COMPARISON OF THE EFFECTIVENESS OF 3% DIQUAFOSOL AND 0,1 % HYALURONATE ACID IN DRY EYE DISEASE

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Abstract: *A dry eye is a disease with morbidity on the ocular surface. Twenty-five percent of patients visiting the eye clinic complained of dry eye symptoms. In Indonesia, the prevalence of dry eye is reported to increase by 27,5% due to some related variables, including age, smoking, and pterygium (Lee AJ. et al., 2002). In Makassar, the case of dry eye is more often found in women than in men, with a ratio of 2:1 (Syawal, 2005). Most patients with dry eyes apply conventional conventional therapy, including supplementary lacrimal using a preserver. Unfortunately the long usage of supplements with preserver in active Ocular Surface Disorders has been reported to increase the vulnerability to toxicity (Gobbels M et al., 1992), (Wilson F et al., 1979). Therefore, it is necessary to carry out a study about the dry eye of patients using diquafosol. This study aims to measure the improvement in the ocular surface structure after administering topical diquafosol 3% based on the degree of dry eye disease. The study employed an experimental design, carried out at the Polyclinic of Dr. Wahidin Sudirohusodo and the University of Hasanuddin Education Hospitals, Makassar, for three months. The research population was patients with dry eyes doing examinations at the Polyclinic While the samples were patients fulfilling the inclusion criteria, including being diagnosed with dry eye, aged 18 years old, and willing to take part in the research by signing an informed consent. While the exclusion criteria are if the patients had allogeneic hematopoietic stem cell transplantation, had done refractive corneal surgery, were contact lens users, and had Stevens-Johnson syndrome and chemical / thermal burns; Have a history of allergies to drugs or health materials used in the study including artificial tears, Schirmer, fluorescein strips; and are possibly uncooperative during the examination. The samples were collected through random controlled trial sampling based on the target sample number (41). Data were recorded and analyzed using a statistical package for social science (SPSS). Results are presented narratively with a table or graph. It is concluded that there is a change in the ocular surface structure leading to the improvement of dry eye disease after the administration of topical 3% diquafosol based on TBUT, Schirmer, and OSDI indicators.*

INTRODUCTION

A dry eye is a disease with morbidity on the *ocular surface*. Twenty-five percent of patients visiting the eye clinic complained of dry eye symptoms. As it develops among societies and is generally found in eye clinics, it becomes an urgent problem. In 1995, dry eye was defined as a group of medical diseases and ocular surfaces caused by decreased lacrimal production and increased lacrimal evaporation (Lemp MA, 1995). In 2007, International Dry Eye Workshop (DEWS) revised the older definition, the scheme of dry eye classification, developed a new definition, and made a new classification based on etiology, mechanism, and the severe levels of the disease (International Dry Eye Workshop (DEWS), 2007). The new definition of *dry eye* is a multifactorial disease on the ocular surface which is indicated by some symptoms including discomfort, visual disturbances, and tear film instability, with an increase on increased tear film osmolarity and inflammation of the ocular surface of the eye

The prevalence of dry eye is estimated between 7,4% and 33,7% (depending on the diagnosis of the surveyed population). A Beaver Dam population-based study found that the prevalence level of dry eye increases to 14% in adults (from 48 to 91 years old. The study also reported that dry eye is more often found in women (16.7%) than in men (11.4%) (Lin PY. et al.). In Indonesia, the prevalence of dry eye is reported to increase by 27,5% due to some related variables, including age, smoking, and pterygium (Lee AJ. et al., 2002). In Makassar, the case of *dry eye* is more often found in women than in men, with a ratio of 2:1 (Syawal, 2005).

The ocular surface depends on the adequacy of the lacrimal layer maintenance. Mucus and fat layers of lacrimal mechanically protect the corneal epithelium, while various growth factors, including vitamins, electrolytes, and *neuropeptide*s, support the growth and migration of cells (Geerling G et al. 2004). Various subjective and objective tests can be used to evaluate patients suspected dry eye. A subjective dry eye examination can use OSDI (*Ocular Surface Disease Index*) questionnaire. On the other hand, the objective examination can use Schirmer, fluorescein, *rose bengal*, *lissamine green*, *or tear-break uptime test*s, and nonroutine dry eye examinations like the Conjunctival impression cytology test. Some studies have shown that the emergence of symptoms is enough to diagnose a dry eye because there is no specific examination for the absolute diagnosis of a dry eye. However, the occurrence of symptoms is not strong enough to diagnose dry eye because there are usually ocular surface and lacrimal disorders which show similar symptoms (Khanal et al., 2008).

In general, dry eye management needs much cost but usually gives inadequate results. Many patients did not experience meaningful relief from the symptoms (Schaumberg et al., 2001). The first step of dry eye management is to identify the etiologies which base it and try to cure them. External topical therapy as the tear film replacement aims to maintain the stability of *the ocular surface* but is limited to relieving the symptoms without curing the etiologies which base it. A synthetic lacrimal is generally made from a buffer solution containing electrolyte, surfactant, preservative, and viscosity, aiming to lubricate the ocular surface (Albelson MB, 1994).

Most patients with dry eyes apply conventional medication to optimize the ocular surface. The ecosystem depends on healthy adnexa dynamic interaction, good blink reflex, normal tear production, and good ocular surface tissue consisting of cornea and conjunctive. Thus, conventional therapy is the right option for ocular surface disordered. In this study, the

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patients had significant coloring on their eyeball surfaces and could not respond to the modality of maximum conventional therapy, including supplementary lacrimal using a preserver. The long usage of supplements with preserver in active *Ocular Surface Disorders* has been reported to increase the vulnerability to toxicity (Gobbels M et al., 1992), (Wilson F et al., 1979).

Diquafosol is a *purinergic P2Y2 receptor agonist*. P2Y2 receptor is found in various *ocular surface*s, including palpebra, conjunctiva bulbar, goblet cell, and adipose, and on epithelium ductus in meibomian glands. Adenosine Triphosphates (ATP) or Uridine Triphosphate (UTP) have been reported to promote aqueous and mucin secretions from the conjunctiva by activating the P2Y2 receptor. Like UTP, Diquofosa also has P2Y2, which can activate agonist receptors and has been reported to have a better solution concentration than ATP or UTP. Topical diquafosol was reported to worsen the cornea disorder in experimented animals with dry eyes, like mice and rabbits, which promotes mucin secretion from the conjunctival tissue.

Considering the high dry eye prevalence as illustrated above and the increasing popularity of dry eye therapy, and the absence of reference related to the effectiveness of the use of *diquafosol* and *hyaluronate acid* by dry eye patients in Indonesia, it is necessary to carry out a study about the dry eye of patients using *diquafosol*. This study aims to measure the improvement in the ocular surface structure after administering topical diquafosol 3% based on the degree of *dry eye disease.*

LITERATURE REVIEW

The ocular surface is a directly exposed mucosa structure but is unique. The surface is protected from environmental exposure, microbes, and other factors which can cause inflammation by stratified epithelium. The conjunctival epithelium has goblet cells which produce the second largest mucus after the digestive tract. It is also the host of various immune system cells like NK cells, dendritic cells, macrophages, and CD4 and CD8 T cells which act as the first anti-microbial defense and are also considered pathogenic for the dry eye. The cornea should always be protected from environmental exposure to keep it comfortable. On the dry eye, there is a disturbance in some mechanisms functioning to keep the ocular surface and gland function balanced. The hyperosmolarity can cause inflammation on the surface of eyeball epithelium which can activate mitogen and stimulate protein kinases (MAPKs), then stimulates the secretion of inflammatory mediators like *cytokines (interleukin 1 & 6, TNF), chemokines,* and *matrix metalloproteinases (MMP)* like *MMP3 and MMP 9* and *induce apoptosis*. (Luo L at al 2004)

On the other hand, dry eye is a multifactorial and heterogeneous disorder, including a wider spectrum of ocular surface damage with various etiology and pathophysiology. A dry eye can be caused by the deficiency of one or more Lacrimal (LAM) layer components or a part of systemic disease, including Sjogren syndrome, lupus, and Stevens-Johnson syndrome (Asbell, 2002 Foster, 2014).

The global definition of the dry eye based on the consensus of *The National Eye Institute (NEI)/Industry Workshop on Clinical Trials in Dry Eye* in 1993-1994 is as follows: "Dry eye is a LAM disorder due to tear deficiency or excessive tear evaporation causing damage on *the ocular surface* of interpalpebral and is related to ocular discomfort symptoms" (Lemp, 2008).

While according to *Dry Eye Workshop (DEWS)* in 2007, *dry eye* is a multifactorial disease on LAM and *ocular surface* which cause discomfort symptoms, visual disturbances, and lacrimal layer instability with potential damage to the ocular surface. An increase accompanies the symptoms on the osmolarity of the lacrimal layer and inflammation on the ocular surface (Foulks, 2007).

Dry eye is a common eye problem and becomes the main reason why patients, especially the elderly, visit a doctor. Earlier epidemiology studies on various populations found that the prevalence of dry eye symptoms was 6% in the Australian population above 40, and it reached 15% of the Maryland, US population above 65 years old. "The Beaver Dam" population-based study found that the prevalence of dry eye was 14% in adults (aged 48-91 years old). The study also found that dry eye is more common in women (16,7%) than men (11,4%). (Guyton, 2009). In Makassar, dry eye case was found more in women than in men, with a ratio of 2:1 (Syawal, 2005). Frequency and clinical diagnosis of dry eye are more often found among Hispanic and Asian populations than Caucasians. In a study carried out in Denmark involving a population aged 30-60 years old, from 514 samples, we found the prevalence of dry eye at 11% according to Copenhagen criteria and 8% according to European criteria. While in Australia, based on the *Melbourne Visual Impairment Project (MVIP)*, from 926 dry eye patients aged 40 years old and above, it was found 10.8% dry eye patients through the rose Bengal examination, 16.3% using Schimer 1 test, and 8.6% with tear break up time test (Nelson, 2006 and Moss, 2000). The prevalence in Indonesia has also been reported by Lee et al. that from 1058 samples, 27.5% of them complain about dry eye symptoms all the time (Lee et al., 2002).

In general, the study reported that the prevalence increases based on age. Gaps among studies tend to be the subjective and objective criteria of dry eye. As it has been mentioned before, dry eye is a multifactorial disorder. The following table presents the risk factors of the dry eye according to *the Dry Eye Workshop Committee*, 2007.

Table 1. Risk Factors of dry eye (*DEWS*, 2007).

Level of Evidence		
Mostly consistent*	**Suggestive†**	**Unclear†**
Older age	Asian race	Cigarette smoking
Female sex	Medications	Hispanic ethnicity
Postmenopausal estrogen therapy	Tricyclic antidepressants	
Omega-3 and Omega-6 fatty acids	Selective serotonin reuptake inhibitors	Anti-cholinergics
Medications	Diuretics	Anxiolytics
Antihistamines	Beta-blockers	Antipsychotics
Connective tissue disease	Diabetes mellitus	Alcohol
LASIK and refractive excimer laser surgery	HIV/HTLV1 infection	Menopause
Radiation therapy	Systemic chemotherapy	Botulinum toxin injection
Hematopoietic stem cell transplantation	Large incision ECCE and penetrating keratoplasty	
	Isotretinoin	Acne
Vitamin A deficiency	Low humidity environments	Gout
Hepatitis C infection	Sarcoidosis	Oral contraceptives
Androgen deficiency	Ovarian dysfunction	Pregnancy

* Mostly consistent evidence implies the existence of at least one adequately powered and otherwise well-conducted study published in a peer-reviewed journal, along with the existence of a plausible biological rationale and corroborating basic research or clinical data.

† Suggestive evidence implies the existence of either: 1) inconclusive information from peer-reviewed publications or 2) inconclusive or limited information to support the association, but either not published or published somewhere other than in a peer-reviewed journal

† Unclear evidence implies either directly conflicting information in peer-reviewed publications, or inconclusive information but with some basis for a biological rationale

RESEARCH METHOD

The study employed an experimental design, carried out at the Polyclinic of Dr. Wahidin

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Sudirohusodo and the University of Hasanuddin Education Hospitals, Makassar, for three months. The research population was patients with dry eyes doing examinations at the Polyclinic While the samples were patients fulfilling the inclusion criteria, including being diagnosed with dry eye, aged 18 years old, and willing to take part in the research by signing an informed consent. While the exclusion criteria are if the patients had *allogeneic hematopoietic stem cell transplantation,* had done refractive corneal surgery, were contact lens users, and had *Stevens-Johnson syndrome* and *chemical / thermal burns*; Have a history of allergies to drugs or health materials used in the study including artificial tears, Schirmer, fluorescein strips; and are possibly uncooperative during the examination. The samples were collected through *random controlled trial sampling* based on the target sample number (41). The sample size was determined based on the following formula:

$$n = \frac{2(Z\alpha + Z_{1-\beta})^2\sigma^2}{\Delta^2}$$

n = the number of samples of a group
Zα = value of Alpha deviation standard (1,96)
$Z_{1-\beta}$ = value of the constant standard value of the research power 80% (0,8416)
σ = deviation standard of the previous studies (1,5)
Δ = the effectiveness of treatment from previous studies (0,76)

The research instruments are Flashlight, Slit Lamp biomicroscope, informed consent sheet, Data collection form, Schirmer, OSDI questionnaire sheet, Fluorescein, and srtificial tears

Data were recorded and analyzed using *a statistical package for social science* (SPSS). Results are presented narratively with a table or graph.

FINDING AND DISCUSSION

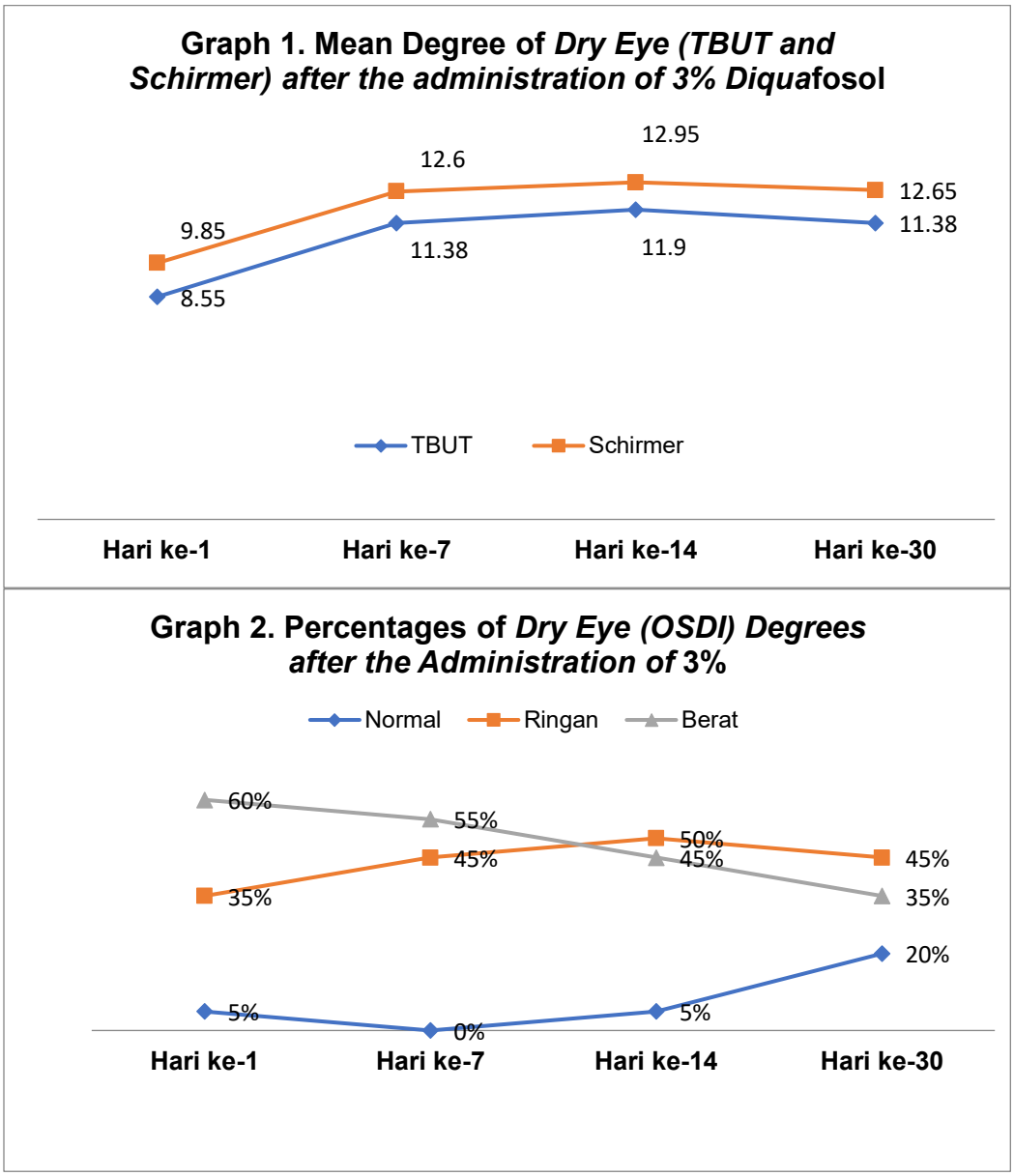
Finding

After carrying out the Ocular Surface test after the implementation of topical 3% diquafosol medical therapy measured based on three indicators of dry eye disease degree in four measuring times, we analyzed data by describing the average value ± deviation standard. While to examine if there is a significant difference before and after the administration of topical 3% Diquafosol, we used the friedman test.

Table 1 Comparison of the average degree of dry eye disease and p-value after administration of Topical 3% Diquafosol

Dry eye degrees	Measurement Times				*p*-value
	Pre Day 1	Post Day 7	Post Day 14	Post Day 30	
TBUT (second)	8,55± 1,89	11,38± 1,75	11,90± 1,89	11,38± 1,75	0,00
Schirmer (mm)	9,85± 2,66	12,60± 2,54	12,95± 1,89	12,65± 1,56	0,00
OSDI:					
- normal	2 (5,0%)	0	2 (5,0%)	8 (20,0%)	0,00
- light	14 (35,0%)	18 (45,0%)	20 (50,)%	18 (45%)	
- medium	0	0	0	0	
- heavy	24 (60%)	22 (55,0%)	18 (45,0%)	14 (35%)	

Note: Data are in average ±SD and frequency percentages



Gambar 2

The table above shows different dry eye average degrees measured four times using TBUT dry eye degree indicators. On the first day before the treatment, they generally showed degrees of 8,55±1,89, indicating that the dry eye ranged from moderate/mild to moderate (scored of 10-6). Then in the second, fourteenth, and thirtieth days, after the administration of topical 3% diquafosol, they were at the averages of 11,38±1,75; 11,90±1,89 and 11.38±1,75 respectively, indicating normal dry eye degrees (scores >10). The table also shows the p-value of the comparison of average TBUT dry eye degree before and after the therapy was 0,00 < alpha 0,05. It means that there is a significant difference in the average TBUT dry eye before and after the administration of 3% diquafosol (days 7, 14, and 30).

The table also shows the average difference of dry eye degrees of research samples measured at four different times using the Schirmer dry eye degree indicator. On the first day

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before the therapy, the average degree was 9,85±2,66, indicating that the dry eye had moderate/mild–moderate degrees (scores = 10-6). Then on days 7, 14, and 30, after the treatment, the average degrees were 12,60±2,54; 12,95±1,89 and 12,65±1,56 meaning that the dry eye had a normal degree (scores > 10). It can also be seen that the p-value of the comparison between average Schirmer dry eye degrees before the administration of topical 3% diquafosol is 0,00 < alpha 0,05. It means there is a significant difference in the Schirmer dry eye degrees before and after the administration of 3% diquafosol to the ocular surface (at days 7, 14, and 30).

Furthermore, the table shows a percentage difference of the research sample frequencies measured four different times using OSDI dry eye degree indicators. On the first day, before the treatment, 24 samples (60,0%) shows heave dry eye degrees. Then, on days 7, 14, and 30, after the administration of topical 3% diquafosol, the dry eye frequency percentages reduced to 22 (55,0%); 18 (45,0%), and 14 (35,0%), respectively. Besides that, the samples with normal dry eye degree before the administration of topical 3% diquafosol were only 2 (5,0%) but increased to 8 (20.0) on day 30 of the treatment.

Based on the table, the p-value of the percentage comparison of dry eye degree frequency before and after the administration of tropical 3% diquafosol was 0,00 < alpha 0,05. It means that the dry eye degrees before and after the administration of 3% diquafosol to the ocular surface on days 7, 14, and 30 are significantly different.

Discussion

Based on the analysis, there is a significant difference in the average dry eye degrees (p-value < alpha value of 0,05) after the therapy with topical 3% diquafosol (on days 1, 7, 14, and 30). Using TBUT, Schirmer, and OSDI indicators, the average degree of samples' dry eye was in categories of moderate/mild and moderate (<10) before the therapy using diquafosol. On days 7, 14, and 30, TBUT and Schirmer dry eye degree indicators show that there is a change in normal dry eye (>10). In contrast, OSDI dry indicators show an increase in the frequency of normal dry eye from 2 (5,0%) to 8 (20,0%) samples and a decrease in heavy dry eye frequency from 24 (60,0%) to 14 (35,0%) samples.

The study is in line with Nam et al. (2017), which found that there was a statistically significant difference in the scores of the Schirmer test (the average difference of 0.74 mm on week 4; 95% CI: 0,24–1,24; l2= 0%), fluorescein stain, rose bengal stain, and TFBUT after treatment using diquafosol compared to the group treated using other eye drops.

Kamiya et al (2012) also explained that diquafosol tetrasodium is effective not only in objectively improving symptoms like breakup time (BUT), fluorescein score, and rose Bengal score but also the subjective symptoms (OSDI) like dry eye sensation, pain, and foreign body sensation.

Diquafosol tetrasodium (“diquafosol”) is a second-generation uridine nucleotide analog P2Y2 receptor agonist. Diquafosol has been approved by Japanese and Korean regulatory agencies (Lau et al., 2014). P2Y2 receptors are a major subtype of purinergic receptors on the ocular surface. Evidence for the existence of P2Y2 receptors in the ocular tissue is the localization of P2Y2 receptors in the conjunctival goblet epithelium, serous cells, Meibom gland acinar cells, and ductal epithelial cells of Rhesus macaque from non-isotopic in situ hybridization (Cowlen et al., 2013). Diquafosol stimulates conjunctival epithelial cells to

secrete fluid and conjunctival goblet cells to secrete mucin on the ocular surface and to stimulate lipids by interacting with P2Y2 receptors to increase the stability of the lacrimal layer (Craig et al., 2017). The binding of diquafosol tetrasodium to P2Y2 receptors increases intracellular calcium and activates chloride ion transport, promoting fluid transport across the epithelial layer (Nichols et al., 2004).

Diquafosol tetrasodium activates the P2Y2 receptor on the ocular and inner eyelid surfaces and increases the natural lacrimal secretion. Lacrimal secretion stimulation using diquafosol releases salt, water, mucin, and other components of the lacrimal layer and hydrates the ocular surface. The administration of diquafosol also increases the pre-lens tear meniscus height/TMH significantly. Diquafosol potentially increases the lacrimal volume on the ocular surface below the contact lens, which can be an alternative for curing dry eye due to contact lenses. Various studies like Tauber et al. prove that the administration of diquafosol on DED shows positive results.

Mun et al. (2018) reported that administering diquafosol 3% improves 78.6% of DED symptoms, tear film breakup time (TFBUT) at 65,7%, and corneo-conjunctival staining at 62,8% in patients with DED type TFBUT. Compared to before treatment, TFBUT increased significantly, and DED symptoms and corneal conjunctival staining scores decreased significantly. The side effects, including stinging sensation and conjunctival chemosis, were experienced only by 4.3% of patients.

CONCLUSION

Based on the findings and discussion above, it can be concluded that there is a change in the ocular surface structure leading to the improvement of dry eye disease after the administration of t*opical 3% diquafosol* based on TBUT, Schirmer, and OSDI test.

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