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Clinical superiority of either of topical 0.5% apraclonidine, 0.2% brimonidine and 0.03% bimatoprost given prophylactically in managing intraocular pressure spikes following Nd:YAG laser posterior capsulotomy

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Abstract
Background: Extracapsular cataract extraction (ECCE) with implantation of posterior chamber intraocular lens (PC IOL) is currently the surgery of choice for cataract, with the success rate of over 95%.
Objectives: To earmark clinical superiority of either of the drugs given prophylactically in managing intraocular pressure spikes following Nd:YAG laser posterior capsulotomy.
Method: The present study was conducted on 100 patients, who had developed posterior capsule opacification following successful cataract surgery with intraocular lens implantation and underwent Nd:YAG laser posterior capsulotomy in the Outpatient Department of Ophthalmology, RMCH.
Results: In Apraclonidine group, pressure differences with control group were evident at 3 hours (ΔP_3) & at 24 hours (ΔP_{24}) that were highly statistically significant; (p=0.0078 & 0.0045 for ΔP_3 & ΔP_{24} respectively). The same were not significantly different (p> 0.05) at 1 hour or day 7 following laser application. The Briminodine group demonstrated significant differences in pressure fluctuations compared with control group at all recorded times with maximum variation noted at 3 hours post capsulotomy (p=0.000015).
Conclusion: It was concluded Both Apraclonidine & Briminodine are found useful drug interventions in laser therapy, but Briminodine clearly scores over former in dampening the IOP rise.

Keywords: posterior capsular opacification, apraclonidine, briminodine, intraocular pressure

Introduction

The incidence of posterior capsular opacification (PCO) has been noted to be varied depending on both patient & surgeon related factors. Boulton *et al.* reported 18-50% incidence of PCO in adults followed up for five years after the in the bag (IOL) implantation [1].

Peng Q *et al.* observed that the development of posterior capsule opacification is a dynamic process [2]. Opacification, stems from continued viability of the lens epithelial cells (LECs) that remain after the removal of nucleus and cortex. The incidence of PCO formation is higher in younger patients. In fact the incidence of PCO formation is near 100% in patients of the pediatric age group that undergo surgery.

The interval between cataract surgery and opacification of posterior capsule varies widely, ranging from 2 months to 5 years [3]. Also the visual symptoms do not always correspond with the observed amount of PCO. Visually significant PCO is managed by creating an opening in the opaque capsule.

Earlier, the treatment of PCO was surgical dissection of the capsule using Zeigler Knife or aspiration of Elschnig pearls or even polishing of posterior capsule with an irrigation and aspiration device. These methods required an intraocular invasive procedure.

Currently the photo-disruptive effect of Neodymium: Yttrium-Aluminium-Garnet laser (Nd:YAG) is employed for posterior capsulotomy [4].

Nd:YAG laser is a solid state laser which contains garnet crystal consisting of yttrium and aluminium oxides in which roughly 1-2% of yttrium ions are replaced by neodymium. An intense light source in this laser activates the electrons to an excited state and the energized ions emit amplified photons of light at a wavelength of 1064 nm.

The incidence of IOP rise after Nd:YAG laser capsulotomy has been reported to vary from 39% to 77% in various studies [4]. Frequency of intraocular pressure elevations greater than 10 mm Hg has been variably observed in 15 to 67% eyes [5].

IOP typically begins to rise immediately after laser capsulotomy, peaks at 3 to 4 hours, then decreases. It may remain elevated at 24 hours but usually returns to baseline at 1 week [6].

A variety of drugs have been used for prophylaxis of IOP rise after Nd:YAG laser posterior capsulotomy, such as Apraclonidine [7], Brimonidine, Timolol, Levobunolol [8], Carbonic anhydrase inhibitors [9] & currently the prostaglandin analogues such as Bimatoprost. Unfortunately, much of their use is empirical in the Nd:YAG procedures adding an element of subjectivity. The present study intends to earmark clinical superiority of either of the three commonly used drugs in this procedure, *viz.* Apraclonidine, Brimonidine & Bimatoprost. It is further intended to explore the pattern of IOP fluctuations following their use which may account beneficial to the treating physician at large.

Methods

This study was conducted in the Department of Ophthalmology, Rohilkhand Medical College and Hospital, Bareilly over a period of 1 year, on 100 consecutive patients of 'Posterior capsular opacification' following uneventful Extracapsular cataract extraction. Permission for the study was obtained from the College authorities prior to commencement. Exclusion criteria were employed for exclusion in the study.

Prior to the procedure, an informed written consent was taken from all the patients. Patients were randomly distributed into four groups of 25 patients each:

- Group I acted as control group in which single drop of topical Ciprofloxacin 0.3% was instilled one hour before Nd:YAG laser posterior capsulotomy.
- Group II acted as the broad study group with three subdivisions of 25 patients each, which were instilled with a single drop of the studied drug, *viz.* 0.5% Apraclonidine, 0.2% Brimonidine & 0.03% Bimatoprost on a similar pattern as of the control group

A uniform standard protocol of the procedure was followed for all patients. This included:

A. Record of demographic details and clinical history of all patients on a clinical proforma.
B. A general physical & systemic examination to explore any co existing morbidity.
C. A detailed Ocular examination to include following key parameters:
   i) Unaided & best corrected Visual acuity of tested eye using Snellen's chart
   ii) Slit lamp examination of anterior segment
   iii) Fundus examination using direct ophthalmoscope & 90 D mirror
   iv) Goldmann applanation tonometry. Measurements were taken 1hour prior to capsulotomy (after dilating the pupil) as well as at the intervals of 1, 3, 24 hours & 7 days post procedure & recorded on the clinical proforma.
D. YAG Laser capsulotomy schedule was similarly placed on uniform guidelines for each of the 100 tested patients.
E. A standard drug regimen of 1% Predinsolone acetate 6 hourly for 7 days was followed for each patient.

Statistical analysis

Data was recorded in a tabulated manner in the Microsoft Excel worksheet and statistical analysis was done using SPSS 21.0 software. Multivariate analysis was performed employing ANOVA while univariate analysis was carried out using the unpaired Student's t test. A p-value<0.05 was considered statistically significant.

Result

All four groups had comparable age, ranging between 62.8 to 63.2 years (p=0.99). A slight male preponderance was seen in the Control group (72%) as against other groups *viz*. 68% in Apraclonidine group, 56% in Brimonidine group and 60% in Bimatoprost group. In all groups, right eye was more commonly affected with an overall approximate ratio of 3:2. Pre-laser BCVA was comparable in all four groups when analysed using one way ANOVA test (p=0.733). On day 7, about 90% patients had a post-laser BCVA of 6/12 or more and results were similar in all groups (p=0.903).

Pre-laser IOP was comparable in all four groups (p=0.820). Post-laser IOP at 1st hour and at 3rd hour showed differences among the groups that were statistically significant (p=0.005 at 1 hour & p<0.001at 3 hours). IOP differences were nevertheless comparable on 1st day (p=0.100) and after 1 week (p=0.570). Comparative analysis of changes in IOP (ΔP) for all groups done at different time intervals revealed highly statistically significant difference (p<0.001).

Comparison of individual study sub-group with control group was done using unpaired Student's t-test. In Apraclonidine group, pressure differences with control group were evident at 3 hours (ΔP_3) & at 24 hours (ΔP_{24}) that were highly statistically significant; (p=0.0078 & 0.0045 for ΔP_3 & ΔP_{24} respectively). The same were not significantly different (p>0.05) at 1 hour or day 7 following laser application. Table 1.

The Briminodine group demonstrated significant differences in pressure fluctuations compared with control group at all recorded times with maximum variation noted at 3 hours post capsulotomy (p=0.000015). IOP fluctuations following prophylactic administration of Bimatoprost followed a pattern similar to Briminodine with highly significant pressure changes compared to the control group (p<0.00001) at 1, 3 & 24 hours post capsulotomy. Employing students t test, the maximum difference was again noted at 3 hours; (t = 7.090, p<0.00001). Table 2.

In addition to the pressure difference (ΔP), even the mean pressure values taken after Bimatoprost instillation were significantly different at 1, 3 & 24 hours. Mean pressure values tended to normalize by day 7 when the effect of the drug waned. Mean pressure value was noted different only at third hour following Briminodine administration and at no time following the use of Apraclonidine. Table 3.

The substantiality of Bimatoprost in pressure control is hence demonstrated at all times as well as its superiority in reverting pressure spikes following YAG capsulotomy. Both Apraclonidine & Briminodine are found useful drug interventions in laser therapy, but Briminodine clearly scores over former in dampening the IOP rise. Table 4.

Table 1: Comparative analysis of IOP change between control group (Group I) and apraclonidine group (Group IIA)

Period	Group	Mean ± SD	T	*P* – value
P0	I	13.12±3.04	-0.9295	0.357
	II A	13.84±2.44		
P1	I	15.2±2.82	0.2110	0.833
	II A	15.04±2.52		
P3	I	16.48±3.17	0.9134	0.365
	II A	15.76±2.33		
P24	I	15.12±2.77	0.8016	0.426
	II A	14.56±2.12		
Pf	I	14.24±2.66	-0.3585	0.721
	II A	14.48±2.02		
ΔP1	I	2.08±1.57	1.7728	0.082
	II A	1.2±1.91		
ΔP3	I	3.36±1.97	2.7747	0.0078
	II A	1.92±1.68		
ΔP24	I	2±1.73	2.9754	0.0045
	II A	0.72±1.27		
ΔPf	I	1.12±1.30	1.4012	0.167
	II A	0.64±1.11		

(Statistical analysis using student's t-test)

Table 2: Comparitive analysis of IOP change between control group (Group I) and brimonidine group (group IIB)

Period	Group	Mean ± SD	T	*P* – value
P0	I	13.12±3.04	-0.3750	0.709
	II B	13.44±3.02		
P1	I	15.2±2.82	1.5	0.140
	II B	14±2.82		
P3	I	16.48±3.17	2.864	0.0061
	II B	14.16±2.51		
P24	I	15.12±2.77	1.3805	0.173
	II B	14.08±2.54		
Pf	I	14.24±2.66	0.6221	0.536
	II B	13.76±2.78		
ΔP1	I	2.08±1.57	3.1026	0.0032
	II B	0.56±1.87		
ΔP3	I	3.36±1.97	4.809	0.000015
	II B	0.72±1.90		
ΔP24	I	2±1.73	3.3023	0.0018
	II B	0.64±1.11		
ΔPf	I	1.12±1.30	2.664	0.0104
	II B	0.32±0.74		

(Statistical analysis using student's t-test)

Table 3: Comparative analysis of IOP change between control group (Group I) and bimatoprost group (Group IIC)

Period	Group	Mean ± SD	T	*P* – value
P0	I	13.12±3.04	-0.6807	0.4993
	II C	13.68±2.80		
P1	I	15.2±2.82	3.3282	0.0016
	II C	12.8±2.23		
P3	I	16.48±3.17	4.2687	0.000092
	II C	13.2±2.16		
P24	I	15.12±2.77	2.341	0.0233
	II C	13.44±2.27		
Pf	I	14.24±2.66	0.883	0.3811
	II C	13.6±2.45		
ΔP1	I	2.08±1.57	6.1173	<0.00001
	II C	-0.88±1.83		
ΔP3	I	3.36±1.97	7.090	<0.00001
	II C	-0.48±1.85		
ΔP24	I	2±1.73	5.3152	<0.00001
	II C	-0.24±1.2		
ΔPf	I	1.12±1.30	3.7796	0.0004
	II C	-0.08±0.90		

(Statistical analysis using student's t-test)

Table 4: Comparative analysis of IOP change between aprclonidine group (Group IIA), brimonidine group (Group IIB) and bimatoprost group (Group IIC)

	Group	Mean	Variance	F	*P* - value
P0	II A	13.84	5.973	0.131944	0.876601
	II B	13.44	9.173		
	II C	13.68	7.893		
P1	II A	15.04	6.373	4.864418	0.010434
	II B	14	8		
	II C	12.8	5		
P3	II A	15.76	5.44	7.642567	0.000978
	II B	14.16	6.306		
	II C	13.2	4.667		
P24	II A	14.56	4.506	1.464138	0.23808
	II B	14.08	6.493		
	II C	13.44	5.173		
Pf	II A	14.48	4.093	0.922388	0.402215
	II B	13.76	7.773		
	II C	13.6	6		
ΔP1	II A	1.2	3.667	8.081013	0.000682
	II B	0.56	3.506		
	II C	-0.88	3.36		
ΔP3	II A	1.92	2.82	10.93117	0.000071
	II B	0.72	3.62		
	II C	-0.48	3.42		
ΔP24	II A	0.72	1.626	4.941176	0.009753
	II B	0.64	1.24		
	II C	-0.24	1.44		
ΔPf	II A	0.64	1.24	3.715736	0.029123
	II B	0.32	0.56		
	II C	-0.08	0.826		

(Statistical analysis using ANOVA test)

Discussion

Most studies have however compared the result in terms of the percentage of patients achieving a significant IOP elevation of 5 mm Hg or more. The lack of standardization of parameters, have contributed to the discrepancy in results. Cullom RD Jr and Schwartz LW when comparing postoperative IOP effects in 53 lasered eyes that received 0.5% Apraclonidine, preoperatively, reported an IOP elevation ≥ 5 mm Hg in only 13% patients while 59% eyes suffered from an IOP elevation above 5 mm Hg in non-recipient group. On a similar note 10 mm Hg elevation was observed in 4% recipients and 27% non-recipients [10]. In normal subjects, apraclonidine produced a significant decrease in IOP beginning 1 hour after its instillation and lasting at least 12 hours [11].

Double masked studies comparing Brimonidine 0.2% with Apraclonidine 0.5% rated equal efficacies of these drugs in preventing IOP elevation. However a distinct advantage of Bimatoprost 0.03% in preventing post laser IOP elevation was suggested by Artunay *et al.* when comparing results with Brimonidine 0.2%. They reported an average peak post-operative IOP elevation of 2.2 ± 3.9 mm Hg with the Bimatoprost group against 3.6 ± 3.1 mm Hg in the Brimonidine group. This difference was statistically significant (p<0.001). Similarly post-operative IOP elevation of 10 mm Hg or more was reported in only 1 (1.56%) of the 195 eyes tested as against 5 eyes (7.35%) in the Brimonidine group. This difference was again statistically significant (p<0.001) [12].

In an Indian study, 0.2% Brimonidine proved efficacious in controlling post capsulotomy IOP spikes in 80% of the subjects [13]. Calli *et al.* [14] in a Turkish trial revealed a significantly lower first hour & first day IOP from baseline in Briminodine group, compared to the pre laser & control group values. Yeom *et al.* documented similar observations where IOP decreased from the baseline in the group instilled with Brimonidine [15]. Our study noted mimimal IOP variation with mean values below 1 mm Hg following Brimonidine usage. The IOP control was less effective with Apraclonidine, where mean IOP levels were 1.2 ± 1.91, 1.92 ± 1.68 & 0.72 ± 1.27 mm Hg above pre-operative levels at 1,3 & 24 hours respectively. Bimatoprost, a synthetic prostamide is known to reduce IOP by promoting both the pressure sensitive as well as the pressure insensitive outflow of aqueous humor. It has no significant effect on aqueous humor formation. Williams RD *et al*, while comparing long term safety & efficacy of 0.3% Bimatoprost with 0.5% Timolol demonstrated a significantly lower IOP reduction with Bimatoprost (7.0 to 8.1 mm Hg) compared to Timolol (3.8 to 5.8 mm Hg) during a 4 year period [16]. Favorable reports of 0.03% Bimatoprost in controlling post laser capsulotomy laser spikes are available. Reported side effects of Bimatoprost like conjunctival hyperemia, growth of eyelashes and ocular pruritus have insignificant role due to a single usage of drug.

Our study while comparing together clinical efficacies of these drugs ensured similarity of sample frame and sizes as well as patient characteristics and procedural uniformity. Employing student's t test, IOP changes following Apraclonidine changes show significance from third hour postoperatively (p<0.05), unlike parallel studies that figure these changes from the first hour itself. A probable explanation for this difference may lie in the configuration of drug administration, where Apraclonidine has been instilled both pre & post laser application. In addition majority of previous studies have used Apraclonidine in a concentration of 1% while we had used 0.5% Apraclonidine for its prophylactic use. Similar analysis for both Briminodine & Bimatoprost groups reveal marked pressure differences, (p<0.01) from first hour itself that seem to revert very gradually even after 1 week. The changes noted with Bimatoprost reveal higher significance, (p<0.00001) at all times of IOP record compared with Briminodine. IOP difference with Bimatoprost use remains highly significant

(p=0.0004) even at 1 week post laser, compared to control group. This highlights the long acting nature of the drug. The marked reduction in IOP following Bimatoprost use has been noticed despite the highest energy deliverance in this group of patients. This fact underscores the importance of pharmacological agent rather than the physical factor of energy deliverance in the modulation of Intra ocular pressure.

Not many studies are available that explore IOP changes following prophylactic use of prostaglandin analogues in laser treatment. Even the trend of usage of this class of drugs like Bimatoprost has not been established probably due to the ill-conceived notion of these drugs abetting inflammatory changes. Nevertheless our limited study underscores their efficacy not only in controlling post LASER IOP spikes but also in reducing IOP levels below baseline for a prolonged period. The latter fact is of special importance in glaucomatous or oculo-hypertensive eyes that remain at a special risk of visual field loss even with minor transient pressure elevations.

Conclusion

The substantiality of Bimatoprost in pressure control is hence demonstrated at all times as well as its superiority in reverting pressure spikes following YAG capsulotomy. Both Apraclonidine & Briminodine are found useful drug interventions in laser therapy, but Briminodine clearly scores over former in dampening the IOP rise.

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Declarations

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Conflict of interest: None

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