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The Effects of Post Cataract Topical Treatment on Anterior Segment Punctal Tomography: An OCT Guided Comparative Study

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Authors' contributions

This work was carried out in collaboration between all authors. Author HAA wrote the protocol, managed the literature searches, recruited the patients legible for the study and performed the follow up examination. Author RSHMA designed the study, performed the statistical analysis, performed the OCT and wrote the first draft of the manuscript. Author RAA designed the study, performed the clinical examination and managed the analyses of the study. Author TIG designed the study, managed the analyses of the study and revised the final draft of the paper. All authors read and approved the final manuscript.

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ABSTRACT

Purpose: To compare the short term effects of preserved prednisolone acetate to preserved nepafenac eye drops on punctum size.
Methods: The punctum size (inner diameter, outer diameter and height) as well as tear meniscus (height & area) were evaluated using AS-OCT in 50 eyes of 48 patients who were scheduled for phacoemulsification. Post operatively, eyes were randomized to receive either prednisolone acetate (group A) or nepafenac eye drops (group B) for 3 weeks. Punctal size and tear meniscus were re-measured at 2 weeks, 1 month and 3 months post-operatively.
Results: Punctum size measurements showed no statistically significant differences between the 3rd month post-operative visit and the pre-operative evaluation in either group (p-values: >0.05). There was no statistically significant difference between both groups (p-value: >0.05 for all the

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parameters). Tear meniscus height and area showed statistically significant increase in both groups compared to preoperative values at the 2nd postoperative visit (p-value = 0.046 and 0.019 in group A compared to 0.001 for both in group B).
Conclusions: Short term preserved prednisolone acetate and nepafenac eye drops have no effect on the lacrimal punctal size. Benzalkonium chloride has a short term effect on tear film stability observed as increased tear meniscus parameters on AS-OCT.

Keywords: Punctal size; AS-OCT; prednisolone; nepafenac; benzalkonium chloride.

1. INTRODUCTION

The assessment of the effects and consequences of medical treatment for different ophthalmological conditions on the lacrimal drainage system has been hugely under-investigated.

Eye drops and their preservatives can cause ocular surface changes that could also affect the punctum and canaliculus being very proximal to the ocular surface. The commonly used prednisolone is believed to play a role in causing progressive punctal narrowing [1].

Preservatives induce, according to their nature, an allergic reaction, but more frequently a cytotoxic reaction (90%) [1]. Further, long term usage of these agents may result in a form of conjunctival scarring known as drug induced pemphigoid or pseudopemphigoid, in which chronic allergic reaction leads to a marked and self-sustaining inflammatory process [2-4]. Preservatives also decrease the precorneal tear film stability [5-7] with subsequent worsening of pre-existing dry eye [8].

It seems likely that similar changes may occur in the epithelium and subepithelial tissues of the lacrimal drainage system, resulting in stenosis. Topical agents, including antiglaucoma medications and antiviral drops as well as systemic medications such as fluorouracil and docetaxel are now considered as risk factors for lacrimal system obstruction [9-16].

Anterior segment optical coherence tomography (AS- OCT) has been established as a new non-invasive modality in punctal assessment. This was first demonstrated by Wawrzynski et al. in 2014 [17].

In 2015, a published work by Allam and Ahmed used this technology to establish normative data in the Egyptian population as regards punctal size and morphology [18].

Moreover, en face AS-OCT was used to study the punctum and vertical canalicular sizes as a step to establish normative data [19].

Topical steroids are established post cataract anti- inflammatory agents. However, NSAIDs eye drops, have also proven their safety and efficacy as potent anti-inflammatory agents for post cataract patients with better protection against post cataract cystoid macular edema [20,21]. Moreover, they were never mentioned in the literature as potential etiology of punctal stenosis.

The current study aims at comparing the effects of short term preserved prednisolone acetate to nepafenac eye drops on the punctal size as evaluated by AS-OCT.

2. PATIENTS AND METHODS

The study has been approved by the Review Board of Ophthalmology department, Faculty of medicine, Cairo University. Data collection conformed to all local laws and was compliant with the principles of the Declaration of Helsinki.

It is an observational, prospective, randomized, blinded and comparative study. Fifty eyes of 48 patients were enrolled in our study. Patients were recruited from the Ophthalmology Department, Kasr Al-Ainy Hospital during the period between December 2014 and September 2015.

Asymptomatic Patients scheduled for cataract surgery, 40-70 years old of both genders were included in the study.

We excluded patients on chronic topical treatment (anti-allergic or anti glaucoma medications), patients with a clinically invisible punctum due to membrane or stenosis, patients already suffering of lacrimal problems (e.g dry eye or epiphora)or who had acquired any condition that may affect the lacrimal punctum during the duration of the study such as blepharitis, previous lid trauma or punctal surgeries, patients having lid margin position abnormalities (entropion, ectropion) and patients with medial lid masses obscuring the punctum. Patients who had to extend the duration of treatment or had to be treated with topical anti glaucoma drugs for increased IOP following cataract surgery were also excluded.

All subjects were clinically evaluated using the slit lamp by one experienced oculoplastic surgeon (R.A).

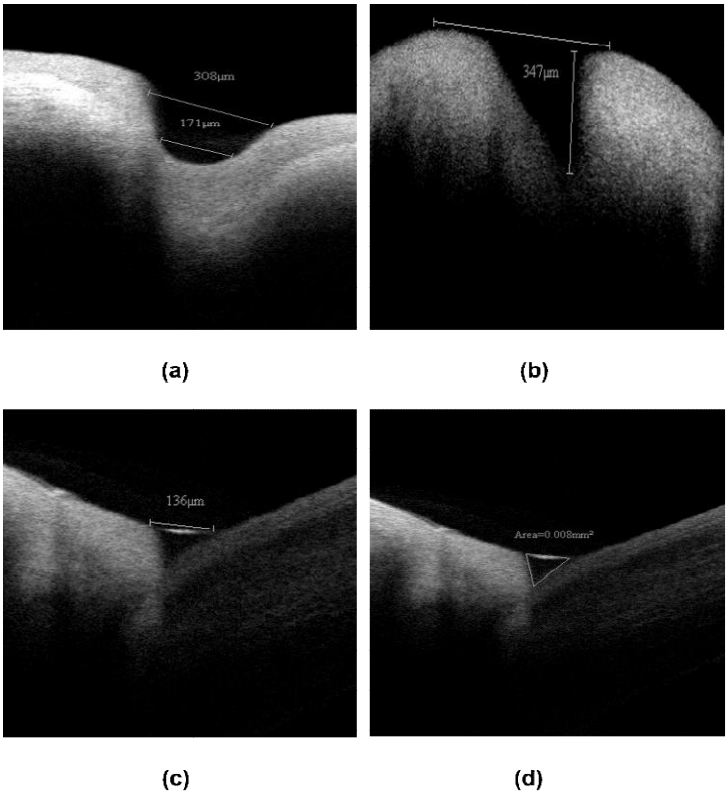
After history taking and full clinical evaluation, patients were photographed preoperatively using spectral domain AS-OCT, RTVue model-RT100 CAM system (Optovue Inc., Fremont, CA, USA) version 6.2 utilizing the cornea/anterior module-short lens (CAM-S) which has a 10mm working distance. Imaging was done by a single investigator (R.S) to accurately measure 5 parameters (punctal inner and outer diameters, punctal height, tear meniscus height and area). All patients were examined clinically and by AS-OCT between 8.30 and 10.00 am on the selected daysfor assessment.

Post-operatively, patients were randomly assigned, using computer software to one of two different post-operative treatment regimens.

Two patients whom were scheduled for bilateral cataract surgeries were not randomized to treatment groups. However, each eye was assigned to a different group than the other eye.

In all postoperative visits, each patient had to answer a yes or no question regarding the presence or absence of epiphora.

All patients received topical Gatifloxacin eye drops (4 times daily the first 5 days, then 3 times daily until completion of a 3 week period) and fusidic acid viscid eye drops (once at night). However in group A that included 25 eyes, patients received Prednisolone Acetate eye drops while the remaining 25 eyes in group B, patients received Nepafenac 0.1% eye drops (both 4 times daily the first 5 days then 3 times daily for the rest of the 3 week period). All eye drops used contained Benzalkonium Chloride (BAC) as a preservative in 0.05% concentration.



SDC 1. (a) AS-OCT of patient 5 of group B (Nepafenac group) showing the outer and inner punctal diameters.
(b) AS-OCT of patient 18 of group A (Prednisolone group) showing measurement of the punctal height.
(c) AS-OCT of patient 12 of group A (Prednisolone group) showing the use of the distance adjustment tool to measure the tear meniscus height.
(d) The area measurement tool is used to measure the tear meniscus area in the same patient

Patients were then examined using AS-OCT at 2 weeks, 1 month and 3 months postoperative. All patients were photographed by a single investigator (Riham S. H. M. Allam) who was blinded as to which group of treatment the patient was assigned.

The lower lid punctum was exposed by everting the medial part of the eyelid without pressure or stretching, to bring the vertical canaliculus into the axial plane. A crossline scan (2 mm × 2 mm) was centered on the punctum for alignment; then a cross-scan was obtained.

For each examined eye 3 scans were obtained, and then the operator selected the images with the deepest measurable diameters and with the clearest details. The outer (towards the lid margin) and the inner (towards the canaliculus) diameters were measured using the distance measurement tool. The depth of the punctum was obtained by drawing a line tangential to the lower lid margin across the punctal outer opening; then a perpendicular line was drawn until the base of the punctum was reached.

The junction of the punctum with the vertical canaliculus was determined by detecting the sudden narrowing in the punctal lumen diameter and/or the thinning of the lining epithelium which was then followed into the beginning of the vertical canaliculus, thus interpreted as the junction between the punctum and the vertical canaliculus [18]. The internal punctal diameter was then identified as the horizontal line drawn just above this junction. The tear meniscus height (TMH) and tear meniscus area (TMA) were also measured (see *supplementary document SDC 1a-d*, which shows how the measurements of the punctal diameters, punctal depth, TMH and TMA were acquired).

2.1 Statistical Analysis

Data were statistically described in terms of mean ± standard deviation (±SD), correlation and percentages when appropriate. Comparison between numerical variables within each group was done using the Wilcoxon signed rank test. Comparison of numerical variables between the two study groups was done using Mann-Whitney U test. Comparison of categorical variables between the two study groups was done using Pearson chi-square or Fisher test as appropriate. Correlation between numerical variables was done by Pearson moment correlation. All statistical calculations were done using computer programs IBM® SPSS® Statistics 21 (Statistical Package for the Social Science).*P*-values less than 0.05 were considered significant.

3. RESULTS

After exclusion of 8 cases for dropouts, 2 patients who needed topical anti-glaucoma drugs and 3 patients for developing blepharitis during the post-operative period, a total of 50 eyes of 48 patients (12 males and 36 females) were enrolled in our study.

The prednisolone group (group A) included 4 males and 20 females with a mean age of 55.86 ± 8.80 years, while the nepafenac group (group B) included 8 males and 16 females with a mean age of 54.75 ± 11.21 years (*P*-values 0.2 and 0.7 for gender and age respectively).

AS-OCT measurements for the punctal size (outer diameter, inner diameter and height) showed no statistically significant differences in any of the groups or between both groups throughout the study (Fig. 1) (Table 1).

The TMH and TMA at 2nd week post operatively showed statistically significant increase in measurements as compared to the preoperative measurements in both groups (*P* value <0.05) . However, this change did not persist throughout the remaining visits. The TMH and TMA distribution in both groups during all visits was statistically insignificant (Table 2). Changes in the height and area are illustrated (Fig. 2).

The number of patients complaining of tearing showed significant increase during the first follow up visit across both groups (Table 3). There were no statistically significant differences between both groups concerning the numbers of symptomatic patients during each visit.

We were able to detect punctal membranes in two patients. In patient 22 of the prednisolone group, this membrane was only detected by AS-OCT (see supplemental Digital Content 2a) but not clinically using slit lamp examination, a condition we like to describe as “occult punctal stenosis”. In patient 24 of the Nepafenac group, the membrane was detected both clinically and in AS-OCT (see supplemental Digital Content 2b). It is worth mentioning that both patients complained of epiphora althrough their follow up visits.

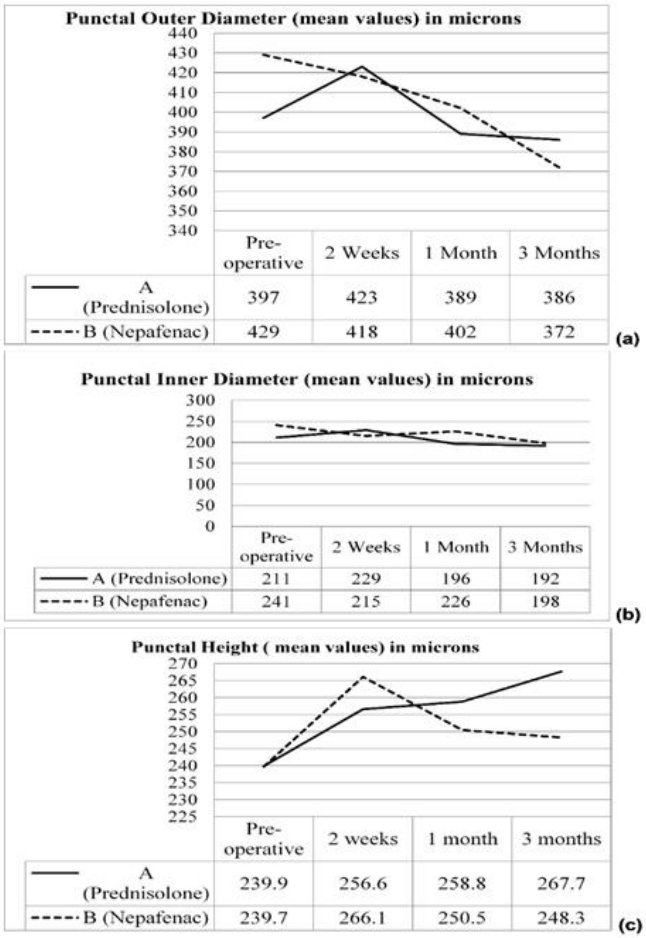


Fig. 1. Line graph showing punctal size changes over follow-up visits. (a) Outer diameter; (b) Inner diameter and (c) Punctal height

Table 1. Punctal size and tear film parameters changes between pre-operative and 3 months post-operative

	Value (Mean change ±SD)	**Group A Prednisolone**	**Group B Nepafenac**	***P*-value (of comparative analysis)**
Outer diameter (microns)	Mean±SD (Range) *P*-value	-10.27±146.3 (-75.15-54.6) 0.987	-56.25±194.06 (-142.3-29.79) 0.236	0.330
Inner diameter (microns)	Mean±SD (Range) *P*-value	-19.09±153.48 (-87.14-48.96) 0.79	-42.70±114.28 (-93.37-7.97) 0.18	0.43
Punctal height (microns)	Mean±SD (Range) *P*-value	27.82±109.33 (-20.66-76.29) 0.14	8.65±85.38 (-29.21-46.51) 0.66	0.2
TMH (mm)	Mean±SD (Range) *P*-value	-3.54±171.93 (-79.77-72.68) 0.338	20.85±86.04 (-17.30-59.00) 0.095	0.707
TMA (mm2)	Mean±SD (Range) *P*-value	-0.011±0.612 (-0.378-0.016) 0.55	0.003±0.020 (-0.005-0.012) 0.07	0.312

Table 2. Tear meniscus height and area changes between pre-operative and 2 weeks post-operative

	Value (microns)	Group A: Prednisolone	Group B: Nepafenac	*P*-value (of comparative analysis)
TMH	Mean±SD	50.3±143.9	101.7±108.3	0.205
	(Range)	(-13.5-114.1)	(53.7-149.7)	
	P-value	*0.046	*0.001	
TMA	Mean±SD	0.013±0.053	0.024±0.029	0.445
	(Range)	(-0.010-0.037)	(0.011-0.037)	
	P-value	*0.019	*0.001	

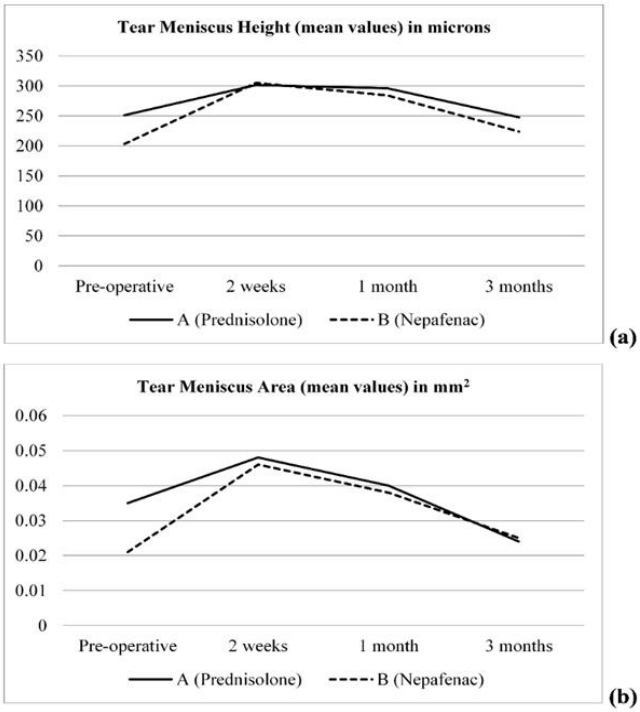


Fig. 2. Line graph showing Tear meniscus (a) height and (b) area changes over follow-up visits

Table 3. Number of symptomatic patients in both groups across the study

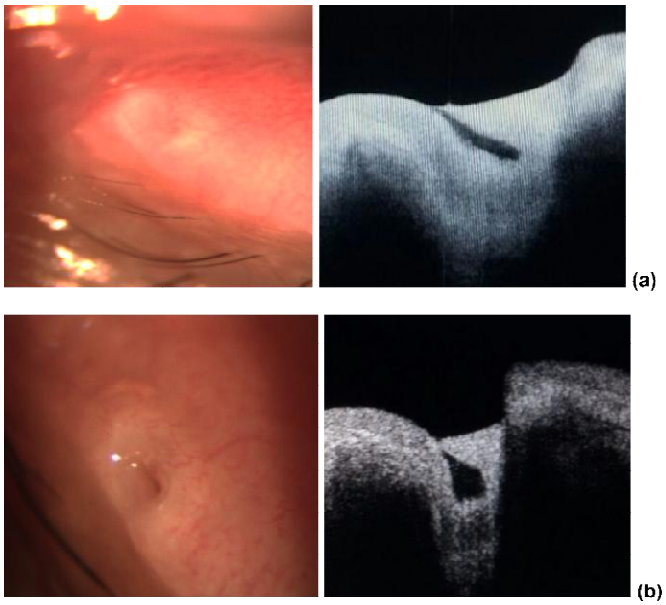
	Pre-operative	2 weeks postoperative	1 month postoperative	3 months postoperative
Group (A) Prednisolone	0	8	6	5
Group (B) Nepafenac	0	6	5	1
P-value	0.945	0.116	0.867	0.101

Figs. 3 and 4 further illustrate the AS-OCT changes in patients of both groups over the study period.

4. DISCUSSION

The current work compared the short term effects of preserved topical steroids (prednisolone) and NSAIDs (nepafenac) on the punctum size using AS-OCT, a subjective tool used for follow up.

Progressive punctal narrowing was observed in many cases of both groups, however, all the studied punctal parameters showed no statistically significant change in both groups throughout the follow up period (p value >0.05).



SDC 2. (a) Left: Punctal membrane slit lamp; Right: AS-OCT shows a punctal membrane; patient 24 in the nepafenac group
(b) Left: An apparently normal punctum on slit lamp; Right: AS-OCT shows a punctal membrane; patient 22 in the prednisolone group

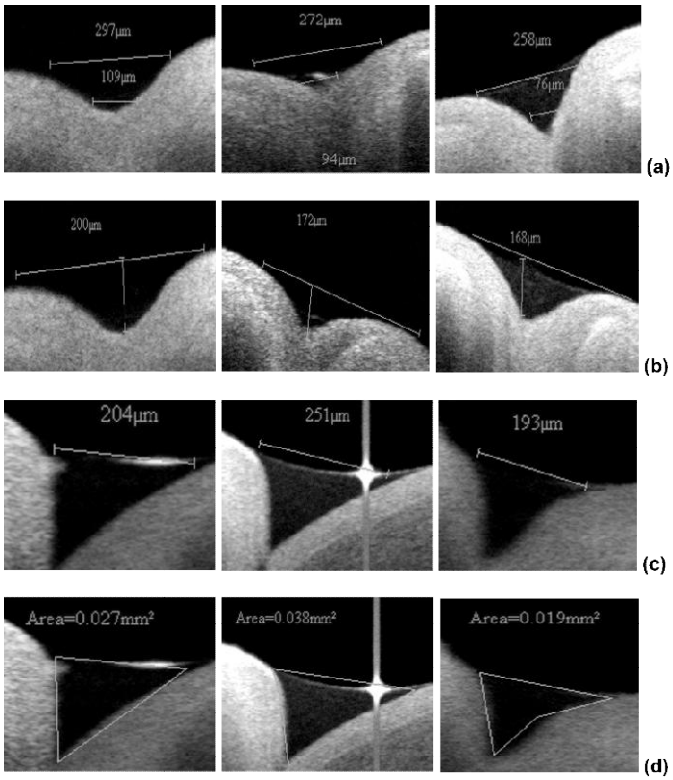


Fig. 3. AS-OCT changes in the (a) Punctal diameters (b) Punctal height (c) tear meniscus height and (d) tear meniscus area in patient 25 of the prednisolone group at pre-operative, 2 weeks and 3 months postoperative visits

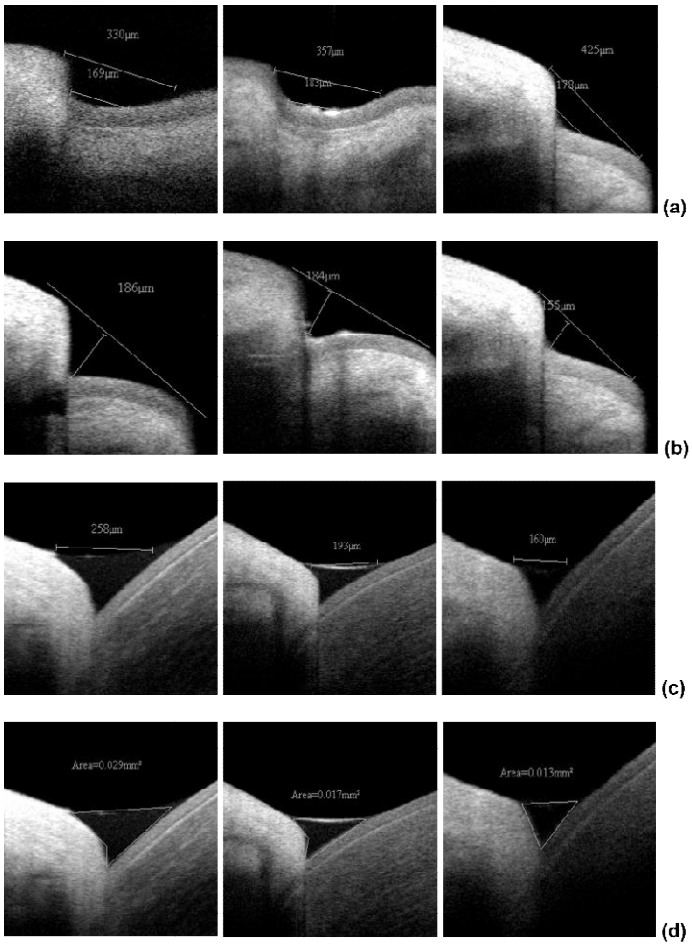


Fig. 4. AS-OCT changes in the (a) punctal diameters (b) punctal height (c) tear meniscus height and (d) tear meniscus area in patient 5 of the nepafenac group at pre-operative, 2 weeks and 3 months postoperative visits

In 1998, McNab reported prednisolone acetate to be one of the culprits in causing punctal narrowing [12] which disagrees with the current study .However, McNab's report included only 5 cases without defining their age group. Besides, the current study included patients between 40-70 years of age. It's possible that in old age, topical medications may act as a catalyst to the involutional changes that occur to the punctum [22-29].

In our study, the duration of treatment was constant at 3 weeks post-operative with an identified frequency of instillation. In McNab's report, the duration of the administered treatment was very wide (3 weeks- 20 years), thereby it's possible that prednisolone can cause stenosis in long-term treatment especially if used in high frequency. This finding may agree with the fact that the remodeling phase of wound healing where collagen contracture and scar reformation occurs usually starts 3 weeks after injury and continues on for years [24,25].

Finally, McNab did not define the method he used for identifying punctal occlusion in his patients. Many various clinical methodologies used for determining punctal size have been shown to be non-objective and inaccurate [26]. However, in the current study we used AS-OCT which was proven to be an accurate objective method [17-19].

The fact that most studies investigated and reported this effect with topical antiglaucoma drugs [27-29] incurs the possibility that this may be due to the long term nature of using these specific drugs and not due to the direct effect of

the drugs themselves, therefore it is possible that any topically administered drug for long term durations may cause the same effects.

Direct chronic tissue damage and/or the chronic low-grade inflammation after long term application of drugs may render components of the basement membrane zone immunogenic, giving rise to an autoimmune reaction resulting in the same sequence of events as in cicatricial pemphigoid [28,30].

Therefore, if topical prednisolone acetate is proven in future studies to cause punctal stenosis in long term durations of treatment, this might be the due to the preservative or the irritant effect of the drug causing cytotoxicity to the conjunctiva and fibrosis of the punctum. Similarly, non-steroidal eye drops as nepafenac will have the same effect. This notion is further supported by Williams et al. [31] and De Saint Jean et al. [32] who reported that in vitro pure topical antiglaucoma medications were significantly less toxic than the commercial drugs with BAC on cultured human tenon's capsule fibroblasts.

Our study reported a statistically significant increase in tear meniscus height and tear meniscus area (P value <0.05) by 2 weeks of topical treatment in both groups. These patients were still using their eye drops and this agrees with Baudouin et al., Baffa et al., as well as Marquardt and Schubert's work where they all showed that the tear breakup time was significantly reduced after using preserved topical antiglaucoma eye drops as opposed to preservative free treatment [5,33,34].

Previous studies reported that BAC had no effect on the tear film lipid layer, but causesa significant reduction in goblet cells as compared to preservative free eye drops [35,36].

It is presumed in the current study that the effect on the tear film might not cause a sheer increase in the aqueous secretion of tears, but rather the uneven distribution of tear film across the ocular surface which might be the reason of the detected increase in tear parameters by AS-OCT since only the central tear meniscus is measured. It is also possible that BAC disturbing the tear film by its surfactant effect causes reflex tearing and therefore an actual increase in our measured parameters [37].

The tear meniscus height and area did not show any significant statistical differences between measurements in the 3 months post-operative visit and the pre-operative evaluation. This leads to the presumption that the effect of BAC on the goblet cells and hence the inner mucoid layer of the tear film is only temporary when the medications are used for 3 weeks only.

A punctal membrane was detected by AS-OCT in 2 cases, one in each group, by 3rd month post operatively, however it was not clinically detected in one of them. This confirms the importance of OCT in detecting subclinical pathologies which could explain the presence of epiphora in patients with no clinically visible punctal pathology.

The relatively small sample size of the current study is a one of its limitations, thereby decreasing the statistical power of our study to 19%. Another limitation is the fact that although AS-OCT has proven its usefulness in punctal photography and assessment, the photography technique remains tedious since it requires good eversion of the punctum to be able to get an axial photo with the widest view of the punctum and therefore obtaining accurately measured parameters. Also, we are still miles away from obtaining an accurate, standardized measure of punctal size with OCT.

Moreover, the short duration of the topical treatment (3 weeks) and follow up (3 months) cannot validate the results for patients with longer durations of treatment and therefore a study design with a longer duration is substantial. However, this study aimed to evaluate postoperative topical medications which seldom exceeds 1 month and so the choice of 3 months as a cutoff period for follow up has been intended to unveil whether the effect of medications was temporary or permanent.

Another limitation is that we still have 6 symptomatic patients at 3 months, which although did not reach statistical significance, but carries a question of reliability on patient's own impression. This could be studied in the future by formulating a more precise questionnaire, particularly that OCT parameters declined by the end of the follow up period.

5. CONCLUSIONS

In conclusion, short term preserved prednisolone acetate and nepafenac eye drops have no significant effect on the lacrimal punctal size. BAC has a short term effect on tear film stability

observed as increased tear meniscus parameters on anterior segment punctal tomography.AS-OCT can objectively compare the effect of topical eye drops on punctal size and tear film measurements, it can also reveal clinically undetectable punctal membranes.

CONSENT

As per international standard or university standard, patient's consent has been collected and preserved by the authors.

ETHICAL APPROVAL

All authors hereby declare that the study has been approved by the Review Board of Ophthalmology department, Faculty of medicine, Cairo University. Data collection conformed to all local laws and was compliant with the principles of the Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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