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ORIGINAL ARTICLE

Effect of brimonidine on anterior-chamber angle in patients with narrow angles

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ABSTRACT

Objective

This study investigated the effect of brimonidine on the anterior-chamber angle in eyes with narrow angles using noncontact three-dimensional anterior-segment analyzer Pentacam.

Methods

Nine eyes with narrow angles were distributed to one of three treatment groups—single topical dose of 0.15% brimonidine tartrate, 0.5% timolol maleate (positive control), or balanced salt solution (negative control)—in a prospective, single-masked, crossover, comparative trial. The primary outcome measure was anterior-chamber angle at baseline, and 2 and 4 hours after instillation of the treatment drug. Secondary outcome measures were pupil diameter, intraocular pressure (IOP), and anterior-chamber depth and volume. After a two-week washout period, eyes were crossed over to the other treatment modes. All baseline and posttreatment measurements were taken. Repeated analysis of variance (ANOVA) was used for statistical analysis.

Results

Anterior-chamber angle, depth, and volume did not differ significantly for all treatment groups. Brimonidine caused a significant decrease in pupil diameter, most notably 2 hours after instillation, from baseline of 2.36 ± 0.37 mm to 2.17 ± 0.35 mm. ($p = 0.03$). There was a significant decrease in IOP from baseline to hour 4 after treatment for both brimonidine (11.4 ± 2.2 to 9 ± 1.8 mm Hg, $p < 0.001$) and timolol (11.9 ± 2.3 to 9.4 ± 2.1 mm Hg, $p = 0.003$).

Conclusion

Brimonidine produced a miotic trend with no significant opening of the anterior-chamber angle in patients with narrow angles.

Keywords: *Brimonidine, Narrow angles, Anterior-chamber angle, Miosis, Intraocular pressure*

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Brimonidine (Alphagan-P 0.15%, Allergan, Irvine, CA, USA) is an antiglaucoma medication believed to work by decreasing aqueous-humor production and facilitating uveoscleral outflow. It is a highly selective α2 adrenergic agonist with a "miotic effect." It exhibits inhibitory mechanism on α1 receptors, thereby modulating noradrenaline release. It inhibits the release of norepinephrine from the sympathetic terminals, and norepinephrine-mediated contraction of dilator muscle through α1 receptor is decreased, thereby inhibiting mydriasis. Thus, miosis is thought to be "passive."[1-2] Several studies have shown that there is no effect on accommodation and anterior-chamber depth.[1, 3]

Recently, brimonidine has been used as an adjunctive therapy for patients suffering from glares and halos, to reduce visual aberrations after refractive surgery. The passive miosis effect is more pronounced in scotopic conditions, since norepinephrine is the main mediator of nocturnal pupil dilatation, when unopposed by the acetylcholine-mediated sphincter muscles.[2]

It has been postulated that since brimonidine has a "miotic" effect, it should have an effect on the opening of anterior-chamber angles. This can be studied using the Pentacam (Oculus Inc., Heidelberg, Germany), which gives cross-sectional images of the anterior-chamber angle and depth, and provides quantitative information regarding the pupil and anterior-chamber volume. Moreover, it has been validated to have similar results with the Anterior Segment-Optical Coherence Tomography (AS-OCT).[4]

This study described the effect of brimonidine on anterior-chamber angle, depth and volume, and pupil diameter among patients with narrow angles using the Pentacam.

METHODOLOGY

Nine eyes of 9 patients, 20 years old and above, with gonioscopically proven narrow angles were included in this prospective, single-masked, crossover, comparative trial conducted from June to September 2010. Narrow angle is defined as not visible or barely visible posterior trabecular meshwork (PTM) for at least 180 degrees on nonindentation gonioscopy with the eye in primary position.[5]

Patients on systemic or topical medication affecting pupil reaction and those with known ocular disease (including glaucoma), peripheral anterior synechiae, previous intraocular surgery (including cataract surgery), systemic condition affecting pupil reaction (e.g. diabetes mellitus, cardiovascular/pulmonary disorders), and allergy to brimonidine or timolol were excluded.

The study adhered to the Declaration of Helsinki. Informed consent was obtained from all participants.

Participants were distributed to either one of three groups: brimonidine, balanced salt solution (BSS) (Alcon, Forth Worth, Texas), or timolol (Celsus, Philippines). One eye was randomly chosen to undergo the Pentacam study. Baseline Pentacam measurements of the anterior-chamber angle, depth and volume, and pupil diameter were taken using the scheimpflug camera after 1 minute of dark adaptation. The nasal and temporal anterior-chamber angles were measured since these were more accessible and less prone to eyelid manipulation. Three measurements were taken by a single operator. A cut-off value of 29.5 degrees was set to discriminate between narrow and open angles, as prescribed in a validation study by Hong et al.[4]

Two measurements of baseline intraocular pressure (IOP) were taken by a single operator with the Goldmann applanation tonometer.

A single dose of the chosen drug was instilled into the chosen eye with punctal occlusion. Repeat measurements of all the parameters were taken after 2 and 4 hours.

After a washout interval of 2 weeks, the patients were crossed over to the other treatment interventions, and baseline and outcome measurements were repeated. The mean of 3 measurements for the Pentacam parameters and the mean of two measurements for the IOP were taken as the readings for a particular time point.

The primary outcome measure was the anterior-chamber angle while the secondary outcome measures were anterior-chamber depth and volume, pupil diameter, and IOP.

Data were analyzed using repeated analysis of variance (ANOVA) and a p value of 0.05 or less was considered significant.

RESULT

Nine patients, all females with mean age of 61 (range, 42 to 83), were included but one did not return for the crossover treatment. There were five right and four left eyes.

The mean nasal anterior-chamber angle at baseline, hour 2, and hour 4 for brimonidine, timolol, and BSS are shown in Table 1. The mean temporal anterior-chamber angle at baseline, hour 2, and hour 4 for brimonidine, timolol, and BSS are shown in Table 2. There were no differences in the anterior-chamber-angle measurements at hours 2 and 4 from baseline across all treatment groups. Likewise, there were no differences in the anterior-chamber angle measurements between brimonidine and timolol (nasal, $p = 0.15$; temporal, $p = 0.63$) and between brimonidine and BSS (nasal, $p = 0.46$; temporal, $p = 0.29$).

There was a 20% decrease in IOP from baseline to hour 4 in the brimonidine group and 21% in the timolol

group (Table 3). Between the 2 groups, the decrease in IOP was similar (p = 0.62). There was no change in the IOP in the BSS group.

There was an 8% decrease in pupil diameter in the brimonidine group at hour 2 (p = 0.03) (Table 4). There was no change in the mean pupil diameter for timolol or for BSS. There was significant miosis in the brimonidine group compared to timolol (p = 0.03) and BSS (p = 0.01).

The mean anterior-chamber depth were similar at baseline, hour 2, and hour 4 for brimonidine, timolol, and BSS (Table 5). It was also similar between brimonidine and timolol (p = 0.74) and between brimonidine and BSS (p = 0.49).

The mean anterior-chamber volume were similar at baseline, hour 2, and hour 4 for brimonidine, timolol, and BSS (Table 6). It was similar between brimonidine and timolol (p = 0.21) and between brimonidine and BSS (p = 0.32).

DISCUSSION

The mean anterior-chamber-angle measurements at baseline were between 22 and 25 degrees. They did not change significantly in the 3 treatment groups at hour 2 and 4.

The miotic effect of brimonidine tartrate 0.15% was observed in all subjects under mesopic conditions after instillation of the drug. This was significant at hour 2 compared with baseline (p = 0.03) and when compared to timolol (p = 0.03) and BSS (p = 0.01). However, no concurrent anterior-chamber-angle opening was observed.

Previous studies have demonstrated that brimonidine 0.15% and 0.20% cause pupil miosis that was greater in scotopic conditions. Miosis was shown to be maximum at 4 hours and lasted for 8 to 12 hours.[2-3] This study showed that miosis peaked and lasted for only 2 hours. The decrease in pupil diameter was 0.2 mm, way below the 1.4 mm observed in some

Table 1. **Within-group comparison of mean nasal anterior-chamber angle (degrees).**

Time	Brimonidine n = 9	p^1	Timolol n = 8	p^1	BSS n = 8	p^1
Baseline	22.01 ± 7.0	-	23.55 ± 5.5	-	22.61 ± 7.5	-
Hour 2	22.19 ± 5.6	0.79	22.94 ± 7.6	0.59	22.33 ± 6.6	0.16
Hour 4	22.00 ± 6.8	0.98	23.15 ± 5.7	0.56	22.01 ± 7.6	0.30

[1]Repeated ANOVA comparing the different time points to baseline.

Table 2. **Within-group comparison of mean temporal anterior-chamber angle (degrees).**

Time	Brimonidine n = 9	p^1	Timolol n = 8	p^1	BSS n = 8	p^1
Baseline	24.48 ± 5.0	-	25.08 ± 4.8	-	24.98 ± 5.8	-
Hour 2	25.11 ± 5.0	0.27	25.00 ± 5.6	0.92	23.99 ± 4.7	0.30
Hour 4	24.97 ± 5.4	0.43	24.46 ± 4.9	0.50	24.81 ± 5.1	0.88

[1]Repeated ANOVA comparing the different time points to baseline.

Table 3. **Within-group comparison of mean intraocular pressure (mm Hg).**

Time	Brimonidine n = 9	p^1	Timolol n = 8	p^1	BSS n = 8	p^1
Baseline	12.3 ± 3.6	-	11.9 ± 2.3	-	13 ± 1.7	-
Hour 2	10.3 ± 3.2	0.000	9.8 ± 2.2	0.002	13 ± 2.1	1.000
Hour 4	9.8 ± 2.9	0.000	9.4 ± 2.1	0.003	13 ± 1.6	1.000

[1]Repeated ANOVA comparing the different time points to baseline.

Table 4. **Within-group comparison of mean pupil diameter (mm).**

Time	Brimonidine n = 9	p^1	Timolol n = 8	p^1	BSS n = 8	p^1
Baseline	2.36 ± 0.37	-	2.36 ± 0.41	-	2.45 ± 0.27	-
Hour 2	2.17 ± 0.35	0.03	2.46 ± 0.33	0.19	2.39 ± 0.29	0.19
Hour 4	2.27 ± 0.57	0.68	2.48 ± 0.40	0.29	2.49 ± 0.40	0.29

[1]Repeated ANOVA comparing the different time points to baseline.

Table 5. **Mean anterior-chamber depth across treatment groups (mm).**

Time	Brimonidine n = 9	Timolol n = 8	p^1	BSS n = 8	p^2
Baseline	1.80 ± 0.45	1.77 ± 0.43		1.80 ± 0.44	
Hour 2	1.79 ± 0.45	1.80 ± 0.45	0.74	1.79 ± 0.43	0.49
Hour 4	1.76 ± 0.47	1.80 ± 0.44		1.81 ± 0.44	

[1]Repeated ANOVA comparing brimonidine vs. timolol.
[2]Repeated ANOVA comparing brimonidine vs. BSS.

Table 6. **Mean anterior-chamber volume across treatment groups (mm^3).**

Time	Brimonidine n = 9	Timolol n = 8	p^1	BSS n = 8	p^2
Baseline	69.6 ± 23.3	70.0 ± 22.1		70.1 ± 20.7	
Hour 2	67.5 ± 21.1	70.2 ± 22.0	0.21	68.9 ± 20.6	0.32
Hour 4	68.3 ± 20.3	70.2 ± 23.9		69.4 ± 19.8	

[1]Repeated ANOVA comparing brimonidine vs. timolol.
[2]Repeated ANOVA comparing brimonidine vs. BSS.

studies.[1] Definite miosis has been shown to occur in photopic, mesopic, and scotopic conditions.[6-7] Even under mesopic conditions, at least 1 mm of miosis was seen in almost all subjects in one study and the effect was stronger in eyes with light irides.[6]

Using the ultrasound biomicroscope (UBM), Lo Presti et al. demonstrated concurrent anterior-chamber-angle opening (3 degrees) 1 hour after brimonidine instillation in patients with open angles.[1] In contrast, Marchini et al. did not find significant angle opening.[3]

This study determined the effect of brimonidine on anterior-chamber angles in patients with narrow angles, which could explain the difference in the degree of miosis observed compared to other studies. Moreover, the instrument used to measure the different parameters was also different.

This study is limited by the small sample size. A larger sample size would make the power of the observations stronger and more conclusive.

In conclusion, there was a trend in brimonidine producing a miotic effect with no significant opening of the anterior chamber angle in patients with narrow angles.

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