Preservative-free tafluprost in glaucoma patients with diabetes.

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Received: 13-2-2021, Accepted: 3-3-2021, Published online:11/3/2021
EJO(MOC) 2021;1:34-39.
Short Running title: Tafluprost in the medical treatment of POAG in patients with type 2 diabetes mellitus

Introduction: Long term glaucoma therapy results in the deterioration of the anterior surface of the eye that it usually negatively affects adherence to prescribed therapy and its efficacy. It is known that type 2 diabetes mellitus (DM) will increase the risk of developing of DED (dry eye disease). Preservative-free (PF) drugs have more gentle influence on the ocular surface with lower risk of local side effects.

Purpose: To study the results of the treatment of primary open-angle glaucoma (POAG) using preservative-free drug Tafluprost 0.0015% (Taflotan®, Santen, Finland) in patients with type 2 diabetes mellitus.

Material and methods: The study included 74 patients aged 50-62 years with newly diagnosed primary open-angle glaucoma (POAG) on initial stage which were divided into two groups: main (52 patients with type 2 diabetes mellitus) and control (22 patients without diabetes mellitus). In both groups patients obtained one instillation of PF Tafluprost 0.0015% (Taflotan®, Santen, Finland) daily. The term of follow up was 12 months. Ophthalmological methods of examination included point contact tonometry, gonioscopy, biomicroscopy and ophthalmoscopy, static automatic perimetry (SAP), optical coherence tomography (OCT) of nerve fiber layer, analysis of the anterior surface of the eye with tear film stability and the simplified OSDI questionnaire.

Results: The results demonstrated that using of PF tafluprost drops has a high percentage of safety as regard possible local side effects, high hypotensive efficacy and adherence. During the entire observation period the state of the anterior surface of eyes almost in all cases was comparable with the initial data and the data of questionnaire. Evaluation of the IOP revealed the sufficient level of IOP reduction by 25-30% in all patients. The SAP data showed a slight decrease of MD index at the level of 0.36 dB, that according to the 5-th edition of «Terminology and Guidelines for glaucoma» corresponds to the positive dynamics of the course of glaucomatous optic neuropathy (GON) in main and control groups.

Conclusions: Long-term use of preservative-free eye drops 0.0015% tafluprost (Taflotan®, Santen, Finland) provided a high hypotensive effect with stable functional state of the optic nerve and safety of the anterior eye surface without the appearance of clinical signs of DED in glaucoma patients with and without 2 type DM. It allows to conclude that PF 0.0015% tafluprost eye drops (Taflotan®, Santen, Finland) as the drug of first choice therapy is reasonable to use in patients with newly diagnosed POAG and type 2 DM to reduce the risk of DED.

Key words: Primary open-angle glaucoma, Diabetes mellitus, Prostaglandin analogs, Tafluprost, efficacy, Adherence.

Introduction

The possibility of implementation of the basic data of «Terminology and Guidelines for Glaucoma» as European recommendation for the diagnosis and the treatment of glaucoma in clinical practice resulted in the definite changes of glaucoma patient care. According to the 4th edition of «Glaucoma Terminology and Guidelines» the 1st choice of glaucoma therapy included all groups of antihypertensive drugs[1]. The results of multicenter studies demonstrated that drugs from the group of PGAs (prostaglandin analogs) have the highest efficiency in ensuring daily control of intraocular pressure (IOP). So, in the 5th edition of «Terminology and Guidelines for Glaucoma» PGAs deservedly took a priority position among the other groups for the first choice for POAG therapy [2].

The very important point in choosing of POAG therapy is the evaluation of the effectiveness to minimize daily IOP fluctuations, to maintain a sufficient level of ocular perfusion pressure (OPP), to ensure the required level of the visual function to lower rate of glaucoma progression[3,4] According to numerous studies aimed to assess the comparative daily effectiveness of the main drugs from the PGAs group widely used in POAG therapy (latanoprost, travoprost, bimatoprost and tafluprost) the minimal daily IOP fluctuations were observed on Tafluprost 0.0015% instillations[5,6]. An important aspect in the choice of the drug is the assessment of its influence on the anterior surface of the eye, since the effectiveness of glaucoma therapy and the patient's adherence to the prescribed treatments largely determined by its quality (initial and subsequent)[7-12].

One should take into account the fact that patients with type 2 DM have a high risk of DED, which greatly complicates the selection of topical pharmacological medication[13]. Taking into the account costs and efficacy of the therapy in 5-th edition of «Terminology and Guidelines for Glaucoma» the therapy for glaucoma patients which have no any manifestations of DED and allergy was recommended to start with generic drugs with preservative. However, in glaucoma patients with clinical signs of allergy or DED original and preservative free drugs were recommended. [2]

Purpose: To study the results of the treatment of primary open-angle glaucoma (POAG) using preservative-free drug Tafluprost 0.0015% (Taflotan®, Santen, Finland) in patients with type 2 diabetes mellitus.

Material and methods

The study included 74 patients aged 50-62 years with newly diagnosed primary open-angle glaucoma (POAG) on initial stage which were divided into two groups: main (52 patients with type 2 diabetes mellitus) and control (22 patients without diabetes mellitus). In both groups patients obtained one instillation of PF Tafluprost 0.0015% (Taflotan®, Santen, Finland) daily. The term of follow up was 12 months. POAG was diagnosed according to European guidelines[1,2].

Ophthalmological examination included ICare point contact tonometry (Tiolat, Finland), gonioscopy with a Goldmann lens, biomicroscopy, ophthalmoscopy in a state of short-term mydriasis, static automatic perimetry (SAP) on the Field Analizer (Humphry, Germany), optical coherent tomography (OCT) of retinal nerve fiber layer (RNFL) on OCT Stratus-3000 (Ziezz, Germany), analysis of the anterior surface of the eye on SLM-6E (Kanghua, China) and a questionnaire survey using a simplified OSDI questionnaire. IOP measurement, VF control and questionnaire were performed before and every 3 months after the start of the treatment, others methods–before and at the end of the course of treatment.

Progression was assessed according to the recommendations of the European Glaucoma Society (5-th edition, 2020), taking into the account the

dynamics of changes of light sensitivity (dB) as the indicator in terms of 1 month (dB / M), 1 year (dB / Y) and 10 years (dB / 10Y) and the fact that age-related loss of light sensitivity should not exceed 0.03 dB per month and, accordingly, 0.36 dB for 12 months (1 year). (Table 1). It is assumed that at the advanced stage, the loss of light sensitivity per year can reach 12.0 dB.

Table 1. The rate of deterioration of the MD index (dB) index in glaucomatous patients according to static automatic perimetry.

Terms	**Dynamics trend**	
	Negative -T	**Positive + T**
1 month	0.05	0.03
1 year	0.6	0.36
10 years	6.0	3.60
Advanced stage POAG: = - 12.0 dB		

Note: T - the tendency of deterioration in light sensitivity.

The exclusion criteria in this study were patients with clinical manifestations of blepharitis and DED. The study completed between September 2018 and October 2019.

This work was carried out according to the requirements of the local ethical committee of Kiev Medical Iniversity, patient consent in compliance and with the principles of the Declaration of Helsinki.

Results

The data of ophthalmological examination revealed that in all patients of both groups the angle of the anterior chamber (AC) was opened and had poor pigmentation. The IOP level was within 26.0-28.5 mm Hg (26.4 ± 1.4). The results of examination of thickness of RNFL and MD index in both groups showed that these parameters were some lower in patients with DM 2 type and POAG (main group) (Table 2).

Table 2. Baseline OCT and SAP parameters in the main and control groups

Parameter (dB, µm)	**Groups**		**P**
	Main	**Control**	
MD index	-2.65	-2.10	0.816
RNFL	72.9	73.1	0.525
RNFL S	86.2	87.9	0.776
RNFL I	94.6	94.8	0.515
RNFL N	70.8	71.1	0.673
RNFL T	67.1	68.8	0.305

Note: MD - the mean deviation measured using standard automatic perimetry (SAP); RNFL - the total thickness of the retinal nerve fiber layer (RNFL); RNFL (S) - thickness of the retinal nerve fiber layer in the upper segment; RNFL (I) - thickness of the retinal nerve fiber layer in the lower segment; RNFL (N) - the thickness of the retinal nerve fiber layer in the nasal segment; RNFL (T) - thickness of the retinal nerve fiber layer in the temporal segment; P - significance of Student's t-test.

Analysis of the anterior surface of the eye did not reveal patients with clinical signs of DED in both groups and control of tear film on the surface of cornea demonstrated that the time of onset and the time of rupture of tear film were on the normal level (Fig. 1, Fig. 1-a).

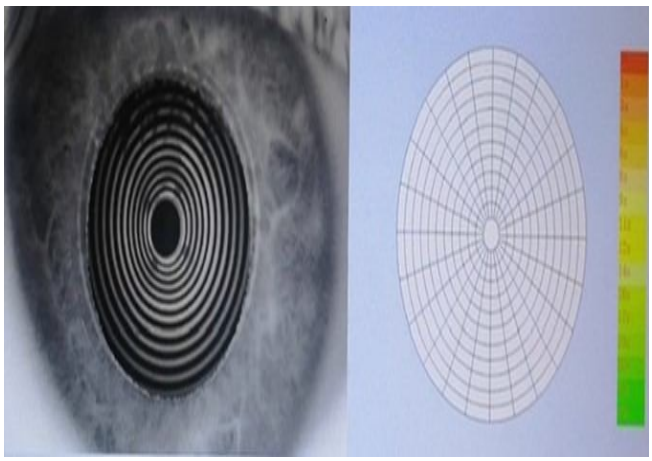

Fig. 1. Tear film rupture map. Patient M (main group)

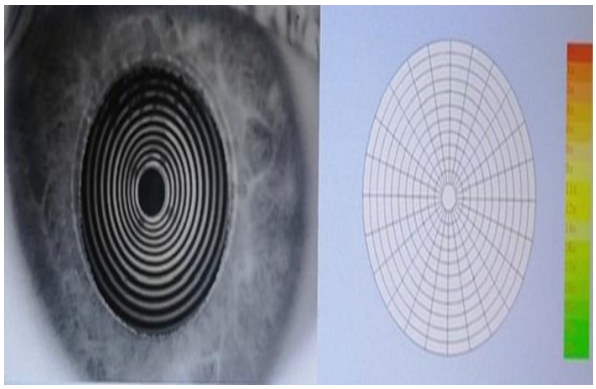

Fig. 1-a. Tear film rupture map. Patient X (control group)

The results of dynamic observation and questionnaire of patients indicated the absence of serious complaints from the anterior surface of the eye. The appearance of some discomfort like as the redness and the feeling of dryness were noted in 3 cases (5.8%) and in 5 cases (9.6%) in 3 and in 6-12 months, respectively, in the main group. In control group similar complaints appeared in less number of cases, in 2 patients (9.1%), and in more late terms, in 6-12 months after the start of instillation of eye drops (Table 3).

The decrease of IOP in both groups was mostly on the high level of 25-30%: in main group 52 patients (100%) and 48 patients (92.3%) - during 6 - 12 months after the start of the therapy. In the control group the same level of lowering of IOP was determined in 100% cases during 6 months and in 95.4% - during 6-12 months. So the number of cases with perfect IOP decrease in control group was on 3.1% larger.

The field analyzer (FA) data revealed a slight decrease of MD index, less than 0.36 dB in 92.3% and in 95.4% cases in main and in control groups, respectively. These data indicated a positive course of glaucoma neuropathy according to the European standards and recommendation and reflected the positive dynamics of the functional state of the optic nerve in both groups [2].

Table 3. The results of the follow-up and questionnaire in both groups.

Parameter	**Groups (n = абс. - %)**							
	Main (n=52)				**Control (n=22)**			
	3	**6**	**9**	**12**	**3**	**6**	**9**	**12**
IOP – 25-30%	52 100	52 100	48 92.3	48 92.3	22 100	22 100	21 95.4	21 95.4
MD (dB)	-	-	-	>0.3	-	-	-	>0.25
Redness, dryness	3 5.8	5 9.6	5 9.6	5 9.6	-	2 9.1	2 9.1	2 9.1
Adherence	52 100	50 96.2	47 90.4	50 96.2	22 100	22 100	21 95.4	21 95.4

Examination of the anterior surface of the eyes in both groups revealed the appearance of slight, local changes of superficial layer of the cornea and the time of rupture of tear film in terms 6 -12 months in 5 patients (9.6%) in main group and in 2 patients (9.1%) in control group. It was demonstrated that the time of beginning and the time of complete rupture of the tear film in these cases were reduced by 1.5-2 times. In none of these cases there were any complaints about the feeling of foreign body or about the pain in the eye, or about the appearance of blurred images (Fig. 2, 2-a).

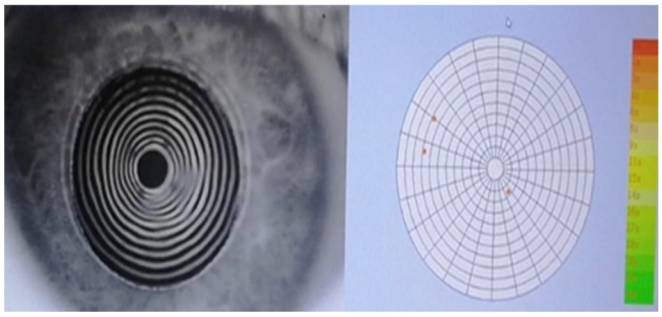

Fig. 2. Tear film rupture map. Patient M (main group)

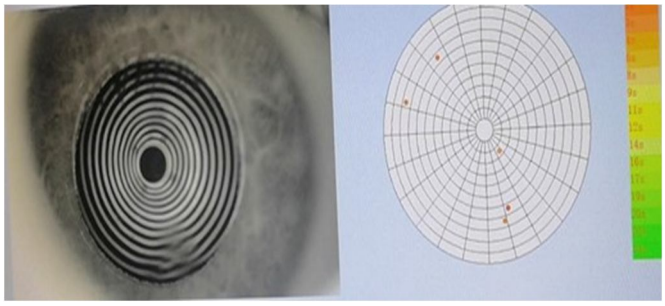

Fig. 2-a. Tear film rupture map. Patient X (control group)

Thus, the obtained data demonstrated a high percentage of safety and hypotensive efficacy of PF Taflotan® eye drops in the main and control groups. The number of cases with small reaction from anterior surface (redness and dryness) in the control group was on 0.5% less. Throughout during the observation period, the condition of the anterior surface of the eye was quite stable and without signs of obvious deterioration. Patients, who noted slight redness of the eyes and transient feelings of the dryness (5 in the main and 2 in the control groups) did not need additional therapy. In both groups, the examined patients confirmed a high level of adherence to therapy: 96.2% and 95.4% in the main and in the control groups, respectively. The majority of patients in the main and control groups assessed the tolerability of Taflotan® eye drops as "excellent" and "good".

Discussion.

The appearance of the insignificant difference in changes of the anterior surface of the cornea, in particular, changes in the time of tear film rupture, as a result of prolonged use of non-preservative eye drops from the group of PGAs in patients with diabetes mellitus compared with control group can be considered as a result of the sparing effect of the drug. This is an extremely important fact for the choosing a drug for long-term therapy of POAG with concomitant diabetes, given the increased risk of DED.

Conclusions. Long-term use of preservative-free eye drops 0.0015% tafluprost (Taflotan®, Santen, Finland) provided a high hypotensive effect with stable functional state of the optic nerve and safety of the anterior eye surface without the appearance of clinical signs of DED in glaucoma patients with and without 2 type DM. It allows to conclude that PF 0.0015% tafluprost eye drops (Taflotan®, Santen, Finland) as the drug of the first choice therapy is reasonable to use in patients with newly diagnosed POAG and type 2 DM to reduce the risk of DED.

No Authors has proprietary interest.

None of the authors has a financial support.

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