

Original Research Article

The Effects of Post Cataract topical treatment on Anterior Segment Punctal Tomography: an OCT guided comparative study

Running title: Topical treatment &AS-Punctal Tomography

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 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

Text:

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

34 conjunctival scarring known as drug induced pemphigoid or pseudopemphigoid, in which
35 chronic allergic reaction leads to a marked and self-sustaining inflammatory process. ⁽²⁻⁴⁾
36 Preservatives also decrease the precorneal tear film stability ⁽⁵⁻⁷⁾ with subsequent worsening of
37 pre-existing dry eye. ⁽⁸⁾
38 It seems likely that similar changes may occur in the epithelium and subepithelial tissues of the
39 lacrimal drainage system, resulting in stenosis. Topical agents, including antiglaucoma
40 medications and antiviral drops as well as systemic medications such as fluorouracil and
41 docetaxel are now considered as risk factors for lacrimal system obstruction. ⁽⁹⁻¹⁶⁾
42 Anterior segment optical coherence tomography (AS- OCT) has been established as a new non-
43 invasive modality in punctal assessment. This was first demonstrated by Wawrzynski et al in
44 2014. ⁽¹⁷⁾
45 In 2015, a published work by Allam and Ahmed used this technology to establish normative data
46 in the Egyptian population as regards punctal size and morphology. ⁽¹⁸⁾
47 Moreover, en face AS-OCT was used to study the punctum and vertical canalicular sizes as a
48 step to establish normative data. ⁽¹⁹⁾
49 Topical steroids are established post cataract anti- inflammatory agents. ⁽²⁰⁾ However, NSAIDs
50 eye drops, have also proven their safety and efficacy as potent anti-inflammatory agents for post
51 cataract patients with better protection against post cataract cystoid macular edema. ^{(20,}
52 ²¹⁾ Moreover, they were never mentioned in the literature as potential etiology of punctal stenosis.
53 The current study aims at comparing the effects of short term preserved prednisolone acetate to
54 nepafenac eye drops on the punctal size as evaluated by AS-OCT.

2. Patients and Methods

The study has been approved by the IRB 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.

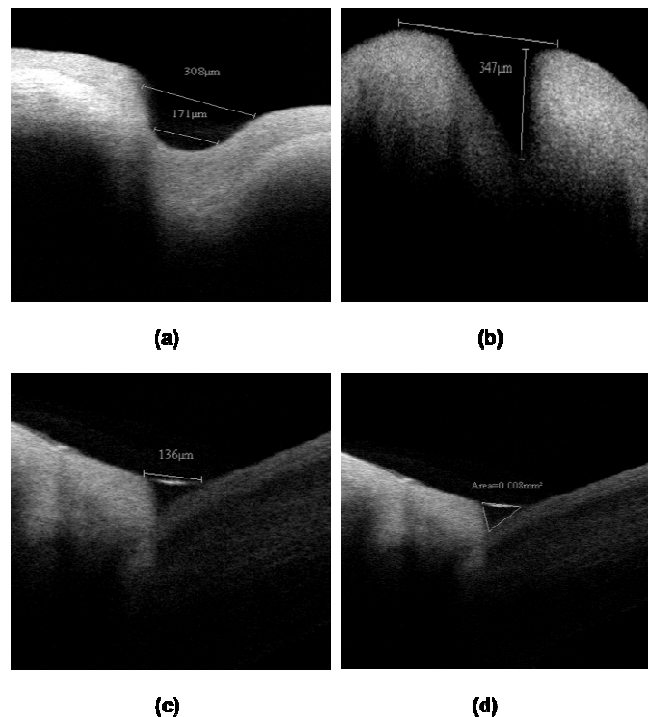
We excluded patients on chronic topical treatment (anti-allergic or anti glaucoma medications), patients with a clinically invisible punctum due to membrane or stenosis, patients already suffering of lacrimal problems or who had acquired any condition that may affect the lacrimal punctum during the duration 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

77 working distance. Imaging was done by a single investigator (R.S) to accurately measure 5
78 parameters (punctal inner and outer diameters, punctal height, tear meniscus height and area).
79 Post-operatively, patients were randomly assigned, using computer software to one of two
80 different post-operative treatment regimens.
81 Two patients whom were scheduled for bilateral cataract surgeries were not randomized to
82 treatment groups. However, each eye was assigned to a different group than the other eye.
83 In all postoperative visits, each patient had to answer a yes or no question regarding the presence
84 or absence of epiphora.
85 All patients received topical Gatifloxacin eye drops (4 times daily the first 5 days, then 3 times
86 daily until completion of a 3 week period) and fusidic acid viscid eye drops (once at night).
87 However in group A that included 25 eyes, patients received Prednisolone Acetate eye drops
88 while the remaining 25 eyes in group B, patients received Nepafenac 0.1% eye drops (both 4
89 times daily the first 5 days then 3 times daily for the rest of the 3 week period). All eye drops
90 used contained Benzalkonium Chloride (BAC) as a preservative in 0.05% concentration.
91 Patients were then examined using AS-OCT at 2 weeks, 1 month and 3 months postoperative.
92 All patients were photographed by a single investigator (Riham S. H. M. Allam) who was
93 blinded as to which group of treatment the patient was assigned.
94 The lower lid punctum was exposed by everting the medial part of the eyelid without pressure or
95 stretching, to bring the vertical canaliculus into the axial plane. A crossline scan (2mm× 2 mm)
96 was centered on the punctum for alignment; then a cross-scan was obtained.
97 For each examined eye 3 scans were obtained, and then the operator selected the images with the
98 deepest measurable diameters and with the clearest details. The outer (towards the lid margin)
99 and the inner (towards the canaliculus) diameters were measured using the distance measurement

100 tool. The depth of the punctum was obtained by drawing a line tangential to the lower lid margin
 101 across the punctal outer opening; then a perpendicular line was drawn until the base of the
 102 punctum was reached
 103 The junction of the punctum with the vertical canaliculus was determined by detecting the
 104 sudden narrowing in the punctal lumen diameter and/or the thinning of the lining epithelium
 105 which was then followed into the beginning of the vertical canaliculus, thus interpreted as the
 106 junction between the punctum and the vertical canaliculus. ⁽¹⁸⁾ The internal punctal diameter was
 107 then identified as the horizontal line drawn just above this junction. The tear meniscus height
 108 (TMH) and tear meniscus area (TMA) were also measured (see *supplementary document SDC*
 109 *1a-d*, which shows how the measurements of the punctal diameters, punctal depth, TMH and
 110 TMA were acquired).



111
 112 **SDC (1):** (a) AS-OCT of patient 5 of group B (Nepafenac group) showing the outer and inner
 113 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.

3. Statistical Analysis: Data were statistically described in terms of mean $\pm$ standard deviation ($\pm$ 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.

4. 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

135 The prednisolone group (group A) included 4 males and 20 females with a mean age of $55.86 \pm$
136 8.80 years, while the nepafenac group (group B) included 8 males and 16 females with a mean
137 age of 54.75 ± 11.21 years (P -values 0.2 and 0.7 for gender and age respectively).
138 AS-OCT measurements for the punctal size (outer diameter, inner diameter and height) showed
139 no statistically significant differences in any of the groups or between both groups throughout the
140 study (figure 1) (table 1).

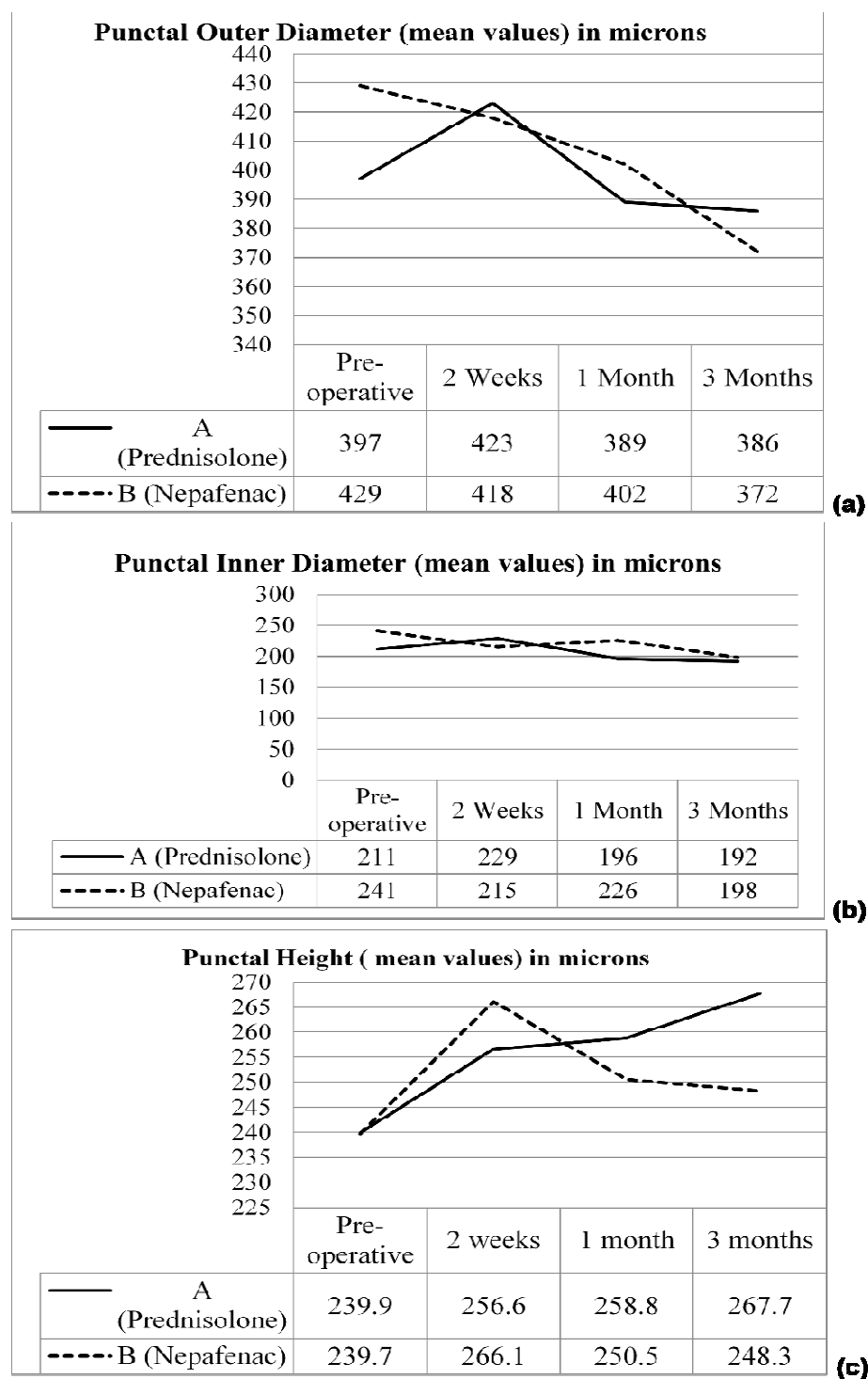


Figure (1): line graph showing punctal size changes over follow-up visits.

(a) Outer diameter; (b) Inner diameter and (c) Punctal height.

145

146 Table (1): Punctal size and tear film parameters changes between pre-operative and 3 months
147 post-operative.

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

148

149

150 The TMH and TMA at 2nd week post operatively showed statistically significant increase in
 151 measurements as compared to the preoperative measurements in both groups (P value <0.05).

152 However, this change did not persist throughout the remaining visits. The TMH and TMA
 153 distribution in both groups during all visits was statistically insignificant (table 2). Changes in
 154 the height and area are illustrated (figure 2).

155 Table (2): Tear meniscus height and area changes between pre-operative and 2weeks post-
 156 operative.

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

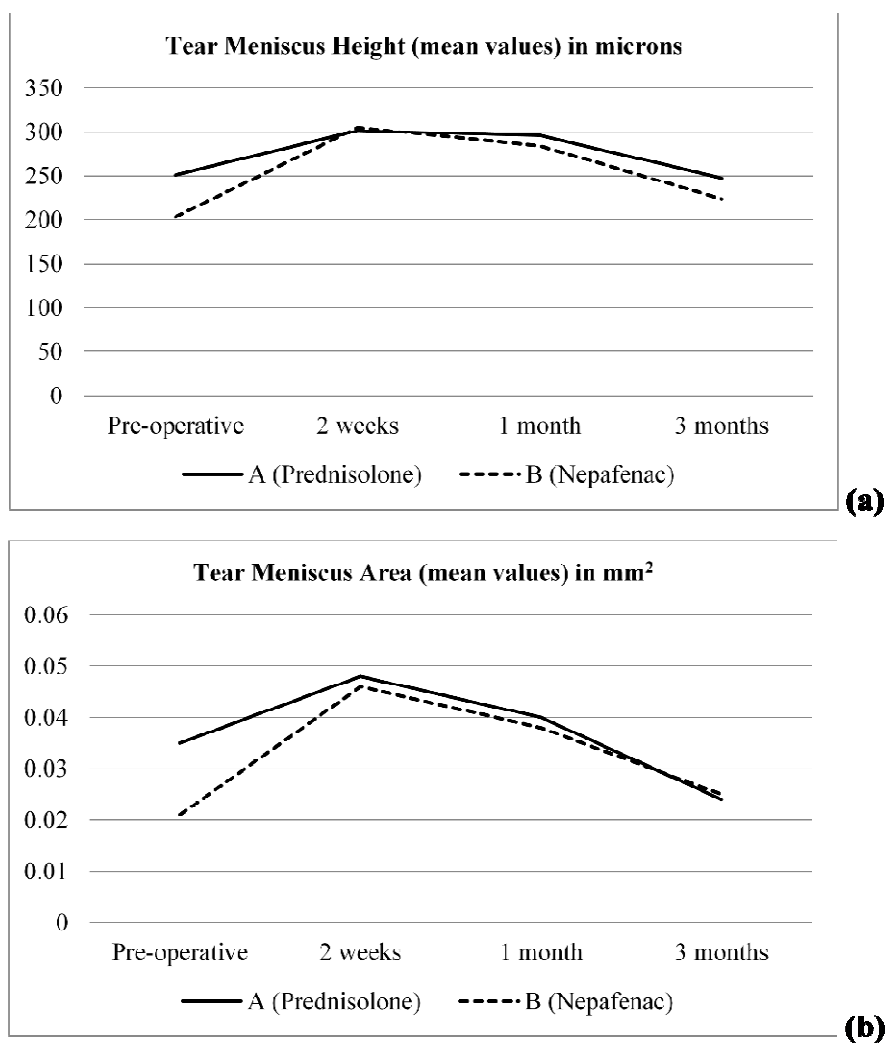


Figure (2): line graph showing Tear meniscus (a) height and (b) area changes over follow-up visits.

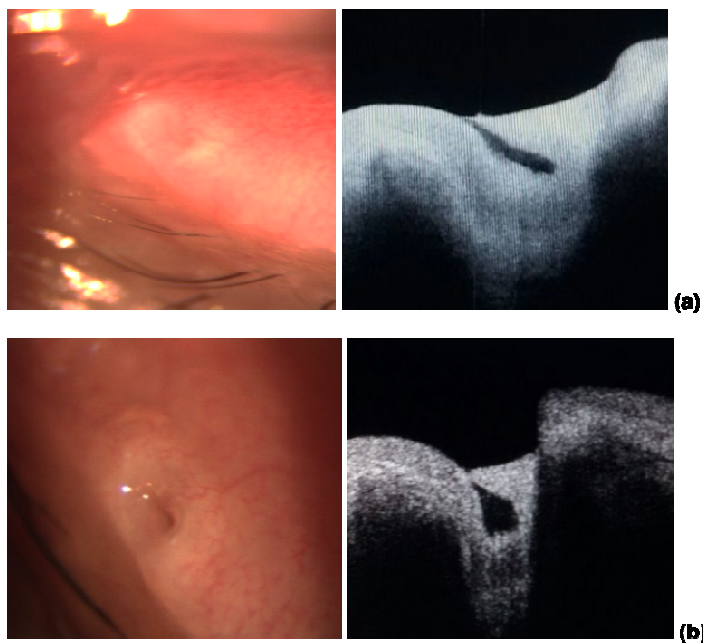
166 The number of patients complaining of tearing showed significant increase during the first
 167 follow up visit across both groups (table 3). There were no statistically significant differences
 168 between both groups concerning the numbers of symptomatic patients during each visit.

169 Table (3): number of symptomatic patients in both groups across the study

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

170

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



177
 178 **SDC (2):** (a) Left: Punctal membrane slit lamp; Right: AS-OCT shows a punctal membrane;
 179 patient 24 in the nepafenac group
 180 (b) Left: An apparently normal punctum on slit lamp; Right: AS-OCT shows a punctal
 181 membrane; patient 22 in the prednisolone group.
 182
 183 Figures (3 & 4) further illustrate the AS-OCT changes in patients of both groups over the study
 184 period

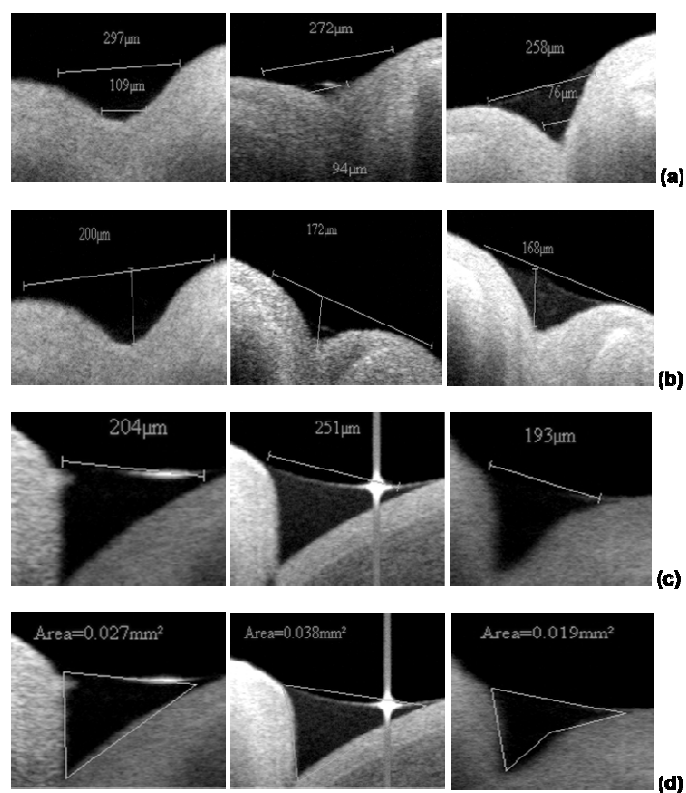


Figure (3): AS-OCT changes in the (a) Punctal diameters (b) Punctal height (c) tear meniscus height and (d) tear meniscus area in patient 25 of the prednisolone group at pre-operative, 2 weeks and 3 months postoperative visits.

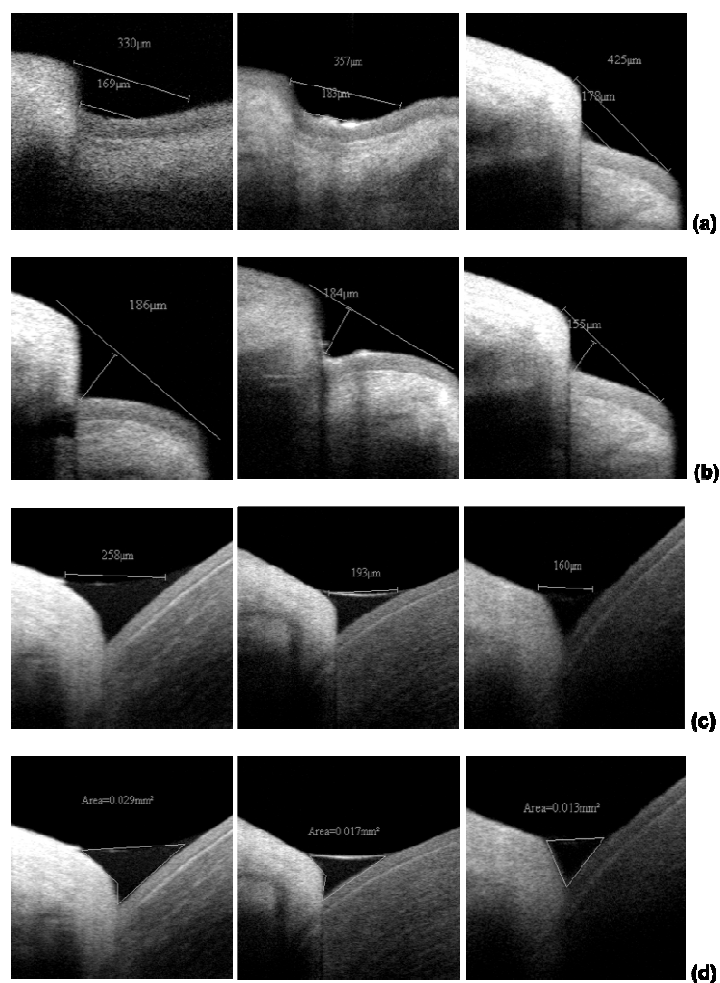


Figure (4): AS-OCT changes in the (a) punctal diameters (b) punctal height (c) tear meniscus height and (d) tear meniscus area in patient 5 of the nepafenac group at pre-operative, 2 weeks and 3 months postoperative visits.

5. 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.

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

202 In 1998, McNab reported prednisolone acetate to be one of the culprits in causing punctal
203 narrowing⁽¹²⁾ which disagrees with the current study .However, McNab's report included only 5
204 cases without defining their age group. Besides, the current study included patients between 40-
205 70 years of age. It's possible that in old age, topical medications may act as a catalyst to the
206 involutional changes that occur to the punctum. ⁽²²⁻²⁹⁾

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

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

217 The fact that most studies investigated and reported this effect with topical antiglaucoma drugs
218 ⁽²⁷⁻²⁹⁾ incurs the possibility that this may be due to the long term nature of using these specific
219 drugs and not due to the direct effect of the drugs themselves, therefore it is possible that any
220 topically administered drug for long term durations may cause the same effects.

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

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

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

237 Previous studies reported that BAC had no effect on the tear film lipid layer, but causes a
238 significant reduction in goblet cells as compared to preservative free eye drops ^(35,36).

239 It is presumed in the current study that the effect on the tear film might not cause a sheer increase
240 in the aqueous secretion of tears, but rather the uneven distribution of tear film across the ocular
241 surface which might be the reason of the detected increase in tear parameters by AS-OCT since
242 only the central tear meniscus is measured. It is also possible that BAC disturbing the tear film

243 by its surfactant effect causes reflex tearing and therefore an actual increase in our measured
244 parameters⁽³⁷⁾.

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

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

253 In conclusion, the punctal parameters mainly size are not affected by topical anti-inflammatory
254 drugs when used for short periods.

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

262 Moreover, the short duration of the topical treatment (3 weeks) and follow up (3 months) cannot
263 validate the results for patients with longer durations of treatment and therefore a study design
264 with a longer duration is substantial. However, this study aimed to evaluate postoperative topical
265 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.

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.

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