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Effect of Enalapril Eye Drops on Intraocular Pressure in Primary Glaucoma Patients: A Clinical Study

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Abstract: *The glaucoma is a diverse group of eye conditions that share the common feature of progressive optic neuropathy or the common feature of occludable drainage angles in the anterior chambers. The most common risk factor known is a raised intraocular pressure (IOP). The objective of the study was to see the effect of instillation of single and multiple doses of 0.5% enalapril eye drop on IOP. Dose-response relationship, response with increased concentration of drug along with side effects, was also analyzed. The study comprised, Group A that included 10 normal volunteers, 40-80 years of age group, having intraocular tension < 21 mmHg, with no optic disc changes or field loss suggestive of glaucoma and Group B that included 20 patients of primary open angle glaucoma, 40-80 years of age, having intraocular tension > 21 mmHg, with optic disc changes or field loss or both. In group A, the peak action of drug was occurred at 6 hrs. intervals after instillation and mean fall of 3.35 mmHg in IOP was observed at 6 hrs. In group B, mean fall was 3.87 (14.55%) and 1.5 (5.6%) mmHg after 6 hrs. and 12 hrs. respectively. Mean fall after 2nd drop instillation at 12 hrs. interval of initial one, was observed at 18 hrs. and it was 3.92 mmHg (14.74%). Mean fall after 24 hrs. was observed 1.42 mmHg (5.34%). There was no statistical significance lowering of IOP after doubling the concentration of drug. Some side effects, stinging and burning sensation, conjunctival hyperaemia, urticarial and rash were seen with 0.5% enalapril on group B patients in one month follow up. Enalapril can be used as adjunctive and neuroprotective agent in the management of glaucoma.*

Keywords: *Glaucoma, IOP, enalapril, optic disc changes*

I. Introduction

Glaucoma is characterized by the slow, progressive degeneration of retinal ganglion cells (RGCs) and optic nerve axons. Glaucoma affects more than 70 million people worldwide with approximately 10% being bilaterally blind, making it the leading cause of irreversible blindness in the world [1]. However, it can be treated if diagnosed at an early enough stage. Since blindness is ultimately induced by the loss of visual field caused by neuronal cell death, understanding the pathology that leads to increased intraocular pressure (IOP), and subsequently to neuronal cell death, is crucial to the development of effective treatments.

The diagnosis of glaucoma depend upon, elevated intraocular pressure, optic nerve head changes like asymmetry of optic cup, C;D ratio > 0.5:1, notching of neuroretinal rim, optic disc hemorrhages etc., and visual field defects like baring of blind spot, Seidel's sign etc. [2]. The lowering of IOP to prevent progression of glaucoma is now the backbone of glaucoma management and is supported by several well-designed randomised controlled trials that have demonstrated that lowering the IOP reduces the rate of glaucomatous damage [3]. Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern recommend lowering the intraocular pressure toward a target level, which is a value or range of values at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease [4]. In general, prostaglandin analogues are the first-line of medical therapy. These drugs reduce intraocular pressure by reducing outflow resistance resulting in increased aqueous humor flow through the uveoscleral pathway [5]. Enalapril and other angiotensin-converting enzyme (ACE) inhibitors have been shown to lower IOP [6]. Topical administration of ACE inhibitors in the form of eye drops may have beneficial effects on the eye without systemic side effects. Such eye drops may have a role in glaucoma and diabetic retinopathy management. The aim of the study was to see the effect of instillation of single and multiple doses of 0.5% enalapril eye drop on IOP. Dose-response relationship, response with increased concentration of drug along with side effects, was also analyzed.

II. Material and methods

The study was carried out over a period of 18 months in the department of Ophthalmology in a tertiary care hospital. The ethical clearance from the ethical committee of the institute was taken to conduct the study. An informed consent was taken from the healthy individuals and patients. In this study the inclusion and exclusion criteria were as follows: Inclusion criteria – male and female patients of age group ≥ 40 years, healthy normal individual as a control, patients with diagnosis of glaucoma (a) IOP should be ≥ 21 mmHg by applanation tonometry (b) glaucomatous changes of Optic nerve hypoplasia (ONH) and peripapaillary retina (c) glaucomatous changes in visual fields. Patients to be labeled primary open glaucoma in addition to above three criteria, angle should be opened gonioscopically. Exclusion criteria were as follows: Patients with aphakia or pseudophakia, advanced lental changes, combined mechanism glaucoma, previous history of glaucoma surgery, and ocular injury.

The current study was done in two groups: Group A – It included 10 normal volunteers, 40-80 years of age group, having intraocular tension < 21 mmHg, with no optic disc changes or field loss suggestive of glaucoma. Group B – It included 20 patients of primary open angle glaucoma, 40-80 years of age, having intraocular tension > 21 mmHg, with optic disc changes or field loss or both.

Preparation of enalapril eye drop: By diluting the Envas injection -1.0 mL (enalaprilat) with water that is used for injection. It contains 1.25 mg enalaprilat and 9 mg of benzyl alcohol as preservative in 1.0 mL.
Preparation of 0.5% enalapril eye drop: 1.0 mL of ampoule contained 1.25 mg of drug and 0.4 mL of it contained 0.5 mg of drug. This 0.4 mL was diluted with 100 mL of 5% dextrose and kept in refrigerator.
Preparation of 1% enalapril eye drop: 1.0 mL of ampoule contained 1.25 mg of drug and 0.8 mL of it contained 1.0 mg of drug. This 0.8 mL was diluted with 100 mL of 5% dextrose and kept in refrigerator.

A detailed clinical history of patient like name, age, sex, history of present illness that included headache, eye ache, pain, redness, diminution of vision, any frequent change in glasses, treatment taken in past, their duration and response, past history of any ocular trauma, surgery, diabetes mellitus, hypertension, cardiovascular or renal disease, any family history of glaucoma etc. All the patients were examined in detail to rule out any associated systemic disease that included cardiovascular, respiratory, central nervous and gastro intestinal system. The distance acuity was charted on snellen's chart. Refractive status of the patient was also measured.

Local examination of eye:
1. Anterior segment examination included lids and conjunctiva, cornea and sclera, anterior chamber. Gonioscopy was done to decide whether the case is of primary open angle glaucoma, primary narrow angle glaucoma, and secondary glaucoma. Sheie's system of angle grading was used [7]. Indentation gonioscopy was done if appositional angle closure was suspected. Grading for nuclear cataract, cortical cataract, posterior subcapsular cataract was done accordingly [8].
2. Posterior segment assessment included fundus and optic disc examination.
3. Intraocular pressure was measured using applanation tonometre.
4. Visual field analysis was done using automated computerized perimetry. Visual field loss is considered significant when; (a) abnormal Glaucoma Hemi Field Test (GHT) on two consecutive tests (b) three abnormal points with $p < 5\%$ one of which should have $p < 1\%$ all being non contiguous with blind spot (c) Corrected Pattern Standard Deviation (CPSD) < 5% if field is otherwise normal on two consecutive tests. Hodapp classification of grading of glaucomatous field loss was used [9].

III. Results

Selected persons were divided into 2 groups, group A and group B for healthy individuals and patients respectively. Group A comprised of 10 individuals, out of which 40% were in the age group of 50-59 years. The age groups, 40-49, 60-69 and 70-80 years were comprised of 20%, 30% and 10% normal individuals respectively. Group A involved 80% male and 20% female individuals. The effect of 0.5% enalapril on IOP, in group A, was shown in table 1. Mean fall of 3.35 mmHg in IOP was observed at 6 hrs. (Table 1). Table 2 showed the mean fall of 0.5 mmHg in IOP in other eye with placebo (5% dextrose). Peak action of the drug was observed at 6 hrs. interval and mean fall of IOP was recorded as 3.35 mmHg (19.18%) which is statistically significant ($p < 0.05$) as compared to placebo drop causing 0.5 mmHg (3.08%) fall in IOP at 6 hrs.

Group B comprised of 20 patients, out of which 50% were in the age group of 50-59 years. The age groups, 40-49, 60-69 and 70-80 years were comprised of 20%, 20% and 10% patients respectively. Group B involved 70% male and 30% female patients. Mean IOP of group B was 26.58 mmHg (Table 3). Mean fall was 3.87 (14.55%) and 1.5 (5.6%) mmHg after 6 hrs. and 12 hrs. respectively. Mean fall after 2nd drop instillation at 12 hrs. interval of initial one, was observed at 18 hrs. and it was 3.92 mmHg (14.74%). Mean fall after 24 hrs.

was observed 1.42 mmHg (5.34%) (Table 3). The drop in IOP at 6 hrs. and 18 hrs. was statistically significant ($p < 0.05$) as compared to 12 hrs. and 24 hrs. drop. There was no statistical significant lowering of IOP after doubling the concentration of drug (Table 4).

A total of 9 (45%) patients were observed fall in IOP (3.1-4 mmHg) even after one month duration whom were instilled with 0.5% enalapril eye drop (Table 5). Common side effects, stinging and burning sensation (50%) followed by conjunctival hyperaemia (20%), urticarial (20%) and rash (10%), were seen with 0.5% enalapril drop twice in a day instillation on group B patients in one month follow up.

Table 1; fall in IOP in group A after single drop instillation of 0.5% enalapril eye drop

S. No.	Baseline IOP (mmHg)	Fall in IOP from baseline (mmHg)					
		After 2 hrs.	After 4 hrs.	After 6 hrs.	After 8 hrs.	After 10 hrs.	After 12 hrs.
1	16.8	1.2	2.2	3.2	2.9	1.7	1.3
2	14.6	1.2	2.1	3.2	3.1	1.8	1.4
3	20.4	1.6	2.6	3.7	3.1	2.1	1.6
4	16.8	1.6	2.1	3.1	2.8	3.0	1.8
5	17.3	1.8	2.4	3.5	3.1	2.4	1.5
6	17.3	1.2	2.1	3.8	3.2	2.9	1.1
7	15.9	1.3	1.9	3.1	2.9	3.1	1.2
8	18.9	2.9	3.1	3.6	3.1	2.8	2.3
9	16.8	1.4	2.2	3.2	3.0	2.2	2.1
10	20.4	2.1	3.1	3.2	3.2	1.7	2.6
Mean (SD)	17.52 (1.86)	1.63 (0.15)	2.30 (0.19)	3.35 (0.25)	3.04 (0.21)	2.37 (0.19)	1.68 (0.15)

Table 2; change in IOP in group A after single drop instillation of placebo (5% dextrose) eye drop in other eye

S. No.	Baseline IOP (mmHg)	Fall in IOP after 6 hrs. (mmHg)
1	16.8	0.2
2	15.6	0.6
3	20.4	0.4
4	16.8	0.7
5	17.3	0.8
6	13.3	0.1
7	15.9	0.3
8	18.9	0.9
9	12.8	0.7
10	20.4	0.3
Mean (SD)	16.25 (1.74)	0.5 (0.27)

Table 3; change in IOP in group B (glaucomatous patients) after instillation of 0.5% enalapril eye drop twice in a day with 12 hourly interval

S. No.	Baseline IOP (mmHg)	Fall in IOP from baseline (mmHg)			
		After 6 hrs.	After 12 hrs.	After 18 hrs.	After 24 hrs.
1	23.2	3.8	1.6	4.2	1.3
2	27.2	3.2	1.8	3.8	1.3
3	24.9	4.0	1.3	4.5	1.2
4	28.6	3.6	1.3	4.6	1.3
5	26.4	3.6	1.2	4.0	1.4
6	27.6	4.0	1.3	4.2	1.6
7	29.8	3.9	1.4	3.6	1.4
8	28.6	4.0	1.4	3.6	1.2
9	23.2	3.4	1.8	4.0	1.3
10	24.9	4.2	1.2	3.8	1.6
11	27.2	3.6	1.5	4.2	1.7
12	26.8	4.0	1.3	3.6	1.4
13	25.6	3.6	1.4	4.0	1.6
14	28.6	3.4	1.8	3.9	1.6
15	24.9	4.2	1.5	4.0	1.2
16	27.2	4.6	1.5	3.6	1.8
17	23.2	4.6	1.5	3.8	1.6
18	28.6	4.5	1.8	4.0	1.5
19	25.9	3.8	1.7	3.2	1.2
20	29.2	4.0	1.8	3.8	1.2

Mean (SD)	26.58 (2.05)	3.87 (0.27)	1.50 (0.21)	3.92 (0.28)	1.42 (0.20)

Table 4; mean effect of 1% and 0.5% enalapril eye drop twice in a day in group B patients

Drug	Mean fall in IOP from baseline (mmHg)			
	After 6 hrs.	After 12 hrs.	After 18 hrs.	After 24 hrs.
1% enalapril	3.96 (14.89%)	1.71 (6.43%)	4.12 (15.49%)	1.56 (5.87%)
0.5% enalapril	3.87 (14.55%)	1.50 (5.60%)	3.92 (14.74%)	1.42 (5.34%)

Table 5; mean fall from previous IOP in patients examined with 0.5% enalapril after one-month duration

S. No.	Fall in IOP (mmHg)	No. of patients	Percentage
1	< 2	3	15
2	2.1-3	5	25
3	3.1-4	9	45
4	4.1-5	3	15

IV. Discussion

The goal of treating glaucoma lies primarily on preventing or delaying the loss of visual field [10]. Since neuronal cell death is irreversible, no cure is available once the visual field is lost. However, since IOP is the primary risk factor causing the loss of RGCs (retinal ganglion cells), the strategies of treatment mostly involve lowering IOP [10]. Current treatments for glaucoma include medication, laser use and surgery. Medications involve inhibiting the inflow of aqueous humor, enhancing the outflow of aqueous humor, protecting the optic nerves and manipulating the osmotic pressure between plasma and the eyes [11,12].

The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects [13]. Several different classes of pressure-lowering medications are available; prostaglandin analogues, β-Adrenergic blockers, α-Adrenergic agonists, carbonic anhydrase inhibitors, cholinergic agonists, calcium channel blockers, hyperosmotic agents and angiotensin converting enzyme (ACE) inhibitors. ACE inhibitors are widely used to treat the systemic hypertension. ACE inhibitors are kininase II inhibitor and thus prevent break down of bradykinin. Bradykinin displays protective actions against neurotoxicity through Bradykinin – β_2 receptors in the cultured retinal neurons [14]. ACE inhibitors blocked the liberation of Angiotensin II fro Angiotensin I. Lower angiotensin II level may have beneficial effects on outcomes by lowering vascular superoxide anion [14]. ACE is primary located on the luminal surface of vascular endothelium cells. ACE is also present in aqueous humor. Angiotensin receptors are found in blood vessels of uveal tract of eye. Here stimulation of angiotensin is associated with vasoconstriction of blood vessels of cilliary body and increased aqueous secretion and IOP [14].

In the present study, the effect of one of the ACE inhibitors, enalapril, was observed in healthy and glaucoma patients. In group A, normal individuals were advised to instill 0.5% enalapril drop in one eye while placebo (5% dextrose) in other eye. IOP was recorded after 2 hrs. interval for 12 hrs. Peak action of the drug was observed at 6 hrs. interval and mean fall of IOP was recorded as 3.35 mmHg (19.18%) which was statistically significant ($p < 0.05$) as compared to placebo drop causing 0.5 mmHg (3.08%) fall in IOP at 6 hrs [Table 1 & 2]. Lotti and Pawlowski (1990) reported that topical administration of enalaprilat produces a decrease in IOP in African green monkeys. Effect may be due to its ability to prevent breakdown of bradykinin and promotes synthesis of prostaglandins. Prostaglandins are known to reduce IOP by increasing uveoscleral outflow [15]. Cafey et al. (2004) studied the effect of topical application of ACE inhibitors and said that ACE inhibitors lower the IOP. Angiotensin induced increase in vascular tone has been implicated as a pathogenic mechanism in glaucomatous cupping and damage to optic nerve [16].

Group B (20 patients) was instilled with 0.5% enalapril eye drop twice in a day at 12 hrs. interval. IOP was recorded at 6 hrs. interval in a day [Table 3]. The drop in IOP at 6 hrs and 18 hrs. was statistically significant (p value < 0.05) as compared to 12 hrs. and 24 hrs. drop in IOP, again suggested that peak action occurred at after 6 hrs. of drug instillation and duration of action was 12 hrs. Watkins et al. (1987) [6] reported that when enalapril topically administered twice daily, caused neither irritation nor alteration of pupil diameter. Inhibition of ocular ACE may represent an effective means of reducing IOP. Shah et al. (2000) [17] studied oculohypotensive effect of ACE inhibitors in acute and chronic models of glaucoma. Prodrugs enalaprilat produced a time dependent decrease in IOP in both acute and chronic models of glaucoma and found that inhibition of ACE in aqueous humor and in ocular tissues, resulting in reduced angiotensin II formation, could be one of the major mechanisms for IOP reduction by ACE inhibitors in rabbit.

Group B patients were also subjected to 1% enalapril drop instillation twice in a day to see the effect of increased concentration of drug on IOP [Table 4]. There was almost negligible increase in IOP lowering efficacy of drug after doubling its concentration that was also statistically insignificant ($p > 0.05$). This suggests that efficacy has been reached with 0.5% enalapril and on further increase in concentration does not produce any beneficial effect. A concentration of 0.5% is sufficient to reach its maximum effect.

To know the long-term effect of 0.5% enalapril that was instilled twice, the IOP of group B patients were recorded after 1 month. A fall of 3.1 to 4 mmHg was recorded even after 1 month in 45% of patients [Table 5]. This suggested that the drug was having tension lowering effect even after one month.

Group B patients were observed some side effects when they followed up after one month. These were stinging and burning sensation (50%) followed by conjunctival hyperaemia (20%), urticarial (20%) and rash (10%). Some authors described adverse side effects of commonly prescribed systemic ACE inhibitors used for the management of hypertension, diabetic nephropathy and congestive heart failure [6]. Ocular side effects were decreased vision, conjunctivitis, photosensitivity, visual hallucinations and subconjunctival or retinal haemorrhages secondary to drug induced anaemia. Eyelids also may have angioneurotic edema, brown discolouration, urticarial, erythema multiformes, exfoliative dermatitis, steven-Johnson syndrome or pemphigoid lesion. However, ACE inhibitors cause angioneurotic edema, hypotension, rash and dry cough but it is good for both diabetes and hypertension [6].

V. Conclusion

Single drop instillation of 0.5% enalapril, in healthy individuals, reduced the IOP and peak action was seen at 6 hrs. On the other hand, in glaucomatous patients with twice daily instillation, peal action was seen at 6 hrs. and 12 hrs. with some side effects like stinging and burning sensation, conjunctival hyperaemia, urticarial and rash. Enalapril (0.5%) has IOP lowering action but due to not achieving the target pressure and high incidence of side effects, it is not useful as the first line therapy. However, it can be used as adjunctive and neuroprotective agent in the management of glaucoma.

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