Influence of Latanoprost on Retinal Microcirculation in Glaucoma

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Abstract: *Purpose*: To test whether latanoprost has an influence on ocular haemodynamics, considering the general reputation of prostaglandins which is frequently associated with vasoconstriction. The effect of latanoprost on the retinal blood supply of treatment-naïve glaucoma patients was tested.

Materials and Methodology: 13 patients (7 male, 6 female) who had just recently been diagnosed with primary open-angle glaucoma (POAG) were treated with latanoprost (0.005%). The average age of our study group was 63.8 years (+/- 2.9 years).

The drug's effect on retinal autoregulation was assessed by flicker test using the Dynamic Vessel Analyzer (DVA). Examinations took place before initializing treatment, after 4 weeks and once again after 4 to 6 months.

Results: In our group of POAG patients, the IOP under treatment was significantly reduced about 25%. No intraindividual differences in systemic blood pressure and heart rate were observed. In DVA measurements of glaucoma patients, the maximum flicker dilation of the arteries was significantly lower than reported for healthy volunteers. Beyond that, POAG patients did not show significant differences in vessel diameters, peak amplitudes as well as maximum dilations of retinal arteries and veins before and under treatment with latanoprost (0.005%).

Conclusion: Latanoprost markedly lowered the IOP but it did not exert a significant effect on retinal haemodynamics. There was neither a tendency towards vasoconstriction nor towards vasodilation. Sustaining reperfusion damage after topical latanoprost therapy thus seems to be highly unlikely. Further studies must show if sole IOP lowering or a dual positive effect – IOP lowering and improvement of retinal vessel autoregulation – have a more positive impact on the long term follow-up of glaucoma patients.

Keywords: Autoregulation, dynamic vessel analyzer (DVA), glaucoma, haemodynamics, latanoprost, vascular dysregulation.

INTRODUCTION

Glaucoma is an optic neuropathy caused by retinal ganglion cell loss leading to typical morphological changes and subsequently to an impaired visual function. While an elevated intraocular pressure (IOP) is regarded as a major risk factor for many though by far not for all cases of glaucoma, there are other contributors to glaucomatous damage as well. Disturbances of the ocular blood flow have been described as an important pathogenetic factor, either as an IOP-independent entity - like the manifestations of a systemic vascular abnormality - or as a result of an elevated intraocular pressure [1]. Low ocular perfusion pressure, caused by high IOP, reduces blood flow due to low systemic blood pressure or a combination of both. It is associated with the onset and the progression of glaucomatous damage [2]. There is accumulating evidence for a multifactorial pathogenesis of glaucomatous optic neuropathy with special emphasis on vascular risk factors. Vascular problems must be suspected particularly in those patients who never have an increased IOP even in 24 h profile measurements corrected for corneal thickness but who nevertheless suffer from glaucomatous optic nerve damage.

While the measurement of IOP is easy, reliable and has been the mainstay of diagnostics in glaucoma for more than a century, another important factor influencing the ocular perfusion pressure has been much more difficult to evaluate: the haemodynamics of the retinal vessels. Only recently, a reliable method to measure and analyze the behaviour of retinal vessels *in vivo* has been developed: the Dynamic Vessel Analysis (DVA) which will be described later.

The primary aim of our current concept of glaucoma therapy is the lowering of intraocular pressure. The rationale behind this strategy which is pursued by administering IOP-

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1874-3641/14 2014 Bentham Open

lowering drugs topically or by surgical intervention is both to reduce "mechanical" pressure on the optic nerve head (a concept which dates back at least to the mid-19th century) and to increase the ocular perfusion pressure by lowering the resistance caused by the IOP. A decreased ocular perfusion pressure is associated with open-angle glaucoma and can be a result of an elevated IOP or acts – particularly in patients with nightly blood pressure dips, sleep apnea syndrome and vascular dysregulations – as an independent risk factor [3, 4]. There is data indicating that reduction of IOP by pharmacological intervention improves optic nerve head blood flow regulation independently of an ocular vasodilator effect [5].

Whereas an increase of ocular perfusion pressure and thus a better blood supply of the optic nerve head and the retina is an aim of successful pharmacological glaucoma therapy, a negative influence of the drug on ocular haemodynamics is not wanted for an antiglaucomatous agent [6]. Almost immediately after their introduction into glaucoma therapy 20 years ago, prostaglandins and their pioneer substance, latanoprost, have become one of the most widely prescribed antiglaucomatous monotherapies in most industrialized countries.

Prostaglandins in general are frequently associated with vasoconstriction, a property that is put to good therapeutical use in some fields of medicine such as, for example, stop of difficult bleedings in obstetrics. *In vitro*, latanoprost also induces vasoconstriction in isolated ocular vessels [7]. It was the goal of our study to find out whether latanoprost has a detrimental effect on the retinal blood vessels of newly diagnosed, hitherto untreated glaucoma patients.

MATERIALS AND METHODOLOGY

We recruited 13 consecutive patients who had only recently been diagnosed with bilateral primary open-angle glaucoma. None of them had received any antiglaucomatous treatment so far. 7 patients were male, 6 patients were female; the average age of our study group was 63.8 years (+/- 2.9 years).

All had significant morphological glaucomatous damage both to the optic nerve head and the visual fields. Damage was documented by optic nerve head photography and optical coherence tomography of the optic disc (FD-OCT 2000, Topcon, Japan), retinal nerve fiber layer analysis by scanning laser polarimetry (GDx Pro, Carl Zeiss Meditec, Dublin, USA) and automated perimetry (Octopus, Interzeag, Switzerland or Twinfield, Oculus, Germany).

Exclusion criteria were:

- history of glaucoma treatment
- history of severe eye diseases and especially
- vascular eye diseases
- history of eye surgery besides uncomplicated cataract surgery
- myopia or hyperopia of more than 3.0 diopters
- astigmatism of more than 3.0 diopters
- unregulated arterial hypertension
- diabetes mellitus

During the study period, systemic medications - if given - were not to be changed.

A first examination took place before treatment was started. It consisted of determining the refraction, visual acuity, slit-lamp examination, corneal thickness, tonometry, binocular funduscopy, fundus photography, perimetry, GDx, spectral OCT and dynamic vessel analysis (DVA). Similar follow-up examinations with an emphasis on tonometry, DVA and funduscopy were repeated after 4 weeks of treatment (visit 1) and again after 4-6 months (visit 2) of therapy, each including a patient report on possible side effects. The patients were treated on both eyes with latanoprost eye drops (0.005%, 50 µg/ml, Pfizer, USA), administered once daily.

To evaluate the drug's effect on retinal vessel changes and autoregulation, we used the Dynamic Vessel Analyzer (Imedos, Jena, Germany).

The DVA combines high end retinal imaging with dynamic and static vessel analysis for examination of vessel state and function. The basis of DVA is given by online measurements of vessel diameters along the vessels and in relation to time by analyzing retina image sequences. The time resolution amounts to 40 ms, lateral resolution is possible down to 10 µm and the measuring resolution is smaller than 1 µm (Retinal Vessel Analyzer, RVA).

For examination of vessel functions and autoregulative behaviour different kinds of provocation or stimulation of retinal microcirculation can be used and vessel response is recorded and evaluated. Flickering light stimulation is the standard stimulation of the DVA.

Vessel parameters are calculated by use of the measured diameters. Vessel parameters describe vascular and autoregulative functions or dysfunctions and enable the physician to detect microvascular risks. Examinations by DVA can quantify the vascular course of diseases or vascular treatment effects. The technology of the Retinal Vessel Analysis has recently proven its value in different eye diseases like glaucoma and diabetic retinopathy.

The flicker light induces diameter changes on the retinal vessels which are recorded over time for all segments of the selected vessel. Flicker-evoked dilation of retinal arteries measured by the DVA has proven to be a parameter that is suitable as a functional parameter of the regulation ability of retinal arteries [8]. Nguyen *et al*. have demonstrated the high reproducibility of DVA for repeated measures over a short period of time on a study group of 33 healthy subjects. The authors reached the conclusion that such measurements may allow non-invasive quantification of endothelial function to study its association with systemic and ocular diseases [9]. A general overview of the use of DVA in research, in a clinical setting, and informed guidelines for its use are given by Garhofer *et al*. [10]. The disturbed dynamics of retinal vessel response and especially the diminished vasodilation of retinal veins in glaucoma patients measured by Retinal Vessel Analysis [11] at increased intraocular pressure have been described recently [12, 13].

After the measurement procedure, the software of the DVA provides several vessel parameters:

- initial baseline value for the width of artery and vein given in measuring units (MU); 1 MU = 1 µm if the eye is fulfilling the conditions of the Gullstrand normal eye. For many eyes this is not the case and interindividual aberrations must be expected. Therefore, no absolute values are given but the term measuring units (MU) is introduced allowing an intraindividual comparison.
- maximum dilation (as % of the initial baseline) of artery and vein during flicker stimulation
- maximum constriction after flicker stimulation
- peak amplitude (difference between dilation and constriction of artery)

Statistical analysis was performed with ANOVA and Bonferroni post-hoc test. $P < 0.05$ was considered the level of significance.

The study was approved by the ethics committee of the Landesärztekammer (LÄK) Münster, the official medical association of the region Westfalen-Lippe, Germany, and each patient gave informed consent according to the declaration of Helsinki.

RESULTS

26 eyes of 13 patients were included in the evaluation. At the beginning of the study, before starting the treatment with latanoprost, average IOP of the glaucoma patients was 22.8 +/-1.0 mm Hg. At the time of visit 1 and visit 2, IOP was significantly ($p<0.01$) reduced by about 25% (visit 1: 17.2 +/- 0.6; visit 2: 17.1+/- 0.6 mm Hg). There was no change of intraocular pressure between visit 1 and visit 2 (Fig. **1a**).

Besides a slight reddening no side effects of the drug were observed or reported.

There was no significant difference in systolic and diastolic arterial blood pressure or heart rate at the three examinations (Table **1a**).

Using DVA, we measured flicker-evoked responses. The maximum dilations of the retinal artery and vein as well as the peak amplitude in both eyes were determined. As an example, the maximum dilation of the artery after flicker stimulation is shown in Fig. (**1b**) at the different time points.

None of these three parameters showed any significant change after the application of latanoprost (Table **1b**).

Additionally, the initial baseline values of artery and vein (ME) did not deviate significantly before and under latanoprost treatment (Fig. **1c**) i.e. we could not observe evident vasoconstriction or vasodilation in glaucoma patients.

Beyond this, it is worth mentioning that the maximum dilation of the arteries at all visits is significantly reduced in comparison to values reported for healthy volunteers.

DISCUSSION

Our results, based on 26 eyes of 13 glaucoma patients, did not reveal a major impact of topical glaucoma therapy with latanoprost on retinal haemodynamics. Despite pronounced IOP lowering of about 25% there was no significant change in retinal vessel diameter or response capacity to increased demand provoked by flicker light.

In earlier studies we could show that surgical interventions such as trabeculectomy and cyclophoto-coagulation have a positive influence on the autoregulative behaviour of retinal vessels. In a group of 26 patients with POAG, an IOP reduction achieved by trabeculectomy led to a distinct increase of dilation capacity in the retinal vessels of most patients. The results suggest that lowering IOP in glaucoma patients improves the reduced retinal vascular dynamics and thus the blood supply of the retinal nerve fiber layer [14].

In a different study [15], we could demonstrate that cyclophotocoagulation (CPC) has a similar effect on retinal perfusion. In a group of 26 patients with advanced glaucoma, laser treatment led not only to an average IOP reduction of about 20% but also to an increase in retinal haemodynamics. Most significant was the ability of the retinal arteries to react with a much more pronounced dilation on flicker light provocation after CPC compared to the pre-operative status [15].

In the last years, dynamic vessel analysis (DVA) has emerged as a helpful tool in measuring retinal blood vessel diameters and their reaction on flicker light provocation to detect disturbances in the autoregulation of retinal vessels. Dynamic Vessel Analysis is considered to have a high diagnostic potential not only in glaucoma, retinal vascular occlusive disease and diabetic retinopathy but also for clinical interdisciplinary cooperation in the field of systemic vessel diseases. Its value for the screening of vasosclerosis and in the diagnostics of arterial hypertension has also been discussed [16]. The benefit of using retinal vessel analysis to monitor a given treatment has been described in cases of systemic therapy [17]. In glaucoma patients, we could show an improved vascular response to IOP lowering in separate studies [14, 15], in which we performed trabeculectomy and cyclophotocoagulation as surgical procedures to reduce IOP. A similar beneficial effect of pharmacological IOP reduction seems to be obvious.

A negative impact of an antiglaucomatous agent on retinal perfusion would be detrimental to the therapeutic strategy. On the other hand, a sudden increase in a previously reduced ocular perfusion – for instance by a too extensive IOP reduction with a high subsequent increase of ocular perfusion pressure – might be avoided as well: some experienced glaucoma researchers have issued warnings of what they call reperfusion damage in glaucoma [18]. Beyond the mechanical damage due to an increased IOP, the fluctuation of both the intraocular pressure and the blood pressure with its characteristic drops, particularly in patients with systemic vascular dysregulation, may lead to short term ischemia, followed by reperfusion damage [19].

Therefore, Zeitz *et al*. postulated that an IOP lowering substance for glaucoma therapy should be at least neutral with regards to the ocular blood supply. Their group assessed the ocular haemodynamics of glaucoma patients who were treated with either latanoprost, bimatoprost or dorzolamide. Primary end-points were the peak systolic and end-diastolic blood flow velocities in the short posterior ciliary artery

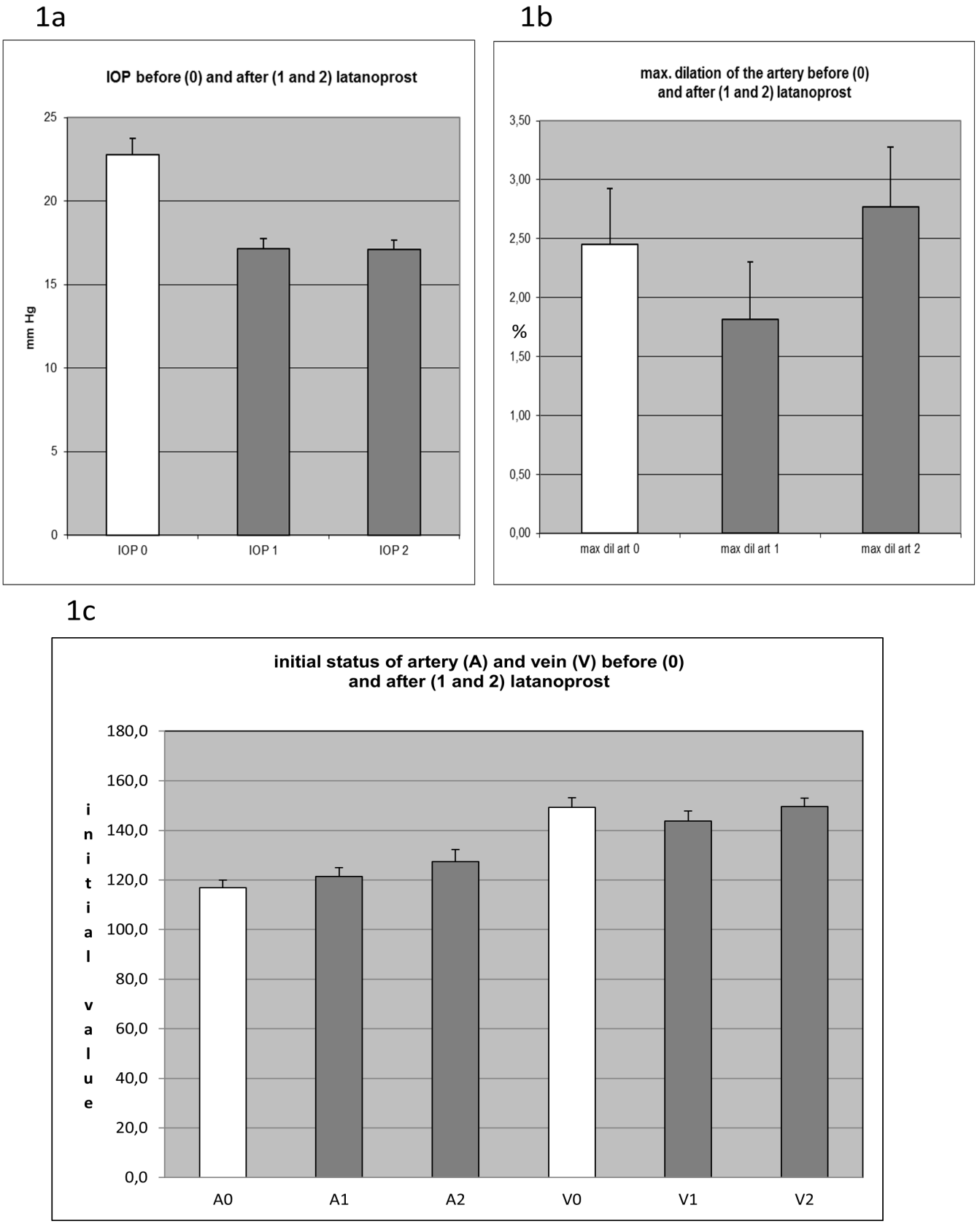

Fig. (1). (**a**) Intraocular pressure before (0) and after (1 and 2) beginning of the treatment with latanoprost; highly significant ($p<0,01$) reduction of IOP by approximately 25%. Bars show mean +/- SEM. (**b**) Maximum dilation of the retinal artery (in %) as measured by DVA after flicker stimulation before (0) and after (1 and 2) beginning of the treatment with latanoprost (+/- SEM); non-significant changes. (**c**) Initial baseline value for the width of artery (A) and vein (V) given in measuring units (MU) assessed by DVA preceding flicker stimulation before (0) and after (1 and 2) beginning of the treatment with latanoprost (+/- SEM); non-significant changes.

Table 1a. Arterial blood pressure and heart rate at the different visits; non-significant changes.

	Visit 0	Visit 1	Visit 2	
Systolic RR	137.3 +/- 4.3	136.9 +/- 2.7	134.6 +/- 2.9	**ns**
Diastolic RR	83.5 +/-1.9	82.3 +/- 1.6	81.9 +/- 1.2	**ns**
Heart rate	70.0 +/- 2.4	70.9 +/- 2.3	73.2 +/-2.6	**ns**

Table 1b. Measurement results of DVA after flicker stimulation before (visit 0) and after beginning of latanoprost therapy (visit 1 and 2); non-significant changes.

	Visit 0	Visit 1	Visit 2	
Max. dilation artery	2.9 +/- 0.5%	1.8 +/- 0.5%	2.8 +/- 0.5%	**ns**
Max. dilation vein	3.6 +/-0.5%	3.3 +/- 0.6%	2.8 +/- 0.5%	**ns**
Peak	2.9 +/- 0.6%	2.1 +/- 0.6%	2.6 +/-0.4%	**ns**

using color Doppler imaging. While dorzolamide accelerated systolic blood flow (without any discernible negative impact), both latanoprost and bimatoprost acted in a haemodynamically neutral manner and had the potential to lower IOP even in patients with normal-tension glaucoma and in those patients with a relatively low initial IOP level [6].

As our present data – which confirm the results of Zeitz *et al*. by using a completely different technology - could establish, latanoprost does not worsen the regulative capacity of retinal vessels on flicker light provocation which is increasing the demand of the surrounding tissue and it does not negatively influence ocular perfusion parameters. Vice versa, however, it also does not *positively influence* retinal autoregulation despite the lowering of IOP.

Our finding that IOP lowering alone by surgery or laser treatment causes a marked improvement of retinal vessel reaction [14, 15] whereas a therapy with latanoprost reveals no significant change of vessel response to flicker light provocation may indicate that the positive effect of IOP lowering may be egalized by a possible vasoconstructive component of latanoprost therapy [7].

Interestingly, Kringelholt and coworkers could show a dual effect of prostaglandins on isolated intraocular porcine ciliary arteries. Whereas prostaglandins PGD2 and PGE2 with affinity to DP1 and EP4 receptors induce relaxation at low concentrations, all tested prostaglandins (PGF2α, PGD2, PGE2, PGI2 and the thromboxane analogue U46619) induced contractions at high concentrations which could be inhibited by blocking the TP receptor [20].

Furthermore, Kringelholt and coworkers found that contractions in intraocular porcine arteries are mediated by α2-adrenoceptors and NPY1 receptors and can be concentration-dependently inhibited by PGE2 acting on prejunctional EP4 receptors but not by an EP1 receptor antagonist [21].

In a recent study on 24 healthy volunteers, the ocular perfusion pressure was manipulated by applying a suction cup to artificially increase IOP. The Austrian study group's data indicated that latanoprost improves choroidal blood flow regulation during both an increase and a decrease in ocular perfusion pressure. Since latanoprost did not affect baseline choroidal blood flow, this effect was regarded as a consequence of latanoprost's ability to significantly decrease IOP and less as an independent vascular effect of the drug [22].

It is well documented that among all current antiglaucomatous drugs, carbonic anhydrase inhibitors (CAI) are the most likely to enhance ocular blood flow by, for instance, decreasing the resistance index in the ophthalmic and short posterior ciliary arteries [23]. Using the suction cup method to artificially increase the IOP during RVA measurements, Nagel, Vilser, and Lanzl reported on a decreased arterial diameter in glaucoma eyes and a significant increase after dorzolamide treatment [24].

Januleviciene and coworkers compared dorzolamide and timolol as add-on therapy to latanoprost in glaucoma patients and found in both an additional IOP lowering effect but dorzolamide showed lower fluctuations in IOP, systolic perfusion pressure and blood pressure. They observed that higher variability of ocular perfusion pressure led to impaired retrobulbar blood flow [25].

In a Japanese study, the combined treatment of latanoprost with carteolol, a beta blocker, was associated with an increased ocular nerve head blood flow [26], whereas a double-masked randomized crossover study from Austria showed an equally effective reduction of IOP but no significant effect on ocular blood flow parameters assessed by laser Doppler flowmetry and color Doppler imaging after 6 weeks of treatment and washout with the combinations Latanoprost/Timolol versus Brimonidin/Timolol [27]. In 27 previously untreated patients with primary open-angle glaucoma, the dorzolamide-timolol fixed combination and latanoprost were administered. Both the combination and latanoprost increased diastolic ocular perfusion pressure, the latter by not effecting diastolic blood pressure and significantly reducing IOP [28].

In a study comparing three different prostaglandins, both latanoprost and travoprost significantly reduced the resistance index of the ophthalmic and the central retinal artery [29].

A Japanese publication showed in 14 myopic patients with normal tension glaucoma and 10 myopic patients without glaucoma 30 to 120 minutes after topical tafluprost administration a significant IOP reduction and an increased mean blur rate in laser speckle flowgraphy [30]. These findings may be a hint in the direction of a positive dual effect of tafluprost but only a small myopic subgroup was enrolled with a short follow-up [30].

In a group of 22 patients with normal tension glaucoma, latanoprost did not effect the ocular perfusion pressure or the blood pressure [31]. A swiss study, however, concluded that latanoprost is effective in normal tension glaucoma as well by lowering IOP and improving the pulsatile ocular blood flow [32]. But these measurements are mainly providing informations on the blood supply of the choroid without autoregulation and only to a small extent on the vessels of the retina and the optic nerve head with autoregulation.

Although the size of our patient group (n=13) is relatively small but homogeneous the results are statistically solid enough to reach the conclusion that topical therapy with latanoprost in glaucoma patients without other vascular eye disease and without major systemic cardiovascular disease (besides treated arterial hypertension) has no significant impact on retinal microcirculation by means of DVA measurements. This fact contributes to the widely accepted safety profile of prostaglandin analogues in glaucoma therapy. The non-interference of an antiglaucomatous drug may be particularly welcome in patients whose blood circulation and general cardiovascular health act as an independent risk factor for ganglion cell death as e.g. in some individuals with arterial hypotension.

Long-time follow-up studies have to show if glaucoma patients have a greater benefit from an intraocular pressure lowering therapy by surgery or laser which leads to an improved dilation of retinal vessels on metabolic demand [14, 15] but which carries with it the danger of reperfusion damage or whether a topical treatment with drugs like latanoprost that does not alter vessel reaction in a statistical significant way is to be preferred. An alternative may be topical IOP lowering drugs with dual effect – IOP lowering and improvement of ocular blood supply [24, 25, 29, 30].

CONCLUSION

Despite IOP lowering, Latanoprost did not exert a significant effect on retinal haemodynamics. There was neither a tendency towards vasoconstriction nor towards vasodilation. Sustaining reperfusion damage after topical latanoprost therapy thus seems to be unlikely, a fact that adds to the known safety profile of this widely used antiglaucomatous treatment option.

Further studies must show if sole IOP lowering or a dual positive effect – IOP lowering and improvement of the regulative response of retinal vessels on demand – have a more positive impact on the long term follow-up of glaucoma patients.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. The only exception is Walthard Vilser who is CEO of IMEDOS Systems UG, Germany.

ACKNOWLEDGEMENTS

Supported by Ernst und Berta Grimmke-Stiftung, Vogelsanger Weg 49, 40470 Düsseldorf, Germany.

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Received: July 17, 2014 Revised: July 21, 2014 Accepted: July 21, 2014