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CLINICAL INVESTIGATION

Comparison of different combinations of maximum medical therapy for lowering intraocular pressure in primary open angle glaucoma: 12-month retrospective consecutive case series

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Abstract

Purpose To compare the efficacy and safety of two combinations of maximum medical therapy for lowering intraocular pressure (IOP) in primary open angle glaucoma (POAG).

Study design A retrospective consecutive case series.

Methods A retrospective consecutive case series study including 82 eyes of 82 subjects with POAG treated with maximum medical therapy to lower IOP. Enrolled patients were divided into 2 groups: the triple maximum medical therapy (TMT) group, comprising POAG patients who were treated with tafluprost, brimonidine and the fixed drug combination (FDC) brinzolamide/timolol; and the double maximum medical therapy (DMT) group, comprising POAG patients who were treated with the FDCs tafluprost/timolol and brinzolamide/brimonidine. We compared the demographics, baseline IOP, IOP reduction rate, and adverse drug reactions (ADRs) between the 2 groups.

Results While the mean IOP reduction rate after 12 months was higher in the TMT group (52.7%) than in the DMT group (50.4%), the difference was not significant (p-value = 0.615). In the TMT group, the rate of proceeding to laser or surgical therapy was 22.2% (DMT group = 37.8%). In the TMT group, the time duration between beginning maximum medical therapy and proceeding to laser or surgical therapy was 10.7 ± 1.3 months (DMT group = 10.3 ± 1.5 months). No serious ADRs were reported in either group. However, the incidence rate of conjunctival hyperemia and dry eye was significantly lower in the DMT group than in the TMT group.

Conclusion DMT is safe and effective for lowering IOP in POAG patients. DMT is not inferior to TMT in POAG patients.

Keywords Maximum medical therapy · Primary open angle glaucoma · Intraocular pressure

Introduction

Elevated intraocular pressure (IOP) is a key risk factor in the development and progression of glaucomatous optic neuropathy, and the only such risk factor that is being modified therapeutically to date [1].

Pharmacological control of IOP with topical ocular hypotensive medications is the standard of care for the initial treatment of open angle glaucoma and ocular hypertension [2]. Typically, the first medical therapy in glaucoma is treatment with one medication (monotherapy) [3]. If the target IOP is not reached, another class of anti-glaucoma eye drops is added [4–7]. In some patients, a four-drug regimen, i.e., maximum medical therapy is used for lowering IOP. If patients treated with maximum medical therapy still show progressing glaucomatous optic disc damage, it is time for surgery [1]. However, many patients refuse to accept or are not candidates for surgical procedures due to surgery-related potential risks. Therefore, many patients continue maximum medical therapy for a long period of time, leading to problems related to the chronic use of medications, such as ocular surface toxicity, high costs, reduced adherence, condition persistence and reduced quality of life [8]. Therefore, it is important to identify combinations of anti-glaucoma eye drops with maximal therapeutic efficacy in reducing IOP and minimal

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adverse drug reactions (ADRs) for promoting patient convenience and adherence.

Many types of anti-glaucoma eye drops are currently available. Recently, various fixed drug combinations (FDCs) have been developed. FDCs provide multiple potential benefits compared to corresponding monotherapies, including the possibility of increased treatment adherence and reduced expo-sure to preservatives [9–11]. FDCs enable new combinations of maximum medical therapy for lowering IOP with minimum dosing in glaucoma patients.

Our clinical protocol of maximum medical therapy for lowering IOP was concomitant treatment with tafluprost, brimonidine, and a brinzolamide/timolol FDC. Two other FDCs were recently developed: tafluprost/timolol, and brinzolamide/brimonidine. We also tested these two combinations as maximum medical therapy regimens.

The purpose of this study was to compare the efficacy and safety of two different combinations of maximum medical therapy for lowering IOP in POAG.

Methods

This study was approved by the Institutional Review Board of Dong-A University (Busan, Republic of Korea). The study adhered to the tenets of the Declaration of Helsinki. We retrospectively reviewed the medical records of consecutive patients diagnosed with POAG who were treated with maximum medical therapy to lower IOP between January 2010 and November 2018 at the Dong-A University Medical Center.

Eligible patients met the following criteria: (1) POAG patients treated simultaneously with tafluprost, brimonidine, and a brinzolamide/timolol FDC; (2) POAG patients treated simultaneously with two other FDCs (tafluprost/timolol and brinzolamide/brimonidine).

The exclusion criteria were: (1) patients who were already using anti-glaucoma drugs or any other eye drops at other clinics; (2) eyes with another visually significant ocular pathology (e.g., visually significant cataracts, diabetic retinopathy, vascular occlusions, macular degeneration); (3) patients on medications (e.g., steroids, hydroxychloroquine) that could affect visual sensitivity and IOP; (4) a history of ocular surgery, including cataract operations; (5) any significant medical problems with ocular manifestations, such as diabetes, hypertension and other systemic diseases that might result in a visual field defect; (6) improper recording of the timing of IOP measurements during the follow-up period; and (7) failure to attend outpatient visits regularly and a duration of maximum medical therapy of less than 6 months.

If both eyes met the eligibility criteria, the right eye was selected for analysis. In monocular cases, the affected eye was used for analysis.

In medically uncontrolled IOP, patients underwent a laser or surgical procedure to lower IOP. The definition of medically uncontrolled IOP was an IOP of > 21 mmHg despite maximum medical therapy or requiring > 3 topical drugs for IOP control (combination drugs were counted as 2 drugs) [12].

The details of anti-glaucoma eye drops' use in our study, including the concentrations, preservatives, and manufacturer name, were as follows: (1) Tafluprost/0.0015%/benzalkonium chloride (BAK)/Taflotan® (Santen,); (2) Brimonidine/0.15%/Purite/Alphagan® P (Allergan Inc.); (3) Brinzolamide/timolol FCD/ - /BAK/Elazop® (Alcon Laboratories Inc,); (4) Tafluprost/timolol FCD/0.0015%/BAK/Tapcom®; (5) Brinzolamide/brimonidine FCD/ - /BAK/Simbrinza® (Alcon).

We divided enrolled patients into two groups: the triple maximum medical therapy (TMT) group, comprising patients who were treated with tafluprost, brimonidine, and a brinzolamide/timolol FDC; and the double maximum medical therapy (DMT) group, comprising patients who were treated with a tafluprost/timolol FDC or a brinzolamide/brimonidine FDC.

Patients receiving tafluprost or tafluprost/timolol were instructed to instill 1 drop of tafluprost or tafluprost/timolol in the eye once daily at 8 PM. Patients receiving brimonidine, a brinzolamide/timolol FDC, or a brinzolamide/brimonidine FDC were instructed to instill 1 drop of brimonidine, brinzolamide/timolol FDC, or brinzolamide/brimonidine FDC twice daily at 8 AM and 8 PM. The total numbers of anti-glaucoma eye drops instilled were 5 in the TMT group and 3 in the DMT group.

The patient demographics, baseline IOP, IOP reduction rates, central corneal thickness (CCT), mean deviation (MD) value from the visual field exam, time interval and rate of need for laser or surgical procedures and ADRs of the two groups were retrospectively analyzed.

A visual field test was performed using the automated perimetry test (Humphrey Field Analyzer, C24-2 Swedish Interactive Thresholding Algorithm [SITA] standard program, Carl-Zeiss Meditec).

Clinical signs of ADRs, such as conjunctival hyperemia, were determined using reference photographs (Contact Lens Research Unit grading scales). Another sign of ADRs, dry eye, was defined as follows: age > 20 years and mild to moderate dry eye corresponding to a dry eye severity level 1 or above, as suggested by the Delphi Panel Consensus for Dry Eye Management and the International Dry Eye Workshop (DEWS) [13, 14].

Statistical analyses were performed using SPSS (version 20.0; SPSS, Inc.). Categorical variables were investigated by

cross-tables and the chi-square test. Student's paired t-test or the Mann-Whitney U-test was used for the analysis of continuous variables. P-values less than 0.05 indicated statistical significance.

Results

During the study period, from January 2010 to November 2018, 98 patients were identified who were treated simultaneously with tafluprost, brimonidine, and a brinzolamide/timolol FDC. Fifty-three patients were excluded because of angle closure glaucoma (n = 7, 7.1%), exfoliation glaucoma (n = 6, 6.1%), neovascular glaucoma (n = 15, 15.3%), and follow-up loss (n = 25, 25.5%). The TMT group comprised 45 patients. Additionally, 72 patients who were treated simultaneously with two other FDCs (tafluprost/timolol and brinzolamide/brimonidine) were identified. Thirty-five patients were excluded because of one of the following: angle closure glaucoma (n = 6, 8.3%), exfoliation glaucoma (n = 4, 5.6%), neovascular glaucoma (n = 10, 13.9%), and follow-up loss (n = 15, 20.8%). Therefore, the DMT group comprised 37 patients.

In the TMT group, the mean age was 65.3 ± 7.2 years, and twenty-five patients (55.5%) were women. The baseline IOP was 35.3 ± 4.5 mmHg, and the baseline MD was −28.7 ± 5.5 dB. The vertical cup-to-disc ratio (CDR) was 0.89 ± 0.08, and the CCT was 540.1 ± 15.4 μm. In the DMT group, the mean age was 63.4 ± 6.9 years, and nineteen patients (51.4%) were women. The baseline IOP was 33.7 ± 5.8 mmHg, and the baseline MD was −27.9 ± 3.8 dB. The vertical CDR was 0.92 ± 0.07, and the CCT was 538.5 ± 16.8 μm (Table 1).

In the TMT group, the baseline IOP and the mean IOP at each follow-up visit are shown in Table 2. The baseline IOP was 35.3 ± 4.5 mmHg, and the mean IOP after 12 months of maximum medical therapy was 16.7 ± 2.6 mmHg. The mean IOP reduction rate after 12 months of maximum medical therapy was 52.7%, which was statistically significant.

In the DMT group, the baseline IOP and the mean IOP at each follow-up visit are shown in Table 2. The baseline IOP was 33.7 ± 5.8 mmHg, and the mean IOP after 12 months of maximum medical therapy was 16.7 ± 3.1 mmHg. The mean IOP reduction rate after 12 months of maximum medical therapy was 50.4%, which was statistically significant.

The mean IOP reduction rate after 12 months of maximum medical therapy in the TMT group was higher than that in the DMT group. However, the difference was not statistically significant (p = 0.615).

In the TMT the rate of proceeding to laser or surgical therapy was 22.2% and in the DMT groups it was 37.8%. The time duration between beginning maximum medical therapy and proceeding to the laser or surgical therapy was 10.7 ± 1.3 In the TMT, and 10.3 ± 1.5 months in the DMT group. These results were not significantly different (Table 3).

Table 1 Clinical and demographic data of the patients

Characteristics	TMT (N = 45)	DMT (N = 37)	p-value
Female, n (%)	25 (55.5%)	19 (51.4%)	0.704†
Age, yrs	65.3 ± 7.2	63.4 ± 6.9	0.100*
Baseline IOP, mmHg	35.3 ± 4.5	33.7 ± 5.8	0.237*
Baseline MD, dB	−28.7 ± 5.5	−27.9 ± 3.8	0.121*
Baseline VFI, %	11.5 ± 2.2	11.2 ± 1.7	0.643*
Vertical CDR	0.89 ± 0.08	0.92 ± 0.07	0.151*
Axial length, mm	23.4 ± 0.8	23.6 ± 0.9	0.727*
Refractive error, diopter	2.36 ± 0.15	2.47 ± 0.19	0.715*
CCT, μm	540.1 ± 15.4	538.5 ± 16.8	0.539*

Values are presented as the mean ± standard deviation unless otherwise indicated

TMT = triple maximum medical therapy; DMT = double maximum medical therapy; IOP = intraocular pressure; MD = mean deviation; PSD = pattern standard deviation; VFI = visual field index; CDR = cup-to-disc ratio; CCT = central corneal thickness; Baseline IOP = intraocular pressure before instillation of antiglaucoma eye drops

†: Chi-square test, statistical significance: $p < 0.05$

*: Paired t-test, statistical significance: $p < 0.05$

The numbers of patients who underwent laser or surgical therapy and had sustained maximum medical therapy in each group at each follow-up period (1, 3, 6, and 12 months) are presented in Table 4.

ADRs reported in each group are presented in Table 5. No serious ADRs were reported in this study. In the DMT group, conjunctival hyperemia (6 patients, 16.2%) occurred with the highest frequency, and additional ADRs were as follows: dry eye (6 patients, 16.2%), eye irritation (7 eyes, 18.9%), allergic conjunctivitis (6 eyes, 16.2%), dry mouth (4 eyes, 10.8%), blurred vision (3 eyes, 8.1%), and foreign body sensation (3 eyes, 8.1%). In the TMT group, conjunctival hyperemia (17 patients, 37.8%) occurred with the highest frequency, followed by dry eye (16 patients, 35.6%), eye irritation (10 eyes, 22.2%), allergic conjunctivitis (7 eyes, 17.8%), dry mouth (5 eyes, 11.1%), blurred vision (4 eyes, 8.9%), and foreign body sensation (4 eyes, 8.9%). The incidence rates of conjunctival hyperemia and dry eye were significantly lower in the DMT group than in the TMT group (conjunctival hyperemia, p-value = 0.031) (dry eye, p = 0.049) (Table 5).

Discussion

In this study, we found that DMT reduced IOP by 50.4% from baseline in POAG patients after 12 months. This reduction in IOP demonstrates that DMT was equal to TMT in POAG patients.

Table 2 Mean IOP and percent change in the mean IOP from baseline

	TMT group (N = 45)			DMT group (N = 37)		
	IOP	Reduction rate (%)†	p-value*	IOP	Reduction rate (%)†	p-value*
Baseline IOP, mmHg	35.3 ± 4.5	N/A	N/A	33.7 ± 5.8	N/A	N/A
1 Month‡	15.7 ± 3.1	55.5	< 0.001	16.8 ± 3.2	50.1	< 0.001
3 Months‡	16.1 ± 2.2	54.4	< 0.001	16.5 ± 2.7	51.0	< 0.001
6 Months‡	15.9 ± 2.5	55.0	< 0.001	16.3 ± 2.8	51.6	< 0.001
12 Months‡	16.7 ± 2.6	52.7	< 0.001	16.7 ± 3.1	50.4	< 0.001

Values are presented as the mean ± standard deviation unless otherwise indicated

IOP = intraocular pressure; TMT = triple maximum medical therapy; Baseline IOP = intraocular pressure before instillation of antiglaucoma eye drops; DMT = double maximum medical therapy; N/A = not applicable

*: Paired t-test, statistical significance: p<0.05, vs baseline

†: vs baseline

‡: F/U period after instillation of antiglaucoma eye drops

Table 3 Incidence rate of proceeding to laser or surgical therapy and time duration between beginning maximum medical therapy and proceeding to laser or surgical therapy

	No. (%)	p-value*	Time duration, months	p-value†
TMT (N = 45)	10 (22.2%)	0.122	10.7 ± 1.3	0.060
DMT (N = 37)	14 (37.8%)		10.3 ± 1.5	

Values are presented as the mean ± standard deviation unless otherwise indicated

TMT = triple maximum medical therapy; DMT = double maximum medical therapy

*: Chi-square test, statistical significance: p < 0.05

†: Paired t-test, statistical significance: p < 0.05

Table 4 The number of patients who underwent laser or surgical therapy and sustained maximum medical therapy

	TMT group (N = 45)		DMT group (N = 37)	
	A (accumulated value)	B	A (accumulated value)	B
1 month	1 (1)	44	1 (1)	36
3 months	1 (2)	42	1 (2)	33
6 months	2 (4)	40	3 (5)	29
12 months	6 (10)	35	9 (14)	23

TMT = triple maximum medical therapy; DMT = double maximum medical therapy

A = number of patients who underwent laser or surgical therapy

B = number of patients who sustained maximum medical therapy

Table 5 Adverse drug reactions

Adverse drug reactions	TMT group (N = 45)	DMT group (N = 37)	p-value*
Conjunctival hyperemia	17 (37.8%)	6 (16.2%)	0.031
Dry eye	16 (35.6%)	6 (16.2%)	0.049
Eye irritation	10 (22.2%)	7 (18.9%)	0.713
Allergic conjunctivitis	7 (17.8%)	6 (16.2%)	0.935
Dry mouth	5 (11.1%)	4 (10.8%)	0.965
Blurred vision	4 (8.9%)	3 (8.1%)	0.900
Foreign body sensation	4 (8.9%)	3 (8.1%)	0.900

TMT = triple maximum medical therapy; DMT = double maximum medical therapy

*: Chi-square test, statistical significance: p < 0.05

TMT consisted of 2 single-agent anti-glaucoma eye drops and 1 FDC. However, DMT consisted of 2 different FDCs. Therefore, DMT required a reduced dosing frequency compared with TMT. To the best of our knowledge, there are no clinical studies comparing different combinations of maximal medical therapy for lowering IOP. However, several studies demonstrate the efficacy and safety of FDCs compared with unfixed combinations [15–17]. Holló G et al. demonstrate that the tafluprost/timolol FDC was clinically as effective as unfixed combinations of tafluprost and timolol [15]. Inoue K et al. conducted a study on switching from concomitant therapy to the tafluprost/timolol FDC. They also demonstrate that the tafluprost/timolol FDC achieved similar IOP control to concomitant therapy with good safety and a high level of patient acceptance [16]. Previously, we conducted a study on the efficacy and safety of the brinzolamide/brimonidine FDC in normal-tension glaucoma (NTG). The results suggested that although NTG patients using unfixed brinzolamide 1% and brimonidine 0.2% switched to fixed brinzolamide 1%/brimonidine 0.2% (BBFC) because of severe ocular surface disease or poor adherence to using multiple drops, the IOP and visual field were preserved [17].

In our study, DMT reduced the IOP by 50.4% from baseline. In addition, this reduction in IOP by DMT was similar to that of TMT in POAG. We confirmed that DMT is efficacious in IOP reduction in POAG. Therefore, clinicians may consider switching from TMT to DMT in POAG patients with poor adherence because of ADRs to anti-glaucoma eye drops.

We investigated the rate of proceeding to laser or surgical therapy, as well as the time duration between beginning maximum medical therapy and proceeding to laser or surgical therapy. In our study, similar incidence rates and time intervals were observed in the DMT and TMT groups. As proceeding to laser or surgical therapy means that maximal medical therapy failed, these results suggest the efficacy of each maximal medical therapy. However, there have been no clinical studies on these outcomes. Our study suggests that DMT is not inferior to TMT regarding the rate of proceeding to laser or surgical therapy or the time duration between beginning maximum medical therapy and proceeding to laser or surgical therapy.

However, the indication for laser or surgical therapy was based only on the medically uncontrolled IOP value. Therefore, patients who had progressing glaucomatous optic nerve damage despite lowering their IOP to less than 21 mmHg were not analyzed. This could be a limitation of our study. In addition, although no statistically significant difference was found between the DMT group and the TMT group regarding the incidence rate of laser or surgical therapy, the incidence rate in the TMT group was lower than that in the DMT group. Therefore, to increase the validity of our results, further studies with larger sample sizes and longer follow-up periods are needed.

In our study, fewer ADRs occurred with DMT than TMT. The incidence rate of conjunctival hyperemia and dry eye was lower in the DMT group than in the TMT group. However, the incidence rate of other ADRs was similar in both groups. This improvement in ocular symptoms may be attributable to reduced exposure to preservatives (e.g., benzalkonium chloride, BAK). In addition, this reduction in ADRs could have been caused by improved patient adherence with the use of fewer drugs. Therefore, DMT could serve as an alternative drug regimen in patients with ADRs from using multiple anti-glaucoma eye drops.

This study has several imitations. First, the retrospective design in a tertiary care setting may have introduced a selection bias. Second, the sample size was small, and the follow-up period was short. Therefore, we believe that additional studies are needed. Third, comparative results for other prostaglandin analogues (PGAs), such as latanoprost, bimatoprost, and travoprost, were absent. Forth, control of adherence to drug use was not evaluated. Fifth, we did not evaluate differences between responders and non-responders to the two combinations of maximum medical therapy. However, little is known about various combinations in maximum medical therapy for lowering IOP in POAG, and our study confirms the clinical efficacy and safety of DMT.

In conclusion, DMT is safe and effective for lowering IOP in POAG patients. DMT is noninferior to TMT in POAG patients.

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Conflicts of interest H. J. Joh, None; S. W. Jin, None.

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