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Role of Nonsteroidal Anti-Inflammatory Drugs in Prevention of Macular Edema after Uneventful Phacoemulsification in Diabetic and Non-Diabetic Patients

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ABSTRACT

Background: Pseudophakic cystoid macular edema is one of the most important complications after cataract surgery. This can result in decreased visual acuity.

Purpose: The study aimed to assess the efficacy of using NSAIDs as a prophylaxis, to prevent macular edema and improvement of visual acuity.

Patients and methods: The study included 100 eyes with cataract and accepted phacoemulsification, classified into: Group 1: Non-diabetic patients were subdivided into: (1A didn't receive NSAIDs, 1B received NSAIDs). Group 2: Type 2 diabetic patients were subdivided into: (2A didn't receive NSAIDs, 2B received NSAIDs).

One drop of nepafenac 0.1% was administrated four times daily for 2 days before surgery, 30-120 minutes prior to surgery. Postoperatively nepafenac was given four times daily for four weeks. SD-OCT was performed to measure CFT before phacoemulsification, repeated 1 week and 1 month postoperatively.

Results: In subgroup 1A; CMT increased through one month, while subgroup 1B, CMT decreased through the same time. There was significant difference in CMT change between preoperative and 1week postoperative as well as between preoperative and 1 month postoperative (p=0.025, 0.037 respectively).

For subgroup 2A; CMT increased through one month. There was significant difference in CMT change (p<0.001) between preoperative and 1week postoperative as well as between preoperative and 1 month postoperative (p<0.008) between subgroup 2B and subgroup2A

Conclusion: The prophylactic use of topical NSAIDs appears to be effective for preventing CMT change after phacoemulsification. It reduces the incidence of PCME in normal and diabetic patients ensures a favorable outcome.

Keywords: Pseudophakic cystoid macular edema, phacoemulsification, nepafenac.

INTRODUCTION

Cystoid macular edema (CME) is one of the most important complications after cataract surgery. It is the main cause of decreased visual acuity, even in patients without risk factors or an uneventful cataract surgery [(1)].

The incidence of clinical CME varies from 0.1% to 2% in patients without risk factors. However, some clinical trials have reported up to 9% angiographic CME which means increased central macular thickness measured by optical coherence tomography [(2)]. The most accepted pathogenesis of Pseudophakic cystoid macular edema (PCME) involves intraocular inflammation with prostaglandin (PG) release and disruption of the blood aqueous and blood retinal barrier [(3)].It can occur in uncomplicated eyes. There are risk factors like PCME in the contralateral eye, diabetes mellitus, uveitis, epiretinal membranes, PG analog use, and aging. That is why, NSAIDs are routinely used in the postoperative period. They inhibit cyclooxygenase (COX-1 and COX-2) enzymes, they prevent PG production and downstream inflammation[(4)].NSAIDs decrease the incidence, severity and duration of macular edema. They provide a very good anti-inflammatory effect apart from maintaining intraoperative mydriasis and decrease postoperative pain [(5)]. Nepafenac is a topical NSAID used for the treatment of pain and inflammation associated with cataract surgery. Nepafenac is a prodrug that rapidly penetrates the cornea and is deaminated into the active metabolite, amfenac, by intraocular hydrolases within ocular tissues, including the ciliary body epithelium, retina, and choroid [(6)].

This bioconversion is targeted to the retina and choroid [(7)]. Macular changes are likely to occur after cataract surgery in diabetic patients, especially those with pre-existing retinopathies, compared with nondiabetic patients, ranging from 31% to 81% [(7)].

Assessing and managing ME after cataract surgery in diabetic patients arises from the fact that two clinical forms of edema can be present, either diabetic macular edema (DME) alone or in combination with Irvine-Gass CME. Retinal capillary hyperpermeability from intraocular inflammation consider the major pathway in the development of this edema. OCT can provide both qualitative and quantitative data to explore the relationship of ME and cataract surgery in patients with diabetic retinopathy [(8)].

Deciding usage of nonsteroidal anti-inflammatory agent to as standard in patients undergoing cataract surgery is important to ensure a favorable outcome [(9)].

PATIENTS AND METHODS

100 eyes of 88 patients with cataract were enrolled in a prospective non-randomized interventional study. This study was conducted in outpatient ophthalmology

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clinics of Al-Azhar University hospitals (Alzahraa and Al Hussin hospitals) during the period from September 2016 to December 2018. The study was adhered to the tenets of the Declaration of Helsinki and was approved by the ethics board of Al-Azhar University and an informed written consent was taken from each participant in the study. The included patients were classified into 2 groups:

Group 1: Non-diabetic patients (50 eyes) were subdivided into 2 subgroups: (1 A who didn't receive NSAIDs and 1B who received NSAIDs).

Group 2: Type 2 diabetic patients (50 eyes) were subdivided into 2 subgroups: (2 A who didn't receive NSAIDs and 2B who received NSAIDs).

Inclusion Criteria were patients 50-60 years of age, Non-diabetic patients or those with type2 diabetic patients with significant cataract (nuclear cataract grade 2-3 according to the Wisconsin grading system [(10)] which grades the level of NC based on opacity and color of lens nucleus) were scheduled for surgery by phacoemulsification with posterior chamber IOL lens implantation. Central macular thickness less than 250 microns.

Exclusion criteria included any of the following conditions: hypersensitivity to the NSAIDs, pre-existing macular edema, central macular thickness more than 250 microns, presence of macular traction and epiretinal membranes. Also media opacity that interfere with preoperative evaluation, congenital cataract, traumatic cataract, macular oedema and/or diabetic retinopathy, previous intraocular surgery, topical glaucoma medications and intraoperative or postoperative complications (e.g. posterior capsular rupture , vitreous loss…)

Methods

- **Ophthalmic examination**

Preoperatively, all patients underwent a thorough ophthalmic examination and review of concurrent medications and medical history. The ophthalmic examination included best-corrected visual acuity (BCVA) (Landot C), slit lamp examination, IOP measurement by Goldmann applanation tonometry, and fundus examination.

- **Macular OCT** using (Spectral-domain OCT (SD-OCT) (NIDEK RS -3000) baseline scan was performed for all patients prior to surgery.

The "Fast Macular Thickness Map" scan and macular line was used to determine the foveal thickness (FT central 1 mm) to detect any macular alteration. Preoperative mydriatic eye drops (1% Cyclopentolate and 10% Phenylephrine) was instilled into all patients. Both subgroups 1B and 2B received topical NSAIDs (one drop of nepafenac 0.1% four times daily for 2 days before surgery). In the day of surgery, 30-120minutes prior to operation nepafenac was given. Postoperatively the drug was given four times per day for four successive weeks.

- **Surgery**

All patients underwent Phacoemulsification cataract surgery with foldable IOL implantation inside the capsular bag using the White star signature (Abbott). Surgeons used the same standardized incision phacoemulsification technique on all patients under local anaesthesia. Phacoemulsification of the nucleus by standard technique (divide and conquer techique) with intraoperative constant parameters. Irrigation aspiration, and implantation of intraocular lens in the bag , finally hydration of the wound and the 2 paracentesis ports. The phaco power and time were recorded to exclude cases with prolonged phaco power and time. Eyes that had any intraoperative or postoperative complications were excluded from the study. Then all patients received the same standard medications for 4 weeks, consisting of a combination of steroid (Prednisolone acetate 1%) and antibiotic (Moxifloxacin 0.5%) eye drops beginning with four times daily, which tapered by 1 drop daily each week. Subgroup 1B and subgroup 2B received (Nepafenac) 4 time daily for 4 weeks. All patients were evaluated postoperatively at 1day, 1 week and 1month after surgery. At each visit BCVA assessment, slit lamp examination of anterior segment, Intraocular pressure (IOP) measurement and fundoscopy were done. Macular OCT was repeated at 1 and 4 week in order to record foveal thickness (FT) and any other macular alteration.

The study was approved by the Ethics Board of Al-Azhar University.

Statistical Methods

The collected data were revised, coded, tabulated and introduced to a PC using Statistical package for Social Science **(IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).**

RESULTS

The present study was conducted on 100 eyes (50 of diabetic and 50 of Non-diabetic patients). Mean age of Non-diabetic group was 56.7, while that of diabetic group was 57.3 years. They were 57 male and 43 Female. Patients of all groups had nuclear cataract grade II with otherwise normal anterior and posterior segment. No significant differences were found in age and gender between Non-diabetic and diabetic groups. Non-diabetic group was 23 left and 27 right eyes, while diabetic group was 22 left and 28 right eyes.

No significant differences were found in baseline ophthalmic examination between diabetic and Non-diabetic groups. Phaco power and aspiration flow rate (AFR) did not differ significantly between diabetic and Non-diabetic patients.

Table (1): Comparison of VA, BVCA, refraction and CMT between Group1 and Group 2.

		Group 1 N=50		Group 2 N=50		*p*
		mean	SD	mean	SD	
VA	**Preoperative**	0.11	0.03	0.12	0.03	0.715ᵗ
	Postoperative after 1 month	0.31	0.07	0.31	0.01	0.824ᵗ
BVCA	**Preoperative**	0.25	0.07	0.27	0.08	0.718ᵗ
	Postoperative after 1 month	0.62	0.20	0.60	0.15	0.730ᵗ
Refraction	**Preoperative**	8.63	2.61	9.66	2.39	0.487ᵗ
	Postoperative after 1 month	1.71	0.29	1.68	0.38	0.858ᵗ
CMT(µm)	**Preoperative**	215.86	16.07	225.72	13.65	0.001ᵗ
	Postoperative after 1 week	223.20	27.67	227.80	22.79	0.366ᵗ
	Postoperative after 1 month	228.74	50.86	238.32	50.86	0.349ᵗ

N, number; SD, standard deviation; ᵗ, t test, VA: visual acuity, BCVA: best corrected visual acuity, central macular thickness (CMT)

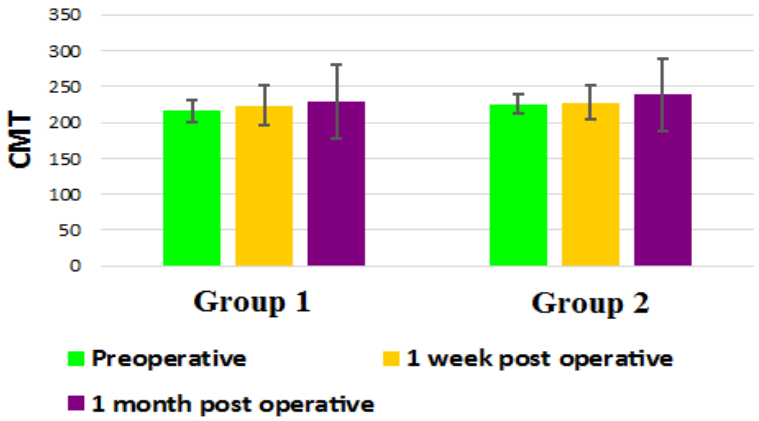


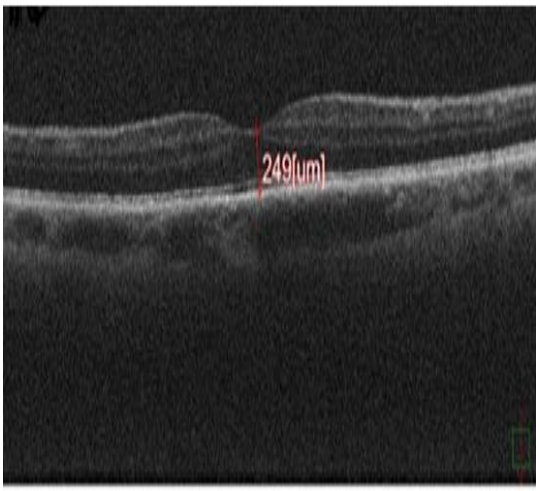
Figure (1): Column chart of CMT in group1 and group2. Column represent mean, error bar represent SD

From **Table (1), Fig.(1),** preoperative central macular thickness (CMT) was significantly higher in group 2 (225.75±13.65um) when compared to group 1(215,86 ±16.07um) (p=0.001). While postoperative CMT at 1 week, 1 month did not differ significantly between both groups. In addition pre and postoperative VA, BVCA, refraction did not differ significantly between both groups.

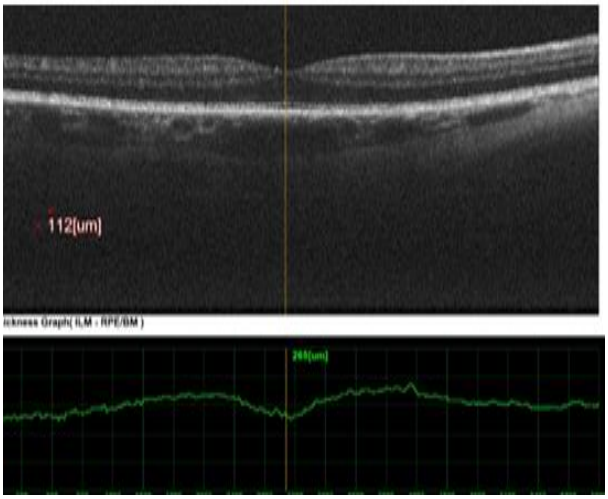
Table (2): Comparison of VA, BVCA, refraction and CMT between subgroup 1A and 1B.

		subgroup 1A N=25		subgroup 1B N=25		*P*
		mean	SD	mean	SD	
VA	**Preoperative**	0.28	0.1	0.20	0.06	0.238ŧ
	Postoperative after 1 month	0.57	0.13	0.67	0.22	0.184ŧ
Refraction	**Preoperative**	9.37	2.3	7.36	2.1	0.355ŧ
	Postoperative after 1 month	1.65	0.53	1.77	0.52	0.603ŧ
BVCA	**Preoperative**	0.11	0.02	0.11	0.03	0.961ŧ
	Postoperative after 1 month	0.28	0.07	0.35	0.11	0.192ŧ
CMT	**Preoperative**	218	17.1	213.7	15	0.342ŧ
	Postoperative after 1 week	232.9	33.9	213.5	14.7	0.011ŧ
	Postoperative after 1 month	244.3	67.8	213.2	13.5	0.029ŧ

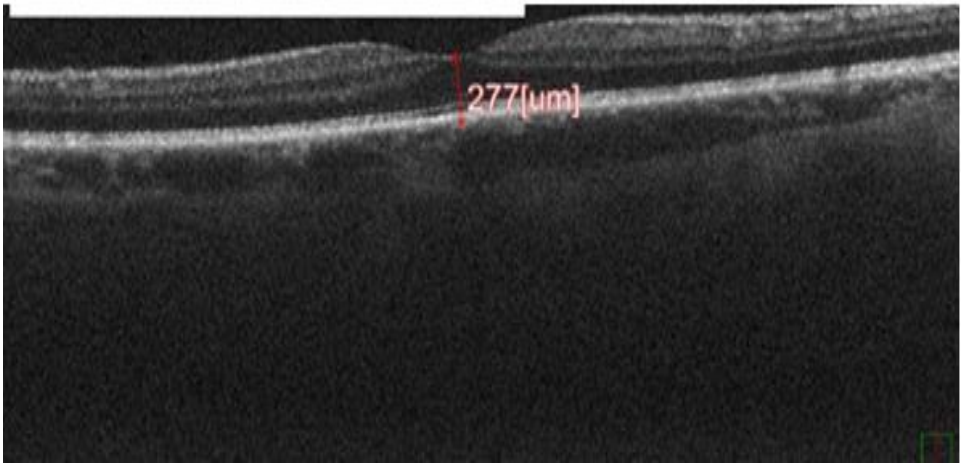
N, number; SD, standard deviation; ŧ, t test, VA: visual acuity, BCVA: best corrected visual acuity, central macular thickness (CMT).



a) Rt eye preoperative CMT was 249um

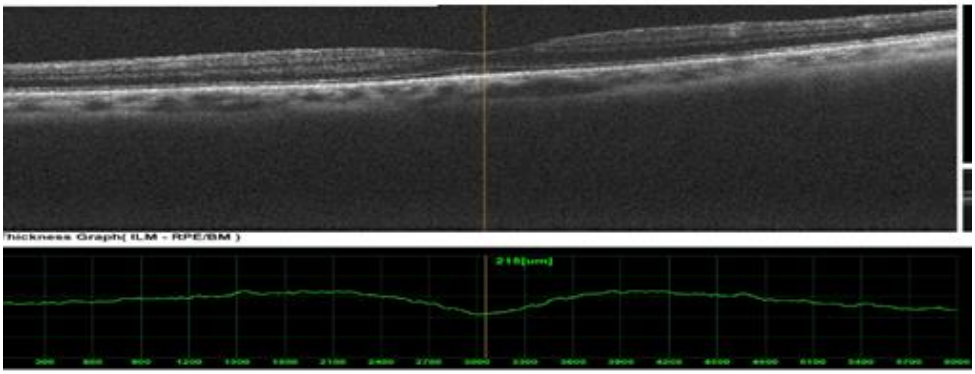


b) 1week postoperative CMT was 265um

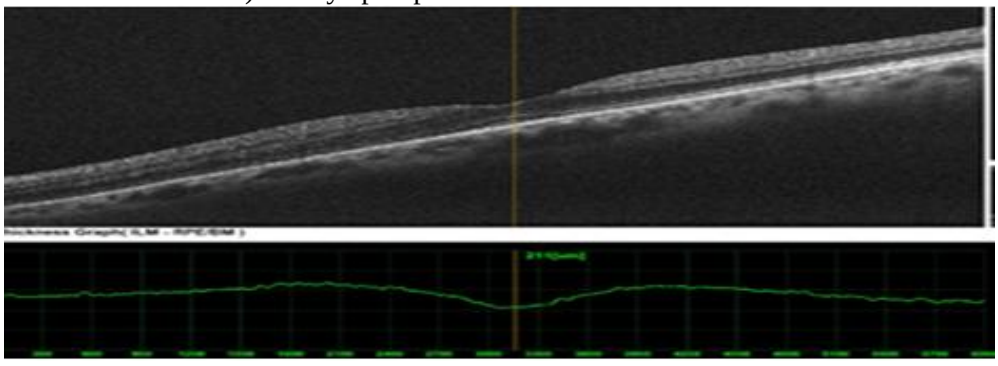


c) 1month postoperative CMT was277um

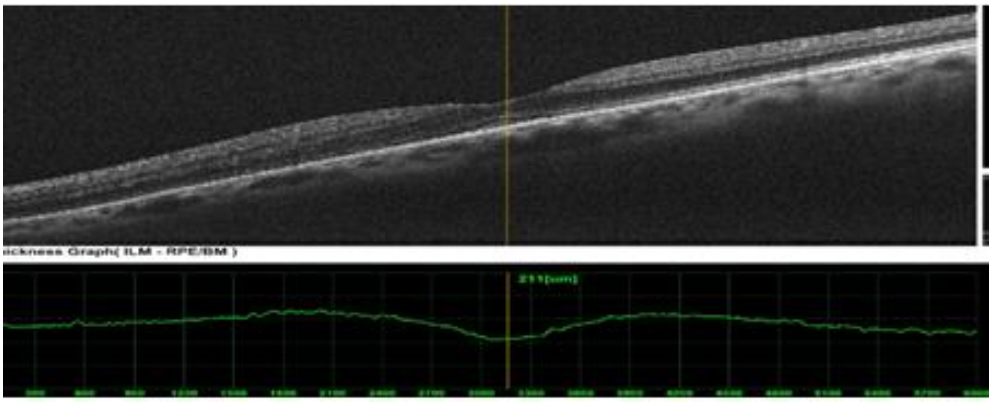
Figure (2) Case 1 from subgroup1A Non-diabetic patient doesnot take NSAIDs



a) Lt eye preoperative CMT was 215um



b) 1 week postoperative CMT was 211um



c) 1month postoperative CMT was211um

Figure (3) Case 2 from subgroup1B Non-diabetic patient takes NSAIDs

From **Table (2).** Both subgroups 1A and 1B showed that VA, BVCA improved, while refraction decreased significantly 1 month post operatively when compared to preoperative values (P<0.001, =0.001, <0.001 respectively). As regard CMT in subgroup 1A CMT increased significantly at 1 week as well as at 1 month post operatively when compared to preoperative values (p=0.016, 0.049 respectively). However, no significant difference was found in CMT between 1 week and 1 month postoperatively **(Figure 2 case number 1)**.

In subgroup 1B no significant difference was found in CMT across follow up period **(Figure 3 Case number 2).**

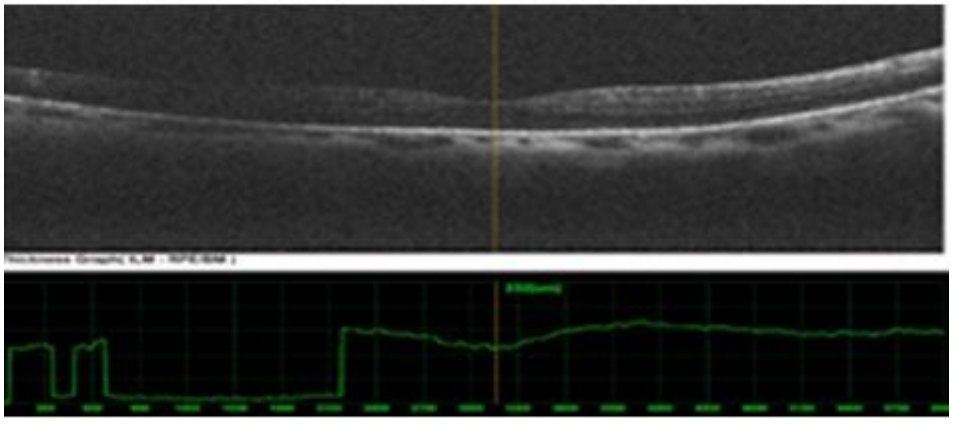
CMT after 1 week and 1 month, showed significantly lower levels in subgroup 1B when compared to subgroup1A (p=0.011, 0.029 Respectively)

Table (3): Comparison of percentage change of VA, BVCA, refraction and CMT between both subgroups 1A&1B

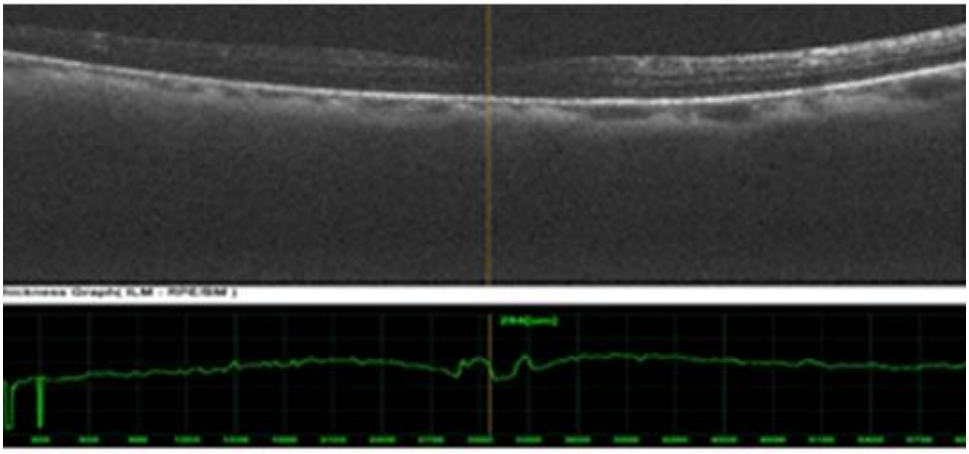
Comparison of percentage change		***P***
VA	**Between preoperative and 1 month postoperative**	0.527ŧ
BVCA	**Between preoperative and 1 month postoperative**	0.102ŧ
Refraction	**Between preoperative and 1 month postoperative**	0.981ŧ
CMT	**Between preoperative and 1week postoperative**	0.025ŧ
	Between preoperative and 1 month postoperative	0.037ŧ
	Between 1 week and 1 month postoperative	0.638ŧ

ŧ, t test, VA: visual acuity, BCVA: best corrected visual acuity, central macular thickness (CMT).

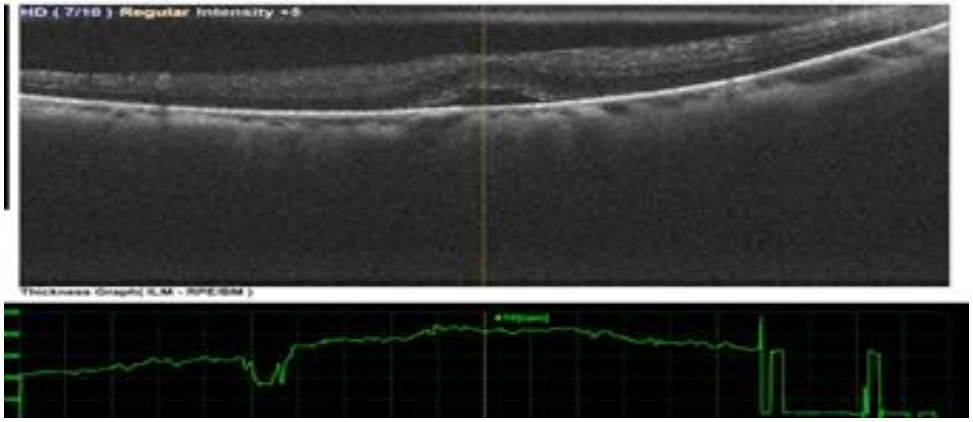
From **table 3** , CMT increased over time in subgroup 1A while in subgroup 1B, CMT decreased overtime. There was significant difference in CMT percentage change between preoperative and 1week postoperative as well as between preoperative and 1 month postoperative (p=0.025, 0.037 respectively).



a) Rt eye preoperative CMT was 232um



b) 1 week postoperative CMT was 294um



c) 1month postoperative CMT was 410um

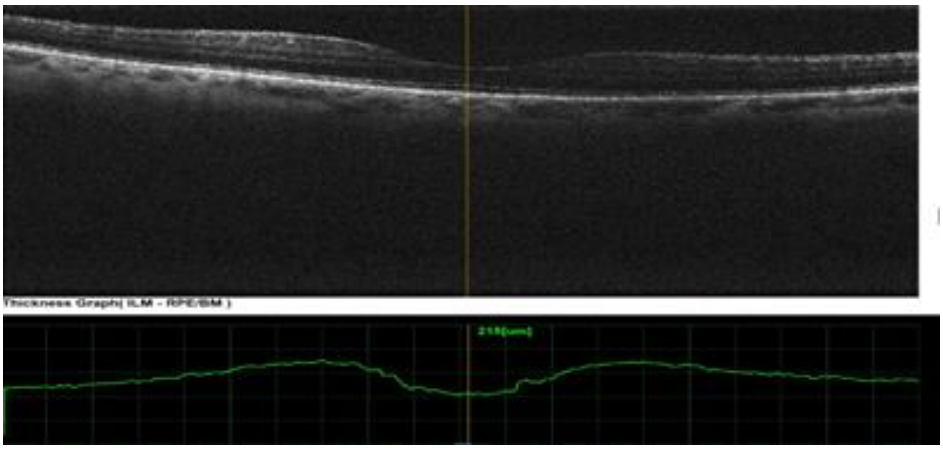
Figure (4): case 3 from sub group 1A Non-diabetic patient doesnot take NSAIDs

In our study three cases in subgroup 1 A (n=3/25, 12%) developed macular oedema with increased central subfield macular thickness and neurosensory detachment following cataract surgery in comparison with the subgroup 1B cases who showed no change in central subfield macular thickness **Figure 4 Case number 3).**

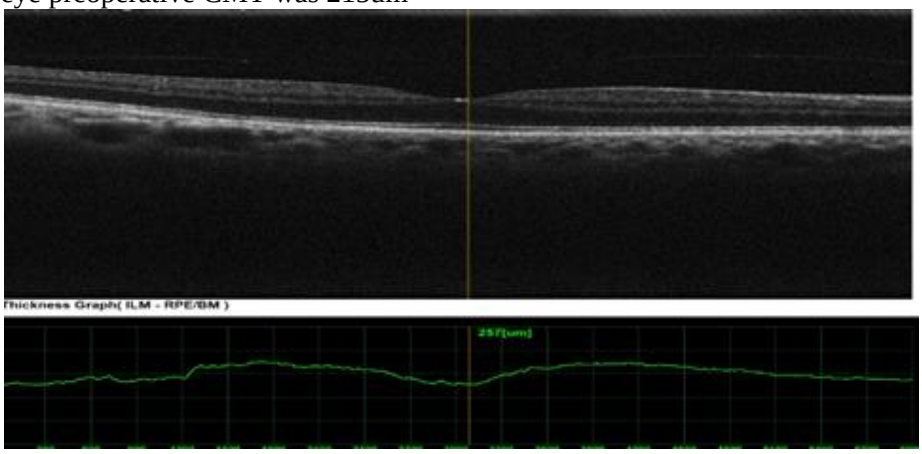
Table (4): Comparison of VA, BVCA, refraction and CMT between subgroup 2Aand 2B

		subgroup 2A (N=25)		**subgroup 2B(N=25)**		***P***
		mean	**SD**	**mean**	**SD**	
VA	**Preoperative**	0.13	0.04	0.11	0.03	0.691 ŧ
	Postoperative after 1 month	0.29	0.09	0.32	0.10	0.365 ŧ
BVCA	**Preoperative**	0.20	0.06	0.32	0.10	0.149 ŧ
	Postoperative after 1 month	0.57	0.09	0.63	0.19	0.159 ŧ
Refraction	**Preoperative**	12.1	3.2	7.7	2.1	0.035ŧ
	Postoperative after 1 month	1.8	0.5	1.6	0.5	0.281ŧ
CMT	**Preoperative**	226.6	14.1	224.8	13.4	0.653ŧ
	Postoperative after 1 week	238.5	25.5	217.1	13.1	<0.001ŧ
	Postoperative after 1 month	256.9	65.9	219.7	14.8	0.008ŧ

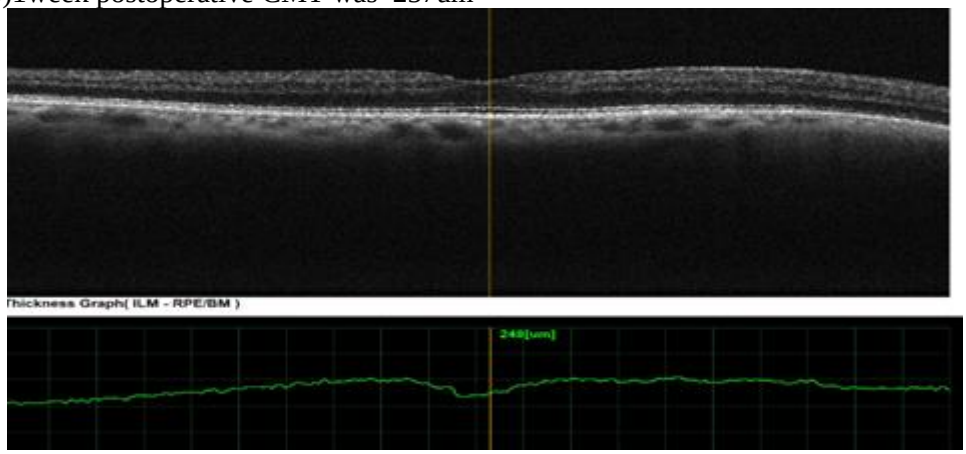
N, number; SD, standard deviation; ŧ, t test, VA: visual acuity, BCVA: best corrected visual acuity, central macular thickness (CMT).



a) Rt eye preoperative CMT was 215um

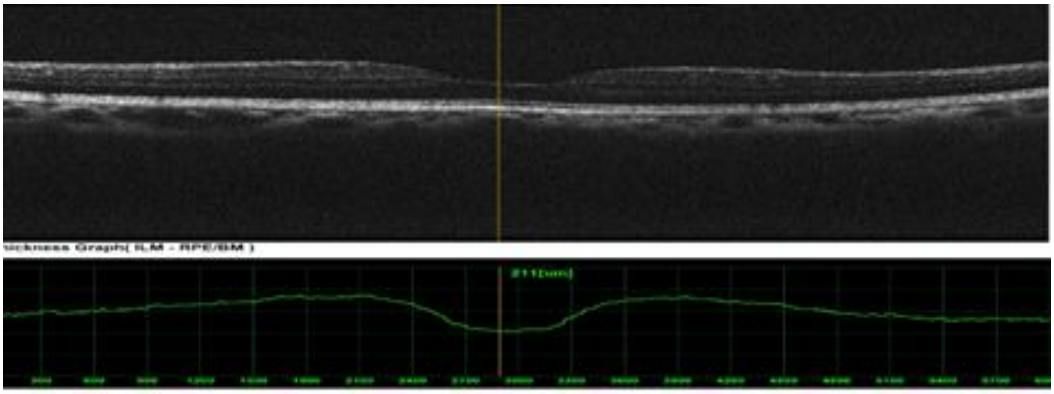


b)1week postoperative CMT was 257um

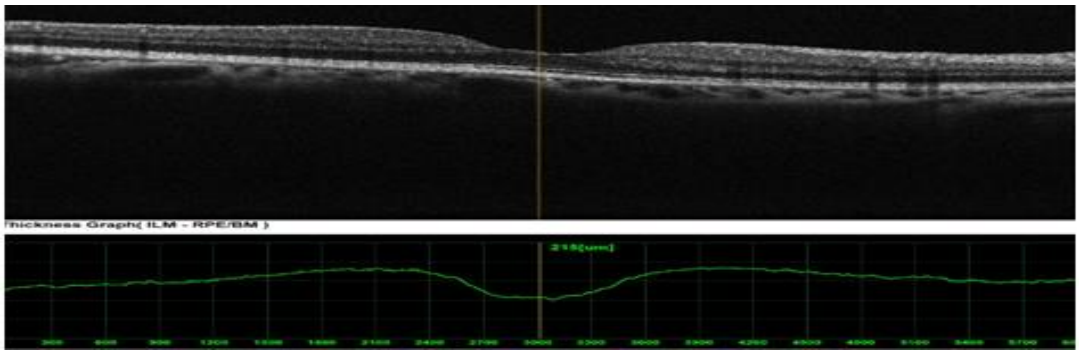


c)1month postoperative CMT was 248um

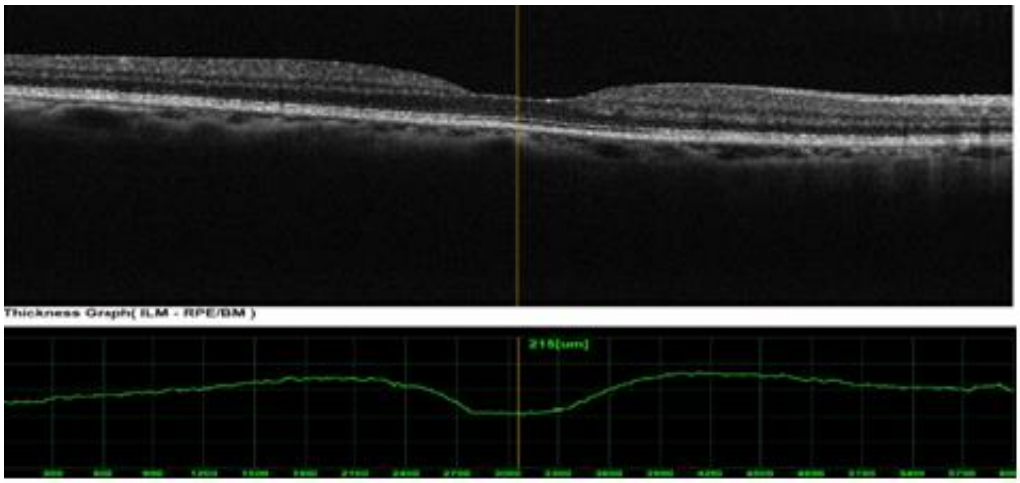
Figure (5): Case 4 from sub group2A diabetic patient doesnot take NSAIDs



a)Rt eye preoperative CMT was 211um



b) 1week postoperative CMT was 215um



c)1month postoperative CMT was215um

Figure (6): Case 5 from subgroup 2B diabetic patient takes NSAIDs

From **table 4**, Both subgroups 2A and 2B showed that VA, BVCA improved with refraction decreased significantly 1 month post operatively when compared to preoperative values ($p<0.001$ for each).

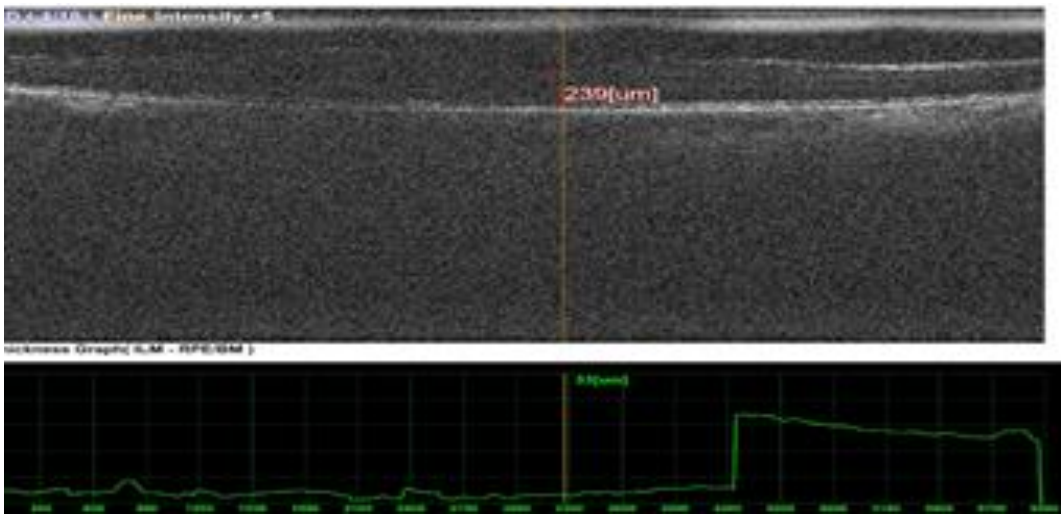
In subgroup 2A CMT increased significantly across time ($p=0.038$), at 1 week as well as at 1 month post operatively when compared to preoperative values ($p=0.012$, 0.028 respectively) (**Figure 5 case number 4**) However, no significant difference was found in CMT between 1 week and 1 month postoperatively while in subgroup 2B CMT differed significantly across time ($p=0.026$). It is decreased at 1 week post operatively when compared to preoperative values ($p=0.013$). However, no significant difference was found in CMT between preoperatively and 1 month post operatively, as well as 1 week and 1 month postoperatively. CMT after 1 week and 1 month, showed significantly lower levels in subgroup 2B when compared to subgroup 2A ($p<0.001$, $=0.008$ respectively).(**Figure 6 case number 5).**

Table (5): Comparison of percentage change of VA, BVCA, refraction and CMT between both subgroups 2A&2B

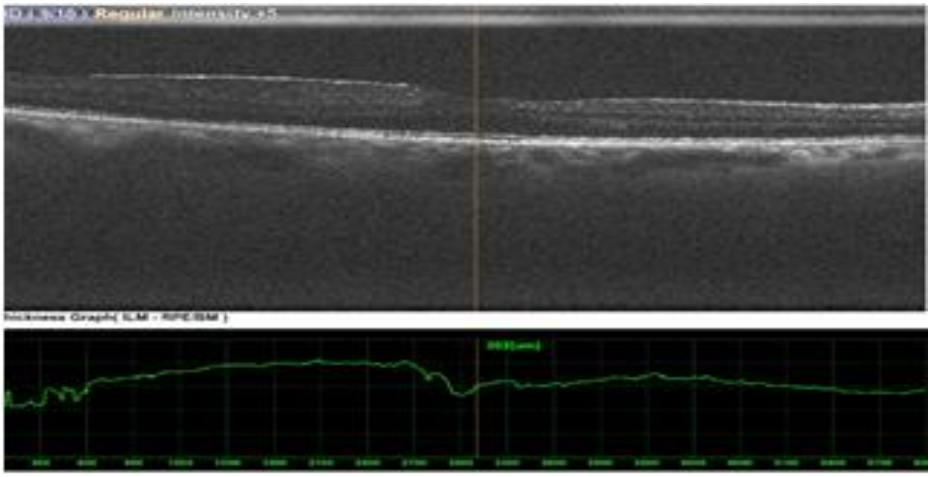
Comparison of percentage change		***p***
VA	**Between preoperative and 1 month postoperative**	0.799ŧ
BVCA	**Between preoperative and 1 month postoperative**	0.313ŧ
Refraction	**Between preoperative and 1 month postoperative**	0.468ŧ
CMT	**Between preoperative and 1week postoperative**	<0.001ŧ
	Between preoperative and 1 month postoperative	0.008ŧ
	Between 1 week and 1 month postoperative	0.141ŧ

ŧ, t test, , VA: visual acuity, BCVA: best corrected visual acuity, central macular thickness (CMT).

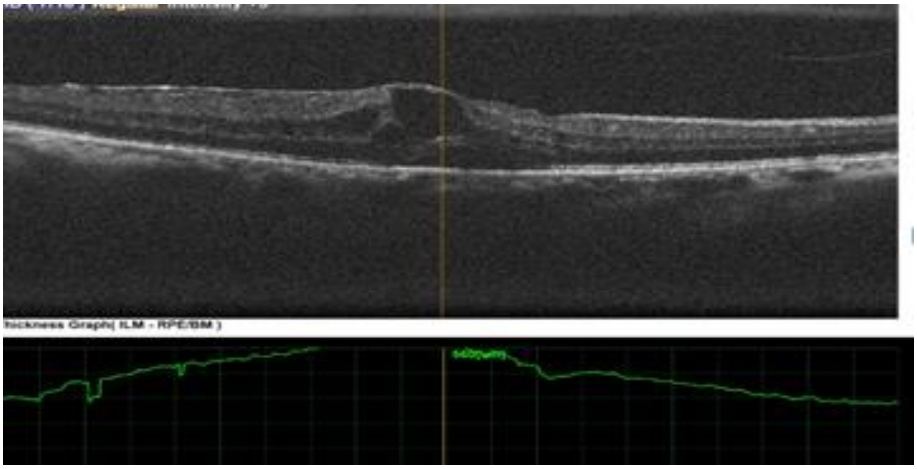
From **table 5,** CMT increased overtime in subgroup 2A. There was significant difference in CMT percentage change between preoperative and 1week postoperative as well as between preoperative and 1 month postoperative between those received nepafenac 0.1% and those did not ($p<0.001$, $=0.008$ respectively).



a)Rt eye peroperative CMTwas 230um



b) 1week postoperative CMTwas 302um



c)1month postoperative CMT was 560um

Figure (7) Case number 6 from subgroup 2A diabetic patient doesnot take NSAIDs

Three cases in subgroup 2 A (n=3/25, 12%) developed macular oedema with increased central subfield macular thickness and neurosensory detachment following cataract surgery in comparison with the subgroup 2B cases only one case(n=1/25, 4%) showed increase in central subfield macular thickness. **Figure 7 Case number 6**

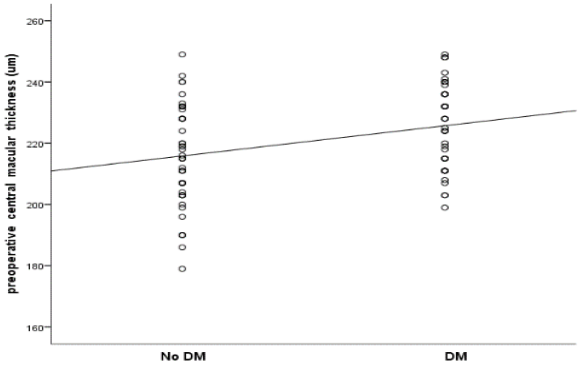


Figure (8). Scatter plot of correlation of preoperative CMT with presence of DM in all studied eyes

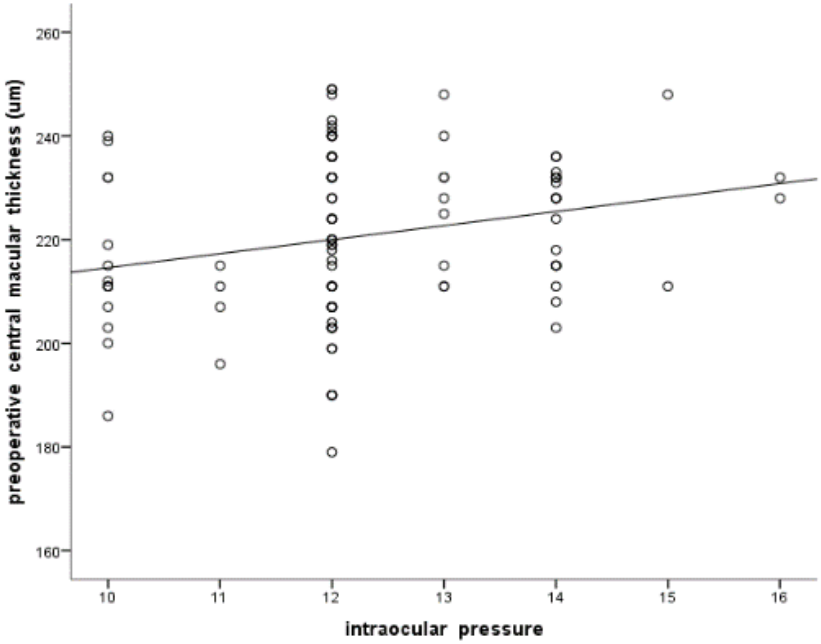


Figure (9). Scatter plot of Correlation of preoperative CMT with IOP in all studied eyes

Preoperative CMT showed significant positive correlation with DM, IOP, and significant negative correlation with biometry.

Table (7): Regression analysis for prediction of CMT change after phacoemulsification.

	p	OR	95% CI	
Age	0.258	2.730	0.478	15.591
DM	0.967	1.580	0.319	9.023
DM duration	0.240	2.502	0.541	11.564
NSAIDs application	<0.001	0.218	0.098	0.485

OR, odds ratio; CI, confidence interval; regression analysis was used.

From **table 7**, CMT change showed significant negative correlation with NSAIDs application. No significant correlations were found between CMT change versus age, DM, DM duration, baseline IOP biometry, change in VA, BVCA and refraction in all studied eyes. Linear regression using generalized linear model was used for prediction of CMT change after phacoemulsification using age, DM, DM duration, nepafenac application as covariates. Nepafenac0.1% application was considered protective factor against CMT change after phacoemulsification.

DISCUSSION

Our study demonstrated the value of addition of two days pre-surgically and 4 weeks postoperatively topical NSAIDs as a prophylactic regimen to the topical corticosteroids after uneventful

phacoemulsification in non-diabetic and diabetic patients. The effect appears obviously on OCT CMT and BCVA.

Our study was in agree with **McCafferty *et al.*** [4] who reported that clinically significant PCME was defined as including both: 1. A loss of two (2) lines of best corrected visual acuity (BCVA) from the expected post cataract surgery BCVA (example: 20/40 BCVA from an expected 20/20 BCVA) or visually symptomatic distortion. 2. OCT, clinical, and angiographic 30% increase in central macular thickness (CMT) from the preoperative baseline**.**

Pollack *et al.* [11] reported that the incidence of ME associated with cataract surgery is higher between patients with diabetes more than those without. More than 75% of patients with mild or moderate DR have vascular leakage after cataract surgery, and more than 3% of patients with diabetes develop ME with decrease in visual acuity within 12 months of surgery, regardless of DR status.

In our present study, Non-diabetic patients and diabetic group showed that VA, BVCA were improved , while refraction decreased significantly 1 month post operatively when compared to preoperative values (P<0.001, =0.001, <0.001 respectively (**tables2,5)**

The results of a study conducted by **Degenring *et al.*** [12] were in agreement with our results for Non-diabetic patients. They found that BCVA increased significantly four successive weeks postoperatively with significantly (p=0.001) higher increase. Also the results of **Petal *et al.*** [13] were agree with our results in diabetic patients.

In our present study, Preoperative CMT was significantly higher in diabetics(mean 225.72± 13.65) (p=0.001) when compared to Non-diabetic group(mean 215.86± 16.07) While postoperative CMT at 1 week, 1 month did not differ significantly between both groups. In addition pre and postoperative VA, BVCA, refraction did not differ significantly between both groups.

Against our study, **Kai and Cheng** [14] demonstrated that there was no difference in preoperative central macular thickness between the two groups, the nondiabetic and diabetic group without diabetic retinopathy.

The current study, subgroup1A showed CMT increased significantly at 1 week as well as at 4 successive weeks post operatively when compared to preoperative values (p=0.016, 0.049 respectively). However, no significant difference was found in CMT between 1 week and 4 successive weeks postoperatively. In subgroup1B was no significant difference in CMT across follow up period.

In agreement with these results **Campa *et al.*** [15] ; **Mathys and Cohen** [16] ; **Wolf *et al.*** [17] concluded that there was significant increase in CMT Compared to baseline (p < 0.01), However, at this time point, four patients (8.3%) of non nepafenac group and none in nepafenac groups developed PCMO (p = 0.016) compared to (12%) in our results. They also reached to the fact that co-administration of nepafenac and steroids in patients who underwent routine cataract surgery is associated with a lower incidence of PCMO compared with steroid monotherapy.

In contrast to our results **Tzelikis *et al.*** [18] found that there was no statistically significant difference in any measurement of CMT between NSAIDs group and control group. They attributed that these results to the fact that these Patients at a low risk factors.

In our present study, subgroup 2A, CMT increased significantly across time (p=0.038), at 1 week as well as at 4 successive weeks post operatively when compared to preoperative values (p=0.012, 0.028 respectively). However, no significant difference was found in CMT between 1 week and 4 successive weeks postoperatively. subgroup2B, CMT differed significantly across time (p=0.026), decreased at 1 week post operatively when compared to preoperative values (p=0.013). However, no significant difference was found in CMT between 1 week and 4 successive weeks postoperatively. CMT after 1 week and 1 month, showed significantly lower levels in subgroup 2B when compared to subgroup2A (p<0.001, =0.008 respectively).

In diabetics; compering between subgroup2A, 2B, there was significant difference in CMT percentage through follow up period compared to preoperative baseline (p<0.001, =0.008 respectively).

Alnagdy *et al.* [19]; **El Gharbawy *et al.*** [20] observed that there was an increase in the CMT starting from postoperative first week until third month. CMT showed a statistically significant difference between control group and NSAIDs groups from postoperative first month until third month (*P*=0.008, 0.027, 0.004).

The results of **McCafferty *et al.*** [4] were against our results . They concluded that topical NSAIDs significantly reduces the incidence of PCME in patients with pre-operative risk factors. There was significant difference between NSAIDs group and control group (p = .0001).

Conclusion:

We concluded that the prophylactic use of topical nonsteroidal anti-inflammatory drugs (NSAIDs) (nepafenac 0.1%) appears to be effective for preventing CMT change after uneventful phacoemulsification. It reduces the incidence of Pseudophakic cystoid macular edema (PCME) in normal and diabetic patients ensures a favorable outcome.

A major limitation of this study was the small number of subjects. However, the results demonstrate findings in the clinical characteristics and outcomes

for this subject group that should be considered for further large scale study.

REFERENCES

1. **Miyake K, Ota I, Miyake G *et al.* (2011):** Nepafenac 0.1% versus fluorometholone 0.1% for preventing cystoid macular edema after cataract surgery. J Cataract Refract Surg ., 37(9):1581–1588.
2. **Quintana N E, Ponce JA, RAllocco A *et al.* (2014):** Non-steroidal anti-inflammatory drugs in the prevention of cystoid macular edema after uneventful cataract surgery. Clinical Ophthalmology, 8: 1209–1212.
3. **Elsawy MF, Badawi N, Khairy HA *et al.* (2013)**: Prophylactic postoperative ketorolac improves outcomes in diabetic patients assigned for cataract surgery. Clin Ophthalmol.,7:1245–1249.
4. **McCafferty S, Harris A, Kew C *et al.* (2017):**Pseudophakic cystoid macular edema prevention and risk factors; prospective study with adjunctive once daily topical nepafenac 0.3% versus placebo. BMC Ophthalmology,17:16.
5. **Yilmaz T, Cordero-Coma M, Gallagher MJ *et al*.** (**2012**):Ketorolac therapy for the prevention of acute pseudophakic cystoid macular edema: a systematic review. Eye (Lond**)**, 26(2):252–258.
6. **Gaynes BI and Onyekwuluje A (2008):** Topical ophthalmic NSAIDs: a discussion with focus on nepafenac ophthalmic suspension. Clin Ophthalmol ., 2:355–368.
7. **Singh R , Alpern L , Jaffe GJ *et al.* (2012):** Evaluation of nepafenac in prevention of macular edema following cataract surgery in patients with diabetic retinopathy.Clinical Ophthalmology , 6 :1259–1269.
8. **Baker C W, Bressler N M, Glassman A R *et al.*** (**2013):** Macular Edema After Cataract Surgery In Eyes Without Preoperative Central-involved Diabetic Macular Edema. JAMA Ophthalmol ., 131(7): 870–879.
9. **Kessel L, Tendal B, Jørgensen K *et al.* (2014):** Post-cataract Prevention of Inflammation and Macular Edema by Steroid and Nonsteroidal Anti-inflammatory Eye Drops. Ophthalmology,121:1915-1924.
10. **Gupta P, Zheng Y, Ting T W *et al. (*2013):** Prevalence of Cataract Surgery and Visual Outcomes in Indian Immigrants in Singapore: The Singapore Indian Eye Study. PLoS ONE, 8(10): e75584.
11. **Pollack A, Staurenghi G, Sager D *et al.* (2017):** Prospective randomized clinical trial to evaluate the safety and efficacy of nepafenac 0.1% treatment for the prevention of macular oedema associated with cataract surgery in patients with diabetic retinopathy. Br J Ophthalmol.,101(4):423-427.
12. **Degenring RF, Vey S, Kamppeter B *et al.*(2007):** Effect of uncomplicated phacoemulsification onth e central retina in diabetic and non-diabetic subjects. Graefes Arch Clin Exp Ophthalmol .,245(1):18-23.
13. **Patel SB, Hartnett ME, Escaravage GK *et al*. (2004):**Qulaity of life after phacoemulsification in patients with Diabetes Mellitus. Invest ophthalmol Vis Sci ., 304.
14. **Kia Y and Cheng KU(2014):** Central macular thickness changes and visual outcome following uncomplicated small incision phacoemulsification in diabetics without diabetic retinopathy patients and nondiabetic patients. Taiwan Journal of Ophthalmology , 4(1):33-39.
15. **Campa C, Salsini G, Perri P *et al.* (2018**): Comparison of the Efficacy of Dexamethasone, Nepafenac, and Bromfenac for Preventing Pseudophakic Cystoid Macular Edema: an Open-label, Prospective, Randomized Controlled Trial. Curr Eye Res .,43(3):362-367.
16. **Mathys KC and Cohen KL (2010):** Impact of nepafenac 0.1% on macular thickness and postoperative visual acuity after cataract surgery in patients at low risk for cystoid macular oedema. Eye (Lond) ,24(1):90-6.
17. **Wolf EJ, Braunstein A, Shih C *et al.* (2007):**Incidence of visually significant pseudophakic macular edema after uneventful phacoemulsification in patients treated with nepafenac. J Cataract Refract Surg .,33(9):1546-9.
18. **Tzelikis PF, Vieira M, Hida WT *et al.* (2015):** Comparison of ketorolac 0.4%and nepafenac 0.1% forthe prevention of cystoid macular oedemaafter phacoemulsification: prospective placebocontrolle d randomised study. Br J Ophthalmol., 99(5):654-8.
19. **Alnagdy AA, Abouelkheir HY, El-Khouly SE *et al.*(2018):**Impact of topical nonsteroidal antiinflam matory drugs in prevention of macular edema follo wingcataract surgery in diabetic patients. Int J Ophthalmol.,18;11(4):616-622.
20. ***El Gharbawy SA , Darwish EA, Abu Eleinen KG et al.* (2018)**: Efficacy of addition of nepafenac 0.1% to steroid eye drops in prevention of post-phaco macular edema in high-risk eyes. Eur J Ophthalmol.,11:206.