Factors predicting response of pseudophakic cystoid macular edema to topical steroids and nepafenac

Sabyasachi Sengupta[1,2], Dhaivat Vasavada[1,3], Utsab Pan[1], Manavi Sindal[1]

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. **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 variables, 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 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. **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.

Key words: Cystoid macular edema, pseudophakia, resolution, topical therapy

With modern cataract surgery, the occurrence of clinical pseudophakic cystoid macular edema (PCME) is uncommon with an estimated incidence of 2%–12%,[1] being marginally higher with complicated cases such as pseudoexfoliation and scleral-fixated intraocular lenses (IOLs).[2] Previous studies performing fluorescein angiography (FFA) have reported a slightly higher incidence.[1,3] With the advent of the optical coherence tomography (OCT), it has become relatively simple to diagnose PCME in a noninvasive manner.

Risk factors for the onset of PCME have been extensively studied in the past. Posterior capsular rupture, vitreous loss, presence of diabetes, and especially, diabetic retinopathy are known to increase the risk of PCME.[1,3-5] Yet, even after uneventful phacoemulsification, PCME can occur occasionally without any apparent cause.[1,3]

Even though diagnosis is easy and risk factors known, the treatment of PCME still remains a challenge. Conventionally, a trial of combination of topical steroids and topical nonsteroidal anti-inflammatory drugs (NSAIDs) is considered to be the first line of treatment.[1,3,6,7] Serial OCT-based assessment of the macular anatomy and thickness along with visual status dictates needs for further treatment such as posterior

sub-Tenon's triamcinolone (PST) or intravitreal steroids (viz., intravitreal triamcinolone acetonide [IVTA] or dexamethasone) in nonresponsive cases.[1,3,8]

Although many studies have been performed to determine the risk factors for onset of PCME, only few studies report on the outcomes of PCME and are limited by a small sample size.[1,3,7,9] Consequently, factors that determine good response with topical medications (i.e., steroids + NSAIDs) alone have not been reported in the past, to the best of our knowledge. We performed a retrospective study to quantify response and determine factors predicting response of PCME to topical medications.

Methods

The study was approved by the ethics committee of the parent institution and was conducted as per the tenets of the Declaration of Helsinki and International Conference on Harmonization–Good Clinical Practice guidelines. Case records of all patients visiting the retina service at our hospital between January 2014 and December 2015 with a diagnosis of acute PCME (International Classification of Diseases-9) were

[1]Vitreoretinal Services, Aravind Eye Hospital and Postgraduate Institute of Ophthalmology, Puducherry, [2]Sengupta's Research Academy, Mumbai, Maharashtra, [3]Vitreoretinal Services, Aakash Eye Hospital, Ahmedabad, Gujarat, India

Correspondence to: Dr. Sabyasachi Sengupta, Sengupta's Research Academy, 1503B, Oberoi Gardens, Thakur Village, Kandivali (East), Mumbai - 400 101, Maharashtra, India. E-mail: drsunny1980@gmail.com

drawn from an electronic database. Two fellowship-trained retina specialists (DV and UP) confirmed the diagnosis of PCME from all the case records received using the following 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 μ) and best-corrected distance vision <6/12 Snellen, and (3) absence of other pathologies such as diabetic macular edema (DME), vein occlusion, or other conditions known to be associated with macular edema. Examining physicians performed fluorescein angiography (FFA) if there was a doubt between PCME and other forms of edema (e.g., DME), and eyes showing FFA features of DME such as leaking microaneurysms and capillary plexus were not labeled as PCME and hence not included in the analysis. Eyes with posterior capsular rent and zonular dehiscence requiring vitrectomy were also excluded from the study. Data from those eyes with complete records and a minimum follow-up of 6 weeks were used for analysis.

Patient demographics such as age, gender, laterality of involvement, systemic status, namely, diabetes, hypertension, and renal disease (yes/no), axial length, duration of visual loss (days), and time since cataract surgery (days) were recorded from the case records. As an institutional policy, all intraoperative findings and early postoperative examinations are routinely recorded as per the Oxford Cataract Treatment and Evaluation Team protocol in our institution.[10] All intraoperative (posterior capsular rupture, vitreous loss, etc.) and postoperative complications (severe inflammation, hypopyon, corneal edema, etc.) documented in the case records were recorded during data collection. Specific intraoperative details recorded were type of cataract surgery (small incision cataract surgery/phacoemulsification/extracapsular cataract extraction), location of incision (superior vs. temporal), type of IOL (Poly[methyl methacrylate] vs. acrylic and hydrophobic vs. hydrophilic), type of capsulotomy (rhexis vs. can opener), and placement of IOL (in the bag vs. sulcus placement).

At the time of presentation with PCME, all patients underwent a comprehensive ophthalmic examination including Snellen's best-corrected visual acuity (BCVA), intraocular pressure measurement using Goldmann applanation tonometry, slit-lamp evaluation to determine the presence of anterior chamber reaction (cells, flare), vitreous in the anterior chamber, position of IOL (in the bag vs. sulcus placement), and dilated fundus examination to document PCME and note other retinal pathology. All patients underwent macular evaluation using spectral domain OCT (5-line raster and macular thickness map, Cirrus OCT, Carl Zeiss Meditec, Dublin, USA). CMT (in microns) obtained from the automated thickness map on the OCT machine and presence of subretinal fluid (yes/no) was recorded during data collection. As per institutional protocol, all patients were initially treated with topical steroids (prednisolone eye drops, Alcon laboratories or generic) four times a day, with or without tapering for 6 weeks, at the treating physicians' discretion. In those receiving tapering regimens, taper was started at 1 week and prednisolone was withdrawn at 6 weeks. In addition, all patients received topical nepafenac drops (Nevanac, Alcon laboratories or generic) three times a day for 6 weeks. Patients were asked to follow up after 6 weeks, and similar data including BCVA and OCT-derived measurements were recorded for analysis at 6-week follow-up.

Outcome measures

Resolution of PCME at 6-week follow-up with combination of topical prednisolone and nepafenac was assessed in terms of complete and any success. Complete success was defined as BCVA ≥6/9 and CMT ≤300 μ with no morphologic retinal edema. Any success was defined anything less than complete success and reduction in CMT by ≥150 μ.

Statistical analysis

All continuous variables were expressed as means + standard deviations and categorical variables were expressed as proportions. Snellen's BCVA was converted into logarithm of minimum angle of resolution for analysis. Group differences in continuous variables were analyzed using Student's *t*-test or the Wilcoxon rank-sum test. Chi-square or Fisher's exact tests were used to determine group differences between categorical variables. Factors influencing complete and any success were 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. This approach identifies the overall best model as well as closely competing models based on the Akaike information criterion (AIC) value. The final model, which resulted in the largest number of statistically significant independent predictors with the lowest AIC value, was chosen. The reduction in CMT (calculated as CMT at baseline–CMT at 6 weeks) was calculated and this was correlated with baseline BCVA as well as improvement in BCVA at 1 month. In addition, linear regression analysis was done to understand the association between improvement of BCVA and CMT reduction at 1 month. Finally, the median CMT reduction value was used to divide the cohort into two groups, and logistic regression was 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).

Results

A total of 69 eyes with PCME were identified during the study period. The median duration of follow-up for those included in the analysis was 81 days (interquartile range = 60–145 days). Complete success with topical medications was seen in 37 eyes (54%) and any success was seen in 55 eyes (80%). Seven eyes (10%) had no improvement in vision and no change or worsening of macular thickness at follow-up. There was no difference in eyes with and without complete success in terms of baseline characteristics [Table 1]. Patients experiencing any success were significantly younger and had much better baseline BCVA than those who did not attain any success [Table 1].

Univariate logistic regression analysis showed that greater interval from time of cataract surgery and lower BCVA at presentation were associated with lower odds of complete success [Table 2], whereas male gender, undergoing phacoemulsification (vs. manual small-incision cataract surgery), and having a nontapering regimen of topical prednisolone were associated with higher odds of complete success [Table 2]. Multivariable logistic regression adjusting for CMT at presentation, gender, and time interval since cataract surgery revealed every one-line decrement of BCVA at baseline (from median) was associated with 17% reduction

in chances of complete success (OR = 0.83, 95% CI = 0.61–0.89, $P = 0.003$). Similarly, BCVA at 6 weeks showed a strong positive correlation (Pearson's correlation coefficient = 0.63, $P = 0.02$) with BCVA at presentation [Fig. 1].

Univariate logistic regression showed that increasing age and BCVA at presentation were significantly able to predict any success [Table 2]. After adjusting for age, gender, CMT at presentation, and topical steroid regimen, every one-line decrement of presenting BCVA was associated with approximately 40% reduction in likelihood of attaining any success with topical medications (OR = 0.61, 95% CI = 0.4–0.9, $P = 0.007$) [Table 2].

There was poor correlation between CMT difference and BCVA at baseline ($r = -0.16$, $P = 0.78$) and with improvement in BCVA at 1 month ($r = 0.19$, $P = 0.81$). Linear regression analysis showed that for every one-line improvement in BCVA, there was 149 μ reduction in CMT (95% CI = −29 μ–327 μ, $P = 0.10$). Dividing the cohort into two equal groups based on the median CMT reduction (mean reduction in CMT = 33 μ vs. 272 μ), logistic regression analysis showed that there was a 54% lower chance of higher CMT reduction with every one-line worsening of BCVA at baseline (OR = 0.46, 95% CI = 0.06 - 3.21, $P = 0.43$).

No differences were noted between success rates of generics and branded drugs, including both prednisolone and nepafenac. Similarly, duration since cataract surgery and macular thickness at baseline did not significantly influence the success rates with topical medications. None of the patients developed steroid-induced glaucoma.

Table 1: Differences in eyes with and without complete success and any success

Variable	Complete success		P	Any success		P
	Yes (*n*=37)	No (*n*=32)		Yes (*n*=55)	No (*n*=14)	
Age (years)	60.7±7.8	63.0±8.9	0.26	61±8	66.8±10.5	0.03
Gender (males), *n* (%)	24 (65)	18 (56)	0.46	33 (60)	9 (64)	0.77
Diabetes, *n* (%)	15 (40)	8 (25)	0.39	20 (33)	3 (21)	0.29
Percentage with DR	7 (19)	4 (13)	0.46	8 (15)	3 (21)	0.53
Percentage eyes with NS >Grade 3	6 (16)	9 (30)	0.27	12 (22)	3 (21)	0.73
Percentage eyes with PSC	13 (35)	7 (22)	0.22	17 (31)	3 (21)	0.48
Technique (phacoemulsification vs. MSICS), *n* (%)	12 (32)	7 (22)	0.23	16 (29)	3 (21)	0.70
Postoperative iritis, *n* (%)	8 (22)	6 (19)	0.36	10 (18)	4 (28)	0.18
Time of onset since cataract Sx (days)	110±23	127±21	0.44	109±76	154±130	0.50
BCVA at presentation (logMAR)	0.41±0.1	0.51±0.2	0.09	0.41±0.2	0.64±0.3	0.001
CMT at presentation (μ)	528±133	589±131	0.11	522±133	571±142	0.84
SRF at presentation, *n* (%)	40 (78)	20 (74)	0.66	51 (78)	9 (69)	0.47
Prednisolone: QID versus taper, *n* (%)	30 (81)	25 (78)	0.76	44 (80)	11 (78)	0.90
Nepafenac: Brand versus generic, *n* (%)	18 (58)	17 (63)	0.70	28 (51)	7 (50)	0.78

Sx: Surgery, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, SRF: Subretinal fluid, MSICS: Manual small-incision cataract surgery, LogMAR: Logarithm of the minimum angle of resolution, PSC: Posterior subcapsular cataract, DR: Diabetic retinopathy, NS: Nuclear sclerosis

Table 2: Univariate and multivariable logistic regression analysis for factors predicting complete and any success with topical medications alone

Variable	Interval	OR (95% CI)			
		Complete success		Any success	
		Univariate	Multivariable	Univariate	Multivariable
Age (years)	5-year increment	0.84 (0.6-1.0)	0.84 (0.6-1.1)	0.66 (0.4-0.9)*	0.73 (0.4-1.2)
Gender	vs. female	1.4 (0.5-3.7)	2.1 (0.6-6.8)	0.83 (0.2-2.8)	1.36 (0.3-6.8)
Diabetes	vs. no DM	2.04 (0.7–5.7)	-	2.09 (0.5-8.4)	-
NS grade	+1 grade increase	1.05 (0.5-1.9)		0.7 (0.3-1.7)	
Technique (phacoemulsification)	vs. MSICS	1.54 (0.9-2.6)	-	1.33 (0.6-2.4)	-
Onset since cataract Sx	1-week increment	0.99 (0.9-1.0)*	0.98 (0.9-1.1)	0.99 (0.9-1.1)	0.99 (0.9-1.4)
BCVA at presentation	1-line worse	0.81 (0.6-0.9)*	0.83 (0.6-0.9)**	0.61 (0.4-0.8)*	0.66 (0.5-0.9)*
CMT at presentation (μ)	100 μ increase	0.70 (0.4-1.1)	0.77 (0.5-1.2)	0.89 (0.5-1.3)	0.82 (0.5-1.4)
SRF at presentation	vs. no SRF	1.27 (0.4-3.8)	-	1.61 (0.4-6.0)	-
Prednisolone: QID	vs. taper	1.2 (0.3-3.8)	1.05 (0.3-3.9)	1.1 (0.2-4.5)	1.46 (0.2-9.1)
Nepafenac: Brand	vs. generic	0.8 (0.2-2.3)	-	1.4 (0.4-4.9)	-

*P<0.05, **Separate model than CMT at presentation. Sx: Surgery, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, SRF: Subretinal fluid, MSICS: Manual small incision cataract surgery, OR: Odds ratio, CI: Confidence interval, DM: Diabetes mellitus, NS: Nuclear sclerosis
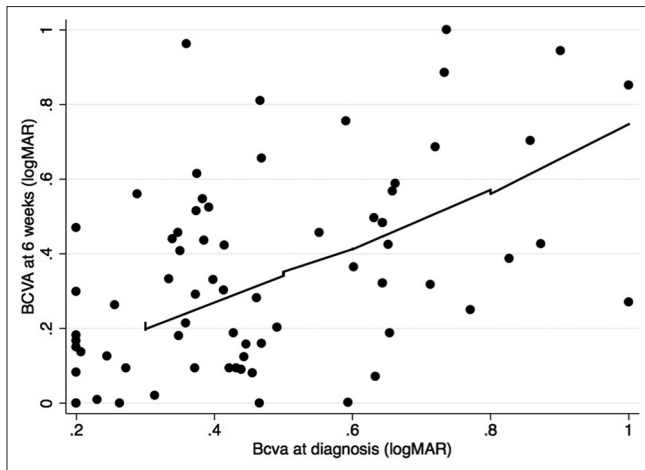
Figure 1: Scatter plot with locally weighted scatterplot smoothing curve showing relationship between vision at baseline and at 6 weeks follow-up

Discussion

Knowledge of baseline factors that predict good response and resolution of acute PCME with topical drops alone can help to alleviate anxiety for patients and their operating surgeons. In addition, this information may also help to counsel potential need for future steroid injections in those who demonstrate risk factors for poor resolution. We found that after uncomplicated cataract surgery, irrespective of surgical technique, eyes with worse vision at baseline (6/18 or worse Snellen's equivalent) experienced unsatisfactory visual and anatomic recovery, thereby increasing the need for invasive treatments such as PST and IVTA.

In a previous study by Heier *et al.*, 28 eyes with PCME were randomized to receiving either topical NSAID (ketorolac) or steroid (prednisolone) or a combination of both.[6] The authors report outcomes from 24 eyes and conclude that combination therapy yielded the best visual outcomes. The authors do not report the resolution rate of CME but mention that two-line improvement in vision was seen in 65% eyes while 8 out of 9 eyes (89%) in the combination group experienced at least two-line improvement. Although the apparent success rate in the combined group was greater than what we report, this study was performed in the pre-OCT era and reported outcomes predominantly based on vision making direct comparisons difficult. In addition, we used a different NSAID (nepafenac) compared to ketorolac used by the authors. Many other studies have evaluated the role of topical NSAID monotherapy or in combination with steroids and some have shown their benefit in resolution rates, but most are limited by their small sample size and hence are unable to perform robust regression analysis for factors predicting response rates.[7,9] In a recent Cochrane review on NSAIDs for treating cystoid macular edema following cataract surgery, Sivaprasad *et al.* observed that study design differed between studies in important aspects, and thus, they could not be combined in a meta-analysis.[7] They concluded that the effect of NSAIDs in acute and chronic PCME remains unclear and needs further investigations.

We found that eyes with lower baseline vision (lesser than median, i.e., 6/18) showed poorer response to topical drugs. Although there was no difference in macular thickness or other OCT-based structural parameters between those with better and worse vision at baseline, it is possible that eyes with lower vision

have some amount of irreversible cellular damage leading to inadequate visual recovery with topical steroids and nepafenac.

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

A drawback of our study, besides its retrospective nature, is the arbitrary allocation of tapering and nontapering regimen of topical steroids to patients. The relatively large sample size and availability of OCT characteristics before and after treatment for meaningful analysis are the strengths of this study.

Conclusion

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

References

1. Guo S, Patel S, Baumrind B, Johnson K, Levinsohn D, Marcus E, *et al.* Management of pseudophakic cystoid macular edema. Surv Ophthalmol 2015;60:123-37.

2. Sindal MD, Nakhwa CP, Sengupta S. Comparison of sutured versus sutureless scleral-fixated intraocular lenses. J Cataract Refract Surg 2016;42:27-34.

3. Yonekawa Y, Kim IK. Pseudophakic cystoid macular edema. Curr Opin Ophthalmol 2012;23:26-32.

4. Chu CJ, Johnston RL, Buscombe C, Sallam AB, Mohamed Q, Yang YC, *et al.* Risk factors and incidence of macular edema after cataract surgery: A Database study of 81984 eyes. Ophthalmology 2016;123:316-23.

5. Daien V, Papinaud L, Domerg C, Lacombe S, Daures JP, Villain M, *et al.* Incidence and characteristics of cystoid macular edema after cataract surgery. Ophthalmology 2016;123:663-4.

6. Heier JS, Topping TM, Baumann W, Dirks MS, Chern S. Ketorolac versus prednisolone versus combination therapy in the treatment of acute pseudophakic cystoid macular edema. Ophthalmology 2000;107:2034-8.

7. Sivaprasad S, Bunce C, Crosby-Nwaobi R. Non-steroidal anti-inflammatory agents for treating cystoid macular oedema following cataract surgery. Cochrane Database Syst Rev 2012;2:CD004239.

8. Shelsta HN, Jampol LM. Pharmacologic therapy of pseudophakic cystoid macular edema: 2010 update. Retina 2011;31:4-12.

9. Wielders LH, Schouten JS, Aberle MR, Lambermont VA, van den Biggelaar FJ, Winkens B, *et al.* Treatment of cystoid macular edema after cataract surgery. J Cataract Refract Surg 2017;43:276-84.

10. Use of a grading system in the evaluation of complications in a randomised controlled trial on cataract surgery. Oxford cataract treatment and evaluation team (OCTET). Br J Ophthalmol 1986;70:411-4.