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BETAXOLOL, BRIMONIDIN AND CARTEOLOL IN THE THERAPY OF NORMAL-TENSION GLAUCOMA

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SUMMARY

Purpose: The purpose of the study was to evaluate influence of betaxolol, brimonidine and carteolol in the progression of the visual field defects during time at patients with normotensive glaucoma (NTG).
Materials and methods: This study included (60 eyes of) 30 patients with NTG. First group consisted of 20 eyes of 10 patients of the average age of 58.5 years, who were treated by betaxolol. Second group also consisted of 20 eyes of 10 patients of the average age of 62.6 years and they were treated by brimonidine. Third group had the same count of the eyes and patients, the average age was 61.1 years and these patients were treated by carteolol. Diagnose of NTG was based on the comprehensive ophthalmological examination including electroretinography and visual evoked potentials. Visual fields were examined by fast threshold glaucoma test using Medmont M700 device. We compared pattern defect (PD) in the visual field for 3 years. The including criteria were: similar visual field findings at the beginning of the study, stable eye therapy (treatment was not changed during the study), uncorrected or best corrected (up to +-3 D) visual acuity of 1,0 of ETDRS, intraocular pressure between 10-15 mm Hg, if present, then compensated cardiovascular disease, no other internal or neurological disorders.
Results: We didn't notice any statistically important difference of PD. The study revealed that brimonidin (p=0,99) and betaxolol (p = 0,81) had the best effect.
Conclusion: Local therapy of betaxolol, brimonidine and carteolol has an essential clinical value in normotensive glaucoma. All the mentioned treatments had a protective effect on the visual field. However, local side-effects of brimonidinu are a question.
Key words: normotensive glaucoma, betaxolol, brimonidin and carteol treatment, pattern defect

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INTRODUCTION

If glaucoma damage (extended excavation of the papilla or loss of the visual field) appears despite the fact that intraocular pressure (IOP) is normal upon repeated measurements, the patient is diagnosed with normal-tension glaucoma (NTG). It is again necessary to emphasise that there is no fundamental difference between hypertensive glaucoma (HTG) and NTG. Both have essentially the same diagnosis and treatment [4].

The results of our studies differ from the above. Today prostaglandins (PG) and beta blockers (BB) are the drugs of first choice for HTG and NTG. When we compared patients with HTG treated with PG, we determined that over a five-year observation period the pattern defect (PD) was statistically unchanged ($p = 0.35$), but the value of the overall defect (OD) approximated statistically significant progression ($p = 0.09$). We recorded a different finding in the case of NTG. The largest changes were in the PD of untreated patients ($p = 0.001$) and in patients treated with PG ($p = 0.04$). In patients treated with BB we did not record any statistically significant progression ($p = 0.7$) [14].

PD and OD are different in HTG and NTG. For the diagnosis and progression of changes in the visual field, OD is more specific for HTG and PD for NTG [11].

On the basis of these findings, we were interested in whether treatment with adrenergic agonists (brimonidin) and beta blockers (BB) would have a different influence on the treatment of NTG. As a result, the purpose of the study was to evaluate the influence of betaxolol, brimonidin and carteolol on the progression of changes in the visual field in patients with NTG over time.

COHORT AND METHOD

Our cohort included 30 patients with NTG. The first group comprised twenty eyes of ten patients with an ave-

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rage age of 58.5 years, who were treated with betaxolol (Betoptic S, Alcon), the second group also twenty eyes of ten patients with an average age of 62.6 years treated with brimonidin (Luxfen, PharmaSwiss), and the third group comprised the same number of patients with an average age of 61.1 years treated with carteolol (Carteol LP 2 %, Bausch and Lomb). The diagnosis was determined by a comprehensive ophthalmological examination, including electroretinography and visual evoked potentials. We examined the visual field by means of a fast threshold glaucoma test using the instrument Medmont M700. We compared the pattern defect (PD) of the visual field over the range of three years. We conducted peripapillary measurement of the retinal nerve fibre layer (RNFL) and vessel density (VD) using the instrument Avanti RTVue XR manufactured by the Optovue company.

The inclusion criteria for the observed cohort were approximately similar visual field at the beginning of evaluation, unchanged eye treatment, visual acuity of 1.0 with correction of less than ± 3 dioptres. All the patients were compensated for cardiovascular disorders and none had any other internal or neurological disorders. IOP was within the range of 10-15 mm Hg throughout the entire observation period. The mean reduction of IOP following the application of treatment was 30 % of the original value.

RESULTS

The average values and their standard deviations of all the evaluated parameters are presented in table 1. The values of PD 0 in the group treated with betaxolol and carteolol are slightly lower than in the group treated with brimonidin. The reason was the assumption of improvement of the perfusion parameters by brimonidin upon determination of the diagnosis. The effect of treatment with brimonidin is documented also by the p value of the Student test (p = 0.99). This is followed by betaxolol (p = 0.81) and carteolol (p = 0.79). Upon a comparison of the individual pharmaceuticals, the smallest difference was between betaxolol and brimonidin (p = 0.79), and carteolol and brimonidin (p = 0.66). Table 2.

DISCUSSION

According to the Normal-Tension Glaucoma Study, the main principle of NTG treatment is the reduction of IOP. This study demonstrated that reducing IOP had a positive influence on progression in comparison with untreated controls with NTG. However, progression in the visual field occurred also after this reduction in 12 % of cases [3]. As a result, IOP cannot be the sole factor in explaining the degeneration of the optic nerve [7]. The current gold standard in the treatment of glaucoma is PG analogues, which are the single most effective drug in the reduction of IOP with corresponding daily control [5].

The fact that this opinion persists at the present time is documented by the study by Symes and Mikelberg, who using a questionnaire survey determined that PG are applied in 88 % of cases of NTG, and brimonidin in 10 % [16]. The results of our studies produced somewhat different conclusions from the above. The first difference is in the effect of prostaglandins. In another study we recorded the largest progression of changes in the visual field (p = 0.001) in untreated patients with NTG. A similar situation applied also in the case of patients using PG (p = 0.04). This is of fundamental significance, since even if a pronounced reduction of IOP occurs after the application of PG, the pathology still progresses further. In the patients treated with BB we did not record any statistically significant progression (p = 0.7) [14]. Another difference is in peripapillary vessel density. In another study, in which we compared the dependency between

Table 1. Summary table for all groups of patients. PD 0 – pattern defect at beginning of evaluation, PD 3 – pattern defect after three years

NTG patients			
medication	**betaxolol**	**brimonidin**	**carteolol**
Number of patients	10	10	10
Average age	58.5 ± 9.87	62.6 ± 10.42	61.1 ± 9.3
Min.	41	52	37
Max.	73	82	70
Mean PD 0	2.48 ± 0.71	3.8 ± 1.8	2.41 ± 1.8
Mean PD 3	2.53 ± 0.67	3.79 ± 1.21	2.28 ± 1.2
p-value	p = 0.81	p = 0.99	p = 0.79

Table 2. p value of Student T-test between individual therapies

medication	**carteolol x betaxolol**	**carteolol x brimonidin**	**betaxolol x brimonidin**
T-test (p-value)	0.39	0.66	0.79

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changes in the visual field and vessel density (VD), we determined that the largest correlation was between the lower half of the visual field and the upper half of VD (r = 0.7, p = 0.001), and the upper half of the visual field and the lower half of VD (r = 0.52, p = 0.001). This means that changes in the visual field have a fundamental influence on blood perfusion in the area of the optic nerve papilla. We did not record such a result in patients with hypertensive glaucoma. As a result, ophthalmological drugs which improve perfusion of the anterior part of the optic nerve also have a protective effect on their nerve fibres. This cannot be asserted in the case of PG [2,19].

Local beta blockers, which reduce the production of intraocular fluid, have the potential to generate significant systemic side effects such as nocturnal hypotension, which may be especially disconcerting in the case of NTG. As mentioned previously, the Low-Pressure Glaucoma Treatment Study indicates that beta blockers could even have a harmful effect in the treatment of NTG [9]. However, we did not record this effect in our patients. Ischaemic change of retrobulbar haemodynamics is one of the important manifestations of NTG. The haemodynamic parameters measured with the aid of colour Doppler imaging may be potential diagnostic tools for NTG [10,20]. A question remains as to what role is played by pulsatile ocular blood flow (POBF). Liu et al. compared the influence of latanoprost and brimonidin on POBF in the case of NTG. After adjustment for IOP they did not determine a statistically significant difference in POBF in any of these pharmaceuticals [12]. The results showed that even local application of timolol did not have a harmful effect on blood flow in the region of the optic nerve papilla in healthy individuals. The application of carteolol increased blood flow to the papilla in a healthy eye [17]. This is attributed to increased ocular perfusion caused by reduced intraocular pressure, as well as to the inhibiting effect on vasoconstriction in the papilla of the optic nerve as a consequence of internal sympathomimetic activity, which prevents a decrease of blood flow to the papilla and thereby also adverse effects on the ocular circulation [13]. Similar conclusions were reached also by Mizuki at al. [15] and Chen et al. [6]. By carteolol hydrochloride binding to alginic acid, its systemic side effects are also reduced [8]. Brimonidin is a highly selective alpha2 adrenergic receptor agonist, which reduces the formation of intraocular fluid and eases its drainage via the uveoscleral pathway. Its effect on the reduction of IOP was similar to the effectiveness of timolol, but higher than betaxolol. However, its side effects are also worthy of mention. Dry eye (30 %), congestion of conjunctivas (26.3 %), burning sensation in eyes (24 %), allergic reaction of conjunctivas (9.6 %). In addition to these local symptoms, users also recorded cardiovascular problems, which however were not statistically significant [1].

Tepelus et al. determined that eyes with NTG also had lower choriocapillary perfusion density than a control group [18].

We may agree with this conclusion also on the basis of our own investigation. We believe that in NTG a very important role is played by the decimation of the capillaries mainly in the region of the optic nerve papilla, above all its anterior part, resulting in the changes of the through-flow parameters determined by Doppler ultrasonography. As yet we are unable to state the process by which this decimation may take place. When we use PG in this reduction of the capillary network, we generate further ischaemia in the region of the optic nerve papilla.

Our current study also demonstrated that pharmaceuticals which positively influence perfusion of the posterior pole of the eye (including the optic nerve) are not the most important in the case of NTG. According to statistical processing, we demonstrated that the best effect was achieved by betaxolol and brimonidin. However, a question remains concerning the adverse local side effects of brimonidin.

CONCLUSION

Local treatment with betaxolol, brimonidin or carteolol is of fundamental significance for NTG. All of the above pharmaceuticals have a protective influence on the visual field.

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