Original

Color Doppler Imaging of Retrobulbar Hemodynamics after Topical Carteolol in Normal Tension Glaucoma

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Background. Carteolol is a nonselective adrenergic blocking agent. The aim of this study was to evaluate the effect of topical carteolol on retrobulbar hemodynamics in patients with normal tension glaucoma (NTG).
Methods. Twelve NTG patients received twelve-week topical treatment of 2% carteolol. Color Doppler imaging (CDI) was used to evaluate the hemodynamic effects before and after drug therapy. Measurements were obtained from the central retinal artery (CRA), the lateral posterior ciliary artery (LPCA) and the medial posterior ciliary artery (MPCA). From each vessel, peak systolic velocity (PSV), end-diastolic velocity (EDV), resistance index (Rl) and Gosling's pulsatility index (PI) were collected and analyzed.
Results. After topical carteolol treatment for twelve weeks, mean resistance index reduced significantly from 0.83 to 0.74 in the CRA (p = 0.03), from 0.74 to 0.68 in the LPCA (p = 0.09). Moreover, mean pulsatility index of the LPCA decreased from 1.45 to 1.26 (p = 0.08).
Conclusions. Twelve weeks of 2% carteoiol treatment may decrease the vascularresistance in NTG patients possibly due to the intrinsic sympathomimetic activity (ISA) of carteolol.
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Normal tension glaucoma is characterized by glaucomatous optic disc cupping, visual field loss in eyes, and consistently normal intraocular pressure (< 21 mmHg) without any other intraocular lesion. The pathogenesis of NTG is still uncertain. Reduced ocular perfusion and hence slow ongoing chronic ischemia of the optic nerve head may give rise to a pale-cupped disc. Those evidences supporting the vascular mechanism include: optic disc hemorrhage,[1] the association with migraines,[2] and spasms of peripheral vessels.[3] Beta-blockers develops specifically as ocular hypotensive agents unquestionably do decrease intraocular pressure. In contrast, their vascular effect on ocular hemodynamics remains controversial.[4,5]

Carteolol hydrochloride is a nonselective beta-adrenergic antagonist with intrinsic sympathomimetic activity (ISA), which is the ability of a drug to partially activate beta-receptors in the absence of catecholamines.[6] In the field of cardiology, ISA has been studied with therapeutic potential to decrease vascular resistance.[7,8] Theoretically, topical carteolol could be expected to decrease vascular resistance and increase ocular blood flow. However, the exact influence of ISA on retrobulbar hemodynamics is not well understood.

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Color Doppler ultrasound imaging allows real-time B-scan ultrasound imaging of anatomic structures in the orbit, displaying superimposed color-coded Doppler frequency shifts resulting from blood flow. Blood flow velocities of the extraocular vessels can then be localized and measured.[9,10] Using this noninvasive technique, we studied the effects of topical carteolol on ocular circulation in twelve patients with NTG.

Methods

Twelve NTG patients (nine male and three female) were recruited for the study. All patients had visual defects in one or both eyes, bilateral glaucomatous optic disc cupping, open anterior chamber angles indicated by gonioscopy, and intraocular pressure less than 21 mmHg with normal diurnal curve measurements. Excluded criteria were history of significant renal or liver disease, bradycardia, congestive heart failure, cardiac conduction defects, reactive airway disease, stroke, and poorly controlled diabetes. Those under systemic beta- adrenergic blockers, alpha-adrenergic agonist or calcium channel blockers were also excluded. Ophthalmic exclusion criteria were history of ocular trauma or surgery, diabetic retinopathy and use of any other anti-glaucomatous medication.

Informed consent was obtained after a full briefing with each patient. Patients were scheduled for a baseline visit between 8 AM and 10 AM, for the procedures including: general ophthalmic examination, intraocular pressure by Goldmann applanation tonometry, blood pressure, and heart rate with digital electronic sphygmomanometry. The averages of three measurements were recorded. After the initial visit, patients were treated with 2% carteolol (Arteoptic, Otsuka Co., Japan); one drop in each eye twice daily for 12 weeks. Patients were asked to return every four weeks at the same time of the day to have the same measurements.

Color Doppler imaging was performed at the initial visit and 12 weeks later. A high-resolution ATL HDI 3000 scanner (Advanced Technology Laboratories, Bothell, Washington, USA) with a 7.5 MHz linear phase transducer was used for Doppler imaging. An experienced ultrasonographer (H.J.C.) performed all the Doppler procedures. During the examination, subjects were in the supine position, with the head tilted forward at about a 30-degree angle. The transducer was applied gently to the closed eyelid using a coupling gel, and care was taken to avoid applying any pressure to the eye.

The central retinal artery (CRA) can be depicted within the anterior part of the optic nerve shadow, about 2 to 3 mm behind the disc surface.[9] Temporal and nasal from the optic nerve shadow, the lateral posterior ciliary artery (LPCA) and medial posterior ciliary artery (MPCA) can be identified. Characteristic Doppler spectra can be obtained from the posterior ciliary arteries with higher diastolic flow velocities because of the low resistance in the choroid supplied.[9,10]

From each vessel, peak systolic velocity (PSV) and end-diastolic velocity (EDV) were defined and recorded. The resistance index (peak systolic velocity minus end-diastolic velocity divided by peak systolic velocity), according to the method of Poucelot[11] and Gosling pulsatility index (peak systolic velocity minus end-diastolic velocity divided by mean velocity),[12] were calculated for each vessel. One eye was selected from each patient for analysis. The paired *t*-tests were used to compare blood flow velocities, resistance indices, blood pressure, heart rate and intraocular pressure before and after drug treatment. A p value less than 0.05 were regarded as statistically significant.

Results

Twelve NTG patients included nine males and three females with mean age 67 years (range 58-76 years). The effects of topically administered 2% carteolol on systemic blood pressure, heart rate and intraocular pressure were studied (Table 1). After three months of treatment, no statistically significant differences in systolic pressure, diastolic pressure and heart rate were noted. The mean intraocular pressure reduced from 15.2 to 14.0 mmHg, which was statisti-

Table 1. Comparison of blood pressure, heart rate and intraocular pressure (means ± SD) in normal tension glaucoma patients before and after 2% carteolol treatment

	Carteolol 2%		
	Baseline	12 week	*p* value
Blood pressure (mmHg)			
Systolic	146.6 ± 27.8	141.8 ± 21.9	0.329
Diastolic	83.5 ± 12.9	80.2 ± 9.8	0.226
Heart rates (beats/min)	69.5 ± 7.5	68.5 ± 12.2	0.797
Intraocular pressure (mmHg)	15.2 ± 1.7	14.0 ± 1.79	0.071

Table 2. Comparison of blood flow parameters (means ± SD) in normal tension glaucoma patients before and after 2% carteolol treatment

	CRA			LPCA			MPCA		
	Baseline	12W	*p* value	Baseline	12W	*p* value	Baseline	12W	*p* value
PSV(cm/s)	8.30 ± 2.42	7.94 ± 2.41	0.499	8.75 ± 2.45	8.48 ± 3.10	0.696	9.07 ± 3.21	9.34 ± 3.70	0.730
EDV(cm/s)	1.54 ± 1.31	1.62 ± 1.06	0.781	2.28 ± 1.40	2.44 ± 1.22	0.610	2.50 ± 2.00	2.67 ± 1.10	0.675
RI	0.83 ± 0.13	0.74 ± 0.19	0.030	0.74 ± 0.13	0.68 ± 0.11	0.090	0.73 ± 0.14	0.71 ± 0.09	0.317
PI	1.80 ± 0.72	1.71 ± 0.64	0.473	1.45 ± 0.37	1.26 ± 0.25	0.081	1.42 ± 0.56	1.34 ± 0.29	0.103

CRA = central retinal artery; LPCA = lateral posterior ciliary artery; MPCA = medial posterior ciliary artery; PSV = peak systolic velocity; EDV = end-diastolic velocity; RI = resistance index; PI = pulsatility index.

cally significant ($p = 0.007$) (Table 1).

As shown in Table 2, the PSV and EDV were not altered after topical carteolol treatment for twelve weeks in any of the three vessels studied. Mean resistance index reduced significantly from 0.83 to 0.74 in the CRA ($p = 0.03$). The reduction was also seen in the LPCA from 0.74 to 0.68 ($p = 0.09$). Moreover, mean pulsatility index of the LPCA decreased from 1.45 to 1.26 ($p = 0.08$).

Discussion

Color Doppler imaging allows information about the flow of blood to superimpose in color on B-mode gray-scale ultrasound image, which enables direct visualization of specific vessels to interrogate to produce a specific spectrum. Using the color image as a guide, the Doppler analysis can quantitatively assess some ocular blood flow parameters- PSV, EDV, RI and PI to evaluate the blood flow in the ophthalmic, ciliary and central retinal arteries for normal and glaucomatous subjects. Previous studies have shown that patients with glaucoma have lower blood flow velocities and higher resistance indices in their retrobulbar vessels compared with normal control subjects.[13,14]

CDI was used by Butt et al.[15] to compare 34 NTG patients with 17 controls. The PI of the ophthalmic artery in the NTG patients was significantly less than in the control group. There was a significant increase in RI of both ophthalmic and central retinal arteries in the NTG group compared with the normal controls. In a similar study, Ranking et al. showed in NTG patients a statistically significant decrease in mean EDV and an increase in mean RI in all vessels studied, most prominently in the central retinal arteries.[16] These results suggest an increased resistance to blood flow in the ophthalmic and central retinal arteries of NTG patients.

In patients with NTG, progressive nerve fiber layer damage and loss of visual function occur despite their normal intraocular pressure. Because both me-

chanical and vascular factors may contribute to NTG, current therapies should be carefully evaluated for both hypotensive and vasorelaxant effects. Topical beta-adrenergic antagonists are widely used for glaucoma therapy. Its vasoconstrictive effect was demonstrated as increased vascular resistance[17,18] and reduction in the pulsatile ocular blood flow.[19] The mechanism responsible for the vasoconstriction of the peripheral circulation of beta-blockers might be an unopposed alpha-vasoconstriction.[20] Concerning the eye, vasoconstriction is presumably due to the blockage of beta-receptors which have shown to exist in the human choroids,[21] anterior optic nerve and optic nerve head,[22] and retina.[23] Carteolol binds to both beta-1 and beta-2 adrenoceptor subtypes and also acts as a partial agonist. Thus its partial agonist action on the vascular beta-2 adrenoceptors could be expected to decrease vascular resistance.

Although topical carteolol might have some effects on ocular blood flow, there were few reports dealing with the subjects. Grunwald and Delehanty reported no effect was found on human retinal circulation of carteolol-treated eyes by laser Doppler velocimetry.[24] Yamazaki and Baba demonstrated a net increase in the pulsatile volume change of the carteolol instilled eyes.[25] Using laser speckle microcirculation analyzer, increased tissue blood velocity in the optic nerve head was observed in twelve healthy volunteers after a single instillation of 2% carteolol.[26] However, the hemodynamic effect of topical carteolol with CDI was not yet reported.

In the present study, color Doppler analysis demonstrates a decrease of vascular resistance indices in NTG patients after topical carteolol treatment for twelve weeks. In evaluating these data, we notice a significant reduction of the resistance index in the CRA ($p = 0.030$). The reduction was also seen in the LPCA ($p = 0.09$). Moreover the pulsatility index of the LPCA is also lower than before treatment ($p = 0.08$). These two index are approaching significance. The tendency for carteolol to increase EDV slightly, while leaving PSV unchanged, resulted in a reduced resistance index in the CRA. Since this is a small sample study, further evaluation for more patients should be done in the future.

Carteolol hydrochloride is a nonselective beta-adrenergic antagonist with intrinsic sympathomimetic activity (ISA). But studies demonstrated that timolol reduces intraocular pressure as much as or more than other beta-blockers, without altering the retrobulbar vascular resistance indices.[27,28] The second possibility is that carteolol exerts ISA effects on blood vessels.

The contribution of ISA to beta-blocker therapeutic potential has been studied extensively in cardiovascular hypertension.[29] Beta-blockers with ISA have shown to decrease vascular resistance in cardiovascular system after acute and chronic exposure.[7,8] Merli et al. compared the long-term vasoactive effects of atenolol and carteolol in human essential hypertension.[30] The results indicated dilation by carteolol and constriction by atenolol of the small resistive vessels of forearm. Because of ISA, carteolol acts as a partial agonist. Its partial agonist action on the vascular beta-2 adrenoceptors might explain in part its vasodilation property on peripheral vessels. Another mechanism for the vasodilation of carteolol is mediated by endothelium function and the action of prostaglandin system as shown by in vitro studies on arterial strips.[31]

In conclusions, our results suggest that twelve weeks of 2% carteolol treatment can decrease the vascular resistance in NTG patients. The vasodilation effect may be due to the partial agonist action of ISA of carteolol.

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