Brimonidine in the Prevention of Intraocular Pressure Elevation Following Argon Laser Trabeculoplasty

Robert David, MD; George L. Spaeth, MD; Charles E. Clevenger, MD; Howard F. Perell, MD; Les I. Siegel, MD; J. Charles Henry, MD; Michael C. Stiles, MD; Michael S. Passo, MD; Robert L. Stamper, MD; John G. Walt, MBA; Elaine P. Kelley; Kuankuan S. Chen, MS

Objective: To evaluate the efficacy of 0.5% brimonidine tartrate, an α_2-adrenergic agonist, in preventing intraocular pressure (IOP) elevation following argon laser trabeculoplasty.

Design: In a multicenter, double-masked, randomized study, 248 patients (248 eyes) who underwent argon laser trabeculoplasty were allocated to four treatment groups: (1) brimonidine administered before and after the procedure; (2) brimonidine administered before the procedure; (3) brimonidine administered after the procedure; and (4) a vehicle administered before and after the procedure.

Results: In the first 3 hours after argon laser trabeculoplasty, only one (0.54%) of the 183 brimonidine-treated patients had a postlaser IOP increase of 10 mm Hg or more, while increases of this magnitude occurred in 13 (23%) of the 56 patients who received only the vehicle ($P<.001$). The three brimonidine-treatment groups demonstrated significant mean reductions in IOP from the pretrabeculoplasty level (−4 to −8 mm Hg), whereas the vehicle-treated group showed an increase in mean IOP (4 mm Hg). Side effects associated with brimonidine treatment included conjunctival blanching (40.9%), lid retraction (7.6%), and a slight lowering of the systolic blood pressure.

Conclusions: One drop of 0.5% brimonidine administered either before or after surgery was found to be efficacious and safe in preventing posttrabeculoplasty elevations in IOP.

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From the Department of Ophthalmology, Soroka University Hospital, Beer-Sheva, Israel (Dr David); Glaucoma Service, Wills Eye Hospital, Philadelphia, Pa (Dr Spaeth); Medical Center Clinic, Pensacola, Fla (Dr Clevenger); Department of Ophthalmology, University of Maryland at Baltimore (Dr Perell); Glaucoma Center of Michigan, Southfield (Dr Siegel); Little Rock (Ark) Eye Clinic (Dr Henry); Hunkler Eye Clinic, Kansas City, Mo (Dr Stiles); Department of Ophthalmology, Oregon Health Sciences University, Portland (Dr Passo); Department of Ophthalmology, California Pacific Medical Center, San Francisco (Dr Stamper); and Department of Ophthalmology Clinical Research, Allergan Inc, Irvine, Calif (Mr Walt and Mss Kelley and Chen). Mr Walt, Ms Kelley, and Ms Chen are employees of Allergan Inc. The other authors have no proprietary interest in either Allergan

ARGON LASER trabeculoplasty (ALT) is a procedure widely used for lowering intraocular pressure (IOP) in patients with glaucoma whose IOP remains unsatisfactorily high despite receiving maximal tolerated medical therapy. For such patients, ALT is a useful option prior to filtration surgery. A major complication with the use of ALT is the immediate IOP elevation that often follows the procedure. This complication has been observed since the procedure became popular in the early 1980s and it has been reported to occur at a magnitude of 10 mm Hg or more in 12% of the cases when ALT is performed over 180° of the angle[1] and in 14% to 50%[2,3] of cases when it is performed over 360° of the angle. This pressure increase may result from mechanical blockage of the trabecular meshwork by cellular debris, pigment dispersion, or inflammatory cells[4]; however, the exact mechanism by which this complication develops is unclear.[5] This immediate IOP increase may be of sufficient magnitude to produce serious complications, including permanent loss of central field.[3,6] In an effort to overcome this complication of a procedure that is otherwise generally safe, clinicians have sought means to control the IOP elevations following ALT. Pressure-lowering drugs that are in common use are reported to have equivocal results. Pilocarpine (4%) was reported to have some effect,[7] but this has not been confirmed by others.[8] Acetazolamide was found to be ineffective in preventing IOP increases.[9] Recently, an α-adrenergic agent, apraclonidine, was found to be effective in preventing IOP elevations following ALT,[10,11] iridotomy,[5] and other anterior segment procedures.[12]

Brimonidine tartrate is a selective α_2-adrenergic agonist that lowers IOP in ex-

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PATIENTS AND METHODS

Two hundred forty-eight patients participated in a multicenter, randomized, double-masked study. To qualify, patients had to be at least 21 years old with useful vision in both eyes. Patients with prior glaucoma surgery or intraocular surgery were not included. Institutional review board approvals were obtained and all patients signed informed consent forms. Each patient was assigned to one of four treatment regimens: brimonidine administered both before and after ALT (B/B); brimonidine administered before and vehicle administered after ALT (B/V); vehicle administered before and brimonidine administered after ALT (V/B); and vehicle administered both before and after ALT (V/V).

The rationale for the selection of treatment regimens was based on the accepted standard clinical practice and recommended for apraclonidine (two instillations) which was to be challenged with the alternatives of treating with a single dose, either before or after the procedure.

The groups were similar with regard to the type of pressure-lowering medications that the patients were receiving prior to enrollment in the study. We did not collect information on optic nerve appearance or visual field status to assess the severity of glaucomatous damage. All four groups received the medication 30 to 45 minutes before and immediately after ALT.

The study consisted of three visits. The first visit usually took place on the day when the ALT was performed. On that day, a baseline eye examination, as well as heart rate and blood pressure measurements, was performed prior to instillation of the first drop of study medication. Argon laser trabeculoplasty was performed according to standard procedures, with 90±28 applications over 360° of the angle. The spot size was 50 μm, the exposure time was 0.1 second, and the intensity varied between 500 and 1500 mW and was aimed at the anterior portion of the trabecular meshwork. The number of applications and the amount of power used were similar in all four treatment groups. Intraocular pressure, heart rate, and blood pressure were measured 1, 2, and 3 hours after ALT. In addition, patients underwent full slit-lamp examinations at these times. If at any stage an unacceptable IOP elevation was observed, the patient received other IOP-lowering medication(s) as needed and was removed from the study. At the second visit scheduled 1 to 2 weeks after ALT treatment, and at the final visit 4 to 6 weeks after ALT, a complete eye examination (including measurement of IOP) was performed, and heart rate and blood pressure were measured.

The data were analyzed with the two-way analysis of variance with Fisher's protected least significant difference test. Within each treatment group, mean changes from baseline at each follow-up visit were analyzed using a paired *t* test. The incidence rate of IOP increases was analyzed using the Cochran-Mantel-Haenszel method. Of the 248 patients enrolled in the study, nine were disqualified from the statistical analysis. Two subjects had been improperly entered into the study and seven were excluded due to study protocol violations. The remaining 239 patients (239 eyes) provided the data for the statistical analysis.

perimental animals[13] and in patients with open angle glaucoma and ocular hypertension.[14] The mechanism by which brimonidine reduces IOP is most likely similar to other α-agonists (clonidine, apraclonidine) by decreasing aqueous humor production.[15] Based on a long-term dose-response study,[16] the 0.5% concentration was identified as the most effective and safe dose for acute IOP lowering and, therefore, this concentration was elected for use in this study.

RESULTS

The four groups were similar with respect to demographics and iris color. The mean IOP before ALT on the day of the procedure in the four groups was 23.3 mm Hg for the B/B group, 23.9 mm Hg for the B/V group, 24.1 mm Hg for the V/B group, and 24.0 mm Hg for the V/V group. Following ALT, IOP increases of 10 mm Hg or more occurred in one (0.54%) of 183 patients in the three groups treated with brimonidine and in 13 (23%) of 56 subjects in the vehicle-treated group. This difference was found to be statistically significant ($P<.001$) (**Table**). As very few brimonidine-treated patients had IOP increases of 10 mm Hg or greater, post-ALT elevations greater than or equal to 5 mm Hg were served in seven (4%) of 183 brimonidine-treated patients and in 23 (41%) of 56 patients who received vehicle alone ($P<.001$) (Table).

Changes in IOP after ALT were also measured (**Figure 1**). The mean of the maximal IOP change (least decrease or most increase) from baseline was −6.5 mm Hg in the B/B group, −4.2 mm Hg in the B/V and V/B groups, and +4.2 mm Hg in the V/V group. The differences between the brimonidine-treated groups and the vehicle-treated group were found to be statistically significant ($P<.001$). As expected, at the subsequent follow-up visits (1 to 6 weeks after ALT) there were no significant differences among the groups. At these follow-up visits, all four groups demonstrated significant mean decreases in IOP from baseline, of 5 to 7 mm Hg, as a result of the procedure ($P<.001$).

Mean IOP at baseline in the contralateral eye was similar in all four treatment groups. Within the first 3 hours after instillation of the medications, there were several significant among-group differences in IOP in the contralateral eye. The B/B group showed a mean decrease in IOP ranging from 2.4 to 3.3 mm Hg; in comparison, the groups that received the vehicle only and brimonidine before and vehicle after laser surgery had a mean decrease in IOP be-

found to be statistically significant ($P \leq .012$). Heart rate was unaffected by brimonidine (**Figure 2**). There was a statistically significant decrease in systolic blood pressure in the B/B group 1, 2, and 3 hours following ALT (**Figure 3**), but these decreases were not clinically significant. To rule out the effect of presurgical anxiety on the blood pressure readings recorded at baseline, we performed an alternative analysis, averaging the data from the second and third visits (1 to 2 weeks and 4 to 6 weeks after ALT) to serve as an alternative baseline. In this alternative analysis, the decrease in systolic and diastolic blood pressure in the B/B group was less than in the original analysis and not significantly different from the other three treatment groups.

Ocular side effects that occurred during the first 3 hours after instillation included conjunctival blanching and lid retraction; the latter was observed in 14 (7.6%) of 183 patients treated with brimonidine. Lid retraction was recorded as moderate in one case; all the others were mild. Conjunctival blanching was noted in 75 (40.9%) of 183 brimonidine-treated patients. Again, the majority of these cases were reported as mild. Blanching was rated as moderate in 16 patients and severe in one patient in the B/B group (at the first post-ALT examination, 1 hour after the second drop of brimonidine). Three cases each of blanching of the conjunctiva and lid retraction were reported (5.4%) in the vehicle group. There were no differences between groups in the other ocular parameters examined (anterior chamber activity, corneal staining, and visual acuity).

COMMENT

The acute IOP elevation that follows ALT is a major hazard of this procedure. The sudden increase in pressure may have a harmful effect, especially if the optic nerve is already severely compromised; serious consequences have been reported.[3,6] Many IOP-lowering agents have been evaluated in an effort to prevent these post-ALT IOP increases. The most successful of these agents has been 1% apraclonidine, an α-adrenergic agonist. It is usually instilled both before and after the procedure, and it has been reported to considerably reduce the frequency of acute post-ALT elevations in IOP.[10-12,17]

The present study considered the safety and efficacy

Overall Incidence of Intraocular Pressure (IOP) Rises*

Treatment Group	No. of Subjects IOP≥5 mm Hg	IOP≥10 mm Hg
Brimonidine/brimondine (n=60)	2	0
Brimonidine/vehicle (n=62)	2	1
Vehicle/brimonidine (n=61)	3	0
Vehicle/vehicle (n=56)	23	13

*The overall incidence of IOP increases of 5 mm Hg or more and 10 mm Hg or more was significantly greater in the vehicle-treated group than

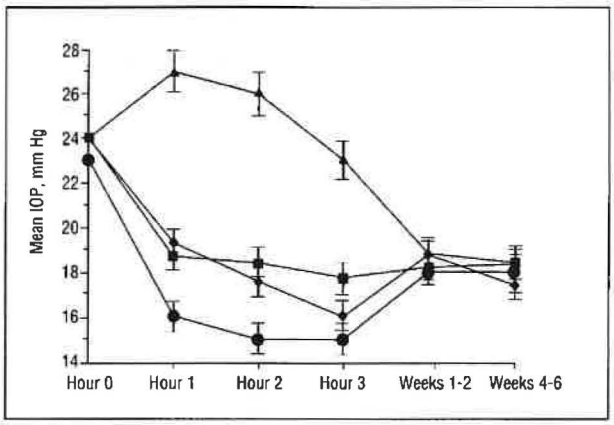

Figure 1. *Mean intraocular pressure (IOP) for 3 hours following argon laser trabeculoplasty and at the two follow-up visits. Solid circles indicate eyes receiving brimonidine both before and after surgery; solid squares, eyes receiving brimonidine only before surgery; solid diamonds, eyes receiving brimonidine only after surgery; and solid triangles, eyes receiving the vehicle. All three brimonidine groups showed a significant reduction (P<.001) from baseline at all three hourly readings whereas the vehicle showed a significant (P=.001) increase at hour 1.*

of another α_2-agonist, brimonidine, for reducing the incidence of IOP increases following ALT. Three different treatment regimens were evaluated: one drop before ALT, one drop after ALT, or two drops (one before and one after ALT). All three regimens were significantly more effective than the vehicle. An increase in IOP of 10 mm Hg or more occurred in only one of the brimonidine-treated patients (0.54%), whereas an increase of this magnitude was seen in 13 vehicle-treated patients (23%). The only brimonidine-treated patient with an IOP increase after ALT did not differ from the rest of the study population. She was a 64-year-old woman with primary open angle glaucoma. Her treated (timolol and pilocarpine) IOP was 19 mm Hg. One hour after ALT, the IOP increased to 30 mm Hg but consequently decreased without any treatment to 26 mm Hg at hour 2 and to 24 mm Hg at hour 3. The incidence of increases that occurred in the vehicle-treated group was similar to that seen in previous reports in the literature.[3,12]

The effect of brimonidine as measured during the first 3 hours following the procedure is most apparent. During this period, the mean IOP in the three brimonidine groups decreased by at least 5 to 8 mm Hg from the baseline mean, while the pressure increased by a mean of 4 mm Hg in the vehicle-treated group. Decreases in IOP from the pre-ALT level of 15 to 23 mm Hg were seen among brimonidine-treated patients several times in the 3 hours after ALT.

There was a slight IOP decrease from baseline in the contralateral eye of patients in the B/B group, but not in the other two brimonidine-treatment groups. This contralateral effect of brimonidine has been reported in monkeys[16] and is known to also occur with apraclonidine.[17] The finding in our study, that only patients from the B/B group had a contralateral effect, may indicate that this is most likely due to the double-dosing within a 45-minute period.

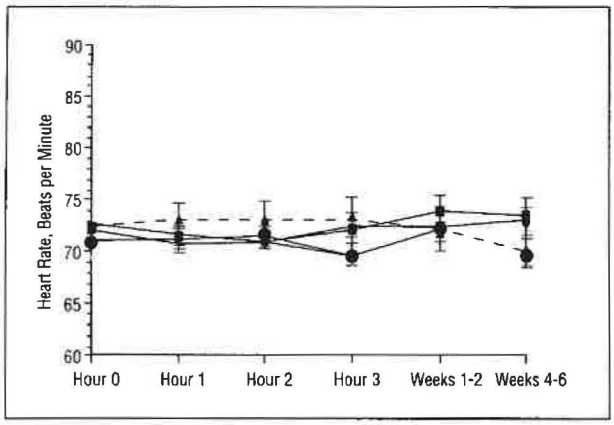

Figure 2. *Mean heart rate for 3 hours following argon laser trabeculoplasty and at the two follow-up visits. Solid circles indicate eyes receiving brimonidine both before and after surgery; solid squares, eyes receiving brimonidine only before surgery; solid diamonds, eyes receiving brimonidine only after surgery; and solid triangles, eyes receiving the vehicle. There were no significant changes from baseline or significant differences among groups.*

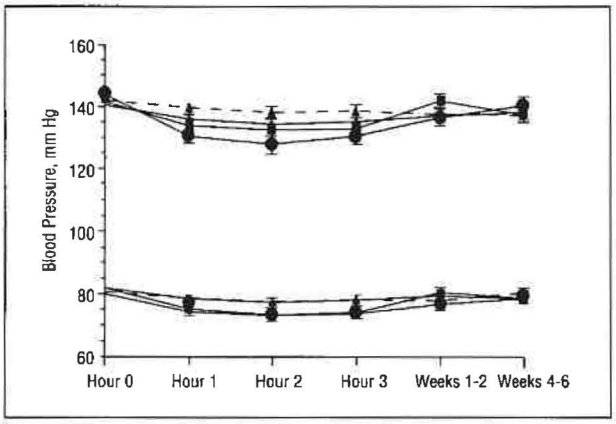

Figure 3. *Mean systolic and diastolic blood pressure for 3 hours following argon laser trabeculoplasty and at the two follow-up visits. Solid circles indicate eyes receiving brimonidine both before and after surgery; solid squares, eyes receiving brimonidine only before surgery; solid diamonds, eyes receiving brimonidine only after surgery; and solid triangles, eyes receiving the vehicle. All three brimonidine groups showed a significant reduction (P≤.010) from baseline at all three hourly readings and the vehicle-treated group showed a reduction at hour 2 in diastolic blood pressure only (P=.010).*

retraction and conjunctival blanching accompanied this treatment. These ocular side effects were mostly mild, were noted 1 and 2 hours after ALT, and had diminished by the 3-hour post-ALT examination. In some cases, the conjunctival blanching was the surgeon's description of what, in fact, appears to be a "normal-looking" eye, as opposed to the usually red, inflamed conjunctiva seen in patients after the manipulations with the contact lens while performing ALT.

The systemic side effects of brimonidine were mild. The drug had no measurable impact on the heart rate. A decrease in systolic blood pressure was statistically significant in the B/B group at the three hourly measurements after ALT. However, this decrease in blood pressure was clinically insignificant; no patient fainted, needed blood pressure changes. As mentioned before, when the baseline blood pressure measurements were averaged with their levels 1 to 6 weeks after the treatment, thus allowing for the anxiety often contributing on the day of ALT, the decrease in the B/B treated patients was not significantly different from that in the other three treatment groups. This suggests that 0.5% brimonidine instilled before and after ALT does have a mild systemic hypotensive effect but that the effect is not as pronounced as the original analysis seemed to indicate.

The fact that a single drop of brimonidine instilled either before or after ALT was as effective as treatment with two drops (one drop before and one after ALT) leaves the treating ophthalmologist the option of any one of the two single-drop modalities and minimizes the possible undesired side effects that a two-drop regimen might produce.

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Reprint requests to Ophthalmology Clinical Research Department, Allergan Inc, PO Box 19534, Irvine, CA 92713-9534 (Mr Walt).

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