

## SAFETY AND EFFICACY OF MONOTHERAPY CHANGE TO FIXED COMBINATION (TRAVOPROST 0,004%/TIMOLOLO,5%) IN 6 MONTHS FOLLOW UP PERIOD

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### SUMMARY

**Purpose:** To assess the safety and efficacy of changing antiglaucoma therapy to the travoprost 0,004%/timolol 0,5% (TTFC) fixed combination from previous monotherapies.

**Methods:** Prospective, open-label, observational, multicenter cohort. A change was done from prior monotherapy at day 0 to TTFC dosed once a day, regardless in the evening or in the morning, without washout period. Active evaluation of systemic and local tolerability (adverse events), and efficacy ie. intraocular pressure (IOP) lowering was done at control 1 (day 30), control 2 (day 90) and control 3 (day 120).

**Results:** 40/155/170 patients (79/309/339 eyes) completed the study (120 days/ 90 days/baseline, respectfully). At control 1 excluded were patients with low tolerability (severe hyperemia (6 patients), discomfort (4), chest pain (1)) and non responders (IOP lowering less than 15% from baseline IOP or target IOP >18 mmHg (4 patients)).

Mean IOP at control 1 was 15,92±1,85 mm Hg (21,66% reduction) for 155 patients (non responders excluded), at control 2 was for 155 patients 15,67±2,17 mm Hg (21,14% reduction), and at control 3 for 40 patients 16,28±1,59 mm Hg (19,86% reduction).

At control 2 analysis of IOP reduction by 4 groups of previous monotherapy (timolol 0,5% (N=33/66), latanoprost 0,005% (N=49/98), betaxolol 0,5% (N=30/60), and travoprost 0,004% (N=43/85) was performed.

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The procedures followed were in accordance with the ethical standards of the institutional or regional responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

40 patients/79 eyes endured to control 3 (after day 90 free samples were not available for all patients). Analysis of IOP reduction by 4 groups of previous monotherapy medications was performed (timolol 0,5% (N=7/14), latanoprost 0,005% (N=14/28), betaxolol 0,5% (N=7/14), travoprost 0,004% (N=12/23)).

**Conclusions:** Changing patients from prior monotherapy to TTFC can provide on average a further reduction in IOP, while demonstrating a favorable safety profile.

**Key words:** *Glaucoma – drug therapy; Ocular hypertension – drug therapy; Intraocular pressure – drug effects; Antihypertensive agents – administration and dosage; Drug combinations*

## Introduction

Glaucoma is a group of ocular diseases characterized by optic nerve damage and visual field loss. While the precise pathophysiology is unknown, the end result of glaucoma is retinal ganglion cell death. Extensive optic nerve injury and visual field loss often have already occurred by the time of diagnosis. Although some glaucoma patients have normal intraocular pressure (IOP), glaucomatous injury is highly correlated with increased IOP. Therefore, reducing IOP is a mainstay of glaucoma therapy.

There are several different classes of glaucoma medications available today (prostaglandin analogues and  $\beta$  blockers among them).

Travoprost is a prostaglandin analogue and a very selective agonist for the prostaglandin FP receptor<sup>1</sup>. It lowers the IOP in patients with primary open angle glaucoma (POAG) and/or ocular hypertension (OH), in cases intolerant or insufficiently responsive to other IOP-reducing medications. It is believed that travoprost reduces IOP by increasing the outflow of aqueous humor through the uveoscleral drainage route, and possibly even with trabecular meshwork resistance reducing<sup>2-5</sup>. It provides effective reductions in IOP with once daily dose, applied in the evening<sup>6,7</sup>. It has been showed that travoprost produces an additional reduction in IOP when used in combination with topical ophthalmic beta blocker timolol<sup>8</sup>.

Beta-blockers have a role in reducing IOP level by slowing the rate of aqueous humor formation<sup>9,10</sup>. These two complementary modes of action are used together in a fixed combination of two drugs. Timolol is often used twice a day in the treatment of POAG and OH. On the other hand, the use of a fixed combination of beta-blocker timolol and prostaglandin analogue in a single ophthalmic solution is provided once daily, with a significant additive effect<sup>11</sup>, also improving patient compliance.

Until introduction of fixed combination travoprost 0,004%/timolol 0,5% (TTFC), in Croatia were commonly used unfixed combinations of those two groups of medications in glaucoma therapy.

This observational, non interventional, open – label multicenter study was designed to evaluate changes in pattern of glaucoma medications prescription of majority of our glaucoma specialists, once this TTFC available in Croatia.

The ophthalmic solution TTFC was prescribed as replacement for previous medication, as judged by investigator, and was applied once daily in the evening or in the morning during a period of 6 months without washout period when the change was done. We observed whether TTFC provides sufficient IOP control (further reduction from baseline) and observed tolerability of new medication in patients with POAG and OH.

## Methods

In this study included were patients with previous diagnosis of POAG or OH, who required a change of previous glaucoma medications therapy according to each investigator criteria from ten glaucoma departments distributed equally throughout Croatia ( 5 in Zagreb, and 1 in Osijek, Split, Rijeka, Zadar and Šibenik, respectfully). Included were patients of both gender (43.2% male, 56.8% female), all caucasian, older than 18 years, whose IOP was not adequately controlled or who were intolerant to previous IOP lowering medications. Definition of adequacy in IOP control was previously determined by consensus: included were patients with IOP at baseline (achieved with any of monotherapies) between 19-35 mmHg in at least one eye (safety reasons for 35 mmHg).

The exclusion criteria were determined in accordance with product labeling (contraindications and possibly pregnant / pregnant women). Visual acuity,

cup/disc ratio, grade of angle closure were recorded, but not corellated to IOP measurement lately. All patients were given informed consent. All investigators had prior the inclusion to the protocol written approval of ethical boards at each site. An analysis of changes in cardiovascular parameters (pulse rate, systolic blood pressure and diastolic blood pressure) has been performed in order to detect systemic adverse events of both beta blocker and prostaglandin analogue component at the control 1 and controls 1, 2 and 3 (these findings were not corellated with IOP changes). No further laboratory measurements were performed in order to detect systemic adverse events.

Participants were grouped into four categories according to previous monotherapy: those on timolol 0,5%, those on betaxolol 0,5%, those on latanoprost 0,005%, those on travoprost 0,004%.

Patients were given one drop of TTFC in the evening at 8 PM or in the morning at 8 AM (according to their preference /lifestyle), during a period of three to six months. No washout period from prior medications was employed because we were obliged by authorities not to intervene in each of investigators practice, just observe pattern of efficacy and safety for the TTFC - mimicking daily clinical practice. All patients were given free samples for 90 days therapy. After that, samples free of charge were available only for 40 patients for another 30 days. TTFC combination was not reimbursed at that time, but was available in pharmacies in Croatia. Patients who were not included in follow up from day 90 to day 120 were instructed to continue with TTFC therapy.

Main outcome measures included mean IOP and tolerability (adverse events) variables.

IOP was measured at Goldmann applanation tonometer for each eye between 9 AM and 11 AM at baseline (day 0) and at three control visits: control 1 ie. day 30, control 2 ie. day 90 and control 3 ie. day 120 of TTFC therapy. In each patient, the eye with the higher baseline level of IOP was chosen for analysis. In cases with equal IOP level in both eyes, the right eye IOP value was analysed.

Responder analysis was performed at day 30 (control 1) in order to exclude non responders. Consensus criteria for non responders was IOP reduction from baseline of 15% or achieved target IOP >18mmHg. An IOP of 18 mmHg was used as the 'target IOP' consistent with the findings of the National Eye Institute

sponsored Advanced Glaucoma Intervention Study (AGIS) which demonstrated that patients with IOP < 18 mmHg at all visits over 6 years had mean changes from baseline in visual field score close to zero during follow-up.

Conjunctival hyperemia was evaluated according to 4 point scale (severe, mild, moderate, none) from CCLRU grading scale<sup>12</sup>.

The Kruskal Wallis test was used for statistical analysis. A P-value of <0.05 was considered to be statistically significant.

## Results

Study included at baseline 170 patients / 339 eyes with POAG and OH (43.2% male, 56.8% female; 76% POAG cases and 24% of patients suffering from OH) and with a similar distribution of adult and elderly (50.3% vs. 49.7%, respectively) patients. All the patients were Caucasian (100%) and majority had brown irides (50.9%).

Analysis was focused on the substitution of one of four common, antiglaucoma medications with TTFC. They included following groups: timolol 0,5% monotherapy (N=35), latanoprost 0,005% monotherapy (N=54), betaxolol 0,5% monotherapy (N=36), travoprost 0,004% monotherapy (N=45) at baseline.

### IOP analysis

The main focus was change in IOP lowering in patients switched from their previous therapy to TTFC, measured at control visits 1 (day 30), 2 (day 90) and 3 (day 120).

At the first control visit, after 30 days of therapy, we recorded individual IOP in each eye in order to exclude non responders (IOP reduction from baseline for each eye less than 15% or not reached target IOP >18 mmHg). Excluded because of criteria of unmet criteria of 15% IOP change from baseline were 4 patients (Figure 1).

At the baseline visit, mean IOP was  $22,1 \pm 2,87$  mm Hg (all medications/ all patients). At the control 1 (day 30), mean IOP was  $15,92 \pm 1,85$  mm Hg (reduction of 21,66%). At the control 2 (day 90), the mean IOP was  $15,67 \pm 2,17$  mm Hg (reduction 21,14%) (Figure 2). At the control 3 (day 120) mean IOP was  $16,28 \pm 1,59$  mm Hg (19,86% reduction) (Figure 2). The differ-

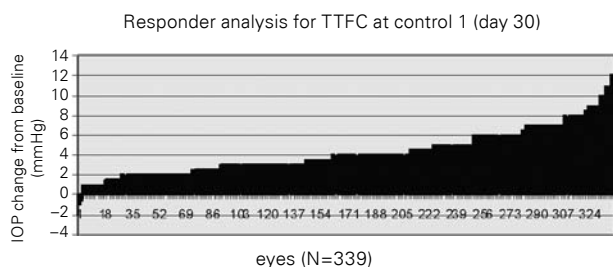


Fig. 1. Responder analysis at control 1 (day 30): IOP change (mm Hg) for each eye from baseline (n=170 patients/ 339 eyes). Four patients (8 eyes) were excluded based on unmet consensus criteria (IOP change by 15% from baseline or IOP >18 mm Hg).

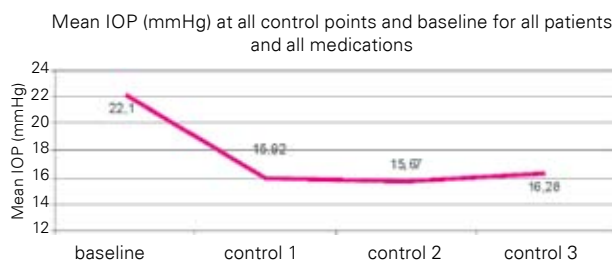


Fig. 2. Mean IOP (mm Hg) in all patients (day 0 and day 30), survivors on day 90 (follow up 2) and survivors on day 120 (follow up 3). Differences in the mean and standard deviation were highly statistically significant ( $P < 0.001$ ) at all control points.

ences (mean±standard deviation) in IOP after 30, 90 and 120 days were all highly statistically significant ( $p < 0,001$ ) compared to baseline values.

In patients switched from timolol 0,5% the change in mean IOP at control 2 (90 days) was  $5,2 \pm 2,7$  mmHg, in betaxolol 0,5% group it was  $5,7 \pm 2,2$  mmHg, in latanoprost 0,005% group it was  $3,8 \pm 2,6$  mmHg, in travoprost 0,004% group  $4,4 \pm 2,8$  mmHg (Figure 3).

Change in mean IOP by all groups of medications at all control points is summarized in table 1, and is highly statistically significant (Table 1).

In total 155 patients (309 eyes) survived the study until control 2 (90 days). At control 2 (day 90) excluded were patients who could not afford to buy TTFC (not reimbursed in Croatia, because free units of TTFC from donation were available for only 40 patients). Until the end of the study endured 40 patients (79 eyes).

In this group of 40 patients (79 eyes), monotherapies prior to the TTFC substitution were as follows: timolol 0,5% (7 patients/14 eyes); betaxolol 0,5% (7

patients/14 eyes); latanoprost 0,005% (14 patients/28 eyes); travoprost 0,004% (13/23 eyes). Measurement of mean change of IOP from baseline was performed for all survivors until day 120: it was for timolol 0,5 group  $3,85 \pm 0,88$  mmHg, betaxolol 0,5% group  $4,09 \pm 0,83$  mmHg, latanoprost 0,005% group  $4,8 \pm 1,63$  mmHg, travoprost 0,004% group  $4,07 \pm 1,38$  mmHg (Figure 4).

#### Tolerability (adverse events)

At control 1 excluded were from further follow up 15 patients with adverse events (severe hyperemia in 6 patients, discomfort of the eye in 4 patients, chest pain 1 in patient). Reported were also mild hyperemia in 4 patients (8 eyes) after 30 days of TTFC therapy, but patients were highly motivated to continue with medication. After 90 days of therapy in those 4 patients hyperemia was not present any more. At control 2 we also report eyelashes growth in 2 patients - 4 eyes, they were not excluded, and all successfully finished the study.

Table 1. Mean IOP (mmHg) by groups of medications at baseline and control 1, 2 and 3.

	Baseline	Control 1	Control 2	Control 3	P*
Betaxolol	20,92 ± 1,62	16,04 ± 0,94	16,21 ± 1,05	16,83 ± 0,83	< 0,001
Latanoprost	21,07 ± 2,77	16,27 ± 1,94	15,90 ± 1,72	16,27 ± 1,63	< 0,001
Timolol	21,46 ± 2,51	16,86 ± 1,15	17 ± 0,73	17,61 ± 0,88	< 0,001
Travoprost	21,11 ± 1,28	17,07 ± 1,64	16,89 ± 1,30	17,04 ± 1,38	< 0,001
P**	0,901	0,059	0,009	0,005	

\* Friedman

\*\* Kruskal Wallis

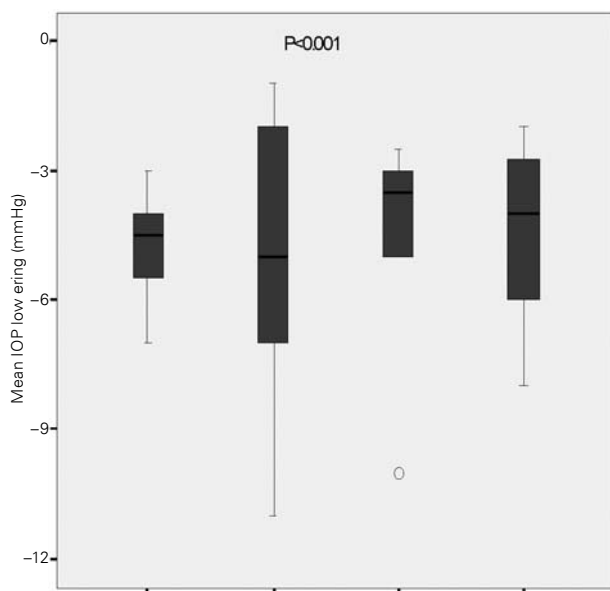


Fig. 3. IOP change (mm Hg) from baseline according to groups of previous medications at follow up 2 (day 90) (Kruskal Wallis analysis).

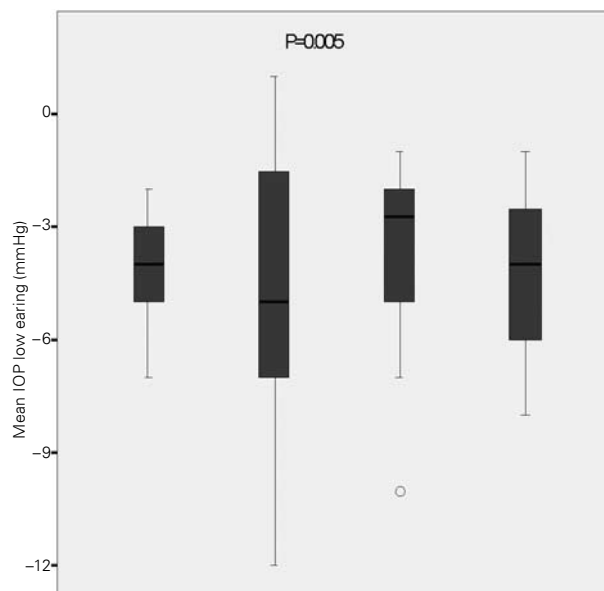


Fig. 4. IOP change (mm Hg) from baseline according to groups of previous medications at follow up 3 (day 120) (Kruskal Wallis analysis).

## Discussion

New TTFC is more effective than any previously used medication (both monotherapy – betaxolol 0,5%, timolol 0,5%, latanoprost 0,005%, travoprost 0,004%) based on IOP lowering efficacy.

In our study ophthalmologists change medication when IOP is not sufficiently controlled or in case of glaucoma disease progression, according to personal clinical experience and European Glaucoma Society guidelines.

Patients in this study, once compared to international (pivotal) studies<sup>13</sup> react to medication with significant IOP lowering, with expected number of responders after 30 days of therapy and maintain efficient IOP control up to 120 days that we managed to follow up our cohort.

The dropouts from the study were because of reported adverse events (severe hyperemia in 6 patients, discomfort in 4 patients, chest pain 1 in patient), and were in range of expected from product labeling.

Exclusions were done by investigators according to consensus on IOP reduction of at least 15% or target IOP <math>< 18\text{mmHg}</math>, necessary to qualify each patient for „responder“ group. Number of responders is consistent to reported in pivotal studies<sup>6-8,13</sup>.

Clinical studies have previously shown that the TTFC produced clinically relevant reduction of IOP, greater than those caused by either travoprost or timolol alone<sup>13</sup>. It has also been shown that the use of TTFC provides safety and efficacy. The concomitant use of both drugs has the same efficacy in IOP-lowering<sup>14-18</sup>. This study demonstrates that patients who underwent a change in therapeutic regimen from other antiglaucomatous therapeutics to TTFC consistently showed a further IOP reduction, regardless of which therapies had been previously used. This could be the consequence of enhanced patient compliance (due to once-a-day usage compared to twice per day timolol 0,5% and betaxolol 0,5%), as well as the predominant IOP reducing role of prostaglandins. Some studies have shown that travoprost has some pharmacologic differences compared to other prostaglandins. According to Hellberg *et al.*<sup>19</sup> travoprost is a potent full agonist to the FP-receptor ( $E_{\text{max}} = 100\%$ ) in comparison to latanoprost ( $E_{\text{max}} = 75\%$ ). Sit *et al.*<sup>20</sup> and Dubiner *et al.*<sup>21</sup> have shown that travoprost exhibits enduring IOP-lowering efficacy. On the other hand, in some patients, the effect of timolol shades away after a period of 24 hours. That provides better IOP control of TTFC comparing to other prostaglandin/timolol fixed combination, according to the endurance

of travoprost which compensates the waning effect of the timolol during the day.

Results in IOP reduction and tolerability (adverse events) in this study follow up expected pattern from published pivotal and observational studies<sup>22-24</sup>.

The mean IOP change after 3 months of therapy with TTFC in our study showed following: in group switched from timolol mean IOP reduction was  $5,2 \pm 2,7$  mmHg, in latanoprost group it was  $3,8 \pm 2,6$  mmHg, and in travoprost group  $4,4 \pm 2,8$  mmHg, in range of results in similar study by Arend *et al.*<sup>22</sup>. The difference from these studies was our analysis of additional group of patients, previously treated by betaxolol, in which we found the mean IOP lowering of  $5,7 \pm 2,2$  mmHg, while Arend *et al.* did not. Barnabey *et al.*<sup>13</sup> found that the TTFC produced clinically relevant reductions in IOP that were greater than those produced by either travoprost or timolol alone. In Konstas *et al.* study<sup>23</sup> the TTFC proved an additional IOP reduction from baseline (mean 24 hour  $9,4$  mmHg) compared to travoprost alone ( $7,1$  mmHg) after 3 months. Stewart *et al.*<sup>25</sup> proved a significant decrease in IOP 3 months after changing to TTFC regardless of prior therapy: travoprost 0,004% ( $16,3 \pm 2,4$  mmHg vs  $22,0 \pm 2,3$  mmHg), timolol 0,5% ( $16,3 \pm 2,4$  mmHg vs  $21,8 \pm 2,1$  mmHg), latanoprost 0,004% ( $16,8 \pm 2,3$  mmHg vs  $22,0 \pm 2,3$  mmHg). In observational study Pfeiffer *et al.*<sup>24</sup> performed at 474 patients in Germany found reduction of IOP after 3 months of TTFC therapy  $5,6 \pm 2,6$  mmHg for all prior treatments (for timolol monotherapy  $5,7 \pm 2,2$  mmHg, for latanoprost monotherapy  $6,3 \pm 2,6$  mmHg).

IOP lowering effect of TTFC in our study was superior in comparison to previous monotherapy with betaxolol, timolol 0,5%, latanoprost and travoprost 0,004%, during 6 months (120 days) period. Mean reduction of IOP was 19,86% after 6 month of therapy. Not many studies report TTFC effective in longer period than 3 months<sup>26-28, 13-16</sup> and only two up to 12 months period<sup>28,29,30</sup>. In Rossi *et al.*<sup>29</sup> 6 month multicenter, observational study on 309 patients IOP was significantly decreased (from  $18,3 \pm 2,9$  to  $16,6 \pm 2,7$  mmHg) after substitution ( $p < 0,0001$ ). 82% patients reached an IOP  $< 18$  mmHg ( $p < 0,0001$ )<sup>29</sup>. In our study, at the control 3 (day 120) mean IOP was  $16,28 \pm 1,59$  mm Hg (19,86% reduction). In study of Danesh Mayee and Topousis<sup>30</sup> (and the Trav/Tim

1-year Study Group) TTFC was compared to previously administered latanoprost 0,005%/timolol 0,5% fixed combination in order to test noninferiority in IOP lowering with new TTFC – IOP lowering effect was significant (compared to the baseline entry) at 6 months and endured to one year. Furthermore, at 9:00 AM, 24 hours after dosing, IOP was statistically lower for travoprost 0.004%/timolol 0.5% pooled across all visits<sup>30</sup>.

The differences (mean  $\pm$  standard deviation) in intraocular pressure values at baseline and after 30, 90 and 120 days were all highly statistically significant ( $p < 0,001$ ). Recent large clinical studies such as Ocular Hypertension Treatment Study (OHTS)<sup>31</sup>, the Early Manifest Glaucoma Trial (EMGT)<sup>32</sup>, and AGIS<sup>33</sup>, have clearly indicated the significance of lowering IOP in preventing the development of open-angle glaucoma in susceptible individuals and the progression of visual field loss in those who already have the disease. TTFC showed endurance of intraocular pressure lowering effect in current study during observed 6 months period. This fixed combination product may, therefore, be of value in patients judged to be inadequately controlled on a prostaglandin analogue or ophthalmic beta-blocker alone.

In current study TTFC was safe and well-tolerated. As with any beta-adrenergic receptor blocking agent, adverse respiratory and cardiac reactions may occur with timolol. An analysis of changes in cardiovascular parameters (pulse rate, systolic blood pressure and diastolic blood pressure) has been performed, the results of which are reassuring with no new or unexpected safety concerns. One patient was excluded from the further follow up after 30 days of treatment with new TTFC, due to the chest pain complaint. In his case no discrepancies were found in pulse rate, systolic or diastolic blood pressure. The complaint resolved with treatment discontinuation, without additional treatment.

Considering that travoprost and timolol are two distinct pharmacological agents, which act by different mechanisms of action and the lack of interaction reports in the literature, support the view that the two agents do not impact significantly on the pharmacodynamics of one another. Reported side effects incidence and occurrence is comparable to reported when those two agents used alone (travoprost 0,004% monotherapy or timolol 0,5% monotherapy)<sup>13</sup>.

Ocular hyperemia, discomfort in the eye and pruritus eye were the most common ocular adverse events reported in pivotal studies<sup>13,14,15,16,17,18</sup>, with incidences of 14.4%, 6.5% and 4.8% in TTFC, 20.8%, 9.9% and 5.4% in travoprost plus timolol, 11.6%, 2.3% and 3.5% in travoprost, 1.7%, 5.7% and 2.3% in timolol and, 4%, 3.6% and 2.5% in latanoprost/timolol fixed combination treatment groups, respectively. Other treatment-related adverse events that occurred with exposure to TTFC in pivotal studies included hair disorder (changes in eyelash), blurred vision, ocular pain, photophobia and keratitis. From this group of ocular adverse events, we reported eyelashes growth in 2 patients (4 eyes), according to expectations with treatment in the group of PGA antiglaucoma medications<sup>13-18</sup>. We did not find any changes of iris color, although expected, most probably due to short time of follow up.

The low discontinuation rate after 6 months indicates a good tolerability profile<sup>28,29</sup>.

## Conclusion

Well designed observational studies can identify clinically important differences among therapeutical options and provide data on drug effectiveness and safety.<sup>31</sup> In our study IOP lowering effect TTFC was superior in comparison to previous monotherapy with betaxolol 0,5%, timolol 0,5%, latanoprost 0,005% and travoprost 0,004%, with statistically significant differences in mean IOP after 30, 90 and 120 days of therapy. TTFC showed indurance of intraocular pressure lowering effect in 6 month observational period.

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## Sažetak

SIGURNOST I UČINKOVITOST FIKSNE KOMBINACIJE (TRAVOPROST 0,004%/TIMOLOL 0,5%)  
UMJESTO MONOTERAPIJE U ŠESTOMJESEČNOM PERIODU PRAĆENJA

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**CILJ:** Zabilježiti sigurnost i učinkovitost promjene antiglaukomske terapije u travoprost 0,004%/timolol 0,5% (TTFC) fiksnu kombinaciju s prethodnih monoterapija.

**METODE:** Prospektivna, otvorena, opservacijska, multicentrična populacija. Promjena s prethodne monoterapije na dan 0 u TTFC, doziran jednom dnevno, ili ujutro ili navečer, bez perioda ispiranja. Aktivno je ocijenjena sistemska i lokalna podnošljivost (popratne pojave), i učinkovitost tj. sniženje intraokularnog tlaka (IOT) na prvoj kontroli (dan 30), drugoj kontroli (dan 90) i trećoj kontroli (dan 120).

**REZULTATI:** 40/155/170 bolesnika (79/309/339 očiju) završilo je studiju (120 dana/ 90 dana/početak). Na prvoj kontroli isključeni su svi bolesnici koji su slabo podnosili lijek: ozbiljna hiperemija (6 bolesnika), neugoda (4), bol u prsištu (1) i ne-responderi tj. sniženje IOT-a manje od 15% od početnog IOT ili ciljnog IOT >18 mmHg (4 bolesnika).

Prosječni IOT na prvoj kontroli je bio 15,92±1,85 mm Hg (21,66% sniženja) kod 155 bolesnika (isključeni ne-responderi), na drugoj kontroli je kod 155 bolesnika bio 15,67±2,17 mm Hg (21,14% sniženja), i na trećoj kontroli kod 40 bolesnika 16,28±1,59 mm Hg (19,86% sniženja).

Na drugoj kontroli je učinjena analiza sniženja IOT-a u 4 grupe prethodno korištene monoterapije: timolol 0,5% (N=33/66), latanoprost 0,005% (N=49/98), betaxolol 0,5% (N=30/60), i travoprost 0,004% (N=43/85).

40 bolesnika/79 očiju praćeno je do treće kontrole. Učinjena je analiza sniženja IOT-a u 4 grupe prethodno korištene monoterapije: timolol 0,5% (N=7/14), latanoprost 0,005% (N=14/28), betaxolol 0,5% (N=7/14), travoprost 0,004% (N=12/23).

**Zaključak:** Promjena terapije s prethodne monoterapije u TTFC može u prosjeku omogućiti dodatno sniženje IOT-a, uz zadovoljavajući profil sigurnosti.

Ključne riječi: *Glaukom – terapija lijekovima; Očna hipertenzija – terapija lijekovima; Očni tlak – učinci lijekova; Antihipertenzivni lijekovi – davanje i doziranje; Kombinacije lijekova*

