Efficacy of the Travoprost/Timolol fixed Combination Versus the Concomitant use of Travoprost 0.004% and Timolol 0.1% Gel Formulation

Aysel Mehmet1, Vassilios Kozobolis1, Aristeidis Konstantinidis1, Harris Sideroudi2, Miguel Teus3

1Department of Ophthalmology, Democritus University of Thrace, Alexandroupolis, Greece; 2Department of Ophthalmology, Eye Institute of Thrace (EIT), Democritus University of Thrace, Alexandroupolis, Greece; 3Department of Ophthalmology, University of Alcala, Madrid, Spain

STUDY DESCRIPTION

In a study conducted by Kozobolis et al. [1] the Intraocular Pressure Lowering (IOP) efficacy of the travoprost 0.004%/Timolol 0.5% Fixed Combination (TTFC group) was compared to that of the concomitant use of each of the constituents of the fixed combination (Travoprost 0.004% and timolol gel 0.1%, Trav+Geltim group) in patients with ocular hypertension and primary open angle glaucoma. The TTFC was administered at 21:00 and in the Trav+Geltim group, the prostaglandin was instilled at 21:00 and the timolol gel 0.1% at 08:00. The patients who were on other glaucoma drops before the study were asked to stop the drops for a wash out period of 14-30 days before participating in the study. The IOP was measured at 4 time points during the day: At 09:00, 12:00, 15:00, and 18:00.

The IOP was measured at 1 and 3 months after initiation of treatment at the same time points. The results showed that there was no statistical difference of the hypotensive effect between the two groups except for the 18:00 time point in the first and the third month where the concomitant use of travoprost and timolol gel showed a higher hypotensive effect.

The authors concluded that the fixed combination of travoprost/ timolol was as effective in lowering the IOP as the concomitant use of travoprost and timolol gel. There was no mention regarding the side effects of the two treatment modalities.

The open angle glaucomas are generally managed with topical IOP-lowering medication, unless the presenting IOP is so high that is unlikely to be sufficiently controlled with eye drops as well as in other types of glaucoma (eg congenital, angle closure) [2]. The most commonly used glaucoma eye drops are the prostaglandin/prostamide analogues, beta blockers, carbonic anhydrase inhibitors, alpha agonists and cholinomimetics [3]. Among these hypotensive agents the first two have shown to have better hypotensive effect [4]. The prostaglandin/prostamide analogues decrease the IOP by increasing the uveoscleral outflow and the beta blockers by decreasing the aqueous production.

A pivotal question regarding fixed combinations is efficacy. Research has proved that prostaglandin/timolol fixed combinations are more potent than the individual components but when the two components are given separately they are more efficacious than the fixed combinations [5]. However the studies mentioned in this paper were characterized by quantitative heterogeneity.

The higher hypotensive effect of the unfixed combination is expected as in fixed combinations both active agents are given at the same time of the day but in the concomitant treatment the medications they are spaced out during the day. Prostaglandin analogues are more effective when taken in the evening [6,7] while timolol is more effective with morning instillation as the sympathic system is more active at this time.

Fixed combinations that do not contain prostaglandin/prostamide analogues include dorzolamide/timolol, brinzolamide/timolol, brimonidine/timolol, brinzomamide/brimonidine. These fixed combinations are as effective as their constituents given separately [8-11].

Although the European Glaucoma Society recommends a monotherapy as the first line treatment for glaucoma, a substantial number of patients will require more than one agent to control the IOP [12]. Multimedication, however, comes with price. Research has shown that adherence is compromised when more drugs are added to the regime of a patient [13,14]. Persistence is also a key factor for the optimal management of glaucoma. A study from Japan by Kashiwagi et al. [15] has shown that persistence decreases with the length of treatment and the more drops the patients use the more the persistence rates fall.

Another issue of major importance in the treatment of glaucoma is the incidence of the Ophthalmic Surface Disease (OSD). The end point of this condition is tear film instability, conjunctival and
concerns epithelial cell damage and inflammation and shares these characteristics with the dry eye disease [16]. A study by Leung et al. [17] showed that about 60% of patients taking glaucoma eye drops had signs and/or symptoms of OSD. A slightly smaller percentage of patients treated for glaucoma reported symptoms of OSD in another study [18]. Both studies agree that the symptoms and signs of OSD were proportional to the number of medications and in the study by Jaenen [18] the symptoms of OSD were diminished when the preservative containing drops were switched to preservative free ones. The main culprit of the OSD has proved to be the commonly used Benzalkonium Chloride (BAC) rather than the active agent itself [16]. Amelioration of the symptoms of OSD (stinging, burning, foreign body sensation) can improve tolerability and adherence. In the study of Kozobolis et al. [1] neither of the glaucoma eye drops used contained BAC. ’Travoprost/timolol fixed combination and travoprost monotherapy drops contain Polyquad and timolol gel 0.1% is preservative free’. Cost effectiveness is another aspect of treating a chronic disease such as glaucoma. Fixed combination eye drops are more cost effective than the concomitant use of the individual constituents [19]

Regarding the recommendation of the scientific bodies EGS states that fixed combination therapy should be preferred to two separate instillations of agents [2]. The UK based National Institute for Health and Care Excellence states that fixed combination therapies are simpler and more convenient to individual monotherapies [20], while the American Academy of Ophthalmology supports that fixed combinations may improve patients’ adherence [21].

CONCLUSION

In summary the fixed combinations and the preservative free eye drops are the way forward for the treatment of glaucoma as they are as efficacious as the unfixed combinations and have better adherence, tolerability and cost-effectiveness.

REFERENCES

1. Kozobolis V, Konstantinidis A, Sideroudi H, Teus M. Efficacy of the travoprost/timolol fixed combination versus the concomitant use of travoprost 0.004% and timolol 0.1% gel formulation. Clin Ophthalmol. 2018;12:2393-2398.
2. European Glaucoma Society. Terminology and Guidelines for Glaucoma (4th edn). In Treatment principles and Options. 2014.
3. Beidoe G, Mousa SA. Current primary open-angle glaucoma treatments and future directions. Clin Ophthalmol. 2012;6:1699–1707.
4. Van der Valk R, Webers CAB, Schouten JSAG, Zeegers MP, Hendrikse F, Prins MH. Intracocular pressure-lowering effects of all commonly used glaucoma drugs: A meta-analysis of randomized clinical trials. Ophthalmol. 2005;112:1177–1185.
5. Quaranta L, Biagioli E, Riva I. Prostaglandin analogs and timolol-fixed versus unfixed combinations or monotherapy for open-angle glaucoma: A systematic review and meta-analysis. J Ocul Pharmacol Ther. 2012;29:382-389.
6. Konstas AG, Mikropoulos D, Katsos K. 24-hour intraocular pressure control obtained with evening-versus morning-dosed travoprost in primary open-angle glaucoma. Ophthalmol. 2006;113:446-450.
7. Alm A, Stjernschantz J. Effects on intraocular pressure and side effects of 0.005% latanoprost applied once daily, evening or morning. A comparison with timolol. Scandinavian latanoprost study group. Ophthalmol. 1995;102:1743-1752.
8. Francis BA, Du LT, Berke S, Ehrenhaus M, Minckler DS. Cosopt Study Group. Comparing the fixed combination dorzolamide-timolol (Cosopt) to concomitant administration of 2% dorzolamide (Trusopt) and 0.5% timolol: A randomized controlled trial and a replacement study. Clin Pharm Ther. 2004;29(4):375-380.
9. Nagayama M, Nakajima T, Ono J. Safety and efficacy of a fixed versus unfixed brinzolamide/timolol combination in Japanese patients with open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2014;8:219-228.
10. Goni FJ. Brimonidine/timolol fixed combination study group. 12-week study comparing the fixed combination of brimonidine and timolol with concomitant use of the individual components in patients with glaucoma and ocular hypertension. Eur J Ophthalmol. 2005;15(3):581-590.
11. Wang N, Da-Wen L, Pan Y, Astakhov Y, Iureva T, Adewale A, et al. Comparison of the intraocular pressure-lowering efficacy and safety of the brinzolamide/brimonidine fixed-dose combination versus concomitant use of brinzolamide and brimonidine for management of open-angle glaucoma or ocular hypertension. Clin Ophthalmol. 2020;14:2121-30.
12. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Kelmner, JL, Miller JP, et al. The ocular hypertension treatment study: A randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. Arch Ophthalmol. 2002;120:701–713.
13. Djafari F, Lesk MR, Harasymowycz PJ, Desjardins D, Lachaine J. Determinants of adherence to glaucoma medical therapy ina long-term patient population. J Glaucoma. 2009;18(3):238–243.
14. Dunker S, Schmucker A, Maier H. Tolerability, quality of life, and persistency of use in patients with glaucoma who are switched to the fixed combination of latanoprost and timolol. Adv Ther. 2007;24(2):376–386.
15. Kashiwagi K, Furuta T. Persistence with topical glaucoma therapy among newly diagnosed Japanese patients. Jpn J Ophthalmol. 2014;58:68-74.
16. Hollo G, Katsanos A, Boboridis KG, Irkec M, Konstas AGP. Preservative-free prostaglandin analogs and prostaglandin/timolol fixed combinations in the treatment of glaucoma: Efficacy, safety and potential advantages. Drugs. 2018;78(1):39-64.
17. Leung EW, Medeiros FA, Weintreb RN. Prevalence of ocular surface disease in glaucoma patients. J Glaucoma.2009;18(3):323–329.
18. Jaenen N, Baudouin C, Pouliquen F, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with prescribed and preservative-free glaucoma medications. Eur J Ophthalmol.2007;17:341–349.
19. Hollo G, Topouzis F, Fechtner RD. Fixed-combination intracocular pressure-lowering therapy for glaucoma and ocular hypertension: advantages in clinical practice. Expert Opin Pharmacother. 2014;15(12):1737-1747.
20. NICE. Glaucoma: Diagnosis and Management of Chronic Open Angle Glaucoma and Ocular Hypertension. 2018.
21. American academy of ophthalmology. Primary open angle glaucoma. Preferred practice pattern. 2016.