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"A Clinical Study of Factors Predicting Response of Pseudophakic Cystoid Macular Edema to Topical Steroid and Nepafenac".

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Abstract
Purpose: The purpose of this study is to determine factors predicting resolution of acute pseudophakic cystoid macular edema (PCME) after 6 weeks of topical prednisolone and nepafenac application.Material and Methods: Case records of patients with a clinical and optical coherence tomography (OCT)‐based diagnosis of acute PCME were retrospectively reviewed for best‐corrected visual acuity and OCT‐based parameters at the time of presentation with PCME. In addition, demographic variable intraoperative and early postoperative factors, and type of treatment prescribed (tapering vs nontapering prednisolone, generic vs. branded prednisolone and nepafenac) were recorded from case records for analysis. Complete and any successes were defined and baseline factors predicting complete success at 6 weeks were analyzed.Results: We analyzed 70 eyes of 70 patients out of which complete success with topical medications was seen in 39 eyes (55.71%) and any success was seen in 58 eyes (82.86%) at 6 weeks. Multivariable logistic regression showed that eyes with lower vision at presentation had a significantly lower likelihood of experiencing both, complete (odds ratio [OR] = 0.00 with one‐line decrement in baseline vision, 95% confidence interval[CI] = 0.00–0.006, P = 0.025) and any success (OR = 0.00, 95% CI = 0.00–0.1, P = 0.01). Baseline OCT thickness did not influence success rates. Conclusion: Topical prednisolone and nepafenac lead to resolution in PCME in half of the eyes at 6 weeks. Baseline vision is the only factor predicting rates of success and PCME resolution with topical medications.

Keywords: *cystoid macular edema ,pseudophakia,,resolution, topical therapy ,oct*

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I. Introduction

Cystoid macular edema (CME) following cataract surgery was first recognized over 4 decades ago by Irvine. 'the report of Irvine represents the first clinical description of CME following cataract surgery as a distinct entity.

'Today, this postoperative complication is frequently referred to as the Irvine-Gass syndrome[2].

It is recognized as the most common cause of decreased vision in patients following cataract surgery with or without the implantation of an intraocular lens'.

Pseudophakic cystoid macular edema [PCME], also known as IRVINE-GASS SYNDROME. It is swelling of fovea due to fluid accumulation, occurring few weeks to months after cataract surgery. Phacoemulsification and small incision cataract surgery have significantly reduced the incidence of pseudophakic CME.[(1,4)]

Definitions(2)- Angiographic pseudophakic CME :- seen on FLUORESCEIN ANGIOGRAPHY [FA] :-it include perifoveal capillary leakage that increase in size and intensity to a "petaloid"appearance,capillary dilation and retinal telangiectasis and late staining of disc.

Clinical pseudophakic CME[2]:- associated with decreased visual acuity.

Acute PCME[2]:-within six months of cataract surgery.

Chronic PCME[2]:-more than six months after cataract surgery.

OCT –PCME[3]:-It is characterized by loss of foveal depression, retinal thickening and cystic hyporeflective area within the macula.

OCT has not replaced the FFA as gold standard in diagnosing pseudophakic CME, because FFA can also ruled out other cause of CME such as diabetic macular edema and retinal vein occlusion.

INCIDENCE[4,5,6]:- Because of heterogenicity of definition and diagnostic criteria its incidence has been reported to be between 1% and 30%,with an incidence of 1%-2% of clinically significant PCME in patient with no risk fectors.

Pathogenesis[7,8,9]:- Pathophysiology of PCME remains uncertain and a multitude of mechanism have been suggested. various factor have been involved in development including inflammation, vascular instability , vitreo-macular traction and light toxicity.

Most researchers agree that postoperative inflammation to be a major cause of PCME.

II. Material & Method

A retrospective clinical study of role of topical prednisolone- 1% & nepafenac-0.1% ophthalmic solution in acute pseudophakic cystoid macular edema.

This study has conducted on 70 eyes of 70 patients in the department of ophthalmology, MBS Hospital Kota. This study duration was 12 months from May 2019 to May 2020.this study was conducted with collaboration of pharmacology department, govt. medical college Kota, Raj.

This study was approved by the ethics committee of the Govt. medical college Kota and associated groups of hospitals and this study has conducted as per the good clinical practice guidelines.

Case records of all patients visiting retina service at our M.B.S. hospital Govt, medical college Kota between May 2019 to May 2020 with diagnosis of acute PCME were taken from discharge ticket of patients .following criteria was used for the confirmation of diagnosis of PCME from all the case records received.

INCLUSION CRITERIA

1. History of in- house cataract surgery within 6 months of presentation .
2. Clinical and OCT- based evidence of cystoid macular edema[central macular thickness(CMT)>250 micro meter.
3. Best corrected distance vision <6|12 Snellen.
4. Patients who give voluntary consent for this study .
5. Data from those eyes with complete records and minimum follow-up of 6 weeks was used for analysis.
6. Patients age above 18 years.

EXCLUSION CRITERIA:

1. Macular edema caused by diabetic mellitus (DME), Retinal vein occlusion, hypertensive retinopathy etc was not included in study.
2. Eyes with posterior capsular rent and zonular dehiscence requiring vitrectomy.
3. Hypersensitivity to topical steroids and Nepafenac.
4. Patients age below 18 years .
5. Patients who did not give voluntary consent.

III. Method :-

This study was conduct in two groups. both groups was assess for acute PCME & one group was treated with topical prednisolone & nepafenac [branded] and other group was treated with topical prednisolone & nepafenac [generic] ophthalmic solution. Two groups namely:-

1. Group A (branded medicine)
2. Group B (generic medicine)

Each patients was given two eye drops bottle of their respective groups that was named according to their group code and instruct to install drop topical prednisolone four times per day and nepafenac thrice a day.

Patient demographics such as age, gender, eye involve, systemic status, namely diabetes, hypertension and renal disease, axial length, duration of visual loss and time since cataract surgery was recorded from case records.All intraoperative and early postoperative examinations was recorded.

Specific intraoperative details wasl recorded viz type of cataract surgery (SICS/phacoemulsification/extracapsular cataract extraction), location of incision(superior v/s temporal), type of IOL (Polymethyl methacrylate v/s acrylic and hydrophilic/hydrophobic), type of capsulotomy (Rhexis v/s can opner) and placement of IOL (in the bag v/s sulcus placement)

At the time of presentation with PCME, all patients were undergo a comprehension ophthalmic examination including :-Snellen's best corrected visual acuity (BCVA) IOP measurement by Goldmann applanation tonometry and non-contact tonometer.Slit lamp examination to determine the presence of anterior chamber reaction (cells, flares), vitreous in anterior chamber, position of IOL ,Detailed fundus examination by slit lamp bio microscopy with 90 D and direct ophthalmoscope for PCME and other retinal pathology.

All patients were undergone macular evalution using spectral domain OCT. Macular thickness was obtained from automated thickness map & 5-line raster on the OCT machine and presence of subretial fluid (yes/no) was recorded during data collection.

As per institutional protocol all patients were treated with topical steroids (prednisolone eye drop conc.1% alcon laboratories /generic) four times a day with or without tapering for 6 weeks .for those who received tapering regimens, taper were started at 1 week and prednisolone was withdrawn at 6 weeks.

All patients were received topical nepafenac eye drops 0.1% (Alcon laboratories / generic) three times a day for 6 weeks.

All patients were undergone follow- up after 6 -weeks and similar data including BCVA and OCT –derived measurements was recorded for analysis at 6-weeks follow- up.

Symptoms like diminution of vision ,photophobia, watering, redness, central scotomas and metamorphopsia etc were graded mild, moderate & severe according to discomfort of the patient.

OUTCOME MEASURES:- Resolution of PCME at 6-week follow-up with combination of topical prednisolone and nepafenac were assessed in terms of complete and any success.

COMPLETE SUCCESS:- Is defined as BCVA >_ 6/9 and CMT <_300 µm with no morphological retinal edema.

ANY SUCCESS:- Is defined as anything less than complete success and reduction in CMT by >150 µm.

STATISTICAL ANALYSIS:-

All continuous variables are expressed as means + standard deviations and categorical variables are expressed as proportions. Snellen's BCVA is converted into logarithm of minimum angle of resolution (LOGMAR) for analysis.

Group differences in continuous variables are analyzed using Student's *t*- test. Chi- square test is used to determine group differences between categorical variables. Factors influencing complete and any success are determined using univariate and multivariable logistic regression analysis and presented as odds ratio (OR) with 95% confidence interval (CI). For logistic regression, multivariable model building used the method of best subsets. The reduction in CMT (calculated as CMT at baseline–CMT at 6 weeks) are calculated and this is correlated with baseline BCVA as well as improvement in BCVA at 1 month. In addition, linear regression analysis is done to understand the association between improvement of BCVA and CMT reduction at 1 month. Finally, the median CMT reduction value is used to divide the cohort into two groups, and logistic regression is performed to look for the influence of vision on CMT reduction. All data were entered into Excel and analyzed using STATA 12.0 I/c (Fort worth, Texas, USA).P value less than 0.05 taken as significiant .

Difference in eyes with and without complete and any success

SN	Variable	Complete	Success	p	Any	Success	p
		Yes (n=39)	No(n=31)		Yes (n=58)	No (n=12	
1	Age (years)	**55.51±10.794**	**68.35+-71.15**	**0.001**	59.47+-11.41	69.58±5.838	0.047
2	Gender (male), n (%)	16 (41.03)	17(54.84	0.36	29(50)	4(33.33)	0.46
3	Diabetes , n (%)	0	2(6.45)	0.6	2(3.45)	0	0.44
4	Percentage eyes with NS>3 grade	19(48.72)	19(61.29)	0.29	31(53.45)	8(66.67)	0.4
5	Technique (PHACO V/S SICS)	8(20.51)	12(38.71	0.16	14(24.14	6(50)	0.14
6	Time of onset since cataract sx (days)	120+-22.71	116.35+-15.90	0.45	120.14 +-21	109.92+-10.24	0.1
7	BCVA at presentation (LOG MAR)	0.66+-0.21	0.79+-0.29	0.03	0.76+-0.30	0.71+-0.24	0.049
8	CMT at presentation (µm)	298.15+-54	379.74+-124.4	0.001	327.10+-94.33	390+-122.6	0.18
9	SRF at presentation, n (%)	8(20.51)	9(29)	0.41	14(24.14)	3(25)	0.95
10	Prednisolone: QID v/s taper, n (%)	24(61.54)	21(67.74)	0.77	35(60.34)	10(83.33)	0.24
11	Nepafenac : branded v/s generic n (%)	20(51.28)	16(51.61	0.83	29(50)	7(58.33)	0.84

Table no 26

Univariate and Multivariable logistic regression analysis for factors predicting complete and any success with topical medications alone.

Variable	interval	Complete success		Any success	
		OR (95%CI)		**OR (95%CI)**	
		Univariate	Multivariable	Univariate	Multivariable
Age (years)==<55	>55years	2.45(0.9-6.5) P= 0.1	0.77(0.6-0.9) P=0.04S	8.93 (1.0 - 73.8) P=0.04 S	0.90(0.7-1.0) P=0.1
Gender(male)	female	1.74(0.6-4.5) P=0.3	9.52(.4-193.2) P=0.1	0.37 (0.1 - 1.4) P=0.2	6.78(.6-68.4) P=0.1
Diabetes mellitus (yes)	No DM	1.79(0.6-5.0) P=0.3	12.52(0.4-362.1) P=0.1	1.83(0.4-7.5) P=0.7	0.68(0.08-5.2) P=0.7
NS grade<3 grade	>3 grade	1.5(0.5-3.9) P=0.5	0.02(0.0-2.9) P=0.1	0.5(0.1-1.7) P=0.4	0.09(0.008-1.1) P=0.06
Technique (PHACO)	SICS	2.33(0.7-7.0) P=0.2	0.06(0.001-3.7) P=0.1	2.25(0.4-11.3) P=0.5	8.36(0.4-152.4) P=0.1
Time since cataract sx<110 day	>110 day	29.00 (5.9 - 140.8) P=	.28(.01-6.6) P=0.4	8.33 (1.0 - 68.8) P=0.05	.04(.001-2.3) P=0.1
BCVA at presentation<=0.8	>0.8 BCVA	0.06(0.02-0.2) P=<0.001	0.00(0.00-0.006) P=0.02S	0.11(0.02-0.5) P=0.008S	0.00(0.00-0.1) P=0.01
CMT at presentation>315µm	<315µm	0.05(0.01-0.28) P=<0.001	0.96(0.9-1.0) P=0.07	0.95(90.2-4.0) P=0.7	1.02(1.0-1.03) P=0.05
Prednisolone (QID)	taper	0.76(0.2-2.0) P=0.7	0.27(0.01-6.6) P=0.4	0.30(0.06-1.5) P=0.2	0.88(0.1-7.1) P=0.9
Nepafenac (brand)	generic	1.01(0.3-2.6) P=0.8	0.008(0.0-0.8) P=0.05	0.46(0.1-1.7) P=0.3	1.87(0.3-11.6) P=0.5

Table No 24

Correlation between baseline BCVA and BCVA at 6th week

		BCVA (LOGMAR) 1st day	BCVA (LOGMAR) 6th WK
BCVA (LOGMAR) 1st day	Pearson Correlation	1	.908**
	Sig. (2-tailed)		.000
	N	70	70
BCVA (LOGMAR) 6th wk	Pearson Correlation	.908**	1
	Sig. (2-tailed)	.000	
	N	70	70

**. Correlation is significant at the 0.01 level (2-tailed).

Significant positive correlation was observed between baseline BCVA and BCVA at 6th week (r=0.908, P<0.001S) .means patients having better baseline BCVA achieved better BCVA at 6th week after successful treatment of six weeks.

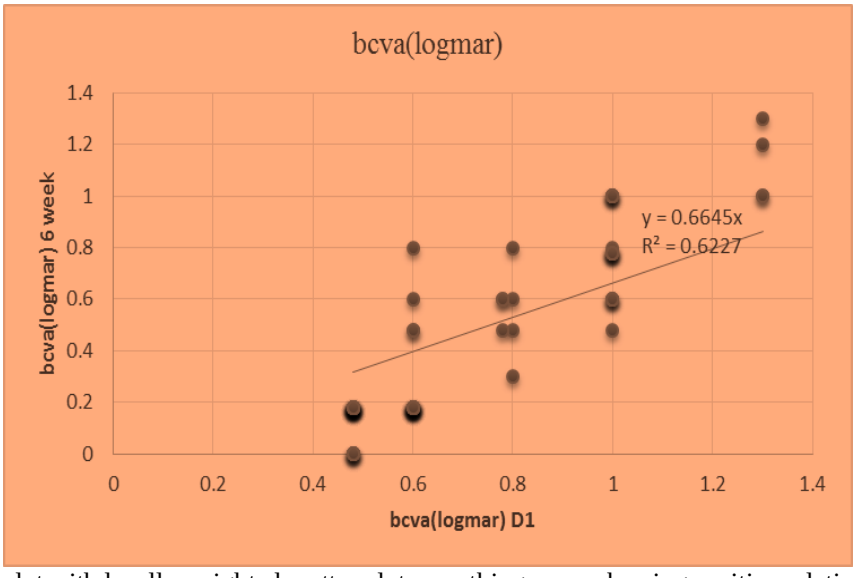

Fig 30 Scatter plot with locally weighted scatter plot smoothing curve showing positive relationship between BCVA at baseline and BCVA at 6th week follow-up.

IV. Results

A total of 70 eyes with PCME were identified during the study period .the median duration of follow up for those included in the analysis is 85 days .

Complete success with topical medications is seen in 39 eyes (55.77 %) and any success is seen in 58 eyes (82.86 %). twelve eyes have no improvement in vision and some eyes shows worsening of macular thickness at follow up.

There is no difference in eyes with and without complete and any success in terms of baseline characteristics (table 25) except age and BCVA at presentation and CMT.

1.Patients experiencing complete success were significantly younger than those who did not attain complete success mean age 55.51<68.35 yrs.and p value is <0.001 significant

2.Patients experiencing complete success were significantly have better baseline BCVA than those who did not attain complete success p value is 0.037 significant ($p<0.05$.

3.Patients experiencing any success were significantly have better baseline BCVA than those who did not attain any success p value is significant ($p<0.05$).

4. P value>0.05 are insignificant means no difference is found in cases in term of baseline characteristics according to any success except baseline BCVA and age of the patients.

5.Univariate logistic regression analysis showed that greater interval from time of cataract surgery (in any success) and lower BCVA at presentation were associated with lower odds of complete success [Table 26], where as male gender, undergoing phacoemulsification (vs. manual small‐ incision cataract surgery), and having a non tapering regimen of topical prednisolone were associated with higher odds of complete success [Table 26]

6. BCVA at 6 weeks showed a strong positive correlation (Pearson's correlation coefficient = 0.908, $P = < 0.001$) with BCVA at presentation (table no 24 & fig 33)

7. Univariate logistic regression showed that increasing age and BCVA at presentation were significantly able to predict any success [Table 26]

8. There was poor correlation between CMT difference and BCVA at baseline (R=0.49, $P = 0.0016$) and with improvement in BCVA at 1 month ($R= 0.087$, $P = 0.52$).

9.univariate and multivariate regression analysis of factors predictating response of topical medicine to PCME shows that BCVA at baseline is only factor which affect the outcome in PCME at 6^{th} week .p value <0.05 in complete as well as any success.(table no 2)

V. Discussion

Knowledge of baseline factors that predicts good response and resolution of acute PCME with topical drops alone can help to remove anxiety for patients and their operating surgeons.

In addition, this information also help to counsel potential needs for future steroids injection needs in those who shows risk factors for poor resolution.

We found that after uncomplicated cataract surgery, irrespective of surgical techniques, eye with worse vision at presentation (less than 6/18) undergoes unsatisfactory visual and anatomical outcome, thereby increasing need for invasive treatments such as PST and IVTA.

In previous study by **Sabyasachi Sengupta[10] et al** they analyzed 69 eyes of 69 patients out of which complete success with topical medications was seen in 37 eyes (54%) and any success was seen in 55 eyes (80%) at 6 weeks. Multivariable logistic regression showed that eyes with lower vision at presentation had a significantly lower likelihood of experiencing both, complete (odds ratio [OR] = 0.83 with one‐ line decrement in baseline vision, 95% confidence interval [CI] = 0.61–0.89, P = 0.003) and any success (OR = 0.61, 95% CI = 0.4–0.9, P = 0.007). Baseline OCT thickness did not influence success rates.

In previous study by **Heier[11] et al**, 28 eyes with PCME were randomized to receive either topical NSAID (ketorolac) or steroid (prednisolone) or a combination of both. The auther reported outcome from 24 eyes and concluded that combination therapy yielded best visual outcomes. The auther do not report the resolution rate of CME but mention that two line improvement in vision is seen in 65% eyes while 8 out of 9 eyes (89%) in the combnation group shows at least two line improvement. Although apparent success rate in the combined group was greater than what we reported. This study was performed in pre OCT era reported outcome predominantly depend on vision, making direct comparison difficult. In addition we used different NSAID (nepafenac).

Seenu M Hariprasad [12]et al in his multicenter retrospective review of 22 CME cases (20 patients) treated with nepafenac 0.1% (six with concomitant prednisolone acetate 1%) from December 2005 to April 2008: three acute pseudophakic CME cases, 13 chronic/recalcitrant pseudophakic CME cases, and six cases of uveitic CME. Pre- and post-treatment retinal thickness and visual acuity were reported.

Following treatment for six weeks to six months, six eyes with uveitic CME showed a mean retinal thickness improvement of 227 ± 168.1 μm; mean best-corrected visual acuity (BCVA) improvement was 0.36 ± 0.20 LOGMAR. All three cases of acute pseudophakic CME improved after four to 10 weeks of nepafenac, with

a mean improvement in retinal thickness of 134 ± 111.0 µm. BCVA improved in two patients (0.16 and 0.22 LOGMAR) but not in the third due to underlying retinal pigment epithelium changes. Thirteen eyes with chronic/recalcitrant pseudophakic CME demonstrated a mean improvement in retinal thickness of 178 ± 128.7 µm after nepafenac and mean BCVA improvement of 0.33 ± 0.19 LOGMAR.

In Cochrane review on NSAIDs for treating cystoid macular edema following cataract surgery, **Shivaprasad[13] et al** concluded that the effect of NSAIDs in acute & chronic PCME remains unclear and needed further investigations.We found that eyes the lower baseline vision less than 6/18 shows poorer response to topical drugs. Although there was no significant difference between macular thickness or other OCT based parameters between those with better and worse vision at base line. It is possible that eyes with lower vision have some amount of irreversible cell damage leading to inadequate visual recovery with topical steroid and nepafenac.

Although PCME is a rare occurrence these days, this study had a relative large sample making it possible to perform regression analysis and determine factors that predicts PCME resolution. We used a combination of anatomic and visual parameters to determine complete and any success. These definition were based on clinical judgement and can be used in future studies reporting on PCME, to help meaningful comparison between studies.

DRAWBACK:- A drawback of our study beside its retrospective nature ,is arbitrary allocation of tapring and non tapring regimen of topical steroids to patients.

STRENGTH OF STUDY:- The relatively large sample size and availability of OCT data before and after treatment for meaningful analysis are the strength of this study.

VI. Summary & Conclusion

A combination of topical steroid and nepafenac lead to complete resolution of acute PCME in just over half of the cases. Best results are seen in those with vision equal and better than 6/18. macular thickness and time since surgery do not influence resolution rate of PCME.

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