

# Effect of prostaglandins and beta blockers on progression of hypertensive and normotensive glaucomas

Klara Maresova<sup>a</sup>, Jan Lestak<sup>b,c</sup>, Martin Fus<sup>b,c</sup>, Iveta Weissova<sup>b,c</sup>

**Aim.** The aim of the study was to evaluate the progression of changes in the visual fields in patients with hypertensive glaucoma (HTG) and normotensive glaucoma (NTG) following administration of prostaglandins and beta blockers, as well as also in NTG without ophthalmological therapy.

**Methodos.** The HTG group included 12 patients (mean age 66 years) with approximately the same changes in the visual field and central corneal thickness (CCT=568um) treated with prostaglandins, and 12 patients (mean age 60 years, CCT=544um) treated with beta-blockers. The IOP ranged from 12 to 18mmHg for the whole follow-up period. The NTG group consisted of three subgroups. The first subgroup consisted of 14 patients (mean age 58 years) who were treated with prostaglandins. The second subgroup consisted of 10 patients (mean age 57 years) who were treated with beta blockers. The third subgroup consisted of 18 patients (mean age 57 years) who underwent no ophthalmological therapy. IOP was within the range of 8-12 mmHg over the whole follow-up period. In all patients, we monitored the pattern defect (PD) and overall defect (OD) within a period of five years. The treatment was not modified during the treatment period. 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.

**Results.** There was no statistically significant difference in HTG during the treatment with prostaglandins in PD ( $P=0.35$ ) and OD ( $P=0.09$ ) or beta blockers ( $P=0.37$  and  $0.23$ , respectively). In NTG, the greatest changes occurred in PD ( $P=0.0001$ ) in untreated patients. OD showed no statistically significant changes ( $P=0.25$ ). Similarly, the patients on prostaglandins had a statistically significant difference in PD ( $P=0.04$ ), while OD did not show statistically significant changes ( $P=0.4$ ). We did not find statistically significant differences in progression in patients with NTG treated with beta blockers PD ( $P=0.7$ ), OD ( $P=0.4$ ).

**Conclusion.** Treatment of glaucoma with prostaglandins and beta blockers has a significant importance in HTG. However, beta blockers have a higher protective effect on the visual field. This is not true in NTG, where we demonstrated this effect only following the administration of beta blockers.

**Key words:** hypertensive glaucoma, normotensive glaucoma, prostaglandins, beta-blockers, visual field, protection

Received: December 6, 2019; Accepted: March 9, 2020; Available online: March 26, 2020

<https://doi.org/10.5507/bp.2020.011>

© 2019 The Authors. This is an open access article licensed under the Creative Commons Attribution License (<https://creativecommons.org/licenses/by/4.0/>).

<sup>a</sup>Department of Ophthalmology, Faculty of Medicine and Dentistry, Palacky University Olomouc, Czech Republic

<sup>b</sup>FBMI CTU Prague, Czech Republic

<sup>c</sup>Eye Clinics JL FBMI CTU Prague, Czech Republic

Corresponding author: Jan Lestak, e-mail: [lestak@seznam.cz](mailto:lestak@seznam.cz)

## INTRODUCTION

An impairment of the ganglion cells and subsequently also of the whole visual tract occurs due to high intraocular pressure (IOP) in hypertensive glaucomas (HTGs). In the case of normotensive glaucoma (NTG), an injury to the anterior part of the visual tract is most probably concerned due to ischaemia.

To date, not every ophthalmologist agrees with this characteristics. The main protective effect on retinal ganglion cells has been a reduction in IOP so far<sup>1</sup>. IOP can be reduced in various ways. In the last ten years, beta blockers and prostaglandins have been used as a first-choice therapy in HTG in Europe<sup>2,3</sup>.

According to the Normal-Tension Glaucoma study, the main principle of therapy in 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<sup>4</sup>. The most commonly prescribed anti-glaucoma agents used in monotherapy in several studies did not achieve the decrease of the IOP proposed by the Collaborative Normal-Tension Glaucoma study.

Prostaglandins increase efflux of intraocular fluid, but they also have a strong vasoconstrictor effect. Beta-adrenoceptor antagonists reduce production of intraocular fluid. In addition, the selective beta blockers improve ocular perfusion<sup>5</sup>. Based on this information, we tried to compare the effect of treatment with beta blockers and prostaglandins on changes in the visual fields. There are only a few studies on the functional assessment of both types of anti-glaucomatous treatment.

**Table 1.**

| Therapy            | Patients with HTG |                   | Patients with NTG |                  | Patients with NTG without therapy |
|--------------------|-------------------|-------------------|-------------------|------------------|-----------------------------------|
|                    | prostaglandins    | $\beta$ blockers  | prostaglandins    | $\beta$ blockers | nothing                           |
| Number of patients | 12                | 12                | 14                | 10               | 18                                |
| mean age           | 66.17 $\pm$ 8.69  | 60.17 $\pm$ 11.25 | 58.2 $\pm$ 10.4   | 57 $\pm$ 10.7    | 58.2 $\pm$ 10.4                   |
| min                | 51                | 46                | 37                | 33               | 37                                |
| max                | 78                | 81                | 75                | 75               | 75                                |
| mean PD 0          | 2.56 $\pm$ 1.54   | 2.23 $\pm$ 0.84   | 2.77 $\pm$ 2.44   | 2.17 $\pm$ 1.0   | 2.2 $\pm$ 0.7                     |
| mean PD 5          | 2.41 $\pm$ 1.23   | 2.16 $\pm$ 0.61   | 3.2 $\pm$ 2.5     | 2.2 $\pm$ 1.3    | 2.9 $\pm$ 1.5                     |
| <i>P</i>           | <i>P</i> =0.35    | <i>P</i> =0.37    | <i>P</i> =0.04    | <i>P</i> =0.7    | <i>P</i> =0.0001                  |
| mean OD 0          | 3.99 $\pm$ 2.43   | 3.39 $\pm$ 1.29   | 2.7 $\pm$ 0.1     | 3.2 $\pm$ 0.6    | 3.2 $\pm$ 1                       |
| mean OD 5          | 3.19 $\pm$ 1.52   | 3.12 $\pm$ 1.11   | 2.8 $\pm$ 1       | 3.5 $\pm$ 0.9    | 3 $\pm$ 1.4                       |
| <i>P</i>           | <i>P</i> =0.09    | <i>P</i> =0.23    | <i>P</i> =0.4     | <i>P</i> =0.4    | <i>P</i> =0.24                    |

## METHODS AND PATIENTS

12 patients (6 females and 6 males, mean age 66 years) with approximately the same changes in visual field and central corneal thickness (CCT-568  $\mu$ m) were included in the HTG group and were treated with prostaglandins, and 12 patients (6 females and 6 males, mean age 60 years, CCT = 544  $\mu$ m) treated with beta-blockers. The intraocular pressure (IOP) ranged from 12 to 18 mmHg during the whole follow-up period.

The NTG group consisted of three subgroups. The first subgroup consisted of 14 patients (8 females and 6 males, of mean age 58 years) who were treated with prostaglandins. The second subgroup consisted 10 patients (5 females and 5 males, of mean age 57 years) who were treated with beta blockers. The third subgroup consisted of 18 patients (8 females and 10 males, of mean age 57 years) who underwent no ophthalmological therapy. The IOP was within the range of 8-12 mmHg over the entire duration of the follow-up period.

In all patients, we monitored the pattern defect (PD) and overall defect (OD) for five years (2014-2019). The treatment was not modified during the treatment period. 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. Diagnosis of HTG or NTG was determined based on a complex ophthalmological and electrophysiological examination. No subject had any eye or systemic disease that could affect changes in the visual field. All patients had approximately the same changes in visual field at the beginning of the assessment. We included patients with HTG with approximately the same corneal thickness (568 and 544  $\mu$ m, respectively). No patient from the HTG group had CCT below 510 $\mu$ m. We made this selection because of the effect of corneal thickness on the changes in the visual fields in HTG (ref.<sup>6</sup>). Corneal pachymetry was performed with a Tomey SP-100 ultrasound device.

We did not find this effect in NTG. The visual field was examined by static perimetry, using a MEDMONT M 700 device with a fast threshold glaucoma program.

We evaluated PD and OD in HTG and NTG. The results of our previous study, where we found that PD was

statistically higher than OD in NTG (*P*=0.0001), led us to this. On the contrary, a statistically higher OD compared to PD was found in HTG (*P*=0.000) (ref.<sup>7</sup>).

## RESULTS

We used a two-selection t-test at the *P*<0.05 level for statistical processing – for prostaglandins with dispersion inequality and for beta blockers with dispersion equality.

All patients from the HTG-prostaglandin group were on latanoprost throughout the follow-up period. With regard to beta blockers, 7 were on carteolol, 3 on timolol and 23 on betaxolol.

In the NTG group, 5 were on betoptic and 5 carteolol, 11 on latanoprost, 2 on tafluprost and 1 on bimatoprost.

## DISCUSSION

In hypertensive glaucomas, the therapeutic effect on the visual field of beta blockers, prostaglandins and combination products has been demonstrated by numerous studies<sup>8-12</sup>.

Our results in HTG are also in compliance with the above-stated studies.

An indispensable finding of this study in HTG is that prostaglandins, although having a greater effect on the decline in IOP, do not have a protective effect on changes in the visual field. PD that is not as distinctive for HTG showed no statistically significant difference over time (*P*=0.35). However, OD that is approaching the limit of statistical significance in our patients (*P*=0.09) is more significant. We did not find a similar effect in beta blockers. PD (*P*=0.37), OD (*P*=0.23).

Mesmer et al. observed visual fields prior to administration of 0.5% timolol or 0.5% betaxolol, and, following that, at intervals of 3, 6, 12 and 18 months. The treatment effect on the visual field was better in the betaxolol-treated group than it was in the timolol-treated group (*P*=0.041) (ref.<sup>13</sup>).

Similar results were obtained by Kaiser et al., who followed 29 patients for three years. They found that the patients treated with betaxolol had significantly smaller

mean defects ( $P<0.05$ ) and higher mean sensitivities ( $P<0.05$ , Wilcoxon rank score test) than did the timolol-treated patients in months 3, 6, 12, and 18 (ref.<sup>14</sup>).

There are not many studies to evaluate only the progression of changes in the visual field in NTG. Tomita et al., who monitored IOP and visual field (mean defect), found that progression was greater after latanoprost  $-0.34\pm 0.17$  (dB/year) than timolol ( $-0.10\pm 0.18$ ). The differences were not statistically significant<sup>15</sup>.

Similarly, Krupin et al.<sup>16</sup> 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 suggest that brimonidine had a relatively protective effect on the visual field.

Hayreh et al.<sup>17</sup> reported 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 concluded 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.

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.

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

## CONCLUSION

Although the treatment of HTG and NTG is generally identical, our results show that prostaglandins and beta blockers have a similar effect in HTG. Beta blockers had a better protective effect on the visual field in HTG. In NTG, we found progression after prostaglandin administration, or in patients without treatment, in contrast to beta blockers, where changes in visual field were statistically insignificant. This conclusion also indicated a different pathogenesis of both diseases.

## ABBREVIATIONS

HTG, Hypertensive glaucoma; IOP, Intraocular pressure; NTG, Normotensive glaucoma; PD, Pattern defect; OD, Overall defect; VF, Visual field.

**Author contributions:** KM, JL, MF, IW: manuscript writing, final approval; KM, JL, MF: literature search, data analysis.

**Conflict of interest statement:** The authors state that there are no conflicts of interest regarding the publication of this article.

## REFERENCES

1. Chang EE, Goldberg JL Glaucoma 2.0: neuroprotection, neurodegeneration, neuroenhancement. *Ophthalmology* 2012;119:979-86.
2. Holmstrom S, Buchholz P, Walt J, Wickstrøm J, Aagren M. The cost-effectiveness of bimatoprost, latanoprost and timolol in treatment of primary open angle glaucoma in five European countries. *Curr Med Res Opin* 2006;22:897-913.
3. Stewart WC, Stewart JA, Mychaskiw MA. Cost-effectiveness of latanoprost and timolol maleate for the treatment of glaucoma in Scandinavia and the United Kingdom, using a decision-analytic health economic model. *Eye (Lond)* 2009;23:132-40.
4. Comparison of glaucomatous progression between untreated patients with normal-tension glaucoma and patients with therapeutically reduced intraocular pressures. *Am J Ophthalmol* 1998;126:487-97.
5. Vasudevan SK, Gupta V, Crowston JG. Neuroprotection in glaucoma. *Indian J Ophthalmol* 2011;59:102-13.
6. Lešták J, Rozsival P. The Influence of Corneal Thickness on Progression of Hypertensive Glaucoma. *J Clin Exp Ophthalmol* 2012;3:8. doi: 10.4172/2155-9570.1000245
7. Lestak J, Nutterova E, Bartosova L, Rozsival P. The Visual Field in Normal Tension and Hyper Tension Glaucoma. *IJSR* 2014;3:49-51.
8. Drance SM. A comparison of the effects of betaxolol, timolol, and pilocarpine on visual function in patients with open-angle glaucoma. *J Glaucoma* 1998;7:247-2.
9. Vainio-Jylhä E, Vuori ML. The favorable effect of topical betaxolol and timolol on glaucomatous visual fields: a 2-year follow-up study. *Graefes Arch Clin Exp Ophthalmol* 1999;237:100-4.
10. Araie M, Azuma I, Kitazawa Y. Influence of topical betaxolol and timolol on visual field in Japanese open-angle glaucoma patients. *Jpn J Ophthalmol* 2003;47:199-07.
11. Pajic B, Pajic-Eggspuehler B, Häfliger IO. Comparison of the effects of dorzolamide/timolol and latanoprost/timolol fixed combinations upon intraocular pressure and progression of visual field damage in primary open angle glaucoma. *Curr Med Res Opin* 2010;26:2213-9.
12. Garway-Heath DF, Crabb DP, Bunce C et. al. Latanoprost for open-angle glaucoma (UKGTS): a randomised, multicentre, placebo-controlled trial. *Lancet* 2015;385(9975):1295-304.
13. Messmer C, Flammer J, Stämpfig D. Influence of betaxolol and timolol on the visual fields of patients with glaucoma. *Am J Ophthalmol* 1991;112:678-81.
14. Kaiser HJ, Flammer J, Stämpfig D, Hendrickson P. Longterm visual field follow-up of glaucoma patients treated with beta-blockers. *Surv Ophthalmol* 1994;38(Suppl):156-9.
15. Tomita G, Araie M, Kitazawa Y, Tsukahara S. A three-year prospective randomized and open comparison between latanoprost and timolol in Japanese normal-tension glaucoma patients. *Eye* 2004;18:984-9.
16. Krupin T, Liebmann JM, Greenfield DS, Ritch R, Gardiner S. Low-Pressure Glaucoma Study Group. A randomized trial of brimonidine versus timolol in preserving visual function: results from the Low- Pressure Glaucoma Treatment Study. *Am J Ophthalmol* 2011;151:671-81.
17. Hayreh SS, Podhajsky P, Zimmerman MB. Beta-blocker eyedrops and nocturnal arterial hypotension. *Am J Ophthalmol* 1999;128:301-9.