UDC 616.7.-007.681-085.27:577.112.385:617.735/.736-018.82-07

The thickness of the retinal ganglion cells complex (gcc) and nerve fibers in the macular area in patients with primary open-angle glaucoma (poag) that received L-arginine in terms of their treatment

Gonchar' E. N. PhD student of the Department of Ophthalmology of Kharkiv National Medical University

Kharkiv National Medical University

Kharkiv, (Ukraine)

E-mail: elena.n.gonchar@gmail.com

Introduction. *In accordance with the contemporary concept, the nature of the glaucomatous damage lies in the accelerated loss of retinal ganglion cells and their axons as optic nerve components, which is associated with the neurons neurotrophic defense reduction, the breach of encephalitic trophic factors transportation to the retinal ganglion cells, as well as with neuroglia involvement, which ensures the optic nerve nutrition.*

Objective: *the study of the thickness of the retinal ganglion cells complex (GCC) and nerve fibers in the macular area in patients with primary open-angle glaucoma (POAG), which received L-arginine in terms of their treatment.*

Material and Methods: 109 patients (192 eyes) with POAG were examined in terms of the study. The patients' age ranged from 40 to 87 years. All patients were randomized into two groups: index treatment group and control group. The index group consisted of 60 patients (102 eyes) with POAG, which received L-arginine treatment along with the background therapy (in accordance with our own proposed scheme — UA 52177 U Ukrainian patent license). The control group consisted of 49 patients (90 eyes) with POAG that received the background therapy. The examination included conventional ophthalmic examination techniques, as well as static computer perimetrium and optical coherence tomography (OCT).

Results: I*t has been established that in patients with POAG that received L-arginine in their treatment, the long-term period stabilization frequency of the nerve fibers average thickness in the macular area was 16% higher than that of the control group (71.6% and 55.6%, respectively), the stabilization frequency of the retinal ganglion cells complex (GCC) average thickness was 23.1% higher than that of the control group (85.3% and 62.2%, respectively), the stabilization frequency of retinal ganglion cells complex (GCC) average thickness in the lower part was 24.6% higher than that of the control group (82.4% and 57.8%, respectively), and the differences were reliable for all parameters ($p<0.05$).*

Conclusion: *The L-arginine use in the treatment of patients with POAG (primary open-angle glaucoma) contributes to the long-term period stabilization of retinal ganglion cells complex (GCC) average thickness, as well as its thickness in the lower part and the macular area nerve fibers thickness.*

Key words: primary open-angle glaucoma, L-arginine, retinal ganglion cells complex (GCC) thickness, nerve fibers thickness in the macular area

Introduction

In accordance with the contemporary concept the nature of the glaucomatous damage lies in the accelerated loss of retinal ganglion cells and their axons [1, 8, 16], as optic nerve components, the main reason of which is associated with the neurons neurotrophic defense reduction, encephalitic trophic factors transportation breach to the retinal ganglion cells, as well as with neuroglia involvement, which ensures the optic nerve nutrition [5, 6, 7].

Liesegang T. J. published histological and electrophysiological evidence proving that retinal ganglion cells are the sole neurons that suffer from glaucoma [14].

Therefore one can hope that neuroprotective therapy, which prevents the retinal ganglion cells destruction, will contribute to the stabilization of visual functions in patients with primary open-angle glaucoma (POAG).

Taking into account that L-arginine reduces the intraocular pressure in healthy individuals [10], relieves vasospasm [15] and helps to reduce the destruction of retinal ganglion cells in terms of experimental disturbed circulation [9], its use in treating patients with primary open-angle glaucoma may be promising.

Objective of the present work lies in the study of the thickness of the retinal ganglion cells complex (GCC) and nerve fibers in the macular area in patients with primary open-angle glaucoma (POAG), which received L-arginine in terms of their treatment.

Material and Methods

The thickness of the retinal ganglion cells (GCL), their thickness in the lower layer (GCL Inf), as well as the thickness of the nerve fibers in the macular area (NFL Th) were studied by means of optical coherence tomography (OCT) technique using the TOPCON 3D OCT-1000 device with the involvement of 109 patients (192 eyes) with POAG. The patients' age ranged from 40 to 87 years. The average age of the patients was (64.2 ± 5.9) years.

All patients were randomized into two groups: index treatment group that consisted of 60 patients (102 eyes) and control group that consisted of 49 patients (90 eyes) with first, second and third stages of POAG. Patients with the fourth stage of POAG and high degree of ametropy were eliminated from the study. All patients received the background therapy (vasoprotectors, antioxidants, vitamins) and antihypertensive therapy according to the protocol of medical care provision to patients with POAG (Order No 117 of the Ministry of Health of Ukraine, dated March 15, 2007). All patients had the normalization of intraocular pressure (IOP) before and during the treatment as well as within the 6 months post-treatment period. The index group patients received L-arginine treatment along with the background therapy in accordance with our own proposed therapeutic regimen (UA 52177 U Ukrainian patent license).

Neither one of the patients in both index and control groups was diagnosed with the optic nerve diseases, hypertensive angiopathy, ocular media deficiency that could complicate the OCT procedure conducting. Patients in both groups were comparable by gender and age regarding the received antihypertensive therapy ($p > 0.05$). In accordance with the identified visual organ co-morbidity the patients were divided as follows: mild myopia (index group – 19, control group – 16 eyes); moderate myopia (index group – 12, control group – 11 eyes); low degree hypermetropia (index group – 16, control group – 14 eyes).

The examination of patients with POAG included conventional ophthalmic examination techniques: visometry, tonometry according to Maklakov, pneumotonometry and pachymetry with the definition of the true intraocular pressure, biomicroscopy, ophthalmoscopy, as well as static computer perimetrium (in accordance with the 30-2 program). The optical coherence tomography (OCT) was performed before the treatment, after the treatment (in 1 month), as well as in the long term period (in 6 months). Before the OCT executing all patients underwent refractive keratoplasty, the data of which were introduced into the research protocol afterwards, and were automatically recalculated. Thus, it prevented the possibility of the analogue picture distortion or unreliable results obtaining.

Statistical analysis was performed using 'Statistica 6.0' (StatSoft Inc., USA) application software. Nonparametric tests, Student criterion (t) and linear correlation analysis were used to determine the significance of differences in comparable groups. The level of significance of the differences $p<0.05$ was recognized as critical.

Results and discussion

The distribution of patients according to the POAG stages is shown in Table 1, the data of which shows that there was no statistical difference in the proportion of the distribution of eyes with different stages of POAG in the index and control groups.

It is established that in one month after the treatment the average thickness of the retinal ganglion cells complex (GCC) in patients with POAG of the index and control groups has not significantly changed. In the index group patients, which received L-arginine in terms of their treatment, the given indicator before and after

Table 1. The distribution of patients according to the stages of POAG in the index and control groups

Group of patients	POAG stages			Total, n (%)
	I stage, n (%)	II stage, n (%)	III stage, n (%)	
Index group	39 (38.2)	36 (35.3)	27 (26.5)	102 (100.0)
Control group	34 (37.8)	31 (34.4)	25 (27.8)	90 (100.0)
p	>0.05	>0.05	>0.05	

Note: n –quantity of eyes, p –level of significance of the differences

Table 2. The stabilization frequency of the retinal ganglion cells complex (GCC) average thickness, its thickness in the lower part and fibers thickness in the macular area in patients with POAG in the long-term period following the treatment

Studied indicators	Index group, % (n)	Control group, % (n)	P
The retinal GCC thickness	85.3 (87.0)	62.2 (56.0)	<0.05
The retinal GCC thickness in the ower part	82.4 (84.0)	57.8 (52.0)	<0.05
Nerve fibers thickness in the macular area	71.6 (73.0)	55.6 (50.0)	<0.05

Note: n –quantity of eyes, p –level of significance of the differences; the retinal GCC – the retinal ganglion cells complex; POAG – primary open-angle glaucoma.

treatment amounted to (64.45±1.49) millimicron and (64.59±1.58) millimicron, respectively (p>0.05). In the control group patients the average thickness of the retinal ganglion cells complex (GCC) decreased from (61.35±1.58) millimicron to (60.19±1.66) millimicron (p>0.05).

It is shown that in patients with POAG that received L-arginine as a part of their treatment the frequency of the retinal ganglion cells complex (GCC) average thickness stabilization was 95.1% and was higher than the same indicator in the control group (91.1%) by 4.0%, but the differences basically had the nature of trend (p> 0.05).

The retinal ganglion cells complex (GCC) average thickness in the lower part in patients with POAG in both study groups also did not change significantly, in the index group before and after the treatment it amounted to (64.46±1.85) millimicron and (64.89±1.87) millimicron, respectively (p>0.05), and in the control group it reduced from (65.61±1.81) millimicron to (64.12±1.89) millimicron (p>0.05).

It has been established that in patients of the index group that received L-arginine as a part of their treatment the stabilization frequency of the retinal ganglion cells complex (GCC) average thickness in the lower part (86.3%) was higher than this indicator in the control group (83.3%) by 3.0% (the differences between the groups basically had the nature of trend, p> 0.05).

Overall, regarding the group, the average thickness of the nerve fibers in the macular area in patients of both groups was not significantly changed. In the index group the given indicator before and after the treatment amounted to (28.12±1.05) millimicron and (27.64±1.08) millimicron, and in the control group it amounted to (30.90±1.08) millimicron and (30.11±1.11) millimicron, respectively (p>0.05).

The stabilization frequency of the nerve fibers average thickness in the macular area immediately following the treatment in patients of the index group was 86.3% of eyes and was higher than the given indicator in the control group (85.6% of eyes) only by 0.7% (the differences basically had the nature of trend, p>0.05).

When analyzing the results of the research in the long-term period following the treatment (in 6 months) it has been established that in patients with POAG that receive L-arginin as part of

their treatment the stabilization frequency of the retinal ganglion cells complex (GCC) average thickness significantly decreased by 9.8% ($p < 0.05$) in comparison with the indicator received immediately after the treatment. At the same time, the stabilization frequency of the retinal ganglion cells complex (GCC) average thickness significantly exceeded the given indicator by 23.1% in the control group (85.3% and 62.2%, respectively, $p < 0.05$) (Table. 2).

It has also been established that in the long-term period following the treatments (in 6 months) in patients with POAG, which received L-arginin as a part of their treatment, the stabilization frequency of the GCC average thickness in the lower part (82.4%) decreased insignificantly (by 4.8%, $p > 0.05$) in comparison with indicators immediately after treatment, but was significantly higher than the said indicator (24.6%) in the control group (57.8%, $p < 0.05$).

The stabilization frequency of the nerve fibers average thickness in the macular area significantly decreased to 71.6% ($p < 0.05$) in patients of the index group in comparison with the indicator immediately following the treatment, but it exceeded the indicator in the control group (55.6%) by 16.0% ($p < 0.05$).

It should be noted that a gradual decrease in GCC density is typical for experimental models of glaucoma caused, in particular, by the IOP periodic increase [12]. Also, significant differences regarding the retinal ganglion cells complex (GCC) indicators have been identified in glaucoma patients compared with the healthy individuals [1].

Recent studies show that the determination of the structural parameters of the retina in the macular area by means of OCT is not inferior to the studies of the thickness of the optic nerve peripapillary nerve fibers in regard to the glaucoma diagnostic accuracy [11, 17, 18, 19]. According to Kim N. R. et al. (2010) the data on the retinal ganglion cells complex (GCC) allow to detect glaucoma at earlier stages, in comparison with the thickness of peripapillary nerve fibers [13].

The decrease in the stabilization frequency of the average thickness of retinal ganglion cells complex (GCC) and the nerve fibers thickness in the macular area in the long-term period, which we have established, both in the index and in the control groups, is consistent with the opinion of Zavgorodniaia N. G. and Pasechnikova N. V. (2010) and other authors regarding the permanent progression of POAG, regardless of the treatment [3, 4].

At the same time, in the long-term period the stabilization frequency of all studied indicators after the treatment with the use of L-arginine in patients with POAG was significantly higher in comparison with the control group.

We have obtained immediate and long-term results of treatment using L-arginine in patients with POAG that to a certain degree are confirmed by Chuman H. et al. studies (2013), which showed that the use of L-arginine in experimental disturbed circulation restored the lowered threshold of the scotopic sensitivity, as well as reduced the destruction of the retinal ganglion cells [9].

Conclusion: Thus, L-arginine use in the treatment of patients with POAG (primary open-angle glaucoma) contributes to the stabilization of the average thickness of retinal ganglion cells complex (GCC) in the long-term period, as well as its thickness in the lower part and the thickness of the nerve fibers in the macular area.

Our findings not only show the effectiveness of L-arginine in patients with POAG treatment, but also open up the prospects of further studies of its neuroprotective properties.

References

1. Akopian VS, Semenova NS, Filonenko IV et al. [The retinal ganglion cells complex (GCC) evaluation in primary open-angle glaucoma]. Oftalmologiya. 2011. 8 (1). p. 20-26. Russian.
2. Zhaboedov GD, Petrenko OV, Parkhomenko EG. [Improving the diagnosis of glaucoma as a result of in-depth understanding of the disease genesis]. Vestnik oftalmologii. 2008. (1). p. 71-73. Russian.
3. Zavgorodniaia NG, Pasechnikova N.V. Primary glaucoma. New look at the old problem. Zaporozhye: Agency Orbita-YUG; 2010. 192 p. Russian.
4. Kunin VD, Redid AA. [The dynamics of the glaucomatous process in patients observing and not observing the follow-up and treatment regime]. Vestnik oftalmologii. 2013. (2). p. 63-68. Russian.
5. Kurysheva NI. [Secondary neuroprotection in terms of glaucoma]. Medical advice. 2008. (3-4). p. 76-77. Russian.
6. Nesterov AP. [Glaucoma: major problems, new opportunities]. Vestnik oftalmologii. 2008. (1). p. 3-5. Russian.
7. Flammer J. Glaucoma. 3rd ed. [Transl. from English] Kovalska M, translator. Lviv: World medicine; 2008. 464 p. Ukrainian.
8. Cellerino A, Вдhr M, Isenmann S. [Apoptosis in the developing visual system]. Cell. Tissue Res. 2000. 301 (1). p. 53-69.
9. Chuman H, Maekubo T, Osako T et al. [Effects of L-arginine on anatomical and electrophysiological deterioration of the eye in a rodent model of nonarteritic ischemic optic neuropathy]. Jpn. J. Ophthalmol. 2013. 57 (4). p. 402-409.
10. Chuman H, Nao-i N et al. [The effect of L-arginine on intraocular pressure in the human eye]. Curr Eye Res. 2000. 20 (6). p. 511-516.
11. Garas A, Vargha P, Hollo G. [Diagnostic accuracy of nerve fibre layer, macular thickness and optic disc measurements made with the RTVue-100 optical coherence tomograph to detect glaucoma]. Eye (Lond). 2011. 25. p. 57-65.
12. Gramlich OW, Lueckner TC, Kriechbaum M et al. [Dynamics, alterations, and consequences of minimally invasive intraocular pressure elevation in rats]. Invest. Ophthalmol. Vis. Sci. 2014. 55 (1). p. 600-611.
13. Kim NR, Lee ES, Seong GJ et al. [Structure-function relationship and diagnostic value of macular ganglion cell complex measuremen using Fourier-domain OCT in glaucoma]. Invest. Ophthalmol. Vis. Sci. 2010. 51. p. 4646-4651.
14. Liesegang TJ [Glaucoma: changing concepts and future directions]. Mayo Clin. Proc. 1996. 71 (7). p. 689-694.
15. Mendrinos E, Petropoulos IK, Mangioris G et al. [Intravitreal l-Arginine injection reverses the retinal arteriolar vasoconstriction that occurs after experimental acute branch retinal vein occlusion]. Exp. Eye Res. 2010. 91 (2). p. 205-210.
16. Nickells RW. [Apoptosis of retinal ganglion cells in glaucoma: an update of the molecular pathways involved in cell death]. Surv. Ophthalmol. 1999. 43 (1). p. 151-161.
17. Rao HL. Babu JG, Addepalli UK et al. [Retinal nerve fiber layer and macular inner retina measurements by spectral domain optical coherence tomograph in Indian eyes with early glaucoma]. Eye (Lond). 2012. 26. p. 133–139.
18. Schulze A, Lamparter J, Pfeiffer N et al. [Diagnostic ability of retinal ganglion cell complex, retinal nerve fiber layer, and optic nerve head measurements by Fourier-domain optical coherence tomography]. Graefes Arch. Clin. Exp. Ophthalmol. 2011. 249. p. 1039-1045.
19. Seong M, Sung KR, Choi EH et al. [Macular and peripapillary retinal nerve fiber layer measurements by spectral domain optical coherence tomography in normal-tension glaucoma]. Invest. Ophthalmol. Vis. Sci. 2010. 51. p. 1446-1452.

Received 07.04.2015