Topical Anti-glaucoma Medications and Lacrimal Drainage System Obstruction

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Abstract

***Purpose*:** To evaluate the effect of topical anti-glaucoma medications on lacrimal drainage system (LDS).

***Methods*:** In a prospective controlled blind observational case series, 627 eyes of 384 patients (219 males, 165 females) were studied. Data recording (demographics and history taking), allocation into case (on topical anti-glaucoma medications) and control (no glaucoma) group, and examinations (eye examination and dye disappearance test) were performed by a senior ophthalmology resident. Exclusion criteria were: epiphora prior to onset of treatment with topical anti-glaucoma medication (just for case group), history of long term usage of topical medications (besides anti-glaucoma medications in the case group), previous intraocular surgery, lacrimal surgery, ocular or periocular trauma, radiation therapy, mucous membrane disorder, eyelid margin malposition, and untreated blepharitis. Diagnostic probing and irrigation of lacrimal drainage system were blindly performed by an oculoplastic surgeon.

***Results*:** After exclusion, there were 130 eyes from 98 patients and 280 eyes from 178 patients in the case and control group, respectively. Case and control groups were matched. There were significantly more LDS obstruction (LDSO) in the case (26/130, 20%) than control (24/280, 8.57%) group (P=0.002). Upper LDSO was significantly more in the case group (P=0.018). Increasing age was associated with significantly more LDSO in just control group (P=0.029). Significant LDSO was found in the eyes taking Timolol + Dorzolamide (P=0.021) and Timolol + Dorzolamide + Pilocarpine (P=0.017) with duration of 2 weeks to 156 months.

***Conclusion*:** Patients on combination of topical anti-glaucoma medications are significantly at risk of developing LDSO. Upper LDSO is significantly more in patients on topical anti-glaucoma drugs.

***Keywords*:** anti-glaucoma medication, glaucoma, lacrimal drainage

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Introduction

Although the pharmacology of anti-glaucoma medications and their effect on conjunctival and sub-conjunctival cell populations have been extensively studied,[1-9] little attention has been given to the lacrimal drainage system effects associated with these medications. Long term use of anti-glaucoma medications induces changes in the conjunctival surface.[2] These changes may be associated with medications themselves, the preservatives, or the duration of topical treatment. Conjunctival metaplasia, decrease in goblet cells, increase in pale cells, macrophages, and lymphocytes within epithelium, and increase in fibroblasts, macrophages, mast cells, and lymphocytes in the substantia properia in the biopsy specimens are significant.[1-9] Multiple-drug topical therapy exerting the greatest effect on the degree of sub-clinical inflammation within conjunctiva.[5]

Some topical anti-glaucoma drugs may cause lacrimal punctal and canalicular stenosis or occlusion.[10,11] Lacrimal drainage system obstructions (LDSO) may also occur as a part of a more widespread cicatrizing process, described as drug-induced pemphigoid, and usually this occurs after long term usage of anti-glaucoma medications.[10]

There are a few reports[10,11] of patients whose LDSO was attributed to the topical anti-glaucoma medications. To our knowledge, there is no study that prospectively compares LDSO in patients taking anti-glaucoma medications with a control group.

The aims of this study were to evaluate the effect of different topical anti-glaucoma medications (single or multiple drops) on lacrimal drainage system, to find the prevalence of asymptomatic and symptomatic LDSO in this group of patients, and to compare the results with a control group in order to high light the at risk patients. This will help to treat this group of patients earlier, before advanced damage to the LDS.

Methods

In a prospective, controlled, blind observational case series, 627 eyes of 384 patients (219 male, 165 female) between March 2003 and May 2005 were enrolled. The case group included patients who were on topical anti-glaucoma medications. The control group included patients who had no history of glaucoma, were free of ocular disease, and were not using topical medications. Both groups were enrolled in a tertiary referral hospital (Rassoul Akram Hospital). Control group were recruited from different age and sex groups in a way to be matched with the case group with no consideration of other variables.

Informed consent was obtained from the all participants. Ethic committee approval was obtained.

Exclusion criteria were: epiphora prior to onset of treatment with topical anti-glaucoma medications (just for the case group, based on history), history of long term usage of topical medications (besides anti-glaucoma medications in the case group), previous intraocular surgery, prior lacrimal drainage system surgery, ocular or periocular trauma, radiation therapy, mucous membrane disorder, eyelid margin malposition, and untreated blepharitis.

Demographic data, history of systemic diseases, intraocular surgery, and usage of topical anti-glaucoma medications were recorded. External eye and slit lamp examinations and dye disappearance test were then performed. Data recording, eye examinations, and categorization of patients into case and control groups were performed by a senior ophthalmology resident (RR). Dye disappearance test was performed with a fluoresceine paper and assessment of remaining dye in the tear meniscus was done after 5 minutes.

Diagnostic probing and irrigation test was performed for all of the participants by an Oculoplastic surgeon (MBK) who was blind to the patients' data and group. External punctal opening size was assessed by slit lamp examination and diagnostic probing according to our previous report.[11]

Diagnostic probing of the canaliculi and irrigation of nasolacrimal duct was performed under topical anesthesia (tetracaine drop 0.5%, Sinadaru, Tehran) in the clinic. According to the severity of the external punctal stenosis, a 25-gauge needle, punctum finder, or punctum dilator was used to open and dilate the punctum and ampulla in order to introduce a #00 Bowman probe. A soft resistance to the probe which could not be

overcome defined as obstruction in canalicular system. Canalicular and common canalicular stenosis were characterized by total narrowing and/or membranous stenosis. Total narrowing of the canaliculi was defined as a snugly fitting probe (#00 Bowman) passing into canaliculus from ampulla to the sac. Membranous stenosis was defined as a resistance to the probe that could be overcome by altering the direction of the probe. The distance from the external punctum was recorded. Both upper and lower canaliculi were probed to differentiate canalicular from common canalicular obstruction. Complete and/or partial obstruction at the level of punctum, canaliculus and/or common canaliculus was defined as upper LDSO (U-LDSO).

Irrigation was performed with a 2 ml syringe, filled with normal saline and a 26 G (1.25") lacrimal canula to evaluate the lower lacrimal system. The canula was passed through the lower punctum into the lacrimal sac and the NLD was irrigated. A Complete NLD obstruction was inferred if saline regurgitated totally through the other punctum. Complete passage of fluid was considered as normal lacrimal drainage system. Forceful irrigation resulting in the passage of fluid into the nostril associated with partial reflux through the other punctum was defined as incomplete NLD obstruction. A complete and/or incomplete NLD obstruction was defined as lower LDSO (L-LDSO). Each eye was defined as a case in this study.

Main outcome measure was any type of LDSO with or without symptom of epiphora.

All data were recorded in especial data forms. Data were entered with soft ware SPSS MS Windows release 11.5 (Chicago). Chi-square test (X^2) and fisher's exact test were used to assess the effect of age interval, sex, systemic diseases, and topical anti-glaucoma medications on lacrimal drainage system. Independent sample T test was used to compare the mean age. Pearson correlation test was used to assess the correlation between age and frequency of LDSO.

Results

One hundred-sixty-seven eyes from 87 patients in the case group and 50 eyes from 25 patients in the control group were excluded mainly because of previous intraocular surgeries. Case group included 130 eyes of 98 patients who were on topical anti-glaucoma medications. Control group included 280 eyes of 178 patients. Two groups were matched regarding to age, sex, and associated systemic disorders (Table 1). There were significantly more LDSO in the case than control group (Table 1).

There was a weak positive and insignificant correlation between the age and frequency of LDSO in the case group. This correlation was stronger, positive, and statistically significant in the control group (Table 2).

The case and control groups with LDSO were also matched (Table 3).

Although symptomatic LDSOs were found to be more in the case group but they did not reach significance in analysis (Table 3).

There was significantly more U-LDSO in the case than control group (Table 3).

A wide variety of drug combination with different durations had been used. Statistical analysis of the effect of different topical anti-glaucoma medications on LDS was performed just for the drug regimens of more than ten participants (Table 4). Table 5 shows the groups with less than 10 eyes in each group of anti-glaucoma medications.

Table 1: Demographic data and frequency of lacrimal drainage system (LDS) obstruction (LDSO) in the case and control groups

	Case Group (130 eyes of 98 patients)	Control Group (280 eyes of 178 patients)	P values*
Age (year)			
Mean	56.52 (SD=17.26)	55.20 (SD=16.97)	0.465
Range	17 to 87	15 to 83	
Sex			
Male	49/98 (50%)	96/178 (53.93%)	0.524
Female	49/98 (50%)	82/178 (46.06%)	
Systemic Diseases	41/98 (41.83%)	66/178 (37.07%)	0.329
LDSO	26/130 (20%)	24/280 (8.57%)	0.002

*: Independent sample t-test for the age and Chi-square test for the other variables

Table 2: Frequency of lacrimal drainage system obstruction (LDSO) with increasing age in both case and control groups

	Mean age of the eyes with LDSO (year)	Mean age of the eyes without LDSO	Pearson correlation test
Case group (130)	57.15 (SD= 18.18)	56.37 (SD= 17.11)	r= +0.018, P= 0.836
Control group (280)	62.42 (SD= 12.34)	54.52 (SD= 17.20)	r= +0.130 P= 0.029

Table 3: Demographic data and the site of lacrimal drainage system obstruction (LDSO) in the case (26 eyes of 23 patients) and control (24 eyes of 22 patients) groups with upper LDSO (U-LDSO), lower LDSO (L-LDSO) or both based on diagnostic probing and irrigation

	Case Group	Control Group	P values*
Mean Age	57.15 (SD=18.18)	62.42 (SD=12.34)	0.241
Sex			
Male	11/23 (47.82%)	10/22 (45.45%)	0.785
Female	12/23 (52.17%)	12/22 (54.54%)	
Systemic Diseases	13/23 (56.52%)	7/22 (31.81%)	0.098
Symptomatic LDSO	12/26 (46.15%)	9/24 (37.80%)	0.578
U-LDSO	20/26 (76.92%)	9/24 (37.50%)	
L-LDSO	5/26 (19.23%)	12/24 (50%)	0.018
Both	1/26 (3.84%)	3/24 (12.50%)	

*: Independent sample t-test for the age and Chi-square test for the other variables

Table 4: Statistical analysis of the effect of topical anti-glaucoma medications (with more than 10 eyes at each group) on lacrimal drainage system (LDS) in comparison to the control group

	eye	Duration range (Month)	Mean duration (Month)	LDS Obstruction	P value (Chi-Square test)
Timolol+Dorzolamide	37	1 - 120 1 - 120	36.56±33.39 20.91±24.69	8/37 (21.62%)	0.021, Odd's ratio=2.941(95% CI= 1.215- 7.142)
Timolol	41	1 M - 120 M	25.34±28.97	6/41 (14.63%)	0.246
Timolol+Dorzolamide +Pilocarpine	17	3 - 156 0.5 - 60 1- 120	49.70±42.45 19.14±21.65 37.94±42.55	5/17 (29.41%)	0.017, Odd's ratio=4.444(95% CI= 1.445-13.698)
Timolol+Dorzolamide +Latanoprost	12	2 - 72 0.5 - 72 1 - 24	22.50±19.32 15.54±19.33 9.16±8.33	2/12 (16.66%)	0.290
Timolol+Pilocarpine	14	5 - 144 5 - 120	49.92±45.44 49.78±36.75	2/14 (14.28%)	0.356

Table 5: Effect of different topical anti-glaucoma medications (with less than 10 eyes at each group) on lacrimal drainage system (LDS)

	eye	Duration range (Month)	Mean duration (Month)	LDS Obstruction
Timolol+Latanoprost	4	0.5 – 24 0.5 – 6	11.25±9.27 2.25±2.23	2/4 (50%) upper LDSO
Timolol+Dorzolamide+Pilocarpine+Latanoprost	2	24- 60 24 - 60 12 - 36 18 – 24	48±20.78 mo 42±21.65 mo 28±13.85 mo 22±3.46 mo	0/2
Latanoprost	2	6,12	----	1/2 (50%) upper LDSO
Latanoprost+Dorzolamide	1	8 6	----	0/1

Discussion

Topical anti-glaucoma medications may induce some inflammatory and fibrotic changes in the conjunctival surface.[3-8]

It seems likely that the same changes could occur in the epithelium and subepithelial tissue of lacrimal drainage system, resulting in stenosis with increasing fibrosis and then occlusion.

Mc Nab[10] reported 14 patients on topical ocular medications (6 were on anti-glaucoma drops) who developed lacrimal punctal and canalicular obstruction. The duration of exposure ranged from 3 weeks to 20 years.[10] They concluded that lacrimal canalicular obstruction may occur after relatively short-term exposure to topical ocular medications or as a part of a more wide spread cicatricial reaction in patients on long-term medication.[10]

In our study, LDSO was found to be significantly more in the case group (Table 1). Age, sex, and history of systemic diseases were not different between case and control

groups in general and in eyes with LDSO in both groups (Tables 1, 3).

Upper lacrimal system is close to the conjunctiva and fornix. Therefore, it is expected to be more affected by topical medications than lower lacrimal system. Parallel to the previous report,[10] upper LDSO was significantly more in the case than control group (Table 3).

A wide variety of topical anti-glaucoma medications with variable durations had been taken by patients in this series. Some patients in the present series had been on topical medications for many years and the effect may be a dose-related phenomenon. In those patients on drops for a much shorter period, it seems more likely that it may be an idiosyncratic reaction.

Two combinations had significant association with LDSO: Timolol + Dorzolamide and Timolol + Dorzolamide + Pilocarpin (Table 4). This study showed that combination therapy has more adverse effect on LDS than single therapy. Timolol and Dorzolamide were present in both combinations. Timolol has been reported to cause lacrimal obstruction[10] and conjunctival fibrosis[1], whereas there is no published data regarding to these complications associated with Dorzolamide.

Although we cannot suggest which drug or preservative or disease process is responsible for LDSO associated with topical anti-glaucoma medications, our data suggest another complication from the use of these medications in the management of glaucoma.

Dalgleish[12] syringed a large series of asymptomatic patients and found that approximately 9% of males and 10% of females over the age of 40 years had nasolacrimal duct and sac obstructions. There is, however, no data for the prevalence of symptomatic or asymptomatic upper LDSO in the literature. We found that 8.5% ($^{24}/_{280}$) of control group aged from 17 to 83 years to have symptomatic and asymptomatic LDSO (Tables 1, 3). Type of obstruction was L-LDSO in 62.5% of them, which seems to be resulted from aging. Increasing age in the control group was significantly associated with increasing frequency of LDSO (Table 3). The type of LDSO and its significant correlation with increasing age are parallel to the literature regarding to involutional LDSO in normal subjects.[13]

Whereas, the type of LDSO in the case group, which was significantly more at upper LDS, and absence of correlation with age show that the etiology is different and may be due to the effect of anti-glaucoma medications.

Since tear secretion decreases with age, many older people will have LDSO with no symptoms.[13] This seems to be the reason why epiphora was observed in about one third of the case and control group with LDSO (Table 3). Patients on anti-glaucoma medications may develop water eye due to irritating effect of the medications and not LDSO. Although, we tried to lower this bias through complete eye examination and specific LDS tests, the symptom could still be attributed in some degree to the anti-glaucoma medications.

Conclusion

In conclusion, results of this study showed that patients on combination therapy with topical anti-glaucoma medications are significantly at risk of developing LDSO. The risk of obstruction is almost twice as general population and significantly more in the upper LDS. Widespread use of these medications necessitates awareness of physician and early recognition and treatment of this side effect to prevent the need for advanced late lacrimal drainage surgeries.

This study included all patients who had used different types of topical anti-glaucoma medications. This made the sample size of each group to be too small to definitely draw a conclusion for all groups of medications. A larger sample size of each group is necessary to confirm the results. The recorded symptoms might somehow be attributed to the topical medications and not LDSO which make the diagnosis of symptomatic LDSO difficult.

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