

Original article

## Discomfort during instillation of antihypertensives and ocular surface condition in glaucoma patients

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**Abstract: Background** — An increase in the frequency of manifestations of dry eye syndrome (DES), against the background of hypotensive therapy, leads to a decrease in treatment adherence. After reformulation in the composition of a preservative-free preparation of a carbonic anhydrase inhibitor (CAI) (sodium benzoate was added), patient complaints of burning sensation during instillation became more frequent, which was the reason for our study.

**Objective** — To evaluate the effect of sodium benzoate on the course of DES during local hypotensive therapy of glaucoma.

**Methods and Results** — Group 1 consisted of 21 eyes with glaucoma receiving hypotensive therapy, Group 2 (20 eyes) included patients with suspected glaucoma not receiving therapy. Patients underwent standard diagnostic methods and examination of the ocular surface condition: tear break-up time test sensu Norn, Schirmer test, vital staining with lissamine green, and a survey based on the Ocular Surface Disease Index (OSDI) questionnaire. When a preservative-free CAI in combination therapy was replaced with the CAI containing sodium benzoate, no statistically significant change in IOP occurred after four weeks of treatment ( $p > 0.05$ ). In both groups, the indicators characterizing the ocular surface condition did not change statistically significantly over the observation period.

**Conclusion** — Replacement of preservative-free CAI in combination therapy of glaucoma with CAI with sodium benzoate does not lead to statistically significant changes in intraocular pressure. The ocular surface condition does not change statistically significantly over a month of observation. Instillation discomfort is not related to the pH of the preparation.

**Keywords:** glaucoma, intraocular pressure, dry eye syndrome, ocular surface, hypotensive therapy, sodium benzoate.

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### Introduction

Diseases of the ocular surface belong to multifactor diseases. They lead to a decrease in the quality of vision and patient complaints due to changes in the epithelium of the conjunctiva and cornea, and in lacrimal and meibomian glands [1, 2]. Manifestations of dry eye syndrome (DES) may increase with prolonged hypotensive therapy [3], systemic medicamentous therapy [4, 5], and after surgical interventions [6-9].

The incidence of glaucoma according to the World Health Organization (WHO) is from 60 to 105 million people worldwide, and in the next 10 years this number is likely to increase by another 10 million (source: <http://www.who.int/ru/>) [10]. The prevalence of glaucoma in people over 50 years of age with diseases of the ocular surface exceeds 10% [11-13]. However, the frequency of DES manifestations in patients receiving local hypotensive therapy, according to some data, reaches up to 60% [14-16]. The occurrence of DES against the background of

hypotensive therapy leads to a reduction in a patient's adherence to the therapy [17-19] and, consequently, to the progression of glaucoma [20, 21].

Hence, the condition of the ocular surface in glaucoma patients has a significant impact on the success of local hypotensive therapy, which can lead to the development and/or intensification of DES manifestations [14, 15, 22].

The toxic effect of hypotensive drops is caused by the preservatives in their content. Several classes of preservatives have been developed to date: benzalkonium chloride (BAC), oxidizing preservative Purite® (Allergan Inc., Irvine, CA, USA), detergent Polyquaternum 1 or Polyquad® (Alcon Research, Fort Worth, TX, USA), ionic buffer preservative SofZia® (Novartis AG, Basel, Switzerland), sodium perborate (GenAqua®), and sodium benzoate. Their prolonged use may aggravate symptoms of ocular surface diseases [23-26]. As a result of changes in the composition of a preservative-free carbonic anhydrase inhibitor (CAI) (Dorzolan Solo, Solopharm, Russia) via adding sodium benzoate preservative,

patient complaints of burning during instillation became more frequent, which was the reason for conducting the study on changes in the ocular surface condition against the background of using CAI containing sodium benzoate.

The objective was to establish the effect of sodium benzoate on the course of DES and the effectiveness of local hypotensive therapy of glaucoma.

### Material and Methods

The study was conducted in the period from September through November of 2020 on the basis of the Municipal Budgetary Healthcare Institution, City Clinical Hospital No. 2, Polyclinic No. 1, and City Glaucoma Office in Chelyabinsk. The data of an analytical, observational case-control study were analyzed. Based on the inclusion and exclusion criteria, 21 patients (41 eyes) were the subject of our study. In all cases, the diagnosis was established *sensu the system of differential diagnosis of diseases* and confirmed by specific research methods. All patients underwent visual acuity examination, iCare tonometry (Tiolat, Finland), elastic tonometry with Maklakov tonometers (weighing 5, 10 and 15 g), computerized perimetry (CP) (Octopus-600, Haag-Streit Diagnostics, Switzerland), optical coherence tomography (OCT) of the macular zone and optic disc (Spectralis OCT, Heidelberg Engineering, Germany).

At the onset of the study and a month after the change of treatment to CAI containing sodium benzoate, patients were examined for the condition of their ocular surface: tear break-up time (TBUT) *sensu* Norn, Schirmer test, vital staining with lissamine green, and a survey based on the Ocular Surface Disease Index (OSDI) questionnaire.

*The inclusion criteria:* city of Chelyabinsk residents; patients with primary open-angle glaucoma (POAG); 45 to 89 old at the time of inclusion in the study (middle, elderly and senile ages *sensu* 2012 WHO classification, [www.who.int/ru](http://www.who.int/ru)); clinical refraction in the range of  $\pm 6.0$  D and astigmatism of  $\pm 1.5$  D; index of the central corneal thickness (CCT) values from 520 to 580  $\mu$ . Hypotensive therapy: a fixed combination of bimatoprost with timolol (FCBT) in conjunction with preservative-free CAI: Dorzolol Solo (Solopharm, Russia).

*The exclusion criteria:* any other form of primary glaucoma than POAG; change of hypotensive therapy during the observation period; opacities of the optical media preventing the performance of perimetric studies; other retinal diseases (any form of age-related macular degeneration, conditions after occlusions, diabetic retinopathy and its complications, as is customary according to the methodology of clinical trials, <https://clinicaltrials.gov>); surgical ophthalmological treatment in anamnesis; injuries and diseases of the eye and accessory visual structures; diabetes mellitus and other common diseases requiring hormone therapy.

**Table 1. Clinical and demographic characteristics of groups**

	Group 1 (n=21)	Group 2 (n=20)	Statistical significance
	M $\pm$ σ; Me (Q25%; Q75%)	M $\pm$ σ; Me (Q25%; Q75%)	
Age (years)	72.2 $\pm$ 9.1; 73.0 (68.4; 78.7)	71.5 $\pm$ 6.6; 70.0 (67.6; 78.7)	W=156; p=0.471
Anamnesis (years)	0.9 $\pm$ 0.23; (0.8; 1.0)	0.73 $\pm$ 0.18; 0.7 (0.6; 0.9)	W=107.5; p=0.006
Male eyes	7	5	X <sup>2</sup> = 0.058978; p=0.808
Eye (OD/OS)	11/10	11/9	X <sup>2</sup> =0; p=1.0
IOL (yes/no)	14/7	10/10	X <sup>2</sup> =0.5862; p=0.443
PES (yes/no)	20/1	20/0	X <sup>2</sup> =1.2e-32; p=1.0
SE (D)	0.48 $\pm$ 3.0; 1.8 (-1.8; +2.6)	-0.26 $\pm$ 4.4; 0.9 (-0.5; +2.2)	W=193; p=0.666
BCVA	0.78 $\pm$ 0.18; 0.8 (0.7; 0.9)	0.73 $\pm$ 0.18; 0.8 (0.6; 0.9)	W=180; p=0.432
AL (mm)	23.7 $\pm$ 0.94; 23.9 (23.6; 24.2)	23.4 $\pm$ 1.2; 22.7 (22.69; 24.5)	W=59.5; p=0.351
CCT ( $\mu$ m)	550 $\pm$ 24; 542 (533; 560)	563 $\pm$ 31; 564 (543; 580)	W=269.5; p=0.123
MD (dB)	-5.5 $\pm$ 6.4; -2.8 (-6.7; -1.4)	-2.4 $\pm$ 4.3; -0.8 (-2.6; -0.5)	W=304; p=0.014
PSD (dB)	4.7 $\pm$ 2.0; 4.5 (2.8; 6.7)	3.3 $\pm$ 1.7; 2.6 (2.2; 3.7)	W=115; p=0.013
OD (mm <sup>2</sup> )	1.9 $\pm$ 0.3; 1.9 (1.7; 2.0)	2.1 $\pm$ 0.5; 1.9 (1.6; 2.5)	W=225.5; p=0.695
RNFL ( $\mu$ m)	74.6 $\pm$ 18.7; 78.0 (64.0; 86.0)	87.7 $\pm$ 23.2; 94.5 (68.5; 104.2)	W=287.5; p=0.044

IOL, intraocular lens; PES, pseudoexfoliation syndrome; SE, spherical equivalent; BCVA, best corrected visual acuity, AL, axial length; CCT, central corneal thickness; MD, mean deviation of retinal photosensitivity; PSD, standard deviation of retinal photosensitivity; OD, optic disc, RNFL, retinal nerve fiber layer.

**Table 2. IOP level at the onset of the study, and after two and four weeks (mm Hg)**

Measurement method	Onset of the study*	4 weeks**	Statistical significance: * vs. **	
Group 1	Po (iCare)	15.2 $\pm$ 4.4; 15.0 (13.0; 18.0)	14.6 $\pm$ 3.1; 15.0 (13.0; 17.0)	V=268, p=0.139
	P5 g	19.3 $\pm$ 3.3; 19.5 (16.5; 21.0)	19.1 $\pm$ 3.1; 18.5 (17.0; 21.0)	V=334.5, p=0.531
	P10 g	24.3 $\pm$ 3.9; 24.5 (22.0; 26.0)	23.6 $\pm$ 2.5; 24.0 (21.5; 25.0)	V=434.5, p=0.212
	P15 g	29.7 $\pm$ 4.0; 29.5 (28.0; 31.0)	29.6 $\pm$ 3.2; 29.5 (27.5; 31.5)	V=327, p=0.716
	Elasticity increase	10.4 $\pm$ 2.1; 10.5 (9.5; 12.0)	10.5 $\pm$ 2.8; 10.5 (9.5; 12.0)	V=249.5, p=0.285
Group 2	Po (iCare)	15.25 $\pm$ 3.8; 15.0 (13.75; 18.0)	15.7 $\pm$ 1.9; 16.5 (14.5; 17.0)	V=14.5, p=0.672
	P5 g	19.2 $\pm$ 3.7; 19.3 (16.1; 21.0)	18.4 $\pm$ 2.2; 18.3 (16.4; 20.5)	V=41, p=0.501
	P10 g	23.6 $\pm$ 5.1; 24.3 (18.5; 25.0)	22.9 $\pm$ 2.2; 24.0 (21.3; 25.0)	V=28, p=1
	P15 g	28.9 $\pm$ 5.3; 29.7 (24.8; 30.6)	28.3 $\pm$ 3.0; 27.8 (26.0; 31.1)	V=41, p=0.905
	Elasticity increase	9.7 $\pm$ 2.8; 9.5 (8.4; 10.7)	9.9 $\pm$ 1.5; 10.0 (9.4; 10.8)	V=25.5, p=0.531
Statistical significance: 1 vs. 2		W <sub>i</sub> =234.5, p <sub>i</sub> =0.814	W <sub>i</sub> =183, p <sub>i</sub> =0.180	
		W <sub>5</sub> =257.5, p <sub>5</sub> =0.814	W <sub>5</sub> =270.5, p <sub>5</sub> =0.609	
		W <sub>10</sub> =279, p <sub>10</sub> =0.488	W <sub>10</sub> =275, p <sub>10</sub> =0.540	
		W <sub>15</sub> =265, p <sub>15</sub> =0.693	W <sub>15</sub> =300, p <sub>15</sub> =0.254	
		W <sub>3</sub> =306, p <sub>3</sub> =0.204	W <sub>3</sub> =301.5, p <sub>3</sub> =0.238	

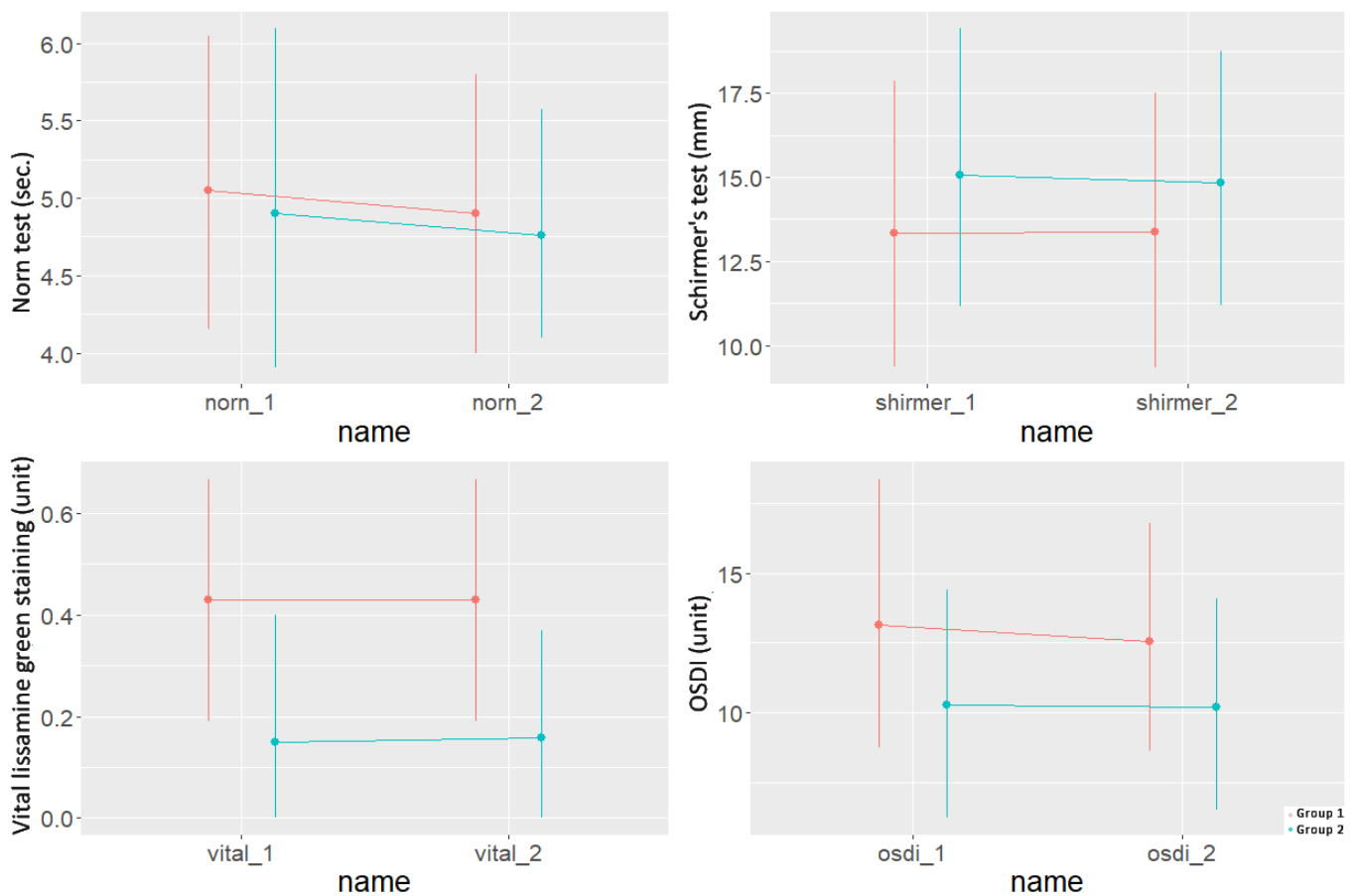


Figure 1. 95% confidence intervals for the Norn test, Schirmer's test, vital lissamine green staining, OSDI questionnaire at the start of treatment and after 4 weeks.

Among examined patients, 15 (71.5%) were women and 6 (28.5%) were men. The mean age of all patients regardless of their gender at the time of enrollment in the study was  $72 \pm 8.3$ ; 72.0 (68.2; 78.7) years; for men, the numbers were  $65.25 \pm 10.4$ ; 65.5 (61.6; 72.8) years; for women, this parameter values were  $74.8 \pm 5.3$ ; 76.3 (70.0; 79.2) years ( $W=272$ ,  $p=0.005$ ). POAG was confirmed for 21 (51.2%) eyes, included in Group 1 (observation group). The patients in this group in terms of their age characteristics were as follows:  $72.2 \pm 9.1$ ; 73.0 (68.4; 78.7) years. Group 2 (control) included patients with suspected glaucoma and ocular hypertension who did not receive any hypotensive therapy: 20 (49.8%) eyes, aged  $71.5 \pm 6.6$ ; 70.0 (67.6; 78.7) years ( $W=156$ ,  $p=0.471$ ). Clinical and demographic data by groups are presented in Table 1.

As expected a priori, the groups differed statistically significantly in their structural and functional characteristics, and duration of observation. There were no statistically significant differences in all other clinical and demographic parameters. The magnitude of intraocular pressure (Po) at the time of inclusion in the study was  $15.2 \pm 4.4$ ; 15.0 (13.0; 18.0) mm Hg in Group 1 vs.  $15.25 \pm 3.8$ ; 15.0 (13.75; 18.0) mm Hg in Group 2 ( $p>0.05$ ) (Table 2). Herewith, elasticity increase, characterizing the biomechanical properties of the eyeball fibrous tunic, was in both groups within average values [27-29] (Table 2).

**Statistical data processing.** Data processing was performed by the R Core Team (2016) (R: A Language and Environment for

Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. Source: <https://www.R-project.org/>. The normality of the data distribution was checked using the Shapiro-Wilk test, while homoscedasticity was examined by the Bartlett's test. Normally distributed parameters are presented in the format:  $M \pm \sigma$ , where M is the mean and  $\sigma$  is the standard deviation of the mean. Parameters with a distribution other than normal are presented in the format:  $Me$  (Q25%; Q75%), where Me is the median, Q25% and Q75% are quartiles. For comparisons of independent groups or repeated intragroup changes with a normal distribution of parameters, the Student's t-test was employed; with a non-normal distribution of parameters, the Wilcoxon test was used for comparing several samples; 95% confidence intervals were calculated as  $M \pm 1.96\sigma$ . The critical level of significance for testing statistical hypotheses was assumed at  $p < 0.05$ .

### Results

When replacing the preservative-free CAI as part of the preservative-free combination therapy with FCBT and CAI with Dorzolano Solo (Solopharm, Russia), containing 0.18% sodium hyaluronate and sodium benzoate, after four weeks of treatment we observed no additional statistically significant change in intraocular pressure ( $p>0.05$ ) (Table 2).

The ocular surface condition sensu TBUT, Schirmer test, vital staining of the ocular surface epithelium with lissamine green, and the OSDI questionnaire at the onset of the study did not differ

statistically significant between the groups (Figure 1). During a month of follow-up, after replacing preservative-free Dorzolol Solo (Solopharm, Russia) containing 0.18% sodium hyaluronate with Dorzolol Solo (Solopharm, Russia) containing sodium benzoate as a preservative, all Group 1 patients noted short-term burning during the instillation. To examine the acidity of both preparation options, we used the pH meter on 12 samples (Liquid analyzer Expert-001, Econix-Expert, Russia), three samples for each bottle, two bottles of preservative-free Dorzolol Solo and Dorzolol Solo containing sodium benzoate preservative. The pH was  $5.67 \pm 0.035$  and  $5.61 \pm 0.04$ , respectively ( $p=0.469$ ), which generally corresponds to the declared acidity of the preparation [30].

Herewith, the indicators characterizing eye surface condition in the observation group did not change statistically significantly over the entire observation period. It is worth noting that over a month of observation, Group 2 did not exhibit statistically significant changes in the eye surface as well (Figure 1).

### Discussion

To reduce the toxic effects of conventional preservatives on the ocular surface, alternative preservatives have been proposed, such as Purite® oxidizing preservative (Allergan Inc., Irvine, California, USA), Polyquaternium-1 or Polyquad® detergent (Alcon Research, Fort Worth, Texas, USA), SofZia® ion buffer preservative (Novartis AG, Basel, Switzerland), sodium perborate (GenAqua®), and sodium benzoate.

Sodium benzoate is considered a relatively safe preservative [31]. Hypotensive medicines containing sodium benzoate as a preservative do not reduce cell viability and do not change the histological integrity of corneal structures after prolonged exposure. However, they can cause a slight disorder of a barrier function [31]. Consequently, sodium benzoate is considered by some authors as a safer preservative for ophthalmic drugs than BAC [32].

Other existing preservatives developed to reduce toxic effects of BAC are also not completely devoid of this effect. For instance, Polyquad (Polyquaternium) represents a family of polycationic polymers. The name Polyquad refers to about 37 different polymers, but it is Polyquaternium-1 that is most often used in ophthalmology, e.g., as a solution for the treatment of contact lenses [33]. Although Polyquad is considered a relatively safe preservative, some studies have shown that its currently used concentration has a strong toxic effect on the barrier function and viability of corneal cells after the prolonged exposure [32].

Preparations containing SofZia do not have toxicity even after prolonged exposure. Since human cells possess cytochrome oxidase and/or catalase enzymes, SofZia is apparently less toxic to human cells [32, 34-36]; however, it still has some detergent effect [35].

In the course of this study, we examined the effect of a preparation containing sodium benzoate on ocular surface condition. Despite the fact that patients complained of a short-term burning sensation during Dorzolol Solo (Solopharm, Russia) instillation, there was no change in the ocular surface condition over the observation period. As far as we know, this is the first study that investigated the effect of Dorzolol Solo (Solopharm, Russia) containing sodium benzoate on the condition of the ocular surface. In patients with glaucoma, diseases of the eye surface caused by a prolonged use of hypotensive drops are more

common, as well as disorders of the tear film due to the filtering bleb. Besides, the presence of concomitant diseases, such as diabetes mellitus, can exacerbate DES [37,38]. Hence, an accurate determination of the potential toxicity of eye drops is of clinical importance in order to avoid unnecessary damage to the eye surface.

### Study limitations

There are several limitations to this study. First, the small sample size of the observation group was partially due to the complexity of the patient inclusion criteria, and to some extent, caused by a burning sensation complaint. Second, we used Dorzolol Solo eye drops (Solopharm, Russia) in this study in combination with a preparation of bimatoprost and timolol, and it is impossible to claim that we were able to identify the individual effects of each of these drugs. Finally, it is possible that a month-long observation period was not long enough to reveal a deterioration in the ocular surface condition.

### Conclusion

Replacement of the preservative-free CAI in combination therapy of glaucoma with a CAI containing the preservative in the form of sodium benzoate and 0.18% sodium hyaluronate (Dorzolol Solo, Solopharm, Russia) did not yield statistically significant changes in intraocular pressure. At the same time, the eye surface condition did not change statistically significantly during a month of observation. The discomfort caused by the instillation of Dorzolol Solo (Solopharm, Russia), containing sodium benzoate as a preservative, was not related to the pH of the preparation.

### Authors' contribution

All authors have contributed equally.

### Financing

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### Conflict of interest

There is no conflict of interest.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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