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Commentary

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

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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 (Travopost 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 clolinomimetics [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 gives 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 sympathetic 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

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corneal 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 Benzalkoniun 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 montherapy 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.

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