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Original Research Paper

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DIURNAL VARIATIONS OF INTRAOCULAR PRESSURE IN PRIMARY ANGLE CLOSURE DISEASE PATIENTS UNDER TREATMENT.

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ABSTRACT

Purpose: To observe diurnal variations in intraocular pressure (IOP) among patients with primary angle closure disease (PACD) who are under treatment. **Materials and Methods:** A cross-sectional study was conducted between July 2018 and April 2019 in which PACD patients including Primary angle closure suspect(PACS),Primary Angle Closure(PAC) and Primary Angle Closure Glaucoma (PACG) patients, who underwent laser peripheral iridotomy or followed by trabeculectomy surgery with or without additional medical antiglaucoma treatment, were included. They underwent applanation tonometry at 4-hourly intervals over a 24 hour period. **Results:** A total of 38 PACD patients (19 males,19 females;75 eyes) were identified and evaluated. An IOP variation of ≥ 8mmHg was considered as significant Diurnal variation test (DVT). Total 41(54.6%) eyes showed significant DVT; 36(48%) eyes showed peak at 4 am out of which 24(66.66%) eyes meeting the criteria of significant DVT(p value =0.04).The mean IOP at 4 am (17.05±7.50mmHg) was significantly higher compared to all other time points. On comparing the groups which showed significant DVT, significant difference was seen between patients with different treatment modality [LPI (65%),LPI with antiglaucoma medication(60.5%), trabeculectomy (28.5%), trabeculectomy with antiglaucoma medication(10%)] (chi square=11.067, p = 0.0009). **Conclusion:** PACD patients show significant diurnal variations of IOP despite it believed to be under control during office-hour measurement, which makes the nature of disease progressive. A simple test such as diurnal variation of IOP measurement may have a prognostic value in PACD patients who are considered being stable for a prolonged period.

KEYWORDS : Diurnal variation in Intraocular pressure, Primary Angle Closure Glaucoma, Primary Angle Closure, Primary Angle Closure Suspects, Primary Angle Closure Disease

INTRODUCTION

Glaucoma is an optic neuropathy characterized by typical visual field defects and structural changes of optic nerve head. Glaucoma is the second leading cause of irreversible yet preventable blindness worldwide, accounting for almost 8% of global blindness[1]. An estimated 80 million people in the world were affected by primary glaucoma in the year 2020[2].

Intraocular pressure (IOP) remains the key clinical parameter for initiating glaucoma treatment and is one of the main targets in daily practice to control the disease and its progression. The intraocular pressure is an easily measurable and only modifiable factor in the treatment of glaucoma.Both high IOP [3-5]and IOP fluctuation [6] are potential risk factors for the onset and progression of glaucomatous optic neuropathy.

IOP fluctuates throughout day reaching its peak in the early morning or supine position as well as throughout the day in healthy individuals or glaucoma patients[7-9]. In normal individuals, diurnal variation in IOP ranges typically from 3mmHg to 6mmHg[10]

The progression of glaucoma despite early diagnosis and timely treatment is not understood completely. Excessive 24-hour fluctuations in intraocular pressure are an independent risk factor for the progression of glaucoma[6,11] .

To the best of our knowledge very few studies have been done to assess the diurnal variations of intra-ocular pressure in primary angle closure disease patients who are already under treatment.[12,13] The present study aims to measure diurnal variations of IOP in primary angle closure disease patients who are already under treatment.

MATERIALS AND METHODS

A cross-sectional observational study was conducted at a tertiary care hospital in Ahmedabad,Gujarat,India from July 2018 to April 2019 in all Primary Angle closure disease(PACD) patients which included Primary angle closure suspect (PACS), Primary angle closure (PAC), Primary angle closure glaucoma (PACG) patients who were on treatment for glaucoma and had controlled IOP during routine outpatient department (OPD) hours from 9 am to 5 pm. Those fulfilling the following criteria were included in the study. Patients were diagnosed to have Primary angle closure suspect (PACS) having greater than 270 degrees of irido-trabecular contact plus absence of peripheral anterior synechiae(PAS),plus normal IOP, disc and visual field. The angle was occludable[14]. Patients were diagnosed to have Primary angle closure (PAC) having greater than 270 degrees of irido-trabecular contact with either elevated IOP and/or PAS plus normal disc and visual field examinations. The angle was abnormal in structure (PAS) or function(elevated IOP) [14]. Patients were diagnosed to have Primary angle closure glaucoma (PACG) having greater than 270 degrees of irido-trabecular contact plus elevated IOP plus disc and visual field damage. The angle was abnormal in structure (PAS) and function(elevated IOP), with optic neuropathy[14].Those patients having secondary glaucomas, ocular hypertension, congenital glaucoma were excluded from the study.

Diagnosis of primary angle closure disease was done on the basis of detailed history and clinical examination including

anterior chamber angle examination by four-mirror gonioscopy lens, IOP readings by handheld Perkin's applanation tonometer,Central corneal thickness (CCT), optic disc evaluation by slit lamp biomicroscopy using 90 dioptre lens and visual field testing. IOP reading was considered after adjusting IOP with CCT correction factor.

Patients were started on appropriate treatment at the time of diagnosis in the form of Nd:YAG (Neodymium-doped Yttrium Aluminium Garnet) laser peripheral iridotomy (LPI).In some patients whose IOP was not under control after LPI, topical antiglaucoma medications was added based on indication and patient factor. Few patient in whom target IOP was not achieved or who showed progression, underwent trabeculectomy surgery based on indication. Topical antiglaucoma medication was added in few patients to achieve target IOP even after trabeculectomy. Drug of choice was prostaglandin analogues and beta blocker followed by carbonic annhydrase inhibitors or alpha agonist based on patient factor . All these patients were on regular follow-up and their IOP was within target limit during out-patient department visiting hours from 9am to 5pm.

Thirty eight PACD patients were included in the study. A written, informed consent was taken. The study adhered to the tenets of declaration of Helsinki and had the approval of the institutional ethical committee.

These patients whose target IOP was achieved with proper treatment were admitted for 24 hours and their IOP measurement was taken by handheld Perkins Applanation tonometer every four hourly at 8am,12 pm, 4 pm and 8 pm in sitting position and at 12am and 4am in supine position by a single observer. .Four hourly sampling in 24 hours was chosen to represent major phase of circadian rhythm(morning, daytime, evening, nocturnal) while minimizing sleep disruption and logistical complexity.Their maximum IOP, minimum IOP, difference between maximum and minimum IOP reading and mean IOP were noted. Difference of IOP value of 8mmHg or more between maximum and minimum IOP was considered as significant Diurnal Variation Test (DVT)[15].

Statistical analysis was performed for each eye using SPSS software (version 25). The statistical tests applied were Chi-square test and ANOVA test.

RESULTS

Thirty eight PACD patients[19 males (50%), 19 females (50%)]total 75 eyes were evaluated for diurnal variation in intraocular pressure in which 3 eyes (4%) belonged to PACS category,19 eyes(25.3%) to PAC category and 53 eyes (70.67%) to PACG category. The mean IOP reading of every 4 hours, with the minimum and maximum IOP recorded is listed in Table 1.

Out of 75 eyes, 41 eyes showed significant DVT and 36 eyes showed peak at 4am. 24 eyes showed significant DVT with peak IOP reading at 4am.The peak mean IOP was measured at 4 am (Figure 1).

The minimum IOP (4 mmHg) and maximum IOP (46mmHg) reading was recorded at 12 am. However the mean minimum IOP across 75 eyes was 11.47 ± 4.47mmHg while mean maximum IOP recorded was 19.49 ± 7.29 mmHg. The difference between minimum and maximum mean IOP was noted as diurnal fluctuation and it was noted as 8.03mmHg which is considered significant in this study[15].(Table 1)

On comparison of mean IOP between various time intervals, the difference between mean IOP at 4 am compared to all other time interval (8 am, 12 pm, 4 pm, 8 pm, 12 am) was statistically significant ($p < 0.05$). This difference was significant even after correcting for the multiple statistical significant tests used (Bonferroni method).[16] While comparison of mean IOP with rest of the time interval was not significant ($p > 0.05$). (Table 2)

IOP fluctuations (difference between minimum and maximum mean IOP) were statistically more significant in females as compared to males(p value = 0.015)(Table 3). However no significant difference was seen between males and females on comparing significant and nonsignificant DVT.(Table 4)

No statistically significant difference in either IOP fluctuations (Table 3) or DVT (Table 4) was seen among phakic and pseudophakic eyes.

On comparing the group of PACS, PAC and PACG group; PACS group showed more fluctuations in IOP followed by PAC and PACG group and this difference was statistically significant (Table 3). However no significant difference was seen in diurnal variation of IOP among them (Table 4).

Out of all patients who underwent LPI, target IOP was achieved in 20 eyes. Thirty-eight eyes required one or more antiglaucoma medications followed by LPI based on indications and contraindication to achieve the target IOP. Seventeen eyes underwent trabeculectomy surgery, of these, seven achieved target IOP without additional medication while ten eyes required topical antiglaucoma treatment to maintain control.(Table 4)

Of treatment group 13 of 20 eyes (65%) treated with laser peripheral iridotomy, 23 of 38 eyes (60.5%) treated with laser peripheral iridectomy plus topical antiglaucoma medication, 2 of 7 eyes (28.5%) treated with trabeculectomy,and 1 of 10 eyes(10%) treated with trabeculectomy plus topical antiglaucoma medication showed significant DVT and this difference was found to be statistically significant (p = 0.0009)(Table 4). However, no significant difference was seen between minimum and maximum IOP i.e IOP fluctuations amongst these patients who were treated by LPI alone or who underwent trabeculectomy with or without additional antiglaucoma medication(Table 3).LPI treated eyes have maximum proportion of eyes with significant fluctuations of IOP of ≥8mmHg.(Table 4).

On comparing peak IOP reading at 4 am with other time, 36 eyes showed peak at 4 am out of which 24 eyes (66.66%) showed significant DVT while 39 eyes showed peak at other time other than 4 am out of which 17 eyes(43.6%) showed significant DVT. This difference was statistically significant with p value 0.04.

DISCUSSION

The diurnal IOP fluctuation is defined as difference between the highest and lowest IOP in a single day. Short term fluctuations are defined as fluctuations within days to weeks, while long term fluctuations include periods from months to years. The intraocular pressure varies on an average of 3-6mmHg in normal individuals,[10] while fluctuations of 8-30mmHg have been detected in untreated glaucoma patients.[17,18] To the best of our knowledge very few studies have been done to assess the diurnal variations of intra-ocular pressure in primary angle closure disease patients who are under treatment.[12,13]

Katavitso[19] suggested that a variation of more than 6.77mmHg or an IOP of more than 23.4 mmHg should be considered pathological. Balaratnasingam et al. showed that short term mean and peak IOP were higher and a diurnal IOP variation of more than 8 mmHg often occured in patients who show progression[15]. In our study we have included IOP variation of 8mmHg or more to be significant. Some primary angle closure glaucoma disease patients shows fluctuations

in IOP even after treatment with laser peripheral iridotomy or trabeculectomy.[12,13,20]. Asrani et al.and others,[6,15,21-23] have shown that large diurnal variation in IOP is a risk factor for the progression of glaucoma. However certain study has shown that IOP fluctuation are not associated with progression of the disease.[24,25]

Sihota et al.[12], have reported that post-LPI peak in IOP in PACD patients occured in afternoon hours which was similar to circadian rhythm of normal eyes; however they did not measure nocturnal IOP and the readings were taken at 7am, 10am, 1pm, 4pm, 7pm, 10pm.

However Katavisto[19]in his work suggested that timings for diurnal variation IOP should be recorded at 4am, 6am, 10am, 2pm, 6pm, and 10pm. In our study 36 eyes (48%) showed peak at 4 am out of which 24 eyes (32%) showed significant diurnal variation($p = 0.04$).The difference in mean IOP at 4 am(17.05 ± 7.50 mmHg) compared to all other reading was also significant.

Barkana et al[26] reported that peak 24-hour IOP was higher than the peak IOP noted during office hours in majority of patients. Studies have shown that the prevailing circadian rhythm is the morning curve ("morning type"), with the IOP peak occurring between 4 and 8 am[27] .

Hirooka and Shiraga[28] found a significant difference between IOP levels measured in the sitting and supine positions, the greater differences being in eyes with more severe visual field loss. It is worth noting that their results suggested that more glaucomatous damage could happen during sleep in the supine position.

It remains unclear whether this peak recorded at early morning is physiological or have some autonomic significance and whether this peak is related to progression of the disease. Knowledge regarding the degree of IOP fluctuations would help in determining therapy, tailoring medications i.e. to assess their efficacy or change in their timings and need for surgical intervention.

Limitation of our study include small sample size. A prospective case-control study would be welcome to confirm whether this 4 am peak is related to glaucomatous progression. IOP reading at 4 am was taken after patients awakens which may not give physiological IOP. Future studies could also compare of effect of various topical antiglaucoma medications on diurnal variation.

CONCLUSION

On treatment and seemingly controlled PACD patients show significant diurnal variations of IOP which makes the nature of the disease progressive. Majority of patients show peak at 12am or 4am. This significant fluctuation which if timely intervened may halt the progression of the disease. Hence measurement of diurnal fluctuations of IOP should be a part of management of glaucoma.Also a further prospective case control study regarding the progression of glaucoma in patients with significant and nonsignificant DVT is needed.

Table 1: The Mean Intraocular Pressure with Standard Deviation in Mmhg Recorded During 24 Hours With Minimum and Maximum Reading of Intraocular Pressure Recorded at that Time in 75 Eyes.

TABLE 1				
	Mean	Std. Deviation	Minimum	Maximum
8AM	13.97	4.818	8	30
12PM	14.17	5.358	6	30
4PM	14.07	5.441	6	30
8PM	14.28	5.689	6	36
12AM	15.13	6.919	4	46
4AM	17.05	7.503	8	40
IOP=Intraocular pressure in mmHg.				

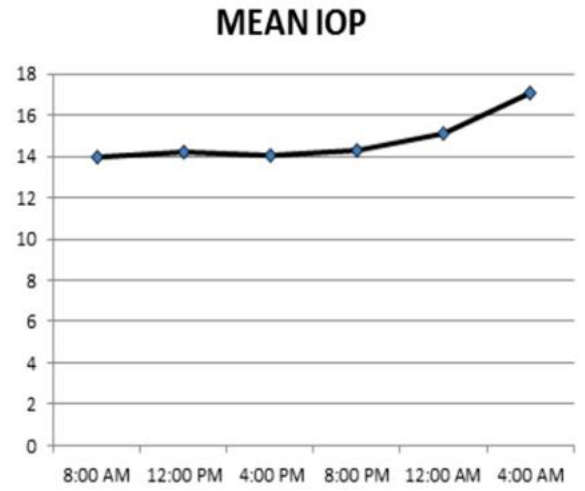

Figure 1: Mean IOP at Different Time Interval.

Table 2: Comparison of Mean Intraocular Pressure Between Various Time Intervals in 24 Hour.

TABLE 2				
Pair wise comparisons Measure- Intraocular pressure				
(I) Time	(J) Time	Mean Difference (I-J)	Std. Error	p value
Mean IOP @8 am	Mean IOP @4 am	-3.080*	0.659	0.000
Mean IOP @12 pm	Mean IOP @4 am	-2.880*	0.677	0.001
Mean IOP @4 pm	Mean IOP @4 am	-2.987*	0.665	0.000
Mean IOP @8 pm	Mean IOP @4 am	-2.773*	0.710	0.003
Mean IOP @12 am	Mean IOP @4 am	-1.920*	0.607	0.034
Mean IOP @4 am	Mean IOP @ 8am	3.080*	0.659	0.000
	Mean IOP @12pm	2.880*	0.677	0.001
	Mean IOP @4 pm	2.987*	0.665	0.000
	Mean IOP @8 pm	2.773*	0.710	0.003
	Mean IOP @12 am	1.920*	0.607	0.034
Based on estimated marginal means				
*. The mean difference is significant at the 0.05 level.				
b. Adjustment for multiple comparisons: Bonferroni.				
Significant p values are shown in bold and highlighted.				

Table 3: IOP Fluctuations(Maximum-minimum) Among Male and Female; Phakic and Pseudophakic Eyes; PACG, PAC and PACS; and Between Eyes Who Underwent LPI or Trabeculectomy with or without Additional Antiglaucoma Medications

TABLE 3			
IOP fluctuations (minimum-maximum) Total =75 eyes	N	Mean in mmHg ± Std.deviation	P value (t test for equality of means)
Sex Male Female	 38 37	 6.74±3.592 9.35±5.329	 P =0.015 (t=-2.497)
Lens Cataract Pseudophakia	 58 17	 8.38±4.712 6.82±4.545	 p = 0.232 t = 1.206
PACD PACG PAC PACS	 53 19 3	 7.47±4.405 8.53±4.892 14.67±4.163	Between groups (ANOVA f = 3.743) p=0.028

Treatment			Between groups
LPI	20	15.92±5.52	(ANOVA f =2.69)
LPI + medical treatment	38	15.71±5.27	p =0.052
Trabeculectomy	7	10.49±3.45	
Trabeculectomy + medical treatment	10	11.55±1.64	

Table 4: Comparison of Groups that Showed IOP Variations ≥8mmHg i.e. Significant DVT Versus <8mmHg i.e. Non Significant DVT.

TABLE 4

Diurnal variation of IOP			Signi-ficant DVT ≥8mmHg	Non-signi-ficant DVT <8mmHg	p value (chi square)
		Total	N (%)	N(%)	
SEX	Male	38	11 (28.9%)	27 (71.1%)	0.29
	Female	37	15 (40.5%)	22 (59.5%)	(1.112)
LENS	Phakic	58	35 (60.3%)	23 (39.7%)	0.068
	Pseudo-phakia	17	6 (35.3%)	11 (64.7%)	(3.329)
PACD	PACG	53	27 (50.9%)	26 (49.1%)	0.239
	PAC	19	11 (57.9%)	8 (42.1%)	(2.864)
	PACS	3	3 (100.0%)	0 (0.0%)	
TREATMENT					0.0009
LPI		20	13(65%)	7(35%)	(11.067)
LPI + medical treatment		38	23(60.52%)	15 (39.47%)	
Trabeculectomy		7	2 (28.57%)	5 (71.42%)	
Trabeculectomy + medical treatment		10	1 (10%)	9 (90%)	
PEAK IOP	@4am	36	24 (66.6%)	12 (33.35)	0.04
		39	17 (43.6%)	22 (56.4%)	(4.023)
	@other time				

Significant p values in bold, IOP: Intraocular pressure; PACD: Primary angle closure disease; PACG: Primary angle closure glaucoma; PAC: Primary angle closure; PACS: Primary angle closure suspect; LPI: laser peripheral iridectomy; Others: cataract surgery or clear lens extraction.

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