Srp Arh Celok Lek. 2015 Sep-Oct;143(9-10):626-631
ПРЕГЛЕД ЛИТЕРАТУРЕ / REVIEW ARTICLE
DOI: 10.2298/SARH1510626B
UDC: 617.7-007.681-085.015.2

Fixed Combinations of Glaucoma Medications

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SUMMARY
The first line treatment in the management of glaucoma is topical medical therapy. Many patients with glaucoma require multiple medications for adequate intraocular pressure control. For patients who need multi-dose regimens to control intraocular pressure, fixed combinations offer convenience, efficacy and safety. This review summarizes the role, efficacy, mechanism of action and indications for use of modern fixed combination of topical glaucoma medications. The review shows the advantages and disadvantages of a prescribing fixed combination in daily clinical practice.
Keywords: glaucoma; fixed combination therapy; drugs

INTRODUCTION

When initiating medical therapy for newly diagnosed glaucoma, it is typically desirable to begin with a single antiglaucoma medication [1]. Topical medical therapy remains the first-line treatment in the management of glaucoma, but over time monotherapy often fails to control intraocular pressure (IOP). The initial monotherapy fails to control IOP within the first two years of treatment in about 50% of glaucoma patients [2] and frequently more than one agent is required to achieve adequate IOP control. If the initial therapy seems to be ineffective or the first choice monotherapy is well tolerated and is effective in lowering IOP but does not succeed in reaching the target pressure, an additional drug is added to the therapeutic regimen [3, 4, 5]. Recent trials, such as the Normal Tension Glaucoma Treatment Study, the Collaborative Initial Glaucoma Treatment Study, and the Ocular Hypertension Treatment Study, demonstrate that in order to reach the target IOP, it is often necessary to use multiple drugs [6, 7]. Patients are often prescribed multiple medications from different classes of IOP-lowering drugs, including α-agonists and carbonic anhydrase inhibitors (CAI) to prostaglandin analogues and β-blockers, to help maintain IOP control. There have been a number of concerns about the use of multiple bottles of glaucoma medications, such as increased toxicity of ophthalmic preservatives in multiple drugs, compliance, costs and washout effects [7, 8]. Complex dosing regimens have been clearly associated with nonadherence to medical therapy. The washout effect depends not only on the increased tear fluid turnover, but also on addition of a second eye drop within a short period. When more than one bottle is used, patients do not always allow adequate time for ocular absorption of their first medication before the second drug is administered [9]. Furthermore, Robin and Covert's study [10] showed that patients using two concomitant drugs often skip one drug in a few days. Low compliance with prescribed long-term glaucoma therapy is universal and impairs treatment outcome [11]. Inadequate compliance greatly diminishes drug efficacy, often leads to aggravation or undertreatment of health problems and inflates the cost of health care. Preservatives, especially benzalkonium chloride (BAK), are toxic to the eye in variety of ways, such as conjunctival inflammation, punctuate keratopathy or dry eye syndrome [8, 12]. These concerns have spurred the search for glaucoma drugs that will work well when put together in one bottle.

RATIONALE FOR FIXED COMBINATION THERAPY

Combining two medications in one bottle may improve compliance by reducing the time required to administer drops, the frequency of use, and the total number of bottles [11, 13]. Additionally, the use of one bottle rather than two significantly reduces the inconvenience of filling prescriptions and reduces daily cost of therapy [14]. For patients who need multi-dose regimens to control IOP, fixed combinations offer convenience, efficacy and safety. Fixed combinations of glaucoma medications offer a reduction in the number of bottles, and reduction in the number of drops per day. They also offer reduced time for drop instillation and potentially greater efficacy by eliminating the washout effect. The cost and time saving can enhance compliance. Instilling two medications in a single drop reduces the amount of preservatives, which may improve the tolerability and eventual surgical outcomes in patients who require filtering procedures [13].

The major limitation of a fixed combination therapy is that dosing of the concomitant medi-

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cation cannot be alerted within the concomitant product. For instance, a twice-daily regimen of a fixed combination product may contain too little or too much of one drug for a given patient. Morning dose may not be ideal for a prostaglandin analogue that seems to have more profound effects on IOP when dosed in the evening. Conversely, β-blockers show little effects on aqueous production during sleep and ideally should be given in the morning. Fixed combination medications may cause problems if a patient is allergic to any constituent of the fixed combination and make difficulties in finding which constituent causes allergy.

Fixed combination often includes timolol, a β-adrenergic antagonist that effectively decreases aqueous humor production and is generally well tolerated. For years these were dominant drugs used in the treatment of glaucoma [15, 16]. When we decide to initiate glaucoma therapy, compliance is of great importance. As the complexity of medical regimen grows, the likelihood of therapeutic adherence falls [7]. An important factor in the maintenance of adequate IOP control is patient's adherence to the prescribed treatment. Studies show that about 50% of glaucoma patients do not comply with dosing instructions and convenience is an important factor contributing to patients' adherence [17]. Simplification of the dosing regimen results in an increase in patients' adherence, but side effects may adversely affect it. A β-blocker, such as timolol, dosed twice daily, may cause cardiovascular, central nervous system, endocrine and pulmonary side effects [15]. Therefore, a once-daily prostaglandin/timolol fixed combination therapy may have important advantages over multi-dose regimens.

Prostaglandin analogues, another class of potent ocular hypotension substances, reduce IOP by increasing uveoscleral outflow of aqueous humor [18, 19]. Many studies showed that prostaglandin administered once daily efficiently lowers IOP in patients with primary open-angle glaucoma (POAG) and ocular hypertension (OHT) [20-23].

The complementary mechanisms of action of a prostaglandin analogue and a β-blocker are likely to show additive IOP-lowering effect in combination when compared with effects of either single agent [24-28].

THE AVAILABLE FIXED COMBINATIONS (TABLE 1)

Latanoprost/timolol

The first fixed combination of a prostaglandin analogue and β-blockers on the market was latanoprost 0.005% / timolol 0.5% fixed combination. Numerous studies have shown greater efficacy in decreasing of IOP compared to individual components. Mean diurnal IOP reduction from baseline was 33.5% and it was achieved in 73.5% of patients. Latanoprost/timolol fixed combination achieved a mean IOP reduction at baseline of -9.4 mmHg [29, 30]. Fixed combination of latanoprost plus timolol is effective in controlling IOP in patients with POAG and OHT who do not tolerate well multiple drops for reaching targeted IOP. The use of latanoprost/timolol fixed combination should reduce the exposure to ophthalmic preservatives compared (less BAK) with concomitant administration of multiple drops. Latanoprost/timolol is indicated in patients with POAG and OHT due to less adverse effects, better compliance and tolerability. Simplification of the regimen to once daily improves the side effect profile.

Table 1. Available fixed combinations of glaucoma medications

Antiglaucoma drug 1	Antiglaucoma drug 2	Commercial name
Bimatoprost 0.03%	Timolol 0.5%	Ganfort®
Latanoprost 0.005%	Timolol 0.5%	Xalacom®, Xalcom®
Travoprost 0.004%	Timolol 0.5%	DuoTrav®
Dorzolamide 2%	Timolol 0.5%	Cosopt®
Brinzolamide 1%	Timolol 0.5%	Azarga®
Brimonidine 0.2%	Timolol 0.5%	Combigan®
Brinzolamide 1%	Brimonidine 0.2%	Simbrinza®

Travoprost/timolol

Travoprost 0.004% / timolol 0.5% is a second-line fixed combination therapy used if treatment with travoprost or timolol as monotherapy fails to reach target IOP, and can replace concomitant administration of non-fixed combination as adjunctive therapy. Clinical studies have found that fixed combination travoprost plus timolol achieved a mean IOP decrease at baseline of 32–38% [27, 31]. A recent study compared the efficacy and safety of the fixed combination of travoprost plus timolol with the fixed combination of dorzolamide plus timolol, and found that the mean reduction from baseline was -8.96 mmHg for the travoprost/timolol fixed combination and -8.07 mmHg for the dorzolamide/timolol fixed combination, with the highest difference of -1.07 mmHg in favor of the travoprost/timolol fixed combination. Mean percentage reduction in diurnal IOP was 36.28% in the travoprost/timolol fixed combination, and 35.66% in the dorzolamide/timolol fixed combination [32]. Travoprost/timolol is the only fixed combination without BAK (travoprost/timolol "BAK-free"). It contains Polyquad ophthalmic preservative, which has far less toxic effect on ocular surface. Fixed combination of travoprost plus timolol is effective in controlling IOP in patients with POAG and OHT who do not tolerate well multiple drops for reaching target IOP. The use of travoprost/timolol fixed combination should be ideal for patients who developed ocular surface disease, due to BAK toxicity. Travoprost/timolol is indicated in patients with POAG and OHT due to less adverse effects, better compliance and tolerability. Simplification of once-daily dosing improves the side effect profile. Travoprost/timolol fixed combination is among the antiglaucoma drugs with the highest efficacy in decreasing IOP, and in certain cases it can be used as initial monotherapy. Travoprost/timolol fixed combination is conveniently dosed once daily in the morning.

Bimatoprost/timolol

Bimatoprost 0.03% / timolol 0.5% is a new fixed combination which represents the second line therapy if treatment

with bimatoprost or timolol as monotherapy does not succeed in reaching the target pressure, and can replace concomitant administration of non-fixed combination as adjunctive therapy. A lot of clinical studies have shown that the average reduction in IOP from baseline was 35% [24, 33, 34]. Fixed combination of bimatoprost plus timolol is effective in controlling IOP in patients with POAG and OHT who do not tolerate well multiple drops for reaching target IOP. The use of bimatoprost/timolol should reduce the exposure to ophthalmic preservatives compared with concomitant administration of multiple drops. [35, 36, 37]. Bimatoprost/timolol is indicated in patients with POAG and OHT due to less adverse effects, better compliance and tolerability. Simplification of the regimen to once-daily dose improves the side effect profile. Bimatoprost/timolol is the most effective antiglaucoma drug with the highest efficacy in decreasing IOP, and in certain cases it can be used as initial monotherapy. Bimatoprost/timolol fixed combination is well tolerated and safe. It is used once daily, in the morning.

Dorzolamide/timolol

Dorzolamide is a topical carbonic anhydrase inhibitor which reduces aqueous humor production and it is frequently prescribed as adjunctive therapy to timolol for additional IOP reduction. In controlled clinical trials, dorzolamide showed additional IOP reduction when used as adjunctive therapy to timolol regardless of which of the two drugs was used as initial therapy [38]. Dorzolamide 2% / timolol 0.5% is a fixed combination product with a convenient dosing regimen for patients requiring multiple medications. The fixed combination of dorzolamide and timolol, dosed twice daily, similarly has been shown to lower IOP more than either of its individual components and has been found to be comparable in efficacy to the concomitant administration of the two medications [39]. Dorzolamide/timolol fixed combination is highly effective in lowering IOP by 34.4–34.6% as initial therapy in patients with POAG and OHT [40]. It is given twice daily.

Brinzolamide/timolol

A fixed combination of brinzolamide 1% plus timolol 0.5% is the latest fixed combination of β-blockers and CAI. Clinical trials have demonstrated that brinzolamide/timolol fixed combination provides clinically meaningful IOP reduction from baseline, non-inferior to those seen with dorzolamide/timolol fixed combination. IOP reduction from baseline was 28.4–34.9% in brinzolamide/timolol group vs. 29.2–33.9% in dorzolamide/timolol group [41]. The advantage of brinzolamide/timolol fixed combination is in a higher safety and tolerability profile. Patients with POAG and OHT prefer the brinzolamide/timolol fixed combination over the dorzolamide/timolol fixed combination. This is likely related to differences in the formulation, specifically differences in pH and buffering system between the two products [42, 43]. Stronger patient's preference for greater comfort of brinzolamide/timolol may lead to better therapeutic compliance. The use of brinzolamide/timolol should reduce the exposure to ophthalmic preservatives compared with concomitant administration of multiple drops. Brinzolamide/timolol is indicated in patients with POAG and OHT due to less adverse effects, better compliance and tolerability. Due to high tolerability and comfort, brinzolamide/timolol fixed combination is a treatment of choice for patients on dorzolamide/timolol treatment who developed intolerability and adverse effects, and should be switched to a new drug. It is dosed twice daily.

Brimonidine/timolol

A fixed combination of brimonidine 2% / timolol 0.5% is a combination of α-agonist and β-blocker. The mechanism of decreasing IOP is complementary, even though both constituents cause IOP decrease by decreasing aqueous humor production by different ways of action. Brimonidine partially increases uveoscleral outflow of aqueous humor as well. The efficacy of IOP lowering ranged from 28% to 33.6% [44, 45]. Clinical studies found that brimonidine/timolol fixed combination is more effective in lowering IOP than any of its individual components and has been found to be comparable in efficacy to the concomitant use of the two medications [46, 47]. A simplified dosing regimen has a potential to improve the compliance. In comparison with dorzolamide/timolol fixed combination, clinical studies found a similar efficacy in IOP lowering, but brimonidine/timolol fixed combination showed better tolerability [47, 48, 49]. In patients on multiple-drug therapy, including prostaglandins, replacement of dorzolamide/timolol with brimonidine/timolol may help achieve a lower IOP of 2 mmHg, while replacement of brimonidine plus dorzolamide/timolol with brimonidine/timolol may help achieve low IOP with fewer medications [50]. It is used twice daily.

Brinzolamide/brimonidine

The newest fixed combination on the market is brinzolamide/brimonidine containing CAI – brinzolamide 1% and α-2 agonist – brimonidine 2% and it is the only fixed combination option that does not rely on a β-blocker to exert its IOP-lowering effect. Its mechanism of action differs from other fixed drug medications. Each component works differently to decrease the elevated IOP; brinzolamide decreases aqueous humor production and brimonidine decreases aqueous humor production and increases uveoscleral outflow. In recent studies, brinzolamide/brimonidine ophthalmic suspension resulted in greater IOP reduction (16.7–20.5 mmHg) than brinzolamide (19.8–21.4 mmHg) or brimonidine (18–22.5 mmHg). Brinzolamide/brimonidine suspension provided an average of 21.4–34.9% reduction in IOP, higher than either of its individual components (16.9–22.6% for brinzolamide; 14.3–25.8% for brimonidine). Patients receiving brinzolamide/brimonidine

doi: 10.2298/SARH1510626B

achieved an average of 5.4–8.8 mmHg reduction of IOP from baseline [51, 52]. It is administered three times a day.

CONCLUSION

In patients with POAG and OHT, fixed combination therapy offers benefits over concomitant therapy, in terms of convenience, costs, and potentially compliance and efficacy. Combination therapy is not recommended as a first-line treatment. However, in some cases, such as advanced glaucoma and/or very high IOP, the requested IOP reduction may exceed their efficacy range when used as a single agent. Therefore, a fixed combination can be used as a first-line therapy. If the combination therapy fails to reduce IOP sufficiently, one can either substitute the second drug or add a third medication to the fixed combination. A fixed combination with addition of a third medication is considered to be maximal medical therapy and at this stage laser or incisional surgery should be considered.

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Фиксне комбинације у терапији глаукома

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КРАТАК САДРЖАЈ

Прва терапијска линија у лечењу од глаукома је медикаментна, у виду капи. Многи болесници који се лече од глаукома захтевају примену већег броја лекова за регулисање интраокуларног притиска. Код болесника којима је потребна употреба већег броја бочица за регулисање интраокуларног притиска, фиксне комбинације нуде једноставност, ефикасност и безбедност у лечењу. Овај ревијски рад приказује улогу, ефикасност, механизам дејства и индикације за примену савремених фиксних комбинација. Рад указује на предности и недостатке код употребе фиксних комбинација у свакодневној клиничкој пракси.

Кључне речи: глауком; фиксне комбинације; лекови

Примљен • Received: 31/03/2015 **Прихваћен • Accepted:** 29/06/2015