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Research Article

The efficacy of local glucocorticosteroid therapy in nonarteritic anterior ischemic optic neuropathy

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BACKGROUND: Non-arteritic anterior ischemic optic neuropathy is the second most common optic neuropathy after glaucoma. The effectiveness of the glucocorticosteroid therapy use for the non-arteritic anterior ischemic optic neuropathy treatment remains a subject of debate. Currently, the search for markers of the disease's "therapeutic window" is under way.

AIM: The aim of this study is to evaluate the use of local glucocorticosteroid therapy as an emergency care for non-arteritic anterior ischemic optic neuropathy.

MATERIALS AND METHODS: 41 patients with non-arteritic anterior ischemic optic neuropathy were enrolled in the study. To evaluate optic nerve head and macula morphometric characteristics, optical coherence tomography was performed, additionally, diameters of arteries and veins were assessed at 4 vascular arcades. Patients were divided into 2 groups according to the presence of intraretinal fluid. The first (main) group consisted of 23 patients with intraretinal fluid, in the second (control) group 18 patients without intraretinal fluid were included. The first group was further divided into two subgroups according to the medical aid recourse periods — up to 5 days, and from 6 to 21 days (subgroup 1 — 9 patients, subgroup 2 — 14 patients).

RESULTS: Correlations between the dynamics of optic nerve head edema changes and the caliber of arteries (negative correlation) and that of veins (positive correlation) were revealed. Sub-tenon injection of long-acting glucocorticosteroid did not lead to morpho-functional improvement in first group patients. Local short-acting glucocorticosteroid therapy accomplished in the acute period of the disease made it possible to achieve an improvement in best corrected visual acuity during the first month in group 1 patients without any further worsening of it.

CONCLUSIONS: When providing emergency care to patients with non-arteritic anterior ischemic optic neuropathy during the first 5 days from the disease onset, the local use of glucocorticosteroid therapy is advisable.

Keywords: nonarteritic anterior ischemic optic neuropathy; optical coherence tomography (OCT); local glucocorticosteroid therapy.

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Научная статья

Эффективность местной глюкокортикостероидной терапии при неартериитной передней ишемической нейрооптикопатии

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Актуальность. Неартериитная передняя ишемическая нейрооптикопатия занимает второе место после глаукомы по распространённости среди всех нейрооптикопатий у пациентов старше 50 лет. Эффективность применения глюкокортикостероидной терапии для лечения неартериитной передней ишемической нейрооптикопатии остаётся предметом дискуссий. В настоящее время продолжается поиск маркеров «терапевтического окна» при данном заболевании.

Цель — оценить целесообразность местного использования глюкокортикостероидов при оказании неотложной помощи пациентам с острой фазой неартериитной передней ишемической нейрооптикопатии.

Материалы и методы. В исследование был включен 41 пациент с неартериитной передней ишемической нейрооптикопатией. Всем пациентам выполняли оптическую когерентную томографию для оценки морфометрических показателей диска зрительного нерва и макулярной области, а также оценивали диаметр артерий и вен по четырём сосудистым аркадам. По наличию интраретинальной жидкости пациенты были разделены на две группы: в основную группу 1 было включено 23 пациента с интраретинальной жидкостью, в группу 2 (контроль) — 18 пациентов без таковой. Группа 1 была дополнительно разделена на две подгруппы по срокам обращения за медицинской помощью: до 5 сут включительно и от 6 до 21 сут (подгруппа 1 — 9 человек, подгруппа 2 — 14 соответственно).

Результаты. Выявлены корреляционные связи между динамикой изменений отёка диска зрительного нерва и калибром артерий (отрицательная) и вен (положительная). Введение пациентам группы 1 в субтеноновое пространство глюкокортикостероидов пролонгированного действия не привело к морфофункциональному улучшению. Местная глюкокортикостероидная терпия короткого действия, проведённая в остром периоде заболевания, позволяла достичь улучшения максимально корригированной остроты зрения в первый месяц пациентам группы 1 без дальнейшего ухудшения данного показателя.

Выводы. При оказании неотложной помощи пациентам с неартериитной передней ишемической нейрооптикопатией в первые 5 сут от начала заболевания местное использование глюкокортикостероидов является целесообразным.

Ключевые слова: неартериитная передняя ишемическая нейрооптикопатия; оптическая когерентная томография (ОКТ); местная глюкокортикостероидная терапия.

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BACKGROUND

Non-arteritic anterior ischemic optic neuropathy (NAION) is an acute ischemia of pre-laminar or laminar part of the optic nerve (ON) induced by the blood circulation impairment in the system of paraoptic short posterior ciliary arteries [1].

The disease manifests by sudden painless monocular visual acuity loss, appearance of altitudinal visual field defects, more rarely central scotomata and other type defects appear. Characteristic signs of NAION are relative afferent pupillary defect on the involved side, pale optic disc edema with compression of retinal vessels and appearance of peripapillary hemorrhages [2].

Among all neuropathies, NAION for its prevalence occupies the second place after glaucoma [3]. The disease is age-related, its maximal incidence is observed between 57–65 years, and only in 23% of cases — before 50 years, and hereby no gender predilection is registered [2, 4].

The pathogenesis of NAION is fairly complex; nowadays in many countries, it is viewed as one of the localizations of acute cerebrovascular accident, considering the optic nerve as a component of the central nervous system [5].

The main role in the pathogenesis of NAION is assigned to the endothelial dysfunction, which is accompanied by hypercoagulation and hypofibrinolysis, local impairment of blood flow autoregulation, decrease of ocular perfusion pressure, and drop in pressure in paraoptic short posterior ciliary arteries. Resulting subclinical ischemia and hypoxia in the anterior part of the optic nerve therefore led to troubles in the axoplasmic transport, to edema of the optic disc and of the peripapillary part of the retina. The compression of optic disc capillaries due to local rise in interstitial pressure increased the ischemia of tissues, hereby forming a "vicious circle" [1].

The presence of local and systemic risk factors predisposes to the NAION development. The acknowledged risk factors are small optic disc dimensions and absence of excavation ("disc at risk"), optic disc drusen, obstructive sleep apnea syndrome, cardiac arrhythmias, as well as various metabolic disorders [6–10].

In 40% of cases, during several weeks after the onset of the disease, some amelioration of visual functions may be observed. There could be several reasons for visual improvement. These include the resorption of subretinal/subfoveal fluid, observed in 10–16% of patients, and of peripapillary subretinal fluid (SRF) — in 64% of patients [11].

The data of studies in mice demonstrating the detection of SRF after the laser-induced NAION during the period of 1 to 7 days in 100% of cases allow to consider its presence as an important marker of the acute phase of the disease [12]. It is beyond argument that the NAION model created in experimental animals could not fully correspond to the clinical picture of human NAION. The structure of laminar vascular net of the optic nerve in mice is characterized by the absence of anastomoses with choroidal vessels, besides in rodents and primates, the number of optic nerve axons and the structure of lamina cribrosa of the sclera vary widely [13]. These differences partly explain absence of the optic disc edema, more frequent observation and earlier resorption of the SRF in experiment on mice. In primates, the optic disc edema is preserved for about 14 days, and in humans in may be observed up to 80 days [14, 15]. Nevertheless, a conclusion beyond argument, based on several experimental studies carried out on mice, rats and primates, is that in NAION development, an immediate significant inflammatory answer occurs, with activation of pro-inflammatory cytokines, which finally during 10.5 days, leads to retinal ganglion cells apoptosis [16].

The presence of an inflammatory reaction in the pre-laminar part of the optic nerve caused by edema and microcirculation impairment, is confirmed by scarce histological studies of eye tissues of patients with NAION history [17, 18].

Actually, the search continues for effective treatment methods aimed to the optic disc capillaries decompression through the elimination of the "compartment syndrome" [19]. In this regard, a surgical decompression of the optic nerve tunics (Ischemic Optic Neuropathy Decompression Trial — IONDT), transvitreal optic neurotomy, as well as vitrectomy aimed to eliminate vitreo- and epipapillary tractions were used [20–22]. However high risk of complications and low efficacy of the above-mentioned methods did not allow them to find a large-scale implementation into clinical practice.

Medical therapy of NAION, as such, is absent. The main treatment method is a symptomatic therapy aimed at restoration of the blood-retina barrier. There are data on the use of angiogenesis inhibitors [23]. Better-known and more clinically spread in the clinical practice is still the glucocorticosteroid (GCS) therapy. Their systemic use in NAION treatment did not show high efficacy [24, 25]. However, medications of the given pharmacological group are actively used as subconjunctival, subtenon, retrobulbar, as well as intravitreal injections. In that regard, most frequently dexamethasone solution or bio-degradable intravitreal implant with dexamethasone (the use of which does not correspond to the approved by state regulatory bodies instruction on medical use — "off-label"), as well as medications with a prolonged effect — betamethasone and triamcinolon [26–28].

GCS have an antiedematous, anti-inflammatory action, could decrease the permeability of capillaries and due to the drop of interstitial pressure decrease the compression of capillaries in the anterior part and the optic disk, and this ameliorates the blood flow and restores the function of ischemic axons in NAION [29].

Some studies give evidence of better functional outcome in early GCS use; however, a large meta-analysis calls the efficacy of this treatment into question [30].

To find the most effective NAION therapy, it is necessary to utilise large-scale clinical studies to prove or to reject the expediency of use of generally accepted treatment methods currently used by ophthalmologists.

An actual objective as well is, based on modern methods of in vivo diagnosis of the optic nerve and the retina status in NAION, to establish a time frame of the "therapeutic window". The experiment shows that even after axonotomy of the optic nerve in 0.5 mm from the eyeball, during 5 days, there are no significant changes of retinal ganglion cells, and only during the following 9 days, their gradual death occurs [16]. Thus, it is possible to assume that there is an "acute" period of the disease, during which one could try to increase the "survival" of ganglion cells.

Aim — to estimate the expediency of GCS local use in emergency care for patients with an acute NAION phase.

The objectives of the study:

1) to determine the time frame of the "therapeutic window", to identify the OCT-markers of the acute NAION period;

2) to determine the influence of the intraretinal fluid (IRF) and of the subretinal fluid (SRF) in NAION on visual functions and prognosis of the disease;

3) to evaluate the efficacy of GCS local use during and beyond the determined "therapeutic window".

MATERIALS AND METHODS

In the open prospective controlled trial, patients with NAION took part, who were treated at the department of ophthalmology of the Academician I.P. Pavlov First St. Petersburg State Medical University and at ophthalmology departments of the City Multifunctional Hospital No. 2 in Saint Petersburg.

Inclusion criteria: no longer than 21 days from the first symptoms of the disease, age older than 18 years, absence of concomitant of the retina, the optic nerve and ocular media, which could confound the interpretation of results, compensation of concomitant systemic diseases.

At initial presentation, after 1 and 3 months, all patients underwent a complete ophthalmological examination including the best corrected visual acuity (BCVA), tonometry (iCare tonometer, Icare Finland OY), perimetry (Octopus 101, Haag-Streit International, G2 program), biomicroscopy, biomicroophthalmoscopy with aspheric lenses 60 and 75 D.

Morphometric parameters of the macular area were investigated using the retinal with image enhanced depth module OCT (Spectralis SD-OCT® Heidelberg Engineering, Germany). In addition, using the spectral tomograph, the peripapillar retinal thickness and the optic disc ("RNFL single exam report" and "ONH" protocols).

Due to the fact that the enlarged diameter of retinal veins during the NAION acute period, is related to the venous outflow impairment caused by the edema of the prelaminary part of the optic nerve, this criterion could be considered as a marker of the optic disc edema, and its dynamic changes — as a response to the carried-out therapy. The diameters of retinal arteries and veins were measured manually on the tomograms obtained before. The evaluation was carried out at 4 vascular arcades at 1.75 mm distance from the optic disc center.

From 2019 through 2022, according to this algorithm, 41 patients with confirmed diagnosis: "Nonarteritic anterior ischemic optic neuropathy" were examined.

The criterion of IRF or SRF presence in patients revealed using the OCT the day of presentation was the basis of patients' division into groups. Because of the absence of SRF in examined patients, the first group consisted of patients with IRF only.

Into the group 1 (main group), 23 patients with IRF were included (14 men and 9 women; age 64 ± 13 years). The group 2 (control group), consisted of the remaining 18 patients (9 men and 9 women; age 62 ± 11 years). The group 1, in its turn, was in addition divided into two subgroups according to the recourse for medical care – up to 5 days inclusively, and from 6 to 21 days. In the subgroup 1, there were 9 patients (7 men and 2 women; age range 58 ± 12 years), in the subgroup 2–14 patients (7 men and 7 women; age range 69 ± 12 years).

All patients, being hospitalized, received 10 daily subconjunctival injections of 0.5 ml (2 mg) dexamethasone solution, or betamethasone sodium phosphate 0.5 ml (1 mg). In patients of the first group, additionally, at the day of discharge, 1.0 ml of triamcinolone hydrochloride was injected into subtenon space.

Statistical analysis of data was carried out using the R language version 4.1.3 in the interact medium R studio.

The results according to category features are presented as the number of patients and percent of the considered group.

Quantitative features are described as mean ± standard deviation (standard deviation).

In comparison of groups, the parametric Student's test with Welch's correction. The analysis of qualitative features was performed using contingency tables and the Pearson's chi-squared test. When the assumption failed to comply with expected values in at least one box of the contingency table, the Fischer's exact test was used. For the analysis, the parametric ANOVA test was also used. Paired comparisons were calculated using the *q*-value method with Bonferroni correction for multiple comparisons. To determine the strength of correlations between variables, the Spearman's rank correlation

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method was used. The significance level for all tests was set as $p < 0.05$.

RESULTS

Data on examination and treatment of NAION patients in presence and in absence of intraretinal fluid.

The formed groups were uniform in sex, age, BCVA, and intraocular pressure (Table 1). However, in comparison of disease prescription between groups, statistically significant differences were revealed. In the group 1, in patients with IRF, mean disease duration was 7.3 ± 4.8 days, while in the group 2, in patients without this feature – 12.9 ± 6.9 days ($p = 0.015$).

Between groups, there was also a tendency towards significant difference in mean height of the optic nerve head (ONH) protrusion – 710 (469–778 μm) in comparison with 440 (371–575 μm), $p = 0.06$. It is worthy of special mention, that a maximal ONH protrusion in the group 1 was revealed in the upper nasal and nasal sectors (545–906 μm and 553–852 μm, respectively), while in the remaining sectors, these values stayed within the interval between 383 and 825 μm. In the group 2, height of ONH protrusion was practically the same in all sectors. Besides, there was a significant difference between groups in mean values of retinal nerve fiber layer (RNFL) thickness in the scanned circumference of the peripapillary area 169 ± 52 compared to 127 ± 48 ($p = 0.024$). Similar to the height of ONH protrusion, the maximal difference between the specified parameters was revealed in the upper nasal (209 ± 81 compared to 145 ± 73 μm, $p = 0.025$) and nasal (161 ± 86 compared to 103 ± 53 μm, $p = 0.020$) sectors.

After one month, the height of ONH protrusion parameter in groups 1 and 2 decreased in all sectors, but there still was a significant difference: 490 μm (422–674 μm) compared to 319 (266–351 μm), $p = 0.008$ — in the central zone; 511 μm (435–595 μm) compared to 366 (316–390 μm), $p = 0.002$ — in the upper sector; 521 μm (434–589 μm) compared to 378 (365–425 μm), $p = 0.011$ — in the nasal sector; 560 μm (436–747 μm) compared to 390 (347–410 μm), $p = 0.009$ — in the lower sector; 394 (319–528 μm) compared to 278 μm (271–298 μm), $p = 0.003$ — in the temporal sector.

Upon discharge from the hospital and after 1 month, the diameter of veins was not significantly different between groups. After 1 month, no differences in the diameter of arteries were found in any of the vascular arcades (Tables 2, 3). At the same time, clear correlation relationships were tracked between the height of the ONH protrusion and retinal vascular caliber (Fig. 1, 2). The diameter of veins had a high direct correlation with the magnitude of the ONH edema (the ONH edema resolution was accompanied by the decrease in diameter of veins). The caliber of arteries, in its turn, had a high negative correlation with the magnitude of the ONH edema (The ONH edema resolution was accompanied by an increase in diameter of arteries).

In spite of the fact that the condition in group 1 patients was more severe, and they received an intensified local GCS therapy (with additional sub-tenon injections), after one month of follow-up, the main parameters characterizing visual functions (BCVA and parameters of the retinal light sensitivity) in them did not differ significantly. The average BCVA was 0.6 (0.23–0.95) compared to 0.5 (0.3–0.88), $p > 0.9$, and mean retinal light sensitivity was 16 ± 8 compared to 16 ± 10 dB ($p = 0.8$).

When comparing structural OCT of the macular area, there were no significant changes in both groups. There was neither IRF, nor SRF. At the same time, in the peripapillar zones in group 1 patients, a significant amount of IRF was detected, which in some cases, occupied a large area (Fig. 3). The maximal duration of the IRF presence was no more than 18 days.

Table 1. Characteristics of groups at the time of the hospital admission
Таблица 1. Характеристика групп при поступлении в стационар

Sign	Group 1	Group 2	*p*
Sex			0.5
• men	14 (61%)	9 (50%)	
• women	9 (39%)	9 (50%)	
Age, years	64 ± 13	62 ± 11	0.5
Best corrected visual acuity	0.38 ± 0.38 (0.01–1.00)	0.38 ± 0.28 (0.02–0.80)	>0.9
Intraocular pressure, mm Hg	17.9 ± 3.3 (10.0–23.0)	16.2 ± 3.9 (10.0–24.0)	0.2
Time of presentation, days	7.3 ± 4.8 (1–18)	12.9 ± 6.9 (1–21)	0.015

Note. Here and in Tables 2–6: group 1 — presence of intraretinal peripapillary fluid; group 2 — absence of intraretinal peripapillary fluid.

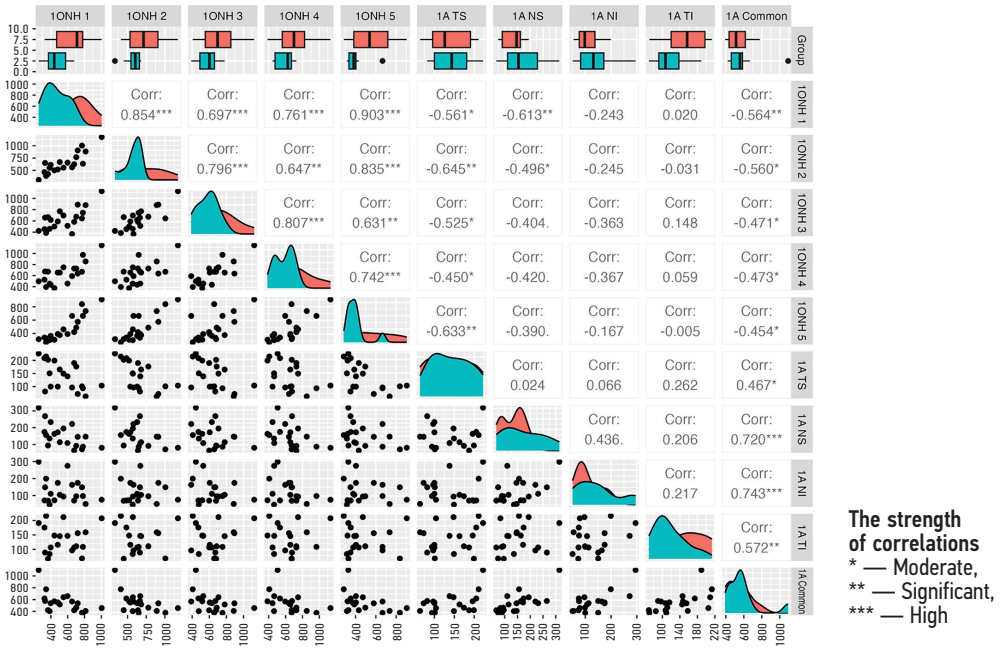


Fig. 1. Correlations between the amount of edema of the optic disc and the diameter of arteries. Groups: red — group 1, green — group 2; A — artery diameter, μm; N — nasal; T — temporal; S — superior; I — inferior; Common — common diameter of vessels of all vascular arcades; optic nerve head prominence, μm: ONH 1 — central sector; ONH 2 — superior sector; ONH 3 — nasal sector; ONH 4 — inferior sector; ONH 5 — temporal sector

Рис. 1. Корреляционные связи между высотой выстояния зрительного нерва и диаметром артерий. Group — группа пациентов (красный — группа 1, зелёный — группа 2); A — диаметр артерии, мкм; N — носовой, T — височный, S — верхний, I — нижний, Common — общий диаметр сосудов во всех сосудистых аркадах; выстояние диска зрительного нерва, мкм: ONH 1 — в центральном секторе; ONH 2 — в верхнем секторе; ONH 3 — в носовом секторе; ONH 4 — в нижнем секторе; ONH 5 — в височном секторе

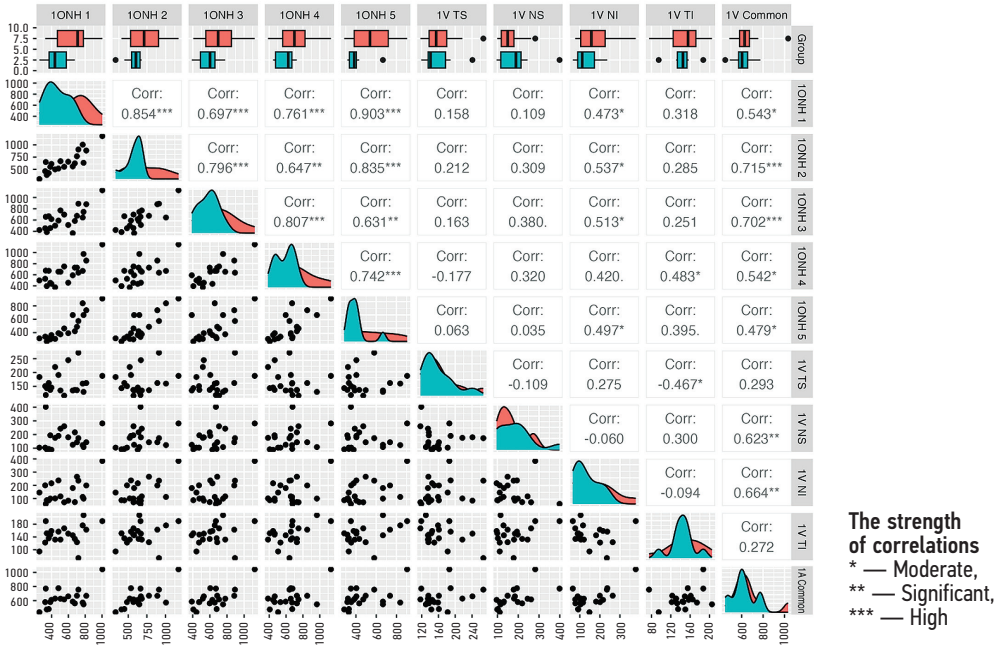


Fig. 2. Correlations between the amount of edema of the optic disc and the diameter of veins. Group: red — group 1, green — group 2; V — vein diameter, μm; N — nasal; T — temporal; S — superior; I — inferior; Common — common diameter of vessels of all vascular arcades; optic nerve head prominence, μm: ONH 1 — central sector; ONH 2 — superior sector; ONH 3 — nasal sector; ONH 4 — inferior sector; ONH 5 — temporal sector

Рис. 2. Корреляционные связи между высотой выстояния зрительного нерва и диаметром вен. Group — группа пациентов (красный — группа 1, зелёный — группа 2); V — диаметр вены, мкм; N — носовой; T — височный; S — верхний; I — нижний; Common — общий диаметр сосудов во всех сосудистых аркадах; выстояние ДЗН, мкм: ONH 1 — в центральном секторе; ONH 2 — в верхнем секторе; ONH 3 — в носовом секторе; ONH 4 — в нижнем секторе; ONH 5 — в височном секторе

Table 2. Diameter of arteries and veins at the time of discharge from the hospital, μm
Таблица 2. Диаметр артерий и вен при выписке из стационара, мкм

Sign	Group 1	Group 2	*p*
A TS	126 (96, 190)	144 (100, 181)	0.9
A NS	146 (90, 161)	154 (111, 228)	0.3
A NI	98 (77, 138)	132 (82, 172)	0.5
A TI	156 (120, 197)	107 (92, 138)	0.031
A total	514 (436, 616)	557 (460, 585)	0.6
V TS	154 (138, 180)	141 (136, 177)	0.8
V NS	149 (118, 180)	189 (116, 214)	0.6
V NI	158 (104, 226)	112 (90, 173)	0.3
V TI	156 (125, 172)	145 (134, 154)	0.6
V total	627 (580, 672)	603 (572, 655)	0.7

Note. A — diameter of artery, μm; V — diameter of vein, μm; N — nasal, T — temporal, S — superior, I — inferior. In brackets, minimal and maximal values are given.

Table 3. Diameter of arteries and veins after 1 month, μm
Таблица 3. Диаметр артерий и вен через 1 мес., мкм

Sign	Group 1	Group 2	*p*
A TS	121 (102, 180)	138 (110, 150)	0.9
A NS	119 (73, 168)	132 (100, 179)	0.5
A NI	80 (65, 146)	94 (72, 142)	0.7
A TI	149 (141, 159)	104 (91, 128)	0.12
A total	486 (408, 594)	480 (458, 584)	0.8
V TS	138 (126, 145)	126 (107, 150)	0.5
V NS	125 (102, 190)	154 (107, 180)	0.9
V NI	124 (95, 199)	102 (80, 139)	0.2
V TI	124 (116, 143)	136 (112, 150)	0.8
V total	566 (504, 648)	525 (506, 561)	0.5

Note. A — diameter of artery, μm; V — diameter of vein, μm; N — nasal, T — temporal, S — superior, I — inferior. In brackets, minimal and maximal values are given.

Besides, in a majority of group 1 patients, many hyperreflective intraretinal dots were found, being a nonspecific sign of both ischemia and inflammation. This sign is found in several diseases, such as diabetic retinopathy with diabetic macular edema, retinal vein occlusions, etc. These changes were preserved in patients during all the follow-up period (Fig. 4).

Data on examination and treatment of patients with different NAION duration.

The baseline data analysis of subgroup 1 patients (disease duration up to and including 5 days) showed the absence of significant differences in all parameters both with subgroup 2 and with group 2.

However, to the day of discharge from the hospital, in the group with the earliest onset of the GCS therapy, BCVA was already statistically significantly higher, and this trend sustained during all the following month (Table 4). During this period of time, the RNFL in these patients was also significantly thicker (Table 5).

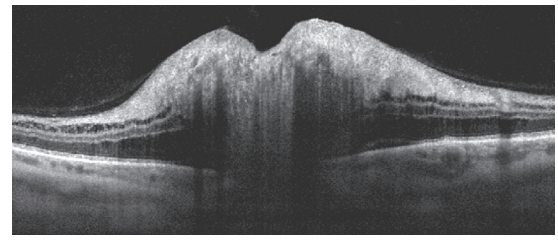
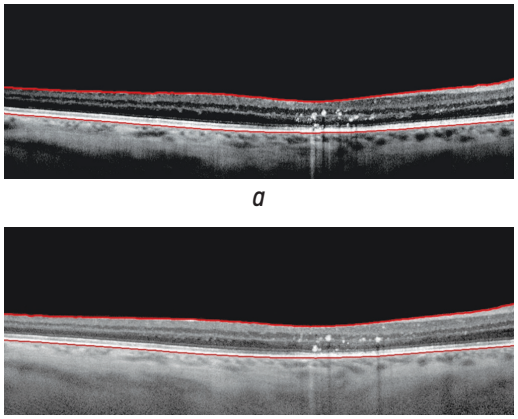


Fig. 3. Intraretinal peripapillary fluid by optical coherence tomography
Рис. 3. Интраретинальная перипапиллярная жидкость по данным оптической когенетной томографии



a

b

Fig. 4. Hyperreflective intraretinal points by optical coherence tomography: *a* — at the discharge from the hospital; *b* — after 3 months

Рис. 4. Гиперрефлективные интраретинальные точки по данным оптической когенетной томографии: *a* — при выписке из стационара; *b* — через 3 мес.

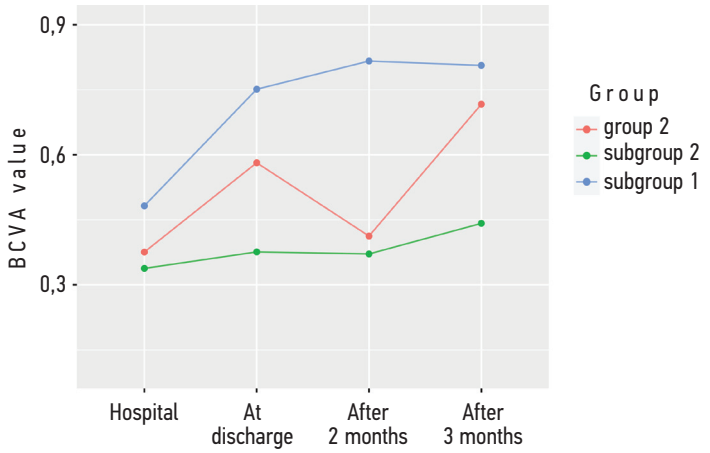


Fig. 5. Dynamics of changes in visual acuity in patients of subgroups 1, 2 and of group 2

Рис. 5. Динамика изменения остроты зрения у пациентов подгрупп 1 и 2 и пациентов группы 2

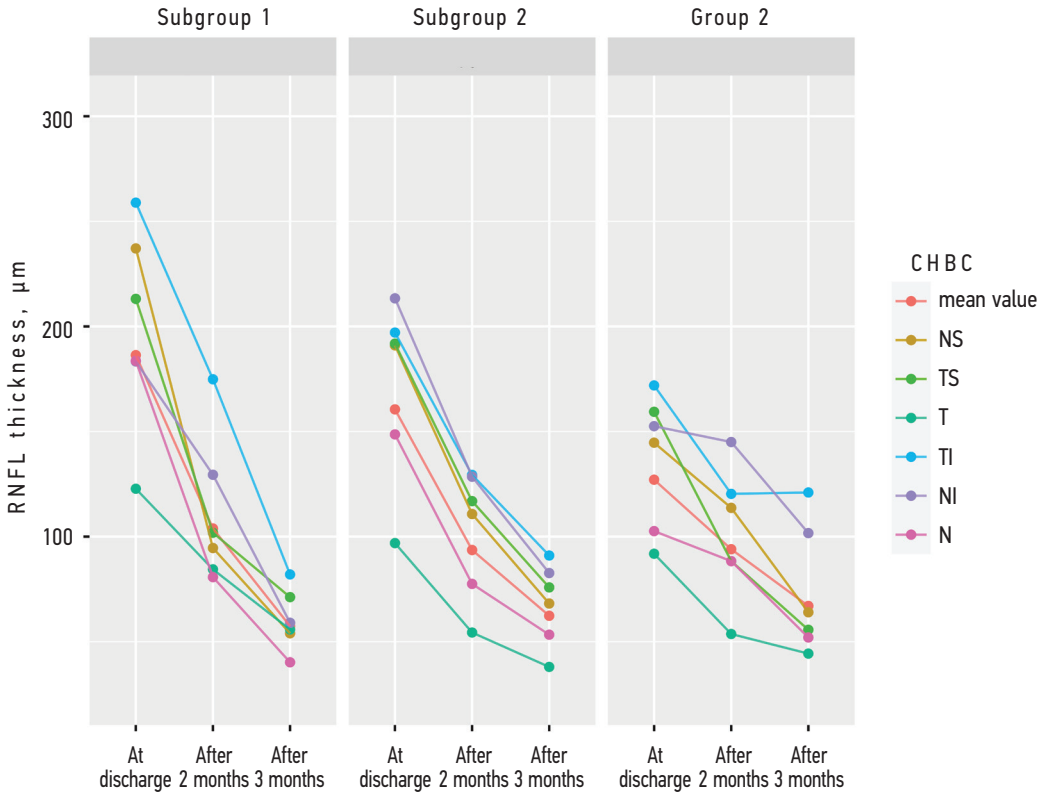


Fig. 6. Dynamics of RNFL thickness changes in the peripapillary area according to the OCT data at various time points. Sectors: NS — nasal superior, TS — temporal superior, T — temporal, TI — temporal inferior, NI — nasal inferior, N — nasal OCT

Рис. 6. Динамика изменений толщины слоя нервных волокон сетчатки (CHBC) в перипапиллярной зоне по данным оптической когерентной томогрфии в различные визиты. NS — верхне-носовой сектор, TS — верхне-височный сектор, T — височный сектор, TI — нижне-височный сектор, NI — нижне-носовой сектор, N — носовой сектор

After 3 months, the difference in BCVA indices (Tables 4, Fig. 5) and in RNFL thickness smoothed over (Table 5, Fig. 6). Regarding other parameters, including the retinal light sensitivity (16 ± 8, 13 ± 8, and 16 ± 10 respectively, $p = 0.8$), there were no significant differences between the studied groups.

DISCUSSION

The study showed that the SRF presence is not a frequent and obligatory marker of the NAION acute phase, whereas IRF detection in patients in such case, could be a sign of a "recent" process, point on the intensity of the inflammatory response, ischemia,

Table 4. Dynamics of visual acuity changes

Таблица 4. Динамика изменения остроты зрения у пациентов в разные сроки

Time of the visit	Group 1		Group 2	*p*
	subgroup 1 (within 5 days)	subgroup 2 (more than 5 days)		
Day of discharge from the hospital	0.75 ± 0.31	0.38 ± 0.31	0.58 ± 0.37	0.05
After 1 month	0.82 ± 0.38	0.37 ± 0.36	0.41 ± 0.41	0.061
After 3 months	0.81 ± 0.5	0.44 ± 0.38	0.72 ± 0.49	0.4

Table 5. Dynamics of RNFL thickness changes in the peripapillary area according to the OCT data at various time points, μm

Таблица 5. Динамика изменений толщины слоя нервных волокон сетчатки в перипапиллярной зоне по данным оптической когерентной томографии в разные сроки, мкм

Sign	Group 1		Group 2	*p*
	subgroup 1	subgroup 2		
At discharge from the hospital	186 ± 57	161 ± 46	127 ± 48	0.032
NS	237 ± 97	191 ± 66	145 ± 73	0.034
TS	213 ± 57	192 ± 63	159 ± 59	0.12
T	123 ± 56	97 ± 40	92 ± 46	0.3
TI	259 ± 74	197 ± 75	172 ± 58	0.022
NI	183 ± 61	213 ± 90	153 ± 77	0.2
N	184 ± 103	149 ± 73	103 ± 53	0.058
After 1 month	104 ± 53	94 ± 36	94 ± 10	0.9
NS	95 ± 33	111 ± 61	114 ± 33	0.8
TS	102 ± 30	117 ± 39	88 ± 11	0.4
T	84 ± 62	54 ± 18	54 ± 5	0.3
TI	175 ± 92	129 ± 73	120 ± 48	0.5
NI	129 ± 82	128 ± 62	145 ± 21	>0.9
N	81 ± 46	78 ± 32	88 ± 3	>0.9
After 3 months	57 ± 16	62 ± 19	67 ± 21	0.8
NS	54 ± 15	68 ± 30	64 ± 25	0.6
TS	71 ± 21	76 ± 40	56 ± 16	0.6
T	56 ± 34	38 ± 8	44 ± 13	0.4
TI	82 ± 28	91 ± 45	121 ± 45	0.4
NI	59 ± 15	83 ± 28	102 ± 26	0.079
N	40 ± 19	53 ± 20	52 ± 32	0.6

Note. NS — superior nasal sector, TS — superior temporal sector, T — temporal sector, TI — inferior temporal sector, NI — inferior nasal sector, N — nasal sector.

and impairment of the internal blood-retinal barrier function.

Peripapillar IRF location was found in 56% of patients during the first 21 days from the NAION onset, at the same time 39.1% of them had the duration of the disease not exceeding 5 days. On the top of the conducted therapy, during 18 days its complete resorption was noted; at the same time, the indices of the ONH height suggesting the optic nerve edema remained practically during the whole follow-up period. The low speed of ONH edema resorption was also evidenced by diameter indices of peripapillary arteries and veins. The diameter of arteries had a negative correlation with the height of ONH protrusion, and the diameter of veins – a positive one. These relationships were revealed in patients with SRF, as well as in those without it. The absence of significant difference in indices of vessel diameter and those of the ONH protrusion between groups after 3 months gives evidence of very slow speed of IRF and interstitial fluid resorption in the prelaminar and laminar parts of the optic nerve, this explains the low therapeutic effect of the "rescue therapy" consisting in subconjunctival injections of GCS.

This kind of therapy, as a matter of fact, does not accelerate the natural duration of ONH edema resorption, which in general average 5.8–11.4 weeks [15].

In our study, we did not find any confirmation of the high prevalence of SRF and serous detachment of the retinal neuroepithelium in the macular area in patients with acute phase of NAION, described in 2008 by T.R. Hedges et al. [11]. Possibly, this was due to a small sample of patients.

The division of NAION group of patients with IRF into subgroups according to the disease duration allowed to determine the timelines, during which the GCS therapy has maximal efficacy.

It was revealed that first 5 days from the first signs of the disease may play a critical role in prevention of the additional optic nerve axons death. In timely treatment, BCVA ameliorates significantly more rapidly, and there is no such rapid RNFL thinning as in comparison groups. At the same time, it's worth noting that the efficacy of 10 daily subconjunctival GCS injections in combination with a single injection into posterior subtenon space of a long-acting GCS does not allow precluding the development of atrophic processes in the optic nerve.

Thus, even on the frame of the "therapeutic window", local GCS therapy does not guarantee the success of NAION treatment.

This study showed that among patients with no IRF, there were those who addressed for care during the first 24 hours from the appearance of complaints. Thus, this feature is the most prevalent, but not obligatory marker of the acute disease period.

Just as important is the choice of the most optimal method of GCS delivery. In our study, all patients received the medication subconjunctivally, and if the IRF persisted to the moment of discharge from the hospital, a single subtenon injection of 1.0 ml of triamcinolone hydrochloride solution was performed.

In posterior segment and optic nerve disease, it is preferable to choose a "targeted" delivery of the medication, and in NAION case, it may be intravitreal, retrobulbar, or subtenon injection. Changing the form and method of medication delivery during the "acute" period could allow to achieve more stable functional response. This is confirmed by a small pilot study by R. Nuzzi and F. Monteu [27], as well as a more large-scale study by H. Fesharaki et al. [31].

To our mind, GCS have to be administered in a maximally effective, but at the same time safe dosage during first 5 days from the onset of the disease. The objective of such "rescue therapy" consists in a complete and rapid resorption of IRF and of the fluid causing compression of optic nerve fibers in its laminar and prelaminar part.

Continuing the GCS therapy at a remote period of time is inadequate, as it does not influence structural changes in the retina and the optic nerve, as well as does not significantly improve visual functions.

As a limitation of our study is a small sample of patients, an impossibility to change the protocols of specialized "emergency" care carried out at a city hospital and corresponding to uniform medical standards, as well as absence of GCS dosage forms, which could allow a rapid targeted delivery of the medication to the optic nerve head, it is necessary to carry on further studies, aimed at the identification of most effective dosage forms and delivery methods for local corticosteroids to treat NAION patients.

CONCLUSIONS

1. IRF in NAION in most cases, is observed at the early phase of the disease and may be considered as an OCT-marker of the "acute" NAION period, which does not exceed 5 days from the disease onset.

2. IRF does not significantly influence visual functions in NAION patients.

3. The GCS use as daily subconjunctival injections in the frame of a certain "therapeutic window" leads to temporary improvement of BCVA, but cannot stabilize the process and preclude the optic nerve's fibers atrophy. The postponed use of GCS (even of those with prolonged action) is useless as it does not lead to significant morphologic and functional changes.

CONCLUSIVE STATEMENT

When rendering urgent medical aid to NAION patients during first 5 days after the onset of the disease, the local use of GCS is reasonable.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of the author: V.A. Antonov — research concept and design, material collection, text writing, statistical data processing, manuscript approval for publication; S.N. Tultseva — research concept and design, text writing and editing; S.Yu. Astakhov — research concept and design, text editing; N.N. Grigorieva — material collection, text editing.

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Consent for publication. Written consent was obtained from the patients for publication of relevant medical information within the manuscript.

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