Research letter

Perimetry criteria for assessing the effectiveness of retinoprotective therapy

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Abstract: *Objective* — To evaluate the effect of the frequency of retinoprotective therapy courses on perimetry parameters, to compare Octopus 900 perimeter with Octopus 600 perimeter, and to assess threshold perimetry results of G-dynamic versus 24-2 programs.
Material and Methods — The study involved 17 patients (34 eyes) diagnosed with primary open-angle glaucoma of advanced stage. Group 1 included subjects receiving a course of Retinalamin every 3 months. Group 2 comprised patients undergoing Retinalamin therapeutics every 6 months.
Results — At the onset of the study via G-dynamic and 24-2 programs, we did not observe any statistically significant differences between the groups in mean deviation of retinal photosensitivity (MD) and pattern standard deviation of mean retinal photosensitivity (PSD). However, the absolute values differed between groups and between programs. On average, the differences in MD and PSD values obtained in the photosensitivity study with G-dynamic vs. 24-2 programs were -0.36 dB (CI 95%: -4.27; 3.54) and 0.63 dB (CI 95%: 2.37; -1.11), respectively. Hence, studies performed via 24-2 and G-dynamic programs yielded comparable results (no statistically significant differences). However, they could not be identical due to different spatial arrangement of points in different programs.
Conclusion — As a result of conducted treatment, retinal photosensitivity did not exhibit statistically significant changes; however, we observed positive dynamics in both groups in MD and PSD parameters of mean retinal photosensitivity. Different devices (Octopus 600 and Octopus 900 perimeters) and different programs (24-2, G-dynamic) yielded different outcomes due to their technical features and capabilities of reproducibility; however, these differences were not statistically significant.

Keywords: glaucoma, retinoprotection, neuroprotection, Retinalamin, optical coherence tomography, perimetry.

Introduction

Glaucoma is a multifactorial disease with neurodegenerative signs of damage to the visual analyzer, which is the cause of irreversible blindness and low vision [1]. It is estimated that more than 60 million people worldwide have glaucoma, of which 8.4 million are blind [2]. In the next 20 years, an increase in the number of patients with glaucoma is expected. Consequently, the number of blind people due to this ailment will increase. Despite the emergence of modern high-tech diagnostic methods, glaucoma is detected mainly at advanced stages of the disease [3], which reduces the effectiveness of its treatment [4].

Computerized perimetry (CP) and optical coherence tomography (OCT) are currently considered the key procedures for diagnosing glaucoma and its monitoring: they allow obtaining fairly objective information about structural and functional parameters [5, 6]. In the treatment of glaucoma, reducing intraocular pressure (IOP) [7-10] remains the only strategy with clinically proven efficacy [11].

However, even when a safe level of IOP is achieved, the death of retinal ganglion cells continues in about 20% of patients, which indicates the progression of glaucoma [12].

In such situations, use of retinoprotective therapy is justified from a medical point of view: it plays an important role in protecting the sensory part of the retina from damaging factors and, as a result, it ensures the safety of visual functions [13, 14].

Since retinoprotective treatment is long-term, most often permanent, preference in choosing medicamentous drugs is given to those that successfully combine efficacy and safety [15].

Typically, as part of a study involving long-term follow-up (lasting 3 years), all patients are regularly (every 3 months) subjected to examination of structural and functional parameters. In some cases, during long-term studies, as a result of a change in

the paradigm of dynamic observation in certain diseases, the diagnostic tactics for monitoring patients may change. For example, in the Ocular Hypertension Treatment Study (OHTS), the Swedish Interactive Threshold Algorithm (SITA) protocol appeared [16,17], which made it possible to somewhat reduce study time. On some occasions, devices may also be changed. Hence, the *objective of our study* was to explore the possibilities of structural and functional research methods in evaluating the effectiveness of retinoprotective therapy.

Material and Methods

As part of a prospective randomized controlled trial in 2019-2020, an expansion of the study was carried out on the basis of the City Clinical Hospital No. 2 of Chelyabinsk on 17 patients (34 eyes) with a diagnosis of the primary open-angle glaucoma of advanced stage, with their IOP brought back to the norm. Patients were randomized via the envelope method into two groups. Group 1 included patients (9 women, 18 eyes) who received a course of retinoprotective therapy in the form of intramuscular injections of Retinalamin; the drug was administered once a day for 10 days 4 times a year (every 3 months). Group 2 comprised patients (6 women, two men, 16 eyes) who received the identical course of intramuscular injections of Retinalamin twice a year (every 6 months).

In addition to routine methods, all patients underwent ophthalmological examinations, including standard automated perimetry using the Octopus device (HaaG-Streit International, Koeniz, Switzerland), structural OCT using Revo NX devices (Optopol Technology SA, Zawiercie, Poland), and Spectralis OCT (Spectralis, Heidelberg Engineering, Heidelberg, Germany) (*Table* 1).

Standard automated perimetry

Prior to enrollment in the study, patients were under dispensary observation, within the framework of which they were under a study using the G-dynamic program on Octopus 600. After inclusion of patients in a multicenter prospective randomized controlled study, an examination was conducted every 3 months using the 24-2 program on Octopus 900 and Octopus 600 perimeters. As criteria for evaluating the effectiveness of Retinalamin, we considered the dynamics of retinal photosensitivity.

Inclusion and exclusion criteria

Inclusion criteria: residency in the city of Chelyabinsk; an advanced stage of primary open-angle glaucoma and normal IOP values; age at the time of inclusion in the study of 45 – 89 years (middle, elderly and senile sensu the 2012 classification by the World Health Organization, www.who.int/ru); clinical refraction in the range of ±6.0 diopters and astigmatism ±1.5 diopters; regimen of topical antihypertensive therapy with medicines without contraindications for their use.

Exclusion criteria: Any other form of primary glaucoma other than the aforementioned; turbidity of optical media preventing the performance of perimetric testing; other retinal disorders (any form of age-related macular degeneration, conditions after occlusions of the retinal vessels, diabetic retinopathy and its complications) in accordance with the methodology for conducting clinical trials (https://clinicaltrials.gov); surgical ophthalmic intervention in anamnesis; injuries and diseases of the eye and its

adnexa; diabetes mellitus and other common diseases requiring hormone therapy.
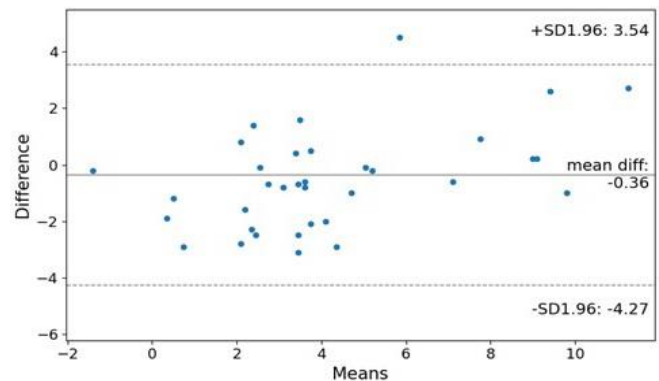

Figure 1. Bland-Altman plot. Mean deviation (MD) of retinal photosensitivity measured with G-dynamic and 24-2 software on Octopus 900 instrument. Mean difference (mean diff) and standard deviation (1.96*SD) of MD parameter.
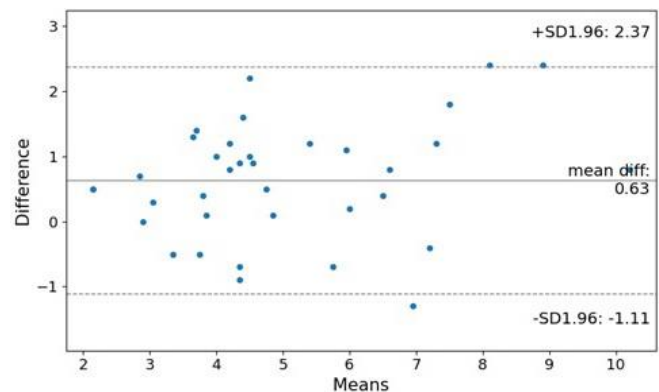

Figure 2. Bland-Altman plot. Standard deviation of mean retinal photosensitivity measured with G-dynamic and 24-2 software on the Octopus 900 instrument. Mean difference (mean diff) and standard deviation (1.96*SD) of PSD parameter (pattern standard deviation of mean retinal photosensitivity) measured on Octopus G-dynamic and 24-2.
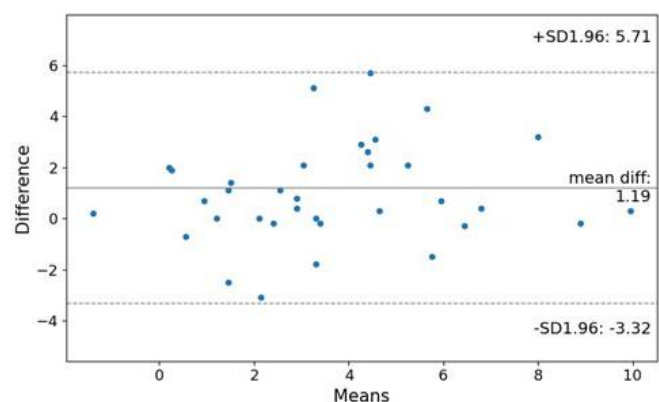

Figure 3. Bland-Altman plot. Mean deviation (MD) of retinal photosensitivity measured with 24-2 program on Octopus 600 and Octopus 900 instruments. Mean difference (mean diff) and standard deviation (1.96*SD) of MD parameter.
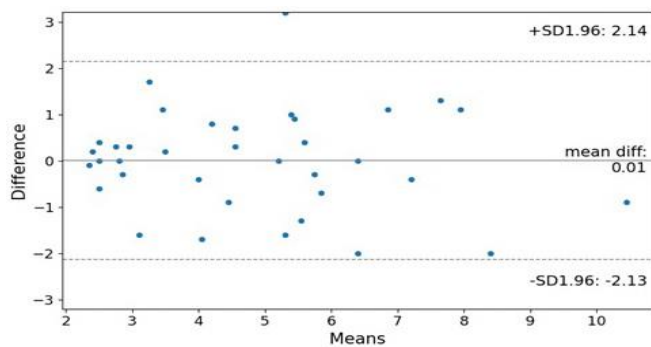
Figure 4. Bland-Altman plot. Standard deviation of mean retinal photosensitivity measured 24-2 program on Octopus 600 and Octopus 900 instruments. Mean difference (mean diff) and standard deviation (1.96*SD) of PSD parameter (pattern standard deviation of mean retinal photosensitivity) measured on Octopus 900 and 600 in 24-2 mode.

Verification of diagnoses

In all cases, the diagnosis was established in accordance with the system of differential diagnosis of diseases and confirmed by specific research methods in the medical records.

Statistical analysis

The obtained data were processed using the Python 3.8 Programming Language. The parameter values are presented in the format of Me (Q25%; Q75%), where Me is the median, and Q25% and Q75% are quartiles. For pairwise intergroup comparisons, the Wilcoxon t-test was used.

The Bland-Altman plot was obtained as follows: the average value for each pair was plotted on the x-axis (the measurement values were obtained via different instruments or using different programs), whereas the difference between the values within the pair was plotted on the y-axis. Further, for the resulting difference of values, the mean and standard deviation were calculated, after which three horizontal lines were drawn on the graph, indicating the mean and mean ±1.96 standard deviation of the measurement difference, which corresponded to 95% confidence interval (CI).

Results and Discussion

At the onset of the study using the G-dynamic and 24-2 programs, there were no statistically significant differences between the groups in mean deviation of retinal photosensitivity (MD) and pattern standard deviation of mean retinal photosensitivity (PSD). However, the absolute values differed both between the groups and between the programs, which was a manifestation of fluctuations in the perimetric testing data.

For instance, the medians for the MD parameter in the G-dynamic program were 3.272 (2.05; 4.05) in Group 1 and 4.866 (2.25; 8.17) in Group 2, W=-0.854; p=0.392; in 24-2 program, the medians were 3.495 (2.45; 5.025) in Group 1 and 5.249 (3.5; 7.37) in Group 2, W=-1.812; p=0.069. The parameter values obtained via two programs did not statistically significantly differ from each other: G-dynamic=4.069 (2.12; 5.52) and 24-2=4.326 (2.925; 5.175); $W_{G \ vs. \ 1}$=-1.205; $p_{G \ vs. \ 1}$=0.228); same was true about the groups (Group 1: $W_{G \ vs. \ 1}$=1.107, $p_{G \ vs. \ 1}$=0.268; Group 2: $W_{G \ vs. \ 1}$=-0.664; $p_{G \ vs. \ 1}$=0.506) (*Table* 2).

The median for the PSD parameter in the G-dynamic program was 5.033 (4.0; 5.98) in Group 1 and 5.627 (4.075; 6.65) in Group 2, W=-0.901; p=0.367; in 24-2 program, the values were 4.375

(2.975; 5.225) in Group 1 and 4.961 (3.8; 6.175) in Group 2, W=-1.315; p=0.188 (*Table* 3).

Between the two programs, the parameter values did not differ statistically significantly: G-dynamic=5.330 (3.975; 6.35) and 24-2=4.652 (3.525; 6.049); $W_{G \ vs. \ 1}$=1.441; $p_{G \ vs. \ 1}$=0.149); same was true about the groups (Group 1: $W_{G \ vs. \ 1}$=1.107; $p_{G \ vs. \ 1}$=0.268; Group 2: $W_{G \ vs. \ 1}$=0.901; $p_{G \ vs. \ 1}$=0.367).

On average, the difference in MD parameter values in the photosensitivity study between G-dynamic and 24-2 programs was -0.36 dB (CI 95%: -4.27; 3.54) (*Figure* 1).

On average, the difference in PSD parameter values in the photosensitivity study between G-dynamic and 24-2 programs was 0.63 dB (CI 95%: 2.37; -1.11) (*Figure* 2).

Thus, the studies performed via the programs 24-2 and G-dynamic yielded comparable results (no statistically significant differences). However, they could not be entirely identical due to the different spatial arrangement of points when using different programs. E.g., the 24-2 program implied the presentation of 56 points of space located at a distance of 6 angular degrees, while the G-dynamic program implied 59 points located along the retinal nerve fiber layer, i.e., located more physiologically.

After six months of observation, patients underwent two-time examination several days apart via 24-2 program on Octopus 600 and Octopus 900 perimeters. The following medians were obtained for MD: on Octopus 900, Group 1 – 3.594 (1.275; 6.149), Group 2 – 5.1 (2.875; 6.675), W=-1.225; p=0.220; on Octopus 600, Group 1 – 2.81 (1.500; 3.675), Group 2 – 3.393 (0.9; 4.275), W=-0.732; p=0.464. For PSD medians were as follows: on Octopus 900, Group 1 – 4.310 (2.7; 5.350), Group 2 – 5.456 (4.475; 6.15), W=-1.941; p=0.052; on Octopus 600, Group 1 – 4.535 (2.8; 6.124), Group 2 – 5.162 (3.774; 6.225), W=-0.827, p=0.407.

The average difference in MD parameter values in the study of photosensitivity sensu 24-2 program on Octopus 600 and Octopus 900 was 1.19 dB (CI 95%: 5.71; -3.32) (*Figure* 3).

The average difference in PSD parameter in the study of photosensitivity sensu 24-2 program on Octopus 600 and Octopus 900 was 0.01 dB (CI 95%: 2.14; -2.13) (*Figure* 4).

The average values of MD and PSD for retinal photosensitivity, according to our study, did not differ statistically among each other when using different models of the Octopus perimeter or when using different examination programs (G-dynamic and 24-2). Hence, both in clinical practice and in clinical research, it is possible to use any model of the Octopus device and use any threshold program.

Comparison of retinal photosensitivity in dynamics

When analyzing photosensitivity of the retina measured by Octopus 900 using the 24-2 program at the onset of the study and 6 months after, we found no statistically significant intergroup and intragroup differences.

In examining intragroup differences in MD values in Group 1, the following values were obtained: W=-1.068, p=0.285. For Group 2, the values were as follows: W=0.015; p=0.987. In the study of intergroup differences in MD at the onset of the study, W=-1.812; p=0.069; at the end of the study, W=-1.125; p=0.260. When we compared the measurements of the MD parameter at the beginning vs. the end of our study for both groups combined, our computations yielded the following values: W=-0.711; p=0.476.

Table 1. Clinical and demographic characteristics of groups

Parameters	Group 1 (n=9; 18 eyes)		Group 2 (n=8: 16 eyes)		$P_{3\ vs.\ 6\ mos.}$
	Me (Q25%; Q75%)	Range	Me (Q25%; Q75%)	Me (Q25%; Q75%)	
Age (years)	72 (68; 69)	64-83	70 (69; 80)	67-83	W=133.5; p=0.767
Gender (m/f)	0/9		2/6		X^2=2.976; p=0.084
BCVA	1.0 (1.0; 1.0)	1.0-1.0	0.8 (0.7; 1.0)	0.5-1.0	W=196; p=0.041
CCT (μm)	508 (499; 514)	476-530	524 (512; 536)	44-536	W=119; p=0.397
P_o (mm Hg)	13 (11.2; 15)	9-18	12.5 (9.75; 16)	6-16	W=159; p=0.6146
CDR	0.645 (0.602; 0.73)	0.3-0.89	0.58 (0.435; 0.69)	0.24-0.86	W=183.5; p=0.1779
OD (mm^2)	1.76 (1.41; 2.08)	1.29-3.51	1.98 (1.85; 2.13)	1.6-3.4	W=91.5; p=0.072
$RNFL_o$ (μm)	77.5 (66.0; 86.2)	66-98	76.5 (71.8; 83.8)	65-91	W=159; p=0.616
$RNFL_s$ (μm)	67 (63; 79)	56-92	71.5 (64.5; 76.2)	52-86	W=139.5; p=0.89

BCVA, best corrected visual acuity; CCT, central corneal thickness; P_o, true intraocular pressure; CDR, cup-to-disc ratio; OD, optic disc; $RNFL_o$, retinal nerve fiber layer measured with Revo NX device (Optopol Technology SA, Zawiercie, Poland); $RNFL_s$, retinal nerve fiber layer measured with Spectralis OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany); $P_{3\ vs.\ 6\ mos.}$, statistical significance of intergroup differences among Group 1 (treatment every 3 months) and Group 2 (treatment every 6 months).

Table 2. Parameters of mean deviation (MD) of retinal photosensitivity and their statistical significance

Program and device	n=17 (34 eyes)	Group 1 (n=9; 18 eyes)	Group 2 (n=8: 16 eyes)	Statistical significance
		Me (Q25%; Q75%)		
md_G_dynamic (600)	4.069 (2.12; 5.52)	3.272 (2.05; 4.05)	4.866 (2.25; 8.17)	W=-0.854; p-value=0.392
md_24_900_1	4.326 (2.925; 5.175)	3.495 (2.45; 5.025)	5.249 (3.5; 7.37)	W=-1.812; p-value=0.069
md_24_900_2	4.673 (2.949; 6.600)	4.135 (2.25; 6.000)	5.272 (3.15; 7.175)	W=-1.125; p-value=0.260
md_24_900_2	4.263(2.075; 6.3)	3.594 (1.275; 6.149)	5.1 (.875; 6.675)	W=-1.225; p-value=0.220
md_24_600	3.069 (1.125; 4.2)	2.81 (1.500; 3.675)	3.393 (0.9; 4.275)	W=-0.732; p-value=0.464
Statistical significance	$W_{G\ vs.\ 1}$=-1.205 $p_{G\ vs.\ 1}$=0.228 $W_{1\ vs.\ 2}$=-0.711 $p_{1\ vs.\ 2}$=0.476 $W_{3\ vs.\ 600}$=1.582 $p_{3\ vs.\ 600}$=0.113	$W_{G\ vs.\ 1}$=-0.964 $p_{G\ vs.\ 1}$=0.334 $W_{1\ vs.\ 2}$=-1.068 $p_{1\ vs.\ 2}$=0.285 $W_{3\ vs.\ 600}$=0.757 $p_{3\ vs.\ 600}$=0.448	$W_{G\ vs.\ 1}$=-0.664 $p_{G\ vs.\ 1}$=0.506 $W_{1\ vs.2}$=0.015 $p_{1\ vs.\ 2}$=0.987 $W_{3\ vs.\ 600}$=1.413 $p_{3\ vs.\ 600}$=0.157	

md_G_dynamic (600), mean deviation of retinal photosensitivity obtained via G-dynamic program on Octopus 600; md_24_900_1, mean deviation of retinal photosensitivity obtained via 24-2 program on Octopus 900 at the beginning of the study; md_24_900_2, mean deviation of retinal photosensitivity obtained via 24-2 program on Octopus 900 after 6 months from the onset of the study; md_24_900_3, mean deviation of retinal photosensitivity obtained via 24-2 program on Octopus 900 several days apart from the study conducted on Octopus 600; W, Wilcoxon T-test of intergroup differences; p-value, statistical significance of intergroup differences; $W_{G\ vs.\ 1}$ and $p_{G\ vs.\ 1}$, Wilcoxon intragroup T-test and statistical significance of difference between md_G_dynamic (600) and md_24_900_1; $W_{1\ vs.\ 2}$ and $p_{1\ vs.\ 2}$, Wilcoxon intragroup T-test and statistical significance of difference between md_24_900_1 and md_24_900_2; $W_{3\ vs.\ 600}$ and $p_{3\ vs.\ 600}$, Wilcoxon intragroup T-test and statistical significance of difference between md_24_900_3 and md_24_600.

Table 3. Parameters of pattern standard deviation (PSD) of mean retinal photosensitivity and their statistical significance

Program	n=17 (34 eyes)	Group 1 (n=9; 18 eyes)	Group 2 (n=8: 16 eyes)	Statistical significance
		Me (Q25%; Q75%)		
psd_G_dynamic (600)	5.330 (3.975; 6.35)	5.033 (4.0; 5.98)	5.627 (4.075; 6.65)	W=-0.901; p-value=0.367
psd_24_900_1	4.652 (3.525; 6.049)	4.375 (2.975; 5.225)	4.961 (3.8; 6.175)	W=-1.315; p-value=0.188
psd_24_900_2	4.944 (3.525; 6.25)	4.72 (3.325; 6.37)	5.194 (3.650; 6.049)	W=-0.657; p-value=0.510
psd_24_900_3	4.819 (3.050; 5.9)	4.310 (2.7; 5.350)	5.456 (4.475; 6.15)	W=-1.941; p-value=0.052
psd_24_600	4.81. (2.875; 6.2)	4.535 (2.8; 6.124)	5.162 (3.774; 6.225)	W=-0.827; p-value=0.407
Statistical significance	$W_{G\ vs.\ 1}$=1.441 $p_{G\ vs.\ 1}$=0.149 $W_{1\ vs.\ 2}$=0.566 $p_{1\ vs.\ 2}$=0.571 $W_{3\ vs.\ 600}$=0.028 $p_{3\ vs.\ 600}$=0.977	$W_{G\ vs.\ 1}$=1.107 $p_{G\ vs.\ 1}$=0.268 $W_{1\ vs.\ 2}$=-0.432 $p_{1\ vs.\ 2}$=0.665 $W_{3\ vs.\ 600}$=-0.446 $p_{3\ vs.\ 600}$=0.655	$W_{G\ vs.\ 1}$=0.901 $p_{G\ vs.\ 1}$=0.367 $W_{1\ vs.\ 2}$=-0.189 $p_{1\ vs.\ 2}$=0.849 $W_{3\ vs.\ 600}$=0.489 $p_{3\ vs.\ 600}$=0.624	

psd_G_dynamic (600), pattern standard deviation of mean retinal photosensitivity obtained via G-dynamic program on Octopus 600; psd_24_900_1, pattern standard deviation of mean retinal photosensitivity obtained via 24-2 program on Octopus 900 at the beginning of the study; psd_24_900_2, pattern standard deviation of mean retinal photosensitivity obtained via 24-2 program on Octopus 900 after 6 months of the study onset; psd_24_900_3, pattern standard deviation of mean retinal photosensitivity obtained via 24-2 program on Octopus 900 several days apart from the study conducted on Octopus 600; W –Wilcoxon T-test for intergroup differences; p-value – statistical significance of intergroup differences; $W_{G\ vs.\ 1}$ and $p_{G\ vs.\ 1}$, Wilcoxon intragroup T-test and statistical significance of difference between psd_G_dynamic (600) and psd_24_900_1; $W_{1\ vs.\ 2}$ and $p_{1\ vs.\ 2}$, Wilcoxon intragroup T-test and statistical significance of difference between psd_24_900_1 and psd_24_900_2; $W_{3\ vs.\ 600}$ and $p_{3\ vs.\ 600}$, Wilcoxon intragroup T-test and statistical significance of difference between psd_24_900_3 and psd_24_600.

In the study of intragroup differences in PSD parameter in Group 1, W=-0.432; p=0.665), and in Group 2, W=0.189; p=0.849. In the study of intergroup differences in this parameter at the onset of our research, W=-1.315; p=0.188; at the end of the study, W=-0.657; p=0.519. When comparing the measurements of MD at the beginning and at the end of the study for both groups combined, W=-0.566; p=0.571.

Thus, there were no statistically significant differences in MD and PSD between the onset and the end of our study.

According to previously published studies, the reproducibility of measurements of retinal photosensitivity via standard automated perimetry was about 2 dB, due to physiological fluctuations and replicability of the study [17, 18]. This finding suggests that the differences obtained during the study may be random, and generally fit within the limits of the earlier described retinal photosensitivity fluctuations. In long-term clinical studies, for a clearer understanding of the trend of changes, it is better to use trends that more obviously reflect the dynamics of the process [13, 19].

Study limitations

Small sample size in our study is an important factor, since in order to identify statistically significant dynamics of retinal photosensitivity according to standard automated perimetry data, changes must be above 2 dB [17, 18], thereby exceeding the physiological fluctuations in standard automated perimetry. With a follow-up period of 6 months, against the background of compensated IOP and presumed stabilization of the glaucoma process, the probability of registering such pronounced changes is very low.

As for the comparison of using two different instruments and different research programs, the sample size becomes not so critical, since all observations are compared for both groups of observations, and the resulting sample size allows using parametric methods of statistical analysis. However, perimetry data are extremely rarely evenly distributed in a sample, to say nothing of a total population. For this reason, nonparametric methods for comparing trends of the mean were chosen, which are in no way inferior in power and efficacy to parametric methods of analysis. For example, the statistical power of the study, when using a two-sided test for comparing devices and programs with a given average value of photosensitivity of 4.0 dB (in our case, 4.069±3.4 dB for the G-dynamic program), standard deviation of 3.0 dB, type I error of 5%, and the sample size of 34 observations is 82%, which is an acceptable power level for this kind of research [20].

Conclusion

As a result of conducting treatment for 6 months in both groups receiving retinoprotective therapy with Retinalamin every 3 (Group 1) or every 6 months (Group 2), the photosensitivity of the retina did not change statistically significantly. However, in both groups, we observed a positive trend in in terms of MD and PSD of the mean retinal photosensitivity, and an increase in indicator values 6 months after the onset of the study. Different instruments (Octopus 600 and Octopus 900 perimeters) and different programs (24-2 and G-dynamic) yielded different results due to their technical features and capabilities of reproducibility, but these differences were not statistically significant. Moreover,

the recorded differences did not exceed the replicability index specified in the published data sources.

Conflict of interest

None declared.

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