Clinical experience of the use of Vasavital® in dry age-related macular degeneration and ischemic optic neuropathy

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Background: *The chronic ischemic process caused by impaired hemodynamics in the eye and brain is a component of the pathogenesis of ischemic optic neuropathy and age-related macular degeneration, and requires prompt and adequate treatment.*
Purpose: *To examine the effect of a one-month course of Vasavital on the function of the visual system and regional hemodynamics in patients with dry age-related macular degeneration and those with ischemic optic neuropathy.*
Material and Methods: *Thirty-two patients with dry age-related macular degeneration (AMD) (mean age, 66 ± 1.5 years) and 22 patients with chronic ischemic optic neuropathy (mean age, 57.0 ± 1.4 years) underwent examination and treatment at the Department of Uveitis and Laboratory for Functional Examination of the Visual System of the Filatov institute. They received a one-month course of Vasavital-only therapy at a dose of one capsule twice a day as an outpatient treatment. Patients reported their complaints and underwent routine eye examination, studies of regional hemodynamics in the eye and brain (by ophthalmic rheography and rheoencephalography with Reocom, the computerized rheography apparatus), and electrophysiological studies of electrically evoked phosphene threshold (EEPT) and critical frequency of phosphene disappearance (CFPD) at two time points: prior to and after a one-month course of Vasavital-only therapy.*
Results: *A one-month course of Vasavital-only therapy resulted in 24% and 9.6%-25% increases in ocular pulse blood filling in patients with chronic ischemic optic neuropathy and patients with age-related macular degeneration with various baseline levels of visual acuity, respectively. In addition, vascular tone in large-and small-caliber ocular vessels decreased significantly, by 12-17%, in patients with chronic ischemic optic neuropathy, and by 10-20%, in patients with age-related macular degeneration, and vascular tone in large-caliber brain vessels (in the vertebral-basilar system) decreased by 21.6% in patients with ischemic optic neuropathy. A course of Vasavital-only therapy resulted in improved optic nerve function in patients with ischemic optic neuropathy, with a 20.5% improvement in electrically evoked phosphene threshold (EEPT), and 22-63% improvement in critical frequency of phosphene disappearance (CFPD); this indicated an improved function of the peripheral as well as central retina.*

Keywords:
Vasavital, dry age-related macular degeneration, ischemic optic neuropathy

Introduction

Age-related macular degeneration (AMD) is a disease that endangers quality of life. According to WHO estimates, worldwide, as many as approximately 50 million people have AMD, of whom approximately 14 million are blind or visually impaired due to the disease [1,2]. AMD is second to cataract as a leading cause of global blindness, and has been attributed to 15.4% and 19.5% of all the causes of blindness in Western Europe and Eastern Europe, respectively [3, 4]. The risk of onset and development of AMD has been associated with genetic variation, aging, and environmental factors like exposure to ultraviolet and blue light. Additional negative factors include low physical activity, smoking, obesity, arterial hypertension and hypercholesterolemia. A high level of oxidative stress plays a key role in the pathogenesis of AMD [5, 6].

Photoreceptor membranes contain high levels of polyunsaturated fatty acids which are a target for free

oxygen radicals. A high level of metabolism, increased retinal blood flow and regular photoreceptor membrane exposure to light contribute to the formation of free radicals. Phagocytosis of the outer segments of photoreceptors and lipofuscin accumulation result in further synthesis of free radicals [6, 7]. Like other tissues of the central nervous system, the retina is particularly susceptible to toxic effects of free-radical oxidation. Damage to the photoreceptor layer not only contributes to the development of AMD, but is also a mechanism of the pathogenesis of retinal damage in macular dystrophy, diabetic retinopathy, glaucoma, and retinal ischemia [4, 5].

Anthocyanins, flavonoids, vitamins A, B, C and E, and carotenoids (especially, lutein and zeaxanthin) may play an important role in the prevention and/or inhibition of the development of AMD [1-4, 6, 8, 9]. Vitamins and microelements are essential for the normal function of the visual system. Diffusion is a mechanism of penetration of these substances into retinal cells. Retinal pigment epithelium (RPE) cells have been found to absorb xanthophylls, microelements, and vitamins through the process depending on Scavenger Receptor Class B type 1 (SR-B1), a surface glycoprotein [10, 11]. SR-B1 mediate penetration of lipids through membranes, particularly of some components of high-density lipoproteins, and, in this way, receptor-dependent transport of lipids, but not proteins of the outer lipoprotein shell takes place. Bioavailability of pharmaceutical substances for the treatment of retinal disorders depends on the entry of actual substances into blood and their subsequent penetration into the retina. An increased antioxidant intake is accompanied by decreased antioxidant absorption. Thus, low-dose intake of lycopene has been found to be more efficacious than high-dose intake of lycopene, with increased lutein intake inhibiting β-carotene absorption [4].

Retinal photoreceptor cells are characterized by the presence of tight cell-to-cell junctions formed by transmembrane molecules. The RPE acts as a highly resistant barrier to diffusion of substances and is easily penetrated by ions, water and proteins under normal conditions, thus regulating and maintaining the environment of retinal cells [12, 13]. Retinal vascular endothelial cells are joined to each other by zonulae occludentes or tight junctions which completely encircle the cells (somatic capillaries). That is, this arrangement forms a barrier that prevents the penetration of large molecules. Water transport is implemented by active mechanisms. Such transport mechanisms exist also for transfusion of some substances [12].

Small lipophobic molecules and ions can pass through the RPE and choroidal capillary walls to reach all layers of the retina. Substance penetration rate is inversely proportional to the molecular weight of the substance. It has been found that pharmaceutical penetration into the eye depended on lipid solubility of the pharmaceutical agent. Liposoluble molecules have ability to cross the blood-ocular barrier (BOB) by passive diffusion and dissolve in membrane lipids [12].

Although there have been advances in the anti-VEGF and stem cell treatment of particular forms of AMD, prevention of retinal cell damage by the use of pharmaceuticals containing natural components seems promising [1, 2 ,6, 9, 14-16].

Ischemic optic neuropathy is a severe clinical manifestation of ocular ischemic syndrome, which, if untreated, results in disability and blindness [17]. Atherosclerosis-associated carotid artery lesions are the major cause of chronic ocular ischemia. Ischemia and resultant hypoxia trigger a series of retinal neuronal damage reactions including oxidative stress, lipid peroxidation of neuronal membranes, excite toxicity, inflammatory cytokine response, and vascular endothelial growth factor (VEGF) expression [17, 18]. Therefore, prevention of the sequelae of retinal damage becomes an important task, and requires coordinated efforts of various specialties.

Although topical administration of pharmaceuticals is common in eye care, oral administration of pharmaceuticals during or after meals is more safe and easy for the patient. An oral medication for the treatment of retinal disorders should not only enable absorption of actual substances by blood, but also provide for their transport to retinal cells, i.e. their ability to cross the blood-ocular barrier (BOB). Medication pharmacokinetics and efficacy are determined by actual substances and pharmaceutical dosage form. A dose of systemically administered medication should be large enough to achieve a therapeutic level in the eye. It is important to bear in mind that the amount of medication reaching the posterior segment is limited by circulation, and, consequently, a systemically administered dose should be rather high. Dose adequacy may be determined by the improvement in visual acuity and/or field of vision and the effect of medication on ocular and brain hemodynamics [19, 20]. The therapeutic effect requires maintenance of high concentrations of active substance in plasma for a long time.

While looking for novel effective and safe agents for the prevention and treatment of ocular lesions in dry AMD and vascular optic neuropathy, we considered Vasavital®. Each Vasavital® capsule contains 40 mg of standardized extract of Ginkgo biloba leaves, 60 mg of bee pollen pellet, and a set of vitamins (thiamine, 1 mg; riboflavin, 1 mg; pyridoxine, 1 mg; ascorbic acid, 30 mg; rutin, 20 mg; and nicotinic acid, 17 mg). Biological effects of some components of Vasavital® are considered below.

The capability of Ginkgo biloba extract to inhibit free-radical oxidation (an important factor for ischemic or hypoxic tissue damage) is responsible for its pharmacological effect. Ginkgo biloba extract influences the formation of vasoactive mediators, thus improving circulation and exerting anti-edematous effects. In addition, it reduces the risk for thrombosis, improves tissue blood supply by regulating blood flow in arteries, veins

and capillaries, and optimizes interneuronal cholinergic and adrenergic mediation.

Bee pollen pellet contains more than 250 biologically active substances, including essential amino acids and unsaturated fatty acids required for cell regeneration. It has a potent antisclerotic effect, reduces blood cholesterol level, and removes cholesterol from the body. Rutin and quercetin, the components of bee pollen pellet, enhance elasticity of blood capillaries, and reduce pathological capillary permeability. Flavonoids also have moderate antihistamine, antioxidant and detoxicant effects.

Ascorbic acid normalizes capillary permeability, improves the protective function of the body, prevents thrombosis, and enhances tissue oxygen saturation. Nicotinic acid (vitamin PP) is involved in body energy metabolism and has a vasodilating effect. Thiamine hydrochloride (vitamin B1) plays a key role in optimal utilization of carbohydrates, a major source of energy for the body, and regulates the function of the peripheral nervous system. Riboflavin (vitamin B2) is involved in growth processes; the active, phosphorylated forms of riboflavin are involved in the regulation of oxidative-reductive processes. Pyridoxine hydrochloride (vitamin B6) is required for metabolism of proteins and fats, promotes red cell formation, and regulates nervous system function. Rutin (vitamin P) is a blood vessel protector and reduces pathological capillary permeability, reinforces the walls of blood vessels, and provides relief of vessel wall edema and inflammation. In addition, it has an antiaggregant effect, improves microcirculation, and inhibits the development of macular dystrophy.

The purpose of the study was to examine the effect of a one-month course of Vasavital on the function of the visual system and regional hemodynamics in patients with dry AMD and those with ischemic optic neuropathy.

Material and Methods

Thirty-two patients with dry AMD (mean age, 66 ± 1.5 years) and 22 patients with chronic ischemic optic neuropathy (mean age, 57.0 ± 1.4 years) underwent examination and treatment at the Department of Uveitis and Laboratory for Functional Examination of the Visual System of the Filatov institute. On completion of the main course of treatment on in-patient basis, they were followed up on out-patient basis, and received a one-month course of Vasavital-only therapy at a dose of one capsule twice a day. Patients reported their complaints and underwent routine eye examination, studies of regional hemodynamics and electrophysiological studies at two time points: prior to and after a one-month course of Vasavital-only therapy. They received visual acuity assessment, IOP measurement, ophthalmoscopy, biomicroscopy, perimetry, and systemic blood pressure and pulse measurement. Optical coherence tomography (OCT) and ocular fluorescein angiography (FA) were performed, if it was required to clarify the clinical diagnosis.

Electrical sensitivity of the visual system (electrically evoked phosphene threshold, EEPT) and lability of the optic nerve (critical frequency of phosphene disappearance, CFPD) were assessed using electric phosphene stimulation with a KNSO-2 apparatus (FOSFEN, Odesa, Ukraine). EEPT was assessed after light adaptation at 1 minute of darkness adaptation. A tip electrode connected both to the current generator and the plate electrode was applied onto the closed eyelid. A patient was exposed to single 10-ms current pulses of increasing current strength until phosphene perception was achieved, and, in this way, an EEPT value was obtained. Thereafter, current strength was increased to 300% or 150% of phosphene threshold, the patient was exposed to current pulses of increasing frequency (10 Hz to 60 Hz) until flickering phosphenes disappeared, and the frequencies obtained in this way were recorded as CFPD3 and CFPD1.5, respectively.

Patients underwent ophthalmic rheography (ORG) and rheoencephalography (REG) with Reocom (KHAI-Medika, Kharkiv, Ukraine), the computerized rheography apparatus, with its operation based on the principle of impedancemetry. ORG included measurements of ocular pulse blood filling (OPBF, expressed as RQ, ‰ rheographic coefficient) and vascular tone (expressed as alpha/T percentage index). In addition, Reocom was used for ORG assessment of the vascular tone in large-caliber vessels in the internal carotid system (ICS) and vertebral-basilar system (VBS) in patients with chronic ischemic optic neuropathy.

The study was conducted in accordance with applicable local laws and the principles stated in the Declaration of Helsinki and the European Convention on Human Rights and Biomedicine.

Statistical analyses were conducted using Statistica 8.0 (StatSoft, Tulsa, OK, USA) software. Data are presented as mean (M), error of mean (m), and standard deviation (SD). A pairwise comparison was performed by using the paired Wilcoxon signed-rank test. Spearman's correlation coefficient was computed for correlation study.

Results

Patients reported that a one-month course of Vasavital was well-tolerated, with no new complaints. In addition, no side effects were observed.

Prior to this treatment, uncorrected visual acuity (UCVA) and best- corrected visual acuity (BCVA) in patients with AMD were 0.39 ± 0.02 and 0.56 ± 0.02, respectively, and in patients with ischemic optic neuropathy, 0.42 ± 0.04, and 0.6 ± 0.04, respectively.

A one-month course of Vasavital resulted in no substantial change in visual acuity.

In addition, in patients with ischemic optic neuropathy, OPBF (expressed as RQ, ‰ rheographic coefficient) was 2.5 ± 0.4‰ at baseline (which was 28% lower than in age-matched normals, $p < 0.05$), and increased by 24% (practically to the level of age-matched normals, $p < 0.05$) after a one-month course of Vasavital (Table 1).

Vascular tone in large-caliber vessels (expressed as alpha1/T percentage index) was 25.9 ± 0.1% at baseline (which was 29.5% higher than in age-matched normals, $p < 0.05$), decreased by 12% after a one-month course of Vasavital, which was still significantly higher than in age-matched normals (Table 1). Vascular tone in small-caliber vessels (expressed as alpha2/T percentage index) decreased by 17% ($p < 0.05$) after a one-month course of Vasavital. Ocular blood flow velocity did not change and remained within a normal range on completion of a course Vasavital therapy [21].

In patients with ischemic optic neuropathy, vascular tone in large-caliber vessels (expressed as alpha1/T percentage index; Table 2) was increased by 53% in the ICS (155.4% in the right ICS, and 151.4% in the left ICS versus 100% in age-matched normals) and by 33% in the VBS (133% versus 100% in age-matched normals) at baseline. In these patients, vascular tone in large-caliber vessels in the VBS decreased by 21.6% ($p < 0.05$) after treatment.

Therefore, a course of treatment with Vasavital resulted in normalization of ocular hemodynamics in patients with ischemic optic neuropathy, and in a 21.6% decrease in vascular tone in large-caliber vessels in the VBS.

In patients with ischemic optic neuropathy, electrically evoked phosphene threshold (EEPT) was 68.2 ± 0.3 μA before treatment (which was 28% greater ($p < 0.05$) than in age-matched normals), and decreased by 25% ($p < 0.05$) after treatment with Vasavital. In addition, after this treatment, critical frequency of phosphene disappearance (CFPD1.5 and CFPD3) increased by 7-9 Hz (22% and 63%, respectively), ($p < 0.05$; Table 3).

Therefore, a course of treatment with Vasavital resulted in an improved function of the visual pathway (particularly, an improved function of the axial bundle of the optic nerve as assessed by CFPD1.5).

Patients with dry AMD were divided into two groups based on visual acuity at the initial examination: group 1 of 16 patients (a visual acuity of 0.3 to 0.4) and group 2 of 14 patients (a visual acuity of 0.5 to 0.6).

In dry AMD patients of group 1, ocular pulse blood filling (OPBF, expressed as RQ, ‰ rheographic coefficient) at the initial examination was 2.4 ± 0.3‰, which was lower than in age-matched normals ($p < 0.05$; Table 4). At the final examination, OPBF in these patients increased by 25% ($p < 0.05$), and was 3.0±0.4%, and vascular tone in large-caliber vessels (expressed as alpha1/T percentage index) decreased by 10% ($p < 0.05$).

Therefore, the ocular hemodynamics and choroidal ischemia improved with treatment with Vasavital in this group of dry AMD patients.

Compared to group 1, group 2 of dry AMD patients had higher visual acuity and, consequently, better regional hemodynamics characteristics at the initial examination. In dry AMD patients of group 1, ocular pulse blood filling expressed as RQ was 3.1 ± 0.4‰ at the initial examination, and increased by 9.6% ($p < 0.05$) with treatment. In addition, vascular tone in large-caliber vessels (expressed as alpha1/T percentage index) decreased by 20% ($p < 0.05$, Table 5).

Therefore, in these dry AMD patients, the ocular hemodynamics was found to be practically normalized as early as on completion of a one-month course of treatment with Vasavital.

Discussion

Ginkgo biloba L, the member of the Ginkgoaceae family, originated more than 250 million years ago, and is among the lineages of gymnosperms with exceptionally long evolutionary histories (a modern living fossil). The curative properties of Ginkgo biloba leaves have been known for thousands of years, and has been used in traditional Chinese medicine as early as five thousand years ago [22].

The neuroprotective effect of this plant has been demonstrated by numerous in vitro and in vivo studies. Bioactive terpenoids and flavonoids from Ginkgo biloba extract protect neurons from the necrosis and apoptosis induced by oxidative stress, calcium overload and NO- and beta-amyloid-induced toxicity [23].

The antioxidative activity of Ginkgo biloba extract can be explained by its capability for absorbing almost all the types of free radicals and inhibiting lipid peroxidation. In addition, as opposed to other antioxidants, its active components (mainly, flavonoids) can act at the mitochondrial level [24].

There have been multiple clinical study reports on the use of Ginkgo biloba extract in the treatment of ocular disorders. Particular attention has been given to the therapeutic potential of Ginkgo biloba for retinal disorders associated with neurodegeneration, with a focus on the lesions induced by oxidative processes. There are, however, very few reports on studies on the effect of Ginkgo biloba for retinal ischemic disorders. These are mostly in vivo studies demonstrating the capability of Ginkgo, its extracts and components, for improving blood flow in various vascular systems and preventing oxidative damage at the cellular level [8].

Isolated studies have demonstrated improved ocular hemodynamics at the level of microcirculation in patients with diabetes mellitus, and improved ocular blood flow velocity in glaucoma patients receiving GBE [25, 26]. In addition, GBE increases ocular blood flow velocity in healthy individuals [27].

In the current study, a one-month course of Vasavital-only therapy resulted in 24% and 9.6%-25% increases in ocular pulse blood filling in patients with chronic ischemic optic neuropathy and patients with AMD with various baseline levels of visual acuity, respectively. In addition, vascular tone in large-and small-caliber ocular vessels decreased significantly, by 12-17%, in patients with chronic ischemic optic neuropathy, and by 10-20%, in patients with AMD, and vascular tone in large-caliber brain vessels (in the VBS) decreased by 21.6% in patients with ischemic optic neuropathy.

The vasodilating effect of Casacital can be explained by the joint effect of Ginkgo biloba extract and nicotinic acid. Particularly, the vasodilatory activity mediated by the release of the relaxing factors of the vascular endothelium and prostacyclin (PGI2) due to the presence of flavonoids, and the antiplatelet activity mediated by diterpenes, might justify the effect of the extract [8].

In ischemic optic neuropathy, visual functions are significantly decreased secondary to the damage to the optic nerve, and there is a characteristic visual field loss due to apoptosis of the retinal ganglion cells. We have previously demonstrated typical regional hemodynamics abnormalities in this disorder [28].

A course of Vasavital-only therapy resulted in improved optic nerve function in these patients, with a 20.5% improvement in electrically evoked phosphene threshold (EEPT), and 22-63% improvement in critical frequency of phosphene disappearance (CFPD); this indicated an improved function of the peripheral as well as central retina. Critical frequency of phosphene disappearance (CFPD) depends on the function of the axial bundle of the optic nerve, and decreases with damage to this bundle [35]. Thus, in patients with ischemic optic neuropathy, CFPD3 and CFPD1.5 were by 22.6% and 52%, respectively, lower than in age-matched normals at the initial examination, and practically normalized after the treatment.

A combination of a set of vitamins (nicotinic acid, vitamin PP; thiamine hydrochloride, vitamin B1; pyridoxine hydrochloride, vitamin B6) and Ginkgo biloba extract might exert a synergic effect on the nervous tissue structures, with improvements both in threshold sensitivity and in lability of the visual system. Bee pollen pellet contains biologically active substances (essential amino acids and unsaturated fatty acids) required for cell regeneration, and contributes to visual system saturation with flavonoids, rutin and quercetin.

Therefore, Vasavital demonstrated prophylactic and treatment effects on various degenerative and pathological vascular processes in the eye, particularly, in dry age-related macular degeneration and ischemic optic neuropathy. Vasavital can be used either as a single-agent therapy or in combination with other medications.

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Table 1. Ocular hemodynamics as assessed by ophthalmic rheography in patients with chronic ischemic neuropathy before and after a one-month course of Vasavital-only therapy

Characteristic	Before treatment	After treatment	Mean values for age-matched normals
Ocular pulse blood filling expressed as RQ ‰	2.5±0.4#	3.1±0.4*	3.2±0.1
Vascular tone in large-caliber vessels, α1/T (%)	25.9±0.1#	22.9±0.6#*	20.0±1.1
Vascular tone in small-caliber vessels, α2/T (%)	15.6±0.4	12.9±0.7*	15.0±1.0
Ocular blood flow velocity, V (ohm/sec)	1.0±0.2	1.1±0.1	1.0±0.1

Note: #, significant difference ($p < 0.05$) compared with age-matched normals; *, significant difference ($p < 0.05$) between post-treatment and baseline

Table 2. Vascular tone in large-caliber brain vessels in the internal carotid artery system (ICS) and vertebral-basilar artery system (VBS) as per rheoencephalography in patients with ischemic optic neuropathy

Characteristic	Vascular tone in large-caliber brain vessels	
	Before treatment M ± m	After treatment M ± m
α (%) Right ICS	155.4 ± 7.3	122 ± 3.0*
α (%) Left ICS	151.4 ± 6.2	119 ± 4.0*
α (%) Right VBS	131.7 ± 7.0	122 ± 5.2
α (%) Left VBS	134.2 ± 7.9*	119 ± 5.2

Note: *, significant difference ($p < 0.05$) between post-treatment and baseline

Table 3. Electric sensitivity and lability of the optic nerve as assessed by electrically evoked phosphene threshold (EEPT) and critical frequency of phosphene disappearance (CFPD) in ischemic optic neuropathy at two time points: prior to and after a one-month course of Vasavital-only therapy

Characteristic	Before treatment M±m	After treatment M±m	Mean values for age-matched normals, M±m
EEPT, μA	68.2 ± 0.3	54.0 ± 0.2*	53.3 ± 1.4
CFPD(3), Hz	41.0 ± 0.6	50.0 ± 0.2*	53.0 ± 1.5
CFPD(1.5), Hz	11.1 ± 0.8	18.1 ± 0.4*	23.0 ± 1.2

Note: *, significant difference ($p < 0.05$) between post-treatment and baseline. Mean values for age-matched normals as per Ponomarchuk (2018) [21].

Table 4. Ocular hemodynamics as assessed by ophthalmic rheography in patients with dry age-related macular degeneration (and visual acuity of 0.3 to 0.4) before and after a one-month course of Vasavital-only therapy

Characteristic	Before treatment M±SD	After treatment M±SD	Mean values for age-matched normals M±SD
Ocular pulse blood filling expressed as RQ ‰	2.4 ± 0.3#	3.0±0.4*	3.2 ± 0.1
Vascular tone in large-caliber vessels, α1/T (%)	23.1±0.1#	21.0 ± 0.2#*	20.0 ± 1.1
Vascular tone in small-caliber vessels, α2/T(%)	16.1 ± 0.7	15.9 ± 0.7	15.0 ± 1.0
Ocular blood flow velocity, V (ohm/sec)	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1

Note: #, significant difference ($p < 0.05$) compared with age-matched normals; *, significant difference ($p < 0.05$) between post-treatment and baseline

Table 5. Ocular hemodynamics as assessed by ophthalmic rheography in patients with dry age-related macular degeneration (and visual acuity of 0.5 to 0.6) before and after a one-month course of Vasavital-only therapy

Characteristic	Before treatment M±SD	After treatment M±SD	Mean values for age-matched normals M±SD
Ocular pulse blood filling expressed as RQ ‰	3.1 ± 0.4	3.4 ± 0.2*	3.2±0.1
Vascular tone in large-caliber vessels, α1/T (%)	25.9 ± 0.1#	21.0 ± 0.6#*	20.0 ± 1.1
Vascular tone in small-caliber vessels, α2/T(%)	15.6 ± 0.4	12.9 ± 0.7*	15.0 ± 1.0
Ocular blood flow velocity, V (ohm/sec)	1.0 ± 0.2	1.1 ± 0.1	1.0 ± 0.1

Note: #, significant difference ($p < 0.05$) compared with age-matched normals; *, significant difference ($p < 0.05$) between post-treatment and baseline