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Influence of apraclonidine and pilocarpine alone and in combination on post laser trabeculoplasty pressure rise

R B Dapling, I A Cunliffe, S Longstaff

Abstract

Apraclonidine and pilocarpine have been shown to be effective in reducing the incidence of intraocular pressure (IOP) spikes following argon laser trabeculoplasty. An additional reduction in the incidence of acute pressure rise might theoretically be expected by combining these two effective agents. In a prospective randomised study we compared the ability of apraclonidine and pilocarpine alone and in combination to prevent post laser pressure spikes. Patients receiving regular pilocarpine to either eye were excluded. Seventy five eyes received either apraclonidine (26 eyes), pilocarpine (23 eyes), or both drugs (26 eyes). Apraclonidine 1% was instilled 1 hour before and immediately after, and pilocarpine 4% immediately after trabeculoplasty. IOP was measured before and at 1, 2, and 3 hours following trabeculoplasty. In only two (8%) eyes receiving combined treatment was a pressure rise observed. This frequency was significantly lower than that seen in eyes treated with apraclonidine alone (38%), or pilocarpine alone (39%). The mean fall in IOP at 1, 2, and 3 hours was significantly greater in those eyes receiving combined treatment than in the other two groups.

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Argon laser trabeculoplasty (ALT) now has an established place in the treatment of raised intraocular pressure (IOP). However, over the past 10 years a number of investigators have reported a transient rise in IOP following this procedure.[1–4] It is now apparent that this elevation in IOP can result in optic nerve damage and the consequent loss of acuity[4] and field.[1,2] In the light of this evidence, acute pressure rises following ALT must be considered as a potential hazard to visual function, and their prevention is clearly desirable.

Medical prophylaxis in patients undergoing ALT may be difficult as many eyes are already receiving topical therapy. Timolol has been shown to prevent pressure rises in patients undergoing primary trabeculoplasty.[5] Conflicting evidence has been reported as to the effectiveness of acetazolamide in suppressing IOP elevations.[2,6,7] Pilocarpine[8] and apraclonidine[9] have both been found to reduce the incidence and level of IOP rise following ALT when compared with placebo. While these studies are clear evidence of the value of prophylaxis, pressure spikes do still occur following ALT, despite treatment.

An additional reduction in the incidence of acute pressure rise might theoretically be expected by combining two effective agents with different mechanisms of action. Apraclonidine hydrochloride is an α2 agonist and lowers IOP by reducing the rate of aqueous production. Pilocarpine increases the rate of aqueous outflow by its mechanical effect on the trabecular meshwork. In this study, we compared apraclonidine and pilocarpine, alone and in combination, in their ability to prevent post ALT pressure spikes.

Patients and methods

All eyes had open angle glaucoma with an IOP greater than 21 mm Hg. Patients were excluded if either eye was currently receiving pilocarpine, or active ocular infection or inflammation was present. Also excluded were patients with unstable cardiovascular disease and any patients taking systemic clonidine. If both eyes required laser trabeculoplasty, then the first eye to be treated was entered into the study. The study had ethical committee approval and patients gave their written informed consent.

All patients received their regular topical treatment before trabeculoplasty. Baseline examination included corrected visual acuity, applanation tonometry using a calibrated tonometer reserved exclusively for study patients, slit-lamp examination, heart rate, and blood pressure. Patients were then randomly allocated to one of three treatment groups. The apraclonidine treated group (group A) received one drop of apraclonidine 1% 1 hour before and immedi-

Table 1 Patient demographic data

	Treatment group		
	Apraclonidine	*Pilocarpine*	*Combination*
Number of patients	26	23	26
Age (years)			
Range	53–84	53–86	46–87
Mean	72·2	68·4	71·3
Eye colour			
Blue	18 (69%)	14 (61%)	16 (62%)
Brown	8 (31%)	9 (39%)	10 (38%)
Glaucoma type			
Number of patients			
Chronic open angle	26 (100%)	19 (83%)	21 (81%)
Pseudoexfoliation	0 (0%)	1 (4%)	4 (15%)
Pigmentary	0 (0%)	3 (13%)	0 (0%)
Fuchs' heterochromia	0 (0%)	0 (0%)	1 (4%)
Glaucoma medication			
Number of patients			
β Blocker			
Carteolol	11 (42%)	8 (35%)	8 (31%)
Timolol	10 (38%)	12 (52%)	15 (58%)
Betaxolol	1 (4%)	0 (0%)	1 (4%)
Levobunolol	1 (4%)	1 (4%)	0 (0%)
Adrenaline	1 (4%)	0 (0%)	0 (0%)
Dipivetrine	2 (8%)	0 (0%)	0 (0%)
No treatment	2 (8%)	2 (9%)	2 (8%)

Department of Ophthalmology, Royal Hallamshire Hospital, Sheffield
R B Dapling
I A Cunliffe
S Longstaff

Correspondence to:
Mr R B Dapling, Department of Ophthalmology, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

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Table 2 Mean intraocular pressures (IOP) and 95% confidence intervals in each group throughout the study period

Time	Treatment group (Mean IOP (95% confidence interval))		
	Apraclonidine	*Pilocarpine*	*Combination*
Preoperative	26·8 (25·1 to 28·5)	26·5 (24·7 to 28·3)	27·4 (25·6 to 29·2)
1 Hour	24·3 (21·9 to 26·7)	26·0 (23·8 to 28·2)	21·1 (19·0 to 23·2)
2 Hours	22·3 (19·5 to 25·1)	21·4 (19·0 to 23·8)	17·2 (15·6 to 18·8)
3 Hours	21·8 (19·1 to 24·5)	19·0 (16·7 to 21·3)	15·6 (14·0 to 17·2)
1 Week	22·6 (21·0 to 24·2)	21·6 (19·8 to 23·4)	23·1 (21·0 to 25·2)

ately after laser treatment. The pilocarpine treated group (group B) received one drop of pilocarpine 4% immediately after laser treatment. The combination treated group (group C) received both the above schedules. Argon laser trabeculoplasty was performed by the same person (RBD) in all cases and consisted of treatment over 180 degrees using between 50 and 60 burns with a spot size of 50 μm placed on the anterior trabecular meshwork. Each application was of 0·2 seconds' duration and between 800 mW and 1000 mW to achieve an end point of blanching or a bubble.

IOP, heart rate, and blood pressure were then recorded at 1, 2, and 3 hours post treatment. Three IOP readings were taken at each recording and their mean calculated. The observer was masked to the study group of the patient. Patients were then examined again at approximately 1 week and the measurements repeated. Probability testing was by analysis of variance[10] and χ^2.

Results

Seventy five eyes were entered into the study. There was no statistically significant difference between the groups with respect to age, eye colour, type of glaucoma, or glaucoma medication (Table 1). All patients had similar disease as judged by single medication, duration of disease, and cumulative treatment. Table 2 and Figure 1 show the mean IOP measurements in each group throughout the study period. There was no statistical difference between the preoperative IOPs in the three groups. At 1, 2, and 3 hours after laser treatment, the mean IOP in group C

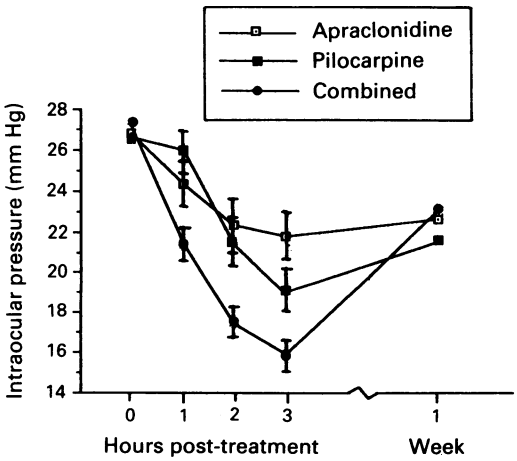

Figure 1 Mean (SE) intraocular pressures in each group preoperatively and at 1, 2, 3 hours, and 1 week following argon laser trabeculoplasty.

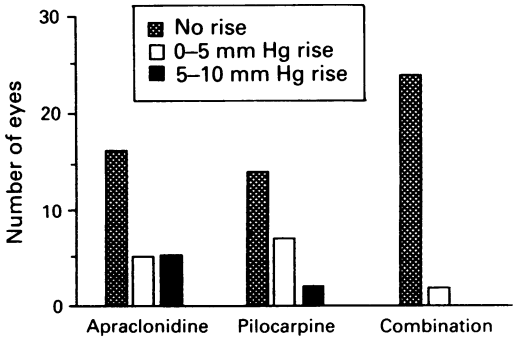

Figure 2 Bar graph showing the number of eyes in each group that had a rise in intraocular pressure following argon laser trabeculoplasty.

was lower than in either groups A or B. The fall in IOP in group C was significantly greater than groups A and B at 1, 2, and 3 hours ($p=0·006$, $p=0·001$, $p<0·001$ respectively). The change in IOP between groups A and B was not significantly different. At 1 week there was no difference in IOP between the groups.

During the first 3 hours, 21 eyes had a rise in IOP (Fig 2). The highest IOP was recorded in 17 (81%) eyes at 1 hour and in two (9·5%) eyes at each of the second and third hours. No rises were greater than 10 mm Hg. Ten eyes in group A and nine eyes in group B had a rise in pressure. Only two eyes in group C had a rise in IOP and in both cases this was less than 1 mm Hg. The frequency of pressure spikes in group C was significantly less than that in eyes in group A or group B ($p\leq0·02$). All eyes in which a pressure rise was seen had chronic open angle glaucoma and 43% had brown irides, compared with 37% in the study as a whole. At 1 week 61 eyes (81%) had a reduction (mean 6·9 mm Hg) in IOP.

Discussion

Transient IOP rise is now a well recognised complication of anterior segment laser treatment. Subsequent loss of vision in such circumstances has been noted following neodymium YAG capsulotomy,[11 12] argon laser iridotomy,[13] and ALT.[4] Visual field loss has also been documented following ALT.[12] Uncontrolled high pressure following cataract surgery has also resulted in loss of visual acuity and central field in a glaucomatous eye.[14] The prevention of these complications is clearly desirable and many prophylactic treatments have been evaluated. The largest study in the literature to date involved a comparison of apraclonidine, timolol, pilocarpine, acetazolamide, and dipiverin in 260 eyes undergoing ALT.[15] In this study, apraclonidine was more effective than other treatments in reducing the incidence of IOP elevation following ALT; however, pressure rises were still observed in all treatment groups. Although topical medications undoubtedly reduce the incidence of post laser IOP spikes, potentially serious rises in IOP are still recorded. Such pressure rises are more likely to occur following ALT when 360 degrees rather than 180 degrees of meshwork are treated.[12] The combining of two effective agents with different mechanisms of action might theoretically be expected to result

in additional reduction in the incidence of acute pressure rises.

In this study, we have shown that apraclonidine and pilocarpine in combination appear to provide significantly better protection against pressure spikes than either alone. A small rise in IOP (less than 1 mm Hg) was seen in two eyes (8%) in group C compared with 10 eyes (38%) in group A and nine eyes (39%) in group B (median 5·5 mm Hg and 2·7 mm Hg) respectively. The rise seen in the two eyes in group C is less than 1 mm Hg which is probably not clinically significant.

In our study, no eyes had a pressure rise of more than 10 mm Hg. We postulate two reasons why this might be so. Firstly, as judged by number of medications our patients had a lower disease severity than in other similar studies where patients were already on maximum tolerated topical therapy. Secondly, we specifically excluded eyes receiving pilocarpine thus ensuring its maximum therapeutic effect.

Patients already receiving regular pilocarpine may not benefit to the same extent from its use at the time of ALT. A study by Robin[15] supports this suggestion. In a group of patients receiving pilocarpine at the time of ALT, he recorded postoperative IOP rises in 57% of cases, higher than the 39% that we observed in our pilocarpine group. However, 54% of eyes in his pilocarpine group were already receiving the drug on a regular basis, whereas we excluded such patients from our study. Even if the prophylactic benefit of pilocarpine is reduced by its regular use before ALT, it would seem appropriate to give an additional dose at the time of ALT to ensure that therapeutic levels are attained at the time when they are most beneficial.

The benefit of apraclonidine and pilocarpine in combination is apparent throughout the 3 hour study period. The fall in IOP which was observed in group C was significantly greater than in groups A and B at 1, 2, and 3 hours (Fig 1). Figure 1 also shows the effect of administering apraclonidine and pilocarpine at different times. The maximum rate of fall in IOP in group A is in the first hour with a slight levelling off during the second and third hours. In group B there is no appreciable change in IOP during the first hour, but a rapid fall in IOP in the second and third hours. This suggests that the maximum effect of apraclonidine occurs before that of pilocarpine. The combination of both drugs in group C results in a rapid fall in IOP that is maintained throughout the 3 hour measurement period. While this gives protection against IOP spikes for 3 hours or more after ALT, most spikes have been shown to occur within the first 2 hours.[16] Our results support these findings with 81% (17 eyes) of IOP spikes occurring in the first hour. Therefore it would seem appropriate to target maximum protection at the first 2 hours following ALT, and to this end perhaps we should have administered pilocarpine 1 hour preoperatively in the same way as apraclonidine.

The use of apraclonidine and pilocarpine in combination in our series of patients has been totally protective against clinically significant pressure spikes following ALT. Such protection will be of particular benefit (i) to eyes with severe optic disc cupping that are at risk of visual field and acuity loss, and (ii) to eyes in which 360 rather than 180 degrees of ALT are contemplated. However, if 360 degrees rather than 180 degrees of ALT are performed then pressure spikes could possibly be higher and even the combined use of apraclonidine and pilocarpine may be inadequate to prevent them completely.

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