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Original Research

To Study The Effect Of Pentoxifylline In Glaucomatous Optic Atrophy

[1]Dr. Khushboo Jaiswal, [2]Dr. Perwez Khan, [3]Dr. Saumya Pande

[1]Assistant Professor, Department of Ophthalmology, Rama Medical College, Kanpur, Uttar Pradesh, India
[2]Professor, Department of Ophthalmology, GSVM Medical College, Kanpur, Uttar Pradesh, India
[3]Consultant, Kanpur Neuro and Eye Clinic, Kanpur, Uttar Pradesh, India

Corresponding Author
Dr. Khushboo Jaiswal
Assistant Professor, Department of Ophthalmology, Rama Medical College, Kanpur, Uttar Pradesh, India

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Abstract
Aim: To study the effect of pentoxifylline in glaucomatous optic atrophy.
Materials And Methods: The present prospective interventional comparative study was conducted among patients attending the out-patient department of Ophthalmology of Lala Lajpat Rai and associated Hospitals, Kanpur were selected. Patients were divided into 2 groups according to best corrected visual acuity (BCVA)-, first group having BCVA ≤20/200(6/60) and second having BCVA >20/200(6/60). In each group further division was made into cases control randomly. 49 eyes (39 patients) were taken in cases and 40 eyes (22 patients) were taken in control group. 33 and 16 eyes were selected for cases having BCVA >20/200 and ≤20/200 respectively. 26 and 14 eyes were selected for control having BCVA >20/200 and ≤20/200 respectively. They underwent detailed history and clinical examination. Patients with primary glaucoma – open angle, closed angle, and normal tension glaucoma were selected. Best corrected visual acuity with logmar chart, IOP with applanation tonometer, baseline IOP, IOP on follow-ups, Fundus examination (ophthalmoscopy), detailed slit lamp examination, visual fields by Humphrey field analyzer, Pachymetry (A scan) and Gonioscopy by Goldmann 3 mirror contact lens was recorded.
Results: Mean improvement of BCVA in first group was 0.02 (SD±0.01) and second group was 0.043 (SD±0.01) in cases (statistically insignificant) at the end of 6 month. In controls, first group had no change in BCVA whereas in second group there was mean deterioration of 0.002 (SD±0.00) (statistically insignificant) at the end of 6 month. Pentoxifylline does not have any significant effect on intraocular pressure.
Conclusion: Patients of glaucomatous optic atrophy on pentoxifylline did not have statistically significant improvement in their BCVA. Pentoxifylline does not have any significant effect on intraocular pressure, fundus picture and visual fields during 6 month of therapy.
Keywords: Pentoxifylline, Glaucoma, Optic atrophy

Introduction:
Glaucoma is a group of acute and chronic, progressive, multifactorial optic neuropathies in which intraocular pressure among other contributing factors are responsible for a characteristic acquired loss of retinal ganglion cell axons leading to atrophy of the optic nerve with demonstrable visual field defects [1]. Damage to the visual system in glaucoma is due to the death of the retinal ganglion cells, the axons of which comprise the optic nerve and carry the visual impulses from the eye to the brain [2]. Glaucoma represents a final common pathway resulting from a number of different conditions that can affect the eye, many of which are associated with elevated IOP. It is important to realize that elevated IOP is not synonymous with glaucoma, but rather is the most important risk factor we know of for the development and/or progression of glaucomatous damage [3].
Keeping in mind vascular theory, many drugs have been proposed in the management of glaucomatous optic atrophy, Pentoxifylline is one among those [4]. Pentoxifylline is a drug commonly sold by Aventis under the brand name Trental. Its chemical name is 1-(5-oxohexyl)-3, 7-dimethylxanthine. Other brand names include Pentox, Pentoxil, and Flexital. Trental® (pentoxifylline) is indicated for the symptomatic treatment of patients with chronic occlusive peripheral vascular disorders of the extremities; In such patients Trental may give relief of signs and symptoms of impaired blood flow, such as intermittent claudication or trophic ulcers [5].
Pentoxiphylline had been used in several studies to restore the normal function of the vasa-vasorum. It also has important role in microcirculation regulation

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and intravascular cell dynamics [6-8]. Pentoxiphylline is also known to increase whole blood filtration rate and deformability of erythrocytesand polymorphonuclear leucocytes in the tissues. So, Pentoxifylline can stop progression in optic atrophy by improving microcirculation and relieving ischemia [9]. The aim of the present study was to evaluate the effect of Pentoxifylline in patients of glaucomatous optic atrophy w.r.t. visual acuity, visual field and intraocular pressure.

Materials And Methods

Study Design: Prospective interventional comparative study

Selection of Patients: Patients attending the out-patient department of Ophthalmology of Lala Lajpat Rai and associated Hospitals, Kanpur were selected. They underwent detailed history and clinical examination. Patients were selected on the basis of following inclusion and exclusion criteria.

Inclusion Criteria:

a. Primary glaucoma – open angle, closed angle, and normal tension glaucoma.
b. Patients willing to undergo study.

Exclusion Criteria:

a. Secondary glaucoma – neovascular glaucoma, lens related glaucoma, pigmentary glaucoma, pseudoexfoliation, traumatic glaucoma, etc.
b. Patients on carbonic anhydrase inhibitors – Brinzolamide and Dorzolamide.
c. Patients not willing to undergo study.
d. Vascular headache – migraine and cluster headache
e. Congenital and juvenile glaucoma.
f. Patients having any other ocular pathology leading to diminuition of vision.

History: Includes history of headache, eye ache, brow ache, diminution of vision, frequent changes of glasses, pain, redness, coloured haloes, any treatment taken in the form of eyedrops and tablets, any history of vascular disease which are frequently associated with primary open-angle glaucoma.

Investigations:

- Best corrected visual acuity with logmar chart.
- IOP with applanation tonometer
  - Baseline IOP.
  - IOP on follow-ups.
- Fundus examination (ophthalmoscopy).
- Detailed slit lamp examination.
- Visual fields by Humphrey field analyzer.
- Pachymetry (A scan).
- Gonioscopy by Goldmann 3 mirror contact lens.

Patients were followed up according to following schedule:

- 1 month.
- 3 months.
- 6 months.
- Best corrected visual acuity by Logarithmic Visual Acuity Chart.
- Intraocular pressure by Applanation tonometer/Schiotz tonometer.
- Fundus examination.
- Visual fields by Humphrey field analyzer at 3rd and 6th month follow-ups.

Data was collected and subjected to statistical analysis.

Results: Patients were divided into 2 groups according to best corrected visual acuity (BCVA)-, first group having BCVA ≤20/200(6/60) and second having BCVA >20/200(6/60). In each group further division was made into cases control randomly. 49 eyes (39 patients) were taken in cases and 40 eyes (22 patients) were taken in control group. 33 and 16 eyes were selected for cases having BCVA >20/200 and ≤20/200 respectively. 26 and 14 eyes were selected for control having BCVA >20/200 and ≤20/200 respectively. Oral pentoxifylline 16 mg/kg in divided doses was started in the cases and were followed up for 6 months period. Study was conducted from January 2012 to June 2013. Patients were included in the study upto December 2012 and were followed up. Number of female was slightly more than the number of male with male: female ratio 6:7.

Table 1: Gender distribution among the study groups

Gender	Case	Control	Total
Male	18 (29.51%)	10 (16.39%)	28 (45.90%)
Female	21 (34.42%)	12 (19.67%)	33 (54.09%)
Total	39 (63.93%)	22 (36.06%)	61 (100%)

Maximum patients 32 (52.45%) were in the age group of 46-50 years old. Only 4 patients (6.55%) were below 40 years. 10 patients (16.39%) were above 50 years old as shown in graph 1.

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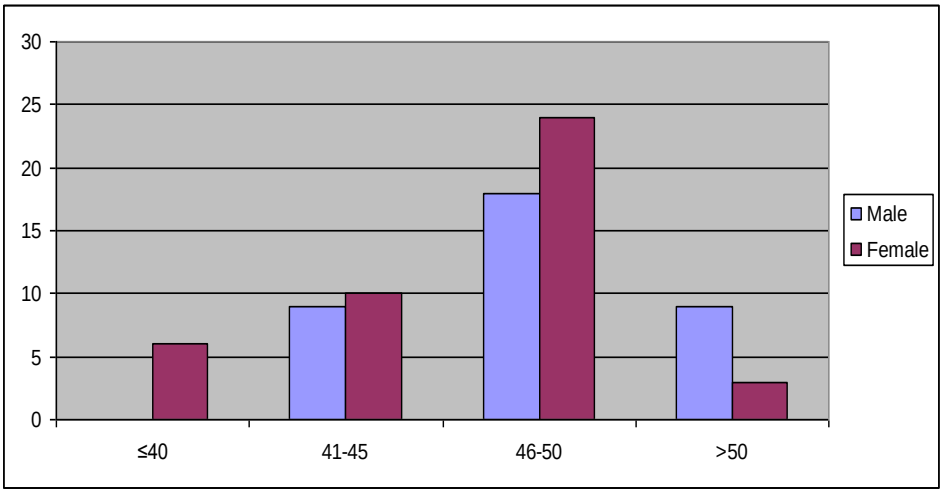

Graph 1: Age and sex distribution

Pre-treatment mean BCVA (Logmar) in the first group was 1.105 (SD±0.12) and post-treatment it was 1.104 (SD±0.11), 1.091 (SD±0.14), and 1.085 (SD±0.14) at 1 month, 3 month, and 6 month respectively (p value >0.05). Pre-treatment mean BCVA (Logmar) in the second group was 0.477 (SD±0.19) and post-treatment it was 0.476 (SD±0.20), 0.467 (SD±0.19), and 0.434 (SD±0.20) at 1 month, 3 month, and 6 month respectively (p value >0.05). The differences between pre-treatment and post-treatment mean BCVA at different intervals was statistically not significant (table 2).

Table 2: Mean visual acuity recordings in cases (in LOGMAR)

Case	Baseline	1 Month	3 Month	6 Month
≤20/200	1.105 ± 0.12	1.104 ± 0.11	1.091 ± 0.14	1.085 ± 0.14
P Value (Compared to Baseline)		>0.05	>0.05	>0.05
>20/200	0.477 ± 0.19	0.476 ± 0.20	0.467 ± 0.19	0.434 ± 0.20
P Value (Compared to Baseline)		>0.05	>0.05	>0.05

Mean BCVA (Logmar) in the first group was 1.142 (SD±0.13) and post-treatment it was 1.142 (SD±0.13), 1.142 (SD±0.13), and 1.142 (SD±0.13) at 1 month, 3 month, and 6 month respectively (p value >0.05). Mean BCVA (Logmar) in the second group was 0.538 (SD±0.21) and post-treatment it was 0.540 (SD±0.21), 0.540 (SD±0.21), and 0.540 (SD±0.21) at 1 month, 3 month, and 6 month respectively (p value >0.05). The differences between mean BCVA at different intervals was statistically not significant (table 2).

Table 3: Mean visual acuity recordings in controls (in LOGMAR)

Control	Baseline	1 Month	3 Month	6 Month
≤20/200	1.142 ± 0.13	1.142 ± 0.13	1.142 ± 0.13	1.142 ± 0.13
P Value (Compared to Baseline)		>0.05	>0.05	>0.05
>20/200	0.538 ± 0.21	0.540 ± 0.21	0.540 ± 0.21	0.540 ± 0.21
P Value (Compared to Baseline)		>0.05	>0.05	>0.05

Mean improvement of BCVA in first group was 0.02 (SD±0.01) and second group was 0.043 (SD±0.01) in cases (statistically insignificant) at the end of 6 month. In controls, first group had no change in BCVA whereas in second group there was mean deterioration of 0.002 (SD±0.00) (statistically insignificant) at the end of 6 month (table 4).

Table 4: Comparison of visual acuity between cases and control

	Baseline		1 Month		3 Month		6 Month	
	Case	Control	Case	Control	Case	Control	Case	Control
≤20/200	1.105 ±0.12	1.142±0.13	1.104 ±0.12	1.142±0.13	1.09± 0.14	1.142±0.13	1.085± 0.14	1.142±0.13
P Value			>0.05		>0.05		>0.05	
>20/200	0.477 ±0.19	0.538±0.21	0.476 ±0.20	0.540±0.21	0.467 ±0.19	0.540± 0.21	0.434± 0.20	0.540±0.21
P Value			>0.05		>0.05		>0.05	

From table 5, it can be said that Pentoxifylline does not have any significant effect on intraocular pressure.

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Table 5: Comparison of intraocular pressure in cases

Duration	Mean IOP in mmHg (by Applanation Tonometer)
Baseline	15.74(SD±3.44)
1 Month	15.60(SD±3.66)
3 Month	14.86(SD±3.81)
6 Month	14.93(SD±2.96)

Most common side effect was nausea (19.2%) followed by headache (15.4%) and vomiting (7.7%).

Discussion: Glaucoma affects more than 67 million persons world-wide, of whom about 10%, or 6.6 million, are estimated to be blind. Glaucoma is the leading cause of irreversible blindness world-wide, and is second only to cataracts as the most common cause of blindness overall. Intraocular pressure is only one of the major risk factors for glaucoma, lowering it via various pharmaceuticals and/or surgical techniques are currently the mainstay of glaucoma treatment.

In cases (pentoxifylline group) with BCVA ≤20/200, 2 patients have improvement of 1 letter and 3 patients of 2 letters.10 patients did not showed any change and 1 patient had deterioration of 3 letters. In cases (pentoxifylline group) with BCVA >20/200, 5 patients have improvement of 1 letter and 2, 3, 5 patients of 3, 2, 5 letters respectively.14 patients did not showed any change and 4 patient had deterioration of 4 letters.

In control with BCVA ≤20/200, all 14 patients did not have any change of BCVA. In control with BCVA >20/200, 24 patients did not have any change of BCVA, 2 patient had deterioration of 2 letters.

Mean improvement of BCVA in cases in first group was 0.02 (SD±0.01) and second group was 0.043 (SD±0.01) (statistically insignificant) at the end of 6 month. In controls, first group had no change in BCVA whereas in second group there was mean deterioration of 0.002 (SD±0.00) (statistically insignificant) at the end of 6 month. In control group mean BCVA remains same during 6 months period but shows around 1 letter gain in cases in first group although it was statistically insignificant. In control group mean BCVA deteriorated very slightly during 6 months period but shows around 2 letter gain in cases in first group although it was statistically insignificant.

Shukla BR et al (1970) [10] reported a case of functional recovery in a patient with hereditary optic atrophy. They kept the patient on vasodilators and vitamin b complex for more than 2 years. For about two years there was no significant objective or subjective improvement. However, at the end of two years, visual acuity started improving rather rapidly.

Schatilova TA et al (1979) [11] studied effect of Pentoxifylline in the treatment of pathological vascular changes in the fundus oculi. This study showed that there were improvements in ocular blood flow after Pentoxifylline and treatment resulted in significant increase in visual acuity, particularly in patients with thrombohaemorrhagic syndrome and with vascular disturbances of the optic nerve.

Iwafune Y et al (1980) [12] studies the clinical effect of pentoxifylline in 23 eyes with retinal haemorrhage caused by disturbances of retinal circulation. It was found that difference in the improvement of visual acuity between the group treated with pentoxifylline and controls was less pronounced.

Kiseleva TN et al (2007) [13] studied the effect of the pentoxifylline retard dosage form Vasonit on ocular hemodynamics in patients with retinal vein occlusions and non-proliferative diabetic retinopathy (DR). After a course of pentoxifylline therapy, the patients were observed to have improved visual functions.

Park CH et al (2007) [14] to determine whether oral pentoxifylline decreases cystoid macular edema (CME) and improves visual acuity in eyes with a perfused central retinal vein occlusion (CRVO). The visual acuity was not significantly changed at 62 letters (20/128 +2) (Student t-test, P = 0.7) at last follow-up. Visual acuity does not appear to change significantly.

Perwez Khan et al (2013) [15] evaluated effect of oral pentoxifylline in optic neuropathies of different etiologies. Oral Pentoxifylline causes functional improvement as suggested by improved BCVA, without causing any gross structural changes in the optic disc. Pentoxifylline causes improvement in visual acuity in cases of optic atrophy of shorter duration. It has no effect on pupillary reaction as well.

From above we can say that non significant improvement of BCVA in our study may be due to the fact that either duration of treatment was small or sample size was not adequate. Its more effective in early glaucomatous optic neuropathy when severe damage has not occurred. As found in the study of Eliseeva TO et al (2000) [16] that subtenon collagen infusion system was most effective followed by parabulbar, we could say that oral may not be efficient. To effectively conclude whether the drug causes any functional improvement in glaucomatous optic neuropathy, studies with larger cohorts and longer duration are required to confirm its role in regaining of visual acuity and its effect on other parameters of vision.

In our study all patients were already on topical anti-glaucoma drugs and their IOP were within normal range. Baseline mean IOP in cases was 15.74 (SD±3.44) and after therapy it was 15.60 (SD±3.66), 14.86 (SD±3.81), 14.93 (SD±2.96). Thus this drug doesn't any significant effect on intraocular pressure. This observation needs to be confirmed in larger trials.

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The drug did not have any effect on the fundus picture and visual field of any patient.
Further studies are needed to assess role of pentoxifylline in glaucomatous optic atrophy.

Conclusion: Results were analyzed and following points were concluded:
1. Patients of glaucomatous optic atrophy on pentoxifylline did not have statistically significant improvement in their BCVA, but they have improvement of 1 letter in those having baseline BCVA ≤20/200 and 2 letter in those having baseline BCVA >20/200 compared to control after 6 month.
2. Pentoxifylline does not have any significant effect on intraocular pressure.
3. Most common side effect of pentoxifylline is nausea followed by headache and vomiting.
4. Pentoxifylline does not have any effect on fundus picture and visual fields during 6 month of therapy.

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