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LABORATORY INVESTIGATION

Comparing Brimonidine 0.2% to Apraclonidine 1.0% in the Prevention of Intraocular Pressure Elevation and Their Pupillary Effects Following Laser Peripheral Iridotomy

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Abstract

Purpose: To compare the effects of brimonidine 0.2% and apraclonidine 1% on intraocular pressure (IOP) and pupil size in patients undergoing laser peripheral iridotomy (LPI).

Methods: Forty patients (40 eyes) with occludable angle or angle-closure glaucoma requiring LPI were recruited. Patients were randomized to receive either brimonidine 0.2% or apraclonidine 1% before and after LPI. The IOPs were measured at 1, 2 and 3 h after LPI, and pupil size was measured before and at 45 min after eyedrop instillation. Both parameters were analyzed using the *t* test.

Results: There were 20 patients in each group. The baseline IOP was 17.1 ± 3.2 mmHg for the brimonidine group and 16.7 ± 2.8 mmHg for the apraclonidine group ($P = 0.67$) (*t* test). The mean IOP 3 h after laser treatment was 18.2 ± 7.8 mmHg for the brimonidine group and 15.7 ± 5.6 mmHg for the apraclonidine group ($P = 0.25$) (*t* test). There was no statistically significant difference between the two groups in the mean IOP changes at 1, 2, or 3 h after LPI. The mean change in pupil size after brimonidine was −0.33 ± 0.37 mm and after apraclonidine was +0.90 ± 0.87 mm. The difference was significant ($P < 0.001$).

Conclusion: Brimonidine 0.2% was found to have an efficacy comparable to that of apraclonidine 1.0% in preventing post LPI IOP spikes. Apraclonidine 1.0% tends to have a pupil dilating effect while brimonidine 0.2% tends to constrict the pupil. **Jpn J Ophthalmol** 2005;49:89–92 © Japanese Ophthalmological Society 2005

Key Words: apraclonidine, brimonidine, intraocular pressure, laser peripheral iridotomy, pupil

Introduction

Laser peripheral iridotomy (LPI) is one of the most commonly performed laser procedures in glaucoma patients in our region. It is indicated in patients with occludable angle to prevent acute angle-closure attack from pupillary block. It may help to prevent closure of the remaining open angle in chronic angle-closure glaucoma. However, postoperative intraocular pressure (IOP) elevation has been reported after this laser procedure.[1]

Apraclonidine 1% (Iopidine, Alcon Laboratories, Fort Worth, TX, USA), an α-adrenoceptor agonist, has been used in the prevention of IOP spike after various laser procedures.[2,3] However, its undesirable pharmacological pupil dilatation effect makes the iris lax and thick, which is not desirable for LPI.[4] Pilocarpine has been used to counteract apraclonidine's mydriatic effect, to keep the pupil constricted and iris taut for LPI.[5] However, the addition of pilocarpine is not without risk and may cause anterior shift of the iris–lens diaphragm and precipitate pupillary block.

Brimonidine tartrate 0.2% (Alphagan, Allergan, Irvine, CA, USA), a highly selective α_2-agonist, is 23 to 32 times

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more selective than apraclonidine.[6,7] It has been studied widely for its effect on aqueous humour dynamics and IOP.[8,9] It reduces IOP by reducing aqueous production and increasing uveoscleral outflow.[10] However, the uveoscleral outflow effect occurs only with prolonged treatment. Thus, a single drop of brimonidine has a pharmacological effect similar to that of apraclonidine.

Brimonidine has also been reported to have a miotic effect in both in vivo and in vitro studies, without associated refractive or visual acuity change.[11,12] An ultrasound biomicroscopy study has shown that the miotic effect is not associated with alteration of the thickness and position of the human lens and does not precipitate pupillary block.[13] Brimonidine decreases the iris thickness with an increase in the posterior chamber depth and iris ciliary process distance with no change in the anterior chamber depth or chamber angle width.[14] Theoretically, the pharmacological effect of brimonidine on the iris may facilitate LPI. Brimonidine has been shown to be effective in controlling IOP spikes after various anterior segment laser procedures.[15–20]

However, owing to the higher lipophilicity of brimonidine compared with apraclonidine, studies have shown a decrease in systolic blood pressure and heart rate after 21 days of continued use of the 0.5% preparation; the 0.2% preparation, however, has only a minimal effect on the cardiovascular and central nervous system.[21] Brimonidine 0.2% may be considered safer than the 0.5% preparation in patients who require LPI.

In this study, we compared brimonidine 0.2% with apraclonidine 1% in the control of post-LPI IOP spikes and their pupillary effect in a prospective, randomized, double-masked clinical trial.

Patients and Methods

This was a prospective, randomized, double-masked clinical trial. Patients older than 21 years of age with either occludable angle on gonioscopy (defined as one in which the trabecular meshwork was visible for less than 90° of angle circumference) who were susceptible to acute angle-closure attack, or who had already developed primary angle-closure glaucoma, were recruited for LPI.

Exclusion criteria specified patients with (1) previous intraocular surgery; (2) abnormal pupil reaction; (3) studied eye being the only eye, that is, fellow eye's visual acuity <0.05; (4) studied eye's visual acuity <0.1 or advanced glaucoma field loss; (5) active ocular inflammation or infection; or (6) current use of medications that might affect pupil size. Approval of the study was obtained from the Tung Wah Eastern Hospital Research and Ethics Committee, and informed written consent was obtained from all participants. Patients on pilocarpine eyedrops were asked to discontinue the drug 5 days before the laser procedure. Patients on pilocarpine for more than 3 months were excluded because their pupils might remain constricted even after stopping the pilocarpine.

On the day of the laser procedure, baseline measurements of IOP by Goldmann applanation (average of three measurements) were recorded. Pupil size was measured in a standard dim room light setting with a designated millimeter caliper and patient fixating at a distant target. Patients were assigned to receive either brimonidine 0.2% or apraclonidine 1% in a randomized, double-masked fashion. An optometrist research assistant gave the appropriate medication, one drop, 45 min before and then immediately after LPI. The patients and the surgeons were masked as to the medications used. The pupil size was measured 45 min after instillation of the eyedrops and just before the laser procedure. The IOP was measured again after laser treatment. The LPI was performed by either of the two author ophthalmologists (SYY or SPH). An argon laser (coherent laser system or the Hgm multiwavelength system) with spot size 50 to 75 μm, exposure time of 0.1 s, and power of 400 to 800 mW with the Abraham iridotomy lens was used. A neodymium:yttrium-aluminium-garnet (Nd:YAG) laser (Carl Zeiss, Oberkochen, Germany), with YAG Abraham lens was added if the argon laser failed to create a full-thickness iridotomy. IOP was then measured at 1, 2, and 3 h after the laser procedure. The IOP changes were analyzed with the independent-sample t test. The change in pupil size after instillation of the eyedrops and before the laser procedure was also compared between the two groups.

Results

Forty Chinese patients (40 eyes) were enrolled in the study. There were 20 eyes in each group. The mean age was 72.1 ± 11.0 years for the brimonidine group and 69.6 ± 10.7 years for the apraclonidine group ($P = 0.47$, t test). There were 17 women and 3 men in the brimonidine group and 15 women and 5 men in the apraclonidine group ($P = 0.36$, χ-squared test). The demographics of these 40 study patients are listed in Table 1. There were six patients in each group using pilocarpine before the laser procedure. The baseline IOP was 17.1 ± 3.2 mmHg for the brimonidine group and 16.7 ± 2.8 mmHg for the apraclonidine group ($P = 0.67$, t test). The argon laser energy used was 3.3 ± 3.0 J for the brimonidine group and 3.6 ± 2.0 J for the apraclonidine group ($P = 0.64$). The Nd:YAG laser energy was 6.9 ± 4.7 J in the brimonidine group and 7.5 ± 6.5 J in the apraclonidine group ($P = 0.74$). The mean IOP changes at 1, 2, and 3 h after LPI were +2.6 ± 5.2, +2.1 ± 6.5, and +1.0 ± 6.6 mmHg in the brimonidine group and +1.6 ± 3.7, +0.5 ± 4.1, and −0.9 ± 4.9 mmHg in the apraclonidine group. There was no statistical difference between the two groups. Table 2 summarizes the parameters studied in the two groups. At 1 h after LPI, nine eyes (45%) in the brimonidine group and five eyes (25%) in the apraclonidine group; at 2 h, seven eyes (35%) in the brimonidine group and three eyes (15%) in the apraclonidine group; and at 3 h, six eyes (30%) in the brimonidine group and three eyes (15%) in the apraclonidine group had IOP elevation ≥5 mmHg.

Table 1. Demographics of study participants

	Brimonidine $n = 20$	Apraclonidine $n = 20$	P value
Mean age ± SD (years)	72.1 ± 11.0	69.6 ± 10.7	0.47*
Sex	17F:3M	15F:5M	0.36**
Mean baseline IOP ± SD (mmHg)	17.2 ± 3.2	16.7 ± 2.8	0.67*
Mean pre-eyedrop pupil size ± SD (mm)	2.8 ± 0.7	2.9 ± 0.6	0.72*
Mean laser energy ± SD (Joules)			
Argon	3.3 ± 3.0	3.6 ± 2.0	0.64*
Nd:YAG	6.9 ± 4.7	7.5 ± 6.5	0.74*

F, female; M, male; IOP, intraocular pressure; Nd:YAG, neodymium: yttrium-aluminium-garnet.
*t test.
**χ-squared test.

Table 2. Study parameters

	Brimonidine $n = 20$	Apraclonidine $n = 20$	P value
Mean post-LPI IOP ± SD (mmHg)			
At 1 h	19.8 ± 6.6	18.3 ± 4.9	0.429*
At 2 h	19.3 ± 7.7	17.2 ± 5.2	0.299*
At 3 h	18.2 ± 7.8	15.7 ± 5.6	0.253*
Number of eyes (%) with Post-LPI IOP ≥ 5 mmHg			
At 1 h	9 (45%)	5 (25%)	0.185**
At 2 h	7 (35%)	3 (15%)	0.144**
At 3 h	6 (30%)	3 (15%)	0.451**
Mean post-LPI pupil size ± SD (mm)	2.5 ± 0.6	3.4 ± 0.7	<0.001*

LPI, laser peripheral iridotomy.
*t test.
**χ-squared/Fisher's exact test.

There was no statistically significant difference between the two groups in the post-LPI IOP peak ($P > 0.05$, χ-squared test and Fisher's exact test).

The mean pupil size decreased by 0.33 ± 0.37 mm in the brimonidine group and increased by 0.90 ± 0.87 mm in the apraclonidine group. The change of the pupil size was statistically significant between the two groups ($P < 0.001$, independent-sample t test). Twelve of the 20 eyes (60%) in the brimonidine group had a detectable pupil constriction of ≥0.5 mm in diameter, whereas 16 of the 20 eyes (80%) in the apraclonidine group showed a detectable pupil dilatation of ≥0.5 mm.

Two patients reported mild stinging with brimonidine. No other adverse reaction was noted in either group.

Discussion

Since the introduction of the selective α_2-agonist brimonidine 0.2%, several clinical studies have shown its effectiveness in controlling IOP spikes after argon laser trabeculoplasty (ALT).[16,17] A few other studies have reported its use in controlling the post-laser IOP spikes in various anterior segment laser procedures such as Nd-YAG LPI and posterior capsulotomy.[15,18,19]

LPI is one of the most commonly performed laser procedures in the Asia-Pacific region, where closed-angle glaucoma is prevalent. It is performed either therapeutically or prophylactically. Apraclonidine 0.5% or 1% eyedrops have been widely used for the prevention of the post-laser IOP spike. However, apraclonidine causes some degree of pupil dilation.[4] This effect may theoretically make laser penetration of the iris more difficult, and may also increase the risk of IOP elevation in occludable angles.

Brimonidine, being 1000-fold more selective for α_2 than α_1-adrenoreceptors, does not cause pupil dilation since the mydriatic effect is mediated mainly through α_1 receptors of the iris dilator muscle. Pharmacological studies reported that brimonidine is 23- to 32-fold more α_2 selective than apraclonidine.[22] Our study was designed to compare the efficacy of brimonidine 0.2% and apraclonidine 1% in the prevention of IOP elevation after LPI as well as their effects on pupil size in angle-closure glaucoma patients.

Our observation of IOP response after LPI for the two drugs showed that both drugs were effective in the prevention of the post-LPI IOP spike. Though apraclonidine appeared to be stronger, the difference was not statistically significant. Our results on the IOP response were similar to the results of another study comparing the efficacy of 0.2% brimonidine and apraclonidine at the lower concentration of 0.5% in the control of post-laser iridotomy IOP spikes.[15,18] The percentage of eyes that had a post-LPI IOP spike of ≥5 mmHg measured hourly for 3 h was not significantly different between the two groups. We also observed

that the highest IOP spike generally occurred at 1 h post-laser for both drug groups, and then IOP returned to baseline level within 2–3 h.

The results of this study showed that apraclonidine dilated the pupil (0.90 ± 0.87 mmHg), whereas brimonidine constricted the pupil (−0.33 ± 0.37 mm). Previously published work substantiated our observation.[11,12] The pupil-constricting effect of brimonidine might give it a theoretical advantage over apraclonidine by making taut the iris tissue for the LPI procedure. This effect, however, might have been due to the small sample size. Nevertheless, the use of brimonidine for the prevention of post-LPI IOP spikes may offer some advantages since only one drug is sufficient without the need of adding pilocarpine to apraclonidine for constricting the pupil. Furthermore, it might be safer to use brimonidine for prophylactic LPI in eyes with occludable angles since it causes minimal change in the anterior chamber anatomy. However, when interpreting the pupil size in this study, one needs to take into account the accuracy of its measurement. The use of the millimeter caliper in this study caused a lower reproducibility and accuracy than other methods such as the Colvard pupillometer or infrared video recording would have.[23] Furthermore, six patients in each group had been using pilocarpine before the laser procedure. The suggested washout period of pilocarpine is 5 to 7 days.[24,25] To minimize the risk of an acute angle-closure attack during the washout period, we chose the shortest washout period for our subjects. Although patients on pilocarpine for more than 3 months were excluded, there could still be residual pharmacological effect after this short 5-day wash-out period.

The IOP change could also be related to the laser energy and the change in pupil size. However, the laser energies used in both groups were similar. The effect of the pupil size could not be confirmed from results of this study. Whether the pupil size contributed to the IOP change or not, the results showed that brimonidine was as effective as apraclonidine in the prevention of IOP elevation after LPI.

In conclusion, brimonidine tartrate 0.2% given before and after laser peripheral iridotomy prevents post-laser IOP elevation as effectively as apraclonidine 1.0%. Brimonidine has a minimal effect on pupil size compared with apraclonidine, which dilates the pupil.

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