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# Influence of artificial tear related with conjunctival goblet cell density in glaucoma patients with latanoprost therapy



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## ABSTRACT

**Purpose:** To know influence of artificial tear related with conjunctival goblet cell density in glaucoma patient with latanoprost therapy.

**Method:** Pre-posttest design with expanded randomized study. This study was performed at Eye Policlinic Sanglah Public Hospital Denpasar and Bali Mandara Hospital from October until December 2015. Forty eyes were taken for impression cytology specimen to search goblet cell density before and 30 days after therapy. Mean difference of goblet cell changes before and after therapy between case and control analyzed with independent t-test.

**Results:** There were enhancements of conjunctival goblet cell mean density on group with artificial tear before and after therapy 83 + 97 cell/mm<sup>2</sup> to 92 + 88 cell/mm<sup>2</sup>. There was reduction of conjunctival goblet cell mean density of group without artificial tear from 144 + 169 cell/mm<sup>2</sup> to 78 + 103 cell/mm<sup>2</sup>. Mean difference between both group in this study differ not significant statistically ( $p=0,178$ ). However, mean difference of conjunctival goblet cell density before and after therapy between both groups differ -75+ 54 cell/mm<sup>2</sup>.

**Conclusions:** Artificial tears have a considerable effect (important), although not statistically significantly.

**Keywords:** artificial tear, goblet cell, glaucoma, latanoprost therapy.

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## INTRODUCTION

Latanoprost is one of the prostaglandin related anti-glaucoma medications that has strong effect to reduce intraocular pressure (IOP) with increasing the outflow through uveosclera.<sup>1</sup> A long term study present that Latanoprost 0.005% which used once daily can decrease IOP that same effectively with  $\beta$ -adrenergic antagonist. Latanoprost can locally well tolerate and has minimal systemic side effect than timolol. Another study results of latanoprost 0.005% once daily in the evening has more significant effective result than twice daily timolol 0.5% in decreasing diurnal IOP after 6 weeks' therapy and has same effective result after 12 weeks of therapy.<sup>1,2</sup>

The side effects that have been complain due to latanoprost is mild. Hyperemic conjunctiva and in long term use can occur iris hyper pigmentation that caused by increasing melanin in melanocytes.<sup>2</sup> Latanoprost contain preservative Benzalkonium chloride (BAC). Benzalkonium chloride is a preservative that generally used in topical anti-glaucoma medicines.<sup>3</sup> Long term use of Benzalkonium chloride can cause toxic effect directly and indirectly on the ocular surface, such as unstable tear layers, squamous metaplasia of the conjunctiva, apoptosis, damage of cornea epithelial barrier, and loss of

conjunctiva goblet cell. Loss of goblet cell can cause decreasing mucin secretion that can trigger unstable tear layers, decreasing nourish of superficial epithelial conjunctiva cell, then produce mechanical damage on the conjunctiva and the superficial cell of the cornea and reduce the ability to distributed tear layers in ocular surface. This thing can cause decreasing visual acuity, foreign body sensation or uncomfortable feeling and can trigger ocular surface disorder or ocular surface disease (OSD).<sup>4,5</sup> The study shows that glaucoma patients is the largest group who need artificial tears compared with other groups.

Therapy with prostaglandin analog often needs artificial tears compared with other anti-glaucoma medicines. The study shows that female with two or more combinations long-term anti-glaucoma therapy increasing needs for artificial tears.<sup>6</sup> Conjunctiva impression cytology is noninvasive technique to take conjunctival sample and epithelial cornea with high sensitivity and specificity, can detect early changes that cannot detect with routine tears function test. Many scientists explain that impression cytology could be first line examination to diagnosed dry eye disease.<sup>7</sup>

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Artificial tears are a first line therapy on dry eye syndrome and very popular because this therapy are noninvasive and has minimum side effect. The mechanism of artificial tears increases tears volume, stabilize tears layer, to keep the humidity of refraction surface, reduce tears osmolarity, and protect the ocular surface with minimize friction between eyelid and cornea.<sup>8</sup>

Artificial tears form a layer to close corneal surface and keep it moist and protected from dryness. The active ingredients in artificial tears are polyvinyl alcohol, cellulose, methylcellulose and their derivate (hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl-cellulose/HPMC, and carboxymethyl cellulose). Other ingredients that common use such as glycerin, polysorbate 80, polyethylene glycol (PEG)-400, dextran 70, povidone, and propylene glycol.<sup>9</sup> Hydroxypropyl methyl-cellulose can cover and protect epithelial surface and also restore the mucin protection function. The side effect can be mild uncomfortable feeling, burn sensation and foreign body sensation.<sup>10</sup> Based on that background, study about influence of artificial tear related with conjunctival goblet cell density in glaucoma patients with latanoprost therapy seemed important for study and clinical concern.

## MATERIAL AND METHOD

### Study Design and Sample Collection

This study is a Randomized Clinical Trial with Double Blind Pre and Post-test Control Group Design to know about goblet cells density between latanoprost eye drop and artificial tears group compare with latanoprost eye drop and placebo group. This study were declared eligible ethics by ethic study commission of Medical Faculty, Udayana University/Sanglah General Hospital Denpasar. This Study were perform at eye clinic of Sanglah General Hospital Denpasar and Bali Mandara Hospital since October 2015 until December 2015.

Samples are all glaucoma's patients that got latanoprost eye drop therapy who come to eye clinic Sanglah General Hospital and Bali Mandara Hospital that appropriate for inclusion and exclusion criteria. Inclusion criterias are more than 40 years old patients, patients diagnosed with glaucoma, patients who need topical anti-glaucoma therapy (latanoprost eye drops with Benzalkonium chloride preservatives), willing to join this study and sign the informed consent. Exclusion criteria are eyelid, corneal, and scleral disorder history, history of systemic disease (Diabetes Mellitus), intraocular surgery history (cataract surgery, refractive surgery, trabeculectomy, Implant devices), routine using contact lens more than 1 year, trauma history (blunt injury, sharp injury, chemical injury, radiation

injury), allergic history disease, pterygium, blepharitis, uveitis. Patients with history of using artificial tears in last three weeks and didn't complete the study because of the side effect or personal reasons were excluded.

Samples were calculated with Pocock obtain 19 samples plus 10% for drop out anticipation. So, obtain 21 samples for each group. The data recorded in main table. The diagnose based on anamnesis and examination. Visual acuity were examine with E chart or Snellen chart. Ophthalmology examination with slit lamp and perform by glaucoma expert. Samples that complete inclusion and exclusion criteria then sign the informed consent and separated became two groups with randomized block permutation to be a latanoprost and artificial tears combination group and latanoprost with placebo combination group, then impression cytology examination was done before therapy. Apply anti-glaucoma eye drops once daily in the evening and artificial tears or placebo one drop 4 times daily. Samples got therapy for 30 days then examine with repeat impression cytology.

To take impression cytology samples, the patients were given with 2% pantocain eye drop, wait until sore sensation was lost. Applicable the blepharostat, applicable nitrocellulose filter paper on limbal-conjunctival area, hold one of the tip with conjunctival forceps, push the paper slowly, wait for 3-5 seconds, then release the paper from the side that hold with conjunctival forceps. Put the filter paper on the object glass with specimen stick on the object glass surface. Release the specimen with rubbing movement, and then fix the specimen with 95% alcohol. The fixated samples send to Histopathology Laboratory Sanglah General Hospital for Papanicolaou staining and examined under microscope. All the subject was follow up at the 15 days during therapy to measure subject obedience and if didn't came, the subject then reminded by phone or direct visitation. The last impression cytology examination was perform at the 30 days during therapy. If the subject has allergic reaction or side effect that cannot tolerated, subject declared drop out. Remain medicine were count to know compliance level. Examination result were interpreted by pathologist expert in Sanglah General Hospital. Goblet cells density result were count under microscope with 400x enlargement, present in cells/mm<sup>2</sup>. After study, the medicine distributor informe the scientist about the A and B medicine composition.

### Statistical Analysis

Data selections are editing, coding and tabulation insert to file navigator using SPSS 17.0. Categorical data scale was described in frequent and percent, numeric data scale in rate and deviation standard.

Normality test using Shapiro-Wilk. For goblet cell count data before therapy was tested with Mann-Whitney test. Rate before and after therapy in groups was analyzed using dependent t-test. Quarrel rate goblet cell changes after and before therapy between the groups was analyzed using independent t-test.

## RESULTS

Examination conducted on 46 glaucoma patients that planned with latanoprost therapy and found 42 eyes that appropriate for inclusion and exclusion criteria, during follow up there are 2 drop out samples in control group so eligible sample totally 40 samples. Basic subject characteristics were present in Table 1.

Mean age of artificial tears group is  $51.52 \pm 14.882$  years old, while in group without artificial tears is  $60.00 \pm 10.344$  years old. In artificial tears group found 16 samples were male and without artificial tears group were 17 samples. The most diagnose in this study is primary open angle glaucoma (POAG) in artificial tears group was 19 samples and in without artificial tears group is 16 samples.

Conjunctival goblet cells density mean before therapy in artificial tears group is  $83 \pm 97$  cell/mm<sup>2</sup> and in group without artificial tears is  $144 \pm 169$  cells/mm<sup>2</sup>. Quarrel goblet cells density between two groups is  $61 \pm 43$  cell/mm<sup>2</sup>. Quarrel

mean between two groups after therapy were not meaningful statistically ( $p = 0.236$ ).

Conjunctival goblet cells mean after therapy in artificial tears group is  $92 \pm 88$  cell/mm<sup>2</sup> and in group without artificial tears is  $78 \pm 103$  cell/mm<sup>2</sup>. Quarrel mean goblet cells between two groups are  $-14 \pm 30$  cell/mm<sup>2</sup>. Quarrel mean between two groups after therapy were not meaningful statistically ( $p = 0.646$ ).

Quarrel conjunctival goblet cells density after and before therapy in artificial tears group is  $8 \pm 120$  cell/mm<sup>2</sup> and in group without artificial tears is  $-66 \pm 216$  cell/mm<sup>2</sup>. Quarrel conjunctival goblet cells density between two groups is  $-75 \pm 54$  cell/mm<sup>2</sup>.

The Difference quarrel mean between two groups were not statistically significantly meaningful ( $p = 0.178$ ).

## DISCUSSION

### Subject Characteristic

This study was done on 40 eyes with inclusion criteria was  $\geq 40$  years old glaucoma patients. In this study found mean age in artificial tears group is  $51.52 \pm 14.882$  years old and in without artificial tears group is  $60.00 \pm 10.344$  years old. There is wide difference mean between two groups because the total samples were small probably the data did not well distributed. Study by Abu-Amero et al.<sup>11</sup> in Philadelphia in 47 POAG patients found the mean age is 67.3 years old. Study by Uusitalo et al.<sup>12</sup> in 264 open angle glaucoma patients that treat with latanoprost, found mean ages 62.4 years old with range 18–88 years old. Study by Aquino et al.<sup>2</sup> in 30 glaucoma and ocular hypertensive patients that treat with latanoprost found mean ages 58 years old with range 21–92 years old. Primary open angle glaucoma occurs more than 40 caused by humor aqueous outflow disorder through trabecular meshwork to the Schlemm canal.<sup>13</sup> Ages known as one of risk factor in glaucoma and generally diagnose for the first time in 60–70. Mean ages of the normal tension glaucoma (NTG) patients in several different study 63.7 until 64.9. Primary

**Table 1 Basic Subjects Characteristics**

Characteristic	Artificial Tears Group n=21	Without Artificial Tears Group n=19
Age (Years)	51.52±14.882	60.00±10.344
Gender		
- Male	16	17
- Female	5	2
Diagnose		
- POAG	19	16
- Chronic PACG	2	3

**Table 2 Conjunctival Goblet Cells Density Changes Before and After Therapy**

Goblet Cells	Artificial Tears Group (n=21)	Without Artificial Tears Group (n=19)	Quarrel Goblet Cells Density (Before-After)	95% CI	P value
Density Before Therapy (Mean±DS)	83±97	144±169	61±43	-26 s/d 148	0.236*
Density After Therapy (Mean±DS)	92±88	78±103	-14±30	-75 s/d 47	0.646
Quarrel Goblet Cells Density (After-Before Therapy) (Mean±DS)	8±120	-66±216	-75±54	-186 s/d 35	0.178

\*Mann-Whitney U Test

open angle glaucoma and NTG prevalence increase occur following the ages. Low-Pressure Glaucoma Treatment Study found 9.5% patients with range age 40–49, 16.3% with range age 50–59, 36.8% with range age 60–69, and 29.5% with range age 70–79.<sup>14,15</sup> Decreasing conjunctival goblet cells density were related with increasing age and trigger the dry eye. Epidemiologic study has been reported that more than 6% of population with age more than 40 suffer dry eye with increasing prevalence until 15% in more than 65 years old population.<sup>16</sup>

Study by Pova et al.<sup>17</sup> in POAG patients found that the most prevalence was female (60.4%). Study by Aquino et al.<sup>2</sup> in 30 patients with glaucoma and ocular hypertension that treat with latanoprost, found that male was more often than female (57%). Study by Suzuki et al.<sup>18</sup> in 124 patients that treat with latanoprost, found that male was more often than female (55,6%). Study by Costa et al.<sup>6</sup> about needed of artificial tears in glaucoma patients found that the most prevalence was in female (56,6%). The study describes that female and glaucoma patients as a risk factor for dry eye syndrome, so the artificial tears is needed.<sup>6</sup> Study by Abu-Amero, et al.<sup>11</sup> in 47 POAG patients found that male were more often than female (55,3%). The study results describe that glaucoma incidence in male are often than female in artificial tears group and artificial tears group. Glaucoma incidence (especially close angle glaucoma) were reported more often in female, because the anterior chamber in females were smaller than males.<sup>9</sup> An epidemiologic study describe about 55% POAG patients were female, but female patients were difficult and rarely agree to referral to secondary facility for diagnose and further examination, so this reason could be related with male were more often suffering glaucoma.<sup>19</sup>

Study by Denis et al.<sup>20</sup> found that POAG incidence were low than ocular hypertensive in intra-ocular pressure less than 24 mmHg or more than 24 mmHg. That result was similar with Suzuki et al.<sup>18</sup> study in 124 POAG and ocular hypertensive patients, with ocular hypertensive incidence is 63,7%. These were similar with this study result that POAG were the most diagnosed in artificial tears group or without artificial tears group. Primary open angle glaucoma found in more than half of whole glaucoma cases in Caucasian North America population and occur in 2% of population with ages more than 45.<sup>17</sup>

Study by Abu-Amero et al.<sup>11</sup> PACGas the most incidence (46.6%), following with Primary angle closure/PAC (17.2%), POAG (12.8%) and secondary glaucoma (13%). Another type of glaucoma like normal tension glaucoma (NTG) (5.9%), childhood glaucoma (2.6%), juvenile glaucoma (1.9%) also reported, but in low incidence.<sup>11</sup> Chronic angle

closure (CAC) can develop after acute angle closure with persistent synechia or gradually angle chamber function progressively.<sup>9</sup>

NTG is a clinical condition that related with abnormality optic disc excavation, visual field disorder appropriate with glaucoma characteristic, within normal limit IOP range. The cause of NTG is unknown, but the level of IOP suspected has a role to trigger NTG. Patients prevalence with NTG are very small, with IOP range between 15 – 20 mmHg.<sup>21</sup>

### Conjunctival Goblet Cell Density Changes Before and After Therapy

Conjunctival goblet cells functions are for synthesis save and produce the mucin that were a glycoprotein complex produced 2–3  $\mu$ L/day. Mucin function is to change the epithelial cornea from hydrophobic to hydrophilic, tear layer stabilization, as a moisture when eyelid rub the eyeball, and to protect the outside surface of the eye from pathogenic agents, chemical and toxin. Goblet cell ability to produce mucin, depend on functional goblet cell count of the conjunctiva. Goblet cell density can be variate and can change by external factors that cause increasing or decreasing cell count. Therapy with topical anti-glaucoma can influence the goblet cell density.<sup>22</sup>

Latanoprost contain Benzalkonium chloride (BAC). Long term use of BAC can cause instability tear layer, metaplasia of the conjunctival squamosa, apoptosis, cornea epithelial barrier damage and loss of conjunctival goblet cell. Loss of goblet cell cause decreasing of mucin secretion that can trigger the tears layer instability, decreasing nutrition to superficial conjunctiva epithelial cell, so that can produce mechanical damage of the conjunctiva and corneal cell surface, and decrease the ability to distribute tears layer on ocular surface. This can cause many manifestations such as decreasing visual acuity, foreign body sensation or uncomfortable feeling and can trigger ocular surface disorder or ocular surface disease (OSD).<sup>4,5</sup> Review by Actis et al.<sup>16</sup> describe that BAC generally had important role to cause ocular surface damage with side effect influence with dose and long term therapy, especially in a combination medicines. Periodical clinical evaluation to prevent the damage that cause by anti-glaucoma eye drop therapy were very necessary.<sup>16</sup>

Study by Kahook, et al.<sup>4</sup> about conjunctival goblet cell quantitative analyzed after topical anti-glaucoma therapy, found that latanoprost with BAC can cause conjunctival goblet cell count decrease significantly compared with travoprost with sofzia and eye drop without preservatives. Moore et al.<sup>23</sup> in the study about dry eye examination in glaucoma, explain that ocular surface can influence by long term topical anti-glaucoma therapy.<sup>23</sup>

Study by Costa et al.<sup>6</sup> explain that female and long term use anti-glaucoma with two or more combinations can increase the need of artificial tear. Artificial tear mechanism increases the volume of tears, stabilization of tears layer, moisture the refraction surface, decrease tears osmolarity and protect the ocular surface by decreased rub between eyelid and cornea.<sup>8</sup> Study by Demiryay, et al.<sup>10</sup> explain the incidence of increasing conjunctiva goblet cell in patients with topical artificial tears therapy (the study use HPMC and Dextran 70 combination). Hydroxypropyl methyl-cellulose can cover and protect the epithelial surface and can restore the mucin protection function.<sup>10,24</sup> Study by Ehrenberg et al.<sup>25</sup> explain that increase effectively occurring in sodium hyaluronate and polyvinylpyrrolidone combination in one packed eyedrop.<sup>25</sup>

Study by Demiryay et al.<sup>10</sup> about topical cyclosporine an artificial tears combination therapy compared with artificial tears on conjunctival goblet cell in dysfunction tears syndrome found the goblet cell density were increase in two of groups after 4 months' evaluation, but the difference between after and before therapy were statistically meaningful only on cyclosporine A group ( $p < 0,001$ ). This study result increasing mean of conjunctiva goblet cell density in group with artificial tears before therapy compared with after therapy is  $83 \pm 97$  cell/mm<sup>2</sup> to  $92 \pm 88$  cell/mm<sup>2</sup>, meanwhile in non-artificial tears group was found decreasing mean of conjunctiva goblet cell density is  $144 \pm 169$  cell/mm<sup>2</sup> to  $78 \pm 103$  cell/mm<sup>2</sup>. The difference of conjunctival goblet cell density in artificial tear group and non-artificial tears group was quite high before therapy. This can cause by topical anti-glaucoma therapy history before the study that more than in dose and length of use in artificial tears groups compared with non-artificial tears group. Besides, small number samples (n) can cause the data opportunities were uneven distributed. Mean difference between the two groups were not meaningful statistically ( $p = 0,178$ ). But the mean difference of conjunctival goblet cell density after and before therapy between the two groups are very great ( $75 \pm 54$  cell/mm<sup>2</sup>). Applicative value of this study can be use as clinical consideration to give artificial tears as additional therapy to the patients with glaucoma who got latanoprost therapy.

The weakness of this study is less period of medicine usage that can cause conjunctival goblet cell density changes were not significant meaningful and the patient compliance due to medicine usage were difficult to monitor because eyedrops usage very difficult to rate the limitation. Moreover, with impression cytologi technic can be obtained variate conjunctival goblet cell count.

## CONCLUSION

Latanoprost eye drop combine with artificial tears were not statistically significant to inhibit the decreasing of conjunctiva goblet cell density compared with latanoprost therapy without artificial tears in glaucoma patients. In this study, artificial tear has important effect. Further study with longer evaluation period (at least 3 months) are needed to know the difference of conjunctival goblet cell density were meaningful statistically. This study may be considered in further study about conjunctival goblet cell density with another anti-glaucoma eye drops. Another study can be done to know about the difference of conjunctiva goblet cell density in patients with topical anti-glaucoma therapy combined with artificial tears compared with artificial tears that contain vitamin A.

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