Original Research Article

Functional and hemodynamic efficacy of non-poliferative diabetic retinopathy treatment by endonasal electrophoresis of Tanakan

ABSTRACT

Aims: To study the effectiveness of the treatment of patients with non-proliferative diabetic retinopathy by tanakan endonasal electrophoresis according to functional and hemodynamic data.

Study design: Cross-sectional comparative analysis

Place and Duration of Study: Department of Ophthalmology, clinic of Tashkent Medical Academy, between 2017 and 2020.

Methodology: We included 66 patients (123 eyes), 23 men and 43 women; age range 18-75 years with non-proliferative diabetic retinopathy. The patients were divided into 2 groups: to receive daily tablets of Tanakan (control), or daily endonasal electrophoresis of Tanakan (main) within ten days. Before and after the course of therapy, the patients underwent determination of visual acuity, Doppler ultrasound imaging of the eye and computer static perimetry.

Results: Improvements in visual acuity were observed in 87,3% of the main group patients, and in 22% of the control group. Statistically significant increase in blood flow velocity and a decrease in the resistance index were observed in the main group ($P < 0.05$). Retinal photosensitivity increased by 22% in the main group, and by 10% in the control group. The mean deviation from the age norm decreased by 33% in the main group and by 12% in the control group. Among the patients of the main group, 30% experienced a decrease in absolute scotomas and 100% in relative scotomas. Among the patients of the control group, 21% and 83% experienced a decrease in absolute and relative scotomas, respectively.

Conclusion: Treatment with tanakan endonasal electrophoresis significantly improved visual acuity, eye hemodynamics, and retinal photosensitivity. This treatment is more effective than the traditional use of ginkgo- biloba tablets.

Keywords: nonproliferativ diabetic retinopathy, endonazal electrophoresis, antioxidant, Color Doppler imaging, microcirculation, systolic velocity, microaneurysms, hemorrhages, intraretinal microvascular abnormalities, photosensitivity, scotomas.

Introduction

Diabetic retinopathy (DR) is the most common and dangerous manifestations of diabetes and, when left untreated, leads to complications such as vitreous hemorrhage and tractional retinal detachment. Early treatment to prevent severe forms of DR may help to avoid vision loss and blindness [1]. Therefore, it is necessary to find a method for the treatment of early forms of nonproliferative diabetic retinopathy (NPDR) [2,3]. Numerous studies of the last decade have been devoted to the use of tanakan (Ginkgo biloba extract EGb 761) in ophthalmology and neurology. EGb 761 has an antioxidant, neuroprotective and blood rheological effect and is used as a pathogenetic agent in the treatment of various forms of DR. [4,5,6,7,8,9,10,11,12]. However, in tablet form, the drug has a delayed cumulative effect, obtained only with long-term systematic use - from 3 to 9 months, which prevents its widespread use due to its high cost. We were interested in studies in which tanakan was used in the form of endonasal electrophoresis in neurology in the treatment of early forms of cerebrovascular diseases and sleep disorders [13,14].

It is known that physical healing factors, which have both local and general effects, activate the body's adaptive reactions, improve microcirculation and normalize metabolic processes. The penetration of drugs into the body is much more intense under the influence of electric current. One of these electropharmacological methods is drug electrophoresis, which is based on a complex, i.e. simultaneous effect on the patient's body of a constant electric current and a medicinal substance entering the blood and lymph with current through the mucous membrane and intact skin. Conventional electrophoresis methods used in ophthalmology (tray and transpalpebral) are not effective enough in the treatment of lesions of the posterior segment of the eye due to the small depth of drug penetration into the eye.

Therefore, a method based on the combined action of galvanic current and a medicinal substance administered by endonasal electrophoresis is very relevant in the treatment of pathology of the posterior segment of the eye. The drug penetrates through the nasal mucous membrane through the perineural slots of the branches of the olfactory and trigeminal nerves and lymphatic vessels directly into the cerebrospinal fluid of the basal cisterns of the brain, and then through the perineural spaces into the optic nerve and retina.

The aim of this study was to explore the efficacy of tanakan endonasal electrophoresis in the treatment of non-proliferative DR.

Material and methods

Clinical studies were carried out during the treatment of 66 patients (123 eyes) with non-proliferative diabetic retinopathy. Age ranged from 20 to 75 years, women - 43, men - 23. The exclusion criteria were eye diseases such as inflammatory eye diseases, eye injury or intraocular surgery, glaucoma, retinal dystrophies, as well as severe somatic diseases such as glucose-galactose malabsorption, kidney or liver failure, hypertensive crisis. [15].

Patients were randomly allocated to receive traditional treatment with daily tablets of EGb 761 (Tanakan, Beaufour Ipsen Industrie, Paris, France) 120 mg as the control group, or daily endonasal electrophoresis of Tanakan 40 mg (permission of the National Ethics Committee of the Ministry of Health of the Republic of Uzbekistan No. 11 of 2.11.2010) as the main group, within ten days.

Procedures

The technique of endonasal electrophoresis. A solution of tanakan EGb 761 in a dose of 1ml was diluted in 10 ml of distilled water at room temperature. To perform

the procedure, gauze turundas, abundantly soaked with the obtained solution of tanakan, were introduced into both nostrils of the patient using tweezers. The free ends of the gauze turundas were brought out onto a rubber plate under the nose above the upper lip and a first electrode in the form of a 1.5 x 3 cm conductive plate connected to the positive terminal of the device was placed on them. A second electrode was placed on the back of the neck. All this was firmly fixed with a bandage. The procedure was carried out from 12 to 20 minutes The current was gradually increased from 1 mA to 3 mA. Number of procedures 10 per treatment course. (Rationalization proposal №604 by 13.05.2011, Tashkent, TMA).
Before and after the course of therapy, the patients underwent determination of visual acuity, Doppler ultrasound imaging of the eye and computer static perimetry. Visual acuity was determined using the Snellen chart. Hemodynamics was studied using an ultrasound system for general clinical HD 11XE (Philips), and HI VISION Preirus (Hitachi) with a linear sensor with a frequency of 7-12 MHz in a pulsed mode.

Visual fields study was conducted using the computer visual field analyzer “Octopus” (Interzeag AG, Switzerland), using the threshold program 60-2 with the determination of the threshold photosensitivity of the retina, deviations from the age norm, the presence of relative and absolute scotomas.

Results & Discussion

The stages of DR were determined using the severity scale of the Early Treatment Diabetic Retinopathy Study (ETDRS), the "gold" standard for a detailed assessment of the fundus condition in scientific studies worldwide. [16,17]. According to the classification, the following stages of NPDR are distinguished: 1. Mild NPDR - the presence of at least one microaneurysm and hemorrhages in one quadrant of the fundus. 2. Moderate NPDR - more retinal hemorrhages in all 4 quadrants of the

fundus (but not more than 20), venous beading are absent or are detected only in 1 quadrant, single hard and soft exudates. 3. Severe NPDR - if at least one of the following signs is detected (rule 4:2:1): more than 20 intraretinal hemorrhages in each of the 4 quadrants of the fundus; venous beading found in at least 2 quadrants; intraretinal microvascular abnormalities (IRMA), arteriovenous shunts in at least one quadrant.

Color Doppler imaging (CDI) were used to visualize blood flow in the ophthalmic artery (OA), central retinal artery (CRA), central retinal vena (CRV), short posterior ciliary artery (SPCA) and register the blood flow spectrum. We determined the following blood flow indicators: maximum systolic velocity (Vs), end diastolic velocity (Vd), resistance index or peripheral resistance (RI), as well as pulsation index (PI), ischemia coefficient and ophthalmo-retinal coefficient.

Patients in both groups tolerated the treatment well. No local or general adverse reactions were noted. Among patients of the main group, 87.3% experienced a significant positive effect as increased visual acuity, and a small percentage (12.7%) of patients did not experience changes. Among patients in the control group, only 22% of patients experienced an increase in visual acuity after completion of the 10-day course of treatment (Table 1).

Table 1. **Dynamics of changes in visual acuity (Mean ± SD)**

Visual acuity range at	Control group (n=32)		Main group (n=34)	
	Baseline	After	Baseline	After
0.01-0.09	0.04±0.01	0.06±0.02	0.05±0.01	0.2±0.07*
0.1-0.9	0.5±0.04	0.55±0.06	0.52±0.02	0.7±0.08*

Notes: * $P < 0.05$; ** $P < 0.01$ – from baseline; SD: Standard deviation.

As previously reported, examination of the fundus revealed a decrease in the number of hemorrhages, foci of soft and hard exudates, the disappearance of macular edema by 24.1% in the main group, and by 8.2% in the control group from baseline [15,18].

A study of the hemodynamics of the eyeball and retrobulbar space revealed an increased blood flow in the CRA and AO at the mild NPDR and a progressive decrease in blood flow in the CRA, SPCA and AO at the moderate NPDR and severe NPDR at baseline.

Patients of the main group experienced a statistically significant increase ($P < 0.05$) in peak systolic velocity (Vs) of CRA from 10.1±1.3 cm/s at baseline to 13.5±0.9 cm/s after treatment, a significant increase ($P < 0.01$) in Vs of CRV from 4.1±0.9 cm/s at baseline to 6.7±0.2 cm/s after treatment, a significant decrease ($P < 0.01$) in RI and PI of CRA from 0.89±0.04 at baseline to 0.65±0.03 after treatment and from 1.7±0.2 at baseline to 1.03±0.04 after treatment, respectively (Table 2). Patients of the control group experienced a nonsignificant increase ($P > 0.05$) in peak systolic velocity (Vs) of CRA from 10.9±1.2 cm/s at baseline to 12.9±1.4 cm/s after treatment, nonsignificant increase ($P > 0.05$) in Vs of CRV from 3.9±0.3 cm/s at baseline to 5.3±0.8 cm/s after treatment, nonsignificant decrease ($P > 0.05$) in RI of CRA from 0.91±0.06 at baseline to 0.78±0.06 after treatment.

Table 2. **Dynamics of blood flow in the vessels of the eye (Mean ± SD)**

	Main group (n=34)		**Control group (n=32)**	
	Baseline	**After**	**Baseline**	**After**
CRA:				
Vs, cm/s	10.1±1.3	13.5±0.9*	10.9±1.2	12.9±1.4
Vd, cm/s	2.6±0.3	3.4±0.1*	2.1±0.2	3.3±0.4*
RI	0.89±0.04	0.65±0.03**	0.91±0.06	0.78±0.06
PI	1.7±0.2	1.03±0.04**	1.7±0.2	1.2±0.06*

CRV:				
Vs, cm/s	4.1±0.9	6.7±0.2**	3.9±0.3	5.3±0.8
SPCA:				
Vs, cm/s	10.3±0.9	13.5±1.2*	11.2±1.2	12.5±0.8
Vd, cm/s	2.6±0.2	4.1±0.7*	2.8±0.7	3.5±0.5
RI	0.82±0.03	0.64±0.03**	0.84±0.04	0.77±0.06
PI	2.8±0.28	1.02±0.3**	3.0±0.29	1.5±0.17**
AO				
Vs, cm/s	30.6±2.2	37.5±2.5*	32.6±4.1	35.3±3.5
Vd, cm/s	5.8±0.5	7.3±0.8	6.0±3.2	7.4±2.2
RI	0.85±0.03	0.76±0.03*	0.83±0.1	0.75±0.07
PI	1.9±0.1	1.3±0.2**	1.85±0.2	1.5±0.06

Notes: $^{*}P < 0.05$; $^{**}P < 0.01$ – from baseline; SD: Standard deviation; Vs: peak systolic velocity, Vd: end-diastolic velocity, PI: pulsatility index, RI: resistivity index, CRA: central retinal artery, CRV: central retinal vena, SPCA: short posterior ciliary artery, OA: ophthalmic artery

In the majority of patients with the mild NPDR, the peak systolic velocity were maintained (12.5 - 14 cm/s) from baseline to month after treatment. Among these patients, two patients with increased blood flow velocity (25.6 and 18.7 cm/s) even experienced a decrease in blood flow velocity to normal values (15.7 and 14.5 cm/s, respectively). Our finding of increased blood flow velocity and increased perfusion in the early years of poorly controlled diabetes associated with hyperglycemia was similar to that of several authors. Prolonged overload of the microvasculature leads to subsequent morphological changes in the vessel wall [19,20,21,22]. Therefore, the normalization of blood flow in the mild NPDR has a positive effect, preventing the progression of DR.

According to static computer perimetry data, the retinal photosensitivity statistically significantly increased by 22% in the main group and nonsignificantly increased by 10% in the control group, the mean deviation from the age norm decreased by 33% in the main group and by 12% in the control group after treatment.

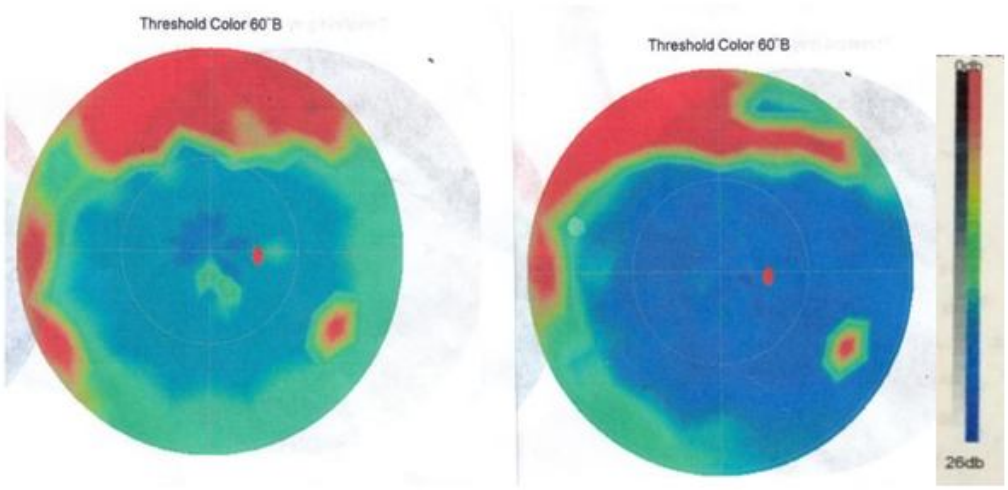
Among the patients in the main group, 30% experienced a decrease in absolute scotomas and 100% in relative scotomas. Among the patients in the control group, 21% and 83% experienced a decrease in absolute and relative scotomas, respectively (Table.3).

Table 3. Indicators of static computer perimetry (Mean ± SD)

Indicators	Main group (n=34)		Control group (n=32)	
	Baseline	After	Baseline	After
MS, dB	13,60±0,63	16,61±0,37**	13,66±0,73	15,05±0,85
MD, dB	9,31±0,60	6,23±0,32**	8,67±0,75	7,6±0,85
absolute. scot.	6,17±2,42	3,12±1,11	8,17±1,5	6,83±1,4
relative. scot.	28,5±2,72	11,5±1,71**	34,5±2,4	26,5±2,5*

Notes: *P < 0,05; ** P < 0,01 – from baseline; SD: Standard deviation; MS – mean retinal photosensitivity; MD – mean deviation from the age norm; dB - decibel

Case example 1. Patient H-va with moderate NPDR. Best-corrected visual acuity OD/OS = 0.5/0.7 at baseline. We found dilated and tortuous veins, narrowed arteries in the fundus. There are microaneurysms, petechial hemorrhages, hard exudates. There is macular edema in the right eye. Mean retinal photosensitivity of the right eye is 14.30 db, the left eye is 17.19 db. The peak systolic velocity in the short posterior ciliary artery (SPCA) on the right is 9.05 cm/s; left 9.06 cm/s. The patient received endonasal tanakan electrophoresis within ten days. Number of procedures 10 per course. After treatment best-corrected visual acuity OD/OS = 0.9/1.0. The patient experienced a decrease in the number and size of hemorrhages and foci of hard exudates, the disappearance of macular edema in the right eye. The mean retinal photosensitivity of the right eye increased to 17.89 db, of the left eye - up to 17.91 db (Fig. 1). Peak systolic velocity in SPCA increased on the right to 18.7 cm/s; on the left up to 13.1 cm/s (Fig. 2, 3)



a b

Figure 1. Retinal photosensitivity of the right eye of the patient H-va with moderate NPDR. a– baseline; b – one month after treatment with tanakan - endonasal electrophoresis.

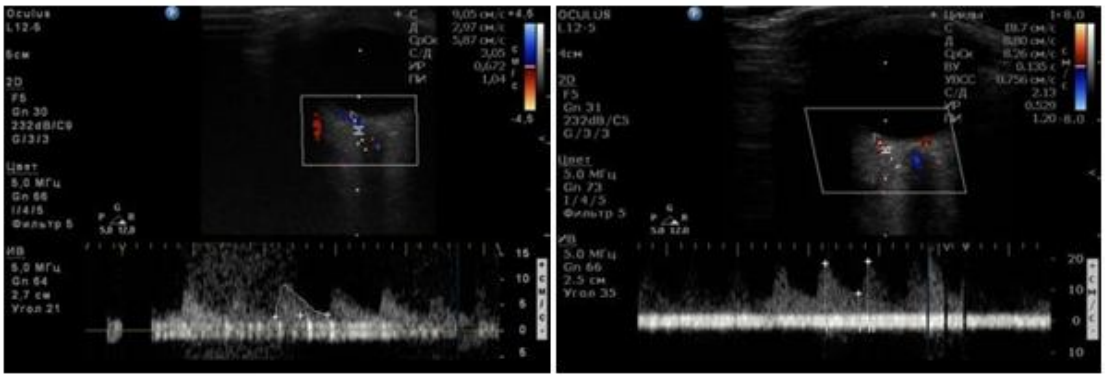


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Figure 2. Color Doppler imaging of the right eye of the patient H-va with moderate NPDR. Peak systolic velocity in SPCA: a– baseline; b – one month after treatment with tanakan - endonasal electrophoresis.

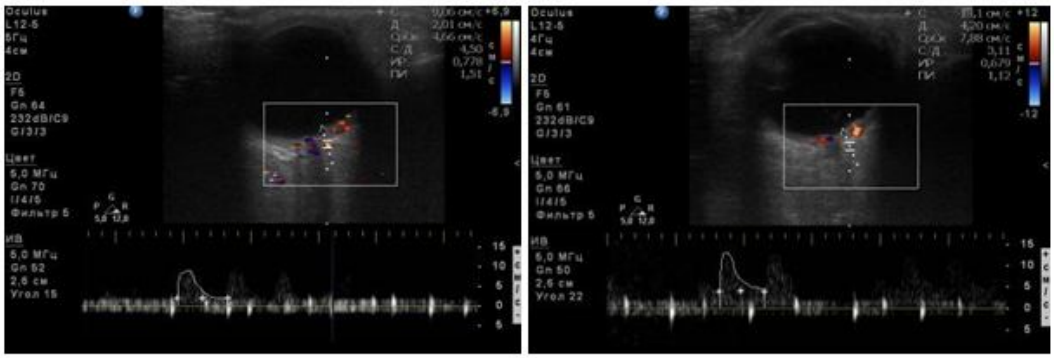

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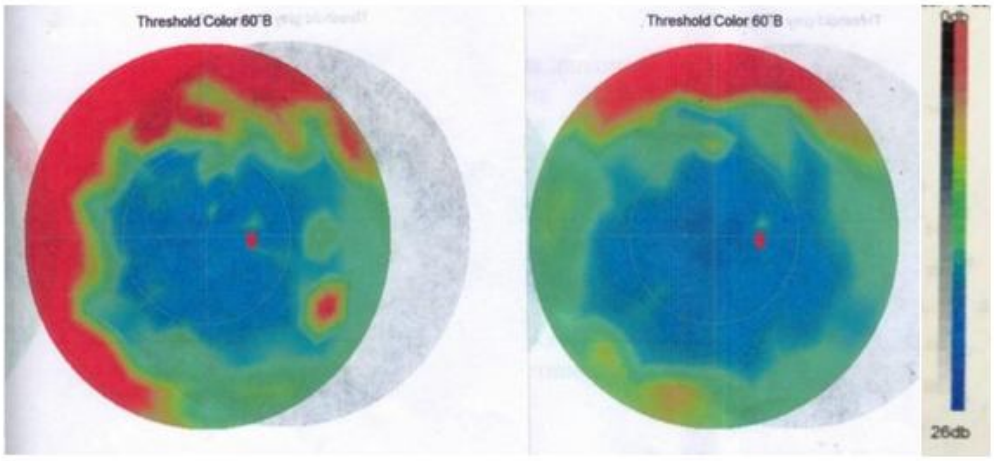
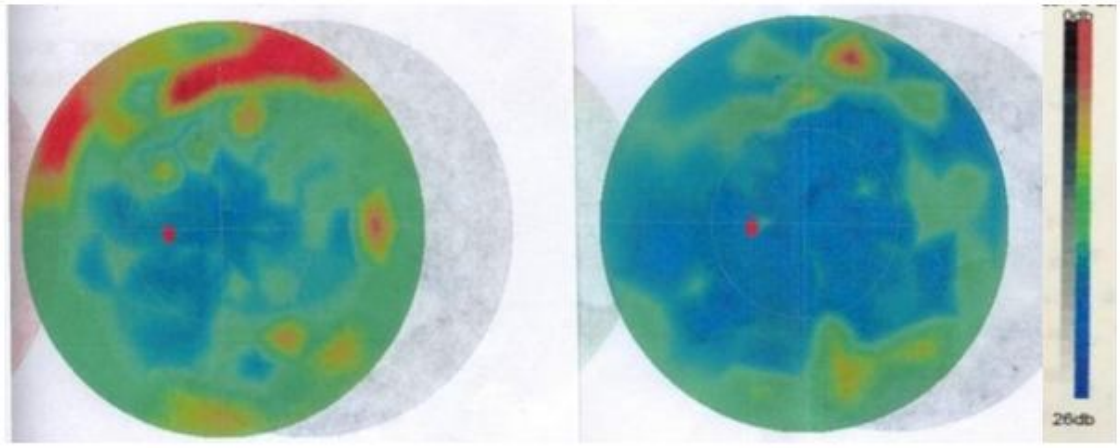
Figure 3. Color Doppler imaging of the left eye of the patient H-va with moderate NPDR. Peak systolic velocity in SPCA: a– baseline; b – one month after treatment with tanakan - endonasal electrophoresis..

Case example 2. Patient I-va with moderate NPDR in the right eye and with severe NPDR in the left eye. Best-corrected visual acuity OD/OS = 0.6/0.4 at baseline. We found dilated and tortuous veins, narrowed arteries in the fundus. There are microaneurysms, petechial hemorrhages, hard and soft exudates. Venous beading and vascular loops were found in the left eye at 2 quadrants of the retina. Mean retinal photosensitivity of the right eye is 14.85 db, the left eye is 14.60 db. The peak systolic velocity in the short posterior ciliary artery (SPCA) on the right is 6.4 cm/s; left 5.79 cm/s. The patient received endonasal tanakan electrophoresis within ten days. Number of procedures 10 per course. After treatment best-corrected visual acuity OD/OS = 0.7/0.5. The patient experienced a decrease in the number and size of hemorrhages and foci of hard exudates, the disappearance of macular edema in the right eye. The mean retinal photosensitivity of the right eye increased to 17.19 db, of the left eye - up to 17.81 db (Fig. 4, 5). Peak systolic velocity in SPCA increased on the right to 15.7 cm/s; on the left up to 12.8 cm/s (Fig.6).



a b

Figure 4. Retinal photosensitivity of the right eye of the patient I-va with moderate NPDR. a– baseline; b – one month after treatment with tanakan endonasal electrophoresis.



a b

Figure 5. Retinal photosensitivity of the left eye of the patient I-va with severe NPDR. a– baseline; b – one month after treatment with tanakan endonasal electrophoresis.

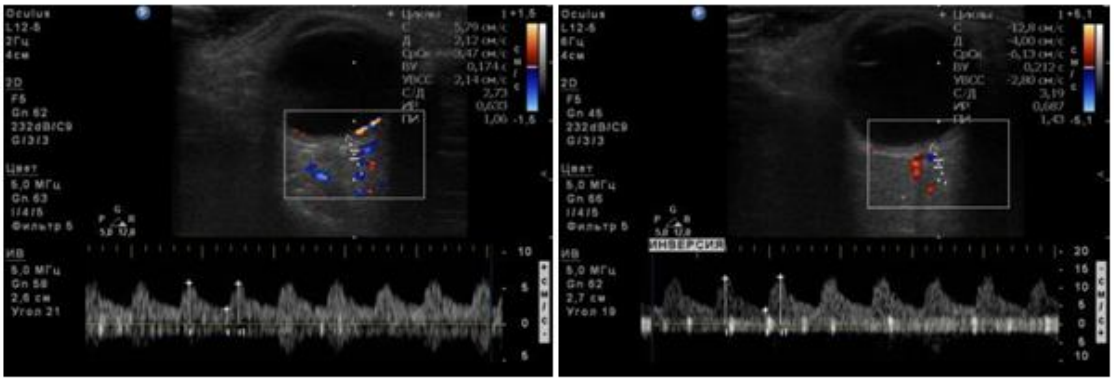


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Figure 6. Color Doppler imaging of the left eye of the patient I-va with severe NPDR. Peak systolic velocity in SPCA: a– baseline; b – one month after treatment with tanakan - endonasal electrophoresis.

Conclusions

The obtained results showed that tanakan endonasal electrophoresis is more effective than tanakan tablets, and leads to faster recovery of visual functions, improvement of hemodynamic parameters, and regression of pathological changes in the fundus. Patients of the main group experienced a significant increase ($P < 0.05$) in peak systolic velocity, and a significant decrease ($P < 0.01$) in RI and PI after treatment, while patients of the control group experienced a nonsignificant change in Vs, RI, and PI after treatment. We observed a significant increase by 22% in retinal photosensitivity in the main group and a nonsignificant increase by 10% in the control group. Taken together, findings from our research have important implications for clinical practice and the management of patients with diabetic eye disease.

Ethical Approval and Consent:

All patients signed informed consent for treatment and examination. The study was conducted according to the principles of the Declaration of Helsinki and the study protocol was approved by the institutional ethics committee. Informed consent was obtained from all participants

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