THE EFFECT OF SIMVASTATIN (ZOCOR°) ON ENHANCEMENT OF OCULAR BLOOD FLOW IN GLAUCOMA PATIENTS

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INTRODUCTION

A reduction in ocular perfusion is known to be associated with and a risk factor for progression of (particularly normal tension) glaucoma [1].

Previous studies have shown that long-term statin therapy may contribute to a reduction in the risk of age-related macular degeneration, diabetic retinopathy, and glaucoma, all ocular disorders thought to be associated with impaired ocular circulation [2, 3]. A very recent study has shown that simvastatin increases retrobulbar flow velocities in patients with diabetic retinopathy [4]. Another recent small-scale study indicated that systemic administration of simvastatin (Zocor°) for seven days in healthy volunteers decreased intraocular pressure (IOP), and increased blood flow velocity in the retinal arteries and veins whereas the diameter of the retinal vessels was unchanged. Plasma nitrite/nitrate levels were elevated after seven days, suggesting improved NO release [5]. In this study, plasma nitrite/nitrate was used as a parameter of endothelial NO (eNOS) synthase activity.

Statins have been shown to have no significant undesirable effects on the lens or other ocular tissues [6-9].

Statins are known to have pleiotropic effects, such as the improvement of endothelium-dependent relaxation by stimulating the nitric oxide (NO) signal pathway. Acetazolamide is known to be the most potent carbonic anhydrase inhibitor and to induce vasodilation through an NO-independent pathway [10 11]. We hypothesize that simvastatin may enhance the increase in blood flow velocity after administration of acetazolamide.

If so, simvastatin may not only lower intra-ocular pressure but also improve ocular blood flow, in particular in conjunction with (oral or topical) carbonic anhydrase inhibitors. Therefore, simvastatin might be a useful drug in the management of glaucoma.

AIM

This study was designed to evaluate the effect of simvastatin (Zocor°) on retrobulbar blood flow velocities after administration of acetazolamide (Diamox°).

HYPOTHESIS

We hypothesized that simvastatin will significantly reduce IOP and increase retrobulbar blood flow velocities after administration of acetazolamide.

STUDY PROTOCOL

Subjects:
Twenty patients with open angle glaucoma (OAG) or normal tension glaucoma (NTG) will be recruited for the study. Glaucoma patients will be defined as having characteristic optic disc damage and visual field loss. For the diagnosis of OAG, an intra-ocular pressure (IOP) ≥ 21mmHg, is required. The Statin and placebo groups will be age- and gender-matched.

Inclusion criteria:
- individuals over 18 years old
- willing to sign an informed consent and able to comply with the requirements of the examination

Exclusion criteria:
- history of ocular trauma or eye disease that cannot be accounted for by refractive error
- best refracted visual acuity less than -1.18 on the logarithmic ETDRS-scale in the study eye
- contra-indications for the use of simvastatin or acetazolamide
- already on statin therapy or need for urgent statin therapy

Measuring devices:
Blood flow velocities will be measured in the ophthalmic artery (OA), the central retinal artery (CRA), and of the temporal and nasal short posterior ciliary arteries (TPCA, NPCA) using CDI. The following parameters analyzed: peak systolic velocity (PSV), end diastolic velocity (EDV) and resistive indices (RI). Moreover, to evaluate the elasticity of the blood vessels, the difference between the PSV and the dicrotic notch will be measured.

Study procedures:
General study setup:
The study will be designed in a prospective, double-masked, placebo-controlled way and will involve two study visits. These visits will be planned around the same time of the day. The subjects will be instructed to avoid caffeine intake, smoking and exercise for three hours prior to each study visit.
During each visit, the following examinations will be performed:

- Blood pressure and heart rate measurements
- Visual acuity, using the ETDRS chart placed in the same location under the same illumination for all subjects
- IOP, using Goldmann applanation tonometry and Pascal Dynamic Contour tonometry
- Color Doppler imaging

Blood will be drawn before the onset of simvastatin/placebo treatment as well as at the end of the study to measure total cholesterol, LDL, HDL, triglycerides and Creatinine Kinase as well as nitrite/nitrate levels.
During the first visit, an informed consent will be signed and a baseline examination will be performed. Color Doppler imaging will be performed before and 1 hour after intravenous administration of 15mg/kg (maximal 500mg) of acetazolamide.
The patient will be instructed to take simvastatin 40mg (or placebo) 1x/d in the morning, and will be fully re-examined after one month (second study visit).

During the second visit, the above mentioned examinations will be performed before and 1 hour after intravenous administration of acetazolamide.

Blood pressure and heart rate measurements:
After five minutes of sitting at rest, heart rate and systemic blood pressure will be measured with the subject in a sitting position. The same arm will be used for all serial measurements. The radial pulse will be taken. Systolic and diastolic blood pressure will be measured with an accurately calibrated mercury sphygmomanometer.

Color Doppler imaging:
CDI is an ultrasound technique that combines b-scan gray scale imaging of tissue structure, colored representation of blood flow based on Doppler shifted frequencies, and pulsed-Doppler measurements of blood flow velocities. Blood flow velocities are assessed in the ophthalmic, central retinal, and short posterior ciliary arteries. In each vessel, peak systolic velocity (PSV) and end-diastolic velocity (EDV) will be calculated. PSV refers to the highest blood flow velocity achieved during systole and is calculated from the frequency of the peak in the Doppler-shifted waveform. EDV refers to the lowest velocity occurring during diastole and is calculated from the frequency of the trough in the waveform. In addition, Pourcelot's resistance index (RI), a measure of peripheral vascular resistance, is calculated for each vessel: RI = (PSV-EDV)/PSV. During the test, subjects are reclined in a chair at about 60 degrees from vertical. Acoustic coupling gel is applied to the probe and the probe is gently positioned on the closed eye. Attention is paid to avoid exerting pressure on the eye. The appropriate vessel is identified, the sample volume placed in the center of the vessel, and several seconds of Doppler waveform recorded. The operator selects the peak and trough of the frequency wave and the device calculates PSV, EDV and RI from these frequencies. Numerous studies have shown that this technique provides reliable and reproducible data.

RESULTS

20 patients (8 female and 12 male) with open angle glaucoma were included in this trial. There was no significant difference in IOP and blood flow velocities between the placebo- and the treatment group with simvastatin after one month after acetazolamide administration.

CONCLUSION

In this study, simvastatin had no effect on IOP and retrobulbar blood flow velocities after administration of acetazolamide.

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