Influence of local application of glaucoma medications-travoprost eye drops on patients' tear film function

Chengpu Zhang*
Department of Ophthalmology, People's Hospital of Zhengzhou, Zhengzhou, China

Abstract: This study discussed about the influence of local application of glaucoma medications--travoprost eye drops to patients' tear film function. We selected 24 patients, 45 eyes with primary open-angle glaucoma or intraocular hypertension. All of the patients topically used the travoprost eye drops for one time every night. After and before the pharmacy, we proceeded 1, 2, 3 mo lines symptom score and Schirmer's test (St), corneal fluorescein staining (FL), breakup time of tear film (BUT). Average value of symptom score and FL of all the patients before pharmacy were 1.32±1. 55, 0.42± 0.68, and 1, 2, 3mo after pharmacy were respectively 2.68±1.59, 0.96±0.81; 4.97±1.62, 1.46±0.62; 6.21±1.33, 1.88 ±0.44. Symptom score and FL of 1, 2, 3 mo patients after pharmacy were all prominent higher than it before pharmacy (P=0.00), and it gradually increased. The average value of patients symptom BUT and St before pharmacy were (7.71±0.87s), (8.32±2.63mm /5min) and 1, 2, 3 mo after pharmacy were respectively (6.93±1.17s), (7.69±3. 33mm /5min); (5.48±1.29s), (6.79±2.94mm /5min); (4.33±1.83s), (5.98±3.11mm/5min). BUT and St value after pharmacy were prominent all lower than the level before pharmacy (P=0.00). And it gradually reduced. Short-term use of travoprost eye drops would aggravate the corneal irritation of patients, and decrease the tear film stability and tear secretion.

Keywords: Glaucoma, intraocular hypertension, travoprost eye drops, tear film function.

INTRODUCTION

Glaucoma is an eye disease with decreased vision and even blindness because of abnormally rising of the intra-ocular pressure and the intraocular hypertension exceed the ceiling for the eye to tolerate then cause the optic nerve and view damage. Local application of the intraocular pressure (IOP) drugs is the important way to treat glaucoma and intraocular hypertension, and some of them need to be used all life time, therefore, its security is most concerned. The studies found that, 20%-40% patients with long-term local application of the glaucoma eye drops might have symptoms such as: Red eye, aningeresting, foreign body sensation, burning senseation, photophoby and lacrimation and it hinted the ocular surface damage in varying degrees (Hui and Juret, 2011; Jiaona *et al.,* 2014; Hong and Pinghua, 2013). Travoprost eye drops (0. 04g/L travoprost eye drops contain with benzalkonium chloride) is a kind of new prostaglandin preparations and it can enduringly give play to the effect of falling the IOP, therefore, the compliance of patients are high, but it is possible to occur the side effect. For this purpose, we observed the ocular surface damage condition of the patients with glaucoma or intraocular hypertension who were treated with travoprost eye drops for short-term local application, in order to further evaluate the security of travoprost eye drops. (Yeshuang *et al.,* 2014; Lina and Haibo, 2009)

Corresponding author: e-mail: zcpzhangp@163.com

MATERIALS AND METHODS

Patients selection

We collected the patients with intraocular hypertension or primary open-angle glaucoma in People's Hospital of Zhengzhou from March 2013 to May 2014 and these cases needed using travoprost eye drops. Standard of patients: having no obvious anomaly on conjunctiva and cornea under the slit lamp examination; Having no obvious other ocular surface disease, such as: Severe xerophthalmia, conjunctivitis, keratitis, blepharitis ciliaris and other ocular region disease which might influence tear film function, such as uveitis, etc; Having no ocular region pharmacy history; having no ocular region operation history; excluding the patients with severe systemic disease. We collected 24 patients within 45 eyes by follow-up visiting 3 mos and the age was in 22-72 (average 56) years. Among them, there were 16 male cases 31 eyes and 8 female cases 14 eyes. The IOP was in 24-33 (average 27.58±3.47) mmHg. This study was approved by Ethic Committee of the People's Hospital of Zhengzhou. Patients have provided their written informed consents.

Therapeutic method

Ophthalmic testing: Includes patients vision, slit lamp, fundus, non-contact intraocular pressure measurement and St, BUT testing, FL, etc. The question about whether the patients had the 8 subjective symptoms of xerophthalmia and its order of severity was asked through a kind of standardization questionnaire and the 8 symptoms were

graded: foreign body sensation, burning senseation, eye keenly feel, easy to be tired, eye bilges feeling, photophoby, red eye, aningeresting. The standard for evaluation was according to the literature (Wang, 2007). The patients were treated by travoprost eye drops (0.04g/L travoprost and corrosion remover benzalkonium chloride, American Alcon Laboratories, Inc) each eye with one drop at 7:00-9:00 in every night and each eye drops should be dropped in conjunctival sac. We uninterruptedly dropped the travoprost eye drops into patients until 3 mo, and respectively checked in the symptom score of the patients in 1, 2, 3 mo before and after pharmacy. The symptom score were including, vision, BUT, FL, St and IOP.

STATISTICAL ANALYSIS

Data analyses were performed using SPSS 13.0 software. Variance analysis of paired data was used, $P<0.05$ was considered to have difference in statistics.

RESULT

IOP

The average basic IOP of patients was 27.58 ±3.47mmHg, and the IOP after using the travoprost eye drops for 1, 2, 3 mo were respectively 16.97±3.28, 17.66±3.75, 17.24 ±3.36mm Hg. It found that, the IOP after pharmacy was prominent lower than basic IOP. It had a significant difference in statistics ($P<0.01$) and it showed that, the travoprost eye drops could effectively reduce the IOP of patients.

Patients symptom score and tear film function

There had a significant difference of subjective symptom and tear film function of the patients before and after treatment and it showed that, the travoprost eye drops had a side effect to patient's eyes (table 1).

DISCUSSION

Glaucoma is a eye disease which is one of the serious threat to human visual function in the world today. IOP one of the important hazards to cause the occurrence and development of the glaucoma, and nowadays, the first choice to treat glaucoma is to reduce IOP by using operation or drug therapy. However, many correlative reports showed that local application of glaucoma medications for long time could influence the ocular surface. Robert J, *et al* (Robert J *et al*., 2004) found through the animal experiment that the glaucoma medications containing benzalkonium chloride as the corrosion remover would damage the cornea epithelium and cause the reduction of the corneal epithelial cells quantity, such as 5g/L timolol, 0.05g/L latanoprost, 20g/L dorzolamide, etc. Researches showed that, slather of glaucoma eye drops might cause the damage of conjunctiva and cornea epithelium, lead to chronic inflammation of conjunctiva and then result in the occurrence and development of the xerophthalmia. In the process of local application in eyes, conjunctiva and cornea tissue play function as a semi permeability protective screen, and conjunctiva tissue may occur the chronic inflammation because of the chronic irritation of the medicine. Then it will lead to the changes such as, epithelial cell keratinize, scarring and neovascularization, etc (Baudouin *et al*., 1994). Therefore, the adverse effect to ocular surface caused by local application of the glaucoma medications is inevitable in theory.

Influence of glaucoma medications can mainly generalize to two aspects, including, the influence caused by corrosion remover and the influence caused by medicine itself. The bases of travoprost eye drops are: Corrosion remover 0.1g/L benzalkonium chloride and 0.04g/L travoprost. Our research showed that, after using the glaucoma medications, dry eye symptoms appear; the breakup time of tear film shortened; tear secretion reduced; cornea staining aggravated. It was showed that, the local application of glaucoma medications would cause the xerophthalmia. Combining with the literature, the influences of corrosion remover to ocular surface may mainly contain two aspects above: (1) Inflammation factor. As everybody knows, glaucoma medications with benzalkonium chloride as a corrosion remover will cause the change of ocular surface (Wilson W *et al*., 1975; Kuppens E *et al*., 1995; Jinghua *et al*., 2007), including, reduction of conjunctiva goblet cell, augment of conjunctival epithelium collagen composure, increase of conjunctiva blood vessel macrophage, fibrocyte, lymphocyte and mastocyte, and diffusion and infiltration of skin reaction factor. The toxic effect of corrosion remover or the secondary change of the inflammatory response, which may cause the high expression of skin reaction factor need further study. (2) Apoptosis mechanism. Some researches reported that, benzalkonium chloride in high concentration caused the necrocytosis of conjunctiva, and benzalkonium chloride in low concentration induced the increase of apoptosis (Debbasch *et al*., 2001). The mode of action is: benzalkonium chloride can implant cytomembrane of cornea and conjunctiva cell, and it will cause the ion resistance variation of the cytomembrane then lead to the increase of cytomembrane permeability; further, it causes the apoptosis and death of the cells. The damage of it to conjunctival epithelium cell shows the dose-dependent (Debbasch *et al*., 2001; Christophe *et al*., 2007), and it also shows dose-dependence to toxic effect of keratocyte.

Travoprost is a new kind of prostaglandins (PG) medicine with an altitudinal selectivity and appetency to PGFP receptor, and it is the analogue of PGF2α. It is a total excited drug. Its mechanism to fall the IOP is: It can be hydrolyzed to active free acid by corneal hydrolase after

Table 1: Comparison of symptom score and tear film function of patients before and after drug therapy

Observational index	Prior treatment	Post-treatment 1mo	Post-treatment 2mo	Post-treatment 3mo	F	P
Symptom score	1.32±1.55	2.68±1.59	4.97±1.62	6.21±1.33	27.65	0.00
BUT(s)	7.71±0.87	6.93±1.17	5.48±1.29	4.33±1.83	20.74	0.00
FL	0.42±0.68	0.96±0.81	1.46±0.62	1.88±0.44	6.86	0.00
St (mm/5min)	8.32±2.63	7.69±3.33	6.79±2.94	5.98±3.11	14.98	0.00

ocular region pharmacy; the free acids widely distribute in the ocular tissue; the PGFP receptor in ciliaris and trabecula cell will be activated when the free acid combine. The activation will cause the effects above: the ciliaris slack and gap of the fascicle increase and collagen reduce I, III and IV type of matrix metalloproteinase increase. The metalloprotease can relieve the extra cellular matrix in the approach of uvea sclera aqueous fluid outflow and reduce the resistance of aqueous fluid outflow. It can increase the uvea drain but not influence the production of the aqueous fluid (Song *et al.*, 2010). In addition, free acid of travoprost can direct act on the eye trabecula cell and increase the aqueous fluid outflow and reduce IOP through the pressure sensitive outflow pathway. It is reported that, the function of PGAs medicine to decrease the IOP is not influenced by the circadian rhythms and it can also fall the IOP at night. Through that, IOP fluctuate can be reduced all day and night, and damage effect of optic nerve can be reduced.

CONCLUSION

The clinical observation found that all the patients appeared ocular surface damage in a short time by using glaucoma medications through, and it was to say that the ocular surface was influenced by the medicine in a short time. The cornea stimulation symptom of patients increased with 1 mo local application and the estimated value of BUT and magnitude of basic tear secretion gradually declined. Therefore, the inspection of ocular surface function before pharmacy and in the early phase after pharmacy is necessary for the patients who will be partly treated with glaucoma medications for a long time. Reduction of the drug use frequency and improvement of the corrosion remover is the effective means to solve the problem of glaucoma medications on ocular surface damage. Nowadays, there have no glaucoma medications without corrosion remover in clinic adhibition and it only can realize through combined application of artificial tears or eye drops and oculentum, which can protect ocular surface cornea. Therefore, in the actual clinical work, most of the ophthalmologists should pay attention to the suggestion that the patients should use the medicine to prevent ocular surface damage if they should use the glaucoma eye drops for a long time. It can not only remit all kinds of discomfort caused by drug-induced xerophthalmia and improve patients' living quality, but also can maintain the form and function of the normal ocular surface. There's no doubt that, in this experiment the lack of control group and less of sample size influence our further research.

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