

Research Article

Prophylactic Use of Nepafenac Versus Triamcinolone Acetonide to Avoid Cystoid Macular Edema Post Phacoemulsification in Diabetic Patients

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Abstract

Introduction: Phacoemulsification is the preferred surgical technique worldwide, in which the eye's internal lens is emulsified with an ultrasonic handpiece and aspirated from the eye. Cystoid macular edema (CME) remains a relatively frequent complication of cataract surgery even after uncomplicated surgery. Aim of this study was to compare effect of prophylactic use of topical nepafenac versus intravitreal triamcinolone acetonide injection in preventing post phacoemulsification cystoid macular edema by optical coherence tomography. **Patients & Methods:** This study was a prospective, interventional comparative study which conducted in department of Ophthalmology, Beni-Suef University hospital from Jan 2010 to Jan 2016. 40 eyes divided into three groups **Group (1):** Nepafenac group included 10 eyes in which prophylactic topical nepafenac one week pre-operatively was used. **Group (2):** Triamcinolone acetonide group, included 10 eyes in which intraoperative prophylactic intravitreal injection of triamcinolone acetonide was used. **Group (3):** Control group, included 10 eyes in which phacoemulsification surgery without prophylactic topical nepafenac nor intravitreal injection of triamcinolone acetonide was done. **Results:** No significant difference was found between studied groups of patients in preoperative Central foveal thickness (CFT) which was 220.1µm in control group, 222.7µm in triamcinolone acetonide and 212.7µm in nepafenac group. There was a significant ($p=0.034$) increase in postoperative CFT in the control group (244.8µm) But, there was no significant difference between pre and post operative CFT in both triamcinolone. acetonide and nepafenac group ($p=0.401$ $p=0.133$ respectively). **Conclusion:** Prophylactic use of topical Nepafenac or intraoperative intravitreal triamcinolone acetonide appears to be a safe intervention to avoid postoperative pseudophakic cystoid macular edema.

Keywords: Prophylactic, Nepafenac, Triamcinolone Acetonide, Cystoid Macular Edema, Phacoemulsification, Diabetic Patients.

Introduction

Phacoemulsification is the preferred surgical technique worldwide, in which the eye's internal lens is emulsified with an ultrasonic handpiece and aspirated from the eye. Aspirated fluids are replaced with irrigation of balanced salt solution, thus maintaining the anterior chamber as well as cooling the handpiece¹.

Despite recent advances in cataract surgery technique and instrumentation, pseudophakic cystoid macular edema (CME) remains a relatively frequent complication of cataract surgery even after uncomplicated surgery². Pseudophakic CME

develops angiographically after uneventful cataract surgery in up to 20-30% of patients after extracapsular cataract extraction/phacoemulsification³.

Inflammation is the major etiologic factor in the development of CME following cataract surgery. Inflammatory mediators such as prostaglandins, cytokines, and other vasopermeability factors induce disruption of the blood-retinal barrier (BRB) after ocular surgery, resulting in increased permeability from the perifoveal capillaries, with resultant fluid accumulation in the perifoveal retina⁴.

Corticosteroids decrease the initial arachidonic acid breakdown by blocking the phospholipase enzyme. Many clinicians routinely use topical or subconjunctival steroids in an attempt to prevent or minimize postoperative inflammation. In addition to their antiphospholipase enzyme activity, corticosteroids may reduce inflammation by inhibiting immune cell function, altering lymphoid inflammatory cell migration, and blocking vasodilatation.

Intravitreal injection of triamcinolone acetonide (TA) has shown a beneficial effect in the resolution of Diabetic Macular Edema (DME). Intravitreal injection of 4 mg TA under sterile conditions in the operating room at the 6 o'clock inferior pars plana via a 25 gauge needle is done. This allows for the chalky white powder to settle in the inferior vitreous cavity away from the visual axis.

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the expression of COX enzymes, thereby reducing the endogenous prostaglandins which cause vasodilation, blood-ocular barrier disruption, pain stimulation, IOP control, and miosis.

Retinal thickness can be assessed by several methods. Optical coherence tomography (OCT) is a method for high resolution cross-sectional imaging of the retina. This non-invasive technique uses interferometry of light reflected from the retina to obtain cross-sectional images of the macula that directly measures changes in the z-plane (depth of the retina) with 10 µm resolution.

The objective of this study was to compare effect of prophylactic use of topical nepafenac versus intravitreal triamcinolone acetonide in preventing post phacoemulsification cystoid macular edema by optical coherence tomography.

Patients and methods

This study was a prospective, interventional comparative study which conducted in department of Ophthalmology at Beni-Suef University hospital from Jan 2010 to Jan

2016. 40 eyes with stable refractive error divided into three groups as follows:

Group (1): Nepafenac group (NP): Included 10 eyes in which prophylactic topical nepafenac one week pre-operatively was used.

Group (2): Triamcinolone Acetonide group (TA): Included 10 eyes in which intraoperative prophylactic intravitreal injection of 4mg in 0.1 ml triamcinolone acetonide was used.

Group (3): Control group (C): Included 10 eyes in which phacoemulsification surgery without prophylactic topical nepafenac nor intravitreal injection of triamcinolone acetonide was done.

Patients were included in this study according to the following:

Inclusion criteria:

1. The patient aged above 40 years old.
2. Senile cataract.
3. Free of any intraocular disease.
4. Free of any systemic disease except diabetes mellitus.

Exclusion criteria:

1. Previous history of intraocular surgery or trauma.
2. Patient with ocular diseases (glaucoma, uveitis, retinal disorders).
3. Patient with systemic diseases as rheumatoid disease.
4. History of topical or systemic corticosteroid administration in last three months.

All patients were subjected to the following:

Ophthalmological examination including the following:

1) Thorough history taking including:

Age, Sex, Type and duration of diabetes, Detailed visual complaints, Past ocular history (disease, surgery, laser photocoagulation) and Other associated systemic diseases.

2) Ocular examination including:

- Best corrected visual acuity (BCVA) in Snellen's line formatting was done preoperatively and then at 30 and 60 days in both groups.
- Preoperative anterior segment examination with slit lamp biome-

crosscopy to assess cataract density of the patient.

- Measurement of intraocular pressure (IOP) with applanation tonometer was done preoperatively.
- Preoperative fundus examination with indirect ophthalmoscopy to assess macular status and peripheral retina.

3) Optical coherence tomography:

- Pupils were dilated for Optical Coherence Tomography (OCT) examination in all cases with 1% tropicamide (Mydriacyl).
- OCT was done preoperatively and then 1 month postoperatively.

Phacoemulsification procedure:

Phacoemulsification and intraocular lens insertion were performed using almost the standard techniques.

After the operation all patients received the same standard medication for 4 weeks, consisting of a combination of steroidal (Prednisolone acetate) and antibiotic (Gatifloxacin or Moxifloxacin) eye drops beginning with six times daily, which were tapered by 1 drop daily each week.

Follow up:

- Clinical examination at one week and one month postoperative.
- OCT was done after one month.

Statistical analysis

Statistical analysis of the data was performed by using SPSS_22 software package. Categorical data parameters were presented in the form of frequency and percent. Quantitative data were expressed in the form of mean, SD. Comparison was performed by chi-square test for categorical data and One Way ANOVA and student T-test for quantitative data. Paired sample t-test was used to test the significance between pre and post operative means of variables. Probability level (P. value) was assumed significant if less than 0.05 and highly significant if P-value was less than 0.01. P-value was considered non-significant if greater than or equal to 0.05.

Results

Regarding demographic data (table,1), the mean age of the control group was 62.2 years (ranged from 53 to 70 years), 63.9 years (ranged from 57 to 71 years) in TA group, 66.6 years (ranged from 53 to 78 years) in NP group.

Random blood sugar mean (RBS) in control group was 130 (mg/dL), in Triamcinolone Acetonide group was (91.2) and in Nepafenac group was 81.4 (mg/dL) with no significant differences between groups.

The mean Central foveal thickness (CFT) in the control group was 220.1um, 222.7um in triamcinolone acetate group and 212.7um in nepafenac group with no significant differences between groups.

Table (1): Demographic data between studied groups:

Variable	Control group (N=10)	Triam. Acetonide group (N=10)	Nepafenace group (N=10)	P. value		
				Control vs. Triam. Acetonide	Control vs. Nepafenace	Triam. Acetonide vs. Nepafenace
Age (year), (M±SD)	62.2 ± 6.9	63.9 ± 0.6	66.6 ± 6.2	0.000 NS	0.006 NS	0.010*
Sex: N (%)						
Males	1 (10%)	1 (10%)	3 (30%)	<0.001*	0.076 NS	0.004**
Females	9 (90%)	9 (90%)	7 (70%)			
Site: N (%)						
Right	0 (0%)	7 (70%)	4 (40%)	0.648 NS	1.000 NS	0.368 NS
Left	0 (0%)	3 (30%)	6 (60%)			

** Significant (p<0.01)

NS Not significant

* Significant (p<0.05)

Table (2): Preoperative measurements in different studied groups:

Variable	Control group (N=10) (M±SD)	Triam. Acetonide group (N=10) (M±SD)	Nepafenace group (N=10) (M±SD)	P. value			
				General	Control vs. Triam. Acetonide	Control vs. Nepafenace	Triam. Acetonide vs. Nepafenace
CFT	220.1 ± 27.6	222.6 ± 30.4	212.6 ± 20.9	0.081 NS	0.844 NS	0.328 NS	0.433 NS

There was no significant difference between groups in all studied variables postoperatively. The mean CFT in the control group was 220.1um, 222.6um in triamcinolone Acetonide group and 212.6um in nepafenac .Results showed that the postoperative mean macular thickness in control group was 288.4um, 273.0um in triamcinolone acetonide group and

278.7um in nepafenac with no significant differences between groups.

The comparison between pre and post operative measurements (table 2) revealed that there was a significant (p<0.05) increase in postoperative CFT in the control group. But, there was no significant difference between pre and post operative CFT in both triamcinolone. acetonide and nepafenace group.

Table (3): Postoperative measurements in different studied groups:

Variable	Control group (N=10) (M±SD)	Triam. Acetonide group (N=10) (M±SD)	Nepafenace group (N=10) (M±SD)	P. value			
				General	Control vs. Triam. Acetonide	Control vs. Nepafenace	Triam. Acetonide vs. Nepafenace
CFT	237.0 ± 30.8	228.6 ± 13.8	223.1 ± 18.0	0.381 NS	0.404 NS	0.172 NS	0.083 NS

Table (4): Postoperative mean macular thickness in different groups:

Variable	Control group (N=10) (M±SD)	Triam. Acetonide group (N=10) (M±SD)	Nepafenace group (N=10) (M±SD)	P. value		
				Control vs. Triamcinolone Acetonide	Control vs. Nepafenace	Triamcinolone Acetonide vs. Nepafenace
Macular thickness	288.4±31.8	273.0±14.6	278.2±20.2	0.194 NS	0.437 NS	0.616 NS

Table (5): Comparison between preoperative and postoperative measurements in studied groups:

Variable		Control group (N=10) (M±SD)	Triam. Acetonide group (N=10) (M±SD)	Nepafenace group (N=10) (M±SD)
CFT	Preoperative	220.1 ± 27.6	222.6 ± 30.4	212.6 ± 20.9
	Postoperative	237.0 ± 30.8	228.6 ± 13.8	222.1 ± 18.0
P. value		0.034*	0.401 NS	0.133 NS

Discussion:

Cystoid Macular Edema (CME) remains a common cause of vision loss after cataract surgery. It was found that the mean incidence of postoperative macular edema was 1.1% in eyes of patients who did not have diabetes at the time of surgery, but found a 2-fold increase in eyes of patients with diabetes⁵.

Optical Coherence Tomography has emerged as an important imaging modality in the evaluation and management of retinal diseases. Since the late 1990s, the interpretation and management of macular pathologies have undergone a major change with the ability of OCT to non-invasively image intraocular structures in vivo⁶.

Although fluorescein angiography has been the traditional method used to confirm presence of macular edema but it is not easily quantifiable and shows only the breakdown of the blood retinal barrier. It does not provide information on the capability of the patient's retina and the retinal pigment epithelium to deal with the resultant extracellular edema. Consequently

the studies utilizing angiographic definitions of CME yield a higher incidence⁷.

OCT was done preoperatively and then 1 month postoperatively as it is reported, From the first week after surgery, there was a significant increase in retinal thickness of the outer macular area with a peak at 1 month, while retinal thickness of the central fovea began to increase from the first month, with a peak at 1¹¹.

Gaynes and Onyekwuluje¹¹ assessed the hypothesis that nonsteroidal antiinflammatory drugs NSAIDs as nepfenac, ketorlac and others may be able to reduce the incidence of CME as well as control postoperative inflammation. In our study we used nepafenac, which is a prodrug that is rapidly converted to the more potent amfenac by intraocular hydrolases. Since nepafenac is a noncharged molecule, it exhibits greater corneal permeability than the other NSAIDs.

In our control group; the mean preoperative foveal thickness of the patients was 270.3±24.2 and then became 288.4±31.8

one month postoperatively. This present study demonstrates that CFT, after uneventful phacoemulsification, in diabetic patients increases significantly.

Similar to our study results, many studies suggested that, for patients with diabetes mellitus, increased retinal thickness has been found in patients without clinical evidence of retinopathy or clinically significant macular oedema¹⁷.

Hayashi et al.,¹⁸ indicated that the foveal thickness in diabetic patients increases after small incision cataract surgery in eyes both with and without DR: the percent increase from baseline was greatest at 3 months after surgery, and then decreased gradually.

Kim et al.,¹⁹ showed that a 40% increase in baseline thickness accurately determined, 100% of eyes with macular oedema and 99% of eyes without macular oedema, and detected that the incidence of postoperative ME was 14% at 1 month for diabetic, uveitic and healthy eyes.

While in triamcinolone acetonide group; the mean preoperative foveal thickness of the patients was 269.0 ± 23.4 and 273.0 ± 14.7 at one month postoperatively, with no significant increase in the macular thickness.

Bunian¹¹ reported that patients undergo intraoperative intravitreal triamcinolone acetonide showed marked reduction of the foveal thickness compared to the control group.

Also, there is no significant increase in the macular thickness in nepafenac group; as; the mean preoperative foveal thickness of the patients was 260.8 ± 21.8 and then became 278.2 ± 20.2 at one month postoperatively.

Kim et al.,¹⁹ reported that the effect of NSAIDs on DME remains controversial among the ophthalmic community, but the data from this DRCR.net study suggest that any beneficial effect of nepafenac on macular edema in patients with diabetes may be limited to a beneficial effect on macular edema associated with recent cataract surgery rather than DME.

Tzelikis et al.,¹⁴ recommended that for at-risk patients, prophylactic use of topical NSAIDs is an efficacious and safe intervention to minimise postoperative macular oedema.

Conclusion

From the previous results it is concluded that:

1. Diabetic patients are at high risk to developed CME post phacoemulsification, so they need to be counseled about it and well prepared preoperatively by OCT to evaluate their condition before the operation.
2. Mean postoperative foveal thickness after uneventful phacoemulsification, in diabetic patients increased significantly.
3. Prophylactic use of topical Nepafenac or intraoperative intravitreal injection of Triamcinolone Acetonide appear to be a safe intervention to avoid pseudophakic macular edema.
4. Further investigation of the influence of these two prophylactic procedures on macula with a larger sample size and longer duration of study and ongoing research brings the promise of newer agents protocols in the near future for preventing postphacoemulsification macular edema.

References:

1. Ruit S, Tabin G, Chang D, Bajracharya L, Kline D C, Richheimer W, Shrestha M, Paudyal G. A prospective randomized clinical trial of phacoemulsification vs manual sutureless smallincision extracapsular cataract surgery in Nepal. *AmJ Ophthalmol* 2007; 143:32-38.
2. Gallego-Pinazo R, Arévalo JF, Udaondo P, García-Delpech S, Dolz-Marco R, Díaz-Llopis M. Prophylaxis of pseudophakic cystoid macular edema with intraoperative pegaptanib. *J OculPharmacolTher.* 28(1):70-8; 2012.
3. Levin DS, Lim JI. Update on pseudophakic cystoid macular edema treatment options. *OphthalmolClin North Am.* 10(4):477-77; 2002.
4. Miyake K and Ibaraki N. Prostaglandins and cystoid macular edema. *Surv*

- Ophthalmol; 47 Suppl 1:S203-18;2002.
6. Mauro Cellini, Alberto Pazzaglia, Eugenio Zamparini and Pietro Leonetti. Intravitreal versus subtenon triamcinolone acetonide for the treatment of diabetic cystoid macular edema. Italy BMC Ophthalmol. 8: 2008.
 7. Turan-Vural E, Halili E, Serin D. Assessing the effects of ketorolac and acetazolamide on macular thickness by optical coherence tomography following cataract surgery. Int Ophthalmol. 34(3):20-31;2014.
 8. Nelson ML and Martinin A. managing cystoid macular edema after cataract surgery. Curr Opin Ophthalmol. 14:39-43;2003.
 9. Cruz Ferreira R, Pereira-da-Silva T, Patrício L, Bezerra H, Costa M. Coronary optical coherence tomography: A practical overview of current clinical applications. Rev Port Cardiol. 2016 Feb; 30(2):10-12.
 10. Vukicevic M, Gin T and Al-Qureshi S. Prevalence of optical coherence tomography-diagnosed postoperative cystoid macular oedema in patients following uncomplicated phacoemulsification cataract surgery. Clin Experiment Ophthalmol. 40(3):282-7; 2012.
 11. Gharbiya M, Cruciani F, Cuozzo G, Parisi F, Russo P and Abdolrahimzadeh S. Macular thickness changes evaluated with spectral domain optical coherence tomography after uncomplicated phacoemulsification. Eye (Lond). 27(5):600-11;2013
 12. Gaynes BI and Onyekwuluje A. Topical ophthalmic NSAIDs: a discussion with focus on nepafenac ophthalmic suspension. Clin Ophthalmol. 2(2):300-68; 2008.
 13. Rebecca S Hunter and Ann-Marie Lobo. Dexamethasone intravitreal implant for the treatment of noninfectious uveitis. Clin Ophthalmol. 2011; 5: 1613-1621.
 14. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. Arch Ophthalmol. 113(3): 320-332; 1995.
 15. Hayashi K, Igarashi C, Hirata A and Hayashi H. Changes in diabetic macular oedema after phacoemulsification surgery. Eye. 23, 289-296; 2009.
 16. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology. 114(5): 881-889; May 2007.
 17. Bunian W. Intraoperative intravitreal triamcinolone acetonide during cataract surgery for the prophylaxis and management of postoperative diabetic macular edema. Thi-Qar Medical Journal 5, 40-59; 2011.
 18. Kim SJ and Toma HS. Inhibition of choroidal neovascularization by intravitreal ketorolac. Arch Ophthalmol. 128(5): 596-600; 2010.
 19. Tzelikis PF, Vieira M, Hida WT, Motta AF, Nakano CT, Nakano EM and Alves MR. Comparison of ketorolac 0.5% and nepafenac 0.1% for the prevention of cystoid macular oedema after phacoemulsification: prospective placebo-controlled randomised study. Br J Ophthalmol. 99(5): 604-8; 2015.