Comparison of the Intraocular Pressure-Lowering Effect and Safety of Preservative-Free And Preservative-Containing Brimonidine/Timolol Fixed-Combination Ophthalmic Solutions in Patients with Open-Angle Glaucoma

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ABSTRACT

Purpose: To compare the therapeutic efficacy and safety of newly developed preservative-free (PF) brimonidine/timolol fixed-combination (BTFC) ophthalmic solutions and a preservative-containing (PC) BTFC ophthalmic solution in patients with open-angle glaucoma.

Methods: This study was conducted as a multicenter, randomized, open-label, parallel-group clinical trial to evaluate the efficacy and safety of PF BTFC as compared with PC BTFC in adult patients (aged ≥ 19 years) with open-angle glaucoma (OAG) and ocular hypertension (OHT). A total of the 106 patients were enrolled, with 53 patients each randomized to the two treatment groups and included in the analysis of the safety set (SS). After a washout period, patients with an IOP below 35 mmHg at 9 a.m. were enrolled. After a full opthalmic and glaucoma examination, a total of 106 OAG and OHT patients were randomized to the PF group or PC group. All subjects were examined 4 and 12 weeks after first administration. At each follow-up visit, IOP was measured at 9 a.m. and 11 a.m. and the efficacy, safety, and compliance were evaluated. Throughout the study, all adverse events were recorded and monitored by the investigators.

Results: The mean IOP changes from baseline to 12 weeks at 11:00 a.m. were −3.45 ± 2.53 mmHg in the PF group and −3.65 ± 2.76 mmHg in the PC group (p < .0001 for both). The difference in mean IOP change between the two groups was 0.20 ± 2.65 mmHg, which was not significantly different. The proportion of patients with IOP reductions ≥ 15% and ≥ 20% and IOP at all-time points in the PF group were not significantly different when compared with the PC group. There were no specific differences between the two groups regarding the incidence of adverse events.

Conclusions: PF BTFC ophthalmic solution shows a similar efficacy and safety profile to that of PC BTFC.

INTRODUCTION

Glaucoma is a chronic progressive optic neuropathy characterized by visual field loss corresponding to the area of optic nerve damage and can lead to irreversible blindness if left untreated. A recent systematic review reported that the global prevalence of glaucoma was estimated to be 3.54% in people aged 40 to 80 years and 3.40% specifically in Asia. In Korea, the number of patients with glaucoma is significantly increased with an estimate of 54.15% from 2008 to 2013. Especially, open-angle glaucoma (OAG) was reported to be a common subtype, which accounts for 56% to 62% of all glaucoma cases. Among the various risk factors, intraocular pressure (IOP) is regarded as the most important factor. Many studies have reported that the reduction of IOP is effective for the management of glaucoma. The Early Manifest Glaucoma Trial showed that the risk of glaucoma progression is reduced by 10% with 1 mmHg of IOP decrease.

The reduction of IOP with ophthalmic solutions is recommended as the primary and first treatment for glaucoma. Brimonidine/timolol fixed-combination (BTFC) therapy has been established as an effective IOP-lowering treatment option for glaucoma, and a recent study reported an approximately two-fold higher IOP-lowering effect was achieved with this medication as compared with 0.5% timolol in normal-tension glaucoma patients. However, much like generally used glaucoma ophthalmic solutions, BTFC ophthalmic solutions also contain benzalkonium chloride (BAK) as a preservative, which may cause ocular side effects such as mucous cell death, tear film instability, and lacrimation, especially in long-term users. Many researchers have recently sought to further elucidate the harmful effect of preservatives, and the European Glaucoma Society now recommends preservative-free (PF) products for use by patients who have severe dry eye or ocular surface diseases.

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Nowadays, PF ophthalmic solutions are preferred and often used because they are likely to reduce or eliminate side effects from the inclusion of preservatives that may affect the compliance of drugs in chronic glaucoma patients. Despite these potential benefits, however, not all glaucoma drugs have been developed PF formulation and sale on the market. In this study, the safety and efficacy of newly developed PF BTFC in Korea were compared to preservative-containing (PC) BTFC ophthalmic solutions for OAG patients.

PATIENTS AND METHODS

Study Design
This study was a multicenter (seven institutions), randomized, open-label, investigator-masked, parallel-group clinical trial designed to evaluate the efficacy and safety of PF/PC BTFC in patients with OAG. The involved sites were Yonsei University Severance Hospital, Kangbuk Samsung Hospital, Kim’s Eye Hospital, Seoul National University Bundang Hospital, Seoul National University Hospital, Catholic University Seoul St. Mary’s Hospital, and Chonnam National University Hospital. This study was conducted from August 2016 to November 2017. The study protocol was approved by the institutional review board of each study site and the trial was performed in accordance with the principles of the Declaration of Helsinki. All patients were fully informed and voluntarily provided written consent before participation. To minimize the bias in measuring the IOP, the investigator was blinded.

Patients
This study enrolled adult patients (aged ≥ 19 years) with OAG/ocular hypertension (baseline IOP < 35 mmHg). We excluded the patients with a best-corrected visual acuity of 20/80 or below on the Snellen chart and/or a medical history of chronic or recurrent intraocular inflammation in progress. Women who were pregnant, planning to become pregnant, currently nursing, or not using a reliable form of contraception were also excluded. Patients with a history of significant ocular trauma or intraocular surgery within 6 months prior to the screening visit, patients diagnosed with advanced glaucoma with a mean deviation of perimeter of −15 dB or less, with any ocular/systemic conditions that may affect IOP, or with visual field defects were additionally excluded. The inclusion and exclusion criteria are presented in Table 1.

| Inclusion | Exclusion |
|-----------|-----------|
| Adult aged ≥ 19 years | BCVA ≤ 20/80 on the Snellen chart |
| Primary open-angle glaucoma/ocular hypertension | Medical history of chronic intraocular inflammation in progress |
| Gonioscopic examination Shaffer grades 3 or 4 | History of significant ocular trauma or intraocular surgery ≤ 6 months from screening visit |
|                                      | Advanced glaucoma (perimetry mean deviation ≤ −15 dB) |
|                                      | Any ocular/systemic conditions that may affect IOP or visual field defects |
|                                      | Women who were pregnant, planning to become pregnant, currently nursing, of childbearing potential, or not using a reliable form of contraception |

BCVA, best-corrected visual acuity; IOP, intraocular pressure.

IOP was measured twice in the same eye with a Goldmann applanation tonometer. If the two measurements differed by more than 2 mmHg, the mean value among three measurements was subsequently chosen for analysis after measuring the IOP once more. Efficacy was evaluated using a single eye of each patient. In patients diagnosed with OAG in both eyes, the eye with the higher baseline IOP value was selected as the study eye, while, when the IOP was the same in both eyes in patients with bilateral OAG, the right eye was chosen to be the study eye.

Statistical Analysis
All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). Concerning the demographic information, continuous variables were presented with descriptive statistics and comparisons between both groups were analyzed using an independent t-test or the Wilcoxon rank-sum test. Frequencies and percentages of categorical variables for both groups were presented as descriptive statistics, compared using the chi-squared test or Fisher’s exact test. The comparison of IOP was performed using a two-sided test with the exception of the comparison of mean IOP changes. All p-values were considered statistically significant when less than 0.05. The noninferiority margin was determined as 1.5 mmHg when considering previous research and the 90% confidence interval was presented using analysis of covariance.
RESULTS

Patients

Table 2 shows the details of the demographics of patients of this study. A total of the 106 patients were enrolled, with 53 patients each randomized to the two treatment groups and included in the analysis of the safety set (SS). The mean IOP at baseline was 15.89 ± 2.84 mmHg in the PF group and 16.27 ± 3.13 mmHg in the PC group. There was no significant difference between groups in terms of mean IOP (p = .57). Six patients (11.32%) had a history of diabetes mellitus in the PF group and seven patients (13.21%) had such in the PC group, while those who had been diagnosed with hypertension numbered 20 (37.74%) in the PF group and 14 (26.42%) in the PC group. There was no significant difference between groups regarding the contents of their medical histories. Patient disposition is presented in Figure 1.

Table 2. Demographics of patients.

|                  | PF (n = 53) | PC (n = 53) | p-value |
|------------------|-------------|-------------|---------|
| Sex, n (%)       |             |             |         |
| Female           | 28 (52.83)  | 28 (52.83)  | 1.0000  |
| Male             | 24 (47.17)  | 25 (47.17)  |         |
| Age (years)      |             |             |         |
|                 | 28 (52.83)  | 28 (52.83)  |         |
|                 |             |             |         |
| Height (cm)      | 165.26 ± 9.09 | 164.33 ± 8.45 | 0.5872 |
| Weight (kg)      | 64.97 ± 11.13 | 64.74 ± 11.72 | 0.7353 |
| BMI (kg/m²)      | 23.69 ± 2.92 | 23.85 ± 3.00 | 0.7913 |
| IOP at baseline  |             |             |         |
| OS               | 15.12 ± 3.01 | 15.31 ± 3.22 | 0.7855 |
| OD               | 15.12 ± 3.01 | 15.31 ± 3.22 | 0.7855 |
| Shaffer grade, n (%) |         |             |         |
| 0                | 0 (0.00)    | 0 (0.00)    | 0.5529 |
| 1                | 0 (0.00)    | 0 (0.00)    |         |
| 2                | 0 (0.00)    | 0 (0.00)    |         |
| 3                | 0 (0.00)    | 0 (0.00)    |         |
| 4                | 0 (0.00)    | 0 (0.00)    |         |
| Best-corrected visual acuity |         |             |         |
| OS               | 22.75 ± 5.10 | 25.38 ± 8.36 | 0.1261 |
| OD               | 23.04 ± 4.98 | 24.17 ± 7.78 | 0.5534 |
| Medical history, n (%) |         |             |         |
| Diabetes mellitus | 6 (11.32)    | 7 (13.21)    | 1.0000 |
| Hypertension     | 20 (37.74)  | 14 (26.42)  | 0.2981 |

Data are presented as means ± standard deviations. PF, preservative-free; PC, preservative-containing; IOP, intraocular pressure; OS, oculus sinister; OD, oculus dexter.

Efficacy

Table 3 reports the mean IOP at each time point and the mean IOP reduction from baseline in both groups. In the per-protocol set (PPS), the mean IOP values recorded at 09:00 a.m. at baseline, 4 weeks, and 12 weeks were 15.89 ± 2.84, 13.09 ± 2.16, and 13.28 ± 2.63 mmHg, respectively, in the PF group and 16.27 ± 3.13, 13.38 ± 2.49, and 13.65 ± 2.92 mmHg, respectively, in the PC group. Additionally, the mean IOP values at 11:00 a.m. 4 and 12 weeks were 11.99 ± 2.24 and 12.45 ± 2.32 mmHg in the PF group and 12.23 ± 2.67 and 12.63 ± 3.03 mmHg in the PC group. Overall, the mean IOP values at each time point were significantly reduced when compared with baseline (p < .0001). The mean IOP reduction from baseline to 09:00 a.m. at 4 and 12 weeks in the PF group were −2.80 ± 2.05 and −2.62 ± 2.26 mmHg and were −2.90 ± 2.44 and −2.62 ± 2.50 mmHg in the PC group. Additionally, the mean IOP reductions from baseline to 11:00 a.m. at 4 and 12 weeks in the PF group were −3.91 ± 2.42 and −3.45 ± 2.53 mmHg, while those in the PC group were −4.04 ± 2.54 and −3.65 ± 2.76 mmHg. The mean IOP reductions were not significantly different between the PF and PC groups at all time points. The results of the full analysis set (FAS) are also presented in Table 3.

Figure 1. Patient selection process. PF, preservative-free; PC, preservative-containing; FAS, full analysis set; PPS, per-protocol set.
We analyzed the responsiveness of each drug based on a 10%, 15% or 20% reduction of baseline IOP. Table 4 shows the proportion of patients with IOP reduced by more than 10%, 15% or 20% at 09:00 and 11:00 a.m. at each time point as compared with baseline. In PPS, the proportions of patients with IOP reduced by more than 10%, 15% and 20% at 09:00 a.m. at 4 weeks were 76.32% (29/38 patients), 63.16% (24/38 patients) and 42.11% (16/38 patients) in the PF group and 69.05% (29/42 patients), 52.38% (22/42 patients) and 45.24% (19/42 patients) in the PC group. Along these lines, the proportions of the same recorded at 11:00 a.m. at 4 weeks were 86.84% (33/38 patients), 73.68% (28/38 patients) and 65.79% (25/38 patients) in the PF group and 85.71% (36/42 patients), 83.33% (35/42 patients) and 66.67% (28/42 patients) in the PC group. Additionally, the proportions of patients with IOP reduced by more than 10%, 15% and 20% at 09:00 a.m. at 12 weeks were 71.05% (27/38 patients), 55.26% (21/38 patients) and 44.74% (17/38 patients) in the PF group and 69.05% (33/42 patients), 61.90% (26/42 patients) and 45.24% (19/42 patients) in the PC group, while those at 11:00 a.m. at 12 weeks were 78.95% (30/38 patients), 71.05% (27/38 patients) and 55.26% (21/38 patients) in the PF group and 78.57% (33/42 patients), 71.43% (30/42 patients) and 59.52% (25/42 patients) in the PC group. There were no significant differences noted between the PF and PC groups regarding observed proportions of patients at all time points. The results of the FAS are also presented in Table 4.

**Safety**

Of the 106 patients in the SS, ocular AEs were observed to have occurred in three patients (three cases). While only one patient (one case) in the PF group experienced corneal erosion, in the PC group, corneal abrasion and vitreous hemorrhage were reported in one patient (one case) each. AEs other than ocular events were noted among 15 patients (17 cases) in the PF group and 13 patients (15 cases) in the PC group. Further details of the reported AEs are presented in Table 5.

**DISCUSSION**

In the present study, PF BTFC demonstrated similar efficacy and safety outcomes as compared with PC BTFC in patients with OAG. There was no significant difference in mean IOP reduction between the PF group and PC group after treatment. Specifically, the difference in the mean IOP reduction between the two groups was 0.20 ± 2.65 mmHg (90% confidence interval: −0.82 to 0.86 mmHg), and the upper limit was lower than the noninferiority margin of 1.5 mmHg. Therefore, this study demonstrated the noninferiority of PF BTFC to PC BTFC by the satisfaction of the noninferiority margin. There was also no significant difference in mean IOP at each time point between the groups.

Ophthalmic solutions are the most commonly used treatment option in glaucoma management. Prostaglandin analogs, β-blockers, α2-agonists, and carbonic anhydrase inhibitors are used as therapeutic remedies in the field of glaucoma. Among these, β-blockers are used as single- or multicomponent agents. Kass et al. showed in their research that after 5 years of using an ophthalmic solution for IOP control, 40% of patients ended
up using two or more drugs to maintain their target IOP. Thus, a combination of two different drugs has been widely used, since, with single-agent treatment, it is not easy to achieve the IOP goal. However, studies have shown that drug adherence decreases as the number of ophthalmic solutions used increases. Therefore, there have been many efforts to develop fixed-combined drugs as part of ways to reduce the number of ophthalmic solutions used while maintaining the same effect.

So far, when generally used, BTFC can be useful for maintaining an IOP goal, yet contains BAK as a preservative for drug stability. BAK is known to demonstrate a critical level of cytotoxicity caused by inflammatory and toxic effects. In an in vitro study, when timolol maleate with BAK was administered to cultured conjunctival epithelial cells, decreases of 40% and 85% in cell viability were observed within 15 minutes and 24 hours, whereas BAK-free timolol did not affect the cell viability. Elsewhere, Cha et al. found that 0.001% or more of BAK reduced cell proliferation and caused apoptosis in corneal epithelial cells. Also, Kwon et al. reported on the corneal endothelial toxicity characteristics of preservatives. Some studies have suggested that BAK increases the levels of interleukin, fibroblast growth factor, platelet-derived growth factor, and tumor necrosis factor alpha in the tear film, and long-term use could lead to apoptosis of conjunctival cells and chronic conjunctival inflammation. In other research, Desbienoit et al. examined the penetration of BAK into the deep ocular structures where, after topical exposure, BAK was found in the conjunctiva as well as in the iris, lens capsule, and trabecular meshwork tissue of rabbits. In terms of its effect on the ocular surface, BAK, when included in topical ophthalmic solutions, induces tear film instability, conjunctival inflammation, subconjunctival fibrosis, epithelial apoptosis, and corneal surface impairment. Pisella et al. reported that the removal of preservatives from ophthalmic solution could lead to improved corneal epithelial barrier function, the prevention of ocular surface inflammation, and a reduction in patient complaints of discomfort. To avoid perpetuating further ocular toxicity and discomfort with treatment, various PF ocular drugs were developed.

Without the preservative, there is a possibility that the discomfort caused by the side effects of the preservative is less, but at the same time, the eye penetration of the drug is reduced, so there is a possibility that the effect of the drug is small. So various studies to date have compared the effects and side effects of existing PC and PF ophthalmic solutions. Pellinen et al. reported similar corneal penetration rates of PC and PF tafluprost were achieved in the aqueous humor of rabbits. Alhara et al.

### Table 4. Proportions of patients with IOP reduced by more than 10% or 15% or 20% at each time point.

| Patients with ≥ 10% IOP reduction | Week 4 | | Week 12 | |
|------------------------------------|--------|----------------|--------|----------------|
|                                    | PF     | PC             | p-value| PF             | PC             | p-value|
| n (%)                              |        |                |        |                |                |        |
| Patients with ≥ 15% IOP reduction  |        |                |        |                |                |        |
| PPS                                |        |                |        |                |                |        |
| FAS 9:00 a.m.                      | 29 (76.32) | 29 (69.05) | 0.4672 | 27 (71.05) | 29 (69.05) | 0.8451 |
| 11:00 a.m.                         | 33 (88.84) | 36 (85.71) | 0.8837 | 30 (78.95) | 33 (78.57) | 0.9673 |
| Patients with ≥ 20% IOP reduction |        |                |        |                |                |        |
| PPS                                |        |                |        |                |                |        |
| FAS 9:00 a.m.                      | 24 (63.16) | 22 (52.38) | 0.3302 | 21 (55.26) | 26 (61.90) | 0.5468 |
| 11:00 a.m.                         | 28 (73.68) | 35 (83.33) | 0.2921 | 27 (71.05) | 30 (71.43) | 0.9704 |

PF, preservative-free; PC, preservative-containing; IOP, intraocular pressure; PPS, per-protocol set; FAS, full analysis set.

### Table 5. Number (%) of patients with ocular and systemic AEs (SS).

| All ocular adverse events | PF n (%) | Events | PC n (%) | Events |
|--------------------------|----------|---------|----------|---------|
| Corneal epithelial defect | 1 (1.89) | 1       | 0 (0.00) | 0       |
| Corneal abrasion          | 0 (0.00) | 0       | 1 (1.89) | 1       |
| Vitreous hemorrhage       | 1 (1.89) | 1       | 0 (0.00) | 0       |
| Total                     | 1 (1.89) | 1| 2 (3.77) | 2       |

**Systemic adverse events**

| Event                        | PF n (%) | Events | PC n (%) | Events |
|------------------------------|----------|---------|----------|---------|
| Chest pain                   | 1 (1.89) | 1       | 1 (1.89) | 1       |
| Bradycardia                  | 0 (0.00) | 0       | 1 (1.89) | 1       |
| Dry mouth                    | 1 (1.89) | 1       | 0 (0.00) | 0       |
| Gastrointestinal disorder    | 1 (1.89) | 1| 0 (0.00) | 0       |
| Toophache                    | 1 (1.89) | 1       | 0 (0.00) | 0       |
| Nasopharyngitis              | 3 (5.66) | 5| 2 (3.77) | 2       |
| Gastroenteritis              | 0 (0.00) | 0| 1 (1.89) | 1       |
| Thermal burn                 | 1 (1.89) | 1       | 0 (0.00) | 0       |
| Rotator cuff syndrome        | 0 (0.00) | 0| 2 (3.77) | 2       |
| Trigger finger               | 1 (1.89) | 1| 0 (0.00) | 0       |
| Somnolence                   | 2 (3.77) | 2* | 2* (3.77) | 2*     |
| Headache                     | 2 (3.77) | 2| 0 (0.00) | 0       |
| Dizziness                    | 1 (1.89) | 1* | 1 (1.89) | 1*     |
| Transient global amnesia     | 1 (1.89) | 1| 0 (0.00) | 0       |
| Insomnia                     | 0 (0.00) | 0| 1 (1.89) | 1       |
| Nocturia                     | 0 (0.00) | 0| 1 (1.89) | 1       |
| Uterusolthiasis              | 0 (0.00) | 0| 1 (1.89) | 1       |
| Reflux laryngitis            | 1 (1.89) | 1| 0 (0.00) | 0       |
| Total                        | 15 (28.30)| 17 | 15 (28.30)| 15    |

*Coding dictionary used MedDRA version 21.0.**

**Duplicated aggregation in the same patient**

PF, preservative-free; PC, preservative-containing; SS, safety set.
suggested a reduced prevalence of superficial punctate keratitis and less hyperemia without significant IOP changes was achieved with BAK-free travoprost in comparison with PC latanoprost during a 12-month prospective study. Rouland et al. noted similar efficacy outcomes with improved local tolerance of PF latanoprost as compared with PC latanoprost. Shedden et al. determined that PF and PC dorzolamide/timolol showed similar degrees of efficacy for changes in trough and peak IOP values and promoted generally similar tolerability levels. In our study, the efficacy was not significantly different between PF and PC BTFC, and this result was comparable with those of previous reports.

In this study, the incidence of systemic side effects was almost similarly small in both groups, which is thought to be because systemic AEs may be caused by active ingredients, not by preservatives. Local ocular AE occurred less in the PF group than in the PC group, but the difference was not statistically significant. There are several possible reasons for these results. The first was that the study cohort size was set based on the analysis of the IOP-lowering effect and may not have been large enough to observe a difference in side effects. Second, the study period was as short as 3 months so the results might be different if a longer period of time was used. Lee et al. reported that the meibomian gland dropout rate caused by glaucoma medication use had a significant correlation with medication duration and preservative status. Finally, there is a possibility that the absence of BAK does not affect the occurrence of side effects in BTFC. Murugesan et al. found that there was no significant difference in tear neuropeptide levels and central corneal/confocal corneal subbasal nerve fiber layer density between BAK-containing and BAK-free antiglaucoma therapies. However, Abegao et al. reported that switching from PC to PF ophthalmic solutions significantly improved the self-reported quality of life of glaucoma patients. To be more clearly understood, further large-scale investigations with long-term follow-up are required.

This study has several limitations that should be noted. First, the sample size may be too small in each group for an adequate safety or adverse effect evaluation to be conducted. Second, the safety follow-up period was not long enough to obtain long-term safety profile data for the drugs. This is probably due to the design which focused on the effectiveness of IOP control rather than safety. Further long-term and large-scale studies are needed. Third, patients could know the information of the investigational medication due to the open-label study design and this may have affected the safety results. However, the researchers who examined IOP amongst the study participants did not know what medications were being used. Finally, there was no objective examination for ocular surface examination including the measurement of tear film break-up time or the evaluation of the status of the cornea/junctiva with staining. Despite the shortcomings mentioned above, this study is meaningful as the first study comparing the effectiveness and safety between newly developed PF BTFC and PC BTFC ophthalmic solutions.

In conclusion, newly developed PF BTFC has demonstrated noninferiority in terms of efficacy and safety as compared with PC BTFC. We anticipated that the side effects of BAK could be reduced by using PF BTFC but the difference in this study in this regard was not clear. Further research will be needed to evaluate the AEs after using PF BTFC for a sufficiently long period of time among enough subjects.

Competing interests
There are no conflict of interest for this study.

Contributors
All listed authors contributed to the conception, design of the work, the acquisition, analysis, and interpretation of data for the work; drafted was made by JMK and All listed authors contributed to revise the draft; and finally approved this version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CYK is responsible for the overall content as a corresponding author.

Patient consent for publication
All patients were fully informed and voluntarily provided written consent before participation.

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