strong evidence for an involvement of RAS in the pathomechanisms underlying diabetic retinopathy.

High blood pressure (hypertension) can lead to and worsen many complications of diabetes including retinopathy and nephropathy. Most people with diabetes develop high blood pressure during their life. Use of ARBs and ACEI in diabetic patients controls the blood pressure and it also prevents the microvascular complications like nephropathy and retinopathy in diabetic patients.

The current study shows that age, duration of diabetes, glycated haemoglobin (HbA1c) levels, systolic and diastolic blood pressure have a positive association with the development of diabetic retinopathy. Prior and ongoing studies like RASS and DIRECT I and DIRECT II have shown that control of above-mentioned factors along with RAS blockers have beneficial effects in the primary and secondary diabetic prevention of diabetic retinopathy.

CONCLUSION AND SUMMARY

Diabetic retinopathy remains a serious clinical problem. Early intervention in patients with mild and moderate NPDR with ARBs help in preventing the progression of DR and vision loss.

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REFERENCES

[1] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy. II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. Arch Ophthalmol 1984;102(4):520-526.

[2] Klein R, Klein BE, Moss SE, et al. The Wisconsin epidemiologic study of diabetic retinopathy III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. Arch Ophthalmol 1984;102(4):527-32.
[3] Wild S, Roglic G, Green A, et al. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(5):1047-1053.
[4] Ramavat PR, Ramavat MR, Ghugare BW, et al. Prevalence of diabetic retinopathy in western Indian type 2 diabetic population: a hospital-based cross-sectional study. J Clin Diagn Res 2013;7(7):1387-1390.
[5] Prasad S, Kamath GG, Jones K, et al. Prevalence of blindness and visual impairment in a population of people with diabetes. Eye (Lond) 2001;15(Pt 5):640-643.
[6] Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. JAMA 2003;290(15):2057-2060.
[7] Klein R, Lee KE, Gangnon RE, et al. The 25-year incidence of visual impairment in type 1 diabetes mellitus the Wisconsin epidemiologic study of diabetic retinopathy. Ophthalmology 2010;117(1):63-70.
[8] Chaturvedi N, Sjolie AK, Stephenson JM, et al. Effect of lisinopril on progression of retinopathy in normotensive people with type 1 diabetes. The EUCLID study group. EURODIAB controlled trial of lisinopril in insulin-dependent diabetes mellitus. Lancet 1998;351:28-31.
[9] Rema M, Pradeepa R. Diabetic retinopathy: an Indian perspective. Indian J Med Res 2007;125(3):297-310.
[10] Fletcher EL, Phipps JA, Ward MM, et al. The renin-angiotensin system in retinal health and disease: its influence on neurons, glia and the vasculature. Prog Retin Eye Res 2010;29(4):284-311.
[11] Chaturvedi N, Porta M, Klein R, et al. Effect of candesartan on prevention (DIRECT-Prevent 1) and progression (DIRECT-Protect 1) of retinopathy in type 1 diabetes: randomised, placebo-controlled trials. Lancet 2008;372(9647):1394-1402.
[12] Sjølie AK, Klein R, Porta M, et al. Effect of candesartan on progression and regression of retinopathy in type 2 diabetes (DIRECT-Protect 2): a randomised placebo-controlled trial. Lancet 2008;372(9647):1385-1393.
[13] Mauer M, Zinman B, Gardiner R, et al. Renal and retinal effects of enalapril and losartan in type 1 diabetes. N Engl J Med 2009;361(1):40-51.