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EXPERT OPINION

The Effect of Magnesium on Retinal Venous Pressure of Patients with Normal-Tension Glaucoma and Flammer Syndrome

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Purpose

To measure the retinal venous pressure (RVP) in both eyes of patients with normal-tension glaucoma (NTG) and Flammer Syndrome before and 6 weeks after treatment with magnesium.

Methods

This retrospective study included 30 patients with NTG and Flammer-Syndrome who were treated with magnesium (12 mmol daily). RVP (mmHg) was measured in all patients bilaterally at baseline and six weeks later using contact lens ophthalmodynamometry. Ophthalmodynamometry was performed by applying increasing pressure on the eye via a contact lens. The minimum force required to induce a venous pulsation is called ophthalmodynamometric force (ODF). The RVP is defined and calculated as the sum of ODF and intraocular pressure (IOP) [RVP = ODF + IOP].

Results

Out of the 30 NTG patients included, 16 were male (53%) and 14 were female (47%). There was no difference in IOP before and 6 weeks after magnesium intake but there was a significant decrease in RPV of 2.15 (95% CI: 1.68–2.62).

Conclusions

Treatment with magnesium may decrease RVP in both eyes of NTG patients with Flammer Syndrome. This effect could be due to the partial inhibition of endothelin-1 (ET-1) by magnesium.

Introduction

Magnesium is the fourth most common mineral in our body and an essential element required as a co-factor for over three hundred enzymatic reactions and therefore necessary for the biochemical functioning of numerous metabolic pathways. Magnesium is a physiological calcium channel blocker and thus functions quite similarly to a calcium channel blocker yet with much fewer side effects than a calcium channel blocker. This makes magnesium an attractive therapeutic agent: it barely has any side effects, is inexpensive, commonly available. For years, it has thus been used to prevent and treat common diseases

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including metabolic syndrome, migraine headache, diabetes, asthma, hyperlipidemia, preeclampsia and normal-tension glaucoma (NTG), particularly when patients are suffering from a vascular dysregulation in the context of the Flammer Syndrome. Flammer Syndrome describes a phenotype characterized by the presence of primary vascular dysregulation together with a cluster of symptoms and signs that may occur in healthy people as well as people with disease. Typically, the blood vessels of the subjects with Flammer Syndrome react differently to a number of stimuli, such as cold and physical or emotional stress.[1,2] People with Flammer Syndrome, especially glaucoma patients, have increased retinal venous pressures as measured by means of ophthalmodynamometry. Retinal venous pressure (RVP) is defined and calculated as the sum of the ocular dynamometric force (ODF) and intraocular pressure (IOP) [RVP = ODF + IOP]. Details of measuring and treating RVP has previously been described[3,4] and reports show that certain therapies lower increased RVP.[5,6]

By acting as a physiological calcium channel blocker, magnesium reduces calcium conduction of calcium channels, increases nitric oxide, induces direct and indirect vasodilation and improves endothelial dysfunction in part by inhibiting endothelin-1 (ET-1). ET-1 is a potent vasoconstrictor and constricts retinal veins locally leading to leading to increased retinal venous pressure as commonly seen in glaucoma patients or in patients with retinal vein occlusions.[7] The relationship between RVP and ET-1 has previously been described.[3]

To see whether treatment with magnesium affects ocular hemodynamics, we retrospectively analyzed retina venous pressures of eyes of NTG patients with Flamer Syndrome who were treated with magnesium at baseline and 6 weeks after treatment.

Methods

Patients

We retrospectively analyzed values of RVP and IOP at baseline and six weeks after treatment with magnesium (12 mmols daily) of 32 NTG patients. No ethical approval was required to measure RVP in glaucoma patients as RVP measurements are always taken in all glaucoma patients. All patients had glaucomatous optic nerve cupping and the absence of alternative causes of optic neuropathy. Neither of the patients had visual field loss due to glaucoma. A total of 22 patients had local drops to reduce eye pressure.

The Flammer Syndrome

FS was defined as being present if it was detected in the patient history and if patients had increased retinal venous pressure measurements as measured by ophthamodynamometry in both eyes.

Evaluation of patient history for FS

FS is defined as present (FS+) in the patient history if the subjects answer five of the following six questions with "Yes", and it is defined as absent (FS-) if the subjects answer less than five questions with "Yes": 1) Do you suffer from cold hands or feet even in summer?[8]; 2) Do you have trouble falling asleep, especially when you are cold?[9]; 3) Are you seldom thirsty, and do you have to remind yourself to drink enough?[10]; 4) Do you suffer from migraine attacks?[11]; 5) Do you have low blood pressure?[12]; 6) Do you identify smells better than others?[13].

Measurement of retinal venous pressure

For all patients, retinal venous pressure was measured in both eyes by ophthalmodynamometry (Meditron GmbH, Völklingen, Germany) at baseline and 6 weeks later. The ophthalmodynamometer consists of a conventional Goldmann contact lens fitted with a pressure sensor at its outer margin, where the Goldmann contact lens is usually held during an ophthalmoscopic examination. The device is connected to an LCD screen. Ophthalmodynamometry is conducted by applying increasing pressure to the eye via the contact lens. Based on a calibration curve, this applied pressure can be read as an IOP increase on the attached LCD screen. The IOP increase that is required to induce a venous pulsation is called the ophthalmodynamometric force (ODF). If a spontaneous venous pulse is present, ODF is said to be 0, if not present, increasing pressure is applied. The RVP is defined and calculated as the sum of the ODF and IOP [RVP = ODF + IOP]. Measurements by the ophthalmodynamometer are reproducible.[14]

Statistical Analysis

Retinal venous pressure (RVP) and intraocular pressure (IOP) are described with means and standard deviations (SD) and graphically with boxplots. T-test was performed to compare the effect of magnesium on RVP and IOP before and after application.

To study the effect of magnesium on RPV we used a mixed-effect model to perform a multiple regression analysis. Adjustment variables sex and age were used to lower variation and to consider possible confounders. Time (pre/post magnesium application) was the variable of interest and patient was entered as a random variable in the regression. Random variables are used when considering repeated measurements on the same patient (pre/post) as in this case. All analyses were conducted using statistical software package R, version 4.0.3. Mixed-effects models are performed using the package lme4.

Results

A total of 30 patients were included in the study, 16 males (53%) and 14 females (47%). The mean age was 61.7 years (SD 13.5). Mean age of male was 60.6 (15.0) and of female 62.9 (11.9). **Table 1** shows the mean and standard deviations of IOP and RPV for left and right eyes before and after application.

Table 1. Mean and standard deviation (SD) of intraocular pressure (IOP) and retinal venous pressure (RPV) for right and left eye, before and after magnesium application.

	Mean (SD) of pressure before magnesium application	Mean (SD) of pressure after magnesium application	p(SD)-value
IOP right	15.23 (1.72)	15.87 (1.07)	0.092
IOP left	15.80 (1.71)	15.83 (1.15)	0.930
RPV right	22.67 (2.12)	20.67 (1.09)	<0.001
RPV left	23.40 (1.81)	21.10 (1.54)	<0.001

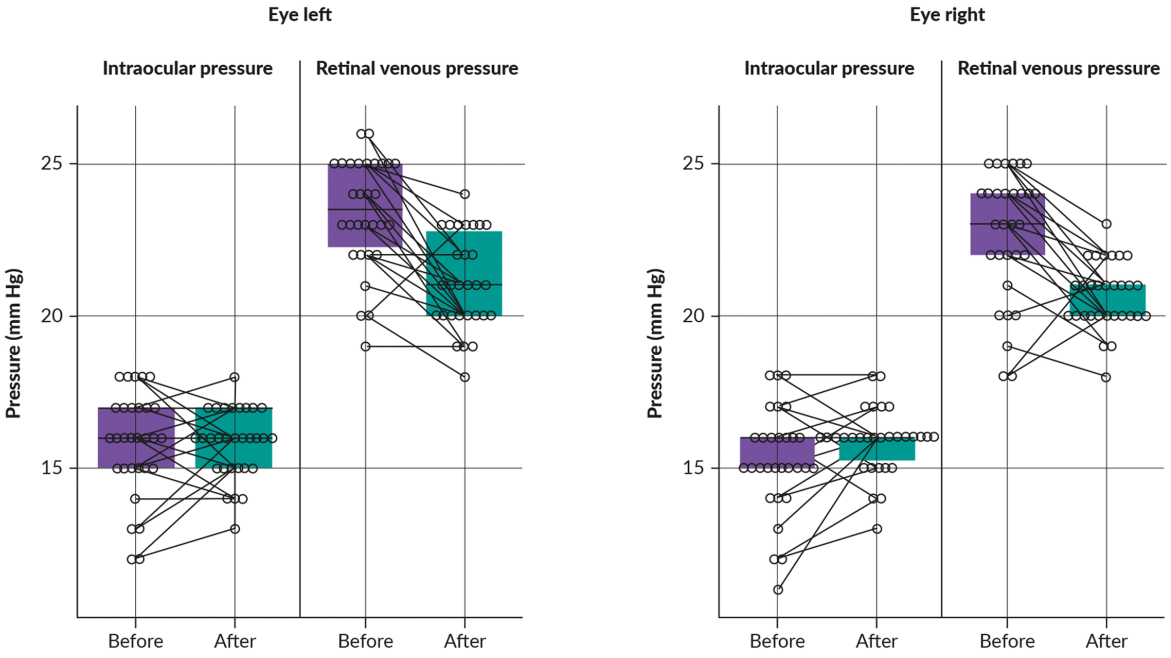

Figure 1. Boxplot of intraocular pressure (IOP) and retinal venous pressure (RPV) showing median, 25%- and 75%-quantiles for right and left eyes.

Each circle is a patient. Lines connect the same patient.

Table 2. Results from regression analysis.

Variable	Estimate (95% CI)	p-value
Intercept 22.8	(22.1–23.5)	<0.001
Centered age (mean=61.7)	-0.0104 (-0.0472–0.0265)	0.593
Female vs male	0.470 (-0.510–1.45)	0.365
Post vs pre	-2.15 (-2.57 to -1.73)	<0.001

Centered age and gender were used as adjustment variables and Time (pre/post magnesium application) as a variable of interest. Patient entered as a random variable.

There was no difference in IOP before and after magnesium intake but there was a significant decrease in RPV of 2.15 (95% CI: 1.68–2.62). **Figure 1** shows the graphical representation of the data.

Regression analysis shows that age and gender are not statistically significant (**Table 2**). The effect of magnesium is statistically significant with -2.15 mm Hg (95% CI: -2.57 to -1.73).

Initially, the site of the eye was entered as random variables (site of eye nested in patient), but since the variation between the eye was close to zero, the site was not considered in the model.

Discussion

Retinal venous pressure (RVP) can be measured non-invasively by means of ophthalmodynamometry. While healthy people have a spontaneous vein pulsation or an RVP slightly above values of intraocular pressure (IOP), those with the ophthalmic or systemic disease commonly have increased RVP.[7,14,15] As such, glaucoma patients particularly those Flammer Syndrome, often have increased RVP.[16,17]

This is the first report showing the possibility of a therapeutic reduction of RVP by magnesium to the best of our knowledge.

At present, the cause of this increased RVP and the fact that it can be therapeutically reduced through magnesium is not fully known. A previous study showed that RVP could be reduced by a low-dose calcium channel blockers (CCB), namely nifedipine.[18]

Magnesium is a physiological CCB and, although weaker and with fewer side effects than a CCB, seems to reduce increased RVP to some extent.

The retinal vessels lack autonomic innervation. The size of the retinal vessels is mainly regulated by vascular endothelial cells. A dysfunction of vascular endothelial cells may occur in various pathologies, such as in glaucoma. Yet it is not likely that a general endotheliopathy may lead to a localized constriction of the veins and thus to a significant increase in RVP. The impact of circulating vasoactive hormones on the retinal vessels is also limited as long as there exists an intact blood-retinal barrier. Vasoactive substances, however, can have a major impact on the retinal vessels from the outside and the likelihood of vasoactive molecules such as endothelin-1 (ET-1) reaching retinal veins from outside, thereby causing vasoconstriction is particularly high around the optic nerve head.[18]

There are various studies that support this hypothesis by showing the effect of CCBs on ocular blood flow. Animal studies show that ONH blood flow is increased after application of CCBs,[19,20] *ex vivo* studies show that CCBs counteract the vasoconstrictive effect of ET-1,[21,22] in glaucoma patients CCBs improved ocular blood flow[23–25] and in glaucoma patients with Flammer Syndrome.

Limitations

This study has certain limitations. Its design lacks a placebo group which thus weakens the conclusion of causality due to the therapeutical effect of magnesium. It is retrospective, only one measurement is done before and after treatment and only patients with elevated RVP were included, thus "a

regression to the mean" can also play a role. Taken together, our results rather support the assumption that an increased RVP may be due to a functional constriction of the vein, which can be at least in part relieved by the therapeutic application of magnesium. Further studies are required to clarify this.

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SUPPLEMENTARY MATERIALS

The Effect of Magnesium on Retinal Venous Pressure of Patients with Normal-Tension Glaucoma and Flammer Syndrome

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