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THE EFFECT OF TOPICAL MEDICATION CONTAININGBENZALKONIUMCHLORIDE ON OCULAR SURFACE DISEASE INGLAUCOMA PATIENTS

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ABSTRACT---Background, *The main cause of the emergence of dry eye and ocular surface disease (OSD) is strongly suspected due to the preservative component of topical medication in the form of benzalkonium chloride(BAK).Various complaints such as uncomfortable, teary, redness, burning and foreign object sensation, glare, often blinking and intermittent blurred vision has-been reported as part of OSD.*

Objective: *The study aimed to investigate the effect of topical medication containing BAK on ocular OSD in glaucoma patients*

Method: *Subject who has been using topical antiglaucomatous medication containing BAK and artificial tears were examined for tear film break up time (TBUT), S I test and corneal staining. Sucject were allowed to close the eyes, then positioned in front of the slit-lamp biomicroscope. Regression test was used to analyze the correlation between each variable.*

Result: *TBUT and S I test were decreased, and corneal staining score was increased, furthermore, BAK is significantly correlated with all of the examination result by using regression test. The effect of the amount and duration of BAK used is significantly correlated with TBUT (p = 0.004). The effect of the amount and duration of BAK used insignificantly correlated with S I test (p = 0.043). This study also has R value as 0.901; >0.05, shows the amount and duration of BAK used is strongly affect TBUT, S I test and corneal staining score.*

Conclusion: *BAK has strong correlation on the event of ocular surface disease.*

Keywords---*benzalkonium chloride, glaucoma, ocular surface disease, Schirmer I test, corneal staining.*

I. INTRODUCTION

Glaucoma is reportedly the leading cause of irreversible blindness in the world, affecting >70 million people worldwide(Leung, Medeiros and Weinreb, 2008).This disease is caused by a group of optic neuropathies that lead to progressive degeneration of retinal ganglion cells. Damage to these neurons results in what is called ‘‘cupping’’ of the optic disk and vision loss(Halasz *et al.*, 2019).The main treatment of glaucoma is the use of topical medication, and often can’t be treated with a single treatment. In a data from the use of topical medication in patients with

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glaucoma in the United States, 49-59% of patients also have dry eyes and ocular surface disease (OSD)(Zhang *et al.*, 2019).

The main cause of the emergence of dry eye and OSD is strongly suspected due to the preservative component of topical medication in the form of benzalkonium chloride(BAK). This additional preservative also functions as bactericidal and increases drug penetration, but can have an unfavorable effect, causing additional complaints and OSD which affecting therapy compliance (Zhang *et al.*, 2019).

Various complaints such as uncomfortable, teary, redness, burning and foreign object sensation, glare, oftenly blinking and intermittent blurred vision has been reported as part of OSD. This occurs due to disruption in the tear, conjunctiva land corneal upper layer with the sign of reduced tear film break up time (TBUT)and Schirmer I test (S I test), also the present of corneal staining(Moss, Klein and Klein, 2000; Kaštelan *et al.*, 2013; Amparo, Schaumberg and Dana, 2015).According to the facts, this study aim is to investigate the effect of topical medication containing BAK on ocular OSD in glaucoma patients.

II. METHODS

This is a cross sectional observational analytic study in the glaucoma division outpatient clinic of Department of Ophthalmology, dr. Soetomo General Hospital Surabaya. This study been held in one month, August 2019. Each subject recruitment and variable examination were conducted at the same day. Ethical clearance was conducted from Ethical Committee Dr.Soetomo Hospital, Surabaya.

After been informed and sign a consent of study. One of the eye were evaluated in order of S I test, TBUT and corneal staining examination. Firstly, without topical anesthesia, Schirmer paper was placed in inferior fornix at lateral area, then after 5 mm, data we recollected in mm unit, as shown by line marker at the paper. Following S I test, TBUT examination were performed by using preservative free sodium fluoresce in 2% stripe and one drop of irrigation water were instilled in the inferior fornix. Subjects that are consist of 23 female and 3 maen were allowed to close the eyes, then positioned in front of the slit-lamp biomicroscope. Once optimal position and lighting in cobalt blue filter is obtained, then subject were instructed to open the eyes, and TBUT were evaluated in second unit.

Subject were instructed to feel comfortable enough to open the eyes for corneal staining evaluation. Corneal staining evaluation uses score protocol from National Eye Institute which divided corneal area into 5 region and certain grading score by its fluoresceinstain. Regression test using SPSS software was used to analyze the correlation between each variable.

III. RESULT

Subjects have been using topical topical antiglaucomatous medication containing BAK for at least 3 months and also artificial tears containing sodium chloride, kalium chloride, and polyquaternium-1 (PQ-1).The more BAK is used, the lower TBUT value and vice versa. The effect of the amount and duration of BAK used is significantly correlated with TBUT ($p=0.004$).The more BAK use, the lower S I test value and the other way around. The effect of the amount and duration of BAK used is significantly correlated with S I test($p=0.043$).

The more BAK use, the highest corneal staining score. The effect of the amount and duration of BAK used is significantly correlated with corneal staining score($p=0.043$).This study also has R value as 0.901; >0.05, shows the

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amount and duration of BAK used is strongly affect TBUT, S I test and corneal staining score. R^2value is 0.812,indicatesthat the amount and duration of BAK used is able to predict the incident of OSD as 81.2%.

IV. DISCUSSION

The result of this study found than TBUT was significantly reduced from baseline by preserved carteolol ($p<0.05$), and non-preserved carteolol usage shows no significant change in TBUT. Another study examined 40 subjects, divided into 2 groups of using anti glaucomatous containing BAK for more and less than 20 weeks, it was found that there were significant correlations between duration of therapy with Schirmer test ($p=0.002$),TBUT ($p=0.004$), Ferning test ($p=0.035$), also correlated with incidence of dry eye syndrome. Another study evaluated 30 subjects using latanoprost containing BAK with abnormal values of tear osmolarity, corneal fluorescein staining, TBUT, and subjective discomfort then switched the therapy with tafluprost preservative free, and reexamined the subjects after 6 and 12 weeks, the result showed tear osmolarity decreased, TBUT increased and discomfort decreased significantly($p<0.005$) (Januleviciene, Derkac and Grybauskiene, 2012).

BAK has detergent molecule, which disrupts lipid layer of bacteria, so it works as preservative but also disrupts lipid layer of ocular surface and lipid layer of tear film. This effect induces inflammation by increasing tumor necrosing factor(TNF), interleukin (IL)-1,5IL-10, IL-2 and C-reactive protein (CRP)(Georgiev *et al.*, 2011; Kaštelan *et al.*, 2013; Artini *et al.*, 2018).Disrupted tear lipid layer causing TBUT to decrease, and the layer below, the aqueous layer, tends to have more evaporation. On the other hand, inflammation on ocular surface also increase tear osmolarity and corneal epithel neurotoxixity then induces vicious scircle on lacrimal gland causing decreased aqueous production of tear film and those mechanism could alter the S-1 test(Rosin and Bell, 2013; Marques *et al.*, 2015; Fidalia, Bahar and Rizki, 2019).

Some studies showed that BAK has no significant effect for Schirmer test, corneal esthesiometer and subjective complain as noted with ocular surface disease index (OSDI) quesionaire (Mathews *et al.*, 2013). On the other hand, our study result was in line with several previous studies as described by Matthews *et al.* in his study, using 123subject consist of glaucoma subject and glaucoma suspect with topical medication of glaucoma showed that corneal staining significantly higher in glaucoma subjects due to number of medication ($p<0.001$)(Mathews *et al.*, 2013). Previous study assed 30 healthy subjects to compare the tolerance of 2% carteolol with and without preservatives in short term use. Examination were performed before, 30, 60, 180minutes and 3 days of after presertative treatment. After 5 days washout, examination were performed with the non preservatives drug.

Disrupted tear film lipid layer increases tear evaporation and affect the protection function of tear film, causing irregularity and disepithelization of cornea and shows positive stain with 2% fluoresce in(Walimbe *et al.*, 2016).All subject has been also using artificial tears with sodium and kalium chloride and PQ-1. PQ-1 itself has toxicity effect to ocular surface, despite the effect is not as great as BAK, indicates currently, this using of artificial tears has not covered the ocular surface disease issue regarding the usage of ant glaucomatous medication containing BAK(Shaarawy *et al.*, 2014).

V. CONCLUSION

In this study it is concluded that the amount and duration of BAK has strong correlation on ocular surface disease manifestation, as TBUT, S I test, and corneal staining score.

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Table 1: Effect of BAK on TBUT

Parameter	The lowest	The highest	Mean	Standard Deviation	Regression Test
Total BAK amount (mcg)	558	58692	1.23×10^4	13334.16	0.004*
TBUT (second)	1	6	3.74	1.65	

Table 2: Effect of BAk on S I Test

Parameter	The lowest	The highest	Mean	Standard Deviation	Regression Test
Total BAK	558	58692	1.23×10^4	13334.16	0.043*

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amount (mcg)					
S I test (second)	1	9	4.51	2.01	

Table 3: Effect of BAK on *Corneal Staining*

Parameter	**The lowest**	**The highest**	**Mean**	**Standard Deviation**	**Regression Test**
Total BAK amount (mcg)	558	58692	1.23×10^4	13334.16	0.014*
Corneal staining score	1	9	5.03	2.008	

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