EFFECT OF BETAXOLOL ON THE RETINAL CIRCULATION IN EYES WITH OCULAR HYPERTENSION: A PILOT STUDY

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SUMMARY

This study investigated the effect of betaxolol, a β1 selective blocker, on the retinal circulation in 10 patients with ocular hypertension. In a masked randomised fashion, one eye of each subject received betaxolol and the fellow eye received placebo (hypromellose). Retinal blood flow (RBF) was determined in a major temporal vein of each eye just prior to instillation of drops and 2 h later, using laser Doppler velocimetry and monochromatic fundus photography. There was an increase of 15.0% in RBF (p = 0.03) in the betaxolol-treated eyes. No significant change was observed in the placebo-treated eyes. Intraocular pressure was reduced by 27.7% in the treated eyes, resulting in an increase of 16.9% in perfusion pressure (p = 0.02) compared with an 8.4% increase in placebo-treated eyes (p = 0.15). This study demonstrated that betaxolol increases RBF in eyes with ocular hypertension; this increase is probably related to the increase in perfusion pressure.

Betaxolol, a β1 selective blocker, is a hypertensive agent which achieves its effect through a reduction in the rate of aqueous humour formation.[1] It is widely used in the management of glaucoma; however, its role in patients with ocular hypertension is less well defined.

Ocular hypertension is generally defined as an elevation of intraocular pressure (IOP) above 21 mmHg in the absence of optic disc cupping and detectable visual field loss. Long-term studies have shown that up to 10% of patients with ocular hypertension develop glaucomatous damage over a 10-year period.[2] There is no clear consensus among ophthalmologists whether these patients would benefit from having their IOP lowered as it is still unclear how raised IOP produces pathology in glaucoma. There are currently two hypotheses. The first, direct mechanical theory suggests that elevated IOP directly damages retinal nerve fibres at vulnerable sites in the optic disc. The second, ischaemic theory proposes that the raised IOP reduces ocular perfusion pressure thereby reducing ocular blood flow.[3] If one believes in the ischaemic theory, it would be reasonable to assume that drugs which increase the perfusion pressure at the disc would have a beneficial effect in patients with ocular hypertension in preventing the onset of glaucomatous damage. In addition optic nerve damage may occur secondary to a reduction in retinal blood flow (RBF) which could cause ischaemic damage to retinal ganglion cells and their axons which in turn constitute the optic nerve;[4] it is thus reasonable to study RBF in patients with ocular hypertension.

Grunwald[5] has shown that timolol maleate causes an increase in RBF in ocular hypertensive eyes. Timolol is a non-selective β-blocker; the effect of betaxolol, a selective β1 blocker, on the retinal circulation is unknown. The aim of this study was to investigate the effect of betaxolol on the retinal circulation in patients with ocular hypertension.

PATIENTS AND METHODS

Ten patients with documented IOP of 22 mmHg or greater on at least two occasions were studied. Two patients were diabetic; 1 of these had no diabetic retinopathy and the other had mild diabetic retinopathy. The other 8 subjects had no other medical or ocular conditions. No patient was receiving any topical or systemic medication (apart for the 2 diabetics, who were on insulin). Slit lamp and funduscopic examinations were normal. No visual field defect was demonstrated using the Humphrey field analyser 30-2 threshold programme. Informed, written consent was obtained from all subjects. The study was approved by the Research Ethical Committee of Hammersmith Hospital.

On the patient's arrival at the hospital, both eyes were dilated with tropicamide 1%; the studies were performed in early afternoon. The RBF was assessed with bidirectional laser Doppler velocimetry and monochromatic fundus photography. A straight segment of the superior or

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inferior temporal vein within 1 disc diameter of the optic disc margin was selected. Particular care was taken to note surrounding anatomical features so as to ensure that the same site was measured each time (see below for details). Polaroid fundus photographs were taken to mark the vessel site for reference. Brachial artery blood pressure and IOP were measured.

In a masked randomised design, one eye of each subject received two drops of betaxolol (Betoptic, Alcon Laboratories) topically, and the other eye received two drops of placebo (hypromellose 0.5%, Isopto Plain, Alcon Laboratories). After 2 h, RBF measurements, blood pressure and IOP were repeated. All measurements, before and after drops, were performed by the same observer. Subjects were asked to refrain from eating or drinking in the interim period.

Blood Flow Measurements

Bidirectional laser Doppler velocimeter (LDV) (Oculix, PA, USA) was used to determine red cell velocity in a retinal vein. LDV consists of a low-power helium–neon laser (wavelength 632.8 nm, irradiance 80 mW/cm^2) which can be focused onto a retinal vein via the illumination path of a Topcon TRC–JE fundus camera (Topcon, Osaka, Japan). The frequency of the laser light scattered by the moving red cells in the vessel is shifted in accordance with Doppler's principle by an amount proportional to the velocity of the red blood cells. Complete details of this method have been published.[6] Previous studies have shown that RBF is similar in the superior and inferior vessels and that a vein drains over 95% of blood supplied by its accompanying artery.[7] Veins rather than arteries were studied because they exhibit minimal pulsatility throughout the cardiac cycle, allowing a more accurate determination of the average velocity. Therefore, flow in a single temporal retinal vein is used as the measure of RBF.[8] The 95% confidence interval for the reproducibility of LDV has been found to be +8.9% to −8.9%.[9]

Vessel Diameter Determination

Monochromatic fundus photographs of the measured vein were taken with a Zeiss 30° fundus camera (Zeiss, Oberkochen, Germany) using Kodak technical Pan film (Kodak, Rochester, NY, USA) through a 570 nm red-free filter. The subjects were positioned to ensure that the vein to be measured was always in the centre of the photographic field; this was achieved with the aid of head rests and target fixation. The photographic negatives were transilluminated on a microscope stage and digitised by a video scanner onto a 512 × 512 pixel screen using a Context Vision image analysis computer (Context Vision, Linköping, Sweden). The site of LDV measurement is indicated by a cursor which cuts across the vessel perpendicularly. The computer then generates a transmittance profile of this site using the mean grey scale intensities from five loci distributed over 10 pixels on either side of the cursor. Background and peak intensity values of this profile are marked from which the computer determines the half-height; the width across the profile at its half-height is taken as the vessel diameter.[10] Vessel diameter was determined from three photographs, each measured three times. The coefficient of variation for this technique has been found to be 0.26%.[11]

Calculations

1. *Retinal Blood Flow*

LDV allows measurement of the maximal centre-line red cell velocity (V_{max}). Dividing V_{max} by 1.6 provides the mean red cell velocity (V_{mean}).[12] Volumetric retinal blood flow was calculated using the following formula:

$$Q = V_{mean} \cdot \pi \cdot D^2/4$$

where Q is blood flow, V_{mean} is mean red cell velocity and D is vessel diameter.

2. *Mean Arterial Pressure and Perfusion Pressure*

The mean arterial pressure (MAP) was calculated as:

$$MAP = 1/3\ (BP_{sys} - BP_{dia}) + BP_{dia}$$

where BP_{sys} is systolic blood pressure and BP_{dia} is diastolic blood pressure.

Retinal perfusion pressure (PP) was calculated by subtracting the IOP from two-thirds of the mean arterial pressure:[13]

$$PP = 2/3\ MAP - IOP$$

Statistical Analysis

The data were tested for normality using the Shapiro–Francia W' test of normality (Minitab Inc. 1989). As all results were normally distributed, further analyses using paired Student's t-test was performed. Regression analysis was used to assess the relationship between changes in blood pressure and IOP with the changes in blood flow parameters. Data are presented as the mean ± SD (unless stated otherwise) and a probability of 0.05 was considered to be statistically significant.

RESULTS

Clinical Data

The changes in mean arterial pressure, IOP and perfusion pressure before and after instillation of betaxolol are shown in Table I. There was no significant change in the mean arterial pressure after the drops. The average IOP decreased significantly by 27.7% in the betaxolol-treated eyes ($p = 0.0005$) and by 13.3% in the placebo-treated eyes ($p = 0.007$). This led to an increase in perfusion pressure of 16.9% in the betaxolol-treated eyes ($p = 0.02$). There was no significant change in perfusion pressure in the placebo-treated eyes ($p = 0.2$). There were no significant changes in systolic or diastolic blood pressure or mean arterial pressure ($p > 0.05$).

Haemodynamic Data

The values of vessel diameter, maximum red cell velocity (V_{max}) and retinal blood flow (RBF) before and after drops

Table I. Average mean arterial pressure (MAP), intraocular pressure (IOP) and perfusion pressure (PP) before and after drops (betaxolol or placebo)

	Baseline	2 h after drops	*p*	% change
MAP (mmHg)	99.30 ± 17.1	99.7 ± 20.7	0.9	0.2
IOP (mmHg)				
Placebo eye	24.4 ± 1.9	21.1 ± 2.9	0.007	−13.3
Betaxolol eye	25.1 ± 1.9	18.0 ± 3.3	0.0005	−27.7
PP (mmHg)				
Placebo eye	43.9 ± 9.0	47.3 ± 10.4	0.2	8.4
Betaxolol eye	43.2 ± 8.1	50.4 ± 11.4	0.02	16.9

Table II. Average diameter (D), red cell velocity (V_{max}) and retinal blood flow (RBF) before and after drops (betaxolol or placebo)

	Baseline	2 h after drops	*p*
Diameter (μm)			
Placebo eye	150.6 ± 34.3	152.4 ± 33.7	0.3
Betaxolol eye	156.4 ± 24.0	156.6 ± 23.3	0.9
V_{max} (cm/s)			
Placebo eye	2.3 ± 0.5	2.1 ± 0.5	0.09
Betaxolol eye	2.2 ± 0.5	2.4 ± 0.5	0.02
RBF (μl/min)			
Placebo eye	16.2 ± 7.7	14.9 ± 8.6	0.4
Betaxolol eye	15.7 ± 5.7	17.9 ± 6.7	0.3

are shown in Table II. V_{max} increased significantly by 13.7% ($p = 0.02$) after instillation of betaxolol. There was no significant change in the placebo-treated eyes ($p = 0.09$). No significant change was detected in the vessel diameter in either group ($p > 0.05$).

Betaxolol led to a 15.0% increase in RBF ($p = 0.03$); the placebo eyes showed no significant change ($p = 0.4$).

There was no correlation between perfusion pressure, IOP and mean arterial pressure with any of the blood flow parameters.

DISCUSSION

In this study, betaxolol increased ocular perfusion pressure by 16.9% due to a decrease in IOP. RBF in the betaxolol-treated eyes increased by 15%, principally from increased red cell velocity; there was no significant change in vessel diameter. The increase in red cell velocity is likely to have resulted from increased perfusion pressure. In contrast, the control eyes showed no significant changes in perfusion pressure, red cell velocity or RBF.

There have been conflicting reports on the effect of beta-blockers on retinal perfusion pressure and RBF. Chio and Chen,[14] studying normotensive and hypertensive rabbit eyes, reported increased RBF with D-timolol. Grunwald recently found an increase in RBF following timolol instillation in healthy subjects[15] and patients with ocular hypertension;[16] he postulated that timolol may affect the capacity of the retina to autoregulate blood flow, thus causing the RBF to increase passively with the increase in perfusion pressure.

Pillunat and Stodtmeister[17] found no change in ocular perfusion pressure in normal eyes treated with timolol or betaxolol, in spite of a significant decrease in IOP. The average IOP reduction in the betaxolol group was 2.1 mmHg; this small change in IOP meant that perfusion pressure was not altered significantly. In the present study the drop in IOP was far greater, which is to be expected as patients with ocular hypertension were studied. Wolf[18] demonstrated increased retinal perfusion pressure with timolol in healthy volunteers. They showed a reduction in IOP of 6 mmHg with no change in blood pressure resulting in increased retinal perfusion pressure.

The retinal vascular bed has been shown to maintain a constant RBF with increasing perfusion pressure of up to 40%.[19] This ability to maintain RBF in the face of changing perfusion pressure is called autoregulation. In the present study, RBF was found to increase by 15% in spite of a change in perfusion pressure of only 16.9%; this suggests an alteration in the autoregulatory capacity of the betaxolol-treated eyes.

Deficient autoregulation of RBF in open angle glaucoma has been reported by Grunwald *et al.*[20] They studied 11 patients with open angle glaucoma and 8 ocular hypertensives using the blue field entoptoscope and found that, in contrast with glaucoma patients, ocular hypertensives maintained the ability to autoregulate. Pillunat *et al.*[21] have similarly shown defective autoregualtion in both primary open angle glaucoma and normal tension glaucoma. The present study subjects had ocular hypertension; autoregulation in this group has not previously been shown to be abnormal. This is upheld by the lack of change in RBF in the control eyes in spite of a significant reduction in IOP. This suggests that autoregulation is preserved in our group of ocular hypertensives, and that betaxolol in some way interferes with the autoregulatory capacity.

It is generally accepted that retinal vessels are not innervated; however, these vessels have been shown to express α1, α2, β1 and β2 adrenergic receptors.[22,23] The exact function and localisation of these receptors are not known. Martin and Rabineau[24] demonstrated that timolol constricted retinal arteries by 4% compared with the untreated contralateral eye. In contrast, Kelly-Hester *et al.*[25] have recently demonstrated that betaxolol possesses a vasorelaxant effect similar to calcium channel blockers. The present study demonstrated no change in retinal venous diameter; it is possible that betaxolol has a direct vasodilatory effect on the small, resistance arteries. If these vessels, which are the principal autoregulators, are partially dilated from a direct effect of betaxolol, it would limit their autoregulatory capacity to prevent an increase in RBF from increased perfusion pressure. Likewise betaxolol may also have an effect on the adrenergic receptors demonstrated on retinal vessels. It is possible that this may also affect their autoregulatory capacity.

The control eyes showed a small decrease in red cell velocity and RBF, though neither was statistically significant. It has been found in some systemic vessels that sometimes when perfusion pressure decreases, RBF occasionally increases and vice versa, i.e. the regulation is overefficient. This phenomenon of 'super-regulation' may explain our findings in the control eyes.

This study has shown that betaxolol increases RBF in

eyes with ocular hypertension. This is likely to result from increased perfusion pressure, aided by possible betaxolol-induced alteration of autoregulatory capacity. This may be beneficial in ocular hypertensive eyes for the following reasons: firstly, if the ischaemic theory is true, increased RBF should prevent the development of glaucomatous damage in these patients. Secondly, these eyes are known to be at risk of developing retinal venous occlusions, and an increase in RBF may be beneficial. Its effect on autoregulation needs to be studied further, as deficient autoregulation may be part of the pathological mechanism in glaucoma.

In conclusion, this pilot study shows that in eyes with ocular hypertension, topical betaxolol produces an increase in blood velocity and blood flow. Its clinical application needs to be evaluated further.

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Key words: Autoregualtion, Betaxolol, Glaucoma, Ocular hypertension, Retinal blood flow.

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