

# Comparison of Evening and Morning Dosing of Travoprost 0.004%/Timolol 0.5% Fixed Combination in 6 Month Period

Smiljka Popović Suić<sup>1,2</sup>, Katia Novak Lauš<sup>3</sup>, Vukosava Maričić Došen<sup>4</sup>, Miroslav Ekert<sup>5</sup>, Zdravko Mandić<sup>6</sup> and Lovro Bojić<sup>7</sup>

<sup>1</sup> Department of Ophtalmology, Zagreb University Hospital Center, Zagreb, Croatia

<sup>2</sup> School of Medicine, Zagreb University, Zagreb, Croatia

<sup>3</sup> Department of Ophtalmology, »Sestre milosrdnice« University Hospital, Zagreb, Croatia

<sup>4</sup> Department of Ophtalmology, »Sveti duh« General Hospital, Zagreb, Croatia

<sup>5</sup> Department of Ophtalmology, Zagreb University Hospital Center, Zagreb, Croatia

<sup>6</sup> Department of Ophtalmology, »Sestre milosrdnice« University Hospital, Zagreb, Croatia

<sup>7</sup> Department of Ophtalmology, Split University Hospital Center, Split, Croatia

## ABSTRACT

*An open label, multi-center, 6 months observational study of new fixed combination (travoprost 0.004%/timolol 0.5%), in order to evaluate both efficacy (intraocular pressure lowering) and tolerability (patient and investigator satisfaction) of two dosing regimens –evening (PM) and morning (AM). After screening for enrollment, to 40 patients (79 eyes with primary open angle glaucoma or ocular hypertension), new fixed combination travoprost 0.004%/timolol 0.5% was prescribed once a day in the evening (PM). Patients were enrolled according to each investigator decision on indication for travoprost 0.004%/timolol 0.5% fixed combination once a day, without washout period after previous medication. Intraocular pressure was measured at 9 AM at all time control points: at baseline, after 1 month, after 3 months and after 6 month. After 1 month, screening for nonresponders (criteria: 20% intraocular pressure lowering) and subjects with major side effects was performed. At second control visit, after 3 months PM dosing, intraocular pressure was measured and patients were instructed to continue once a day the same medication, but in the morning (AM) for consequent 3 months. After 1 month, reduction in mean intraocular pressure value was 21.66%. At the visit after 3 month, the mean intraocular pressure was 15.67±2.17 mm Hg (reduction 21.14%). 3 month after dosing regimen changed to AM (6 month after beginning of travoprost 0.004%/timolol 0.5% combination therapy), reduction in intraocular pressure value was 19.86%. The differences (mean±standard deviation) in intraocular pressure values after 1, 3 and 6 month were all highly statistically significant compared to baseline values. The tolerability was evaluated in five steps (Likert scale) ranging from unsatisfactory to excellent by both patient and investigator – taken at 3 and 6 month control visit. 95% of patients and 100% of investigators were satisfied with the possibility of choosing dosing regimen for travoprost 0.004%/timolol 0.5% fixed combination. Travoprost 0.004%/timolol 0.5% fixed combination proved sufficient intraocular pressure control dosed either PM or AM with no statistically significant difference between two dosing regimens. Possibility to choose between two dosing regimens gives each practitioner additional reassurance that glaucoma therapy will be individualised to needs of each patient.*

**Key words:** travoprost 0.004%/timolol 0.5%, glaucoma, dosing regimen

## Introduction

Glaucoma is potentially blinding, multifactorial optic neuropathy characterized by progressive loss of optic nerve tissue with associated visual field loss. Elevated intraocular pressure is often observed in glaucomatous eyes and is a strong risk factor for the development and progression of glaucoma<sup>1</sup>. Therapeutically reducing intraocular pressure is the only proven way to reduce the risk of developing glaucoma as well as slowing the progression of the disease once it is present<sup>2,3-7</sup>. Topical  $\beta$ -adrenergic blocking agents, such as a timolol, have been widely accepted as a first line therapy for glaucoma and ocular hypertension<sup>8,9</sup>.  $\beta$ -blockers reduce intraocular pressure by slowing the rate of aqueous humor formation<sup>10</sup>. In recent years, a new family of drugs, the prostaglandin analogues, has become mostly prescribed. Studies have shown that travoprost 0.004% ophthalmic solution is a potent FP receptor agonist in human ciliary muscle and trabecular meshwork cells<sup>11,12</sup>. Unlike  $\beta$ -blockers, prostaglandin analogs reduce intraocular pressure by increasing both uveoscleral and conventional aqueous humor outflow<sup>13</sup>. Travoprost is a prostaglandin analog product approved for once-daily dosing in patients with open-angle glaucoma or ocular hypertension. Travoprost has been shown in many large-scale, multicenter clinical trials to produce clinically relevant reductions of baseline intraocular pressure that are better than timolol with a safety profile comparable to other prostaglandin analogs<sup>14,15</sup>.

As many as 40% of patients treated for glaucoma are unable to achieve adequate control of intraocular pressure with a single medication<sup>16</sup>. Patients are often prescribed multiple medications from the different classes of intraocular pressure – lowering therapies. While multiple medications can achieve acceptable intraocular pressure levels for many patients, the use of more than one dosing bottle is associated with several concerns, including increased preservative exposure of multiple drops, greater patient cost for multiple prescriptions, reduced compliance, and potential washout from multiple dosing<sup>17</sup>. In a 6-month study of concomitant therapy with travoprost 0.004% and timolol 0.5% in patients with inadequately controlled intraocular pressure with timolol 0.5% alone, has been demonstrated efficacy and safety of this combination<sup>18</sup>. Side effects of concomitant therapy were mild. These findings have led to the development of a fixed combination of travoprost 0.004% and timolol 0.5%, which has advantage because majority of glaucoma patients require more than one medication. When used as first-line therapy for open-angle glaucoma and ocular hypertension, timolol is often dosed twice daily. However, the use of a fixed dose combination of timolol and a prostaglandin analogue in a single ophthalmic solution dosed once daily has been demonstrated to provide a significant additive effect<sup>19</sup> and has the potential to improve patient compliance. This study was designed to evaluate the efficacy and tolerability of a fixed combination ophthalmic solution of travoprost 0.004% and timolol 0.5%, given once daily, in patients with

open-angle glaucoma or ocular hypertension and to determine whether there is any significant difference between morning (AM) or evening (PM) dosing. The primary objective was to demonstrate that morning and evening dosing produce equivalent intraocular pressure-lowering effect. The secondary objective was to evaluate patient and investigator satisfaction with two dosing regimens.

## Materials and Methods

This study was a multicenter, prospective, clinical observational study, open-label to both-patients and investigators. Patients eligible for inclusion were of either sex (22 male, 18 female) and one ethnic group (all caucasian), older than 18 years of age, diagnosed with either open-angle glaucoma (37 patients) (without pseudoexfoliative or pigmentary glaucoma) or ocular hypertension (3 patients), and were currently treated with a pressure-lowering monotherapy (timolol 0.5%, betaxolol 0.5%, travoprost 0.004%, latanoprost 0.005%). Patients were enrolled according to each investigator decision on indication for travoprost 0.004%/timolol 0.5% fixed combination, without washout period after previous medication, if IOP values at baseline with monotherapy were over 20 mm Hg. In all enrolled patients, best corrected visual acuity was over 0,6 on both eyes, C/D ratio over 0,8, and anterior chamber angle grade was 3 or 4 (measured by gonioscopy). Patients were without severe central visual field defects on both eyes. Women of childbearing potential were excluded from the study if they were currently pregnant, had a positive urine pregnancy test at the screening visit, intended to become pregnant, were breast feeding, or were not using highly effective birth control measures. Patients were also excluded if they had a history of chronic or recurrent severe inflammatory eye disease; a history of ocular trauma within the preceding 6 months or ocular infection or inflammation within the preceding 3 months; a history of clinically significant or progressive retinal disease, other severe ocular pathology that would have precluded the administration of a topical prostaglandin analogue, or severe or serious hypersensitivity to any components of the study medication; had undergone intraocular surgery within the preceding 6 months or ocular laser surgery within the preceding 3 months; or had a best-corrected visual acuity worse than 0,6, anterior chamber angle grade 1 or 2 (measured by gonioscopy), a C/D ratio greater than 0,8, or severe central visual field loss in either eye. In addition, patients could not take part if they were taking glucocorticoids or any additional topical or systemic ocular hypotensive medication; had a history of severe, unstable, or uncontrolled cardiovascular, hepatic, or renal disease or bronchial asthma or severe chronic obstructive pulmonary disease.

After screening for enrollment, to 40 patients (79 eyes) with primary open angle glaucoma or ocular hypertension, fixed combination travoprost 0.004%/timolol 0.5% was prescribed once a day in the evening at 8 PM

(PM dosing regimen). No washout period was planned for any of previous medications, because intention was to observe clinical pattern of performance of new fixed medication, without interrupting or modifying investigators personal decision on necessity to change medication. Intraocular pressure was measured always at 9 AM: at baseline, and after 1, 3 and 6 months. At second control visit, after 3 months of PM dosing regimen, patients were instructed to continue administration of the same medication once a day in the morning at 8 AM (AM dosing regimen) for next 3 months. After 1, 3 and 6 month there were no nonresponders (criteria: IOP lowering 20%) and no subjects with major side effects. Minor side effects were not reason to terminate therapy. Reported minor side effects were: eyelashes growth (2 patients – 4 eyes) and mild hyperemia (4 patients – 8 eyes). Tolerability was evaluated by the patient and the investigator on a five-point scale, ranging from unsatisfactory to excellent, taken after 3 and 6 month travoprost 0.04%/timolol 0.5% fixed combination therapy. If the tolerability was judged as good, very good and excellent, this finding was evaluated as satisfactory (Likert scale)<sup>20</sup>.

Doctors were satisfied with therapy when IOP dropped by 20% and if patients had no major topical and none systemic side-effects. Patients were satisfied with the therapy if it is efficient and if they had none or only minor topical side effects, burning, or hyperemia. All 40 patients finished the study. The Friedman's CHI square and Wilcoxon test were used for statistical analysis. A p-value of <0.001 was considered to be statistically significant.

## Results

### Intraocular pressure analysis

The focus of the intraocular pressure analysis was any change in intraocular pressure when travoprost 0.004%/timolol 0.5% fixed combination was substituted for one of four common intraocular pressure-lowering medication(s). In this group of 40 patients (79 eyes), therapeutic regimens prior to the travoprost 0.004%/timolol 0.5% fixed combination substitution were as follows: timolol 0.5% monotherapy (14 eyes); betaxolol 0.5% monotherapy (14 eyes); latanoprost 0.005% monotherapy (28 eyes); travoprost 0.004% monotherapy (23 eyes). At the baseline visit, mean intraocular pressure value was 22.1±2.87 mm Hg. After 1 month, mean intraocular pressure value was 15.92±1.85 mm Hg (reduction for 21.66%). At the visit after 3 month, the mean intraocular pressure was 15.67±2.17 mm Hg (reduction 21.14%). 3 month after dosing regimen changed to AM (6 month after beginning of travoprost 0.004%/timolol 0.5% combination therapy), mean intraocular pressure value was 16.28±1.59 mm Hg (19.86% reduction). The differences (mean±standard deviation) in intraocular pressure values after 1, 3 and 6 month were all highly statistically significant ( $p < 0.001$ ) compared to baseline values. Figure 1 provides a summary of the intraocular pressure changes observed after the substitution of travoprost 0.004%/timolol 0.5%

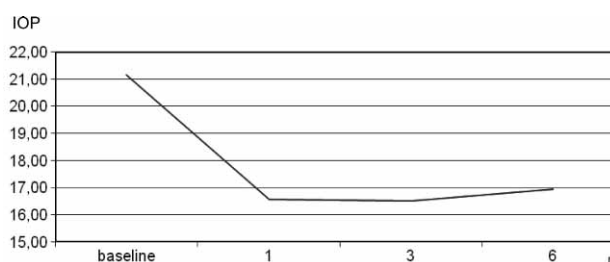


Fig. 1. Intraocular pressure values during 6 months of travoprost 0.004% / timolol 0.5% fixed combination therapy – difference from baseline and at 1.3 and at 6 months was statistically significant. IOP= mean intraocular pressure, m= month,  $p < 0.001$ , Friedman's  $\chi^2 = 136$ .

for the previous antiglaucoma therapy in 6 months period. Figure 2 shows comparison of intraocular pressure mean values between two dosing regimens of travoprost 0.004%/timolol 0.5%: in the evening (PM) and in the morning (AM) after 3 month therapy with each dosing regimen. We found no statistically significant differences in mean intraocular pressure values comparing these two dosing regimens.

### Tolerability

Travoprost 0.004%/timolol 0.5% fixed combination was well accepted by the patients and their doctors. We noted mild hyperemia in 4 patients (8 eyes) after 1 month therapy, but patients were motivated to continue with medication. After 3 months of therapy in those 4 patients hyperemia was not present any more. These 4 patients were not excluded from the study. We also report eyelashes growth in 2 patients-4 eyes, and all successfully finished the study. No other side effect were noted.

On Likert scale 90% of the patients were satisfied with therapy (5% good, 10% very good and 75% excellent) and the 90% of doctors (5% good, 10% very good and 75% excellent) judged the tolerability of the therapy as satisfactory after first 3 month of evening (PM) dosing (figure 3). After next 3 month, when dosing regimen changed to morning (AM) administration, 95% patients were satisfied with therapy (10% very good and 85% ex-

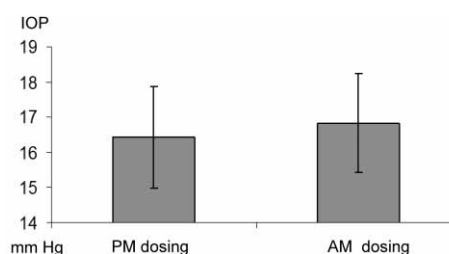


Fig. 2. Evening and morning dosing of travoprost 0.004%/timolol 0.5% fixed combination – comparison of mean intraocular pressure values after 3 months therapy of each dosing regimen. IOP= intraocular pressure, PM=evening dosing, AM=morning dosing, no statistically significant difference, Wilcoxon test:  $z = 2.72$ ,  $p = 0.06$



Fig. 3. Patient's and investigator's satisfaction with travoprost 0.004%/timolol 0.5% fixed combination after 3 month of PM dosing therapy.

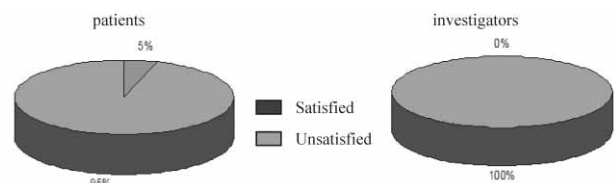


Fig. 4. Patient's and investigator's satisfaction with travoprost 0.004%/timolol 0.5% fixed combination after 3 month of AM dosing therapy.

cellent) and 100% investigators (5% good, 20% very good and 75% excellent) were satisfied with the therapy (Figure 4).

## Discussion

Prostaglandin analogs are today the most prescribed antiglaucoma monotherapy because of their potent intraocular pressure reduction and good tolerability. 40% of patients treated for glaucoma are unable to achieve adequate control of intraocular pressure with monotherapy<sup>16</sup> and combination of several drugs are very common. Several clinical studies that evaluate the clinical efficacy and safety of fixed combination travoprost 0.004%/timolol 0.5% have been completed and this combination is safe and stable<sup>20–23</sup>. The first of these by Barnebey<sup>21</sup> was a randomized, prospective, multicenter, double-masked, parallel group study of 263 patients with either open angle glaucoma or ocular hypertension. After a variable washout period during which all ocular hypotensive medications were held, the patients were randomized to receive either: daily (AM) fixed-combination travoprost/timolol with vehicle (placebo) in the evening, twice daily timolol or daily (PM) travoprost with vehicle (placebo) in the morning. They were treated for a total of 3 months while their intraocular pressures were monitored at nine different time periods. Results showed that fixed-combination travoprost/timolol lowered intraocular pressure 1.9–3.3 mm Hg more than timolol alone, and 0.9–2.4 mm Hg more than travoprost alone. The adverse event profile was similar among all three study arms. Intraocular pressure reduction from baseline ranged 32–38% for the fixed-combination medication, compared with 29–32% for travoprost alone and 25–30% for timolol alone. These results suggest that fixed-combination travoprost/timolol produced clinically relevant intraocular pressure re-

ductions greater than either agent alone, whereas the incidence of adverse events was comparable.

The present study demonstrates that patients undergoing alteration in therapeutic regimen from other intraocular pressure lowering drugs showed a further reduction in intraocular pressure value. Reductions in mean intraocular pressure from baseline up to 21.6% were observed in the current study. Intraocular pressure lowering effect of fixed combination travoprost 0.004%/timolol 0.5% was superior in comparison to previous monotherapy with betaxolol, timolol 0.5%, latanoprost and travoprost 0.004%, during 6 month period. Reduction of intraocular pressure after administration travoprost 0.004%/timolol 0.5% fixed combination therapy was 21.66% after 1 month, 21.14% after 3 month and 19.86% after 6 month of therapy. After 3 month of PM therapy when dosing regimen changed to AM (6 month after beginning of travoprost 0.004%/timolol 0.5% combination therapy), mean intraocular pressure value was 16.28±1.59 mm Hg. The differences (mean±standard deviation) in intraocular pressure values at baseline and after 1, 3 and 6 month were all highly statistically highly significant ( $p < 0.001$ ). Recent large clinical studies such as Ocular Hypertension Treatment Study<sup>24</sup>, the Early Manifest Glaucoma Trial (EMGT)<sup>3</sup>, and AGIS<sup>25</sup>, have clearly indicated the significance of lowering intraocular pressure 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. Fixed combination travoprost 0.004% and timolol 0.5% 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 the fixed combination of travoprost 0.004%/timolol 0.5% was safe and well-tolerated when dosed either in the morning or the evening. Intraocular pressure was sufficiently controlled after switch from PM to AM dosing regimen after 3 month of PM therapy, at 6 month control point. We found no statistically significant differences in mean intraocular pressure values comparing these two dosing regimens.

Pharmacologic approach of travoprost 0.004%/timolol 0.5% fixed combination is synergistic providing different mechanisms of action: reduce aqueous inflow by the  $\beta$ -blocker and outflow improvement by prostaglandin analog. Because  $\beta$ -blocker has reduced efficacy at night, as well as the potential for nocturnal hypotension, this fixed combination is likely to have better efficacy if dosed in the daytime. Data suggest that prostaglandin analogues may offer slightly more intraocular pressure reduction when dosed in the evening compared to the morning<sup>26</sup>. Konstas and colleagues<sup>27</sup> compared AM versus PM dosing of latanoprost/timolol fixed combination and found better intraocular pressure reduction during daytime hours when the combination was given in the evening and better intraocular pressure reduction during nighttime hours when combination was given in the morning.



Denis and colleagues<sup>28</sup> compared morning *versus* evening dosing of fixed-combination travoprost/timolol in a prospective, randomized study of 92 patients. After 6 weeks of treatment, the mean intraocular pressure ranged 16.5–16.7 mmHg in the morning group, as compared with 16.1–17.2 mmHg in the evening group. The mean percentage of intraocular pressure reduction from baseline in both groups was 32–38%, with no statistically significant difference.

An important factor in the maintenance of adequate intraocular pressure control is patient's adherence to prescribed treatment. Studies show that as many as 50% of glaucoma patients do not comply with dosing instructions and that dosing frequency and convenience are important factors contributing to patient adherence<sup>28,29</sup>. Tsai and associates<sup>7</sup> used patient questionnaires to identify situational obstacles to medication adherence. They found regimen factors to be an obstacle to adherence for 32% of the glaucoma patients they studied. In current study, travoprost 0.004%/timolol 0.5% fixed combination was well accepted by the patients and their doctors. 90% of the patients and the doctors judged the tolerability of the therapy as satisfactory after first 3 month of evening (PM) dosing. After consecutive 3 month, when dosing regimen changed to morning (AM) administration, 95%

patients and 100% investigators were satisfied with the new therapy regimen. Patients and investigators were also satisfied with the possibility of choosing the dosing regimen, which has good impact on compliance and adherence.

## Conclusion

Well designed observational studies can identify clinically important differences among therapeutical options and provide data on drug effectiveness and safety<sup>30</sup>. In our study intraocular pressure lowering effect of fixed combination travoprost 0.004%/timolol 0.5%, 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 intraocular pressure values after 1, 3 and 6 month of therapy. Fixed combination travoprost 0.004%/timolol 0.5% showed indurance of intraocular pressure lowering effect in 6 month observational period, with no statistically significant differences in mean intraocular pressure values comparing AM and PM dosing regimen. 95% patients and 100% investigators at 6 month control point were satisfied with both, AM and PM dosing regimens, and with the possibility of choosing the dosing regimen.

## REFERENCES

1. CHEN PP, *Ophtalmology*, 110 (2003) 726. — 2. HATTENHAUER MG, JOHNSON DH, ING HH, *Ophtalmology*, 105 (1998) 2099. — 3. LE-SKE MC, HEIJL A, HYMAN L, BENGTSSON B, *Ophtalmology*, 106 (1999) 2144. — 4. MUSCH DC, GILLESPIE BW, NIZIOL LM, CASHWELL LF, LICHTER PR, *Ophtalmology*, 114 (2007) 1965. — 5. MORLEY AM, MURDOCH I, *Br J Ophtalmol*, 90 (2006) 640. — 6. STEWARD WC, GARRISON PM, *Arch Intern Med*, 158 (1998) 221. — 7. TSAI JC, McCLURE CA, RAMOS SE, SCHLUNDT DG, PICHERT JW, *J Glaucoma*, 12 (2003) 393. — 8. LeBLANC RP, KRIP G, *Ophtalmology*, 88 (1981) 244. — 9. ZIMMERMAN TJ, KAUFMAN HE, *Arch Ophtalmol*, 95 (1981) 601. — 10. REISS GR, BRUBAKER RF, *Ophtalmology*, 90 (1983) 1369. — 11. SHARIF NA, KELLY CR, CRIDER JY, *Invest Ophtalmol Vis Sci*, 44 (2003) 715. — 12. SHARIF NA, CRIDER JY, HUSAINS, KADDOUR-DJEBBAR I, ANSATIAR, ABDEL-LATIF AA, *J Ocular Pharm Ther*, 19 (2003) 437. — 13. BRUBAKER RF, SCHOFF EO, NAU CB, CARPENTER SP, CHEN K, VANDENBURGH AM, *Am J Ophtalmol*, 131 (2001) 19. — 14. NETHLAND PA, LANDRY T, SULLIVAN EK, ANDREW R, SILVER L, WEINER A, MALICK S, DICKERSON J, BERGAMINI MV, ROBERTSON SM, DAVIS AA, *Am J Ophtalmol*, 132 (2001) 472. — 15. FELLMAN RL, SULLIVAN EK, RATLIFF M, *Ophtalmology*, 109 (2002) 998. — 16. KASS MA, HEUER DK, HIGGINBOTHAM EJ, *Arch Ophtalmol*, 120 (2002) 701. — 17. WEINREB RN, *J Glaucoma*, 1 (1992) 134. — 18. ORENGO-NANIA S, LANDRY T, VON-TRESS M, *Am J Ophtalmol*, 132 (2001) 860. — 19. HIGGINBOTHAM EJ, FELDMAN R, STILES M, *Arch Ophtalmol*, 120 (2002) 15. — 20. AREND KO, BABER T, *J Ocul Pharm Ther*, 24 (2008) 414. — 21. BARNABY H, ORENGO-NANIA S, FLOWERS BE, *Am J Ophtalmol*, 140 (2005) 1. — 22. HOMMER A, *Eur J Ophtalmol*, 17 (2007) 53. — 23. HUGHES BA, BACHARACH J, CRAVEN ER, *J Glaucoma*, 14 (2005) 392. — 24. BRANDT JD, BEISER JA, KASS MA, GORDON MO, *Ophtalmology*, 108 (2001) 1779. — 25. The AGIS INVESTIGATORS, *Am J Ophtalmol*, 130 (2000) 429. — 26. ALM A, STJERN-SCHANTZ J, *Ophtalmology*, 102 (1995) 1743. — 27. KONSTAS AG, NAKOKS E, TERSIS I, *Am J Ophtalmol*, 133 (2002) 753. — 28. DENIS P, ANDREW R, WELLS D, FRIREN N, *Eur J Ophtalmol*, 16 (2006) 407. — 29. PATEL SC, SPAETH GL, *Ophtalmic Surg*, 26 (1995) 233. — 30. SILVERMAN SL, *Am J Med*, 122 (2009) 122.

S. Popović Suić

Department of Ophtalmology, Zagreb University Hospital Centre, Kišpatičeva 12, 10 000 Zagreb, Croatia  
e-mail: spopovic@kbc-zagreb.hr

## **USPOREDBA VEČERNJEG I JUTARNJEG DOZIRANJA FIKSNE KOMBINACIJE TRAVOPROST 0,004%/TIMOLOL 0,5% S OBZIROM NA UČINKOVITOST U SNIŽAVANJU OČNOG TLAKA I ZADOVOLJSTVO BOLESNIKA LIJEČENJEM KROZ 6 MJESECI**

### **S A Ž E T A K**

Cilj istraživanja ove multicentrične, opservacijske studije je bio ustanoviti učinkovitost u snižavanju očnog tlaka i podnošljivost (zadovoljstvo lijekom bolesnika i liječnika) fiksne kombinacije travoprost 0,004%/timolol 0,5%, primijenjene jedanput dnevno ujutro ili navečer. 40 bolesnika (79 očiju) sa primarnim glaukomom otvorenog kuta ili očnom hipertenzijom, čiji ciljni očni tlak nije bio postignut monoterapijom (betaksololom, timololom 0,5%, latanoprostom i travoprostom), počeli su primjenjivati fiksnu kombinaciju travoprost 0,004%/timolol 0,5% jedanput dnevno navečer, bez »wash-out« perioda. Očni tlak izmjeren je prije uključivanja novog liječenja kao i na kontrolnim pregledima nakon 1, 3 i 6 mjeseci, uvijek u 9 sati ujutro. Na prvom kontrolnom pregledu nakon mjesec dana, bolesnici u kojih nije došlo do 20% snižavanja vrijednosti očnog tlaka, kao i bolesnici sa neugodnim popratnim pojavama liječenja, su isključeni (2 bolesnika). Prilikom drugog kontrolnog pregleda nakon 3 mjeseca primjene lijeka navečer, izmjeren je očni tlak i bolesnici su upućeni na primjenu lijeka ujutro, počevši od slijedećeg dana, slijedećih 3 mjeseca, nakon čega je vrijednost očnog tlaka izmjerena. Početna srednja vrijednost očnog tlaka (postignuta prethodnim liječenjem) je bila  $21,13 \pm 2,18$  mm Hg. Nakon 1 i 3 mjeseca primjene fiksne kombinacije travoprost 0,004%/timolol 0,5% jedanput navečer, postignuto je sniženje očnog tlaka za 21%. Promjenom načina primjene, davanjem lijeka ujutro kroz slijeda 3 mjeseca, srednja vrijednost očnog tlaka ostala je snižena je za 19% u odnosu prema početnoj vrijednosti. Razlike početne vrijednosti očnog tlaka prema vrijednostima nakon 1, 3 i 6 mjeseci su statistički značajne. Zadovoljstvo liječenjem je ocijenjeno od strane liječnika i bolesnika nakon 3 i 6 mjeseci liječenja, uporabom Likertove ljestvice zadovoljstva liječenja u 5 kategorija, od nezadovoljavajućeg do odličnog. 95% bolesnika i 100% njihovih liječnika je bilo zadovoljno liječenjem fiksnom kombinacijom travoprost 0,004%/timolol 0,5%, kao i sa mogućnošću izbora primjene lijeka, ujutro ili navečer, što omogućava individualni pristup primjene liječenja prema potrebama bolesnika.