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Article

Topical Treatment of Elevated Intraocular Pressure in Patients with Graves' Ophthalmopathy

Magdalena Gumińska, [1] Roman Goś, [2] Janusz Śmigielski and [3] Michał S. Nowak,[1,4,*]

[1] Provisus Eye Clinic, 112 Redzinska str., Częstochowa 42-209, Poland; e-mail mguminska@op.pl
[2] Department of Ophthalmology and Vision Rehabilitation, Central Veterans Hospital, Medical University of Lodz, 113 Zeromskiego str., Lodz 90-549, Poland: e-mail rgos@poczta.onet.pl
[3] Department of Statistics, State University of Applied Science in Konin, 1 Przyjazni str., Konin 65-510, Poland; e-mail janusz.smigielski.stat@gmail.com
[4] Saint Family Hospital Medical Center; 19 Wigury str., Lodz 90-302. Poland; e-mail michaelnovak@interia.pl
ORCID: 0000-0001-6304-1545
* Correspondence: Michał S. Nowak, Provisus Eye Clinic, 112 Redzinska str. Częstochowa 42-209, Poland; e-mail michaelnovak@interia.pl, Tel +48 888 801010
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Abstract: Purpose: The evaluation of the efficacy of topical hypotensive treatment and/or systemic corticosteroids therapy in patients with elevated intraocular pressure and Graves' orbitopathy (GO).

Methods: 172 eyes in 86 individuals with duration of GO ≥ 3 months, intraocular pressure in either eye ≥ 25.0 mmHg and GO ranked ≥ 3 at least in one eye in modified CAS form, were included. The study subjects were divided into three treatment subgroups: subgroup I was administered latanoprost QD; subgroup II was administered a combined preparation of brimonidine and timolol BID; subgroup III was the control group, not receiving any topical hypotensive treatment. All the study participants received systemic treatment – intravenous corticosteroid therapy at the same dose, according to the EUGOGO guideline

Results: On the final visit, the mean IOP value was significantly lower in all treatment subgroups comparing to the initial values. In both subgroups receiving topical treatment the IOP reduction was higher than in the control group receiving systemic corticosteroids only. However, the latanoprost eye drops decreased intraocular pressure more effectively than drops containing brimonidine and timolol.

Conclusion: Topical ocular hypotensive treatment is effective in reducing intraocular pressure in GO and decreases intraocular pressure more effectively than systemic corticosteroid therapy alone.

Keywords: Graves' ophthalmopathy; exophatlmos; intraocular pressure; topical medications

1. Introduction

Thyroid-associated orbitopathy is an autoimmune, inflammatory disease of the orbital tissue. It is caused by autoantibodies against the thyrotropin receptor on endothelial cells of the thyroid follicles and against a subpopulation of orbital fibroblasts. It occurs in about 25-50% of patients with Graves' disease (GD) [1-5]. It is estimated that elevated intraocular pressure (IOP) in the course of thyroid-associated orbitopathy affects 3.7%-24% of patients. It is also known that in most cases it stabilizes following immunosuppressive therapy. However, in clinical practice, persisting increases in IOP, despite general treatment, are often observed. It is still not proved whether thyroid-associated orbitopathy predisposes to developing glaucoma, or just to intraocular hypertension [1,6-11].

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Elevated IOP present in GD is a very significant sign, not included in the disease severity classification. In consequence, it may result in glaucomatous optic neuropathy, because (according to the European Glaucoma Society guidelines) ocular hypertension is the most important risk factor for the development of glaucoma [12]. According to various authors, glaucoma may occur in the course of Graves' orbitopathy in 0.8 to 13% of patients [1,6-8,10-11] and the number of studies concerning the elevated IOP treatment in patients with Graves' orbitopathy is also limited [13-17].

Due to the fact, that Graves' orbitopathy results in the inflammation of the ocular surface, the ideal choice of hypotensive treatment (in subjects with elevated IOP) seems to be very important. The ideal hypotensive drug in Graves' orbitopathy should combine the best intraocular pressure lowering effect with the best tolerance to ensure patient's compliance [18-20].

The aim of the present study was the evaluation of the efficacy of ocular hypertension treatment with the use of topical therapy with a prostaglandin-group drug and a complex drug being a combination of a α2-mimetic and a β-blocker and/or systemic corticosteroids therapy applied according to the European Group of Graves' Orbitopathy (EUGOGO) guidelines in patients with orbitopathy in the course of Graves' disease.

2. Materials and Methods

A prospective study was conducted at the Department of Ophthalmology and Vision Rehabilitation, Central Veterans Hospital, Medical University of Lodz, in the period between June 2011 and June 2013. The study, performed within the doctoral thesis, included 172 eyes in 86 individuals, 25 males and 61 females, patients of the Department of Endocrinology, Medical University of Lodz with Graves' orbitopathy. The Clinical Activity Scale (CAS) by Mourits & Weetmann, in an individually modified version, was used for the assessment of Graves' orbitopathy activity. All participants were interviewed and information regarding brief details of medical history and the eye conditions as well as demographic data was collected. Comprehensive ophthalmic examination included: distance visual acuity (VA) testing, a cover test, binocular and color vison assessments, exophthalmos (EXO) measurements with Hertel exophthalmometer, intraocular pressure (IOP) measurements with the Goldman applanation tonometry, ultrasound pachymetry as well as slit lamp and indirect ophthalmoscopic evaluation of the anterior and posterior segments and other examinations where needed. Inclusion criteria included: person aged ≥ 18 years, duration of orbitopathy at least 3 months, intraocular pressure in either eye equal to or exceeding 25.0 mmHg, ocular Graves' orbitopathy in modified CAS form ranked ≥ 3 at least in one eye. The exclusion criteria included: pregnancy or lactation period, topical hypotensive treatment prior to the study, closed or narrow angle glaucoma, pseudoexfoliation syndrome (PEX), rubeosis iridis, intraocular surgery in the study eye within 3 months prior to screening, medical history of any uveitis and ocular trauma, uncontrolled heart disease, severe respiratory syndrome, liver failure and known allergy to a prostaglandin-group drugs or a α2-mimetic and a β-blocker drugs. The study subjects were divided into three treatment subgroups, i.e. subgroup I – 20 patients (7 males and 13 females) with Graves' orbitopathy qualified for the study were administered a prostaglandin, latanoprost, taken once daily, in the evening, same time, at 8 p.m.; subgroup II – 20 patients (6 males and 14 females) with Graves' orbitopathy qualified for the study were administered a combined preparation of brimonidine and timolol (Combigan) taken twice daily, same time, at 9:00 a.m. and 4 p.m.; subgroup III – 46 patients (12 males and 34 females) with Graves' orbitopathy and intraocular pressure exceeding 25.0 mmHg were qualified for the control group, not receiving any topical hypotensive treatment. All the study participants received systemic treatment – intravenous corticosteroid therapy at the same dose, according to the EUGOGO guidelines, i.e. methylprednisolone 0.5 mg weekly for the first six weeks, and then methylprednisolone 0.25 mg for the next six weeks. The observation period of the patients lasted 12 weeks.

The study was approved by the institutional review board of the Medical University of Lodz (Ethical Approval Code RNN/488/11/KB) and informed consent was obtained from all included subjects. All participants were counseled about the prognosis for their condition and the nature and possible consequences of the treatment were explained. For statistical analysis, the demographic

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data were anonymously recorded and all procedures used adhered to the tenets of Declaration of Helsinki.

Data management and statistical analysis:

Data was entered into Microsoft Excel database and commercially available software STATISTICA v. 10.1 PL (StatSoft Polska, Krakow, Poland) was used to perform all statistical analyses. The statistical analysis included demographic data as well as medical history data and patients' tests results obtained on both the screening and the final visits. The sex distribution was explored by Chi squared (χ^2) test. Other non-parametric methods based on ranks were used for the analyses of participants' age, BMI, GD duration time, CAS inflammation values, EXO values and IOP measurements values. The Kruskal-Wallis analysis of variance was used to examine the differences between all treatment subgroups. The comparison between particular subgroups was done using the Mann-Whitney U-test and the Dunn test because of the Bonferroni's correction. Multiple logistic regression model was used to investigate the association of sex and the duration of Graves' orbitopathy (GO) with EXO values on the screening visit. Differences were considered significant at $p<0.05$ with a 95% confidence interval.

3. Results

The demographic analysis of the study population is presented in Table 1 and Table 2. A total of 86 white subjects, most of whom live or have lived in the city of Lodz, in central Poland were enumerated and included into the study. There were 25 men (29.1%) and 61 women (70.9%). Our study subjects were divided into 3 subgroups. Subgroup I included 7 men (35.0%) and 13 women (65.0%). Subgroup II included 6 men (30.0%) and 14 women (70.0%). Subgroup III included 12 men (26.1%) and 34 women (73.9%). Statistical analysis revealed that our three subgroups did not vary significantly in gender (χ^2 test p= 0.760). An analysis of data on the screening visit showed that the mean age of the study subjects was 54.91 years $\pm$ 8.25 years (range, 29-73 years). The mean BMI value was 25.67 ± 3.86 in the females and 26.45 ± 3.12 in the males (range, 19.26 – 35.43). The mean GO duration time was 22.59 months ± 23.13 in the females and 19.32 ± 21.55 months in the males (range, 3 – 12 months). A comparative analysis between Subgroup I (latanoprost treatment), Subgroup II (therapy with Combigan complex preparation) and Subgroup III (observation without any pharmacotherapy) based on the Kruskal-Wallis test revealed that differences in age, BMI value and GO duration time between the studied subgroups were not statistically significant (p=0.954, p=0.851 and p=0.851) (Table 3, Table 4).

The exophthalmos (EXO) secondary to Graves' ophthalmopathy ranged from 12.0 to 28.0 mm at the screening visit **(Table 5).** The mean EXO value in the right eye was 19.18 mm ± 3,58 mm in the females and 21.08 mm ± 2.48 mm in the males. The mean EXO value in the left eye was 19.34 mm ± 3.82 mm in the females and 20.88 mm ± 2.83 mm in the males. The CAS inflammation values ranged from 2 to 6 at the screening visit. The mean CAS value in the right eye was 3.54 ± 0.85 in the females and 3.44 ± 0.65 in the males **(Table 6).** The mean CAS value in the left eye was 3.70 ± 0.78 in the females and 3.56 ± 0.71 in the males. A comparative analysis between Subgroup I, Subgroup II and Subgroup III based on the Kruskal-Wallis test revealed that the differences in the CAS inflammation values and EXO values between the studied subgroups were not statistically significant either in the right eye (p=0.741 and p=0.279) or in the left eye (p=0.262 and p=0.12). Multiple regression analysis also revealed the values of exophthalmos were statistically significant associated with female gender and duration of GD. Female gender decreased exophthalmos by 1.808 and longer duration of GD increased exophthalmos by 0.028 (p= 0.002 and p=0.016 respectively).

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Table 1. Analysis of sex of the study population divided into three subgroups.

Sex	Subgroup I Topical treatment with latanoprost and steroids iv.		Subgroup II Topical treatment with Combigan and steroids iv.		Subgroup III Control group steroids iv. only		All participants	
	No	%	No	%	No	%	No	%
Men	7	35,00	6	30,00	12	26,09	25	29,07
Women	13	65,00	14	70,00	34	73,91	61	70,93
All	20	100,00	20	100,00	46	100,00	86	100,00
Statistical analysis	Chi squared test = 0,55 p =0,7603							

Table 2. Analysis of age of the study population divided into three subgroups.

Age [years]	All participants		
	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46
Minimum	42,00	36,00	29,00
Maksimum	67,00	73,00	73,00
Median	56,00	55,00	55,00
Mean	54,95	55,35	54,70
Standard deviation	5,47	10,23	8,46
Asymmetry coefficient	-0,15	-0,26	-0,73
Statistical analysis	Kruskal-Wallis test: H =0,095 ; p=0,954		

Table 3. Analysis of BMI parameters in the study participants at the screening visit.

BMI value	All participants		
	Subgroup I	Soubgroup II	Subgroup III
No of subjects	20	20	46
Minimum	19,26	19,82	20,07
Maksimum	34,81	34,21	35,43
Median	25,55	25,50	25,19
Mean	26,01	26,33	25,66
Standard deviation	3,55	4,34	3,45
Asymmetry coefficient	0,75	0,50	0,85
Statistical analysis	Kruskal-Wallis test: H =0,32 ; p= 0,851		

Table 4. Analysis of Graves' orbitopathy (GO) duration time in the study participants at the screening visit.

Duration time of GO at the screening visit (months)	All participants		
	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46
Minimum duration	3,00	6,00	3,00
Maksimum duration	72,00	72,00	96,00
Median duration	8,00	17,00	12,00
Mean duration	21,95	24,00	20,48
Standard deviation	24,61	21,74	22,50
Asymmetry coeffitient	1,24	1,19	1,79
Statistical analysis	Kruskal-Wallis test: H =1,47 ; p=0,851		

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Table 5. EXO values analysis in the study participants' right and left eyes at the screening visit.

Exophthalmos values at the screening visit	Right eyes			Left eyes		
	Subgroup I	Subgroup II	Subgroup III	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46	20	20	46
Minimum (mm)	12,00	13,00	13,00	14,00	16,00	10,00
Maksimum (mm)	22,00	26,00	28,00	24,00	27,00	27,00
Median (mm)	20,00	21,50	20,00	19,00	21,50	19,00
Mean (mm)	19,15	20,65	19,59	19,10	21,20	19,48
Standard deviation	2,81	3,59	3,52	3,11	3,37	3,82
Asymmetry coeffitient	-1,10	-0,66	0,07	-0,01	-0,14	0,01
Statistical analysis	Kruskal-Wallis Test: H =2,55 ; p=0,279			Kruskal-Wallis Test: H =4,21 ; p=0,122		

Table 6. Modified CAS inflammation form analysis in the study participants' right and left eyes at the screening visit.

Modified CAS Inflammation values at the screening visit	Right eyes			Left eyes		
	Subgroup I	Subgroup II	Subgroup III	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46	20	20	46
Minimum	3,00	2,00	2,00	3,00	3,00	3,00
Maksimum	6,00	5,00	5,00	6,00	5,00	5,00
Median	3,00	3,00	3,00	3,00	4,00	4,00
Mean	3,45	3,60	3,50	3,50	3,80	3,67
Standard deviation	0,83	0,88	0,75	0,89	0,83	0,67
Asymmetry coeffitient	2,05	0,43	0,82	1,75	0,41	0,49
Statistical analysis	Kruskal-Wallis Test: H =0,60 ; p= 0,741			Kruskal-Wallis Test: H =2,68 ; p= 0,262		

The mean IOP parameter in the right eye was 26.72 mmHg ± 1.23 mmHg in the females and 26.32 mmHg ± 0.80 mmHg in the males, at the screening visit **(Table 7).** The mean IOP value in the left eye was 26.89 mmHg ± 1.93 mmHg in the females and 26.52 mmHg ± 1.61 mmHg in the males. A comparative analysis between Subgroup I, Subgroup II and Subgroup III based on the Kruskal-Wallis test and Dunn's test showed that the differences in the OIP value in the right eye between the studied subgroups on the screening visit were not statistically significant (p=0.450). Whereas, as for the left eye, they were statistically significantly higher in Subgroup I and Subgroup II as compared to Subgroup III (p=0.030 and p=0.020). The difference in the initial IOP in the left eye between Subgroup I and Subgroup II was not statistically significant (p=1.000).

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Table 7. IOP measurements values analysis in the study participants' right and left eyes at the screening visit.

IOP values at the screening visit (mmHg)	Right eyes			Left eyes		
	Subgroup I	Subgroup II	Subgroup III	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46	20	20	46
Minimum (mmHg)	25,00	25,00	25,00	25,00	25,00	25,00
Maksimum (mmHg)	29,00	29,00	29,00	35,00	34,00	29,00
Median (mmHg)	26,00	26,50	26,00	27,00	27,00	26,00
Mean (mmHg)	26,75	26,80	26,46	27,40	27,45	26,22
Standard deviation	1,25	1,24	1,03	2,21	2,04	1,38
Asymmetry coeffitient	0,71	0,60	1,28	2,33	1,84	1,02
Statistical analysis	Kruskal-Wallis Test: H =1,60 ; p=0,450			Kruskal-Wallis Test: H =11,59 ; p=0 ,0030		
Statistical analysis				Test Dunna =		
Subgroup I					0,127	2,581
Subgroup II				0,127		2,730
Subgroup III				2,581	2,730	
				p =		
Subgroup I					1,000000	0,029565
Subgroup II				1,000000		0,018978
Subgroup III				0,029565	0,018978	

On the final visit, the mean IOP value in the right eye decreased by 35.7% to 17.20 mmHg ± 3.61 mmHg among the patients receiving prostaglandin treatment (Subgroup I); in the patients administered with combined drug, Combigan (Subgroup II) it decreased by 28.2% to 19.25 mmHg ± 2.0 mmHg and in the control group (Subgroup III), not receiving any topical treatment, it decreased by 17.6% to 21.80 mmHg ± 4.98 mmHg **(Table 8).** Similarly, in the left eye the mean IOP value decreased by 39.1% to 16.70 mmHg ± 3.88 mmHg in Subgroup I, in Subgroup II it decreased by 28.2% to 19.70 mmHg ± 2.41 mmHg and in Subgroup II it decreased by 17.2% to 21.72 mmHg ± 5.11 mmHg I. A comparative analysis between Subgroup I, Subgroup II and Subgroup III based on the Kruskal-Wallis test and Dunn's test revealed that the differences in IOP value in both eyes on the final visit were statistically significantly lower in Subgroup I as compared to Subgroup III (p=0.001 and p=0.001). The final IOP in Subgroup II was also lower than in Subgroup III (in both eyes), however, the difference between Subgroup II and Subgroup III was not statistically significant (p=0.140 and 0.593). The difference in the final IOP in both eyes between Subgroup I and Subgroup II was not statistically significant either (p=0.496 and 0.115), however, the prostaglandin eye drops decreased intraocular pressure more effectively than Combigan drops containing brimonidine and timolol. Topical ocular hypotensive therapy was well-tolerated by the patients, both on the check-up appointment and the final visit.

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Table 8. IOP measurements values analysis in the study participants' right and left eyes at the final visit.

IOP values at the final visit (mmHg)	Right eyes			Left eyes		
	Subgroup I	Subgroup II	Subgroup III	Subgroup I	Subgroup II	Subgroup III
No of subjects	20	20	46	20	20	46
Minimum (mmHg)	10,00	15,00	12,00	10,00	15,00	12,00
Maksimum (mmHg)	23,00	22,00	30,00	23,00	24,00	32,00
Median (mmHg)	18,00	20,00	22,00	17,50	20,00	21,50
Mean (mmHg)	17,20	19,25	21,80	16,70	19,70	21,72
Standard deviation	3,61	2,00	4,98	3,88	2,41	5,11
Asymmetry coeffitient	-0,58	-0,56	-0,23	-0,17	-0,51	0,05
Statistical analysis	Kruskal-Wallis Test: H =21,05 ; p=0, ,0008			Kruskal-Wallis Test: H =14,11 p =0,0009		
Statistical analysis	Dunn Test =			Dunn Test		
Subgroup I		1,387	3,642		2,074	3,737
Subgroup II	1,387		2,005	2,074		1,288
Subgroup III	3,642	2,005		3,737	1,288	
	p =			p =		
Subgroup I		0,496561	0,000812		0,114299	0,000560
Subgroup II	0,496561		0,134977	0,114299		0,593070
Subgroup III	0,000812	0,134977		0,000560	0,593070	

4. Discussion

The previously published studies revealed that elevated IOP in the course of thyroid-associated orbitopathy (TAO) is related to compression of the eyeball by enlarged extraocular muscles, the elevated intraorbital pressure (as result of the proliferation of intraorbital connective tissue) and the enlargement as well as swelling of extraocular muscles. However, orbital decompression and extraocular muscle surgery are effective in lowering the IOP in patients with TAO [9,13-16], there is a lack of studies concerning topical hypotensive treatment in patients with TAO and our study fills this gap. Guminska et al. have published a pilot study which proved that prostaglandin drug latanoprost is effective in lowering IOP in patients with TAO on a small group of subjects without a control group in year 2014 [17]. The present study, performed within the doctoral thesis, included 172 eyes in 86 individuals, divided into three treatment subgroups including control group without topical hypotensive treatment.

One of the inclusion criteria was CAS inflammation score ≥ 3 in at least one eye, because previously published studies by Behrouzi et al. and Cockerham et. al have showed that active TAO may results in ocular hypertension and/or progression of glaucoma [7,10]. Due to the fact, that all included subjects have active TAO, all of them received systemic treatment – intravenous corticosteroid therapy at the same dose, according to the EUGOGO guidelines.

Other important inclusion criterion was IOP ≥ 25 mmHg in both eyes at the screening visit. The results of The Advanced Glaucoma Intervention Study (AGIS) showed that an increase of IOP to 26 mmHg or more increases the risk of glaucoma twelve times in long term follow-up [21]. On the other hand, the results of Early Manifest Glaucoma Trial (EMGT) showed that 25% reduction of IOP from the initial values (maintained throughout follow-up) reduced the risk of glaucoma by near 50% [22]. However, the observation period of the patients in our study lasted only 12 weeks, the results of previously published studies showed that prevalence of ocular hypertension in patients with TAO is higher than in the general population [7-8,10-11]. Some studies showed that TAO was associated with the higher prevalence of open angle glaucoma [7,11], but other showed that prevalence of open angle glaucoma in patients with TAO was similar to that in the general population [8], though their findings were not consistent.

Spierer & Eisenstein have showed that an increase of IOP in patients with active TAO correlated positively with the severity of exophthalmos [23] and the results our study showed female gender

decreased exophthalmos by 1.808 and longer duration of GD increased exophthalmos by 0.028 (p= 0.002 and p=0.016 respectively), at the screening visit.

On the final visit, the mean IOP value was significantly lower in all treatment subgroups comparing to the initial values. In both subgroups receiving topical treatment the IOP reduction was higher than in the control group receiving systemic corticosteroids only. However, the difference in the final IOP in both eyes between prostaglandin (latanoprost) subgroup and Combigan subgroup was not statistically significant either (p=0.496 and 0.115), the latanoprost eye drops decreased intraocular pressure more effectively than Combigan drops containing brimonidine and timolol. Topical ocular hypotensive therapy was well-tolerated by the patients, both on the check-up appointment and the final visit. Our results were in agreement with the results of other previously published studies that showed good ocular-tolerability profile of both types of eye drops [24-26]. Although, the study by Katz et al. showed fixed-combination brimonidine-timolol was as effective as latanoprost in reducing IOP in patients with glaucoma or ocular hypertension [26], the results of the present study showed better efficacy in lowering IOP of latanoprost versus fix-combination brimonidine-timolol in patients with TAO.

The limitation of the current study include low number of participants and short period of follow-up but it likely had only a minor impact on the study findings. Our study group included only subjects with active Graves' disease and elevated intraocular pressure and obtained results were in agreement with the results of other studies from Poland and worldwide.

5. Conclusions

Topical ocular hypotensive treatment in the form of latanoprost (prostaglandin) eye drops or the combined preparation of brimonidine and timolol is effective in reducing intraocular pressure in patients with orbitopathy in the course of Graves' disease and decreases intraocular pressure more effectively than systemic corticosteroid therapy alone. Latanoprost eye drops lower intraocular pressure more effectively than those containing the combined preparation of brimonidine and timolol in patients with increased intraocular pressure in the course of orbitopathy associated with Graves' disease. Topical pharmacotherapy is well-tolerated and does not cause any serious side effects.

Author Contributions: Magdalena Gumińska and Roman Goś conceived and designed the experiments. Data was collected by Magdalena Gumińska and Janusz Śmigielski. The results were analyzed by Michal S. Nowak, Janusz Śmigielski and Roman Goś. The first and final drafts were written by Magdalena Gumińska. The defects of draft were critiqued by Michał S. Nowak. All authors agreed on the final draft of this study.

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Conflicts of Interest: The authors declare no conflict of interest

Ethics approval: the study was approved by the institutional review board of the Medical University of Lodz (Ethical Approval Code RNN/488/11/KB)

Consent to participate: informed consent was obtained from all included subjects.

Availability of data and material: the source data is available at Department of Ophthalmology and Vision Rehabilitation, Central Veterans Hospital, Medical University of Lodz, 113 Zeromskiego str., Lodz, Poland

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