Efficacy of Brimonidine 0.2 Per Cent as Adjunctive Therapy to Beta-Blockers: A Comparative Study between POAG and CACG in Asian Eyes†

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Abstract

Objective : To compare the efficacy and safety profile of brimonidine as adjunctive therapy to beta-blockers between primary open angle glaucoma (POAG) and chronic angle closure glaucoma (CACG) in Asian eyes.

Design : Three-months, open-label, prospective study.

Participants : Twenty-three patients (35 eyes) with POAG and 25 patients (39 eyes) with CACG were enrolled in the study.

Intervention : Patients with POAG or CACG post iridectomy whose IOP was inadequately controlled with topical beta-blocker monotherapy were included. Then, brimonidine 0.2 per cent was added twice daily in both groups. Study visit occurred at weeks 2, 4, 8, and 12. Complete ophthalmic examinations were performed in all visits.

Main Outcome Measures : Efficacy was determined by reduction in IOP from baseline and tolerability was assessed by reports of adverse events.

Results : After 3 months of brimonidine adjunctive treatment, the mean (± SEM) IOP reduction were 4.37 ± 0.34 mmHg (19.4%) in POAG and 4.54 ± 0.37 mmHg (20.1%) in CACG (p= 0.741). No serious ocular or systemic adverse event was reported.

Conclusion : Brimonidine was well tolerated, efficacious and provided additive IOP reduction in POAG and CACG.

Key word : Primary Open Angle Glaucoma (POAG), Chronic Angle Closure Glaucoma (CACG), Topical Beta-Blocker, Brimonidine, Adjunctive Therapy

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Many patients with glaucoma who were treated with topical beta-blockers eventually require adjunctive therapy to adequately reduce intraocular pressure (IOP)[1-3]. Patients in need of additive agents to further lower IOP present a special challenge to physicians, since several agents currently are available. In recent years, a number of new pharmacologic agents have become available that have varying degrees of IOP lowering efficacy. One of these new ocular hypotensive agents is brimonidine tartrate, a highly sensitive alpha-2- adrenergic agonist[4-6]. Introduced in the United States in 1996, brimonidine 0.2 per cent is now available in >50 countries world wide for the lowering of IOP in patients with ocular hypertension or open angle glaucoma. Brimonidine effectively lowers IOP when used as monotherapy [7-11], or when used adjunctively with other antiglaucoma medications[12,13]. However, these previous studies demonstrated the efficacy of brimonidine in primary open angle glaucoma (POAG) and ocular hypertension. Currently, no study has shown the efficacy of brimonidine in chronic angle closure glaucoma (CACG).

In Western countries, the most common type of glaucoma is POAG, but in Asian countries, the prevalence of CACG is higher. From Siriraj Hopital, Mahidol University, Bangkok, Thailand, the investigators performed an epidemiologic study of glaucoma in the elderly (age ≥60 years) to assess the prevalence and different forms of glaucoma in Thailand. (This study was part of the Integrated-Health Research Program for the elderly supported by the National Research Council of Thailand and has been in process for publication). This epidemiologic study revealed that the prevalence of glaucoma in the elderly was 6.1 per cent which were POAG 47.6 per cent, CACG 41.4 per cent, normotension glaucoma 9.4 per cent, and secondary glaucoma 1.6 per cent. Therefore, it demonstrated that CACG is one major form of glaucoma in Asia. For the benefit of glaucoma patients in Asia, new antiglaucoma drugs should be studied for their efficacy in CACG.

This study aimed to compare the efficacy and safety profile of brimonidine as adjunctive therapy to beta-blockers between POAG and CACG in Asian eyes. This was also the preliminary study of brimonidine in CACG.

PATIENTS AND METHOD

Study design

This study was a 3 month, prospective, open-label, comparative clinical trial between POAG and CACG. The study protocol was approved by the Ethics Committee, Faculty of Medicine, Siriraj Hospital, Mahidol University, based on the declaration of Helsinki. Each patient gave written informed consent before entering the study.

Anterior chamber angle grading

A gonioscopic examination was performed at the pre-study visit by using a Goldmann or a Zeiss four-mirror gonioprism. The criteria for POAG was a wide open angle demonstrating scleral spur and or ciliary body band. The criteria for CACG were primary angle closure at least 180°, either appositional or synechial, where at least half the trabecular meshwork is blocked, some peripheral anterior synechial or synechial angle closure must be present. Evidence of glaucomatous optic neuropathy and/or visual field defect must also be present in both groups.

Patient selection

Patients were eligible for inclusion in the study if they were men or women aged >18 years with a clinical diagnosis of POAG or CACG (as described above), currently treated with topical beta-blocker monotherapy in one or both eyes, with the ability to follow study instructions and complete all required visits. All CACG had received iridectomy at least 3 months before entering the study. An uncontrolled IOP of ≥20 mmHg up to not more than 34 mmHg at baseline visit and best-corrected visual acuity of 20/400 or better were required. If the patients had been treated with dual-therapy (beta-blocker plus a second drug), the second drug should be washed out for up to 30 days. The wash out period depended on the type of drug : prostaglandin for 30 days, adrenergic agonist for 15 days, carbonic anhydrase inhibitor and pilocarpine for 5 days. IOP measurement after wash out of the second drug should be ≥20 mmHg and <34 mmHg before the study started (baseline visit). The exclusion criteria were any uncontrolled systemic diseases, contraindications to the use of brimonidine, post laser or intraocular surgery within the past 3 months, active ocular diseases, wearing contact lenses and corneal abnormalities that would prevent accurate IOP readings. Women who were pregnant, nursing or planning a pregnancy also were excluded.

Examination schedule and treatment

Possible study patients should be screened for eligibility at pre-study visit within 4 weeks prior to the study (baseline visit). If the patient had dual

therapy of IOP reducing medications (beta-blocker plus second drug), the second drug had to be completely washed out before baseline visit. Then, qualified patients were enrolled in the treatment schedule. The treatment period comprised 5 visits: baseline (visit 1), and follow-up visits in week 2 (visit 2), week 4 (visit 3), week 8 (visit 4) and week 12 (visit 5). At baseline visit, eligible patients were recommended to apply beta-blocker twice daily at 8 a.m. and 8 p.m. then apply brimonidine adjunctively to beta-blocker 15 minutes later (8.15 a.m. and 8.15 p.m. respectively). The patients were scheduled to follow-up at week 2, 4, 8 and 12. At all 5 visits, complete eye examinations were performed as follows: visual acuity, IOP measurements, slit-lamp biomicroscopy and fundoscopy. All IOP measurements were performed (using a calibrated Goldmann applanation tonometer) at 10 a.m. which were IOP at peak level. At each visit, blood pressure and heart rate were recorded and patients were queried regarding the occurrence of adverse events. The efficacy was determined by IOP reduction from baseline, tolerability was assessed by reports of adverse events. The authors used program n Query pair *t*-test for statistical analysis.

RESULTS

The study was conducted in the Department of Ophthalmology Siriraj Hospital, Mahidol University, Bangkok, Thailand. The enrolled population included 23 patients (35 eyes) with POAG and 25 patients (39 eyes) with CACG. All qualified patients were Asian. According to patient demographics (Table 1), there was no significant difference between the groups for age. In POAG: the number of males and females was nearly equal whereas, in CACG: the number of females was higher than males.

At all visits, IOP measurements were recorded at 10 am which was approximately 2 hours after applying beta-blocker and brimonidine. This was the peak effect of IOP lowering efficacy of both drugs. At the baseline visit (with beta-blocker monotherapy), the mean (±SEM) IOP in POAG and CACG were 22.5 ± 0.34 mmHg and 22.5 ± 0.27 mmHg respectively. The mean baseline IOP in both groups was nearly the same (p=0.902). The mean IOP after adding brimonidine in weeks 2, 4, 8 and 12 is shown in Table 2.

Table 1. Patient demographics.

	POAG	CACG
No. of patients	23	25
No. of eyes	35	39
Male	11	5
Female	12	20
Mean age (years ± STD*)	60.0 ± 17.2	62.6 ± 8.4

*STD = standard deviation

After 1 month of adjunctive therapy, patients achieved IOP reduction of 4.2 ± 0.34 mmHg in the POAG group and 4.9 ± 0.29 mmHg in the CACG group (p=0.741). At the 3-month visit, the mean IOP reduction was 4.37 ± 0.34 mmHg in POAG and 4.5 ± 0.37 mmHg in CACG (p=0.136) (Fig. 1). There was no statistically significant difference of IOP reduction at every visit between the two groups (p>0.005). The reduction in IOP was sustained nearly 20 per cent from week 2 to week 12 in both groups. The pattern of IOP reduction during the study period is shown in Fig. 2.

The adverse events in each group are demonstrated in Table 3. The common adverse events were oral dryness, insomnia, eye irritaton, and conjunctival follicles. No patient had corneal change or visual acuity change during the study. All patients tolerated brimonidine and completed the study. No serious drug-related adverse events were reported in either

Table 2. Mean IOP measurents (mmHg).

	POAG Mean IOP ± SEM	CACG Mean IOP ± SEM	P-value
Baseline	22.5 ± 0.37	22.5 ± 0.27	0.902
Weeks 2	18.2 ± 0.31	18.0 ± 0.40	0.622
Weeks 4	18.2 ± 0.28	17.6 ± 0.33	0.171
Weeks 8	18.4 ± 0.26	17.9 ± 0.30	0.269
Weeks 12	18.1 ± 0.23	18.0 ± 0.33	0.780

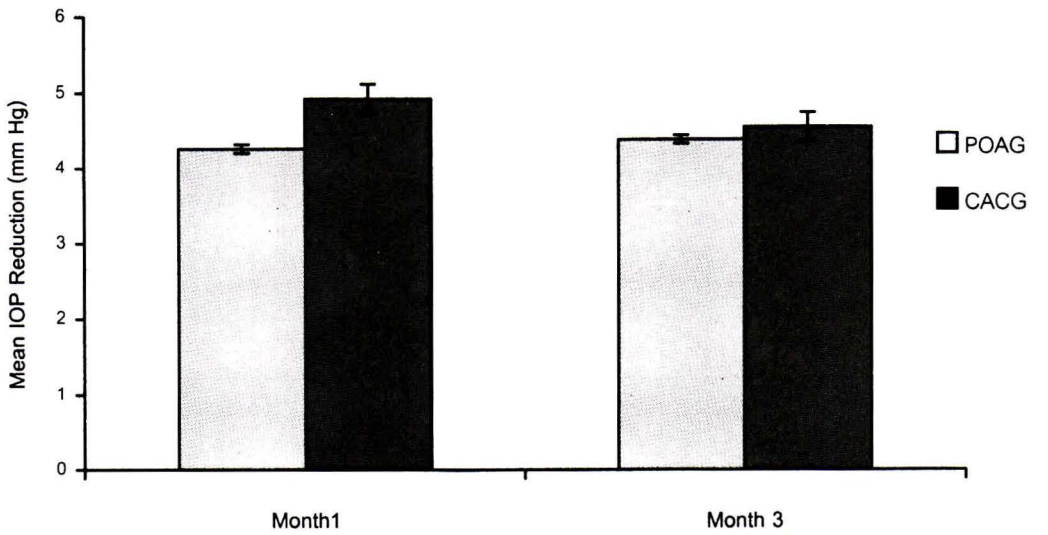

Fig. 1. Reduction in intraocular pressure (mean ± SEM) at month 1 and month 3 in primary open angle glaucoma (POAG) and chronic angle closure glaucoma (CACG).

group and no patient was discontinued during the study. No patient showed clinically relevant changes in blood pressure or heart rate during the study.

DISCUSSION

Currently, clinical evaluations have shown that brimonidine is efficacious and well tolerated as adjunctive therapy with other classes of agents, such as beta-blockers. Brimonidine 0.2 per cent b.i.d. was found to have comparable additive ocular hypotensive efficacy to that of pilocarpine 2 per cent t.i.d., when given in combination with beta-blocker therapy (12). Moreover, brimonidine 2 per cent b.i.d. was significantly more efficacious than dorzolamide 2 per cent t.i.d. when given in combination with beta-blockers(13). Other reports have suggested that brimonidine has similar efficacy as latanoprost when used as adjunctive agent(14,15). However, all of these previous studies demonstrated the efficacy of brimonidine in POAG and ocular hypertension. No clinical study has revealed the efficacy of brimonidine in CACG. This present study showed the preliminary results of brimonidine in CACG and demonstrated the efficacy of brimonidine as adjunctive therapy to beta-blockers comparable between POAG and CACG in Asian eyes.

Angle closure glaucoma is significantly more prevalent in Asian populations than in Caucasian populations(16-18). Lowe and Rich reported that the ratio of CACG to POAG could be as high as 3:1 in Asians, while in Caucasions the ratio was found to be 1:3(19). The epidemiologic study of glaucoma in Thailand revealed that the ratio of CACG to POAG was approximately 1:1. Angle closure glaucoma is characterized by partial or total obstruction to aqueous outflows resulting from the closure of the anterior chamber angle by the peripheral iris or peripheral anterior synechiae (PAS). The IOP rises rapidly in acute angle-closure glaucoma (AACG) because of a relatively sudden blockage of the trabecular meshwork by the iris. After attacks of AACG or when the chamber angle closes gradually and the IOP elevates, patients may develop CACG, in which portions of the anterior chamber angle are permanently closed by PAS and the IOP is chronically elevated to damage the optic nerve head. It is therefore important to study the efficacy of antiglaucoma medications in both POAG and CACG.

In POAG, the findings of this study are consistent with the results of a previous clinical trial(13) in which brimonidine demonstrated additive mean reduction in IOP of 5.95 mmHg (27.6%) at peak

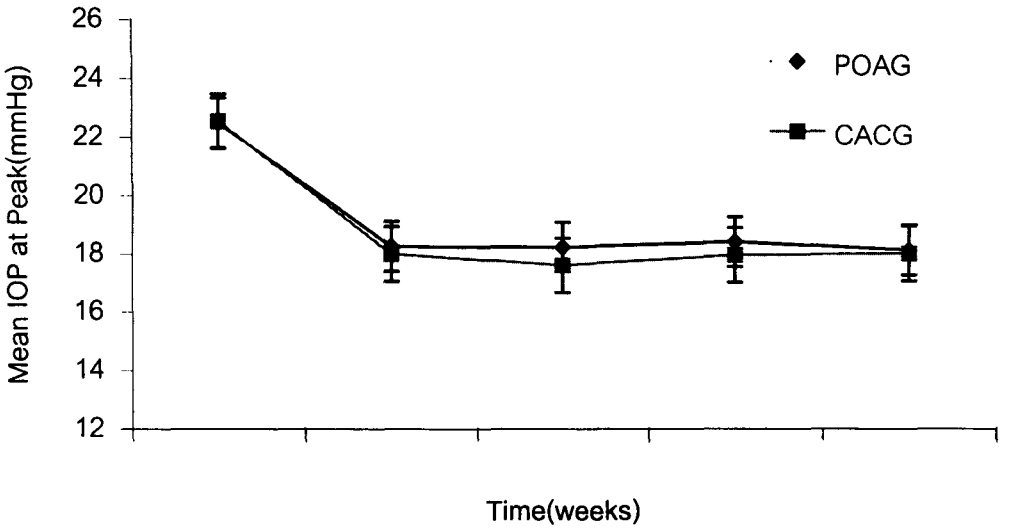

Fig. 2. Mean (± SEM) intraocular pressure at peak from baseline to month 3 in primary open angle glaucoma (POAG) and chronic angle closure glaucoma (CACG).

Table 3. Adverse events occurring during study peroid (3 months).

Adverse events	POAG n=23	%	CACG n=25	%
Oral dryness	3	13	3	12
Insomnia	4	17.4	3	12
Eye irritation	2	8.7	2	8
Conjunctival follicles	2	8.7	1	4

effect and 2.39 mmHg (13.6%) at trough effect when added to beta-blocker monotherapy. In this study, mean (± SEM) reduction in IOP at peak was 4.25 ± 0.34 mmHg (18.9%) at month 1, and 4.37 ± 0.34 mmHg (19.4%) at month 3. The present results in Asians had a little bit less IOP reduction than the results in Caucasians.

In CACG, this study showed that additive mean IOP reductions at peak were 4.92 ± 0.29 mmHg (21.8%) at month 1 and 4.54 ± 0.37 mmHg (20.1%) at month 3, which showed no statistically significant difference when compared to the results in POAG (p=0.136, and p=0.741 respectively).

The mean baseline IOP was comparable between two groups. The pattern of IOP reduction in weeks 2, 4, 8 and 12 were similar in both groups (p>0.005 in all visits). Therefore, this comparative study revealed that the additive IOP reduction of brimonidine twice daily as adjunctive therapy to beta-blockers was nearly equivalent (~ 20%) between POAG and CACG in Asian eyes. The adverse events found in this study were similar to those reported in previous studies(11,20).

SUMMARY

Brimonidine 2 per cent is a useful additive to the armamentarium for the treatment of glaucoma and it enhances the choices for the optimization of patient safety and quality of life. Brimonidine is well tolerated, efficacious and provides additive IOP reduction as adjunctive therapy in POAG and CACG. However, further study in a larger population is required.

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ประสิทธิภาพของยาหยอดบริโมนิดีน 0.2% เมื่อให้ร่วมกับยาหยอดบีต้าบล็อคเกอร์ในการรักษาผู้ป่วยต้อหินมุมเปิดและต้อหินมุมปิด†

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การศึกษาประสิทธิภาพของยาหยอดบริโมนิดีน 0.2% เมื่อให้ร่วมกับยาหยอดบีต้าบล็อคเกอร์ ในการรักษาผู้ป่วยต้อหินที่ไม่ทราบสาเหตุชนิดมุมเปิดและมุมปิด การศึกษานี้เป็นการศึกษาแบบไปข้างหน้า ในระยะเวลา 3 เดือน พบว่าผู้ป่วยต้อหินมุมเปิด 23 ราย (35 ตา) และผู้ป่วยต้อหินมุมปิด 25 ราย (39 ตา) ที่ได้รับการรักษาด้วยยาหยอดบีต้าบล็อคเกอร์แล้วไม่สามารถควบคุมความดันตาให้อยู่ในระดับที่ปกติ เมื่อได้รับยาหยอดบริโมนิดีนเพิ่มเข้าไป และตรวจวัดความดันตาเป็นระยะพบว่าที่ระยะ 3 เดือน ความดันตาผู้ป่วยต้อหินมุมเปิดและต้อหินมุมปิดลดลงจากเดิม 4.37 $\pm$ 0.34 มม. ปรอท (19.4%) และ 4.54 $\pm$ 0.37 มม. ปรอท (20.1%) ตามลำดับ ซึ่งไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ อีกทั้งไม่พบข้อแทรกซ้อนที่รุนแรงของยาในการศึกษานี้ ดังนั้นยาหยอดบริโมนิดีนจึงเป็นยาที่มีประสิทธิภาพและปลอดภัย ในการช่วยลดความดันตาในผู้ป่วยต้อหินมุมเปิดและต้อหินมุมปิด

คำสำคัญ : ต้อหินมุมเปิด, ต้อหินมุมปิด, ยาหยอดบีต้าบล็อคเกอร์, ยาหยอดบริโมนิดีน, ความดันตา

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