

Changes in Visual Fields in Normotensive Glaucoma

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ABSTRACT

To find the effect of prostaglandins and beta blockers on medium-term progression of changes of visual fields in normotensive glaucoma in a retrospective study. We evaluated three groups of patients with normotensive glaucoma (NTG). The first group consisted of 28 eyes of 14 patients (8 females and 6 males) of mean age 58 years (37-75 years) who were treated with prostaglandins. The second group consisted of 20 eyes of 10 patients (5 females and 5 males) of mean age 57 years (33-75 years) who were treated with beta blockers. The third group consisted of 36 eyes of 18 patients (8 females and 10 males) of mean age 59 years (37-75 years) who underwent no ophthalmological therapy. All patients were compensated for cardiovascular status and had no other internal or neurological disease. Visual acuity was 1.0 with a possible correction (less than 3 dioptres) in all patients.

If hypotensive ophthalmological therapy was initiated, it had remained stable for the last five years. In all patients, central corneal thickness (CCT), excavation of the optic nerve papilla (c/d), ganglion cell complex (GCC), retinal nerve fiber thickness (RNFL), pattern defect (PD) and overall defect (OD) of visual field were monitored by us. Statistical analysis found the highest progression of changes in the visual fields (PD) in patients without therapy ($p=0.0001$) and in patients treated with prostaglandins ($p=0.04$). In patients who were treated with beta blockers, the progression of changes in the visual fields was statistically significant ($p=0.7$). We did not find a statistically significant progression in any group. The correlation analysis found the highest correlation with GCC in PD ($r=0.33$; $p=0.004$). We did not find any correlation between the evaluated parameters in OD. Our results show that therapy with beta blockers is more convenient for NTG, compared to prostaglandins or no topical therapy.

Introduction

Normotensive glaucoma (NTG) is defined as progressive optic neuropathy with glaucomatous disc of the optic nerve and visual field in which IOP is equal or lower than 21mmHg [1]. Differences compared to hypertensive glaucoma (HTG) were described in the previous paper [2]. In 2013, we referred to the effects of pharmacological therapy on the progression of changes in the visual fields in hypertensive glaucoma (HTG). We did not find differences between therapy with prostaglandins or beta blockers [3]. Because NTG is pathophysiologically a different disease, we were interested in determining whether the finding would be similar to that of HTG after a 5-year follow-up of the changes in visual fields without local therapy. This was the purpose of our study.

Materials and Methods

We evaluated three groups of patients with NTG. Diagnosis was determined by means of complex ophthalmology examination, including the IOP curve and electrophysiological examination. The first group consisted of 28 eyes of 14 patients (8 females and 6 males) of mean age 58 years (37-75 years) who were treated with prostaglandins. The second group consisted of 20 eyes of 10 patients (5 females and 5 males) of mean age 57 years (33-75 years) who were treated with beta blockers. The third group consisted of 36 eyes of 18 patients (8 females and 10 males) of mean age 59 years (37-75 years) who underwent no ophthalmological therapy. All patients were compensated for cardiovascular status and had no

other internal or neurological disease. Visual acuity was 1.0 with a possible correction (less than \pm dioptres) in all patients.

The IOP ranged between 10-15mmHg in all patients. If hypotensive ophthalmological therapy was initiated, it had been stable for the last five years. In all patients, we monitored CCT, excavation in the papilla (c/d), ganglion cell complex (GCC), thickness of the retinal nerve fibre layer (RNFL), pattern defect (PD) and overall defect (OD) of the visual field. In 2013, changes in the visual fields were approximately the same in all patients. We compared the results of the visual fields after five years, i.e. the results were found in 2018. Central corneal thickness (CCT) was measured, using the ultrasound pachymeter Tomey SP-100. GCC and RNFL, using optic coherence tomography SD-OCT RTvue-100, and the visual field using the glaucoma fast threshold program with the MEDMONT M 700 device. For statistical consideration, we used the paired test and correlation analysis.

Results

Patients Treated with Prostaglandins

Number of patients: 14

Mean age: 58.2 ± 10.4

Lowest: 37

Highest: 75

Mean PD 0: 2.77 ± 2.44

Mean PD 5: 3.2 ± 2.5

$p=0.04$

Mean OD 0: 2.7 ± 1

Mean OD 5: 2.8 ± 1

$p=0.4$

Therapy

xalatan 9

monopost - 2

taflotan - 2

bimican - 1

System changes

Hypertension - 4

Hypotension - 4

Patients Treated with Beta Blockers:

Number of patients: 10

Mean age: 57 ± 10.7

Lowest: 33

Highest: 75

Mean PD 0: 2.17 ± 1

Mean PD 5: 2.2 ± 1.3

$p=0.7$

Mean OD 0: 3.2 ± 0.6

Mean OD 5: 3.5 ± 0.9

$p=0.4$

Therapy

betoptic - 5

carteol - 5

System Changes

hypertension - 1

hypotension - 2

Patients without Therapy:

Number of patients: 18

Mean age: 59.5 ± 16.1

Lowest: 37

Highest: 75

Mean PD 0: 2.2 ± 0.7

Mean PD 5: 2.9 ± 1.5

$p=0.0001$

Mean OD 0: 3.2 ± 1

Mean OD 5: 3 ± 1.4

$p=0.24$

System changes

Hypertension - 1

Hypotension - 2

CAD - 2

From the above Table 1, we can see that the GCC variable correlates mostly with the progression of changes in PD ($r=0.3255$; $p=0.04$). Therefore, it is a proportional correlation. No variable correlates statistically significantly with the progression of changes in OD. Furthermore, it can be concluded that GCC strongly correlates with RNFL ($r=0.73$; $p=0.0001$) and weakly with c/d ($r=0.32$; $p=0.05$). The correlation with CCT is also interesting ($r=0.3$; $p=0.009$). We found a similar correlation between the changes in visual fields and CCT also in HTG [4].

Table 1: Final correlation coefficients' data of the evaluated variables. PD-pattern defect, OD-overall defect, CCT-central corneal thickness, c/d-cup/disc ratio, GCC-ganglion cell complex, RNFL-retinal nerve fibre layer.

Variable	Correlations (Data) Marked correlations are significant at $p < 0.05000$ N=86 (Case wise deletion of missing data)					
	PD (before-after)	OD (before-after)	CCT	c/d	GCC	RNFL
PD (before-after)	1	0.1192	0.1454	0.0123	0.3255	0.1951
	p=---	p=0.305	p=0.210	p=0.916	p=0.004	p=0.091
OD (before-after)	0.1192	1	0.0244	-0.0319	0.0256	-0.0149
	p=0.305	p=---	p=0.835	p=0.785	p=0.826	p=0.898
CCT	0.1454	0.0244	1	-0.0519	0.2959	-0.0259
	p=0.210	p=0.835	p=---	p=0.656	p=0.009	p=0.824
c/d	0.0123	-0.0319	-0.0519	1	-0.3224	-0.1662
	p=0.916	p=0.785	p=0.656	p = ---	p=0.005	p=0.151
GCC	0.3255	0.0256	0.2959	-0.3224	1	0.7374
	p=0.004	p=0.826	p=0.009	p=0.005	p = ---	p=0.000
RNFL	0.1951	-0.0149	-0.0259	-0.1662	0.7374	1
	p=0.091	p=0.898	p=0.824	p=0.151	p=0.000	p = ---

Discussion

According to the Normal-Tension Glaucoma study, the main principle of therapy of NTG is a decrease of the IOP. This study showed that a decrease of the IOP had a positive effect on the progression of this disease, compared to untreated controls with NTG. Progression of changes in the visual fields occurred even after this decrease in 12 % of cases [5]. The most commonly prescribed anti-glaucoma agents used in monotherapy in several studies did not achieve a decrease of the IOP proposed by the Collaborative Normal-Tension Glaucoma study. Prostaglandin analogues (latanoprost and bimatoprost), beta blockers and alpha-adrenergic agonists decrease IOP by 16 % to 20 % during monotherapy [6,7]. Administration of dorzolamide/timolol and brimonidine/timolol for 12 weeks resulted in a decrease of the IOP by 20 % and 23.7 %, respectively [8,9]. Tomita et al. monitored a decrease of IOP for three years, and the changes in visual fields in latanoprost and timolol-maleate. The decrease of IOP was 13-15 % in both groups. Progression of changes in visual fields (MD) for latanoprost was (dB/year) -0.34 ± 0.17 and -0.10 ± 0.18 for timolol. The differences were not statistically significant [10].

Krupin et al. [11] compared the effect of brimonidine and timolol on the changes in the visual fields and found a higher progression in NTG when timolol was used. The authors state that beta blockers can even have a detrimental effect on NTG. Although these conclusions should be interpreted with caution, due to the high number of discontinuations in the brimonidine group, the results suggested that brimonidine had a relatively protective effect on the visual field. Hayreh et al. [12] report that topical beta blockers induce a significant decrease in mean diastolic blood pressure at night, and that patients with NTG treated with beta blockers had visual field progression more frequently than those who did not. They conclude that beta blockers are a risk factor for

patients with NTG. This is also the reason why our group treated with beta blockers is so small and timolol-maleate is not used.

The possibilities of pharmacological treatment in progressive cases include betaxolol eye drops, which, in addition to reducing IOP, have a beneficial effect on the optic nerve blood flow. Other beta blockers and adrenergic agents (such as dipivefrin) should be excluded, due to the likelihood of nocturnal systemic hypotension and optic nerve hypoperfusion. Prostaglandin derivatives tend to have a higher IOP decreasing effect, which can have a fundamental significance [13]. Carteolol is a non-selective beta blocker with intrinsic sympathomimetic activity (I.S.A.) Carteolol had no effect on nocturnal IOP, but significantly helped to reduce daytime IOP, maximum IOP, mean 24-h IOP, and the 24-h IOP range. The drug exerted no statistically significant effect on the pulse rate [14]. Brinzolamide and betaxolol significantly increased the thickness of choroidal in healthy individuals, while latanoprost had no effect [15]. With regard to the undesirable effects of beta blockers, a study by the authors who monitored 1112 patients with the diagnosis of AV block should be stated.

A permanent pacemaker was implanted in 946 cases (84.3%) during the follow-up period. Of this number, 13 patients were taking topical beta blockers (7 patients applied timolol, 4 betaxolol and 2 carteolol). The mean time of therapy using ophthalmological beta blockers was 30.1 ± 15.9 months. Eight patients had a complete AV block and 5 patients had a high degree of AV block during electrocardiographic study. Following discontinuation of treatment in 10 patients, the block persisted, and a permanent pacemaker had to be implanted. One patient needed implantation of a pacemaker during the follow-up period. Pacemakers were implanted in a total of 11 out of 13 patients [16]. Messner et al. studied the changes in the visual fields in HTG during therapy with timolol and betaxolol. The effect of treatment on the visual fields was better in the

betaxolol group than in the timolol group ($P=0.04$) [17]. Carenini et al. [18] studied pulsatile ocular blood flow (POBF) in patients with HTG treated with timolol and betaxolol.

They found that POBF was significantly decreased during the 12-month observation period in patients treated with timolol, while remaining stable in patients treated with betaxolol [18]. The study by Melena et al. [19] who investigated the possible blockade of calcium entry into the cells on isolated rat retinas, by stimulating the NMDA receptors using anti glaucoma tics (betaxolol, carteolol, levobunolol, timolol, brimonidine, dorzolamide, latanoprost and pilocarpine), is also interesting. We found that beta blockers could affect this process with the highest effect in betaxolol [19]. The neuroprotective effect of betaxolol on isolated rat retinas was also demonstrated by the study of Osborn et al., who investigated the influx of calcium into the cells. They found a significant reduction of the increased Ca^{2+} values following the administration of kainite [20]. Both beta blockers (betoptic and carteolol) we evaluated in our studies had a positive effect on the changes in visual fields in NTG. We did not have to change this therapy in any patient during the follow-up period with regard to possible general problems. We are aware of the smaller groups in which we used beta blockers, which is a limitation of this work. Following their effect on the progression of the disease, we will consider a more frequent administration and, perhaps after five years, will perform a similar assessment.

Conclusion

Our results show that therapy with beta blockers (betaxolol and carteolol) is more suitable for patients with NTG vs prostaglandins or without topical therapy.

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