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Al-Shifa Journal of Ophthalmology

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Factors affecting corneal penetration of drugs

Muhammad Sadiq

While treating anterior segment of the eye in ophthalmological practice, topical medications are the most commonly prescribed medications. The current issue has three studies related to the efficacy or side effects of topical medications used in the management of various anterior and posterior segment diseases. The intraocular bioavailability is very low due to very rapid drainage of drug from the ocular surface and only few minutes are available for the drug to be absorbed. In most cases the topically administered ocular drugs do not reach the posterior segment of the eye like retina, vitreous and choroid and these can be treated by using intravenous or intra-vitreal routes of drug administration[1]. Only 1-7% of dose of the drug can reaches into the aqueous humor because corneal epithelium can effectively limit the drug delivery into the eye[2].

The penetration of drugs through cornea is very important clinically because it is the major determinant of the efficacy of drug topically applied to the eye. Ocular preparations in majority are formulated in an aqueous vehicle and the bioavailability of drugs from aqueous based products is mainly affected by the factors which are categorized in to the following three groups.

1- Physiological factors
2- Physicochemical factors
3- Formulation factors[3]

1- Physiological factors

Physiological factors include some pre-corneal factors and membrane factors.

Pre-corneal factors like tears secretions turn over, ocular drainage of the instilled drug, non-corneal absorption (Conjunctival absorption), protein binding and corneal absorption rate are the contributing factors in the net pre-corneal drug loss. These factors collectively lead to corneal contact time of the drug 2-4 minutes in human for an instilled solution. Normal tears volume is only 7 µl and tears wash out at the rate of 16% per minute. The pre-corneal area can hold approximately 30 µl including tears when eye is not blinking. When drug is instilled, the excess of volume is spilled out or drain through the nasolacrimal apparatus. Normally tears contain 0.7% of protein and this level increases during inflammation or infection. As tears are replaced quickly, so they remove both free and bound from of drug. Conjunctiva has 17 time greater surface area & higher permeability as compared to cornea. The absorption of drugs through the tissues other than cornea are considered as nonproductive absorption.

Thicknesses, porosity, tortuosity of the cornea, surface area available for absorption and lipophilicity / Hydrophilicity balance are the major membrane factors contributing in the ocular absorption of drugs. The lipophilic drugs have greater penetration through cornea as compared to hydrophilic drugs.

2- Physicochemical factors

Partition coefficient, solubility, ionization constant and molecular weight are the main physicochemical factors contributing in the ocular penetration of drugs[4]. Partition coefficient is the parameter used for the penetration of drugs through different biological membranes. The corneal permeability of any drug depends upon its lipophilic characters (Partition coefficient). The maximum penetration of a drug is the multiplicative factor of permeability coefficient and tears

solubility. The concentration of poorly soluble drug in the pre-corneal tears film may be limited which can result in low corneal absorption. The ionization constant (pKa) of a drug is important factor for its corneal penetration. The extant of ionization can influence the diffusion of drugs across the membranes. Most of the drugs are week acids or weeks bases and are partially ionized at physiological pH. The ionized form of drug is poorly lipid soluble (Limited corneal penetration) and if this proportion is high then it is difficult for a drug to achieve therapeutic concentration. Molecular weight is a less critical factor because ophthalmic preparations have very low and narrow molecular weight range. Drugs having molecular weight greater than 500 Da offer poor corneal penetration and vice versa.

3- Formulation factors

Concentration, particle size, shape & dissolution rate, pH & tonicity and viscosity are the formulation factors that can affect the corneal penetration of the drugs. By increasing the solution concentration, corneal penetration can be enhanced. Particle size & shape is mostly concerned with the use of ophthalmic suspensions. Drug particles can be deposited at the outer surface of the eye which can cause irritation & abrasion upon movement through eye lids while blinking. Increase in particle size can leads to poor corneal penetration. Irregular particles or edged particles can cause more irritation as compared to spherical particles. Concentration, size & shape of the particles together can determine the irritation potential of the suspended particles. The human tears pH ranges from 7.14-7.28 and possess relatively weak buffer capacity. The hypotonic solution can increase the corneal permeability while instillation of hypertonic solution can decrease the permeability of the corneal epithelium. The hypotonic solution can create an osmotic gradient between the tears film and surrounding tissues. The corneal epithelium has greater tolerability to large variations in the pH and tonicity. It is generally believed that by increasing the viscosity of the ophthalmic solution, corneal penetration can be increased because it can increase the contact time of the drug with corneal epithelium. The most commonly used viscolizing agents in ophthalmic preparations are hydroxy propyl methyl cellulose (HPMC) and Poly vinyl alcohol (PVA) etc. Penetration enhancers like actin cytoskeleton inhibitors (like Cytochalasin B) [5], Surfactants (like Benzalkonium Chloride, Sodium Lauryl Sulphate), Chelators (Like EDTA) and preservatives (like Benzalkonium chloride, organomercurials) etc. can be used in the ophthalmic preparations to enhance the corneal penetration by one or another mechanism.

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ORIGINAL ARTICLE

Trabeculectomy versus Combined Trabeculectomy and Cataract Surgery in Pseudoexfoliation Glaucoma

Yousaf Jamal Mahsood[1], Hussain Ahmad[2], Muhammad Naeem[3], Irfan Ullah[4], Saima Farooq[3], Muhammad Sadiq[4], Farah Akhtar[4]

ABSTRACT

Aims: To compare the success rate of trabeculectomy versus combined trabeculectomy plus cataract extraction augmented with 5-Fluorouracil in pseudoexfoliation glaucoma.

Study Design: Case control study.

Methods: Past records of patients with pseudoexfoliation glaucoma (PXF-G) who had undergone trabeculectomy with 5-Fluorouracuil (5-FU) (Group 1) or combined trabeculectomy and cataract extraction (Group 2) with5-FU were obtained and analyzed. All those patients were included who were stable for at least 6 months before entering into the study. To avoid bias in the results, those patients were excluded who had intraoperative complications like posterior capsular rupture, vitreous loss, zonular dialysis etc. A total of 40 patients were included with 20 in each group. The primary outcome, effect on intraocular pressure (IOP), was compared between the two groups.

Results: The Group 1 had significant reduction in IOP ($p < 0.02$) with mean pre-treatment IOP of 30.72 $\pm$ 7.44 mm of Hg to final IOP of 15.30 $\pm$ 5.43 mm of Hg. Similarly, Group 2 had also significant reduction in IOP ($p < 0.032$) with mean pre-treatment IOP of 31.20 $\pm$ 7.68 mm of Hg to final IOP of 16.01 $\pm$ 5.55 mm of Hg. When both groups were compared for final IOP, it was not significant ($p < 0.3$). The success rate of group 1 was 83.5 $\pm$ 5.5% while that of group 2 was 80.4 $\pm$ 4.3 %.

Conclusion: Both techniques achieved good IOP reduction and combined trabeculectomy plus cataract surgery with 5-FUis a safe option in patients with PXF-G and cataract. *Al-Shifa Journal of Ophthalmology 2016; 12(3): 131-134.*

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Introduction:

Pseudoexfoliation (PXF) syndrome is an age related process which results in abnormal collagen deposition in ocular structures like conjunctiva, iris, lens, cornea, ciliary body and epithelium.[1] It is the most common identifiable cause of secondary open angle glaucoma (SOAG) and accounts for 20-25% cases worldwide.[2] The increased intraocular pressure is due to blockage of trabecular meshwork by PXF material released from the epithelium but it may also be due to peripheral anterior synechiae formation causing angle closure.[3] It has also been investigated that there is always some sort of ischemia and decreased level of ascorbic acid in anterior chamber of PXF

patients which can accelerate the cataract formation.[4,5]

The treatment of PXF-G is similar to primary open angle glaucoma (POAG) but sometimes both the problems like cataract and glaucoma coexist and it is strongly felt that a combined (trabeculectomy and cataract)surgery should be offered to the patient. Risks of cataract surgery in PXF are widely studied which show higher complication rates than a non-PXF cases.[6] So it is thought that doing a combined procedure in such cases may add more injury and incite factors which can compromise the IOP control. There have been reports which compared combined procedures with phacoemulsification in PXF-G patients[7]or combined surgeries alone [8]to look for IOP control but to our knowledge no such study have been done to compare IOP lowering effect of trabeculectomy versus combined procedure. So, we have designed this study to compare the IOP lowering effect of both procedures.

Subjects and Methods:

This study was conducted at Glaucoma Clinic, Al-Shifa Trust Eye Hospital, Rawalpindi. The records of patients with PXF-G who underwent trabeculectomy with 5-FU (Group 1) and combined surgery (Group 2) were identified between 1st March 2014 and 30th June 2016. A total of 40 patients with 20 in each group were included. Group 1 was allocated to those patients who underwent trabeculectomy with 5-FU while group 2 had those patients who underwent trabeculectomy with 5-FU and cataract surgery in one setting. Group 2 patients were those who had significant cataract and PXF-G and met anyone of the following indications: uncontrolled glaucoma despite maximally tolerated medical therapy; polypharmacy (two or more) of anti-glaucoma medications; poor compliance with medical treatment; or, in case of advanced glaucomatous damage, to avoid post cataract surgery IOP spikes. Those patients were excluded who had intraoperative complications which can compromise the success of filtering procedure. The surgeries were done by 4 glaucoma surgeons with expertise in trabeculectomy and cataract surgery. The primary outcome was to compare the IOP lowering effect between the both groups. The success was defined as IOP of $\leq$21 mm of Hg with no treatment or $\leq$16 mm of Hg with not more than one topical anti-glaucoma drug.

Results:

Out of 40 patients, 25 (62%) were male and 15 (38%) were female (Figure 1). The mean age of our patients was 70.4 $\pm$ 6.3 years with mean follow-up 16.3 (8-24) months. The Group 1 had significant reduction in IOP ($p < 0.02$) with mean pre-treatment IOP of 30.72 $\pm$ 7.44 mm of Hg to final IOP of 15.30 $\pm$ 5.43 mm of Hg. Similarly, Group 2 had also significant reduction in IOP ($p < 0.032$) with mean pre-treatment IOP of 31.20 $\pm$ 7.68 mm of Hg to final IOP of 16.01 $\pm$ 5.55 mm of Hg (Table I). When both groups were compared for final IOP, it was not significant ($p < 0.3$). The success rate of group 1 was 83.5 $\pm$ 5.5% while that of group 2 was 80.4 $\pm$ 4.3 %.

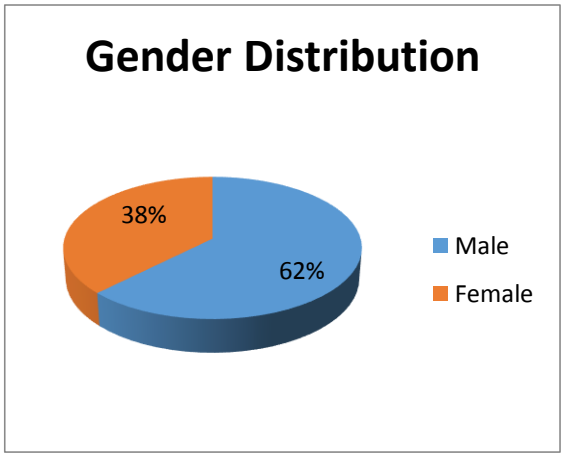

Figure 1: Gender distribution

Table 1: Group wise success rate

Group	Initial IOP (mm of Hg)	Final IOP (mm of Hg)	p value	Success rate (%)
Group 1	30.72 ± 7.44	15.30 ± 5.43	< 0.02	83.5 ± 5.5
Group 2	31.20 ± 7.68	16.01 ± 5.55	<0.032	80.4 ± 4.3

Discussion:

Pseudoexfoliation syndrome was first described by Lindberg in 1917.[1] It is the most common identifiable cause of secondary glaucoma and it behaves aggressively than primary open angle glaucoma (POAG).[2] As PXF is an entity primarily presented in elderly patients, it is not uncommon that cataract may also coexist in the same patient. Whether cataract is related to PXF itself is a debatable topic because it has been reported that there may be some relation between the two.[9,10] Cataract surgery in PXF patients is always been challenging to ophthalmologists due to higher complication rate in these eyes. PXF-G is treated in the same way as of POAG and it has been reported that filtration procedures like trabeculectomy have same success rate in terms of IOP control as in POAG but it has never been compared to combined procedures in PXF-G with cataracts.

Trabeculectomy with 5-FU alone have same success when compared to combined trabeculectomy and cataract surgery. Our results are consistent with the previous reports that have showed similar results with trabeculectomy in PXF-G. Combined procedure in our patients resulted in significant IOP control and was comparable to group 1. Combined procedure has advantages over sequential surgeries in terms of one time intervention, low cost and patient psychological satisfaction. However there are few disadvantages of combined procedures which are more in PXF-G than in POAG, like complications of cataract surgery in PXF which can be causative factor in failure of IOP control. We didn't include patients who got complicated during surgeries so that there should be a fair comparison between the two groups. It is to highlight here that if we had included all the cases of both groups then we may have got higher failure rate in group 2. Other disadvantage of combined procedure could be that patients with PXF have been found to have low endothelial cell count probably because it is disease of elderly patients and this may delay visual rehabilitation. Patients having combined procedures must understand the need for more frequent post- operative follow-up visits than patients having trabeculectomy alone.

We included both types of cataract procedures in group 2 depending upon the surgeon's choice and expertise. If we had included only phacoemulsification surgery in group 2 then may be the results were different but this cannot be said with certainty without clinical evidence. Multiple surgeons' inclusion may also be a factor which could have influenced the results. The benefits of combined procedure cannot be overlooked in cases of coexisting cataract and PXF-G especially in advanced cases where

occasional IOP spikes may be detrimental to optic nerve.

Conclusion:

Both groups achieved same success rate and we conclude that combined surgery is a safe option in patients with coexisting PXF-G and cataract. However there are few limitations in the study because of retrospective design, only uncomplicated surgeries included and multiple surgeons involved. So we recommend that in future with randomized control trials these shortcomings can be addressed.

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Drafting: Yousaf Jamal Mahsood, Hussain Ahmad, Irfan Ullah
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Critical revision: Farah Akhtar

ORIGINAL ARTICLE

Prophylactic Diclofenac versus Betamethasone in Preventing Postoperative Cystoid Macular Edema After Uneventful Phacoemulsification

Anique Ahmad[1], Adnan Aslam Saleem[2], Yawar Iqbal [3]

ABSTRACT

Purpose: To compare the effectiveness of a topical non-steroidal drug (diclofenac 0.1%) and a topical steroidal drug (betamethasone 0.1%) in preventing cystoid macular edema (CME) after phacoemulsification cataract surgery and foldable intraocular lens (IOL) implantation.

Settings: Study was done in Armed Forces Institute of Ophthalmology, Rawalpindi, Pakistan, from August 2014 to April 2015.

Methods: This randomized study comprised 60 eyes, 30 in each group. After cataract surgery, patients were randomly divided into two groups. Group A was given Diclofenac Sodium 0.1% eye drops; Group B was given 0.1% Betamethasone eye drops. Change in central macular thickness (CMT) before and 6 weeks after surgery was compared between two groups. Drug was considered effective if the CMT didn't increase more than 15 microns (µm) from baseline value, 6 weeks after cataract surgery.

Results: All the patients completed the follow up. Six weeks after surgery, mean CMT increase in Diclofenac group was 12.57± 4.93 microns, whereas Betamethasone group showed mean increase of 23.73± 12.51 microns. Efficacy of topical Diclofenac Sodium 0.1% eye drops was seen in 83.3% of cases while that of Betamethasone was seen in 26.7% of cases ($p<0.05$).

Conclusions*:* 0.1% Diclofenac Sodium eye drops is more effective than 0.1% Betamethasone eye drops in reducing frequency of pseudophakic cystoid macular edema. We recommend that non-steroidal anti-inflammatory agents should be considered for routine treatment of eyes having cataract surgery. *Al-Shifa Journal of Ophthalmology 2016; 12(3), 135-141*. *© Al-Shifa Trust Eye Hospital, Rawalpindi*.

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Introduction:

Age related cataract remains the single major cause of blindness in Pakistan. Despite advances in cataract surgery, the most common cause of decrease in central vision after cataract surgery is cystoid macular edema(CME). The exact mechanism of CME is undetermined. Proposed factors include hypotony, inflammation, photo damage and vitreous traction. However in uncomplicated cases, significance has been given to postoperative inflammation.[1]

Surgical procedure itself causes release of numerous inflammatory mediators like prostaglandins (PG) and leukotrienes.

Diclofenac sodium is a potent NSAID that block synthesis of prostaglandins by inhibiting cyclo-oxygenase (COX) pathway. CME is divided into clinical and subclinical types. Clinical CME refers to macular edema associated with decreased visual acuity of 6/12 or less. Subclinical CME refers to macular edema seen on fluorescein angiography (FFA) resulting in decrease in contrast sensitivity with variable visual loss. The incidence of clinical CME has been reported up to 6% and of angiographic CME up to 54.7%. [2]

FFA has traditionally been utilized for detecting CME. Optical coherence tomography (OCT) is a newer, non-invasive modality; it has proved to be as effective as FFA in detecting CME with good reproducibility. [3]The purpose of this study is to determine the effectiveness of Diclofenac Sodium 0.1% eye drops in preventing development of CME and thus stressing its importance in post cataract surgery drug regimen.

Subjects and Methods:

The study sample was collected from outpatient department, Armed Forces Institute of Ophthalmology Rawalpindi. Patients planned to undergo phacoemulsification and posterior chamber IOL implant were selected. After informed consent, all patients underwent a comprehensive ophthalmic assessment. Examination included, unaided vision, pinhole vision, best corrected visual acuity (BCVA) testing using Snellen chart at 6 m, pupillary reactions, slit-lamp examination and fundus using 90 D lens.

This randomized control trial included 60 eyes of 60 patients. Inclusion criteria included patients aged 50 to 80 years of either gender. Moderate cataract density (N4C5P5 or less - LOCS III Classification) and good OCT signal strength (Q factor of 50 or higher).Exclusion criteria includedpatients having allergy to NSAIDs, preexisting macular pathology, intraocular disease other than cataract such as pseudoexfoliation syndrome, uveitis, glaucoma, retinal detachment, age related macular degeneration, central serous retinopathy and macular hole. Cases which had intraoperative complications such as prolonged surgery, posterior capsule rupture, vitreous loss and lens fragments in the vitreous were also excluded.

Pre-op OCT (*Fourier Domain 3D OCT-1000 Topcon*) was performed on each patient making sure the good OCT signal was obtained. If signal strength of OCT (Q-Factor) was below 50 the patient was excluded from study. Baseline central macular thickness (CMT) in microns/µm was noted for each patient. First 60 cases that satisfied the study criterion were included.

Surgery was performed by two surgeons using similar techniques and utilizing same Phacoemulsification platform (Infinity, Alcon, Inc.). In all patients surgery was conducted through a 2.75 mm clear corneal superior incision. A well-centered 4.5 to 5.0 mm capsulorhexis was created and the IOL implanted in the capsular bag.

After phacoemulsification surgery, patients were assigned into two groups randomly. Group A was given Diclofenac sodium 0.1 % eye drops 6 hourly while group B received Betamethasone 0.1% eye drops in same frequency. Drugs were administered to each patient for six weeks after surgery. Concomitant antibiotic agents were also given to each patient as per post-op protocol. At the end of six weeks follow-up, CMT was measured via OCT.

Statistical analyses were performed with SPSS software (version 17, SPSS Inc. Chicago, IL). Independent-samples t-test was applied to compare the mean difference in CMT at 6 weeks from the baseline in both the groups**.** Paired samples t-test was used to determine the difference in mean CMT at baseline and six weeks in

both the groups. Chi-Square test was used to compare the efficacy of two groups. P-value of ≤ 0.05 was considered statistically significant.

Results:

All the patients completed the follow-up to 6 weeks postoperatively. Group A had 21 males and 9 females while group B had 20 males and 10 females. Both groups were comparable with respect to gender (p=0.781). Mean age of group A was 62.03 years (SD=7.513) whereas that of group B was 60.07 (SD=6.878). At baseline mean CMT in group A was 220.73 microns (SD= 3.619) while in group B it was 220.43 microns (SD 4.321). Insignificant difference was observed between two groups regarding baseline, p=0.772. (Table 1)

At six weeks post-operative follow up, in group A the mean CMT was 233.30 microns (SD= 6.634) while in group B, the mean CMT was 244.17 microns (SD = 12.068). Mean difference in CMT from the baseline when compared in either groups shows a highly significant result, p=0.001. Paired t-test revealed a significant difference, p=0.001 when applied to the baseline mean CMT and CMT at six weeks postoperatively in Group A. Similarly, significant difference between baseline CMT and CMT at six weeks postoperatively, p=0.001 was shown in Group B. (Table 2)

Drug was considered effective if the CMT didn't increase more than 15 microns from baseline value, 6 weeks after cataract surgery. In Group A, post-op CMT remained below 15 microns in 25 cases (83.3%) while 5 cases (16.7%) showed increase in CMT. In Group B, 8 cases (26.7%) showed stable CMT while CMT increased above 15 microns in 22 cases (73.3%). Using Chi-Square test this difference was found to be highly significant (p=0.001). There were no cases of treatment related ocular adverse events observed during study. (Table 3)

Table 1: Comparison of Mean CMT (in Microns) Between Both the Groups

	Mean CMT (InMicrons)		p Value
	Group A (n = 30)	Group B (n = 30)	
At Baseline	220.73 ±3.61	220.43± 4.32	0.772
Six weeks postoperatively	**233.30 ±6.63**	**244.17 ± 12.06**	**0.001**

Table 2: Comparison of Mean Difference in CMT (in microns) between the two groups

	Mean CMT (InMicrons)		p Value
	Group A (n = 30)	Group B (n = 30)	
Mean Difference	**12.57 ±4.93**	**23.73 ±12.51**	**0.001**

Table 3: Efficacy of Drug

	Efficacy of Drug		Total
	CMT remained stable*	CMT Increased**	
Group A	25 (83.3%)	5 (16.7%)	30
Group B	8 (26.7%)	22 (73.3%)	30
*CMT increase less than 15 microns from baseline			
** CMT increase more than 15 microns from baseline			

Discussion:

CME has traditionally been defined as a characteristic leakage in the macula, associated with visual acuity of 20/40 or worse. In present era, the importance of visual acuity after uneventful phacoemulsification has shifted more from quantity to quality of vision. If a patient develops even subtle macular thickening, that by traditional definition is not considered CME, quality of vision is decreased. Subtle contrast sensitivity deficits, reading speed deficits or color deficits are a part of a patient's subjective appraisal after cataract surgery. Increasingly patients are demanding better outcomes after cataract surgery. Now more than ever, preventing theses subtle changes in macular thickness has become a priority for cataract surgeons.

Studies that report increase in macular thickness following cataract surgery are found to be plentiful in literature. *Z Biro et al* in a prospective study on 71 eyes showed that after uneventful cataract surgery, a significant increase could be detected on the postoperative 7, 30, and 60 days in the peri-foveal 3.0 and 6.0 mm sectors. The initial (preoperative) average value of 234.1±2.6 μm in the 6.0 mm peri-foveal region increased to 242.5±2.6μm (P<0.01) 1 week, to 247.7±4.6μm (P<0.01) 1 month and to 246.0±5.9μm (*P*<0.05) 2 months after surgery, which proved to be significant.[4] Compared to our study, we had baseline macular thickness of 220.43$\pm$4.32 μm which after 6 weeks increased to 244.17$\pm$12.06 μm in steroid group with (P<0.001).

Blanco et al conducted a prospective study of 260 consecutive cataract surgeries. Eyes were divided in three groups: group A, with 208 eyes of non-diabetic patients, group B with 42 eyes of diabetic patients with or without retinopathy, and group C with 10 eyes of diabetic patients with persistent macular edema. CMT increase was noted in all categories however in this study group A was comparable to our study. The mean and standard deviation (SD) of the baseline macular thickness on OCT in Group A was of 204.6 µm (SD 21.8) while in our study it was 220.43$\pm$ 4.32. After 5 weeks the macular thickness increased to 217.1 (SD 42) while in our study group B had increase of macular thickness up to 244.17 $\pm$ 12.06, six weeks

after cataract surgery. They did not detect any patient with clinically significant CME, but in 4 eyes (1.92%) they detected an increase of macular thickness ≥ 43.74 μm while in our study 5 eyes from group B develop macular thickness > ≥41 μm. [5]

At the time when we established the protocol for our study, it had already been established that Diclofenac penetrates into vitreous and retina effectively to achieve a good therapeutic concentration. [6] Earlier investigators reported favorable effects of Diclofenac and other NSAIDs in preventing and treating pseudophakic macular edema. The effectiveness of topically administered NSAIDs is proved by several studies and their use is suggested as alternative to steroids when possible due to the well-known side effects after long-term administration of steroids particularly elevation of IOP. [7,8]
In a recent study to evaluate the efficacy of prophylactic ketorolac 0.5% versus nepafenac 0.1% versus placebo on macular volume 1 month after uneventful phacoemulsification; the authors found that at one month after uneventful phacoemulsification, there was no difference in macular volume between the placebo, ketorolac, and nepafenac. Ketorolac and nepafenac were well tolerated with minimal side-effect profiles. They concluded that in patients without risk factors having routine surgery, prophylactic topical NSAIDs are not recommended.[9]These results are contrary to ours where we found much stable macula post cataract surgery. However it can be deliberated that topical NSAIDs should be reserved in high risk cases such as diabetics and uveitic patients.

Asano et al conducted a study on 142 eyes. One group was given Diclofenac eye drops after cataract surgery while other group was given Betamethasone eye drops. Five weeks after cataract surgery subclinical CME was detected in 18.8% eyes in the Diclofenac group and 58.0% eyes in the Betamethasone group. The difference between groups was statistically significant (P<.001). These results were in accordance with our study in which subclinical CME developed in 5 eyes out of 30 (16.7%) in diclofenac group while in betamethasone group, edema developed in 22 eyes out of 30 (73.3%). The difference between groups was highly significant in our study (P<0.001). [10]

Miyake et al conducted a prospective, double-masked study of 50 patients, in which patients were randomized to use diclofenac or the corticosteroid fluorometholone for 5 weeks after cataract surgery, in which they supported the idea that NSAIDs reduce the risk of CME by maintaining the integrity of the blood-aqueous and blood-retinal barriers. Two weeks postoperatively, it was found that the patients who used fluorometholone had reduced choroidal blood flow compared with those who used diclofenac. Based on the hypothesis that the exposure to prostaglandins can diminish choroidal blood flow and the observation that the patients who used the NSAID had less aqueous flare than those who used the steroid, the investigators concluded that diclofenac prevented CME more effectively than fluorometholone in pseudophakic eyes during the early postoperative period. [11]

Many studies advocated use of NSAIDs/Steroid combination is more effective in preventing macular edema. Wittpenn et al conducted a study on 546 patients in which after cataract surgery patients were randomized to receive either prednisolone acetate 1% 4 times daily (QID) alone or prednisolone 1% QID plus ketorolac 0.4% QID for approximately four weeks postoperatively. No patients in the ketorolac/steroid group and five patients in the steroid group had clinically apparent CME (*P* = .032). Based on OCT, no ketorolac/steroid patient had definite or probable CME, compared with six steroid

patients (2.4%; *P* = .018). In the ketorolac/steroid group, mean retinal thickening was less (3.9 μm vs. 9.6 μm; P = .003), and fewer patients had retinal thickening of more than 10 μm as compared with the steroid group (26% vs 51%; P < .001). [12]

In this study, we specifically discussed acute or subclinical CME evident on OCT. Many studies in literature have provided with variable results regarding incidence of subclinical macular edema. Asano et al in a study on 142 eyes showed that 5 weeks after surgery incidence of angiographic CME was about 58.0%[11]. Ursell et al investigated the existence of angiographic CME after phacoemulsification on the 60th day after surgery; they reported lesser incidence of 19% of angiographic CME in 103 eyes, with no development of clinical CME in any of these eyes[13].

In at least one large series comparing postoperative CME after ECCE and phacoemulsification in patients with no underlying systemic disease, no significant differences were found between the two techniques. Even though the angiographic CME was slightly higher for ECCE, the clinical incidence was similar (0-6% for phacoemulsification compared to 0-7.6% for ECCE). [14] Increase incidence of CME in our study of about 73.3% is due to utilization of OCT to quantify macular thickness which is highly sensitive in detecting any change in macula as compared to angiography which was used as a diagnostic tool in previous studies. Although a reliable diagnosis for CME has been elusive, pre and postoperative OCT imaging could change how we approach prevention.

In conclusion 0.1% Diclofenac sodium eye drops is more effective that 0.1% Betamethasone eye drops in reducing frequency of CME following uneventful phacoemulsification surgery. The key to success in dealing CME lies in its prevention. In light of increasing evidence for adequate and improved efficacy of NSAID monotherapy compared with corticosteroids, a postoperative regimen consisting solely of an NSAID may replace combination therapy as the primary regimen for CME prophylaxis. By doing so and reducing the frequency of CME, we can improve surgical outcomes and provide our patients with better quality of vision.

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ORIGINAL ARTICLE

Comparison of Intravitreal Bevacizumab with Combined Intravitreal Triamcinolone and Bevacizumab in the Treatment of Clinically Significant Macular Edema

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ABSTRACT

Objective: Objective was to compare mean central macular thickness after a single injection of intravitreal bevacizumab (Avastin) opposed to intravitreal injection of triamcinolone plus an injection of bevacizumab in the treatment of clinically significant macular edema (CSME).

Methods: This Randomized Control Trial was conducted in Retina Clinic of Al Shifa Trust Eye Hospital, Rawalpindi from July 2013 to August 2014.Five sixty patients were randomly assigned either to IVB or to IVB plus IVTA treatment. Patients with CSME were followed for four weeks to note any reduction in central macular thickness (CMT).

RESULTS:560 patients with mean age 49.15 ± 5.4 year were included and randomly assigned. There was equal distribution of age, gender and pre-operative macular thickness in both groups. Both treatment options i.e. IVB and IVB+IVTA significantly reduced macular edema when pre injection and post injection macular thickness was compared using paired sample t test (p value < .001). There came out to be a non-significant difference in mean reduction in post-injection CMT (p value 0.125).

CONCLUSION: It is concluded that IVB and IVB+IVTA are equally effective and comparable in reducing central macular thickness in patients with clinically significant macular edema. *Al-Shifa Journal of Ophthalmology 2016; 12(3), 142-148. © Al-Shifa Trust Eye Hospital, Rawalpindi.*

Introduction:

Diabetic retinopathy (DR) is one of the most important causes of visual loss worldwide and is the principal cause of impaired vision in patients between 25 and 74 years of age. DME is a main reason that leads to decreased visual acuity (VA) in patients diagnosed with DR. [1] DME is defined as a retinal thickening by pathological accumulation of extracellular fluid in the macular area. Histologically, edema fluid is present in the outer plexiform layer and the internal nuclear layers of the retina. Its prevalence in patients has been reported to be 2.7–11.0 %. [2,3]

DR is divided into two major forms: non-proliferative and proliferative, named for the presence or absence of abnormal new blood vessels emanating from the retina. DME can occur at any stage of DR. DME is primarily caused by increased vascular permeability and increase in concentration of growth factors such as vascular endothelial growth factor (VEGF). Optical coherence tomography (OCT) is most sensitive and reliable method for measuring the thickness of the edematous retina.

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Glucocorticoids are used to treat DME for their anti-inflammatory effects; stabilizing the capillary wall with consequent improvement of endothelial barrier function. Intravitreal bevacizumab (avastin), a monoclonal anti-VEGF antibody is being used in DME because of its anti-angiogenic and anti-exudative effects.Although still an off-label drug but its use has risen probably due to its efficacy and economic considerations. This study is structured to see; if intravitreal triamcinolone acetonide (IVTA) given along with intravitreal avastin (IVB), is there any added benefit or not.

Subjects and Methods:

The study was conducted after approval by the hospital ethical committee. An informed consent was taken from all the patients. In this randomized clinical trial all patients diagnosed with DME/CSME by clinical exam and graded on Optical Coherence Tomography (OCT) were included. Both type1 and 2 diabetics of any age and gender were included. Complete ophthalmic examination including slit lamp and dilated fundus exam was performed. Central macular thickness (CMT) was measured by OCT (OCT III, Stratus, Carl Zeiss). Three vertical and horizontal manually assisted OCT scans were obtained to locate the foveal thickness.

Clinically significant macular edema (CSME) was defined as per ETDRS as one of the following conditions; retinal edema localized at less than 500 µm from the center of the macula, hard exudates at less than 500 µm from the center of the macula associated with adjacent macular thickening and at least one disc diameter retinal thickening located at less than a disc diameter from the center of the macula.

Exclusion criteria were history of intraocular surgery during last 6 months, history of retinal laser photocoagulation, high refractive errors (> 6 diopters of sphere or > 3 diopters of cylinder), media opacity affecting VA and OCT measurements, history of glaucoma or intraocular pressure more than 22 mmHg, ischemic or inflammatory optic neuropathy, uveitis, retinal vascular occlusion, vitreo-macular interface disorders and the need for pan-retinal photocoagulation. Both eyes of each participant were enrolled if both eyes met the inclusion criteria.

The patients were selected for the study by systematic random sampling taking into consideration the inclusion and exclusion criteria. Patients were randomly allocated to either group based on computer generated table of random numbers. Group A was given monotherapy i.e. only injection avastin and group B received both intravitreal avastin and IVTA by a blinded retina consultant.

Intravitreal injections of bevacizumab and intravitreal triamcinolone were administered in retina clinic under sterile conditions. *Group A* received intravitreal injection of 1.25mg/0.05ml bevacizumab and Group B received intravitreal triamcinolone acetonide 2 mg/0.05 ml plus 1.25mg/0.05ml bevacizumab. After instillation of a drop of proparacaine, one drop of 5% povidone-iodine was instilled in the fornix. The lids were kept open by the surgeon, no speculum was used. The patients were asked to look at the contralateral shoulder. Triamcinolone Acetonide and Avastin injection were given with a TB syringe (30 G) in the inferotemporal quadrant via pars plana, 3-3.5 mm for pseudophakes and 3.5-4.0 mm for phakic patients. Patients started using ofloxacin eye drops four times per day one day before the injection/ injections and continued to do so for four days after the injection. Follow up after completion of therapy was done in the retina clinic of the hospital at 1 month.

Statistical analyses were performed with SPSS software (version 17, SPSS Inc. Chicago, IL). *Paired sample t-test* was used to compare pre and post injection CMT. *Independent sample t-test* was used to compare the mean CMT (difference between baseline and at 1 month) in both groups. A *p* value ≤ 0.05 was considered as statistically significant.

Results:

560 patients with mean age 49.15 ±5.4 year ranging from 40-62 years were included in the study pre-operative macular thickness was 483.8 ± 35.8 µm ranging from 390-535 µm while after intravitreal injection macular thickness reduce to 403.6 ± 21.2 µm with range from 320-465 µm. 324 included persons (58%) were male and 489 were diabetic.

Distribution of diabetes and hypertension was almost equal in both groups along with gender. To check significant reduction for each treatment individually paired sample t test was applied on both groups which showed significant reduction (p value < 0.001) both for IVB and IVB + IVT combination group. (Table 1, II)

478 were hypertensive showing prevalence of both chronic diseases. Mean age distribution in treatment group came out similar (p= 0.746). Similarly macular thickness before the intervention was equally distributed in both groups (p= 0.125). But post-operative macular thickness was non-significantly different in both treatment groups. (Table III)

Table I : Efficacy of IVB treatment

	Mean	N	Std. Deviation	Std. Error Mean
Pre op Macular Thickness	481.49	280	37.682	2.252
Post op Macular Thickness	403.36	280	21.555	1.288
p value < 0.001 (at 95% CI mean difference 72.965 to 83.278)				

Table II : Efficacy of Combined IVB + IVTA treatment

Treatment Group - IVB+IVTA	Mean	N	Std. Deviation	Std. Error Mean
Pre op Macular Thickness	486.12	280	33.651	2.011
Post op Macular Thickness	403.89	280	21.006	1.255
p value < 0.001 (at 95% CI mean difference 77.6 to 86.8)				

Table III: Post-Injection Macular Thickness Difference In Both Groups

	Treatment Group	N	Mean	Std. Deviation	Std. Error Mean
Post Inj Macular Thickness	IVB	280	403.36	21.555	1.288
	IVB+IVTA	280	403.89	21.006	1.255
p value= 0.125					

Discussion:

DME is responsible for significant visual impairment in diabetic patients. Laser photocoagulation has been the mainstay of treatment until recently. The current treatments for DME target reducing vascular leak in the macula once it has taken place, they do not attempt to treat the basic pathology. Pharmacological treatments are aimed at antagonizing VEGF or non-VEGF inflammatory pathways. These include intravitreal injections of anti-VEGFs (ranibizumab, aflibercept or bevacizumab) or steroids (dexamethasone, triamcinolone or fluocinolone) as single therapies.

The available evidence suggests that each individual treatment modality in DME does not result in a completely dry macula in most cases. The ideal treatment for DME should improve vision and improve morphological changes in the macula for a significant duration, reduced adverse events, reduced treatment burden and be well tolerated by patients. This article evaluates combined efficacy of both intravitreal triamcinolone and bevacizumab as treatment modality in CSME in our local population.

The Pan-American Collaborative Study Group in their study on eyes with CSME performed repeated IVB, after a mean of 13.8 weeks for the second injection and after 11.5 weeks for the third injection.IVB was used as a primary treatment for DME at doses of 1.25 mg or 2.5 mg and results showed that within 1 month after the initial bevacizumab injection mean BCVA improved from 0.87 to 0.6, a difference that was statistically significant (P<0.0001). [4]

The current study showed that patients with DM developed CSME early in their life (50 years of age). Most patients were both hypertensive and diabetic with increased pre-operative macular thickness. Age and gender were equally distributed in both treatment groups showing effective randomization procedure. More male patients presented with CSME possibly showing vasculo-protective action of estrogen in the female population. Prevalence data regarding the gender difference in macular edema may help making policy regarding screening of individuals. Our results show that both procedures significantly reduce the macular thickness thus preventing further deterioration in VA. However there was no statistically significant difference between intravitreal injections of bevacizumab appose to intravitreal injection of triamcinolone plus bevacizumab as independent sample t-test came out non-significant.

In the studies by Chakrabarti and later by Marey, the response to therapy with bevacizumab showed superiority compared with triamcinolone for DME. [5,6] However, these studies differed from that of Paccola, Isaac, Lim and Song who demonstrated that intravitreal triamcinolone was more efficient in reducing DME relative to bevacizumab.[7,8,9,10]

A study showed earlier and more frequent macular edema recurrences in the eyes treated with IVB compared with the ones treated with IVTA. IVTA was found to provide more efficient and long-standing effect in terms of reducing CMT compared with the IVB. [11] Another study concluded that IVB/IVTA is more effective for improving VA and decreasing CMT at 3 months in DME. A single injection of IVTA along with the first IVB could improve outcome within 3 months, but this is not sustained at 6 months. [12]

Pharmacokinetic data suggest a single intravitreal injection of 1.25 mg bevacizumab is effective for 6-7 wk. Kreutzer suggested that a single triamcinolone injection may be as effective as a 3 injections of bevacizumab for the treatment of DME. [13] Less number of injections of triamcinolone reduces injection-related complications and improves the patient compliance. According to the literature, the reduction in CMT after IVB can be maintained only for about 1 month even with 2.5 mg injection, macular thickness begins to increase again and require a second injection after 1 month. [14,11]

In a systematic review results of analysis showed IVT had a statistically significant improvement in vision over IVB at 1 month and 3 months ($P<0.01$). However, the reduction was not significant regarding CMT during the earlier (1 month and 3 months) follow-up period ($P=0.12$, $P=0.41$, respectively).With regards to IVT versus IVB combined with IVT, there were no significant differences in CMT at 1 month ($P=0.86$) and 3 months ($P=0.06$) as our results also show. [15,16]

There are only a few studies which compare triamcinolone acetonide and bevacizumab therapies in the same patients. Shimura applied single dose of bevacizumab 1.25 mg in one eye of each of the 14 patients with bilateral persistent DME, while delivering single dose of triamcinolone acetonide 4 mg on the contralateral eye, after which the patients were followed-up for 24 weeks. Triamcinolone acetonide was found to provide more efficient and long-standing effect in terms of reducing CMT and increasing visual acuity compared with the bevacizumab. [17]

In a one year study on IVB and IVTA, both proved equally effective in reducing CMT in early DME. After 6 months, rehabilitation of vision was comparable in both treatment arms, whereas at the final follow-up at 12 months, BCVA was superior in the IVB than in the IVTA sample. This may be related to cataract development following steroid treatment, as well as to substance-specific mechanisms within the angiogenic versus the inflammatory cascade. [18]

The limitations of this study included a relatively short duration of follow-up. Any regression in terms increase in CMT in follow up period could not be taken into account. However the initial visual and anatomical responses were apparent during the follow-up time. Patients with CSME were taken irrespective of associated severity of diabetes as determined by HbA1c. We also didn't include intraocular pressure as a factor which may affect the choice of treatment. The strengths of this study include; the prospective design, the relatively large number of patients and the careful follow-up. Most studies on

intravitreal injection of bevacizumab included only very limited numbers of patients and were designed as retrospective analyses.

The therapeutic mechanisms of the drugs are comparable but not identical. IVB even if delivered in minimal intravitreal concentrations, down regulates VEGF plasma levels and may provoke cardiovascular events; as diabetic patients are intrinsically predisposed to increased cardiovascular risk factors. [19,20] The direct comparison in this setting provide indirect evidence that both independent pathways; anti-angiogenic and anti-inflammatory contributed to a therapeutic effect. The current study also showed that earlier diagnosis of CSME is essential so we may intervene early; earlier intervention may help improved outcome. It is concluded that single injection of IVB is equivalent to IVTA plus IVB in the treatment of CSME in terms of reducing mean CMT.

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ORIGINAL ARTICLE

Pattern of Posterior Capsular Opacification in Extra Capsular Cataract Extraction versus Phacoemulsification Using Different Types of Intraocular Lenses

Mohammad Siddique[1], Faisal Rashid[1], Hina Khan[2], Mahmood Saeed[1]

ABSTRACT

Objectives: The objectives of this study were to find out the Pattern of posterior capsular opacification in extra capsular cataract extraction Vs Phacoemulsification using different types of IOLs as well as to find status of Diabetes on incidence of PCO and Pigmentation on IOL.

Subjcts and Methods: This descriptive type cross sectional comparative study was conducted at ophthalmology department of Sheikh Zayed Medical College/Hospital Rahim yar khan from June 2015 to June 2016. A total of 130 subjects were included in this study by using non-probability convenient sampling technique.

Results: A total of 130 subjects of both genders, referred from different ophthalmic centers, having PCO were included in the study. 92 (70.8%) had undergone ECCE and 38 (29.2%) had undergone phacoemulsification.102 (78.5%) had PMMA IOL implanted while 28 (21.5%) had Foldable intraocular lens implanted in their eyes. 81 (62.3%) were having fibrosis type PCO while 49 (37.7%) were having Elschnig pearls. 20 subjects having pupillary capture, 19 (95%) had undergone ECCE while 1 (5%) had undergone phacoemulsification ($p<0.005$). Pigmentation on IOL was more commonly found in Diabetics as compared to non- diabetics ($p<0.005$).

Conclusion: Fibrous pattern of Posterior Capsular Opacification was found to be more common in Extra-capsular Cataract Extraction than Phacoemulsification. Phacoemulsification was established as better surgical technique to lower the incidence of PCO and pupillary Capture due to in-bag IOL implantation. Diabetics were at higher risk of early development PCO and Pigmentation on IOL. *.Al-Shifa Journal of Ophthalmology 2016; 12(3), 149-155. © Al-Shifa Trust Eye Hospital, Rawalpindi*.

Introduction:

Posterior capsule opacification (PCO) is a common complication of any type of cataract surgery[1].It occurs in about 50% of cases within two years of cataract surgery[2].Capsular opacification is different from the intraoperative opacification that takes place in the intact lenses. It is known as a plaque that can either be in the anterior and/or posterior capsule. Posterior Capsular Opacification is also known as secondary cataract or after cataract which develops over the clear posterior capsule a few months to many years after uncomplicated cataract surgery. It is different from primary capsular opacification in which the posterior capsule is opacified in intact crystalline lens and found to be well differentiated intraoperatively[3].PCO results from the abnormal proliferation of lens epithelial cells mostly from the equatorial part of the

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capsule. These epithelial cells move to the central part of visual axis resulting in decrease vision. PCO occurs mostly in two patterns i.e; elschnig pearls and fibrosis while rarely in combination. Microscopic examination of fibrous PCO shows the presence of extra cellular matrix and myofibroblast cells [4]. Histology ofpearl shows swollen opacified, differentiated lens epithelial cells known as bladder or Wedl cells[2]. The mechanism of PCO formation comprises of migration[5].Differentiation[6] and proliferation of lens epithelial cells[7].

The risk factors for PCO include age[8-9], diabetes mellitus[10], uveitis[11], myotonic dystrophy[12], retinitis pigmentosa[13]and trauma[14].PCO can be reduced by a-traumatic cataract surgery, continuous curvilinear capsulorhexis[10],thorough cortical clean-up[15], use of hydro-dissection and rotation of nucleus[16], polishing of anterior and Posterior capsule[17-18]in bag fixation[19-20]specific IOL designs[21]and haptic design and angulation[22].

The treatment of PCO can be surgical and non-surgical. The non-surgical treatment includes Neodymium: Yttrium Aluminum Garnet (Nd-YAG) laser capsulotomy which is most commonly used worldwide. The need of treatment depends upon the symptoms like decrease vision, glare and monocular diplopia[23]. The complications of Nd-YAG laser capsulotomy are corneal burn, rise in intra ocular pressure, pitting and chipping of lens, cystoid macular edema and retinal detachment[24]. The surgical capsulotomy is usually done in children, mentally retarded patients, head nodding patients and nystagmoid patients. It is performed by the use of needle capsulotomy, Vanna scissor and by viteractomy cuttor.

The objectives of this study were to find out the Pattern of posterior capsular opacification in extra capsular cataract extraction Vs Phacoemulsification using different types of IOLs as well as to find status of Diabetes on incidence of PCO and Pigmentation on IOL.

Subjects and Methods:

This descriptive type cross sectional comparative study was conducted at ophthalmology department of Sheikh Zayed Medical College/Hospital Rahim yar khan from June 2015 to June 2016. A total of 130 subjects were included in this study by using non-probability convenient sampling technique. Informed and written consent was taken from all the patients. A thorough history and complete ocular examination was performed prior to treatment. All the patients were treated by using YAG Laser, (OSRAM HLX 64251) performing circular pattern opening in the posterior capsule. Patients of both genders having age more than 5 years who underwent any type of cataract surgery having PCO referred from any private or government setup were included in the study. The data was recorded on a self-made proforma and was analyzed by using SPSS 20.0 software.

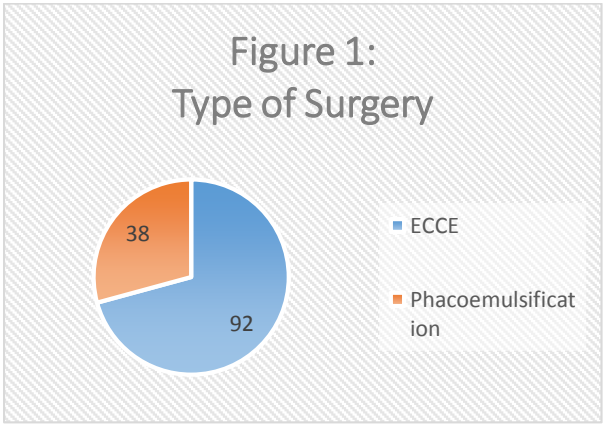
Results:

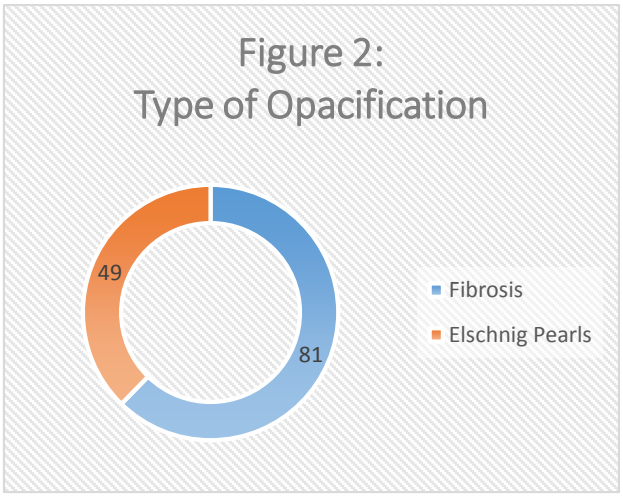
A total of 130 subjects of both genders having PCO were included in the study.

Figure 1 shows that out of total 130 subjects, 92 (70.8%) had undergone ECCE and 38 (29.2%) had undergone phacoemulsification. Table 1 shows that out of total 130 subjects 102 (78.5%) had PMMA IOL implanted while 28 (21.5%) had Foldable intraocular lens implanted in their eyes. Figure 2 shows out of total 130 subjects, 81 (62.3%) were having fibrosis while 49 (37.7%) were having Elschnig pearls. Table shows that out of total 81 subjects having fibrosis, 65 (80.2%) had undergone ECCE while 16 (19.8%) had undergone phacoemulsification. This shows high significance of fibrosis with ECCE ($p<0.005$). Figure 3 shows that out of total 130 subjects, 46 (35.4%) were

diabetic while 84 (64.6%) were non-diabetic.

Table 3 shows that out of total 130 subjects, 31 (23.8%) had pigmentation on IOL while 99 (76.2%) had no pigmentation on IOL. Table 4 shows that out of total 31 subjects having pigmentation on IOL, 25 (20%) were diabetic and 5 (3.8%) were non-diabetic. This shows statistically significant difference of pigmentation between diabetics and non-diabetic patients ($p<0.005$).





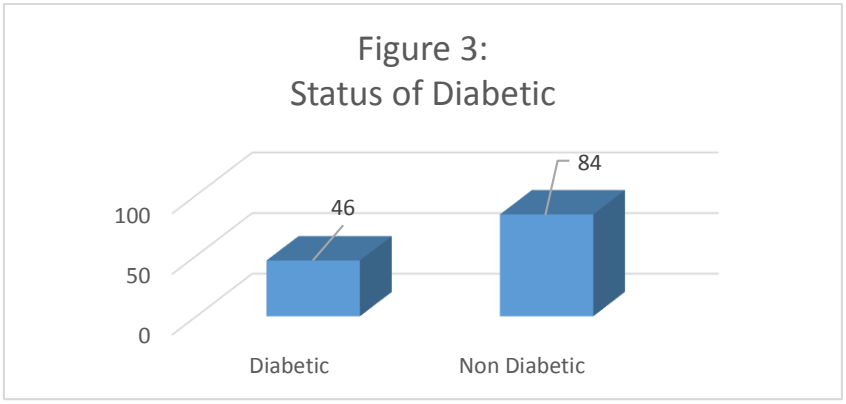


Table 1:PMMA Vs Foldable IOLs		
IOL Type	**No. of Patients**	**Percentage**
PMMA	102	78.5%
Foldable	28	21.5%
Total	**130**	**100%**

Table 2: Fibrosis in ECCE Vs Phaco			
	Patients with Fibrosis	**Percentage**	**P-value**
ECCE	65	80.20%	P<0.005
Phacoemulsification	16	19.80%	
Total	**81**	**100%**	

Table 3:Pigmentation on IOL: Diabetic Vs Non-diabetic			
Pigmentation on IOL	**No. of Patients**	**Percentage**	**P-value**
Diabetic	25	20%	<0.005
Non-diabetic	5	3.8%	
Total:	**30**	**23.8%**	

Table 4:Pigmentation on IOL		
Pigmentation on IOL	**No. of Patients**	**Percentage**
Present	31	23.8%
Absent	99	76.20%
Total	130	100%

Discussion:

Posterior capsule opacification (PCO) is a common complication of any type of cataract surgery. The risk factors for PCO include age, diabetes mellitus, uveitis, myotonic dystrophy, retinitis pigmentosa and trauma. PCO can be reduced by a-traumatic cataract surgery, continuous curvilinear capsulorhexis, thorough cortical clean-up, use of hydro-dissection and rotation of nucleus, polishing of anterior and Posterior capsule in bag fixation specific IOL designs and haptic design and angulation. In our study total 130 subjects were enrolled, out of which 92 (70.8%) had undergone ECCE and 38 (29.2%) had undergone phacoemulsification whereas 102 (78.5%) had PMMA IOL implanted while 28

(21.5%) had Foldable intraocular lens implanted in their eyes. 81 (62.3%) were having fibrosis type PCO while 49 (37.7%) were having Elschnig pearls. This resembles with the study of Angli Siathia et al which showed 60.90 % had fibrosis type of Posterior capsular opacification and 16.30 % had Elschnig pearls[25]. Similar findings were reported by Hayashi et al.[26]. A study conducted by Sanjoy Chowdhary et al reported similar results in their study[27].Out of total 81 subjects having fibrosis, 65 (80.2%) had undergone ECCE while 16 (19.8%) had undergone phacoemulsification. This shows high significance of fibrosis with ECCE ($p<0.005$).

Out of total 20 subjects having pupillary capture, 19 (95%) had undergone ECCE while 1 (5%) had undergone phacoemulsification ($p<0.005$). This shows that capsulorhexis, hydro-dissection, nucleus rotation and in bag IOL implantation in phacoemulsification not only decreases the incidence of PCO but also reduces the chances of pupillary capture. Ram et al had similar findings in their study[28].

In this study, out of total 31 subjects having pigmentation on IOL, 25 (20%) were diabetic and 5 (3.8%) were non-diabetic ($p<0.005$). This resembles with the study of Ebihara et al[10]andJonathan G.F[29].

The objectives of this study were to find out the Pattern of posterior capsular opacification in extra capsular cataract extraction Vs Phacoemulsification using different types of IOLs as well as to find status of Diabetes on incidence of PCO and Pigmentation on IOL. The study showed higher significance of PCO in ECCE as compared to Phacoemulsification. Fibrotic pattern was found to be more common than Elschnig's pearls in ECCE as compared to Phacoemulsification. The study also revealed that Pigmentation on IOL was more commonly found in Diabetics as compared to non- diabetics. Additionally Results exhibited pupillary capture to be more abundantly found in ECCE as compared to Phacoemulsification.

Conclusion:

Fibrous pattern of Posterior Capsular Opacification was found to be more common in Extra-capsular Cataract Extraction than Phacoemulsification. Phacoemulsification was established as better surgical technique to lower the incidence of PCO and Pupillary Capture due to in-bag IOL implantation. Diabetics were at higher risk of early development PCO and Pigmentation on IOL.

Recommendations:

This study by no means is an Exhaustive study due to lack of time and resources. More studies need to be conducted on this topic on larger scale. With the help of results and conclusions following recommendations may be made:

1. Phacoemulsification should be the surgery of choice for the treatment of Cataract.

2. Posterior Capsular Opacification can be reduced by following proper steps of phacoemulsification like continuous curvilinear capsulorhexis, hydro-dissection, rotation of nucleus, thorough cortical clean up, polishing of anterior and Posterior capsule, in bag fixation,specific IOL designs, and heptic design and angulation.

3. Patients with diabetes undergoing cataract surgery should be advised for early follow up as they are at the higher risk for developing PCO as well as pigmentation on IOL.

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ORIGINAL ARTICLE

Cyclosporine A Eye Drops: Its Effects and Complications in Vernal Keratoconjunctivitis

Hussain Ahmad[1], Yousaf Jamal Mahsood[2], Muhammad Naeem[3], Muhammad Sajid Khan[1], Maqsood Ahmad[1], Ubaid Ullah[1]

Objective: To evaluate the efficacy, safety, and therapeutic effect of topical cyclosporine A drops in vernal keratoconjunctivitis patients.

Materials and Methods: This study was conducted in Department of Ophthalmology, Khyber Teaching Hospital, Peshawar from 1st April 2015 to 31st March 2016.Forty patients with active vernal keratoconjunctivitis diagnosed at least one year before and treated with a variety of topical medications including steroids were included in the study. All patients were treated with 0.05% cyclosporine eye drops four times daily in both eyes for 4weeks. Symptoms (itching, watering, photophobia, mucous discharge and foreign body sensation) and signs (conjunctival hyperemia, limbal edema, epithelial punctate keratitis and palpebral conjunctival papillae) of vernal keratoconjunctivitis were recorded before treatment and at the end of treatment period.

Results: There was a statistically significant improvement in itching, photophobia, mucous discharge, conjunctival hyperemia, punctate keratitis and conjunctival papillae after 4 weeks treatment period. No significant adverse effect of treatment with topical cyclosporine was observed except for mild to moderate stinging upon administration.

Conclusion: Topical cyclosporine A seems to be safe and effective in alleviating signs and symptoms of severe VKC refractory to topical steroid treatment. *Al-Shifa Journal of Ophthalmology 2016; 12(3), 156-163. © Al-Shifa Trust Eye Hospital, Rawalpindi.*

Introduction

Allergic conjunctivitis is a local allergic condition centered mainly in the ocular area, although sometimes it is also associated with rhinitis. The disease ranges in severity from mild to severe forms. Mild can still interfere significantly with quality of life, while severe cases are characterized by potential impairment of visual function, especially if the cornea is involved[1]. Vernal Keratoconjunctivitis (VKC) is one severe chronic form of seasonally exacerbated allergic conjunctivitis. It is more common in children and young adults having an atopic background. Aside from being one of the most severe forms of ocular allergy, VKC can be considered the childhood form of allergic conjunctivitis due to the fact that the condition affects mainly children in their first decade of life and young adults[1-3]. The disease is usually bilateral and is seen more commonly among males[4].

Patients with vernal keratoconjunctivitis may suffer from symptoms throughout the year, but the intensity of the disease may

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increase in spring and summer. The precise immunopathogenic mechanism is unknown but it is thought to be more complex than a simple type I hypersensitivity reaction [5]. By itself, the IgE-mast cell mediated process does not explain the entirety of the clinical and histopathological changes associated with VKC; there are other mediators and cells involved in the initiation and perpetuation of the ocular allergic inflammation [2].

Therapeutic measures are required to control signs and symptoms of VKC and to avoid the initiation of longstanding permanent inflammatory sequel that may lead to fibro vascular reaction, new collagen deposition, tissue remodeling and permanent visual damage. There are a variety of drugs currently used to treat VKC, including anti-histamines, mast-cell stabilizers, dual acting agents, corticosteroids and immunomodulators or immunosuppressants, but none have been shown to be sufficient to treat all aspects of the complex pathophysiology of VKC [1,6]. Steroids can be highly effective, but may cause unwanted elevation of intraocular pressure in steroid responders and increase the risk of corneal infection through local immunosuppression. In addition, induction of cataract and delayed wound healing can be problematic[6].

Cyclosporine A is an immunomodulator that specifically inhibits CD4_ T lymphocyte proliferation via inhibition of interleukin-2 receptor expression[7].Cyclosporine A also has direct inhibitory effects on eosinophil and mast cell activation and release of mediators, which seem to be important in its role in the treatment of allergic inflammation[8,9]. Topical cyclosporine has been used in several formulations in an effort to reduce steroid dependence. A placebo controlled trial using topical cyclosporine 2% in maize oil showed it to be an effective and safe steroid sparing agent, but its use was limited by frequent intense stinging in the patients [10].

To avoid the complications of current treatment of severe VKC (especially steroid), the efficacy of cyclosporine regarding the control of symptomatology of VKC was studied.

Subjects and Methods:

The study was conducted at Ophthalmology Department, Khyber Teaching Hospital Peshawar from 1st April 2015 to 31st March 2016. A total of 40 patients were included in this Quasi experimental study. Patients included in the study were known cases of active palpebral or limbal vernal keratoconjunctivitis diagnosed at least one year before and treated with a variety of topical medications, except cyclosporine with poor response. Written informed consent was obtained from all patients. Patients with moderate to severe steroid dependent VKC who met the inclusion criteria according to previously established definitions were included in the study (Table 1).

VKC was diagnosed based on the presence of itching, mucus discharge, papillae on the superior tarsal conjunctiva and changes in the limbal area. At the time of inclusion in the study, all the patients were disease positive in an active stage and they were under treatment with topical steroids (loteprednol etabonate, prednisolone or dexamethasone), and in about 5% of cases, the disease had remained refractory to treatment with steroids for more than two weeks. The eligibility approval for all the subjects was determined after concluding the clinical evaluation in the basal visit. A complete washout period was then initiated for all study participants, which consisted in the use of only physical measures during 1 week. For all the patients the use of topical steroids was discontinued during the washout; after this

period topical steroid use was not re-initiated. All patients were given 0.05% cyclosporine eye drops four times daily in both eyes. Symptoms and signs were recorded before treatment and after 1st, 2nd and 4th week of treatment. Symptoms and signs were graded as shown in table 2.

Main outcome measures of the study were the efficacy and safety of the treatment, effect of the treatment on clinical grades and rate of recurrences. Statistical analyses were performed using SPSS software for Windows version 15.0 (Statistical Package for the Social Sciences, SPSS, Inc., Chicago, IL).

Table 1: Eligibility criteria for VKC patients

INCLUSION CRITERIA
Patients with a clinical diagnosis of Steroid-Dependent Vernal Keratoconjunctivitis
Patients of either gender, 4 years or older.
EXCLUSION CRITERIA
Patients with only one eye.
Patients with visual acuity of 6/60 or worst in any of both eyes without a justifying cause.
Patients with any other ocular inflammatory disease besides of VKC.
Patients receiving medication like systemic NSAIDs, systemic steroidal anti-inflammatory drugs, systemic immunosuppressants which interfere with results of the study.
Patients with history of hypersensitivity to cyclosporine.
Contact lenses users.
Patients who don't want to participate in this study.

Table 2: Grading Scale for Ocular Signs and Symptoms in VKC study

SYMPTOMS	0	1	2	3
Itching	No itching	Occasional itching	Frequent itching	Constant itching
Tearing	Normal tears	Sensation of fullness of the conjunctival sac without tears spilling over the lid margin	Intermittent, infrequent spilling of tears over the lid margin	Constant, or nearly constant, spilling of tears over the lid margin
Foreign body Sensation	Absent	Mild, similar to fine dust sensation	Moderate, similar to sand sensation, with mild tearing and blinking	Severe, similar to big foreign body sensation, with constant tearing and blepharospasm
Photophobia	No Photophobia	Mild difficulty with light	Moderate difficulty, necessitating dark glasses	Extreme photophobia causing the patient to stay indoors; cannot stand natural light even with dark glasses
Stinging	Absent	Mild	Moderate	Severe

SIGNS	0	1	2	3
Conjunctival Hyperemia	Absent	Mild	Moderate	Severe, with hyperemia in all conjunctival surface
Conjunctival Discharge	Absent	Small amount of discharge	Moderate amount of yellow or green-yellowish discharge	Severe, with blood traces in the lower cul-de-sac and
Tarsal conjunctival Papillary hypertrophy	No evidence of papillary formation	Mild papillary hyperemia	Moderate papillary hypertrophy with edema of the palpebral conjunctiva and hazy view of the deep tarsal vessel	Severe papillary hypertrophy obscuring the visualization of the deep tarsal vessels
Chemosis	Absent	Mild	Moderate	Severe, involving all conjunctival surface

Results:

In our study 40 patients were enrolled in which 33(82.5%) were male and 7 (17.5%) were female. Patients had mean age of 8.4 years (ranged 4 to 17 years). Twenty six (65%) of 40 patients were 8 years of age or younger (Table 3).

Patients after using topical cyclosporine remained comfortable. No significant side effect occurred, except for mild to moderate stinging and burning upon administration. There was statistically significant improvement in itching and photophobia. Also there was improvement in watering and foreign body sensation, although not statistically significant. Thirty eight (95%) patients had decrease in itching after treatment with topical cyclosporine ($p<0.05$). Tearing improved in 30(75%) patients after treatment with topical cyclosporine ($p<0.05$). Photophobia improved in 34(86.5%) patients ($p<0.02$) while Foreign body sensation improved in 30(81.1%) patients ($p>0.05$).Stinging occurred in 4 patients (Table 4).

There was a statistically significant improvement in the conjunctival and corneal signs after using topical cyclosporine. Bulbar conjunctival hyperemia improved in 39(97.3%) patients ($p<0.01$). Conjunctival discharge improved in 35(91.9%) patients ($p<0.02$). Chemosis improved in 34(89.2%) patients ($p>0.05$).Tarsal conjunctival papillae showed improvement in 28(51.4%) patients ($p>0.05$) (Table 5).

Table 3: Age and Gender distribution

Age	4-8 years	26(65%)
	9-12 years	9 (22.5%)
	13-17 years	5 (12.5%)
Gender	M	33(82.5%)
	F	7(17.5%)

Table 4: Improvement in symptoms

Symptoms	No of patients improved
Tearing	30 (75%)
Itching	38 (95%)
F.B sensation	33 (82.5%)
Photophobia	34 (85%)

Table 5: Improvement in signs

Signs	No of patients improved
Conjunctival Hyperemia	39 (97.5%)
Conjunctival Discharge	36 (90%)
Tarsal conjunctival Papillary hypertrophy	35 (87.5%)
Chemosis	28 (70%)

Discussion:

VKC is characterized with bilateral inflammation of ocular and periocular tissue in response to ocular allergic stimulus and is commonly seen in male pediatric population. The presence of associated allergic diseases in many patients with VKC points a common underlying
immunological process where Th2-driven, IgE dependent and independent pathways are involved [11]. Type I and IV hypersensitivity reactions are involved in VKC. Antigen presenting cells such as Langerhan's cells, Th2 cells, B cells ex-pressing CD21, CD23 and CD40 and IL-8 have particular importance during multifactorial pathogenesis of VKC [12].

The management of VKC often is difficult and is determined by availability of medications, safety and cost effectiveness [13]. Milder cases can often be treated with tear substitutes, topical vasoconstrictors or topical antihistamines. More advanced cases may be treated with combinations of topical mast cell stabilizers and topical corticosteroids but unsupervised treatment may lead to glaucoma and cataract[14]. Therefore a drug which is effective in advanced cases of VKC with no or little side effects is highly desirable.

Cyclosporine which was isolated from Tolypocladium inflatum Gams acts is a cyclic polypeptide calcineurin inhibitor which inhibits primarily the action of T cells through down regulation of expression of IL-2 receptors [15, 16]. It also displays as an inhibitor of histamine release, and early phase reaction in type- I allergy, and reduces conjunctival fibroblast proliferation rate [11, 17]. Cyclosporine was also showed to be effective in reducing eosinophilic infiltration by interfering type IV allergic reaction in conjunctiva [18]. The efficacy of topical cyclosporine in the treatment of VKC is controversial. Many studies showed the high efficacy of topical cyclosporine in VKC [19, 20]. However, Daniell et al [21] evaluated the efficacy, safety and therapeutic effect of topical cyclosporine A in steroid dependent allergic conjunctivitis and showed that it had no benefit over placebo as a steroid sparing agent.

Hingorani et al. investigated the immunomodulatory effect of topical cyclosporine A after 3 months of treatment through superior tarsal conjunctiva specimens[6]. They found that the in-crease of T cells which express IL-2 and IFNγ, and the decrease in CD4-CD8 ratio which indicated the potential effect of topical cyclosporine on ocular immune profile. Keklikci et al demonstrated that topical cyclosporine A 0.05% caused a significant decrease of conjunctival inflammatory cell count by using conjunctival impression cytology[22].

Our clinical trial demonstrated that topical cyclosporine was effective is controlling the symptoms and signs of patients with VKC. Statistically significant improvement was observed for symptoms (itching, photophobia) and signs (conjunctival hyperemia, conjunctival discharge) of VKC. There was also improvement for other symptoms (tearing, foreign body sensation) and signs (chemosis, tarsal conjunctival papillae)of VKC, although statistically not significant. These results are comparable with the studies carried out by Gupta et al and secchi et al [23, 24].

Topical cyclosporine was well tolerated by all of our patients. No significant side effects occurred, except for mild stinging and burning upon administration, which was also noted in studies carried out by Hingorani et al and Secchi et al[10, 24]. However in study carried out by Bleik et al, no adverse effects and no detectable levels of cyclosporine were noted in the blood in the cyclosporine treated groups[25]. Literature shows that topical cyclosporine is not going to be absorbed into the systemic circulation in sufficient concentration to reach therapeutic or toxic dosages and therefore is not associated with any systematic side effects. Prolonged use of topical 2% cyclosporine has been reported, and the only serious side effects reported are lid maceration and corneal epitheliopathy, both of which resolve on cessation of treatment and which do not necessarily preclude further use of cyclosporine. Topical cyclosporine appears to carry none of the serious, sight threatening complications of topical steroids, such as glaucoma, cataract and exacerbation of corneal infection [26].

Topical cyclosporine has been used to treat a number of anterior segment conditions including Sjogren's syndrome, ligneous conjunctivitis, ocular cicatricial pemphigoid, Mooren's ulcer and autoimmune corneal melting. It also has been used in high risk penetrating keratoplasty and is also under trial for the treatment of steroid dependent atopic keratoconjunctivitis[10]. It is available commercially at 0.05% concentration (Ristases, Cylor, Ropsol) in our country and has been reported to be effective for allergic conjunctivitis[27]. We would suggest that topical cyclosporine 0.05% is safe and effective therapy in patients with VKC who are resistant to conventional treatment or when there is danger of developing complications with conventional treatment.

Conclusions

Topical cyclosporine is effective in controlling the symptoms and signs of patients with vernal keratoconjunctivitis who are refractory to conventional treatment and can be used safely without any significant side effect.

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ORIGINAL ARTICLE

Association between Dry Eyes and Anti-glaucoma Medications: A Case Control Study

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Abstract

Objective:

To identify the association between dry eye syndrome and anti-glaucoma medications, to detect the effect of duration of anti-glaucoma medications use on producing symptoms of dry eye and to compare the frequency of dry eye symptoms in anti-glaucoma medications users and control group.

Subjects and Methods: A case control study at the Glaucoma department of Al-Shifa Trust Eye Hospital Rawalpindi, in which hundred patients on anti-glaucoma medications and hundred controls were enrolled. Tear break up time (TBUT), Schirmer test and Tear meniscus height were used to evaluate dry eye. All the information was recorded on a structured proforma and data was analysed using SPSS version 13.

Results: In results of TBUT, 78% dry eyes were found in cases and 30% in control group. Schirmer test results showed 62% dry eyes in cases and 34% in control group. Tear meniscus height showed 85% dry eyes in cases and 37% in control group. Results were statistically significant with P <0.005. Regarding the duration of use, 34% dry eyes were found in Glaucoma patients using medications for 2-3 years and 75% in those who were using medicines for more than 5 years and results were statistically significant with p <0.005.

Conclusion: This study concludes that there is an association between the use of anti-glaucoma medications and dry eyes. Increase in duration of medications use leads to increase in symptoms of dry eye. *Al-Shifa Journal of Ophthalmology 2016; 12(3), 164-169. © Al-Shifa Trust Eye Hospital, Rawalpindi.*

Introduction

Dry eye syndrome is a group of disorders that affects various component of ocular surface. Basically it is described as a condition that affects the stability and function of tear film in different ways [1]. Some of the common causes of dry eyes include environmental factors, blepharitis, meibomian gland dysfunction, age use of oral contraceptives and anti-histamine as well as preservative-containing eye drops. Dry eye is also reported in the patients using anti-glaucoma medications.

Glaucoma is among the leading causes of blindness all over the world. The estimated prevalence of glaucoma is about 0.8-7.0%. Glaucoma is treated with anti-glaucoma medications, lasers and surgeries to lower the IOP. Medical therapy for glaucoma is usually achieved by topical medicines[2]. Preservatives are used in topical anti-glaucoma medications, due to which topical glaucoma medications are associated with ocular surface disorders [3].

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In literature prevalence of dry eye is diverse, ranging between 7.8% in one study from western countries and 93.2% in one study from Asia [4]. One of the studies from Canada shows the prevalence of dry eye about 28.7%, while in China it is about 21%. Three different studies from India show dry eye prevalence about 18.4 - 40.8% [5.]

Patients with dry eyes usually present in OPD with general discomfort, itching, dryness, redness of the eye, burning sensation, foreign body sensation, visual disturbance, difficulty in reading or working in front of a computer and photophobia [6]. Anti-glaucoma medications are not the only reason to cause dry eye but the preservatives used in medications are the main source of the dry eye in anti-glaucoma therapy. The common preservative used in glaucoma topical is benzalkonium chloride. This preservative has a detergent-like activity. In the long-term, because of their detergent nature, preservatives such as benzalkonium may cause damage to the conjunctiva epithelial cells, decrease goblet cell density, and cause dry eye. [7]

In addition, the preservative may penetrate the epithelium to the conjunctival stroma and cause an inflammatory action in the deeper tissues by activating a cascade of pro-inflammatory cytokines released from inflammatory cells such as lymphocytes. Release of inflammatory cytokines might result in activation of conjunctival fibroblasts resulting in conjunctival fibrosis. Some of these lymphocyte-related cytokines belong to the interleukin family and have a marked pro-inflammatory effect. The cornea may also be affected from chronic use of glaucoma. A keratoepitheliopathy has been reported that occurs as a result of decreased tear volume and the tear film instability, perhaps through toxic effects to the surface of the eye.[8]

Glaucoma patients have different tolerance to topical medication and in those with coexistent dry eye instillation of preserved drops may deteriorate signs and symptoms of OSD and further decrease the quality of life. Additionally, side effects of treatment and intolerance to drops may reduce adherence to the prescribed treatment regimen and contribute to the progression of disease. Moreover, if severe dry eye is left untreated then it can cause scarring on the surface of eyes [6].

Objectives of this study were to identify the association between dry eye syndrome and anti-glaucoma medications, to detect the effect of duration of anti-glaucoma medications use on producing symptoms of dry eye and to compare the frequency of dry eye symptoms in anti-glaucoma medications users and control group.

Subjects and Methods:

This was a case control study carried out at Al-Shifa trust eye hospital form 1st July 2015 to 31st December 2015.

Inclusion criteria

- Both genders were included with age between 20-50 years.
- In cases group, 100 eyes of patients visiting glaucoma clinic of Al-Shifa trust eye hospital for last 2 years or more were enrolled.
- In control group 100 eyes of subjects visiting general OPD and not using any eye drops were enrolled.

Exclusion criteria

- Patients with age above 50 years were excluded.
- Patients with the history of glaucoma surgery were excluded.
- Patients with any Systemic diseases like DM, arthritis and use of oral contraceptives
- Patients with any ocular disease which can be the risk factor for dry eye like pterygium, keratitis. Adenoviral and eye lid disorder were excluded.

Three tests were used to diagnose dry eye in these participants. These included TBUT, Schirmer test and Tear meniscus. TBUT was used to measure tear film stability. Schirmer test was used to measure maximum basic and reflex secretion of tears. Descriptive as well as inferential statistics were applied for analysis. All the information was recorded on a structured Performa.

Statistical analysis was done by using SPSS version 13. Chi-square test was applied to find out the association between dry eye and anti-glaucoma medications. P values < 0.05 were considered as statistically significant.

Results

Itching was found to be the most frequent complaint compared to other symptoms of dry eye. Figure 1 shows frequency of various complaints associated with the use of anti-glaucoma medications. The most frequently prescribed medication was the combination of timolol + dorzolamide, followed by latanoprost and brimonidine. Figure 2 shows frequency of various anti glaucoma medications prescribed in the glaucoma clinic. In results of TBUT, 78% dry eyes were found in cases and 30% in control group. Tear meniscus height showed 85% dry eye in cases and 37% in control group (Table No. 1). Schirmer test results showed 62% dry eye in cases and 34% in control group (Table No. 2). Results were statistically significant with P <0.005. Regarding the duration of use, 34% dry eyes were found in Glaucoma patients using medications for 2-3 years and 75% in those who were using medicines for more than 5 years and results were statistically significant with p <0.005 (Table No. 3).

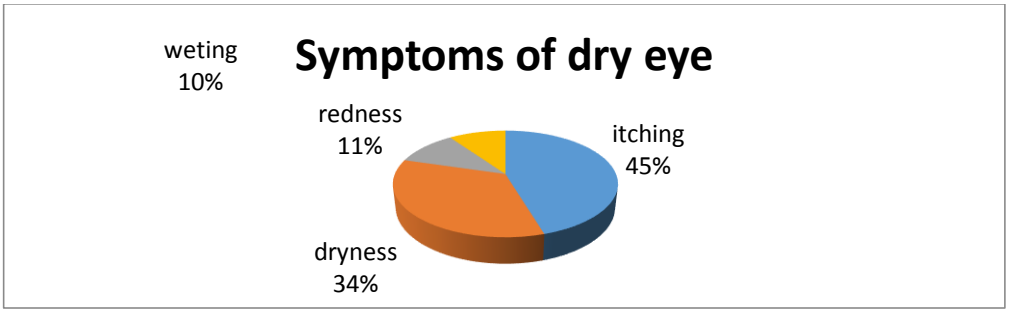

Fig. 1: Percentage of different symptoms of dry eye

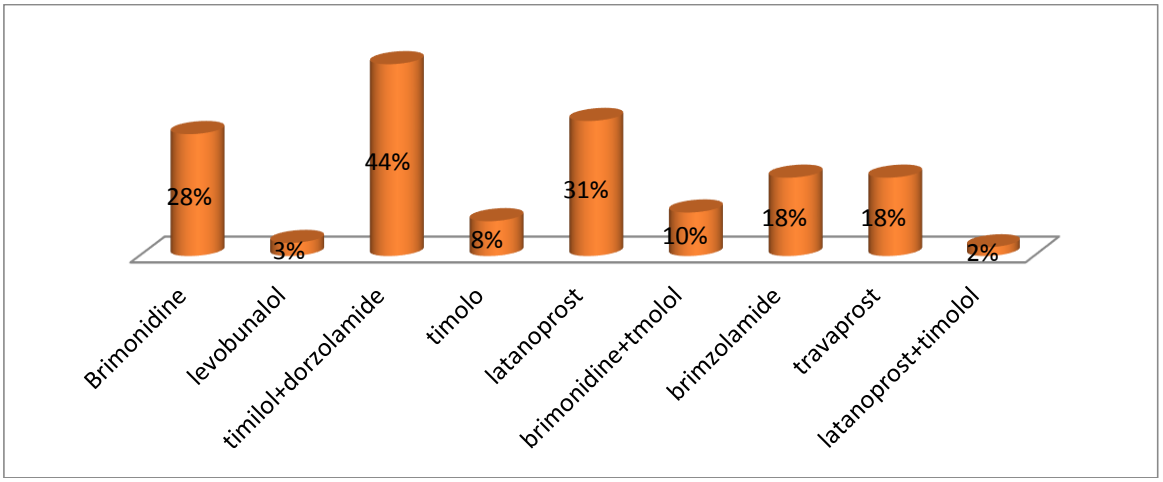

Fig.2: shows the different anti-glaucoma percentage

Table.1 Severity of dry eye according to Tear Meniscus Height in case and control group

tear meniscus height	Case group	control group	χ^2
<1mm severe dry eye	52	20	
1mm mild dry eye	33	17	P=<0.001
>1mm normal	15	63	

Table No.2 Severity of dry eye using Schirmer test in case and control group

Schirmer test	Case group	Control group
<3mm very severe	16	5
3-6mmsevere dry eye	19	9
6-9mm moderate dry eye	12	14
10mm mild dry eye	15	6
>10mm no dry eye	38	66

Table.3 Association between dry eye and duration of Anti-Glaucoma medications

Duration of anti-glaucoma medications	**N**	**Dry eye present**	**Dry eye not present**	**P value**
2-3 years	34	11	23	0.270
4-5 years	42	31	11	<0.001
>5 years	24	18	6	<0.001

Discussion

Diagnosis of dry eye in clinical practice is usually based on the presence of dry eye symptoms, Schirmer test, TBUT fluorescein staining and tear meniscus height. This study found that dry eye syndrome was present significantly more in case group as compared to control group.

Christophe Baudouinu et al reported that 59% patients on glaucoma medications had symptoms of dry eye in at least one eye, Schirmer test showed 61% patients with decreased tear production and 78% showed abnormal tear quality in TBUT [9]. Similar results showed by the study of Zeomba M in which prevalence of dry eye is 63% in case group [10].

There were statistically significant differences between the glaucoma-treated patients and control group in all the clinical tests used to diagnose dry eye syndrome. In this study Schirmer test was significantly reduced in glaucoma patients compared to control group (62% vs 34%) . TBUT and tear meniscus height were also reduced in glaucoma patients in this study. Another study reported that only TBUT and fluorescein staining grade were significantly altered in glaucoma treated patients as compared to untreated control group, but for Schirmer test there was no significant difference in both groups[11]. According to our study there was a significant difference in Schirmer test of both groups. This might be explained by various factors like environmental conditions, number of medicines and types of preservatives used in the medicines. Fechtner et al concluded that mean OSD score varied significantly with the number of topical IOP lowering used and higher OSD score in patients using multiple IOP-lowering[12]. We could not determine the relationship between the number of medicines and the severity of dry eyes because of frequent switching of therapy by different physicians in different hospitals, clinics and regions.

Stewart et al concluded in their study that OSD is common in medically treated glaucoma patients causing symptoms and sign of dry eye that may impact on a patient's quality of life[13]. Ghosh S et al showed in their study that signs and symptoms of dry eye in glaucoma population were 70.3% and in control group 33% with $p<0.001$[14]. In this study we included the patients below 50 years of age because above this age many other factors cause dry eye. Moreover, patients with systemic diseases were also excluded. So risks of dry eye due to other cause were lower and only glaucoma effect was expected to be the cause of dry eye.

This study showed that longer treatments with glaucoma medications have a higher risk of dry eye. In a comparative retrospective study using in vivo confocal microscopy, cases were divided according to the number of glaucoma drops instilled per day (1, 2, or 3). The prevalence of dry eye was reported as 40% in patients using 3 drops/day, 39% in patients using 2 drops / day, and 11% in patients using 1 drop/day. Furthermore, OSDI questionnaires revealed that 15% of patients using 3 drops / day and 8.7% of those using 2 drops/day developed severe OSD. Moreover, the prevalence of ocular symptoms and signs related to dry eye were dose dependent, increasing with the number of preserved anti-glaucoma drops[4].

A few limitations of this study are short time duration of study, while the sampling was convenient rather than random sampling. This study was done in a single setting, so limited numbers of patients were included in this study. More research work need to be done in this field to overcome all the above mentioned limitations.

Conclusion

Our study indicates that dry eye is more in glaucoma patients using anti-glaucoma eye drops then control group. Schirmer test, TBUT and tear meniscus height is less than normal in majority of glaucoma patient.

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