

# Efficacy of Combined Administration of 0.2% Brimonidine and 0.5% Betaxolol in Treatment of Primary Open Angle Glaucoma and Ocular Hypertension

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## Abstract

**Purpose:** To observe the efficacy of combined use of brimonidine and betaxolol in treatment of primary open angle glaucoma (POAG) and ocular hypertension.

**Methods:** A total of 54 patients (90 eyes) with POAG and ocular hypertension were randomly divided into three groups (receiving betaxolol, brimonidine and combined administration of betaxolol and brimonidine respectively). The administration was given twice daily in all groups (0.5% betaxolol, 0.2% brimonidine and 0.5% betaxolol combined with 0.2% brimonidine). The changes in intraocular pressure (IOP) were observed before, and 2, 4, 6, and 8 weeks after treatment. In addition, the adverse reactions were also recorded post-treatment.

**Results:** The mean IOPs at all the time points after treatment were significantly reduced compared with pre-treatment levels ( $P < 0.05$ ). Patients receiving brimonidine had a greater reduction in IOP compared with their counterparts in the betaxolol group but the difference was not statistically significant. The IOP decline was significantly higher in the combined therapy group than in the other two groups ( $P < 0.01$ ). Few cases presented with slight discomfort, such as sensation of foreign bodies, ocular irritation, dizziness, headache, fatigue, and dryness of mouth and nose. No severe adverse reactions were noted following administration.

**Conclusion:** Combined use of brimonidine and betaxolol is an efficacious treatment of reducing IOP without severe side effects. (*Eye Science* 2013; 28:190-194)

**Keywords:** primary open angle glaucoma; brimonidine; betaxolol; combined therapy

Intraocular pressure (IOP) is one of the major risk factors resulting in the incidence and progression of glaucoma and is the only risk factor that can be properly controlled<sup>1,2</sup>. Hence, the success of glaucoma treatment mainly relies upon IOP control new types of IOP-reducing agents have been applied in clinical settings. For example, the use of a selective  $\alpha_2$ -adrenoceptor agonist is highly recognized by patients due to its favorable IOP-reducing effects. This is especially the case with brimonidine (0.2% brimonidine tartrate), which has the following characteristics: 1. It has a selectivity for  $\alpha_2$ -adrenoceptor agonist 20 to 30 times higher than apraclonidine. Pupillary dilation and vasoconstrictor action of bulbar conjunctiva are seldom observed. It exerts almost no effect upon systematic vascular and respiration systems. 2. It plays a role in reducing IOP via two underlying mechanisms: decreasing the production of aqueous humor and promoting the outflow of aqueous humor through the uveoscleral pathway. 3. Administration of therapeutic doses of brimonidine eye drops exerts a neuroprotective effect on glaucoma<sup>3-8</sup>.

Betaxolol is a selective  $\beta_1$  adrenoceptor blocker

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that has the following characteristics: 1. It has a relative selectivity for the  $\beta_1$  receptor (heart) and relatively weak blocking activity for the  $\beta_2$  receptor. It exhibits almost no topical anesthesia effect. 2. It does not induce arterial vascular contraction. It can block calcium ion-induced vasoconstriction to reduce IOP and improve blood supply in the eyes. 3. Recent studies reveal that betaxolol can block the calcium ion channel located on the ganglion cell membrane and exhibit a protective effect on optic nerves. 4. It avoids the side effects caused by non-selective  $\beta$  receptor blockers and seldom affects the cardiovascular system<sup>9,10</sup>. Previous findings indicate that single use of brimonidine or combined administration of brimonidine and a  $\beta$ -receptor blocker can both effectively reduce IOP. This study was designed to observe the efficacy and safety of the combined use of brimonidine and betaxolol eye drops in reducing IOP.

## Subjects and methods

### Study subjects

**Study subjects:** A total of 54 patients (90 eyes) diagnosed with POAG and ocular hypertension were enrolled in this study. All participants were randomly assigned into three groups (betaxolol, brimonidine, and combined therapy groups). The eyes of patients with bilateral high IOP were included in the same group.

**Inclusion criteria:** The subjects diagnosed with POAG and ocular hypertension with an IOP ranging from 22 and 34 mmHg (1 mmHg= 0.133 kPa); normal cornea observed under slit-lamp microscope; corrected visual acuity of the selected eye > 0.3; either sex; age ranging from 18 and 70 years; willing to comply with clinical protocols.

**Exclusion criteria:** The subjects with any eye diseases affecting the reliability of this clinical test; those undergoing intraocular or laser surgery in the previous three months; corneal lesions affecting the measurement of IOP; those wearing corneal contact lens; allergic to any ingredient contained in the drugs; asthma or bradycardia (the resting heart rate of under 60 beats per minute); pregnant and lactating women with severe heart, lung, liver and renal function barriers; those receiving systemic or topical

medication affecting the efficacy evaluation (other IOP-reducing agents and adrenal corticosteroids). The subjects could withdraw from the test if they had poor IOP control, poor compliance, or their own willingness.

### Methods

**Drug administration:** In the betaxolol group, 0.5% betaxolol (Alcon, America) was administered twice daily, one drop per each time; 0.2% brimonidine was given in the brimonidine group (Alcon, America), twice per day, one drop per each administration. In the combined therapy group, one drop of betaxolol was administered and then brimonidine was given 5 minutes later, twice daily for 8 weeks.

#### Treatment methods and observation indexes

The history of illnesses, ocular symptoms and physical signs were recorded during the screening period. IOP measurement was conducted by Goldmann applanation tonometer three times, and the mean value was obtained. The corrected distance visual acuity was measured. Fundus examination was performed by a direct ophthalmoscope. The anterior segment and lens were observed by slit-lamp microscopy. After screening procedures, medication therapy was initiated. Re-examination was conducted at 2, 4, 6, and 8 weeks ( $\pm 1$  d) after treatment, at 9 $\pm$ 1 a.m. The examined indexes included IOP, visual acuity, anterior segment and fundus examination, subjective symptoms and objective physical signs, combined medication, and adverse events. All indexes were observed by physicians.

### Statistical analysis

SPSS 10.0 software was utilized for data analysis. All factors were analyzed using single-factorial ANOVA.  $P < 0.05$  was considered as statistical significance.

## Results

### General clinical information

Fifty four patients (90 eyes), aged 46 years on average, 29 males and 25 females, participated in this study. Eighteen (29 eyes) were allocated to the betaxolol group, 18 (31 eyes) to the brimonidine group, and 18 (30 eyes) to the combined therapy group. No statistical significance was noted among three groups in terms of age, sex composition, and

**Table 1** General clinical information

Group	No. of cases( <i>n</i> )	Gender( <i>n</i> )		Age(year)	Diagnosis( <i>n</i> )	
		Male	Female		POAG	Hypertension
Betaxolol	18	11	7	48±18	13	5
Brimonidine	18	9	9	44±13	12	6
Combined administration	18	9	9	46±15	14	4

other general information (Table 1).

### Treatment efficacy

Patients in all three groups had a significant decrease in IOP at 2, 4, 6, and 8 weeks post-treatment ( $P<0.05$ ). In the betaxolol group, the mean IOP declined from (24.07±2.54) to (18.96±2.31) mmHg after medication therapy, with a decrease rate from 13.8% to 21.2%. In the brimonidine group, IOP decreased from (24.09±4.21) to (17.95±2.74) mmHg with a

decrease rate from 19.8% to 25.5% and dropped from (24.69±2.68) to (16.50±3.24) mmHg with a decrease rate from 22.2% to 33.2% in the combined therapy group, as shown in Tables 2 and 3. The IOP-reduction efficacy and reduction rate were significantly higher in the combined therapy group than in the betaxolol or brimonidine group, suggesting that combined therapy is superior to single use of betaxolol or brimonidine regarding IOP reduction.

**Table 2** IOP-reducing effects before and after administration

Time of administration	Betaxolol	Brimonidine	Combined administration
Before administration	24.07±2.54	24.09±4.21	24.69±2.68
2 weeks after administration	20.76±3.34	19.32±3.56	19.20±2.67
4 weeks after administration	19.86±2.78	18.41±2.56	17.73±2.98
6 weeks after administration	19.27±2.50	18.20±2.84	17.20±3.25
8 weeks after administration	18.96±2.31	17.95±2.74	16.50±3.24

**Table 3** Comparison of mean IOP reduction among three groups (%)

Time of administration	Betaxolol	Brimonidine	Combined administration
2 weeks after administration	13.8	19.8	22.2
4 weeks after administration	17.5	23.6	28.2
6 weeks after administration	19.9	24.4	30.3
8 weeks after administration	21.2	25.5	33.2

### Safety evaluation

Following medication treatment, only three patients presented with the sensation of ocular foreign bodies and irritation (1 in the brimonidine group and 2 in the combined therapy group), two cases had dizziness, headache, fatigue and dryness of the mouth and nose (each in the brimonidine and combined therapy groups), which did not interrupt drug administration. No apparent changes were noted in visual acuity, anterior segment, and ocular fundus. No significant abnormalities were observed in iris color. Topical adverse reactions were alleviated by effective treatments. No participants withdrew from this investigation due to local adverse events. No systemic adverse reactions were found. No statistical

significance was found among patients from three groups.

### Discussion

Commonly used IOP-reducing eye drops include  $\beta$ -receptor blocker, adrenoceptor agonist, miotic, carbonic anhydrase inhibitor, prostaglandin derivatives and hyperosmotic agents, *etc.*<sup>11,12</sup>. In the mid-1960s, an  $\alpha$ -adrenoceptor agonist was first applied in ophthalmic studies. The topical administration of clonidine HCl has been confirmed to reduce IOP with a reduction rate of 20-30%. However, this drug also induces severe side effects, such as dryness of nose, dizziness, *etc.*, which constrains its scope of clinical application<sup>13</sup>. Much attention has been paid

therefore to decreasing the side effects induced by  $\alpha$ -receptor agonist. Apraclonidine, an amido derivative of clonidine, has a low lipid solubility, thereby exerting no effect on blood pressure. However, a variety of adverse effects such as pupillary dilation, conjunctival edema, and sensation of foreign bodies, have prevented the long-term application of apraclonidine<sup>14</sup>. Brimonidine, as a new-generation  $\alpha$ 2-adrenoceptor agonist, has a high selectivity for the  $\alpha$ 2-adrenergic receptor and can effectively lower IOP through an underlying mechanism whereby it selectively binds with the  $\alpha$ 2-adrenergic receptor on the cell membrane, alters the biological characteristics of cells via the second messenger of receptor-G-protein-mediated signal transduction, decreases the production of aqueous humor, and increases the outflow of aqueous humor. Additionally, it can also reduce the resistance against the outflow of aqueous humor by increasing uveoscleral outflow. Experts have indicated that 0.2% brimonidine is efficacious in reducing IOP, and induces only slight adverse effects almost without any harm to cardiovascular function. In addition, it potentially exerts a protective effect on the optic nerves. Previous studies have indicated that brimonidine is efficacious in reducing IOP of patients with POAG and ocular hypertension and yields few adverse reactions<sup>3-8</sup>, making it now widely utilized as an anti-glaucoma agent. This present study also concludes that brimonidine has a high efficacy for lowering IOP, with slight adverse effects noted in a few patients.

Betaxolol, as a selective  $\beta$ 1-receptor blocker, not only effectively reduces IOP, but it also significantly increases the blood flow in the fundus and protects retinal ganglion cells<sup>15,16</sup>. Compared with timolol, betaxolol has a slightly lower efficacy in reducing IOP<sup>17</sup>, but it induce fewer adverse effects and is more suitable for patients with cardiovascular illnesses who cannot tolerate timolol. This clinical trial compares the IOP-reduction efficacy between betaxolol and brimonidine and indicates that betaxolol has a slightly lower efficacy than brimonidine in terms of IOP reduction after 8 weeks of administration (21.2% vs. 25.5%), whereas betaxolol has a high tolerability and induces no systemic adverse reactions.

Scholars have verified that combined application of brimonidine and timolol can reduce IOP in a significant and stable manner<sup>18</sup>. Topical administration of betaxolol can increase the blood flow in central retinal artery and posterior ciliary artery while reducing IOP, improving the nutritional status of the optic nerves, and yielding few systemic adverse events. Consequently, 0.2% brimonidine combined with 0.5% betaxolol was employed to treat POAG and ocular hypertension for two months. Clinical outcomes revealed that combined administration of brimonidine and betaxolol twice daily can reduce IOP in a significant and stable pattern. The IOP-reduction rate achieved up to 33.2% at 8-week following medication treatment. The IOP-reducing efficacy of combined use of brimonidine and betaxolol is significantly higher compared with brimonidine (25.5%) or betaxolol (21.2%) alone. Another advantage of combined therapy is the few adverse effects. During the whole observation period, only slight symptoms, such as sensation of ocular foreign bodies, ocular irritation, dizziness, headache, fatigue and dryness of mouth and nose, and conjunctival hyperemia, were noted. These adverse reactions did not lead to discontinuation of the treatment.

However, the duration of this clinical trial was only two months. The long-term efficacy and safety of combined use of 0.2% brimonidine and 0.5% betaxolol remain to be further elucidated.

To sum up, combined administration of 0.2% brimonidine and 0.5% betaxolol twice per day can effectively reduce IOP in patients with POAG and ocular hypertension and causes no severe topical or systemic adverse events.

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