EVALUATING THE EFFECTIVENESS OF FRUCTOSE-1,6-DIPHOSPHATE IN TREATING OF OCULAR ISCHEMIC SYNDROME

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ABSTRACT
The purpose of this study was to evaluate the efficacy and safety of FDP in patients with ocular ischemic syndrome.

Material and methods. The material for this study is based on results of a comprehensive examination and treatment of 53 patients with a diagnosis OIS. The average age of the patients was 57.8 ± 6.82 year. 19 of them women, 34 men. 27 patients entered to the main group (1) which received standard therapy in combination with intravenous FDP (fructose 1,6-bisphosphate). 26 patients in the control group (2) received standard treatment.

Results. In applying the FDP combined with comprehensive therapy in the main group resulted in increased of visual acuity by 32.8%, parameters of retinal sensitivity by 17.8%, reducing the area of scotomas compared with patients of the control group. Optical coherence tomography registered significant changes in the dynamics in patients of the main group - reducing the edema and restoration of RNFL and ONH. Recovery of visual function may have contributed neuroprotective activity of the drug FDP by a protective effect on nerve tissue, reducing the effects of hypoxic stress.

Conclusions. The use of standard therapy in combination with FDP in the treatment of ocular ischemic syndrome has a positive effect on the course of the disease, thereby, increase of visual acuity, a decrease in sectoral loss in vision fields, the positive dynamics OCT parameters, improving hemodynamic parameters at Doppler imaging in dynamics.

UDC CODE & KEYWORDS
UDC: 617.7:616-008.6-005.4-08 ■ Ocular ischemic syndrome ■ The treatment of ischemic diseases of the eye ■ FDP ■ Metabolic therapy of ocular ischemic syndrome

INTRODUCTION
Ocular ischemic syndrome is a rare condition, which is caused by ocular hypoperfusion due to stenosis or occlusion of the common or internal carotid arteries. Atherosclerosis is the major cause of changes in the carotid arteries (Kearns & Hollenhorst, 1963). OIS occurs mostly in patients with poor collateral circulation between the internal and external carotid arteries or between the two internal carotid arteries (Mendrinos, Machinie & Pournaras 2010, Mizener, Podhajsky & Hayreh, 1997). Since OIS is associated with atherosclerosis, patients usually have other related co-morbidities. Hypertension is found in 73% of the patients and diabetes mellitus in 56% (Sharma & Brown, 2006). Myocardial infarction occurs in approximately 4% of patients with OIS (Sharma & Brown, 2006). The mortality rate is as high as 40% within 5 years of onset (Sharma & Brown, 2006). Cardiovascular disease is the main cause of death (approximately 66%), followed by stroke as the second leading cause of death (Ryan, Hinton & Schachat, 2004), which is why patients with OIS should be referred to the cardiologist, for imaging studies of the carotid arteries, and to the vascular surgeon (Barbara, Terelak-Borys, Katarzyna, Skonieczna, Iwona & Grabska-Liberek, 2012).

Therefore, during treatment of OIS, to eliminate hypoxic and ischemic processes, and improve metabolic processes should be performed courses of conservative therapy with drugs that improve metabolic processes in the tissues, as well as reduce the hypoxic manifestations in organs and tissues of the eye.

Such drug is the FDP, which is used in cardiology, neurology and pediatric neurology in ischemic processes of organs and tissues (ischemic stroke, myocardial infarction, and others).

Fructose-1,6-diphosphate (FDP) is a key intermediate in anaerobic glycolysis and is the product of the major regulatory enzyme in the pathway (phosphofructokinase). Preclinical and clinical data suggest that FDP has substantial cytoprotective effects in a variety of ischaemia-reperfusion injury scenarios. Evidence indicates that FDP has a direct effect on ATP pools, reduces ischaemia-induced tissue damage and has positive inotropic effects on heart function. The clinical data suggest that FDP may be a useful drug in a variety of ischaemic and inflammatory clinical settings where acute management of tissue injury is desired (Marangos, Fox, Riedel, Royston & Dzwilawonska, 1998).

According to the literature, intravenous injection of FDP during cerebral hypoxia and ischemia restores vital energy of brain cells, the ion gradient of neuronal membranes, thereby minimizing damage of the cerebral cells (Karaca, Klic, Yazici, Demir & Torre, 2002). In addition, the "surviving" effect of FDP is also demonstrated in ischemia of the kidneys, small intestine, coronary heart disease, brain disease, as well as with lower limb ischemia (Karaca, Klic, Yazici, Demir & Torre, 2002; Riedel, Gal, Ellis, Marangos, Fox, & Royston, 2004).

Considering the above we conducted a study, where as an anti-ischemic and neuroprotective drug in patients with ocular ischemic syndrome used FDP.

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Purpose
Evaluate the efficacy and safety of fructose-1,6-diphosphate in patients with ocular ischemic syndrome.

Material and Methods
The material for this study is based on results of a comprehensive examination and treatment of 53 patients with a diagnosis OIS. The study was conducted in the Republican Clinical Eye Hospital under the Ministry of Health of the Republic of Uzbekistan (Tashkent) from 2012 to 2014.

General examination of patients consisted of complaints, medical history, as well as the measurement of blood pressure, heart rate. In all patients was performed a comprehensive ophthalmologic examination, including visometry, tonometry, computerized static perimetry, gonioscopy, biomicroscopy, fundus ophthalmoscopy. Special methods of investigation include ultrasound dopplerography of vessels of the organ of vision and the brachiocephalic trunk.

Visometry according to EN ISO 8596 (European standard) conducted on Snellenstable (20/200) or Landolt rings. Tonometry was performed by the method of Goldman. Biomicroscopy of the eyeball conducted slit lamp company «Carl Zeiss». Fundus ophthalmoscopy were performed by ophtalmoscope «Heine» and fundus-camera «Carl Zeiss».

Computer static perimetry was performed using the perimeter of Humphrey Field Analyzer 740i (Carl Zeiss Meditec inc.) by programme central threshold test 30-2 and peripheral test 60-4. All results were recorded using a digital marking with the general analysis of indexes MD (mean deviation sensitivity of the retina) and PSD (pattern standard deviation). The distance between the test points was 6°.

To estimate the parameters of the optic nerve (optic disk) all patients underwent examination optical coherence tomography (OCT) Cirrus HD - OCT (Zeiss, Spectral Domain Technology). Explored the area of the optic nerve (protocol ONH) and the area of the retina (RNFL).

Ultrasound examination with color Doppler mapping in 3D mode was performed by transpalpebral contact method using multiultrasonic instrument («VOLUSON 730 PROGE»). Doppler of the extracranial and intracranial segments of the main vessels of the brachiocephalic trunk was performed to analyze the state, caliber, patency and hemodynamics at the internal, external and common carotid arteries. In order to visualize blood flow in the ophthalmic artery, central retinal artery and its branches used ophtalmodopplerography.

The studies were conducted in the dynamics: before treatment, after treatment and 3 months after treatment. All patients were randomized by the method of stratification by diagnosis, age, sex, visual function, and concomitant diseases.

Statistical Methods
We used a variational methods of parametric and nonparametric statistics with the calculation of the arithmetic mean of the studied parameter(M), standard deviation(σ), standard error of the mean (m) and relative values (frequency,%). The statistical significance of the measurements by comparing the mean values was determined by Student’s test (t) with the calculation of the probability of error (P) when checking normality of distribution (by the excess) and the equality of the population variance (F - Fisher’s exact test). For statistically significant changes have taken level of confidence P < 0.05.

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**Results**

According to the study in 12 patients the diagnosis OIS was based on central retinal artery occlusion combined with anterior ischemic optic neuropathy. In 11 patients was observed pseudoxplofoliative syndrome in combination with occlusion of the central retinal artery and cataract. In 11 patients central retinal vein thrombosis combined with anterior ischemic neuropathy. In 10 patients occlusion of the central retinal artery developed in conjunction with anterior ischemic neuropathy and open-angle glaucoma. In 9 patients there was occlusion of the central retinal artery in combination with open-angle glaucoma and cataract. All patients with the above nosologies were evenly divided in the main and control groups for therapeutic measures.

In the main group visual acuity of patients before treatment was 20/340 on average. In the control group the visual acuity of patients before treatment was 20/320 on average.

Ophthalmoscopy of the fundus: optic disk was round shape in 25 (47.16%) patients, oval - in 28 (52.83%) patients, paley-pink in 7 (13.2%) patients, pale - 43 (81.13%) patients, hyperemic - 3 (5.66%) patients.

The boundaries of the optic disc are distinct in 3 (5.66%), indistinct - in 17 (32.07%), were not detected in 33 (62.26%) patients. Papilledema was observed in 45 (84.9%), peripapillary edema in 26 (49.05%) cases. Narrowed artery in 47 (88.67%), normal-caliber veins in 8 (15.09%), the veins are narrowed in 31 (58.49%), expanded in 14 (26.41%) patients. In 23 (43.39%) patients were visualized locuses of hemorrhages. Cotton-like locuses were observed in 17 (32.07%) patients. Spontaneous pulsation of the arteries was observed in 23 (43.39%) patients.

In 47 (88.67%) patients in the OCT before treatment showed an increase in the thickness of the neuroretinal area, high edema ONH and peripapillary zone.

Analysis of the data computed perimetry showed an absolute scotoma in 23 (43.39%), concentric narrowing of the visual field in 21 (39.62%) patients. In the main group the mean deviation of retinal sensitivity (MD) before treatment was $-14.17 \pm 1.29$ dB, pattern standard deviation (PSD) - $6.24 \pm 0.51$ dB (p <0.05). In the control group before treatment MD was $-13.93 \pm 1.42$ dB (p <0.05), PSD - $6.51 \pm 0.49$ dB (p <0.05).

At Doppler ultrasound of the eyes revealed hemodynamically significant asymmetry of the velocity parameters of blood flow in the central retinal artery in 24 (45.28%) patients, the posterior short ciliary arteries in 28 (52.83%) in the ophthalmic artery in 42 (79.24%) patients. In 47 (88.67%) patients had a decrease in blood flow velocity parameters by ophthalmic artery with signs spasm of the peripheral arterioles.

In these patients the aforementioned changes combined with an increase of resistivity index by the central retinal artery and posterior short ciliary arteries varying degrees, indicating that the deterioration of the blood supply in the organ of vision.

In the main group before treatment hemodynamic parameters averaged: ophthalmic artery - $V_{\text{max}} 36.2 \pm 2.13$ cm/s, $V_{\text{min}} 10.9 \pm 1.12$ cm/s, RI $0.51 \pm 0.01$; central retinal artery - $V_{\text{max}} 8.9 \pm 0.97$ cm/s, $V_{\text{min}} 3.2 \pm 0.21$ cm/s, RI $0.43 \pm 0.02$; posterior short ciliary arteries - $V_{\text{max}} 12.4 \pm 0.78$ cm/s, $V_{\text{min}} 5.3 \pm 0.13$ cm/s, RI $0.47 \pm 0.07$, while in the control group: ophthalmic artery - $V_{\text{max}} 12.1 \pm 0.81$ cm/s, $V_{\text{min}} 9.3 \pm 1.19$ cm/s, RI $0.42 \pm 0.01$; central retinal artery - $V_{\text{max}} 8.9 \pm 0.97$ cm/s, $V_{\text{min}} 3.2 \pm 0.21$ cm/s, RI $0.41 \pm 0.05$; posterior short ciliary arteries - $V_{\text{max}} 12.1 \pm 0.81$ cm/s, $V_{\text{min}} 5.1 \pm 0.19$ cm/s, RI $0.46 \pm 0.09$.

After the course of the treatment changes in the blood pressure and heart rate were not revealed.

In patients of both groups after treatment was a decrease in edema of the optic disc and peripapillary zones, areas of hemorrhage and colton-like locuses.

After treatment in the main group visual acuity of patients in the affected eye improved by 32.8% and amounted to 20/60, the intraocular pressure in the normal range. In the control group the visual acuity in the affected eye improved by 9.4%, the intraocular pressure in the normal range. In the control group the visual acuity in the affected eye improved by 9.4%.

After treatment in patients of the main group MD and PSD increased by 17.8% and amounted: $-9.29 \pm 1.18$ dB, $-11.18 \pm 1.09$ dB, $-12.51 \pm 1.12$ dB, $-13.93 \pm 1.42$ dB respectively, while in the control group MD and PSD increased by 9.2% and amounted: $-9.29 \pm 1.18$ dB, $-11.18 \pm 1.09$ dB, $-12.51 \pm 1.12$ dB, $-13.93 \pm 1.42$ dB (p <0.05) (table 1). On the computer perimetry absolute scotoma in dynamics decreased in both groups.

On optical coherence tomography papilledema and peripapillary zone in dynamics decreased in both groups.

After treatment in the main group noted improvement in blood flow in main arteries of eye by 16.57%, after 3 month was 17.95% from the initial level. In the control group hemodynamic parameters in main arteries of eye after treatment was improved by 7.2%, after 3 month 7.4% (tables 1,2,3).

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**Table 1:** Parameters of computed perimetry

<table>
<thead>
<tr>
<th>Parameters of computed perimetry</th>
<th>Main group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>After treatment</td>
<td>After 3 months</td>
</tr>
<tr>
<td>Before treatment</td>
<td>After treatment</td>
<td>After 3 months</td>
</tr>
<tr>
<td>MD dB</td>
<td>$-14.17 \pm 1.29$ dB</td>
<td>$-13.93 \pm 1.42$ dB</td>
</tr>
<tr>
<td>Vmax cm/s</td>
<td>$42.2 \pm 1.13$ cm/s</td>
<td>$42.1 \pm 1.13$ cm/s</td>
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<tr>
<td>Vmin cm/s</td>
<td>$9.3 \pm 1.17$ cm/s</td>
<td>$9.3 \pm 1.17$ cm/s</td>
</tr>
<tr>
<td>RI</td>
<td>$0.51 \pm 0.013$</td>
<td>$0.44 \pm 0.021$</td>
</tr>
</tbody>
</table>

*Statistically significant changes are level of confidence $P<0.05$

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**Table 2:** Hemodynamic parameters in ophthalmic artery

<table>
<thead>
<tr>
<th>Hemodynamic parameters in ophthalmic artery</th>
<th>Main group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before treatment</td>
<td>After treatment</td>
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</tr>
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<td>After treatment</td>
<td>After 3 months</td>
</tr>
<tr>
<td>Vmax cm/s</td>
<td>$36.2 \pm 1.19$ cm/s</td>
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<tr>
<td>Vmin cm/s</td>
<td>$10.3 \pm 1.17$ cm/s</td>
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<td>RI</td>
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</table>

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### Table 3: Hemodynamic parameters in central retinal artery

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Central retinal artery</th>
<th>Main group Before treatment</th>
<th>After treatment</th>
<th>After 3 months</th>
<th>Control group Before treatment</th>
<th>After treatment</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vmax cm/s</td>
<td>8.9±0.97*</td>
<td>10.7±0.95*</td>
<td>11.6±0.96*</td>
<td>9.2±0.61*</td>
<td>9.7±0.74*</td>
<td>9.9±0.47*</td>
<td></td>
</tr>
<tr>
<td>Vmin cm/s</td>
<td>3.2±0.21*</td>
<td>4.8±0.15*</td>
<td>4.97±0.21*</td>
<td>3.40±0.12*</td>
<td>3.5±0.21*</td>
<td>3.9±0.59*</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.43±0.021*</td>
<td>0.49±0.019*</td>
<td>0.53±0.020*</td>
<td>0.41±0.071*</td>
<td>0.46±0.031*</td>
<td>0.47±0.071*</td>
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</tr>
</tbody>
</table>

*Statistically significant changes are level of confidence P < 0.05

Source: Author

### Table 4: Hemodynamic parameters in posterior short ciliary arteries

<table>
<thead>
<tr>
<th>Hemodynamic parameters</th>
<th>Posterior short ciliary arteries</th>
<th>Main group Before treatment</th>
<th>After treatment</th>
<th>After 3 months</th>
<th>Control group Before treatment</th>
<th>After treatment</th>
<th>After 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vmax cm/s</td>
<td>12.4±0.78*</td>
<td>13.3±0.91*</td>
<td>14.2±0.87*</td>
<td>12.1±0.81*</td>
<td>12.8±0.78*</td>
<td>12.9±0.97*</td>
<td></td>
</tr>
<tr>
<td>Vmin cm/s</td>
<td>5.3±0.13*</td>
<td>5.5±0.11*</td>
<td>5.5±0.17*</td>
<td>5.1±0.15*</td>
<td>5.3±0.13*</td>
<td>5.3±0.27*</td>
<td></td>
</tr>
<tr>
<td>RI</td>
<td>0.47±0.071*</td>
<td>0.5±0.078*</td>
<td>0.56±0.061*</td>
<td>0.46±0.091*</td>
<td>0.46±0.078*</td>
<td>0.48±0.081*</td>
<td></td>
</tr>
</tbody>
</table>

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Source: Author

In evaluating the safety of the FDP in both groups, adverse events that threaten the patient’s life, was not registered. Events that do not threaten the life of the patient in the main group were 12: of these - dyspepsia in 4 patients, headaches in 3, dizziness in 3, feelings the tide in 2. In the control group recorded 13 cases: of these, dyspepsia in 3, headaches in 4, vertigo in 2, feelings the tide in 2, allergic reactions in the form of small rashes in the limbs in 2 patients. This indicate that is not statistically significant incidence of adverse events.

### Discussion

Today the OIS is an urgent problem of ophthalmology, despite numerous works on the development of diagnostic and therapeutic measures performed in different countries.

The most frequent clinical manifestations of OIS were combination of anterior ischemic neuropathy, central retinal artery occlusion, ischemic central retinal vein thrombosis and glaucoma. In comparison with literature data the average age of patients was lower than 5.4 years.

In applying the FDP combined with comprehensive therapy in the main group resulted in increased of visual acuity by 32.8%, parameters of retinal sensitivity by 17.8%, reducing the area of scotomas compared with patients of the control group. This is confirmed by computed tomography. Optical coherence tomography registered significant changes in the dynamics in patients of the main group - reducing the edema and restoration of RNFL and ONH. Recovery of visual function may have contributed neuroprotective activity of the drug FDP by a protective effect on nerve tissue, reducing the effects of hypoxic stress (Karaca, Kilic, Yazici, Demir & Torre, 2002).

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Odero, Kunkl, Cugnasca, De Amics & Marchetti, 1985; Marchezani, Valerio, Dardes, Viglianti & Sanguinetti, 2000), also showed a significant recovery of peripheral haemocirculation in patients with lower limb ischemia, improvement of respiratory function in the treatment of malfurnished patients with chronic obstructive bronchitis of lung, especially in strengthening the respiratory muscles.

Should be noted that when using this drug in patients of the main group side effects such as changes in blood pressure and heart rate were not detected. In the works of Angel K. et al. 1997, noted anti-ischemic effect FDP without increasing the respiratory muscles.

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### CONCLUSION

1. The use of standard therapy in combination with FDP in the treatment of ocular ischemic syndrome has a positive effect on the course of the disease, thereby, increase of visual acuity, a decrease in sectoral loss in vision fields, the positive dynamics OCT parameters, improving hemodynamic parameters at Doppler imaging in dynamics.

2. Application FDP in patients with OIS is safe because, in patients of the main group were not recorded statistically significant indicators of adverse events in both groups, it may be noted about the safety and efficacy of the drug FDP.

### REFERENCES


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