

Efficacy and tolerability of brinzolamide/brimonidine suspension and prostaglandin analogs in patients previously treated with dorzolamide/timolol solution and prostaglandin analogs

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Objective: Fixed combination glaucoma medication is increasingly used in glaucoma treatment. There is a lack of comparative study in the literature of non-beta blocker combination agents used adjunctively with a glaucoma agent in a different class. The objective of this study is to evaluate the effect of intraocular pressure (IOP) control and tolerability of non-beta blocker combination suspension with prostaglandin analogs (PGA) in patients with open angle glaucoma who were previously treated with beta blocker combination solution with PGA.

Design: Open-label retrospective review of patient records.

Patients and methods: This study looked at patients with open angle glaucoma taking dorzolamide/timolol solution with PGA that were switched to brinzolamide/brimonidine combination suspension with PGA. This study reviewed the charts of all patients who were at least 21 years old with a clinical diagnosis of open-angle glaucoma or ocular hypertension in at least one eye. Patients needed to have been treated with concomitant use of PGA and dorzolamide/timolol solution for at least one month. Patients using dorzolamide/timolol solution plus PGA with medication related ocular irritation were switched to brinzolamide/brimonidine suspension with the same PGA. Best-corrected visual acuity, ocular hyperemia grading, slit lamp biomicroscopy and Goldmann applanation tonometry measurements, and patient medication preferences were assessed at baseline, 1 month and 3 months.

Results: Forty eyes with open angle glaucoma. The mean age of the patients was 68 and 60% were females. The IOP before the switch was 17.2 and 16.5 ($P=0.70$) following the switch at 3 months. We found a decreasing trend of ocular hyperemia ($P=0.064$) and strong preference ($P=0.011$) for non-beta blocker combination suspension but no difference of visual acuity and slit lamp findings.

Conclusion: Brinzolamide/brimonidine combination suspension when used adjunctively with PGA is equally effective. Patients in this study reported greatly reduced ocular redness and shorter duration of stinging with non-beta blocker combination suspension. Their preference of it over dorzolamide/timolol combination solution makes it a viable treatment option, particularly for the aging glaucoma patient with comorbidities that restrict the beta blocker use.

Keywords: Open angle glaucoma, brinzolamide, brimonidine, dorzolamide, timolol, prostaglandin analogs, side effects

Background

Optimal control of intraocular pressure (IOP) has been shown to reduce the risk of glaucoma-related optic nerve damage and visual field loss.¹⁻⁴ Prostaglandin analogs (PGA) are the most commonly prescribed agents to lower IOP.⁵ A single IOP-lowering

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medication may not provide sufficient IOP control, thus resulting in the need for multiple IOP-lowering medications to reach the target IOP.⁶ β -blockers with PGA are often employed for lowering the IOP and have been found to be effective.⁷ Up to 30% of glaucoma patients require adjunctive therapy within 1 year, and there is a general increase in the number of patients prescribed three or more agents for IOP control.^{5,6}

Although β -blockers are frequently employed along with PGA, in the United States, the most common fixed-combination IOP-lowering medication consists of β -blockers with carbonic anhydrase inhibitors (CAIs; eg, brinzolamide and dorzolamide) or α_2 -adrenergic agonists (eg, brimonidine).⁸ Recently, a non- β -blocker combination solution that consists of a fixed combination of brinzolamide and brimonidine suspension has been approved.⁹

To our knowledge, there is no comparative study of non- β -blocker combination agents against β -blocker combination agents when used adjunctively with a glaucoma agent in a different class.

In this study, patients previously taking dorzolamide/timolol solution and PGA for IOP control with medication-related ocular irritation and intolerance who were switched from dorzolamide/timolol solution to brinzolamide/brimonidine while concomitantly taking the same PGA were analyzed. The impact of this change on IOP control and tolerability was investigated.

Methods

This was a retrospective, open-label chart review of patients with a diagnosis of open-angle glaucoma or ocular hypertension treated with PGA, but needing a combination agent to meet target IOP. Dorzolamide/timolol solution was added to PGA. Patients using dorzolamide/timolol solution with PGA who reported medication-related ocular irritation were switched to brinzolamide/brimonidine suspension while concomitantly on the same PGA. The PGA consisted of latanoprost, travoprost, or bimatoprost. The Institutional Review Board of the University of Hawaii approved the study. Data collection and reporting were in compliance with all Health Insurance Portability and Accountability Act requirements.

Patients

The charts of all patients who met the study criteria were reviewed. Data were collected for patients who were at least 21 years old with a clinical diagnosis of open-angle glaucoma and/or ocular hypertension in at least one eye. They needed

to have been treated with concomitant use of PGA and dorzolamide/timolol solution for at least 1 month.

Patients using dorzolamide/timolol solution plus PGA with medication-related ocular irritation were switched to brinzolamide/brimonidine suspension with the same PGA. Best-corrected visual acuity (BCVA), ocular hyperemia grading (scale of 0–3), slit-lamp biomicroscopy, and Goldmann applanation tonometry measurements were all recorded at the visit when medications were altered.

Patients taking brinzolamide/brimonidine suspension plus PGA were seen at baseline and 1 and 3 months later. Data were analyzed for the groups that had office visits at 3 months.

A two-tailed paired Student's *t*-test was used to calculate statistical significance of IOP change, hyperemia level, visual acuity, and preference of medication while taking dorzolamide/timolol solution plus PGA at the baseline visit as compared to brinzolamide/brimonidine suspension with the same PGA after 3 months. A *P*-value less than 0.05 was considered to be statistically significant.

Results

Forty eyes of 20 patients, eight males (40%) and 12 females (60%) aged 32–87 (68±14) years, were included. All had a diagnosis of open-angle glaucoma (100%). Seven (35%) patients were on latanoprost, seven (35%) patients were on travoprost, and six (30%) patients were on bimatoprost with dorzolamide/timolol solution. Table 1 shows the baseline demographics of the patients included in this study.

As shown in Table 2, there was no significant difference in baseline mean IOP (17.2±1.5 mmHg) as compared to brinzolamide and brimonidine suspension with PGA at 3 months (16.5±1.6 mmHg, *P*=0.20). No significant difference was noted in mean ocular hyperemia (1.2±0.4 vs 1.1±0.3, *P*=0.064). No significant changes in visual acuity, corneal staining, or slit-lamp biomicroscopy findings were noted. Two treatment-related adverse events were reported: one episode of increased ocular hyperemia and one occurrence of allergic conjunctivitis. The symptoms resolved after discontinuing the brinzolamide/brimonidine suspension.

Table 1 Baseline demographics of patients

Mean age (years ± SD)	68±14
Sex, n (%)	
Male	8 (40%)
Female	12 (60%)
Baseline characteristics	
Open-angle glaucoma	20 (100%)
Cataract	6 (30%)

Table 2 Efficacy and ocular measures of brinzolamide/brimonidine suspension plus PGA versus dorzolamide/timolol solution plus PGA

Measurement	Dorzolamide/ timolol + PGA	Brinzolamide/ brimonidine + PGA	P-value
Intraocular pressure (mmHg)	17.2±1.5	16.5±1.6	0.20
Hyperemia	1.2±0.4	1.1±0.3	0.064
Visual acuity (LogMAR)	0.33±0.05	0.34±0.06	0.45
Medication preference	6	14	0.011

Notes: Data are presented as mean ± SD. Bold text indicates statistical significance of a P-value less than 0.05.

Abbreviations: PGA, Prostaglandin analogs; LogMAR, logarithm of the minimum angle of resolution.

The patients were restarted on dorzolamide/timolol solution without further events.

Significantly more patients reported less stinging and preferred the brinzolamide/brimonidine suspension compared with the dorzolamide/timolol solution (14 vs 6, $P=0.011$).

Discussion

Multiple IOP-lowering medications with separate bottles can be difficult for patients to manage.^{10–12} In addition to the risk of preservative-induced ocular symptoms, the drops, if not properly spaced apart, may introduce a washout effect.¹³ There is a trend toward increased use of a fixed-combination agent as the first-line adjunctive therapy, because it provides convenience and improved adherence versus concomitant use of multiple separate bottles.^{6,10} Because glaucoma is a chronic disease, the long-term tolerability of the eye drops determines a patient's adherence, persistence, and willingness to take the prescribed medication.¹⁴

Previous studies confirmed the greater IOP-lowering effect of the brinzolamide and brimonidine combination compared with brinzolamide or dorzolamide monotherapy.^{9,15} The safety profile and tolerability of brinzolamide and brimonidine, like other fixed-combination IOP-lowering medications, is consistent with its individual components.^{9,15}

Fixed-combination solutions were more effective than timolol monotherapy. Adding a fixed-combination eye drop to a PGA provides an alternative therapeutic benefit for patients with glaucoma needing multiple drug therapy.⁶ The two types of fixed-combination eye drops appear to have different ocular and systemic side effect profiles.¹⁶

In this study, patients who were unable to tolerate dorzolamide/timolol fixed combination with PGA were switched to brinzolamide/brimonidine suspension

while maintaining the same PGA. There was no significant change in IOP 3 months after transitioning from dorzolamide/timolol solution to brinzolamide/brimonidine suspension, suggesting brinzolamide/brimonidine suspension with PGA is a viable option for IOP control especially in patients with comorbidities restricting the use of β -blockers.

The results of our chart review demonstrated significantly less stinging of shorter duration with brinzolamide/brimonidine suspension versus the dorzolamide/timolol solution. This is believed to be a result of a more neutral pH (6.5) in the brinzolamide/brimonidine suspension than the acidic pH (5.6) of the dorzolamide/timolol solution.¹⁷ In addition, eye drops with dorzolamide use sodium citrate as a buffer, whereas drops with brinzolamide do not.¹⁷

There were two treatment-related adverse events, one episode of increased ocular hyperemia and one occurrence of allergic conjunctivitis. But no serious treatment-related adverse effects were observed. Fixed combination of PGA and timolol was shown to have less conjunctival hyperemia than when used separately.⁷ In our study, patients also reported less redness with the brinzolamide/brimonidine suspension and preferred it to the dorzolamide/timolol solution. The mechanism may be due to α -adrenergic agonist effect. Reduction of ocular symptoms associated with the prescribed medication would have a beneficial effect on patient preference and may increase adherence of glaucoma medication. Despite this, we found no statistically significant difference ($P=0.064$) in redness with the brinzolamide/brimonidine suspension versus dorzolamide/timolol solution, irrespective of the PGA concomitantly used, most likely due to the small sample size of this study.

The brief duration of dorzolamide/timolol solution plus PGA therapy prior to transitioning to brinzolamide/brimonidine suspension in this study may not have allowed enough time to observe difference in IOP and adverse effects between treatments. A previous study revealed no change in mean blood pressure regardless of non- β -blocker combination or individual components used.¹⁵ In this study, we did not look at the effect on blood pressure in our subjects when they were switched from topical β -blocker combination to non- β -blocker combination solution. A similar study with a longer duration of use of dorzolamide/timolol solution with PGA use prior to switching might produce differences in other parameters that were not evident in the current study. However, the fact that our patients had a strong preference for brinzolamide/brimonidine suspension after taking dorzolamide/timolol solution for a relatively short time strongly increased tolerability of brinzolamide/brimonidine

suspension versus dorzolamide/timolol solution when used with a glaucoma agent in a different class.

Conclusion

Our study, albeit limited by small sample size, confirms that all currently available fixed-combination IOP-lowering medications have similar IOP-lowering efficacy. Patients with open-angle glaucoma and/or ocular hypertension requiring multiple medications can be switched from dorzolamide/timolol solution plus PGA to brinzolamide/brimonidine suspension plus PGA with similar IOP control with benefits of improved compliance owing to increased tolerability. Brinzolamide/brimonidine suspension is β -blocker free, making it a viable treatment option for our aging glaucoma patients with comorbidities restricting β -blocker use.

Disclosure

The authors report no conflicts of interest in this work.

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