THE ROLE OF APRACLONIDINE HYDROCHLORIDE IN LASER THERAPY FOR GLAUCOMA*

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INTRODUCTION

WITHIN THE LAST DECADE LASER IRIDOTOMY AND TRABECULOPLASTY have become commonplace. We have recently appreciated some potentially serious complications associated with these procedures. One relatively frequent sight-threatening problem common to both is a transient postoperative intraocular pressure (IOP) elevation. We cannot predict who will experience this complication. The best prophylaxis is still unknown. Thus, this thesis will consider a new drug to manage this problem.

INTRAOCULAR PRESSURE RISE FOLLOWING ARGON LASER IRIDOTOMY

Pollack and Patz[1] were the first to notice an acute IOP rise following argon laser iridotomy. Later others[2-7] observed that over one-half of treated eyes had some IOP elevation in the immediate postoperative period. About one-third had an IOP rise greater than 10 mm Hg over baseline within the first 3 hours, while one-eighth of these treated eyes had an IOP elevation greater than 20 mm Hg over baseline. Although the post-surgical IOP usually returned to normal within 24 hours, this elevation resembled a self-limited attack of acute pupillary-block glaucoma.

To date, no preoperative or immediate postoperative variable has accurately predicted which eye will have an IOP elevation following iridotomy.[2,3,8] Ancillary parameters such as the total amount of energy applied, iris color, and preoperative IOP do not correlate with its occurrence. Neither has the incidence correlated with the type of laser used: neodymium-YAG or argon.[2,3]

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INTRAOCULAR PRESSURE RISE FOLLOWING ARGON LASER TRABECULOPLASTY

Transient IOP elevations which complicate argon laser trabeculoplasty were first documented in 1982.[9] In contrast to iridotomy, this IOP rise may correlate with the amount of energy delivered to and absorbed by the trabecular meshwork.[10,11] Sufficient energy applied to the monkey trabecular meshwork can cause glaucoma.[10,11] In human eyes, the IOP spike also covaries with the energy delivered per laser pulse,[12,13] and the total energy applied to the trabecular meshwork.[14] Decreasing the energy or number of pulses delivered reduces the frequency of this complication. These changes do not, however, totally eliminate the acute IOP elevation.

The placement of laser energy applications is another variable that effects the frequency of large IOP elevations.[15] Posterior treatment within the trabecular meshwork causes more frequent IOP increases than treatment of the anterior meshwork. However, marked IOP elevations still occur often with anterior burn placement.

The preoperative coefficient of outflow also may correlate with the acute IOP elevation following trabeculoplasty.[16] However, tonography is neither practical to do routinely, nor is it always reliable.[17] We, therefore, still cannot predict which eye will experience an acute, and possibly dangerous, IOP elevation.

The IOP rise apparently does not correlate with the extent of the trabecular meshwork treated. Weinreb and co-workers[14] initially noted the following: over one-third of eyes experienced an IOP rise of at least 10 mm Hg over baseline following 360° argon laser trabeculoplasty. Fewer eyes receiving 180° treatment experienced a similar IOP rise. This led many investigators to believe that it was safer to treat only 180° in one session. Subsequent investigations found no marked difference in IOP elevation when comparing 180° and 360° treatment.[15] Krupin and coworkers[18] documented that 14% of eyes having 360° treatment experienced a clinically significant IOP elevation. This is similar to the 12% to 21% of eyes in separate studies undergoing 180° treatment that experienced a large IOP elevation.[19-21]

In addition, 180° treatment does not offer enough long-term IOP control in many eyes. A second treatment session may be necessary.[22-26] Studies evaluating this repeated argon laser trabeculoplasty differ about both its efficacy and its potential to produce an IOP rise. Brown and coworkers[23] found the risks of a second treatment large, with 12% of eyes having very marked IOP rises (10 to 37 mm Hg over baseline). Retreatment was only successful in 38% of eyes. These results, however, are controversial.[22-26] It may be preferable to treat 360° of the trabecular meshwork in one session.

The IOP rise following trabeculoplasty also may not be dependent on whether the type of laser used is argon or neodymium-YAG.[27] Both photocoagulation and photodisruption cause frequent IOP elevations.

ETIOLOGY OF THE INTRAOCULAR PRESSURE RISE

The etiology of the acute IOP rise following both laser trabeculoplasty and iridotomy is unknown. Breakdown of the blood aqueous barrier may be a contributing feature.[28-30] This may release leucotrienes and other serum factors not normally present in aqueous humor. Laser irradiation of rabbit irides elicits an acute inflammatory response, partially mediated by prostaglandins.[31,32] However, all attempts to blunt the IOP rise in humans with topical corticosteroids and nonsteroidal anti-inflammatory agents have been unsuccessful.[19-21,33]

Particulate matter and high molecular weight protein are capable of obstructing the trabecular meshwork.[34,35] Iris pigment and blood products block the trabecular meshwork following iridotomy.[36] Similarly, capsule and lens debris, and red blood cells impede the trabecular meshwork following experimental neodymium-YAG laser posterior capsulotomy in monkeys.[37] No animals in either model had acute IOP rises through the tonographic outflow decreased in one report.[37] It could be that monkeys are not a good model to investigate the acute IOP elevation,[38] or that additional features, other than particulate debris, may also be responsible for the acute IOP rise in humans.

MEDICAL PROPHYLAXIS OF THE INTRAOCULAR PRESSURE RISE

Although its etiology is unknown, many investigators believe that the postoperative IOP elevation is one of the most serious acute complications associated with these laser procedures.[2,6,9,14,18,39] Moster and co-workers[40] documented that eyes undergoing cyclocryotherapy with extensive glaucomatous damage may be most susceptible to large IOP elevations. In their study, a transient IOP elevation resulted in a loss of at least 1 line of Snellen visual acuity in 25% of treated eyes. This may, or may not, be clinically significant. Likewise, authors have conclusively linked the IOP elevations following argon laser anterior segment glaucoma surgery with progressive optic nerve damage, visual field loss, and visual acuity loss.[9,18] This IOP rise can necessitate emergency filtering surgery.[41] Since this problem can be sight-threatening, a relatively safe prophylaxis is desirable.

Until recently, no medications have been consistently or adequately effective in preventing IOP rises following iridotomy. Schrems and coworkers[7] found that pilocarpine hydrochloride markedly decreased the

incidence of the postoperative IOP rise associated with iridotomy. However, 60% of eyes still experienced some IOP rise despite pilocarpine therapy.[2-6] The combination of oral methazolamide and topical timolol maleate reduced the incidence of IOP elevations in a small pilot study.[5] No one has investigated prophylactic epinephrine since it might cause mydriasis and could produce pupillary-block in susceptible eyes.

Similarly, no chronic glaucoma medications have conclusively prevented the acute IOP rise following argon laser trabeculoplasty. Here medical prophylaxis of the acute IOP elevation may be more difficult as many eyes are already receiving maximum tolerated medical therapy. Most are on a combination of beta-blockers, pilocarpine, epinephrine, and carbonic anhydrase inhibitors before laser treatment.

In a study involving 44 eyes,[42] the addition of another drop of pilocarpine appeared better than placebo in dampening the IOP rise. Seventy-three percent of placebo-treated eyes compared to 36% of pilocarpine-treated eyes had IOP spikes. It would be desirable to further reduce this 36% incidence. In another study, Leung and Gillies[43] found no difference between pilocarpine and placebo-treated eyes in either the frequency or severity of IOP spikes. Robin and co-workers[44] also found that preoperative pilocarpine did not adequately prevent large IOP elevations. Pilocarpine pretreatment could also have the disadvantage of further narrowing the approach to the trabecular meshwork. This could decrease the surgeon's visualization of the treatment area.

Hoskins and co-workers[39] have found that oral carbonic anhydrase inhibitors have little value in suppressing the IOP elevation. Other investigators have found that they may be effective.[43,45] We do not definitely know whether these medications are capable of suppressing the IOP elevation.

One topical medication that consistently diminishes the postoperative IOP rise following anterior segment laser surgery is apraclonidine hydrochloride (formerly known as ALO 2145, para-aminoclonidine hydrochloride, or aplonidine hydrochloride).[46-49] The combined results of two separate independent studies involving argon laser trabeculoplasty, showed that 14 of 76 (18%)[46,48] placebo-treated eyes experienced IOP rises larger than 10 mm Hg. Only 4 of 80 (5%) apraclonidine-treated eyes developed large IOP rises. The results were equally striking for eyes requiring argon laser iridotomy.[47,48] Ten of 33 (30%) placebo-treated eyes had IOP elevations larger than 10 mm Hg over baseline. None of the 13 apraclonidine-treated eyes suffered a large IOP elevation. This difference in the frequency of large IOP spikes, when comparing apraclonidine to placebo, for both trabeculoplasty and iridotomy was highly significant.

In previous reports, investigators evaluated the IOP lowering ability of apraclonidine following argon laser iridotomy and trabeculoplasty by comparing it to a placebo.[46-48] No authors have compared it to any other IOP lowering medications. It is important to know the efficacy of these other agents, compared with apraclonidine, in preventing an IOP elevation. This might help us to treat patients better and to better understand the mechanism of the postoperative IOP rise.

Apraclonidine may have another advantage besides IOP lowering in these eyes. Many alpha-agonists cause iris vasoconstriction and may selectively decrease blood flow to the anterior segment.[50-53] Apraclonidine 1.5% decreased blood flow to the iris, conjunctiva, and sclera by over 50% in monkeys.[54] There was no significant decrease in the choroidal, retinal, or optic nerve blood flow. Clinically, apraclonidine causes conjunctival vasoconstriction.[51] Iris vasoconstriction may be advantageous in procedures such as neodymium-YAG laser iridotomy where bleeding occurs often[2-5] and may lead to serious complications.[55] Neodymium-YAG laser iridotomy may be a good model to test the clinical value of apraclonidine's iris vasoconstriction.

PURPOSE OF THIS STUDY

This study will attempt to provide information pertinent to a fuller understanding of the short-term uses of 1% apraclonidine. It will compare apraclonidine therapy to commonly used glaucoma medications in preventing postoperative IOP rises in humans. This investigation consists of three distinct original prospective studies: the first two in humans, the third in monkeys. The first compares the effects of apraclonidine hydrochloride to timolol maleate, dipivefrin hydrochloride, pilocarpine hydrochloride, and acetazolamide on the IOP elevation following argon laser trabeculoplasty. The second compares the IOP lowering capability of apraclonidine to timolol following argon laser iridotomy. Finally we shall examine the clinical efficacy of topical 1% apraclonidine hydrochloride on iris bleeding in a monkey model, following Q-switched neodymium-YAG laser iridotomy.

SUBJECTS AND METHODS

ARGON LASER TRABECULOPLASTY

All patients' eyes had various forms of open-angle glaucoma with disk and visual field damage. All had poor IOP control despite maximum tolerated medical therapy. Patients were of legal age. The study excluded patients with asthma, sulpha allergy, unstable cardiovascular disease, allergy to

any of the test medications, and eyes which had prior argon laser trabeculoplasty. If both eyes had elevated IOP and required trabeculoplasty, the study included only the eye treated first.

All patients gave written informed consent. Patients took their glaucoma medications as usual. A baseline examination included: applanation tonometry, Snellen visual acuity, slit-lamp examination, and resting heart rate. A computer generated random-number table assigned eyes to treatment groups. The randomization allowed about four times more eyes to receive topical 1% apraclonidine than either timolol 0.5%, pilocarpine 4%, dipivefrin 0.1%, or 250 mg acetazolamide, individually. This was done intentionally to increase our experience with the use of apraclonidine. The investigator was masked to which medication each subject received.

This study does not evaluate the usefulness of prophylactic therapy with either oral glycerin or intravenous mannitol. These two medications have limited potential for routine prophylaxis. Oral glycerin also may only delay the onset rather than prevent the IOP elevation.[56] No eyes were treated with placebo since studies have already proven it is less effective than apraclonidine.

One hour before trabeculoplasty, one of the following medications was administered in a masked fashion to the treated eye (patient): topical 1% apraclonidine, topical 0.5% timolol, topical 4% pilocarpine, topical 0.1% dipivefrin, or oral acetazolamide 250 mg. Topical anesthesia was applied to the eye. A one-mirrored contact lens was placed on the eye and 360° of argon laser trabeculoplasty was performed using a total of 80 laser applications. Each application was 800 mWatts and placed within the anterior third of the trabecular meshwork. Blue-green argon laser light was used for all treatments (Coherent laser model 900, or 920 laser). Within minutes of completing the procedure, one drop of 0.1% dexamethasone alcohol was placed on the eye. The patient also took an additional dose of the study medication at this time. IOP, the degree of anterior segment inflammation, and resting heart rate were measured hourly for the next 3 hours.

If the IOP rose to a dangerous level, considering the eye's pre-existing optic nerve damage, oral glycerin was administered. These eyes were followed until the IOP began returning to baseline.

Patients' discharge instructions included continuation of their preoperative glaucoma medications. They also used topical 0.1% dexamethasone alcohol four times daily for the following 4 days. Patients returned for evaluation at 1 week and at 1 month after therapy. Visual acuity, IOP, and anterior segment inflammation were recorded at these visits.

ARGON LASER IRIDOTOMY

Enrollment included patients with phakic primary chronic pupillary-block glaucoma with either disk or visual field changes. Dark room prone provocative testing confirmed the diagnosis in all cases. If both eyes required therapy, only the first treated eye was included for analysis. All eyes had been treated with varying concentrations (1% to 4%) of pilocarpine 2 to 4 hours before laser therapy. No patient had any contraindication to beta-blocker or alpha-agonist administration. All patients gave written informed consent.

Baseline evaluation included measurement of Snellen visual acuity, IOP, and resting heart rate. Argon lasers (Coherent models 900 or 920) were used to create iridotomies. Topical anesthesia was applied to the eye. An Abraham contact lens (Ocular Instruments; Bellevue, Washington) was placed on the globe. All pulses were applied to a midperipheral iris crypt in the superior nasal or temporal quadrant using the following laser settings: 50 μ spot size, 0.2 second duration, and 1000 mWatt power. Repeated well-focused burns were continued until the anterior lens capsule was seen clearly through the iris opening.

One hour before the iridotomy, all eyes randomly received either one drop of 1% apraclonidine or 0.5% timolol in a double-masked fashion. Neither epinephrine nor acetazolamide were included as comparative treatments. Epinephrine treatment could provoke an acute angle-closure attack. The patient population was not large enough for an acetazolamide treatment arm.

The treated eye received a second drop of the appropriate study medication immediately following iridotomy formation. I performed applanation tonometry, slit-lamp examination, and measured resting heart rate hourly for the next 3 hours. Eyes received dexamethasone alcohol 0.1% after the iridotomy and were instructed to take this four times daily for the next 4 days. If there was a large acute IOP rise, the patient was not discharged until his IOP returned to baseline. If the eye's IOP rise was felt to be dangerous, oral glycerin was administered. Patient instructions included continuation of his preoperative glaucoma medications throughout the study. A follow-up examination was given 1 week and 1 month later.

PRIMATE STUDIES

Six cynomolgus monkeys (*Macaca fascicularis*) of similar weight and of either sex were anesthetized with intramuscular ketamine and intravenous pentobarbital. This investigation conformed to the ARVO resolution on the use of animals in research. The preoperative evaluation

included slit-lamp biomicroscopy and IOP examination done with the Alcon pneumatonograph. In addition, one drop of 2% pilocarpine was instilled on both eyes 1 hour before laser therapy. Five minutes later, one eye received a drop of either 1% apraclonidine hydrochloride or its vehicle (placebo). The fellow eye received the other medication in a double-masked randomized fashion. A drop of the same test medication was placed on both eyes 30 minutes later.

One hour after the first application of the study medication, each eye received one drop of proparacaine hydrochloride 0.5%. An Abraham YAG iridotomy laser contact lens (Ocular Instruments; Bellevue, Washington) was used to create a peripheral iridotomy in the superior nasal quadrant of each eye in the midperiphery. Repeated spots of well-focused 10 mJ (one monkey) or 15 mJ (five monkeys) energy with a burst mode of 1 were used until a patent iridotomy was created. Visualization of the lens beneath the iris opening was the criteria for iridotomy patency. The right eye was always treated first. Digital pressure was not placed on the contact lens if iris bleeding occurred.

Before removing the contact lens, the eye was observed through the laser's slit-lamp for about 3 minutes. The extent and duration of bleeding from the iridotomy site were evaluated. Iris bleeding was graded according to the following ordered scale: (0) no bleeding or a drop of blood at the iridotomy margin, (1) a small flow of blood from the iridotomy margin, or (2) extensive bleeding from the iridotomy margin. The duration of bleeding was timed in seconds and IOPs were measured 1, 2, and 3 hours later.

STATISTICAL ANALYSIS

Descriptive statistics were calculated as mean ± 1 standard deviation (SD). For probability testing, Student's *t*-test, linear regression analysis, and chi-square analysis were used, when appropriate. The resulting *P* values must be interpreted with some caution and were not considered clinically significant unless they were less than .05.

RESULTS

TRABECULOPLASTY

Two hundred sixty eyes (260 patients) were treated. There were no significant preoperative differences in race, age, sex, eye color, or preoperative types of glaucoma between the five treatment groups (Table I).

Between 90% and 94% of eyes were already being treated chronically with a beta-blocker prior to trabeculoplasty (Table II). There were also

TABLE I: DEMOGRAPHIC DATA TRABECULOPLASTY

VARIABLE	TREATMENT GROUP				
	APRACLONIDINE	TIMOLOL	PILOCARPINE	ACETAZOLAMIDE	DIPIVEFRIN
Total number of treated eyes	125	35	37	31	32
Race, number of patients					
White	90 (72%)	29 (83%)	28 (76%)	19 (61%)	20 (63%)
Black	35 (28%)	6 (17%)	9 (24%)	12 (39%)	12 (37%)
Age (yrs)					
Range	24–92	53–92	49–84	24–79	29–86
Mean ± 1 SD*	66.5 ± 12.2	68.4 ± 10.3	67.6 ± 8.9	63.0 ± 13.1	65.5 ± 14.0
Sex, number of patients					
Male	55 (44%)	15 (43%)	14 (38%)	11 (35%)	16 (50%)
Female	70 (56%)	20 (57%)	23 (62%)	20 (65%)	16 (50%)
Eye color, number of eyes					
Blue	65 (52%)	16 (46%)	18 (49%)	10 (32%)	13 (41%)
Brown	60 (48%)	19 (54%)	19 (51%)	21 (63%)	19 (59%)
Glaucoma type, number of eyes					
Chronic open-angle	98 (78%)	24 (68%)	27 (73%)	17 (55%)	20 (63%)
Chronic angle-closure after iridotomy	20 (16%)	9 (26%)	7 (19%)	8 (26%)	8 (25%)
Pigmentary glaucoma	5 (4%)	1 (3%)	1 (3%)	1 (3%)	2 (6%)
Pseudoexfoliation	1 (1%)	1 (3%)	0 (0%)	2 (6%)	1 (3%)
Others	1 (1%)	0 (0%)	2 (5%)	3 (10%)	1 (3%)
Preoperative IOP (mm Hg)					
Range	22–49	23–44	21–50	22–37	22–36
Mean ± 1 SD*	27.2 ± 5.1	27.6 ± 4.1	27.1 ± 5.1	25.9 ± 3.0	25.7 ± 3.9

*SD is 1 standard deviation.

TABLE II: PERCENT* OF EYES UNDERGOING TRABECULOPLASTY RECEIVING EACH CHRONIC GLAUCOMA MEDICATION

PREOPERATIVE CHRONIC GLAUCOMA MEDICATION	TREATMENT GROUP				
	APRACLONIDINE	TIMOLOL	PILOCARPINE	ACETAZOLAMIDE	DIPIVEFRIN
Beta-blocker	94	91	92	90	94
Pilocarpine	74	69	54	74	88
Carbonic anhydrase inhibitor	23	23	22	16	25
Epinephrine	77	77	86	84	72

*Percent total more than 100% for each group as many eyes required multiple different medications.

similarities between groups in the percentage of eyes receiving chronic preoperative epinephrine and acetazolamide. Between 16% and 25% of eyes were on chronic acetazolamide therapy. Fewer eyes randomized to the pilocarpine treatment group (54%) were on chronic pilocarpine than eyes in other groups (69% to 88%). This difference was only significant ($P < .05$) when comparing eyes randomized to apraclonidine treatment with those randomized to pilocarpine treatment. Fig 1 documents the total number of different chronic glaucoma medications taken by patients in all treatment groups. More than 50% of the eyes in each treatment group received three different chronic glaucoma medications prior to laser surgery. One eye randomized to timolol treatment was unable to tolerate any glaucoma medication on a long-term basis. There was no significant difference between groups.

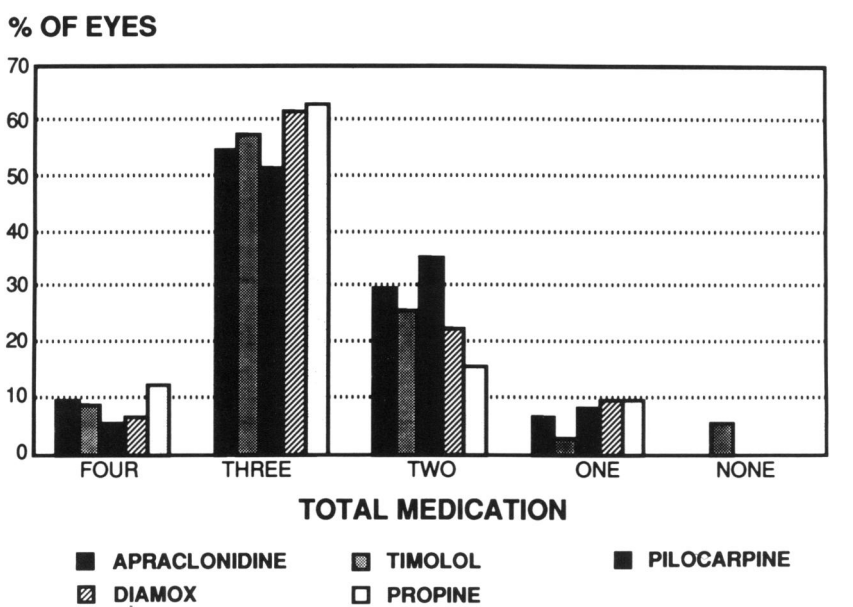

FIGURE 1

Bar graph comparing the number of different glaucoma medications that eyes in each study group (apraclonidine, timolol, pilocarpine, acetazolamide, and dipivefrin) required before argon laser trabeculoplasty. X axis represents total number of IOP lower medications which an eye received prior to argon laser trabeculoplasty. (If a patient's maximum medical therapy was the combination of timolol and pilocarpine, he required two different medications.) Y axis represents percent of all eyes, in each study group, receiving that number of different medications. Distribution is not significantly different when comparing different treatment groups.

The mean preoperative IOPs were not statistically different (Fig 2). During each of the first 3 hours, mean IOPs were significantly lower in apraclonidine-treated eyes than in any of the other treatment groups ($P < .01$). There were no significant differences at the first postoperative week and month. Apraclonidine administration significantly lowered mean IOP from baseline while treatment with other medications allowed an initial increase in mean IOP. There was no significant difference in mean IOPs at any time when comparing the groups of eyes treated with timolol, dipivefrin, pilocarpine, and acetazolamide.

Eyes treated with apraclonidine always had larger ($P < .01$) decreases in IOP after trabeculoplasty (Fig 3). During the first 3 postoperative hours only four (3%) eyes treated with apraclonidine had IOP rises > 5 mm Hg (Table III). One of these four eyes had an IOP rise > 10 mm Hg. This

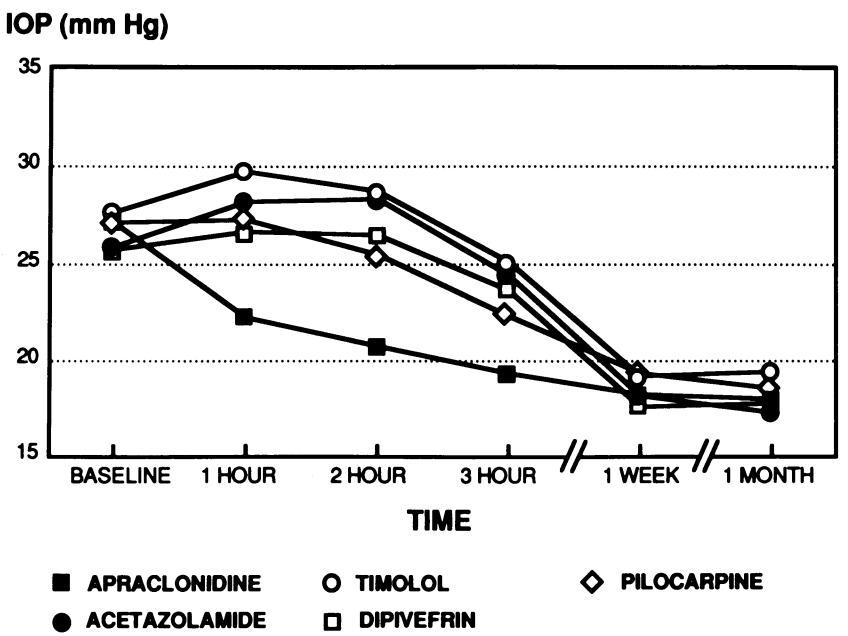

FIGURE 2

Line graph comparing mean IOP of eyes treated with apraclonidine, timolol, pilocarpine, dipivefrin, and acetazolamide after argon laser trabeculoplasty. There is no significant difference in preoperative IOPs. Mean IOP of apraclonidine treated eyes is only significantly lower ($P < .01$) than mean IOP of other groups' eyes at the first, second, and third postoperative hours. There is no statistically significant difference at these times between any of the nonapraclonidine treatment groups.

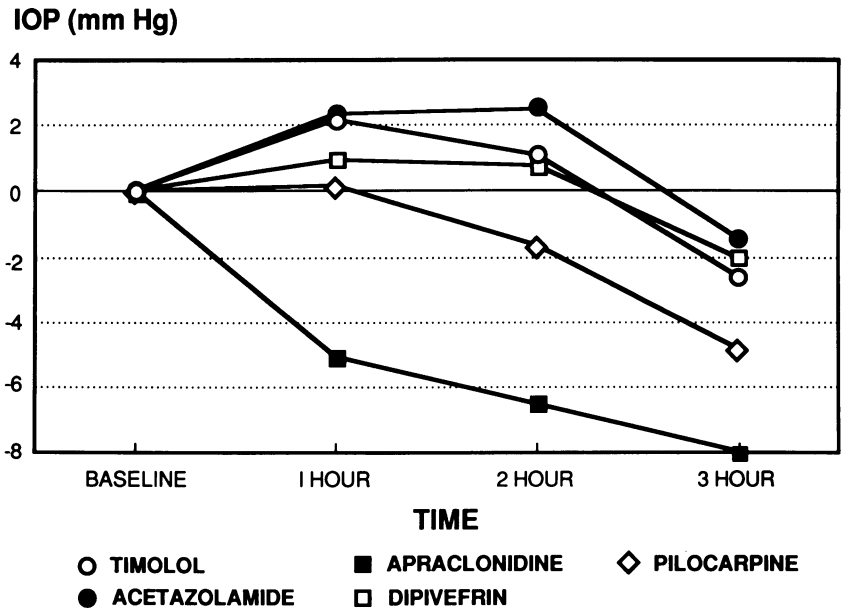

FIGURE 3
Line graph comparing mean IOP changes from baseline during the first 3 postoperative hours after trabeculoplasty in eyes treated with apraclonidine, timolol, pilocarpine, dipivefrin, or acetazolamide. Mean IOP change of apraclonidine-treated eyes is significantly lower ($P < .01$) than mean IOP changes of other groups' eyes.

TABLE III: IOP ELEVATIONS DURING FIRST 3 POSTOPERATIVE HOURS AFTER ARGON LASER TRABECULOPLASTY

MAXIMUM IOP ELEVATION	TREATMENT GROUP*				
	APRACLONIDINE	TIMOLOL	PILOCARPINE	ACETAZOLAMIDE	DIPIVEFRIN
No IOP elevation	86% (107)	34% (12)	43% (16)	26% (8)	47% (15)
1–5 mm Hg	11% (14)	34% (12)	24% (9)	35% (11)	15% (5)
6–10 mm Hg	2% (3)	17% (6)	30% (11)	26% (8)	22% (7)
> 10mmHg	1% (1)	15% (5)	3% (1)	13% (4)	16% (5)
Total of eyes	100% (125)	100% (35)	100% (37)	100% (31)	100% (32)

*Percent (number) of eyes.

frequency of larger IOP spikes is significantly ($P < .001$) less than eyes treated with any of the other medications. Twelve (39%) eyes treated with acetazolamide, 12 (33%) eyes treated with pilocarpine, 11 (32%) eyes treated with timolol, and 12 (38%) eyes treated with dipivefrin had an IOP rise > 5 mm Hg. The highest IOP elevation over baseline in an apraclonidine-treated eye was 14 mm Hg. The largest IOP elevation over baseline were 24 mm Hg, 26 mm Hg, 23 mm Hg, and 15 mm Hg for eyes treated with timolol, dipivefrin, acetazolamide, and pilocarpine, respectively.

Linear regression analysis of one variable at a time showed no correlation between preoperative IOP and maximal IOP change during the first 3 postoperative hours. Table IV documents the characteristics of eyes with IOP elevations greater than 10 mm Hg. All received nonspecific beta-blockers and 14 (87%) received three or more IOP lowering medications. Three (19%) had preoperative IOPs greater than 30 mm Hg. More eyes had brown irides (13) than blue (3).

Dangerously high IOP levels requiring oral glycerin administration were not observed in any apraclonidine-treated eye. Three eyes in the timolol treatment group, one in the pilocarpine group, two in the acetazolamide group, and one in the dipivefrin group had these larger IOP rises. Despite oral glycerin, and later intravenous mannitol, the IOP was unable

TABLE IV: PATIENTS WITH IOP* ELEVATIONS > 10 mm Hg AFTER ARGON LASER TRABECULOPLASTY

TREATMENT GROUP	PATIENT AGE (Y†)/SEX/ RACE/EYE COLOR	PREOPERATIVE IOP (mm Hg)	MAXIMUM IOP RISE DURING FIRST 3 HOURS (mm Hg)	GLAUCOMA MEDICATIONS‡
Dipivefrin	58/F/white/brown	24	+26	B/P/E
Timolol	58/M/white/brown	25	+24	B/P/E
Timolol	62/F/white/brown	44	+23	B/P/C
Acetazolamide	73/F/white/blue	25	+23	B/P
Timolol	66/F/white/brown	34	+19	B/P/C
Dipivefrin	72/F/white/brown	24	+18	B/P/E
Acetazolamide	69/F/black/brown	26	+18	B/P/E
Pilocaropine	82/F/white/brown	28	+15	B/P/E
Timolol	61/F/black/brown	30	+14	B/E/C
Acetazolamide	57/F/white/brown	28	+14	B/P/E
Dipivefrin	86/F/white/blue	26	+14	B/P/C
Dipivefrin	73/F/black/brown	23	+14	B/P/E
Apraclonidine	58/F/white/brown	38	+14	B/P/E
Acetazolamide	53/F/white/blue	27	+13	B
Dipivefrin	58/M/black/brown	26	+11	B/P/E
Timolol	53/M/white/brown	26	+11	B/P/E/C

*IOP indicates intraocular pressure.
†Y indicates years of age.
‡Medications: B, beta-blocker; C, carbonic anhydrase inhibitor; E, epinephrine; P, pilocarpine.

to be lowered with medical management in one pilocarpine-treated eye. This eye required an emergency surgical trabeculectomy.

There was no significant change from baseline in the mean resting heart rates in any group (Table V). There was no adverse systemic reactions in any eye treated with any medication. There was no significant difference among groups in the degree of anterior segment inflammation (cell and flare). The postoperative visual acuity did not differ more than 2 Snellen lines from the reoperative acuity in any eye.

IRIDOTOMY

Fifty-four eyes (54 patients) were treated. There was no significant preoperative differences in race, age, sex, eye color, or mean preoperative IOPs (Table VI). Indentation gonioscopy disclosed no eye with peripheral anterior synechiae involving more than 25% of the angle. Twelve eyes randomized to treatment with apraclonidine and nine eyes randomized to timolol treatment already received a topical beta-blocker. No eyes in either treatment group received chronic epinephrine. Three eyes in the timolol treatment group were on carbonic anhydrase inhibitors while no eyes in the apraclonidine treatment group were on this oral medication. The difference in total medications received between both treatment groups is not significant.

The mean number of laser pulses required to complete an iridotomy was 53 ± 45 in the apraclonidine-treated eyes (range, 10 to 195 pulses). In the timolol-treated group the mean number of pulses was 53 ± 28 (range, 12 to 102 pulses). Nine (32%) apraclonidine-treated eyes and 13 (50%) timolol-treated eyes required more than 50 pulses to complete an iridotomy.

There was always a decrease in mean IOP during the first 3 postoperative hours in apraclonidine-treated eyes (Fig 4). There was an increase in mean IOP in timolol-treated eyes. This difference was highly significant ($P < .001$) at all three time intervals. There was no significant difference in mean IOP at the 1 week or 1 month visits.

The mean IOP change from baseline during the first 3 postoperative hours in the timolol-treated eyes was an increase (Fig 5). This varied from an increase of 21% ± 28% at 1 hour to a 10% ± 28% increase at the third postoperative hour. The change seen in apraclonidine-treated eyes was an IOP decrease. The IOP decrease in these eyes varied from 12% ± 20% at the first postoperative hour to 20% ± 20% at the third hour. This difference between the two treatment groups was highly significant ($P < .001$).

TABLE V: MEAN HEART RATE*: ARGON LASER TRABECULOPLASTY STUDY

TREATMENT GROUP	TIME					
	PREOP	1 HR	2 HR	2 HR	1 WK	1 MO
Apraclonidine	72.7 ± 10.5	72.4 ± 10.4	72.6 ± 10.1	72.3 ± 10.3	71.2 ± 9.6	72.8 ± 9.5
Dipivefrin	77.5 ± 11.9	76.2 ± 11.2	73.7 ± 9.2	76.0 ± 12.7	71.0 ± 9.7	70.0 ± 10.6
Acetazolamide	73.4 ± 12.9	70.3 ± 12.0	71.0 ± 13.3	69.6 ± 10.5	69.7 ± 9.2	70.5 ± 9.0
Pilocarpine	72.1 ± 11.2	70.6 ± 11.8	72.2 ± 10.2	69.6 ± 11.6	71.7 ± 9.0	70.7 ± 9.3
Timolol	70.6 ± 10.4	68.9 ± 10.3	68.5 ± 10.4	69.5 ± 10.6	70.0 ± 12.8	72.0 ± 10.6

*Beats per minute ± 1 standard deviation.

TABLE VI: DEMOGRAPHIC DATA: IRIDOTOMY

VARIABLE	APRACLONIDINE GROUP	TIMOLOL GROUP
Total no. of eyes	28	26
Race, no. of patients		
White	26 (93%)	25 (96%)
Black	2 (7%)	1 (4%)
Age (yrs)		
Range	34–95	34–89
Mean ± 1 SD	68.2 ± 15.6	66.5 ± 14.3
Sex, no. of patients		
Male	7 (25%)	6 (23%)
Female	21 (75%)	20 (77%)
Eye color, no. of eyes		
Blue	17 (61%)	16 (62%)
Brown	11 (39%)	10 (38%)
Preoperative IOP (mm Hg)		
Range	16–34	12–35
Mean ± 1 SD	22.3 ± 4.1	23.4 ± 4.7

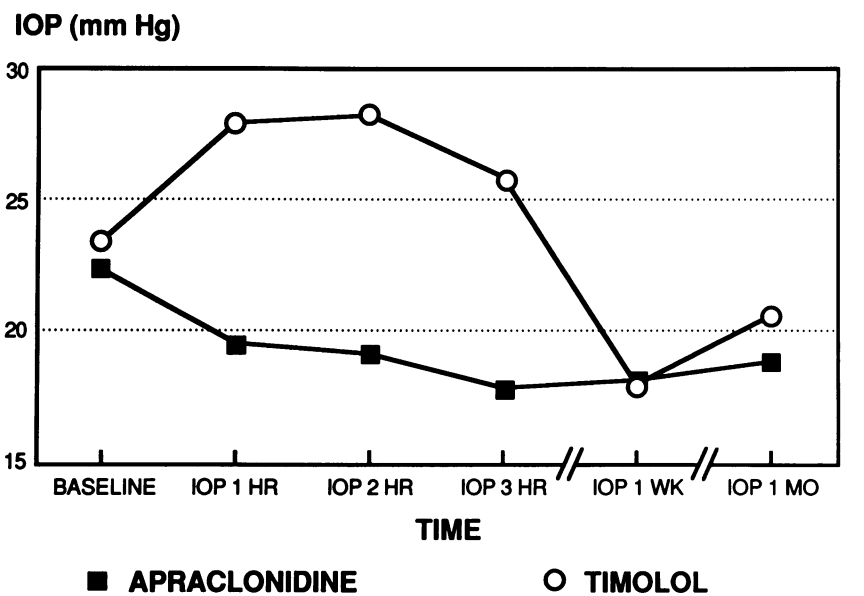

FIGURE 4

Line graph comparing mean IOP of eyes requiring argon laser iridotomy treated with apraclonidine and timolol. There is no significant difference in preoperative IOPs. Mean IOPs of apraclonidine-treated eyes are significantly lower ($P < .001$) than mean IOPs of eyes treated with timolol at the first, second, and third postoperative hours. There is no significant difference between apraclonidine and timolol-treated eyes at the 1 week and 1 month visits.

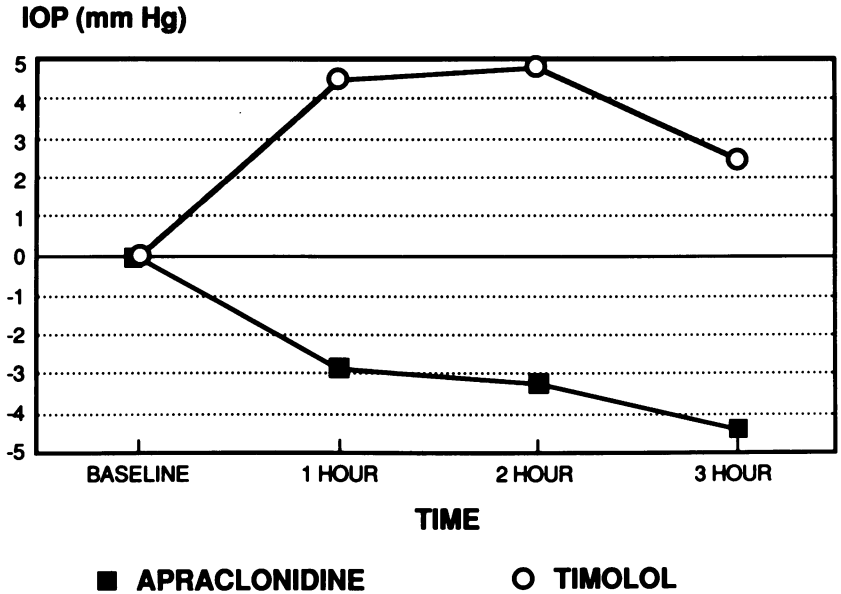

FIGURE 5

Line graph comparing mean IOP changes from baseline in eyes undergoing argon laser iridotomy treated with apraclonidine and timolol. The mean IOP change of apraclonidine-treated eyes is an IOP decrease. Mean IOP response of timolol-treated eyes is an IOP increase. Difference between these two treatment groups is significant ($P < .001$) at first, second, and third postoperative hours.

TABLE VII: MAXIMUM IOP ELEVATION DURING FIRST 3 POSTOPERATIVE HOURS AFTER ARGON LASER IRIDOTOMY

	TREATMENT GROUP*	
MAXIMUM IOP ELEVATION	APRACLONIDINE	TIMOLOL
No IOP elevation	86% (24)	19% (5)
1–5 mm Hg	7% (2)	27% (7)
6–10 mm Hg	7% (2)	27% (7)
> 10mmHg	0% (0)	27% (7)
Total no. of eyes	100% (28)	100% (26)

*Percent (number) of eyes.

The difference in the distribution of IOP changes from baseline during the first 3 postoperative hours, between apraclonidine- and timolol-treated eyes (Table VII), was highly significant ($P < .001$). Twenty-four (86%) eyes treated with apraclonidine had an IOP decrease during the first 3 postoperative hours. Five (19%) timolol-treated eyes experienced an IOP decrease. Four (80%) of these eyes were not receiving timolol prior to iridotomy. No apraclonidine-treated eyes had an IOP elevation greater than 10 mm Hg during the first 3 hours. Only two (7%) apraclonidine-treated eyes experienced an IOP elevation greater than 5 mm Hg during this time. More timolol-treated eyes had larger IOP elevations. Seven (27%) had IOP elevations greater than 9 mm Hg were reviewed (Table VIII). There was no correlation of age, sex, eye color, or preoperative IOP with large IOP elevations.

There was no difference in anterior segment inflammation between treatment groups. No eye had a visual acuity change greater than 1 Snellen line. Mean heart rate in either treatment group was not significantly different from baseline at any interval (Table IX). There were no drug related adverse reactions in either group of eyes.

One timolol-treated eye required oral glycerin. The preoperative IOP was 27 mm Hg. The IOP increased to 54 mm Hg 3 hours later. The IOP slowly returned to baseline. Preoperatively, this eye received a beta-blocker, carbonic anhydrase inhibitor, and pilocarpine.

PRIMATE STUDY

Six monkeys received bilateral iridotomies. Eyes treated with apraclonidine received the following energy applications to create a patent iridotomy: 1 pulse of 10 mJ (one eye), 1 pulse of 15 mJ (two eyes), 2 pulses of 15 mJ (one eye), and 5 to 6 pulses of 15 mJ (two eyes). In the eyes treated

TABLE VIII: PATIENTS WITH IOP* ELEVATIONS ≥ 10 mm Hg AFTER ARGON LASER IRIDOTOMY

TREATMENT	PATIENT AGE (Y†)/ SEX/RACE	EYE COLOR	PREOPERATIVE IOP (mm Hg)	MAXIMUM IOP RISE DURING FIRST 3 HOURS AFTER OPERATION (mm Hg)
Timolol	64/M/white	Blue	27	+27
Timolol	57/F/white	Brown	27	+16
Timolol	84/F/white	Brown	18	+16
Timolol	65/F/white	Blue	23	+13
Timolol	65/F/white	Blue	19	+13
Timolol	89/F/black	Brown	24	+12
Timolol	86/F/white	Blue	21	+12

*IOP indicates intraocular pressure.
†Y indicates years of age.

TABLE IX: MEAN HEART RATE*: ARGON LASER IRIDOTOMY STUDY

TREATMENT GROUP	TIME					
	PREOP	1 HR	2 HR	3 HR	1 WK	1 MO
Apraclonidine	76.1 ± 11.4	73.5 ± 10.0	73.4 ± 10.2	73.2 ± 9.6	75.2 ± 10.5	73.1 ± 8.8
Timolol	75.9 ± 13.3	70.5 ± 9.1	73.6 ± 11.0	71.8 ± 10.8	71.6 ± 8.8	74.6 ± 9.1

*Beats per minute ± 1 SD.

TABLE X: MEAN IOP IN NEODYMIUM-YAG IRIDOTOMY STUDY

TREATMENT GROUP	IOP*			
	PREOPERATIVE	1 HR AFTER IRIDOTOMY	2 HR AFTER IRIDOTOMY	3 HR AFTER IRIDOTOMY
Apraclonidine	15.0 ± 2.2	13.2 ± 5.6	12.8 ± 3.4	10.8 ± 1.3
Placebo	14.7 ± 2.4	13.3 ± 2.6	12.8 ± 2.1	13.8 ± 2.2

*Mean ± 1 SD (mm Hg).

with vehicle, one eye received a single 10 mJ pulse, one eye received a single 15 mJ pulse, and four eyes required 2 or 3 pulses of 15 mJ. The mean total energy to create an iridotomy was 39 ± 31 mJ for eyes treated with apraclonidine and 32 ± 15 mJ for eyes treated with placebo. This difference was not statistically significant ($P > .7$).

Although there was no significant difference in preoperative IOPs (Table X), the mean IOP decreased during the first 3 hours after iridotomy in both the apraclonidine and placebo-treated eyes. The maximum IOP fall from baseline was greatest at the second postoperative hour in placebo-treated eyes (11% ± 14%) and the third postoperative hour in apraclonidine-treated eyes (27% ± 12%). This IOP decrease was greater in the apraclonidine-treated eyes at the third postoperative hour and approached statistical significance ($P < .1$). No eyes had any IOP rises greater than 3 mm Hg.

Two apraclonidine-treated eyes had no bleeding and the four others had a small drop of blood at the iridotomy margin. All placebo-treated eyes bled. Two had a drop of blood at the margin, one had a small amount of blood flow, and three demonstrated moderate bleeding. This nonparametric difference in bleeding was significant ($P < .05$, chi-square analysis). No eye had a clinically detectable hyphema. One apraclonidine-treated eye had bleeding lasting longer than 1 minute (62 seconds). Four placebo-treated eyes bled longer than 1 minute ($P < .1$). The mean time for bleeding to stop was 31.5 ± 23.8 seconds in the apraclonidine-treated eyes and 68.2 ± 44.5 seconds in placebo-treated eyes ($P < .1$).

DISCUSSION

SAFETY

Clonidine is a relatively selective alpha-2 agonist[57] and is a potent and effective IOP lowering medication.[52,58-63] The IOP lowering of the 0.125% and 0.25% solutions is comparable to 2% pilocarpine hydrochloride.[59] However, topical clonidine is not well accepted because it was found to lower diastolic blood pressure up to 30 mm Hg in 50% of volunteers.[52,58,59] Lower concentrations, delivered as mini-drops, do not satisfactorily reduce the frequency of this cardiovascular complication.[60]

Apraclonidine is a clonidine derivative and is also an alpha-2 agonist.[57] The only difference between clonidine and apraclonidine is the amino group ($-NH_2$) on the C_4 position of the benzene ring (Fig 6). This alteration decreases the lipophilicity of apraclonidine. This lowers its corneal penetration coefficient, increasing its degree of ionization at

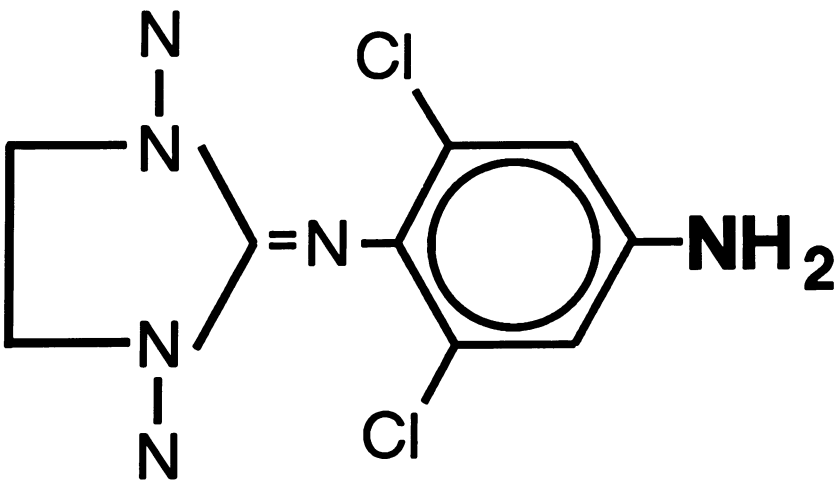

FIGURE 6
Chemical structure of apraclonidine hydrochloride. Amino group (*bold*) on the C_4 position of benzene ring differentiates this drug from clonidine.

physiological pH.[54] It would also be expected to have decreased penetration through the blood brain barrier. This may be responsible for the lack of adverse reactions seen in the present study. No significant effects on resting heart rate were noted. There was no difference in anterior segment inflammation. The frequency of laser-induced corneal and lens burns was not unusual. This profile of apraclonidine's safety agrees with other published reports.[46-49,51,64-66]

There were no significant differences between the heart rates of timolol and apraclonidine-treated patients in either the iridotomy or trabeculoplasty studies. Some studies also have noted that timolol has no effect on resting heart rate.[67-69] Other studies have shown that nonspecific topical beta-blockers can decrease the resting pulse rate.[70] The lack of any difference in the present study may be attributable to the sample size or the brief period (3 hours) of heart rate measurements.

IOP ELEVATION

The literature suggests that large IOP elevations occur more often following iridotomy than trabeculoplasty.[2,3,5,6,8,9,14,15,18-21,33,39,41-48] Although no intentional direct comparison is made, the results of the present study

agree with these observations. In eyes not treated with apraclonidine, 7 (27%) of the 26 eyes undergoing iridotomy had IOP elevations greater than 10 mm Hg compared to only 15 (11%) of the 135 eyes having trabeculoplasty.

Eight (35%) of these 22 eyes with large IOP rises undergoing either procedure required oral glycerin postoperatively. These large elevations might have been missed had the IOP not been measured during the immediate postoperative period. This study reinforces the importance of IOP measurement during the hours immediately following anterior segment laser surgery.[71]

The results of the present study, in eyes treated with apraclonidine, are similar to the results of other studies.[46-48] Apraclonidine effectively lessens the frequency and magnitude of IOP elevations following both argon laser trabeculoplasty and iridotomy. Most eyes treated with apraclonidine had IOP decreases within the first 3 postoperative hours. Only six (4%) apraclonidine-treated eyes in both human studies experienced an IOP elevation greater than 5 mm Hg. Only one (0.7%) had an IOP elevation greater than 10 mm Hg.

Eighty-six percent of apraclonidine-treated eyes undergoing iridotomy and trabeculoplasty had no IOP increase during the first 3 postoperative hours. This was significantly better than timolol-treated eyes. More than 60% of timolol-treated eyes undergoing either procedure had an IOP elevation, rather than an IOP decrease. This IOP response found in timolol-treated eyes does not appear clinically different from that seen in eyes treated with either pilocarpine, dipivefrin, or acetazolamide. Following trabeculoplasty, over 50% of eyes treated with these other agents experienced some IOP elevation during the first 3 hours following laser surgery. The frequency of larger IOP elevations (> 5 mm Hg) in apraclonidine-treated eyes following trabeculoplasty (3%) is significantly ($P < .001$) better than the frequency in eyes treated with timolol (32%), pilocarpine (33%), acetazolamide (39%), and dipivefrin (38%).

Not only was apraclonidine more effective than other medications in decreasing the frequency of IOP spikes, but it was also more effective in lowering the mean IOP. Mean IOP decreased a minimum of 5.0 ± 4.9 mm Hg during the first 3 postoperative hours in apraclonidine-treated eyes undergoing argon laser trabeculoplasty. Mean IOP increased at some time during the first 3 postoperative hours in eyes treated with timolol, dipivefrin, acetazolamide, and pilocarpine. The difference in mean IOP between these non-apraclonidine-treated eyes and eyes treated with apraclonidine was significant ($P < .01$). There was no significant difference in mean IOP between eyes treated with any of the for non-apraclonidine medications.

The large mean IOP decrease in apraclonidine-treated eyes found in this study does not appear markedly different from the decrease found in other studies.[46-48] Here, the mean IOP decrease following iridotomy ranged from 2.8 ± 4.2 mm Hg to 4.4 ± 5.0 mm Hg during the first 3 hours. In a different study,[47] the mean IOP decreased from 4.4 ± 4.5 mm Hg to 5.0 ± 4.1 mm Hg. In a prior study[46] the mean IOP decreased 4.3 ± 4.8 mm Hg to 6.4 ± 5.4 mm Hg following argon laser trabeculoplasty. This is similar to the 5.1 ± 4.9 mm Hg to 7.9 ± 5.0 mm Hg in this study.

Mean IOPs increased during the first 3 postoperative hours when timolol was used following argon laser iridotomy. This change from baseline ranged from 2.5 ± 6.9 mm Hg to 4.8 ± 6.5 mm Hg, and does not appear markedly different from the 3.8 ± 6.6 mm Hg to 4.6 ± 9.4 mm Hg IOP increases previously seen in placebo-treated eyes.[47]

PREVENTING THE IOP ELEVATION

If we knew prospectively which eyes would develop an IOP rise, we could selectively treat these with apraclonidine. However, no known patient characteristic reliably predicts this complication. In a retrospective analysis of 120 eyes undergoing argon laser trabeculoplasty, Schultz and co-workers[72] found that no preoperative patient characteristics correlated positively with this complication. Similarly, no aspects predict which eye undergoing an argon laser iridotomy will experience an acute IOP elevation.

All eyes undergoing trabeculoplasty were on maximum tolerated medical therapy. However, because of allergy or intolerance, many eyes received three or less of the four possible chronic glaucoma medications (Fig 1). Some of these might not have required trabeculoplasty if they could have tolerated additional IOP lowering medications.

Thirteen (87%) of the 15 non-apraclonidine-treated eyes with large IOP elevations (Table IV) were receiving at least three different medications on a chronic basis. It is probably not the increased number of medications, that correlates with the likelihood of an IOP rise. This agrees with the work of Keightley and co-workers.[16] They felt that an IOP rise is more likely in an eye with a decreased coefficient of outflow. This is a reasonable conclusion because poorer-functioning trabecular meshworks might require more medications. These same eyes might not be able to tolerate any additional insult to the trabecular meshwork. Further trabecular meshwork damage might then result in a transient IOP elevation.

Apraclonidine's ability to prevent IOP elevations is important. All eyes undergoing either argon laser iridotomy or trabeculoplasty in this study

had glaucomatous optic nerve damage. These eyes probably lost a minimum of 30% of their axons before developing clinically detectable visual field loss.[73,74] Laser surgery was done to prevent or retard further progression of optic nerve damage. Elevated IOP, even as a transient spike, could conceivably cause further damage.

Since the postoperative IOP rise following argon laser trabeculoplasty and iridotomy occurs frequently and can be sight-threatening, it is ideal to use apraclonidine prophylactically to minimize the frequency of this complication. This increases the laser procedures' safety as apraclonidine is both relatively safe and the most effective agent available. The risks of no prophylaxis appear greater than the risks of unnecessary therapy. It is probably better to prevent this spike from occurring than to wait for treatment until after this complication occurs. IOP lowering might be still more difficult if the IOP spike was high enough to collapse Schlemm's canal.

Apraclonidine's ability to prevent IOP elevations following trabeculoplasty appears better than that of timolol, pilocarpine, acetazolamide, and dipivefrin. Apraclonidine also appears more effective than timolol in preventing the IOP rise associated with iridotomy.

APRACLONIDINE'S MECHANISM OF ACTION

The ocular hypotensive effect of apraclonidine appears primarily due to decreasing aqueous humor flow.[75] I can neither explain why timolol nor acetazolamide, both aqueous humor suppressants, did not alter the postoperative IOP as much as apraclonidine. There appears to be no difference in efficacy in preventing the IOP elevation between these two aqueous suppressants, and pilocarpine and epinephrine, both drugs which increase aqueous outflow.

One reason that timolol may have had less effect than apraclonidine was because 32 (91%) of the eyes in the group randomized to timolol treatment were already being treated with chronic topical beta-blockers. Chronic beta-blockers therapy might have already maximally suppressed aqueous humor production linked to beta-blockade so that the addition of still more beta-blocker achieved no further effect. Another application of timolol in these eyes, at the time of laser surgery, had no apparent clinical value. Acetazolamide, like timolol, was not apparently additive if an eye was already receiving chronic beta-blocker therapy.

On the other hand, 117 (94%) eyes randomized to apraclonidine treatment received preoperative beta-blockers. Twenty-two (19%) of these eyes on beta-blockers also received carbonic anhydrase inhibitors. Two

eyes (2%) were on a preoperative carbonic anhydrase inhibitor but were not on a beta-blocker. Apraclonidine appeared to have an additive effect despite the presence of these other aqueous humor suppressing medications.

Apraclonidine's additivity to beta-blockers may result from several factors. First, apraclonidine has no effect on tonographic outflow facility.[51] Therefore, its IOP-lowering activity should not diminish if there is beta-receptor blockade within the trabecular meshwork. Second, apraclonidine decreases aqueous humor production by as much as 35%,[75] presumably through stimulation of alpha-receptors within the ciliary body. Because apraclonidine is relatively specific for the alpha-2 receptor,[57] its effect on IOP might be less easily antagonized by concurrent beta-blocker therapy. In addition, both beta-agonists and increased sympathetic tone may accelerate aqueous humor production.[76-80] This presumably results from stimulation of beta-receptors, which then activate the enzyme adenylate cyclase, resulting in increased cyclic AMP synthesis.[81] Alpha-2 stimulation by clonidine inhibits adenylate cyclase in the ciliary epithelium and other tissues.[82-84] Since beta-blocking agents would also decrease adenylate cyclase activity, apraclonidine and beta-blockers in combination, may be synergistic. Both medications may lower IOP by inhibition of this enzyme, a controlling step in the formation of aqueous humor.

If aqueous humor suppression alone could significantly alter the postoperative IOP response, one would expect acetazolamide to have a marked effect. Twenty-six (84%) of the eyes which were randomized to acetazolamide treatment did not receive carbonic anhydrase inhibitors on a chronic basis prior to the study. Eighteen (69%) of these 26 eyes had some IOP elevation. Eight (31%) had an IOP elevation greater than 5 mm Hg. This incidence of IOP elevations is greater ($P < .001$) than that seen with apraclonidine treatment. In addition, separate fluorophotometric studies show similar aqueous flow inhibition by both topical timolol and apraclonidine.[75,77] However, 81% of timolol-treated eyes undergoing iridotomy experienced an IOP rise compared to only 14% of apraclonidine-treated eyes. Factors other than increased aqueous humor suppression may also be required to blunt the postoperative IOP rise.

Although only 3% of pilocarpine-treated eyes had large (10 mm Hg) IOP elevations, 30% had IOP elevations between 6 and 10 mm Hg. This does not appear different from the results reported by Ofner and coworkers.[42] It is surprising that pilocarpine did not have a greater effect since only 54% of eyes randomized to this treatment received chronic pilocarpine before trabeculoplasty.

Most eyes randomized to treatment with either of the aqueous outflow enhancing agents (pilocarpine or dipivefrin) were already receiving one of

these medications chronically. Only four (11%) pilocarpine-treated eyes and one (3%) dipivefrin-treated eyes were not receiving either chronic pilocarpine or epinephrine therapy. Twenty (25%) pilocarpine-treated eyes received both chronic pilocarpine and epinephrine before trabeculoplasty. The addition of either more pilocarpine or dipivefrin had no apparent effect on the frequency of large IOP elevations. There is the possibility that the top of the dose response curve for both medications was already reached. Additional drops would then have no better effect. This lack of efficacy could also be attributable to significant pre-existing trabecular meshwork damage, which might prevent increased outflow by the further addition of these agents. This would also indirectly support the hypothesis that poor outflow correlates with an increased incidence of IOP spikes.[16]

Our studies did not test what effect apraclonidine might have on an IOP rise once it has occurred. Our human studies also did not compare the relative efficacy of timolol, acetazolamide, pilocarpine, or dipivefrin to placebo. This study suggested no significant difference between these other glaucoma medications. Apraclonidine was clinically more effective in preventing the IOP spike than any of these agents used alone.

PRIMATE STUDIES

In the primate study there was no significant difference in postoperative IOP elevations between apraclonidine- and placebo-treated eyes. Other studies also note that it is unusual for primate eyes to experience IOP elevations following anterior segment laser procedures.[36-38] Human studies have shown that apraclonidine treatment of one eye can cause an IOP lowering of the fellow, untreated eye.[51] This contralateral effect might have decreased the IOP in placebo-treated eyes, lessening the difference between the two eyes. The IOP lowering seen in the apraclonidine-treated eye might have appeared relatively greater if this medication did not cause contralateral IOP lowering. It is interesting to note that when apraclonidine is used, the maximum percent IOP change from baseline at the third postoperative hour was similar in both the human eyes undergoing argon laser iridotomy (20% ± 20%) and monkey eyes undergoing neodymium-YAG laser iridotomy (27% ± 12%).

We do not know the mechanism of this contralateral effect. We know that other topical medications, such as clonidine[85,86] and timolol,[87] may also cause IOP lowering in fellow untreated eyes. We do not know whether this effect on the nontreated eye is limited to IOP lowering. Perhaps other properties such as vasoconstriction can occur in a fellow eye.[88]

Apraclonidine applied to one eye may have a vasoconstrictive effect on the fellow eye. If this is the case, the difference in bleeding between apraclonidine- and placebo-treated eyes would have appeared even greater if only one eye of each animal had been treated or if more animals were treated. Bleeding in apraclonidine-treated eyes lasted for a shorter time and was present to a lesser degree. Apraclonidine 1.5% decreases iris blood flow by approximately 70% 1 hour after its topical application.[54] This was detected in an investigation using tritiated microspheres. The technique was similar to one previously used to study clonidine.[53] Our study supports this finding in that there was less bleeding after neodymium-YAG laser iridotomy in apraclonidine-treated eyes.

The grading used to quantify iris bleeding in this study was admittedly arbitrary. The results (both a decreased quantity and duration of bleeding) which were almost statistically significant, suggest that apraclonidine does acutely decrease iris blood flow or increase hemostasis in monkeys. This hemostasis might be helpful during neodymium-YAG laser iridotomy in humans where bleeding is a frequent complication.[2,3] Bleeding following neodymium-YAG iridotomy is rarely severe enough to cause total hyphema, requiring surgical intervention.[55] This vasoconstriction might theoretically benefit a surgeon during cataract and corneal surgery, where anterior segment bleeding can also be a serious problem. We need further studies to determine the clinical value of apraclonidine-induced vasoconstriction in humans. We also should determine whether the same IOP lowering apraclonidine affords for eyes treated with argon laser iridotomy also occurs following Q-switched neodymium-YAG laser iridotomy.

FUTURE USES FOR SHORT-TERM 1% APRACLONIDINE

Short-term apraclonidine may have a role in other procedures involving glaucomatous eyes. A transient IOP spike and iris bleeding can also complicate Q-switched neodymium-YAG laser posterior capsulotomy. Preoperative miotics would decrease visualization of the posterior capsule. The efficacy of postoperative miotics is controversial.[89,90] Timolol and levobunolol hydrochloride are both effective prophylactic agents against the IOP spike accompanying capsulotomy.[90-92] However, these studies exclude glaucomatous eyes and the eyes of patients with systemic disease in which topical beta-blockers are contraindicated. Apraclonidine is effective in preventing the IOP rise following posterior capsulotomy in eyes both with and without pre-existing glaucoma.[48,49] Further studies might prove that apraclonidine prevents this IOP rise in glaucomatous eyes, and also decreases bleeding.

Bleeding and IOP elevation complicate cataract surgery. In nonglaucomatous eyes, topical and intracameral miotics decrease the frequency of the IOP rise.[93-95] This complication still occurs despite the use of these miotics. The addition of topical beta-blockers adds only slightly in some series[92,96,97] but much more in another study.[98] We need studies to evaluate whether apraclonidine is additive to miotics and beta-blockers in normal and glaucomatous eyes undergoing cataract surgery. Apraclonidine's mydriatic and vasoconstrictive effects could also be helpful in these eyes.

CONCLUSION

This study accurately characterizes the present value and role of short-term 1% apraclonidine therapy for laser trabeculoplasty and iridotomy. Apraclonidine does not totally eliminate IOP elevations following laser surgery. However, it is significantly more effective in preventing the IOP spike following argon laser trabeculoplasty than either timolol, pilocarpine, acetazolamide, or dipivefrin. It is also more effective than timolol in minimizing acute IOP elevations following argon laser iridotomy. Apraclonidine appears effective when added to chronic medical therapy: both aqueous suppressants and outflow enhancers. The two apraclonidine drops required for adequate prophylaxis appear safe and well-tolerated.

There are many potential applications for short-term apraclonidine therapy. The primate study suggests that apraclonidine may have a clinical value in decreasing iris bleeding associated with neodymium-YAG laser iridotomy. Studies are currently underway to further investigate the potential benefits which this drug offers.

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