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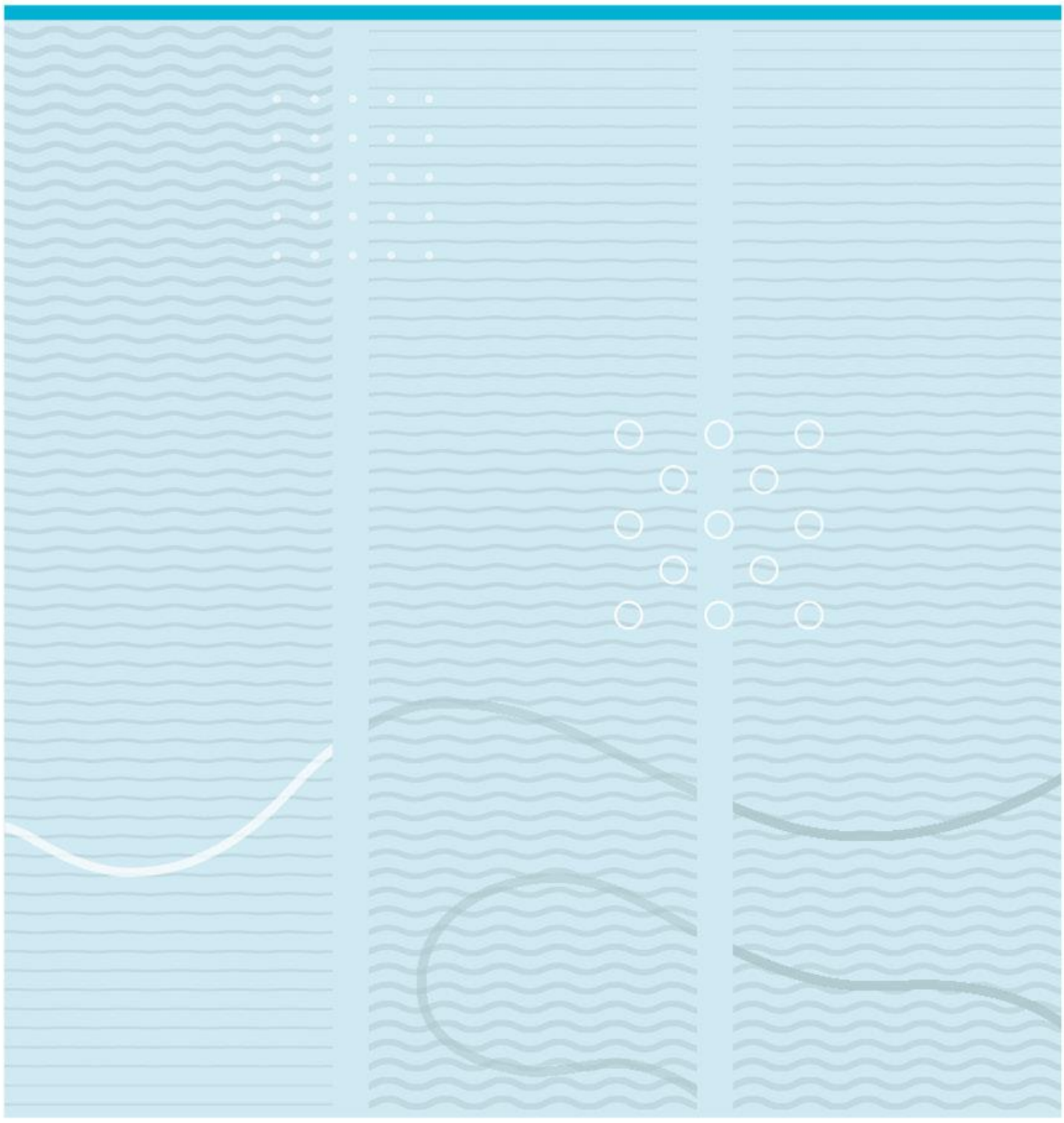
Ocular surface complications in primary open-angle glaucoma

Occurrence of the ocular surface complications in primary open-angle glaucoma patients treated with IOP lowering eye drops



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This thesis is worth 30 study points.

Summary

Purpose: To determine the occurrence of symptoms and signs of ocular surface disease (OSD) in primary open-angle glaucoma patients (POAG) currently treated with one topical intraocular pressure (IOP) lowering agent for at least three months. A secondary objective was to explore the relationship between treatment compliance and the severity of symptoms and signs of the OSD.

Methods: This was a cross-sectional clinical study. POAG patients age 50 to 75 underwent a comprehensive tear film evaluation of both eyes. OSD symptoms were investigated with validated questionnaires: OSDI (≥13) and SPEED II (>5). Signs of OSD included hyperosmolarity, defined as values higher than 308 mOsm/L in either eye or a difference between eyes of 8 mOsm/L or more, reduced NIKBUT (<10s), mild or more severe ocular surface staining (OSS) according to Oxford grading scale and reduced Schirmer 1 test values (<10mm). The patients were asked to estimate their compliance to the prescribed treatment during a short interview, whereas information about age, gender, duration of the treatment, and the active pharmacological substance were collected from the patient journals. Frequencies of symptoms and signs and their association with the active substance, treatment duration, and compliance were analyzed. All statistical tests of hypotheses employed a significance level of $p<0.05$.

Results: All study participants (n=31) were under treatment with a single unpreserved active IOP-lowering substance, of which forty-eight eyes (77%) were treated with prostaglandin analogs and fourteen (23%) eyes treated with beta-blockers. The mean ± SD treatment duration was 77±51 months, age of the participants was 68±6 years, of which 61% were female. Symptoms of OSD were reported by nine (29%) of study participants utilizing the OSDI questionnaire, whereas fourteen (45%) participants reported symptoms utilizing SPEED II. A total of twenty-one (68%) patients exhibited hyperosmolarity. Thirteen (41%) participants had reduced NIKBUT in at least one eye, with significantly shorter break-up values found in the beta-blocker compared to the prostaglandin analog group ($p=0.004$). Twenty-one (68%) study subjects had reduced Schirmer I test results indicating reduced tear production, while eight (26%) participants exhibited only mild OSS. We found no association between treatment duration or compliance and severity of OSD, with 29 of 31 (94%) study participants reporting missing a dose no more than once or twice a month.

Conclusion: To the best of our knowledge, this is the first study where all subjects were currently treated with an unpreserved active ingredient that allowed us to examine the effect of a single active ingredient on the ocular surface. This study observed a high occurrence of OSD signs in POAG patients under treatment with unpreserved prostaglandin analogs and beta-blockers, whereas the frequency of symptoms (OSDI) was reported in considerably fewer participants. The relationship between treatment compliance and severity of OSD symptoms and signs remains inconclusive. Further studies are warranted.

Keywords: ocular surface disease, OSDI, glaucoma, treatment compliance

Sammendrag

Hensikt: Å bestemme forekomsten av symptomer og tegn på okulær overflatesykdom (OSD) hos pasienter med primær åpenvinkelglaukom (POAG) som for tiden behandles trykksenkende øyedråper (IOP) i minst tre måneder. Et sekundært mål var å utforske forholdet mellom behandlingsetterlevelse og alvorlighetsgraden av symptomer og tegn på OSD.

Metoder: Dette var en klinisk tverrsnittsstudie. POAG-pasienter i alderen 50 til 75 gjennomgikk en omfattende tårefilmevaluering av begge øyne. OSD-symptomer ble undersøkt med validerte spørreskjemaer: OSDI (≥13) og SPEED II (>5). Tegn på OSD inkluderte hyperosmolaritet, definert som verdier høyere enn 308 mOsm/L i et av øynene eller en forskjell mellom øyne på 8 mOsm/L eller mer, redusert NIKBUT (<10s), mild eller mer alvorlig okulær overflatefarging (OSS) i henhold til Oxford skala og reduserte Schirmer 1 testverdier (<10mm). Pasientene ble bedt om å estimere etterlevelsen av den foreskrevne behandlingen under et kort intervju, mens informasjon om alder, kjønn, behandlingens varighet og det aktive farmakologiske stoffet ble samlet inn fra pasientjournalene. Hyppigheten av symptomer og tegn og deres assosiasjon med virkestoffet, behandlingsvarighet og etterlevelse ble analysert. Alle statistiske tester av hypoteser brukte et signifikansnivå på $p<0,05$.

Resultater: Alle studiedeltakerne (n=31) var under behandling med et enkelt ukonservert aktivt IOP-senkende stoff, hvorav førtiåtte øyne (77 %) ble behandlet med prostaglandinanaloger og fjorten (23 %) øyne behandlet med betablokkere. Gjennomsnittlig ± SD-behandlingsvarighet var 77±51 måneder, deltakernes alder var 68 ± 6 år, hvorav 61 % var kvinner. Symptomer på OSD ble rapportert av ni (29%) av studiedeltakerne ved å bruke OSDI-spørreskjemaet, mens fjorten (45%) deltakere rapporterte symptomer ved bruk av SPEED II. Totalt tjueen (68%) pasienter viste hyperosmolaritet. Tretten (41%) deltakere hadde redusert NIKBUT i minst ett øye, med signifikant kortere break-up verdier funnet i betablokkergruppen ($p=0.004$). Tjueen (68%) studiepersoner hadde reduserte Schirmer I testresultater som indikerte redusert tåreproduksjon, mens bare åtte (26%) deltakere viste mild OSS. Vi fant ingen sammenheng mellom behandlingsvarighet eller etterlevelse og alvorlighetsgraden av OSD, med 29 av 31 (94 %) studiedeltakere som rapporterte at de ikke misset en dose mer enn én eller to ganger i måneden.

Konklusjon: Så vidt vi vet, er dette den første studien der alle forsøkspersoner for tiden ble behandlet med en øyedråpe uten konserveringsmiddel som gjorde at vi kunne undersøke effekten av en enkelt aktiv ingrediens på øyeoverflaten. Vi observerte en høy forekomst av OSD- funn hos deltakere med mild POAG under ukonservert IOP-senkende monoterapi, mens forekomsten av symptomer (OSDI) ble rapportert hos betydelig færre deltakere. Vi fant ingen klar sammenheng mellom behandlingsoverholdelse og alvorlighetsgraden av OSD-symptomer og tegn. Ytterligere studier er berettiget.

Nøkkelord: okulær overflatesykdom, OSDI, glaukom, behandlingsoverholdelse

Abbreviations

A.M. = Andrea Mihovilović

BAK = Benzalkonium chloride

DED = dry eye disease

DSAEK = Descemet stripping automated endothelial keratoplasty

GSS = The Glaucoma Symptom Scale

IOP = intraocular pressure

IPL = intense pulse light

LASEK = laser-assisted epithelial keratomileusis

LASIK = laser-assisted in situ keratomileusis

MDLT = micropulse diode laser trabeculoplasty

MG = meibomian glands

MGD = meibomian gland dysfunction

MIGS = minimal invasive glaucoma surgery

NIKBUT = non-invasive Keratograph tear break-up time

NSD = Norsk senter for forskningsdata (Norwegian Centre for Research Data)

OHT = ocular hypertension

OS = ocular surface

OSD = ocular surface disease

OSDI = Ocular Surface Disease Index

OSS = ocular surface staining

PDG = pigment dispersion glaucoma

PEX = pseudo exfoliation glaucoma

PGA = prostaglandin analog

PLT = pattern scan laser trabeculoplasty

POAG = primary open-angle glaucoma

REK = Regionale komiteer for medisinsk og helsefaglig forskningsetikk (Regional Committees for Medical and Health Research Ethics)

SD = standard deviation

SLT = selective laser trabeculoplasty

SPEED II = Standard Patient Evaluation of Eye Dryness II

TMH = tear meniscus height

TFOS = Tear Film and Ocular Surface Society

TM = trabecular meshwork

TSLT = titanium sapphire laser trabeculoplasty

Contents

Foreword

This thesis is the final step of a three-year journey towards completing my master's study in general practice optometry at the University of South-Eastern Norway after moving to Norway in 2018. I am incredibly proud of the work that went into this thesis, and I hope the reader will enjoy it as much as I enjoyed creating it.

I want to thank my supervisor, Per Lundmark, for his excellent guidance. Also, express gratitude to my partner Thomas and family for their support and care.

Haugesund, 29.04.2022
Andrea Mihovilović

1 Introduction

Glaucoma is a family of optic neuropathies characterized by progressive retinal ganglion cell death and optic nerve fiber layer loss, which results in structural changes of the optic disk followed by irreversible, but preventable deterioration of the visual field's function (Allison, Patel, & Alabi, 2020). Glaucoma is a significant public health issue as a second leading cause of blindness after cataracts (Allison et al., 2020). The social and economic burden of the disease is expected only to increase in a rapidly aging global population with a longer life expectancy (Allison et al., 2020; King, Azuara-Blanco, & Tuulonen, 2013). Although the exact number is unknown, Tham et al. (2014) estimated the number of people with glaucoma (aged 40 to 80 years) to be increasing from 64.3 million in 2013 to 76.0 million in 2020 and 111.8 million in 2040. A recent "World report on vision" by the World Health Organization (2019) estimated that 6.9 million (10.9%) of those suffering from glaucoma have moderate to advanced vision impairment or even blindness subsequent to late diagnosis or inability to receive or to adhere to appropriate treatment.

The term ocular surface disease (OSD) represents a group of chronic multifactorial disorders of the cornea, conjunctiva, lacrimal and meibomian glands such as dry eye disease (DED), blepharitis, meibomian gland dysfunction (MGD), ocular allergies, and topical medication toxicity (Kastelan, Tomic, Metez Soldo, & Salopek-Rabatic, 2013; X. Zhang, Vadoothker, Munir, & Saeedi, 2019). It is often a result of inadequate tear production, tear film instability, and consequently increased tear evaporation that may lead to symptoms of discomfort and decreased visual acuity through different inflammatory mechanisms (Garcia-Feijoo & Sampaolesi, 2012; X. Zhang et al., 2019). Both ocular surface disease and glaucoma have an age-dependent prevalence, meaning that the OSD in glaucoma patients occurs even more frequently with advancing age (Baudouin et al., 2013). However, its prevalence as a comorbidity of glaucoma is higher, at 49-59%, compared to the general elderly population, with an estimated OSD prevalence of 5-50%, depending on the study population and diagnostic criteria (Actis & Rolle, 2014; Kastelan et al., 2013; Stewart, Stewart, & Nelson, 2011). Ystenæs, Sand, and Sundling (2021), estimated a prevalence of OSD/DED symptoms in the general Norwegian population seen in everyday optometric practice to be as high as 59% utilizing the Ocular Surface Disease Index (OSDI) questionnaire.

In order to further clarify the relationship between these two debilitating conditions, we designed a cross-sectional study investigating symptoms and clinical signs of OSD in primary open-angle glaucoma (POAG) patients aged 50 to 75 currently treated with only one intraocular pressure (IOP) lowering agent. The goal of the study was to 1) document the occurrence of symptoms and signs of OSD in POAG patients under treatment with topical IOP-lowering eye drops for a minimum of three months and whether it is related to added preservatives, active substances, or treatment duration. We also set out to 2) investigate the relationship between compliance and symptoms and signs of the OSD (Mihovilovic, 2021).

1.1 Primary open-angle glaucoma

Primary open-angle glaucoma is considered the most common type of glaucomatous optic neuropathies, with a global prevalence of 3.5% in the population aged 40 to 80 years (Tham et al., 2014). In Europe, prevalence is estimated to be slightly lower at 2.5%, and 7.8 million people affected (Allison et al., 2020). According to the first nationwide study of glaucoma prevalence and incidence in Norway by Slettedal et al. published in 2020, the prevalence of treated glaucoma in the general Norwegian population, based on the prescription of anti-glaucoma medication in 2018, was 1.4%, rising to 8% in the population aged 70 years and older (Slettedal, Traustadóttir, Sandvik, & Ringvold, 2020). Common risk factors for developing POAG are increasing age, history of POAG in the first-degree relative, myopia, diabetes, black ethnicity, and elevated intraocular pressure (King et al., 2013). Early detection of the disease through regular ocular health assessments by primary health care professionals, like optometrists, and timely treatment initiation, is critical. The onset of the POAG can be insidious, as patients are often asymptomatic and typically unaware that they are affected until irreversible damage has occurred (King et al., 2013). As the disease progresses, glaucoma patients may experience difficulties performing visual tasks like reading and driving or even encounter mobility difficulties inside and outside the home (Allison et al., 2020). A study done by McGinley et al. found that patients with glaucoma are at higher risk of being admitted to the hospital due to fall injuries than patients that do not have glaucoma (McGinley, Ansari, Sandhu, & Dixon, 2020). In addition, there is a strong correlation between glaucoma and anxiety and depression due to reduced quality of life (Zhang et al., 2017; X. Zhang et al., 2019).

The goal of glaucoma treatment is to preserve satisfying visual function and associated quality of life by preventing irreversible manifest glaucoma injury to the optic nerve through

reduction of the IOP, the only modifiable risk factor, as shown by several significant studies done on the topic (Collaborative Normal-Tension Glaucoma Study Group, 1998; Gordon & Kass, 1999; Miglior et al., 2002). For instance, a meta-analysis done by Maier et al. in 2005 demonstrated a significant prophylactic effect of reducing IOP on the progression of glaucoma and delay in visual field deterioration (Maier, Funk, Schwarzer, Antes, & Falck-Ytter, 2005). Even though laser and surgical treatments have become safer and more approachable, topical IOP lowering eyedrops are widely accepted as a standard course of treatment for most patients (Kastelan et al., 2013). Several topical agents are available today, with prostaglandin analogs and beta-blockers often being an initial choice due to the greatest efficacy in attaining target IOP[1] and often having the lowest side effect profile (King et al., 2013). The success of the glaucoma treatment is highly dependent on the patient's motivation and ability to consistently self-administer eye drops for a condition that is chronic and generally asymptomatic; however, Wolfram et al. reported that as many as 30% of glaucoma patients fail to adhere to prescribed treatment (Wolfram, Stahlberg, & Pfeiffer, 2019). Genuine reasons for such high rates of non-adherence to the treatment of potentially blinding disease are highly variable, but forgetfulness, traveling, and side effects are the most probable (Kholdebarin, Campbell, Jin, & Buys, 2008). Lemij et al. have found a strong association between ocular surface disease and patients' dissatisfaction with glaucoma treatment (Lemij, Hoevenaars, van der Windt, & Baudouin, 2015). In addition, Lee et al. found that the development of MGD can have a negative impact on glaucoma treatment compliance (Lee, Sung, Heo, & Park, 2018).

1.2 Ocular surface disease (OSD) and glaucoma

Ocular surface disease (OSD) can be a comorbidity of many ocular and systemic conditions. It is unclear whether the high occurrence (estimated at 49%-59%) of this condition in glaucoma patients is a novel disease, occurring as a consequence of instigation of topical glaucoma treatment, or if it is a pre-existing condition that is further aggravated by the topical treatment (Garcia-Feijoo & Sampaolesi, 2012; X. Zhang et al., 2019). A study done by Kuppensz et al. has found that even untreated POAG patients are at higher risk for developing OSD due to a 22% lower basal tear turnover rate[2] than individuals without glaucoma, which indicates that glaucoma may also be a factor playing a role in the development of OSD (Baudouin, Kolko,

[1] calculated level of IOP associated with minimal likelihood of glaucoma progression (Popovic-Suic et al., 2005)
[2] the percent decrease of fluorescein dye concentration in the tears per minute after the instillation of fluorescein dye (Sorbara, Simpson, Vaccari, Jones, & Fonn, 2004)

Melik-Parsadaniantz, & Messmer, 2021; Kuppens, Van Best, Sterk, & De Keizer, 1995). Regardless of the underlying cause, research agrees that even a single installation of preserved IOP-lowering topical eye drops can have a hazardous effect on the ocular surface homeostasis (Terai, Müller-Holz, Spoerl, & Pillunat, 2011). Development of OSD in glaucoma patients is associated with reduced density of goblet cells, squamous metaplasia of the conjunctival epithelium, dysfunction of meibomian glands, conjunctival and corneal desquamation, and overexpression of proinflammatory cytokines (Baudouin et al., 2021; Boso, Gasperi, Fernandes, Costa, & Alves, 2020).

Several factors play a significant role in developing OSD among topically treated glaucoma patients. For example, the duration of the treatment and the number of drops instilled is directly correlated to both the prevalence and severity of the OSD (X. Zhang et al., 2019). Since glaucoma is chronic and progressive, many patients may need two or more topical intraocular pressure-lowering agents over extended periods, increasing the risk of developing severe OSD exponentially (Baudouin et al., 2012; X. Zhang et al., 2019). Other factors associated with OSD development are age, female gender, autoimmune diseases, systemic use of antidepressants, antihistamines, or antihypertensives, contact lens use, and different environmental factors (Kastelan et al., 2013). Signs and symptoms of the ocular surface disease (OSD) commonly seen in topically treated glaucoma patients are shown in Table 1. The number of glaucoma patients on topical hypotensive drops complaining of OSD symptoms such as burning, itching, tearing, light sensitivity, and blurred vision is usually significantly higher in clinical practice than the one reported in prospective clinical trials due to their short duration and exclusion of subjects that are already presenting with OSD (Garcia-Feijoo & Sampaolesi, 2012; Kastelan et al., 2013). Decreased tear film stability, tear osmolarity, conjunctival and corneal damage, and conjunctival hyperemia are just some of the signs of this debilitating condition; however, the mechanisms involved are not well understood and are presumed to be allergic, toxic, or proinflammatory nature (Baudouin et al., 2012; Baudouin et al., 2021; Garcia-Feijoo & Sampaolesi, 2012).

Symptoms	Signs
* Blurry/unstable vision * Dry eyes sensation * Tearing/Epiphora * Foreign-body sensation * Stinging or burning sensation * Photophobia * Red eyes * Itchy eyelid edge * Frequent/repeated blinking * Difficulty wearing contact lenses * Difficulty with nighttime driving	* Abnormal tear osmolarity (308 mOsm/L * in either eye or a difference * between eyes 8 mOsm/L) * Abnormal tear break-up time test (TBUT) (<10s) * Abnormal Schirmer test (<10mm) * Corneal and/or conjunctival staining * Limbal and/or bulbar hyperemia * Meibomian gland dysfunction/dropout * Reduced meibomian gland quality * Reduced meibomian gland expression * Lid margin vascularization * Lid margin irregularity's

Table 1 Signs and symptoms of the ocular surface disease (OSD) commonly seen in topically treated glaucoma patients. Table information adapted from: (Kastelan et al., 2013).

1.3 Prevalence of OSD in topically treated glaucoma patients

Ocular surface disease related research relies mostly on the same criteria used to diagnose and manage Dry Eye Disease (DED) as suggested in TFOS Dry Eye Workshop II (Tear Film and Ocular surface Society) from 2017 (Craig et al., 2017; Wolffsohn et al., 2017). Several studies, as presented in Table 2, have tried to document the prevalence of ocular surface disease in topically treated glaucoma patients using different diagnostic tests, questionnaires, and surveys (Asiedu & Abu, 2019). The most popular diagnostic tool is the Ocular Surface Disease Index (OSDI) questionnaire, which can accurately differentiate between normal, mild to moderate, and severe dry eye disease (Schiffman et al., 2000). One of the first relevant studies on this subject was published in 2006 by Tsai et al., and it reported a high prevalence (65.7%) of glaucoma in patients with severe OSD than was previously assumed (Tsai, Derby, Holland, & Khatana, 2006). In 2008, the first large multicenter cross-sectional study (20,506 subjects) was done by Erb et al. in Germany. They found a correlation between the occurrence of the OSD (in subjects with glaucoma) and age, female gender, concomitant disease, number of different eye drops used, type of glaucoma, and its duration (Erb, Gast, & Schremmer, 2008). The same year, Leung et al. performed a cross-sectional study on 101 patients with POAG and ocular hypertension (OHT) using the OSDI questioner. Sixty (59%) patients reported symptoms of a

dry eye in at least one eye, of which 27% presented with severe symptoms. Tear break-up time (TBUT) was reduced in 78% of patients, Schirmer test results were abnormal in 61% of patients, and conjunctival staining with lissamine green was seen in 22% of patients (Leung, Medeiros, & Weinreb, 2008). They also demonstrated that each additional benzalkonium chloride (BAK) preservative containing eyedrop was linked to nearly double odds of presenting with positive ocular surface staining (Leung et al., 2008). The reader should keep in mind that all of the mentioned prevalence studies included mostly glaucoma patients under treatment with several, BAK preserved topical agents, as shown in Table 2.

In 2010, Fechtner and associates examined the prevalence of OSD in POAG and OHT patients using the OSDI questionnaire. They found that 48% of study subjects presented with OSD symptoms, where higher OSDI scores were directly correlated to the greater number of prescribed topical glaucoma eyedrops (Fechtner et al., 2010). Moreover, Garcia-Feijoo and Sampaolesi (2012) included 448 treated glaucoma and OHT patients in a multicenter, international study and observed an overall prevalence of OSD of 59% symptoms using OSDI questioner. They also observed a correlation between OSDI scores, duration of the treatment, and the number of IOP-lowering drugs. The same year, in a first case-control study, Ghosh and colleagues reported a significantly higher prevalence of OSD (70%) in the glaucoma population when compared with controls (Ghosh, O'Hare, Lamoureux, Vajpayee, & Crowston, 2012). They also reported that treatment duration and the number of IOP-lowering agents are the main predictors of OSD severity (Ghosh et al., 2012). In 2013, Rossi et al. enrolled 233 topically treated glaucoma patients in a cross-sectional study. They found an overall prevalence of OSD symptoms of 42% (Rossi et al., 2013). The presence of the OSD was statistically related to the number of IOP-lowering agents used, prolonged use of preserved medications, and total BAK exposure (Rossi et al., 2013).

Authors	Study design	Study population (n, age)	Country	Type of glaucoma	Active substance	Preservatives (BAK)	Clinical tests	OSDI	TBUT	Schirmer	OSS
(Erb et al., 2008)	Multicenter cross-setional	20,506 (N/A)	Germany	POAG PEX PDG	One or more	Yes	TMH LIPCOFs Bulbar redness OSS (fluorescein) TBUT Schirmer II test	N/A	N/A	N/A	N/A
(Leung et al., 2008)	Cross-sectional	101 (18+ y.o.)	USA	POAG OHT	One or more	Yes	OSS (lissamine green) TBUT Schirmer I test	59%	78%	61%	22%
(Fechtner et al., 2010)	Multicenter cross-sectional	630 (18+ y.o.)	USA	POAG PEX PDG OHT	One or more	Yes	None	85%	N/A	N/A	N/A
(Garcia-Feijoo & Sampaolesi, 2012)	Multicenter cross-setional	458 (19.90 y.o)	International	All	One or more	Yes	None	59%	N/A	N/A	N/A
(Baudouin et al., 2012)	Multicenter cross-sectional	516 (18+ y.o.)	France	POAG OHT	One or more	Yes	Custom	N/A	N/A	N/A	N/A

(Rossi et al., 2013)	Cross-sectional	233 (18+ y.o.)	Italy	POAG PEX PDG OHT	One or more	Yes	OSS (fluorescein) TBUT	N/A	30%	N/A	32%
(Saade, Lari, Berezina, Fechtner, & Khouri, 2015)	Controlled, cross-sectional	61 (18+ y.o.)	USA	POAG Vs. Controll	One or more Vs. None	Yes Vs. No	OSS (lissamine green) TBUT	68% vs. 13%	68% Vs. 17%	N/A	65% Vs. 3%
(Ramli et al., 2015)	Controlled, cross-sectional	203 (45+ y.o.)	Malaysia	Glaucoma Vs. Controll	One or more Vs. None	Yes Vs. No	OSS (fluorescein) TBT Schirmer II test	37% Vs. 26%	91 % Vs. 81 %	39 % Vs. 25 %	63% Vs. 36 %
(Pérez-Bartolomé et al., 2017)	Controlled, Cross-sectional	262 (N/A)	Spain	POAG, OHT Vs. Controll	One or more Vs. None	Yes Vs. No	OSS (fluorescein) TMH NIKBUT	41% Vs. 26%	N/A	N/A	27% Vs. 0%
(Ruangvaravate, Prabhasawat, Vachirasakchai, & Tantimala, 2018)	Cross-sectional	109 (N/A)	Thailand	N/A	One or more	Yes	OSS (fluorescein and rose Bengal) TBUT Schirmer test	39%	99%	73%	32%
(Portela et al., 2018)	Controlled, cross-sectional	57 (N/A)	Brazil	POAG	One or more Vs. None	Yes Vs. No	NIKBUT Meibography Bulbar redness TMH	50%	N/A	N/A	N/A

Table 2 Overview of the study population, information about inclusion criteria relating to IOP-lowering medications and preservatives, clinical tests and frequency of the most common symptoms and signs in relevant prevalence studies. (NIKBUT = non-invasive Keratograph tear break-up time, OHT = ocular hypertension, OSDI = Ocular Surface Disease Index, OSS = ocular surface staining, PDG = pigment dispersion glaucoma, PEX = pseudo exfoliation glaucoma, POAG = primary open-angle glaucoma, SPEED II = Standard Patient Evaluation of Eye Dryness II,TMH = tear meniscus height)

More recently, in 2017, Perez-Bartolome and associates found significantly higher OSDI scores (41%vs.26%) and corneal staining (27%vs.0%) in glaucoma patients on topical treatment compared to the control group (Pérez-Bartolomé et al., 2017). As previous authors, they identified treatment duration, preserved topical IOP-lowering agents, and age as major risk factors (Pérez-Bartolomé et al., 2017). In 2018, Ruangvaravate et al. recruited 109 glaucoma patients in a cross-sectional study where 39% of patients reported symptoms of OSD utilizing an OSDI questionnaire. Abnormal TBUT was found in 99% of patients, positive fluorescein and rose Bengal staining were found in 32% and 39%, respectively, and decreased tear film production was observed in 73% of patients (Ruangvaravate et al., 2018). Portella et al. reported a significantly higher occurrence of keratitis and conjunctival hyperemia in a glaucoma group than in the control. Also, this is one of the first studies that attempted to estimate OSD prevalence of signs using objective parameters measured by Keratograph analysis (Portela et al., 2018). Lastly, Wong et al. (2018), in a cross-sectional, paired eye study recruited thirty-three glaucoma subjects treated in only one eye, whereas the other eye served as a control. They found that treated eyes had poorer NIKBUT, tear film osmolarity, bulbar redness, TMH, and Schirmer values.

1.3 Benzalkonium chloride and OSD

Benzalkonium chloride (BAK), the most commonly used preservative in ophthalmic preparations, has consistently demonstrated a toxic effect on the ocular surface, both in vitro and in vivo (Baudouin et al., 2021; Baudouin, Labbe, Liang, Pauly, & Brignole-Baudouin, 2010). The continuous exposure to BAK can destabilize tear film by disrupting the lipid layer and causing swift evaporation of aqueous component, consequentially inducing squamous metaplasia of the conjunctival epithelium, disrupting the corneal epithelium by reducing epithelial cell density, and increasing stromal keratocyte activation (Baudouin et al., 2010; Kastelan et al., 2013; X. Zhang et al., 2019). For example, a study done by Ramli et al. (2015) found three times higher rates of abnormal OSDI scores in glaucoma patients under treatment with topical IOP-lowering drops containing BAK preservative compared to control subjects treated with Purite-preserved or non-preserved eye drops. Baudouin et al. reported that even a short-term treatment with BAK-preserved topical medication could induce tear film hyperosmolality, conjunctival hyperemia, ocular surface changes, subconjunctival fibrosis, and epithelial apoptosis (Asiedu & Abu, 2019; Baudouin et al., 2021; Baudouin et al., 2010). Asiedu et al. reported that BAK could decrease the stability of the precorneal tear film, as it has a

detergent effect on the lipid layer, resulting in premature evaporation (Asiedu & Abu, 2019). In addition, Baudouin et al. found that long-term administration plays a role in the trabecular meshwork (TM) cell loss through oxidative stress, chronic inflammatory changes, and apoptosis within the glaucomatous TM, hypothesizing that it leads to a significant reduction in aqueous humor outflow and increase in IOP (Ammar & Kahook, 2011; Baudouin et al., 2021). Hence, leading to the use of several IOP-lowering agents, more preservatives, and greater ocular inflammation and toxicity (Baudouin et al., 2021). Furthermore, several studies suggested that TM cell loss can result in failure in filtration glaucoma surgery (Baudouin, Denoyer, Desbenoit, Hamm, & Grise, 2012; Baudouin et al., 2021; Hamard, Valtot, Sourdille, Bourles-Dagonet, & Baudouin, 2002). BAK may also be included in slowing corneal wound healing, leaving the ocular surface vulnerable to further injury (Shen, Huang, & Yang, 2019). Induced ocular toxicity is time and concentration-dependent with lower concentrations of BAK, resulting in fewer symptoms and signs of OSD though it is also less effective in preventing microbial growth in the multidose containers (Baudouin et al., 2021; X. Zhang et al., 2019). Improvement of OSD symptoms and signs after switching from BAK-preserved drops to preservative-free treatment alternatives has also been documented (Boso et al., 2020; Katz, Springs, Craven, & Montecchi-Palmer, 2010; Kuppens, De Jong, Stolwijk, Van Best, & De Keizer, 1995). Since POAG and OSD are most prevalent in elderly patients at higher risk of contaminating preservative-free drops in multiuse containers due to difficulties with correct installation, the benefits of prescribing preservative-free should be evaluated against drop safety (X. Zhang et al., 2019). There is some evidence that new generations of preservatives like Polyquad, Purite, and the sofZia have a less toxic effect on the ocular surface than BAK, but this needs to be further researched (Stewart et al., 2011; X. Zhang et al., 2019).

1.4 Active substance and OSD

Prostaglandin analogs (PGAs) and beta-blockers are usually the first choices of POAG and OHT treatment; however, each currently available ocular hypotensive agent has specific potential systemic and ocular side effects, as pointed out in Table 3 (Kastelan et al., 2013). For example, prostaglandin analogs give a considerable IOP-lowering effect, need less frequent dosing, and have fewer systemic side effects, but PGAs have traditionally been preserved with benzalkonium chloride (BAK). Fortunately, preservative-free formulations have become more widely available in the past few years (Lee et al., 2018). Nevertheless, recent studies have demonstrated a high prevalence and severity of obstructive meibomian gland dysfunction (MGD) connected to long-term administration of preserved PGAs (Arita et al., 2012a; Lee et al., 2018; Mocan, Uzunosmanoglu, Kocabeyoglu, Karakaya, & Irkec, 2016). Lee et al. (2018) have also found MGD to be negatively correlated to PGA monotherapy compliance, meaning that the development of MGD might negatively affect treatment compliance. On the other hand, with or without preservatives, beta-blockers reduce basal tear turnover, compromising the integrity of precorneal tear film and inducing damage to the ocular surface, such as superficial punctate keratitis (Servat & Bernardino, 2011; X. Zhang et al., 2019). Brimonidine tartrate, the most commonly used alpha-adrenergic agonist, has a higher incidence of ocular allergies that often result in drug discontinuation (Servat & Bernardino, 2011; X. Zhang et al., 2019). Also, multiple studies have found that topical carbonic anhydrase inhibitors, such as dorzolamide, cause a significant increase in central corneal thickness in patients with compromised corneal endothelium (Servat & Bernardino, 2011). Finally, it can cause severe periorbital dermatitis, induce tear film instability, blurred vision, and superficial punctate staining (Servat & Bernardino, 2011).

	Ocular side effects
Prostaglandin analogs (Latanoprost, Travaprost, Bimatoprost, Tafloptost)	Conjunctival hyperemia, lengthening, thickening and hyperpigmentation of the eyelashes, irreversible hyperpigmentation of the iris, hyperpigmentation of periocular skin
Nonselective beta-blockers (Timolol, Betaxolol, Levobunolol, Carteolol, Metipranolol)	Burning, stinging, aching, photophobia, foreign-body sensation, redness, superficial punctate keratitis, corneal anesthesia
Alpha-2 agonists (Brimonidine, Apraclonidine)	Itching, ocular allergies, redness, pupillary dilatation, and lid retraction
Carbonic anhydrase inhibitors (Brinzolamide, Dorzolamide)	Stinging, irritation, red eyes, allergic blepharoconjunctivitis

Table 3 The most common ocular side effects of topical IOP-lowering eyedrops. Table information adapted from (Bowling, Kanski, Nischal, & PearsonBowling, Kanski, Nischal, & Pearson, 2016, pp. 230-232; Kastelan et al., 2013; Servat & Bernardino, 2011).

1.5 Treatment compliance and OSD

Patients with lifelong asymptomatic diseases, such as glaucoma, are often prone to poor compliance and treatment adherence due to dissatisfaction with the treatment, poor tolerability, numerous side effects, cost, denial, forgetfulness, frequent traveling, etc. (Kholdebarin et al., 2008). Motivation to persevere with the treatment can vary severely during the patient's life as the principal goal of the treatment is the preservation and not improvement of the visual function (Joseph & Pasquale, 2017). Cyclic behavior, such as white coat syndrome, where patients are best at complying with prescribed therapy several days prior to the doctor's appointment and then compliance declines gradually over the following months, is a well-recognized occurrence in the medical community (Schwartz & Quigley, 2008). As mentioned, Wolfram et al. reported that as many as 30% of glaucoma patients fail to adhere to the prescribed treatment (Wolfram et al., 2019), but the number could be even higher, as the patients tend to overestimate their adherence (Schwartz & Quigley, 2008; X. Zhang et al., 2019).

A number of studies have confirmed a correlation between ocular surface disease and reduced quality of life in glaucoma patients that may impact adherence and inevitably contribute to further visual impairment, depression, and anxiety (Portela et al., 2018; Quaranta et al., 2016). A major challenge, therefore, is adding multiple drops to a topical regimen of the patient with a severe form of glaucoma that is already presenting with OSD, as the disease severity is associated with poorer glaucoma-related quality of life and higher exposure to BAK (Conlon, Saheb, & Ahmed, 2017; Skalicky, Goldberg, & McCluskey, 2012). However, prescribing once-daily treatment options has a higher adherence rate than agents that require multiple drop instillations a day (Kastelan et al., 2013).

1.6 Significance of the study

In recent years, OSD has been recognized as one of the most common glaucoma comorbidities, with a large body of evidence indicating that the long-term use of preserved IOP-lowering agents almost always results in a high occurrence of ocular surface symptoms and signs. Due to the multifactorial nature of the condition reported prevalence varies highly thought literature but has been estimated to 49-59% (Actis & Rolle, 2014; Kastelan et al., 2013; Stewart et al., 2011). Lemp et al. (2011) reported already in 2010 that our understanding of pathogenesis, classification, and characteristics of OSD characteristics has expanded considerably. However, its diagnosis and ability to differentiate between early stages and normal variations have been hindered by the lack of objective tests with adequate sensitivity and specificity, sufficient repeatability, ease of performance, and suitability for the clinical practice setting. When faced with the medical necessity of treating a potentially vision-threatening condition such as glaucoma, prevention, and treatment of ocular surface disease are often overlooked (Baudouin et al., 2012). An optometrist may play an essential role in identifying ocular surface disease in glaucoma patients and potentially supervise the management of mild and moderate presentations. Awareness of the high prevalence of the ocular surface disease among glaucoma patients and associated life quality could lead to better management options for OSD and glaucoma and increased patient satisfaction. Patients satisfied with the therapy are more likely to take an active role in their care and comply with prescribed therapies.

In order to attain more clarity on the issue and in an attempt to fill the knowledge gap, we set out to investigate the occurrence of OSD in the POAG population in a cross-sectional study, the first of its kind (to the best of our knowledge) having recruited only patients under unpreserved glaucoma monotherapy, conducting a comprehensive evaluation of symptoms, and clinical signs. Including only relatively young patients, age 50 to 75, with early/mild POAG diagnosis, will hopefully help debunk the common belief that OSD is problematic only in glaucoma patients of age or those with a severe presentation using several eyedrops and BAK preservatives. This study's results are expected to further improve understanding of the connection between glaucoma treatment with IOP-lowering eye drops and ocular surface disease. Recognition and a better understanding of the problem may help individualize treatment options for patients in agreement with personalized medicine. Consequentially, this could positively affect glaucoma treatment outcomes due to better treatment compliance and general improvement of patient life quality.

2 Research objectives and significance

The study's primary objective was to build knowledge about the occurrence of symptoms and signs of ocular surface disease in patients who are on treatment with topical IOP-lowering eye drops.

The main objective of the study was based on the following research questions:

1. What is the occurrence of symptoms and signs of ocular surface disease (OSD) in patients with primary open-angle glaucoma (POAG) who have been on treatment with IOP-lowering eye drops for at least three months?
2. Is the occurrence of symptoms and signs of OSD in patients with POAG related to added preservatives in the IOP-lowering eye drops?
3. Is the occurrence of symptoms and signs of OSD in patients with POAG modified by the active pharmacological substance in the IOP-lowering eye drops?
4. Is the occurrence of symptoms and signs of OSD in patients with POAG related to the duration of the treatment with the IOP-lowering eye drops?

Based on research questions 2-4. the following hypotheses were formulated:

1. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of symptoms of OSD, defined as OSDI index $\geq$ 13 or SPEED II values >5, is greater in patients that are on eye drops with preservatives compared with those that are not.
2. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of signs of OSD, defined as hyperosmolarity, reduced NIKBUT, ocular surface staining, or reduced Schirmer 1 test, is greater in patients that are on eye drops with preservatives compared with those that are not.
3. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of symptoms of OSD is modified by the active pharmacological substance in the IOP-lowering eye drops.

4. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of signs of OSD is modified by the active pharmacological substance in the IOP-lowering eye drops.
5. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of symptoms of OSD is related to the duration of the treatment with an IOP-lowering eye drop of a specific pharmacological category (prostaglandin analogs, beta-blocker, carbohydrase inhibitor or alfa-2-agonist).
6. In a sample of patients with POAG, who have been on treatment with IOP lowering eye drops for at least three months, the frequency of signs of OSD is related to the duration of the treatment with an IOP-lowering eye drop of a specific pharmacological category (prostaglandin analogs, beta-blocker, carbohydrase inhibitor or alfa-2-agonist).

The secondary objective of this study was to investigate a relationship between compliance and symptoms and signs of ocular surface disease.

The secondary objective of the study was based on the following research questions:

1. Is the occurrence of signs and symptoms of OSD in patients with POAG related to self-reported compliance to the treatment with the IOP lowering eye drops?

2. Is the occurrence of signs and symptoms of OSD in patients with POAG independently related to self-reported compliance to the treatment with the IOP lowering eye drops?

Based on these research questions, the following hypotheses were formulated:

1. In a sample of patients with POAG who have been on treatment with IOP lowering eye drops for at least three months, the frequency of symptoms of OSD is different in patients with self-reported poor compliance, defined as single dose skipped or forgotten more than once a week (Robin & Grover, 2011), compared with patients with good self-reported compliance.
2. In a sample of patients with POAG who have been on treatment with IOP lowering eye drops for at least three months, the frequency of signs of OSD is different in patients

with self-reported poor compliance, defined as single dose skipped or forgotten more than once a week, compared with patients with good self-reported compliance.

3. In a sample of patients with POAG who have been on treatment with IOP lowering eye drops for at least three months, the frequency of symptoms of OSD is different in patients with self-reported poor compliance, defined as single dose skipped or forgotten more than once a week, compared with patients with good self-reported compliance, when adjusted for preservatives, pharmacological substance, and duration of treatment.
4. In a sample of patients with POAG who have been on treatment with IOP lowering eye drops for at least three months, the frequency of signs of OSD is different in patients with self-reported poor compliance, defined as single dose skipped or forgotten more than once a week, compared with patients with good self-reported compliance, when adjusted for preservatives, pharmacological substance, and duration of treatment.

Parts of this thesis has been presented in the project protocol as the final exam in MRES019 Research methods and project description (Mihovilovic, 2021) at USN (unpublished).

3 Methods

3.1 Study design and study population

This study was designed as a single-center, cross-sectional clinical study with prospective data collection over a period of six months, from August 2021 to January 2022. It was carried out at the private ophthalmology practice Ifocus Øyeklinikk in Haugesund, Norway, as a sub-study study of an "Ocular Surface and glaucoma. A randomized clinical study of IOP reducing eye drops versus surgical intervention" study (REK no. 253485). The study was conducted in accordance with the Declaration of Helsinki after approval was attained from the Regional Committees for Medical and Health Research Ethics (Regionale komiteer for medisinsk og helsefaglig forskningsetikk (REK)). The project protocol was registered at the Norwegian Centre for Research Data (NSD: Norsk senter for forskningsdata) under a reference number: 924566.

Participants were recruited consecutively from subjects who consented and were eligible to participate in the main study without any attempt to select cases, especially patients motivated by ocular surface symptoms. Therefore, the following recruitment methods were applied for both studies and performed simultaneously. Eligible patients were (1) men and women of any ethnicity; (2) age 50 to 75; (3) with a clinical diagnosis of a mild POAG, currently treated with IOP-lowering eye drops in both eyes (>3 months); and (4) with the ability to read and complete the Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation of Eye Dryness II (SPEED II) questionnaire written in Norwegian. Primary open-angle glaucoma (POAG) had to be diagnosed according to the European guidelines for glaucoma diagnoses and staging of the disease as mild/early with MD loss of less than 5 dB on visual field examinations (European Glaucoma Society, 2021). Subjects eligible for the main study, and thereafter this study (sub-study) were identified from the patient journal system and approached via telephone by the investigator (A.M.), informed about the content of both studies, and then offered an appointment for the comprehensive tear film evaluation.

During a telephone call, recruited subjects were instructed to abstain from taking therapeutic or diagnostic drugs at least two hours before the set appointment (this is relevant for studies to avoid confounding the results). At the beginning of the study appointment, participants were given oral and written information about the studies together with consent forms. Time was allocated to answer any questions related to the research studies. Informed

consent (Annex 1) was obtained from all participants prior to the data collection for both studies. The investigator stored the original signed documents as a permanent part of the subject's medical record. All study subjects were provided with a signed copy of consent forms to ensure transparency. The participants' names were replaced with unique randomized four-digit ID numbers to ensure the anonymity of the participants.

Patients exhibiting any ocular or systemic condition that has OSD as comorbidity and could confound the results of this study (such as Sjogren's syndrome, Rheumatoid arthritis, connective tissue disease, clinically significant atopic disease, lid deformities, manifest corneal disease, dystrophy, or ectasia) were identified from patient journals and excluded from the recruitment process. Additionally, subjects who underwent recent intra- or extra-ocular surgery, had a history of refractive procedures (such as LASIK, LASEK, or radial keratotomy) or previous corneal transplants (DSAEK, lamellar keratoplasty, or similar procedure) were also excluded. The method section was written with respect to the approved project protocol (Mihovilovic, 2021)**.**

3.2 Data collection

After signing informed consent forms, participants underwent a comprehensive tear film evaluation of both eyes. Study participants had to complete two validated questionnaires (OSDI and SPEED II) and were asked (interview) to describe their compliance to the prescribed treatment. After that, a battery of unmasked clinical examinations was performed by the investigator (A.M.) in a fixed order from the least to the most invasive one: Tear film osmolality, Non-invasive Keratograph tear break-up time (NIKBUT), Bulbar redness, Tear Meniscus Height (TMH), Schirmer 1 test, Ocular surface staining (OSS), Meibum quality, Meibum expressibility, Corneal sensitivity, Meibomian gland dropout (Wolffsohn et al., 2017). This is graphically described in Figure 1. Information about age, sex, duration of the treatment, the active pharmacological substance, and the preservatives in the topical IOP-lowering medication were collected from the patient journals. The whole study appointment took 40 to 60 minutes.

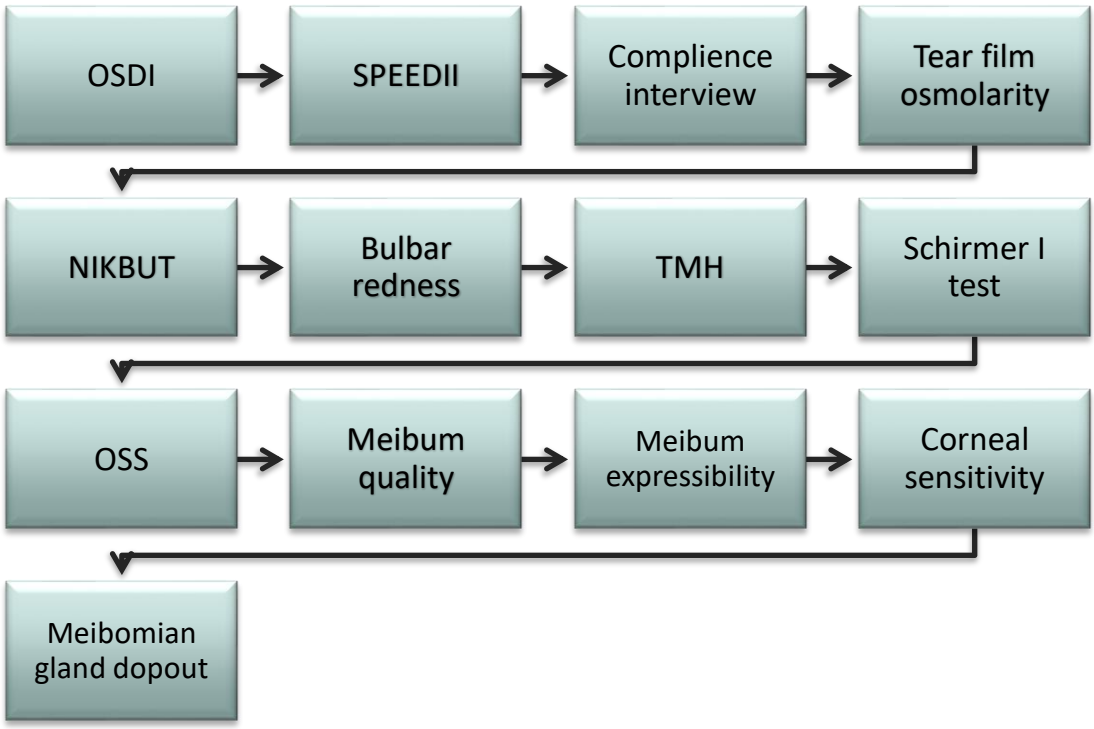


Figure 1 Study subjects were asked to complete two validated questionnaires (OSDI and SPEED II) before a battery of unmasked clinical examinations was performed in the fixed order from the least to the most invasive one.

The Ocular Surface Disease Index (OSDI)

The ocular surface disease index or OSDI (Annex 2) is a 12-item, disease-specific diagnostic tool used in research and clinical practice to quickly assess the severity of OSD symptoms and their impact on a patient's vision-related quality of life. It has demonstrated excellent reliability (0.7) and can accurately differentiate between normal, mild to moderate, and severe dry eye disease (Schiffman, Christianson, Jacobsen, Hirsch, & Reis, 2000). Ocular discomfort, vision-related function, and environmental triggers are quantified with one week recall period. Each response was recorded using a scale that ranged from 0 (none of the time) to 4 (all of the time). The average OSDI scores were then transformed to a scale ranging from 0 to 100 using the following formula:

$$\frac{(\text{sum of scores for all questions answered}) \times 25}{\text{total \# of questions answered}},$$

with higher scores representing greater disabilities (Schiffman et al., 2000). The severity of OSD was then assessed as normal (scores of 0–12), mild (scores of 13–22), moderate (scores of 23–32), or severe (scores of 33–100) (Wolffsohn et al., 2017). Participants were given approximately five minutes to complete the questionnaire independently, where the examiner was allowed to provide only general explanations and was not allowed to interpret or rephrase the questions.

Standard Patient Evaluation of Eye Dryness II (SPEED II)

Standard Patient Evaluation of Eye Dryness or SPEED II (Annex 3) is another validated questionnaire used for research and clinical purposes to investigate OSD symptom changes over the course of 3 months (Ngo et al., 2013). SPEED II was used in this study as it is concurrent with OSDI but better at distinguishing MGD-related dry eye (Wolffsohn et al., 2017). The questionnaire has eight items that assess the type, frequency (0=never, 1=sometimes, 2=often, 3=always), and severity of symptoms (0=not problematic, 1=tolerable, 2=uncomfortable, 3=bothersome, or 4=intolerable). A total scores therefore range from 0 to 28. Values >5 were considered indicative of OSD. Additional five minutes were given to the participants to complete the questionnaire independently.

Compliance interview

Study participants were asked in a short interview to describe their compliance to the prescribed treatment by estimating how often they might forget or skip a single dose. Four possible options were read out to the participants, and they had to choose the one that best describes their compliance (0=less than once or twice a month, 1=once or twice a month, 2=approximately once a week, 3=more than once a week (Robin & Grover, 2011)). The answer was recorded on the data registration sheet.

Ocular surface assessment

All clinical examinations were first performed on the right eye, followed by the left eye in a fixed order.

Tear film osmolarity was measured with calibrated TearLab Osmolality System (TearLab Corporations) from one 50 µl tear sample collected at the temporal part of the lower eyelid margin. In order to collect the sample, participants were instructed to sit with a chin tilted upward and look toward the ceiling (Wolffsohn et al., 2017). Different diagnostic criteria for DED/OSD have been suggested in the literature, from 305 mOsm/L to 316 mOsm/L, with reported sensitivities ranging from 64% to 91% and specificities from 78% to 96% (Potvin, Makari, & Rapuano, 2015; Wolffsohn et al., 2017). In the present study, values above 308 mOsm/L in either eye or a difference between eyes of 8 mOsm/L or more were considered a sign of mild to moderate OSD, whereas values higher than 316 mOsm/L were considered a sign of a moderate to severe presentation (Wolffsohn et al., 2017). The TearLab Osmolarity System has a precision (CV) of 1,5% with a standard deviation (Stdev) of 5.0 mOsm/L and accuracy of r^2=0,95 according to the TearLab Osmolality system Clinical Utility Guide (TearLab™ Osmolarity System).

Non-invasive Keratograph tear break-up time (NIKBUT), **Bulbar redness**, and **Tear Meniscus Height (TMH)** were measured with The Oculus Keratograph 5M by OCULUS, Inc. All of the participants received short instructions about the NIKBUT examination and were helped to place the head correctly in the chinrest to assure comfort and quality measurements. When the Keratograph was aligned with the pupil center, participants were told to blink twice. After the second blink, the measurement of the NIKBUT started automatically. The participants

were verbally encouraged to keep their eyes open as long as possible without blinking to ensure an accurate measurement. The device was calibrated to automatically stop the measurement if the participant moves or blinks (Koh & Tresia De Jager, 2015). The Keratograph 5M provides the time to the first break-up in the tear film after a blink (NIKBUT first) and the average time of all break-ups (NIKBUT average) during a single measurement, and both were registered. Tear break-up time of 10 seconds or less (NIKBUT average ≤10s) was considered indicative of OSD (Wolffsohn et al., 2017). The lower median break-up value (NIKBUT average) of the two eyes was considered when identifying participants with positive findings and diagnosing OSD as advised by the TFOS DEWS II Diagnostic Methodology report from 2017. NIKBUT average exhibits a good correlation to other dry examinations and has acceptable sensitivity (68%), specificity (70%), and repeatability (Wang & Craig, 2018).

Bulbar redness was measured and graded automatically and objectively by taking a picture with the Oculus Keratograph 5M. Integrated R-Scan detects the blood vessels in the conjunctiva and evaluates the degree of redness. Bulbar and limbal redness were measured in 0.1 steps (0 to 4.0), where 0 represents no bulbar redness and 4.0 represents severe bulbar redness according to the integrated JENVIS Pro Dry Eye Report (Oculus Keratograph 5M, OCULUS, Inc.) software grading scale (Koh & Tresia De Jager, 2015). Values ≥2.5 were considered as abnormal bulbar redness (Pult, Murphy, Purslow, Nyman, & Woods, 2008).

Tear Meniscus Height (TMH), the height of the tear prism on the lower eyelid margin, was measured objectively in line with the pupil center from the picture taken with Oculus Keratograph 5M, which has an integrated ruler and various magnification options (Koh & Tresia De Jager, 2015). The diagnostic cutoff for a diagnosis of OSD, based on measurements of tear meniscus height (TMH), was set to <0.1 mm, whereas values between 0.2 and 0.4 mm were considered within normal limits (Wolffsohn et al., 2017).

Schirmer 1 test was performed without anesthetics. The participants were asked to look up, and the free end of the non-toxic calibrated filter paper (TearFloTM) was placed in the temporal part of the lower eyelid of both eyes. To minimize the potential for inducing ocular surface staining and reducing the influence of the vertical gaze position and horizontal eye movements on the test results, participants were asked to hold their eyes gently closed for 5 minutes (Wolffsohn et al., 2017). At the end of the 5-minute interval, the paper strips were removed from each lower eyelid, and the amount of wetting of the paper was noted. Several diagnostic

cut-offs have been proposed in the literature. However, this study considered values under 10 mm in 5 minutes (10mm/5mm) as abnormal and values under 5mm/5min as a definite sign of OSD (Wolffsohn et al., 2017).

Slit-lamp examination of the anterior segment was performed to evaluate **Ocular surface staining (OSS)**. A quantified 5 µl of 2% Fluorescein sodium (MINIMS® Fluorescein Sodium 2%, Bausch&Lomb) was instilled into each conjunctival sac with a micro-pipette (using a sterile tip), and then observation of the ocular surface was done with a slit-lamp (HUVITZ Microscope Slit-lamp HS-7000) using a yellow filter and cobalt blue light. Assessment of the OSS was based on the Oxford schema (Bron, Evans, & Smith, 2003), commonly used to estimate surface damage in dry eye disease. Staining was subjectively assessed and graded in 0.5 steps from 0 (absent) to 5 (severe). Values equal to or higher than 2.0 were set as a diagnostic cut-off and considered indicative of mild OSD.

Meibum quality and **Meibum expressibility** were evaluated during the slit lamp exam using the white light of moderate intensity. Meibum quality was assessed by applying moderate digital pressure on each of the eight glands of the central third of the lower lid with a Q-tip for 10 seconds. It was estimated and graded on a scale from 0 to 3 for each gland: 0=clear, 1= cloudy, 2= cloudy with debris (granular), and 3= thick, like toothpaste (total score range, 0–24) (Nichols et al., 2011). Meibum expressibility was assessed in the five central glands in the lower lid by applying pressure on the lid with a Q-tip. It was estimated on a scale from 0-3 (0= all glands expressible; 1=3-4 glands expressible; 2=1-2 glands expressible; 3=no glands expressible) according to the number of glands expressible (Nichols et al., 2011). Evaluation of the meibum expressibility was performed simultaneously with an evaluation of the meibum quality.

Cochet–Bonnet Aesthesiometer (Luneau Technology Group) was utilized to measure **corneal sensitivity** (Chao, Stapleton, Badarudin, & Golebiowski, 2015)**.** Fine nylon filament (0.12 mm), the length of which can be adjusted (60 mm to 5 mm), was used to apply different intensities of stimuli on the corneal apex. The filament is first extended to a maximum length of 60 mm and thereafter retracted in 5 mm steps until the patient can feel the stimuli. The shortest length[3] of the filament that the patient reacted to was noted.

[3] shorter length of the filament indicates decreased sensation

Meibomian gland dropout (Meibography) was examined by taking infrared photos of the lower eyelid with Oculus Keratograph 5M (OCULUS, Inc) with minimal discomfort to the participant. Gland tissues were made visible by everting the lower eyelid with a Q-tip and using Meibo-Scan (infrared trans-illumination) and classified on the Meiboscale grading scale (Pult & Riede-Pult, 2013) that ranges from 0 to 4 (0=0% loss; 1=≤25%; 2=26%-50%; 3=51%-75%; 4=>75% loss).

3.3 Analyses

The results were recorded in the patient journal system (Infodoc Plenario) used at the Ifocus Øyeklinikk, Haugesund, Norway. The data collected with the Oculus Keratograph 5M by OCULUS, Inc. was stored in a separate database called Oculus Patient Data Management. Once measurements were performed, data related to the study was transferred from the patient journal to a data registration form (Annex 4) in a paper format. The names of the patients were replaced with ID numbers. Thereafter, all data was transferred to and organized in a database (Excel, Microsoft Inc.). To identify empty cells or unrealistic values, an algorithm in Excel flagged the cells in question. A quality-assured version of the database constituted the basis for statistical analyses performed using IBM SPSS version 26. Descriptive statistics presented as frequencies and percentages were used to summarize the demographic data of the study subjects, such as sex, active substance, and preservative, whereas age and treatment duration summaries included mean, standard deviation (SD), minimum and maximum. For most of the predictor variables, we provided central and spread of the raw data (mean, standard deviation, median, minimum, and maximum) on eye level, in addition to frequencies of data categorized regarding the set cut-off values. Frequencies regarding meibomian gland expressibility and Meiboscore was calculated on eye level, whereas the frequency of other symptoms and signs was calculated on a person level, always selecting the worse eye as the basis for the analysis. The normality of distributions was verified using the Shapiro-Wilk normality test. The association between OSD symptoms and signs and treatment duration was analyzed using logistic regression models and a chi-square test. The frequency of symptoms was compared between active substance groups. Linear mixed-effect models that account for the correlation between eyes from the same subjects were also used to test whether the difference between groups is statistically significant. . All statistical tests of hypotheses employed a significance level of $p<0.05$.

4 Results

The present study completed a comprehensive tear film evaluation on sixty-two (n=62) eyes of thirty-one (n=31) participants. Demographic characteristics of the study population are reported in Table 4. The mean age of the participants was 68±6 years, with the youngest participant being 52 years old and the oldest one 75 years old. Twenty-one (68%) participants were in the 65-75 age group, and 61% were female. The mean treatment duration was seventy-seven months with a standard deviation (SD) of 51 months (77±50 months), ranging from only 4 to 236 months of use. When the study was conducted, all participants were under treatment with only one active IOP-lowering substance, with forty-eight eyes (77%) treated with prostaglandin analogs and fourteen (23%) eyes treated with beta-blockers. All of the participants were prescribed an unpreserved topical agent.

Number of participants	31 (62 eyes)
Age (mean±SD) Range	68 ± 6.5 years 52-75 years old
Treatment duration (mean±SD) Range	77.23±50.66 months 4-236 months
Sex: Female Male	 19 (61%) 12 (39%)
Active substance: Prostaglandin analogue Beta-blockers	 24 (77%) 7 (23%)
Preserved formulation	0 (0%)

Table 4 Demographic characteristics of the study population

4.1 Occurrence of symptoms and signs

The overall person-related occurrence of OSD varied from 29% to 68%, depending on the specific test evaluated. When utilizing the OSDI questionnaire (≥13) to evaluate the occurrence of the OSD symptoms, nine (29%) participants reported symptoms. However, when utilizing the SPEED II questionnaire (>5), fourteen (45%) reported symptoms of different intensities. A summary of questionnaire results is presented in Table 5.

Twenty-one (68%) participants presented with hyperosmolarity due to high discrepancies between the eyes of the same participant. Mild to moderate hyperosmolarity was seen in seventeen (55%) participants, whereas severe hyperosmolarity (>316 mOsm/L), considered a moderate to severe presentation, was seen in only 13% of participants (Table 6).

	Mean	Standard deviation	Median	Minimum	Maximum
OSDI	11.65	13.75	8	0	56
SPEED II	5.19	4.36	4	0	16

Table 5 A summary of questionnaire results

(n,%)	OSDI	Osmolarity	NIKBUT	Schirmer I test	OSS
Normal	22, 71%	10, 32%	18, 58%	10, 32%	9, 29%
Mild	2, 6%	17, 55%	9, 29%	8, 26%	14, 45%
Moderate	4, 13%				8, 26%
Severe	3, 10%	4, 13%	4, 13%	13, 42%	0, 0%

Table 6 Occurrence and severity of the symptoms and clinical signs of OSD

A total of thirteen (41%) participants had reduced average NIKBUT (>10s) in at least one eye. Furthermore, four (12%) participants exhibited abnormal bulbar redness (>2.5) (Pult et al., 2008) in at least one of the eyes. Six (18%) participants had abnormal TMH values in at least one eye, whereas none of the subjects met a suggested diagnostic cutoff for aqueous deficiency OSD of TMH less than 0.1 mm. Twenty-one (68%) participants had Schirmer 1 test values below 10 mm/5min in at least one eye, whereas thirteen (42%) had severe aqueous deficiency (<5mm/5min), as shown in Table 6.

	Mean	Standard deviation	Median	Minimum	Maximum
Tear film osmolality (mOsm/L)	296.7	12.2	295.5	275	340
NIKBUT average (s)	14.7	6.2	15.8	2.78	24
NIKBUT first (s)	9.9	6.4	7.7	1.2	24
Bulbar redness	1.7	0.57	1.75	0.6	3.0
TMH (mm)	0.27	0.15	0.23	0.11	1.14
Schirmer I test (mm)	10.29	8.55	8	1	35
Corneal sensitivity (mm)	56.6	4.5	60	45	60

Table 7 Descriptive statistics for numerical variables

Twenty-two (71%) participants exhibited a certain degree of ocular surface staining (OSS). The highest percentage of subjects (45%) had minimal OSS (in at least one of the eyes), 26% of the subjects exhibited mild OSS, and the rest of the subjects (29%) staining was absent (Table 6).

Eighteen participants (58%) had decreased (cloudy/cloudy with debris) meibum quality, while the other thirteen (42%) presented with clear meibum in both eyes on the day of the exam. No more than eight eyes (13%) were graded as having all glands expressible. Twenty-seven eyes (44%) had grade 1 expressibility, eighteen eyes (29%) were classified as grade 2, and nine eyes (15%) were grade 3 or non-expressible. Only two eyes (3%) were found to have no meibomian gland loss, whereas nineteen eyes (31%) were classified as Grade 1, thirteen eyes (21%) as grade 2, thirteen (21%) as Grade 3, and fifteen eyes (24%) were classified as grade 4.

4.2 Occurrence of symptoms and signs in relation to the added preservatives

We were unable to explore the relationship between preservatives and occurrences of OSD symptoms and signs, as all of the consecutively recruited subjects were prescribed with an unpreserved active agent.

4.3 Occurrence of symptoms and signs in relation to the active pharmacological substance

When evaluating the active substance of the currently prescribed treatment as an independent risk factor for development of OSD in this study population, no significance was attained to the occurrence of symptoms using an independent t-test. Average NIKBUT was also found to be significantly longer in participants treated with prostaglandin analogs (p=0.0043) as presented in Table 8.

	Prostaglandin analogue (n=24, 77%)	Beta-blockers (n=7, 23%)	Prostaglandin analogue (mean±SD)	Beta-blockers (mean±SD)	p-value
OSDI	6, 25%	2, 29%	12.63±14.82	8.29±8.82	0.18
SPEED II	12, 50%	2, 29%	5.46±4.39	4.29±4.29	0.38
Tear film osmolarity	15, 63%	6, 86%	296.70±12.87	296.71±10.0	0.999
Average NIKBUT	8, 33%	5, 71%	15.99±5.73	10.17±5.64	0.0043 *
Schirmer I test	18, 75%	3, 43%	9.68±8.66	12.35±8.08	0.433
OSS	5, 21%	3, 43%	0.63±0.7	1.07±0.73	0.08

Table 8 Relationship between active substance and the occurrence of the symptoms and signs of OSD.

4.4 Occurrence of symptoms and signs in relation to treatment duration

The relationship between duration of treatment and symptoms and signs of OSD is displayed in Table 9. Duration of the treatment may be effecting first NIKBUT (r= 0.29, p= 0.023), but not average NIKBUT (r= 0.23, p= 0.067).

OSDI	r= 0.02, p= 0.929
SPEED II	r= 0.14, p= 0.295
Tear film osmolarity	r= 0.004, p= 0.978
Average NIKBUT	r= 0.23, p= 0.067
Schirmer I test	r= -0.2, p= 0.121
OSS	r= -0.06, p= 0.648

Table 9 Correlation of the predictor variables to the duration of the treatment

4.5 Occurrence of symptoms and signs and their relationship to treatment compliance

The relationship between the treatment compliance and symptoms and signs of OSD is displayed in Table 10. Treatment compliance was not significantly affected by OSD symptoms and signs as 94% of participants reported missing a dose no more than once or twice a month.

OSDI	r= 0.14, p= 0.267
SPEED II	r= 0.06, p= 0.656
Tear film osmolarity	r= 0.06, p= 0.637
Average NIKBUT	r= -0.07, p= 0.574
Schirmer I test	r= -0.08, p= 0.528
OSS	r= -0.03, p= 0.788

Table 10 Correlation between treatment compliance and symptoms and signs of OSD

5 Discussion

This cross-sectional study set out to investigate symptoms and clinical signs of OSD in early primary open-angle glaucoma patients treated with only one unpreserved intraocular pressure lowering agent. This gave us a unique opportunity to explore the effect of a single unpreserved active agent on the ocular surface. The main finding in this study was a high occurrence of OSD signs, whereas the frequency of symptoms (OSDI) was reported in significantly fewer participants than in other relevant studies. Symptoms of OSD were reported by nine (29%) of study participants utilizing the OSDI questionnaire, whereas fourteen (45%) participants reported symptoms utilizing SPEED II. A total of twenty-one (68%) patients exhibited hyperosmolarity. Thirteen (41%) participants had reduced NIKBUT in at least one eye, with significantly shorter break-up values found in the beta-blocker group ($p=0.004$). Twenty-one (68%) study subjects had reduced Schirmer I test results indicating reduced tear production, while only eight (26%) participants exhibited mild OSS. Interestingly, all subjects showed signs of meibomian gland dysfunction (MGD). However, we found no association between treatment compliance and severity of OSD, with twenty-nine (94%) of study participants reporting missing a dose no more than once or twice a month.

Most of the relevant studies chose the OSDI questionnaire to estimate the prevalence of OSD symptoms and their impact on vision-related quality of life, as it is user-friendly and cost-effective. In this study, 29% of patients reported OSD symptoms utilizing OSDI, with only 10% presenting with severe OSD. OSDI scores below the diagnostic cut-off indicative of OSD (≥ 13) were less prevalent than those reported in the literature but still higher than the prevalence reported in the age-matched general population, which is why we suspect that the cumulative effect of preservatives such as BAK might not be the “whole story” as all of the participants in this study were treated with a single unpreserved active ingredient. OSDI scores were not correlated to any of the clinical tests performed, which is in agreement with previous studies. It has been postulated that this discrepancy could be related to the driving mechanism, as signs are often caused by tear film hyperosmolality, decreased lubrication, and inflammatory markers (Bron et al., 2017). In contrast, visual symptoms studied with OSDI usually develop secondary to ocular surface irregularities and shorten the tear break-up time (Bron et al., 2017). A significant overlap between mild to moderate forms of the disease and the inability to accurately differentiate them from normal variations in the population has made it hard for researchers and

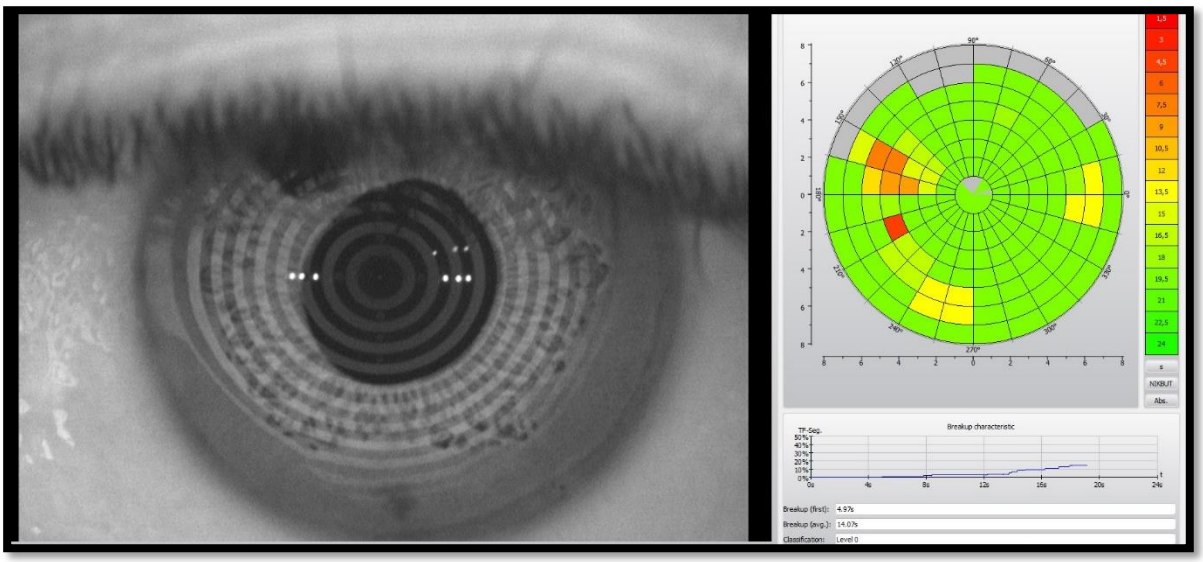
clinicians to determine the true prevalence and incidence of ocular surface disease (OSD) among glaucoma patients.

The occurrence of OSD symptoms was somewhat higher when utilizing the SPEED II questionnaire, with 45% reporting symptoms of different severity. Even though OSDI and SPEED II are both effective for detecting OSD, they cannot be compared directly since SPEED II questions seem to correlate more with parameters of evaporative dry eye compared to OSDI, which is more interrelated with parameters for aqueous tear-deficiency dry eye (Finis et al., 2014; Wolffsohn et al., 2017). SPEED II has not been used on glaucoma patients in earlier prevalence studies and yet has to be verified as appropriate to use in the glaucoma population. However, as more recent research has shown that glaucoma patients experience a high frequency of MGD, SPEED II was chosen to further explore the exact nature of OSD symptoms.

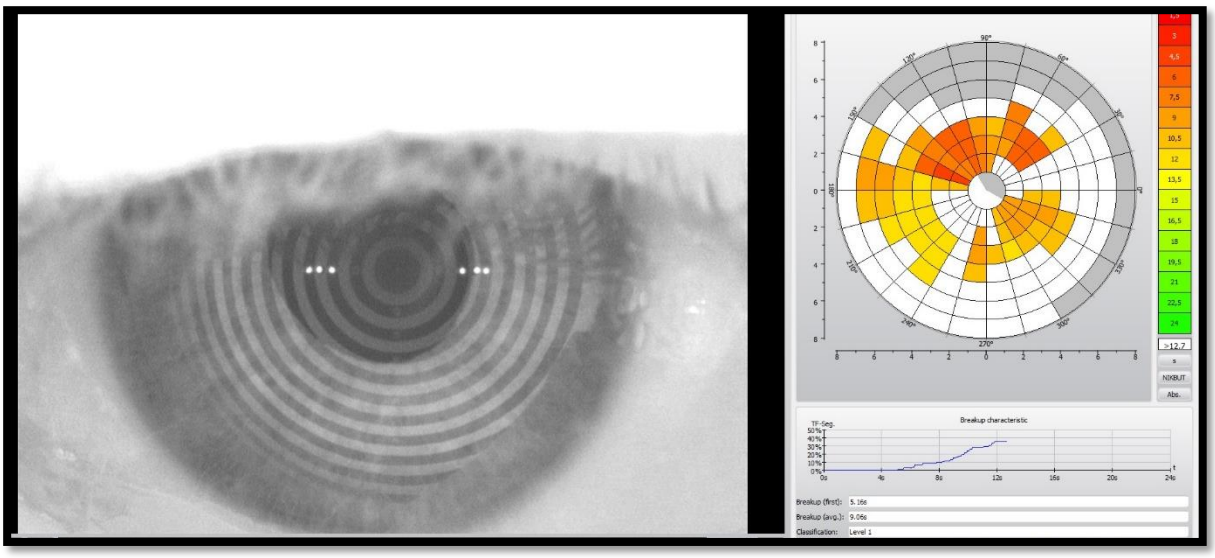
Clinical tests in this study were done to respect diagnostic ability, minimal invasiveness, objectives, and clinical applicability. Tear film osmolality has been described as the single best metric to diagnose and classify OSD, as it is a global marker of the disease that has a higher sensitivity and correlation to the severity of the disease than any other clinical tests (Lemp et al., 2011). In the present study, 68% of the subjects presented with hyperosmolarity values due to high inter-eye variability, a hallmark of an early OSD not seen in the healthy subjects. Tear osmolality variability is highly reflective of the tear film instability that will eventually result in tear hyperosmolality, which can have a devastating effect on the ocular surface epithelium through activation of a cascade of inflammatory events with an increase in inflammatory tear cytokines, increasing apoptotic cell death in surface cells and initiating alterations in mucin expression (Lemp et al., 2011; Wolffsohn et al., 2017). Values over 316 mOsm/L, considered moderate to a severe presentation (Wolffsohn et al., 2017), were recorded in only 13% of our study subjects. Tear film hyperosmolarity has been described in the literature regarding glaucoma patients, but these studies are not comparable due to different study designs and populations. For example, Wong et al. (2018), in a cross-sectional, pair-eye study, found a significantly higher tear film osmolality in the eye that is treated with IOP-lowering agents compared to a fellow eye (313 ± 12mOsmol/L versus 305 ± 11mOsmol/ L, p=0.04). In addition, Lebbe et al. found a statistically significant correlation between tear osmolarity and the number of drugs, the number of installations, and the number of installations of preserved eye drops (Labbe, Terry, Brasnu, Van Went, & Baudouin, 2012). Unfortunately, tear film osmolality as a biomarker is unable to differentiate between aqueous deficiency and evaporative dry eye. Since

the study was performed in Norway in the winter months, environmental factors (temperature, humidity, airflow) could have contributed to increased variability, even though the impact of environmental triggers on tear film osmolality appears to be unclear through literature (Potvin et al., 2015).

Tear break-up time (TBUT) is the most frequently used test in clinical practice due to its practicality and cost-effectiveness. However, it has been argued that TBUT, Schirmer test, and corneal staining lack the power to differentiate mild to moderate forms and, as such, are only helpful in detecting a severe form of the disease. Forty-one percent (41%) of subjects in this study had reduced average NIKBUT (<10s) in at least one eye, whereas only four (12%) subjects had average NIKBUT under five seconds in at least one eye. This is in agreement with previous studies that found a high occurrence of reduced TBUT in 30.5-78% of study subjects; however, these studies included patients treated with multiple preserved active agents where it is expected to see a higher occurrence of tear film instability due to presence of Benzalkonium chloride (BAK) (Leung et al., 2008; Rossi et al., 2013). Interestingly, this study found indications that active substances may play a role in the reduction of TBUT, as a significantly higher average NIKBUT was found in the participants treated with prostaglandin analogs (p=0.004) compared to beta-blockers.

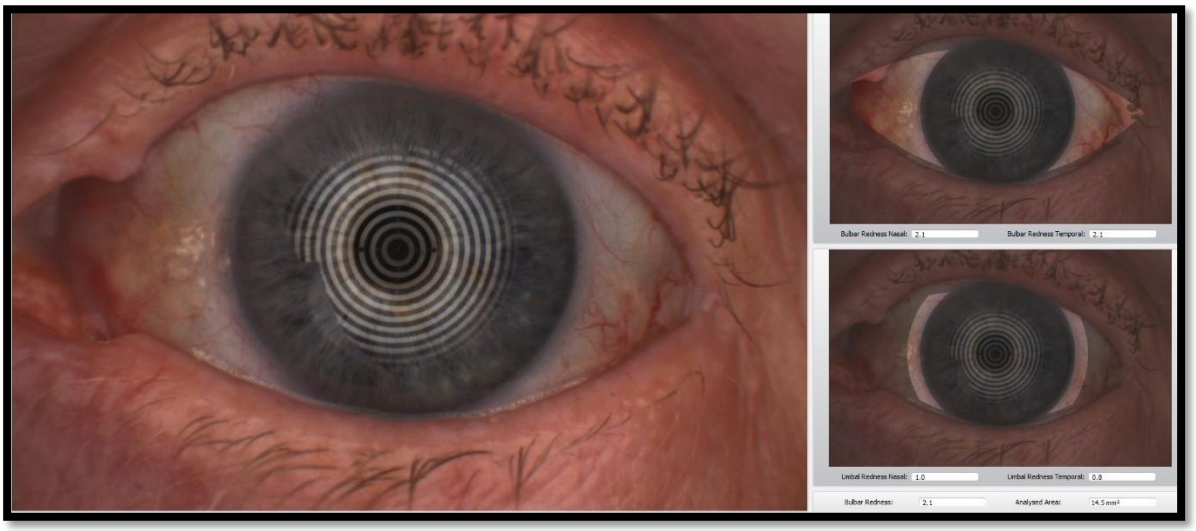


Picture 1 Graphic representation of “normal” average NIKBUT in a glaucoma patient treated with a single unpreserved IOP-lowering agent, with some indication of tear film instability in the nasal part of the cornea.



Picture 2 Graphic representation of “abnormal” first and average NIKBUT in a glaucoma patient treated with a single unpreserved IOP-lowering agent

Abnormal tear meniscus height was found in only 18% of the subjects, whereas bulbar conjunctival hyperemia was seen slightly more frequently than the age-matched general population, which is in agreement with the literature (Portela et al., 2018; Wong et al., 2018). Some authors hypothesized that this is an indicator of ocular surface inflammation as the expected prostaglandin analog-related conjunctival hyperemia usually disappears within a month of use (Wong et al., 2018).



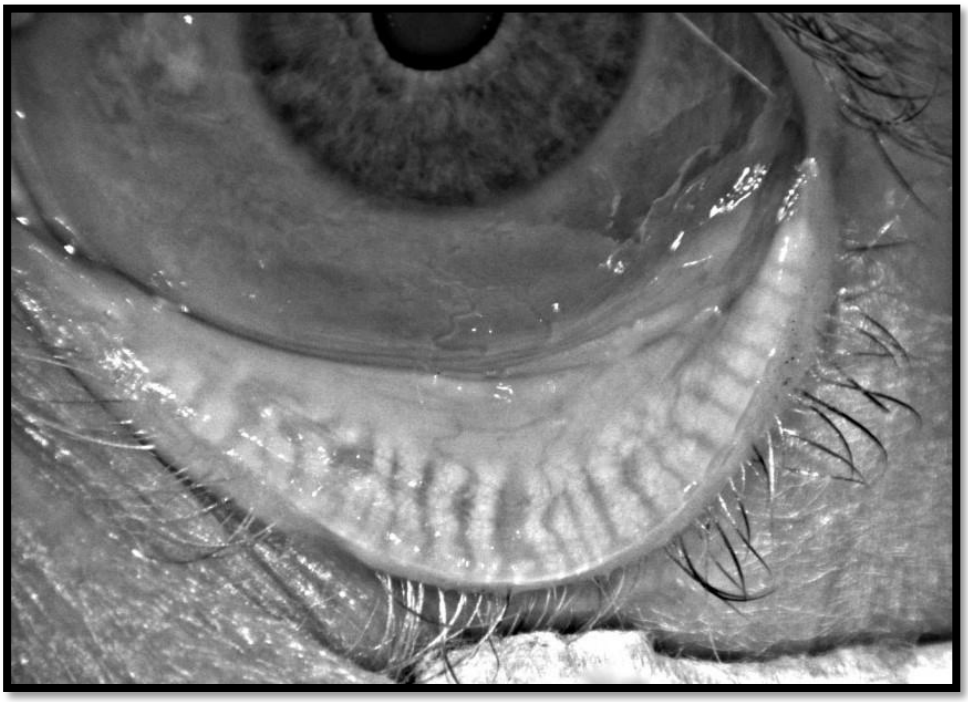
Picture 3 Mean bulbar redness in one of the participants measured by means of Oculus Keratograph

Schirmer I test continues to be one of the most commonly used methods for detection and diagnosis of the dry eye up to date even though it is recommended only for confirming severe aqueous deficiency dry eye due to its invasiveness, length, and variability (Wolffsohn et al., 2017). We measured values below diagnostic cut-off (<10mm) in at least one eye in 68% of the study subjects, where 42% presented with severe tear deficiency. This is in agreement with current literature, where Leung et al. found 61% of patients to have decreased tear production, of which 35% had severe tear deficiency (Leung et al., 2008); however, these studies, even though similar, are not entirely comparable due to different study population, mostly under treatment with preserved IOP-lowering agents.

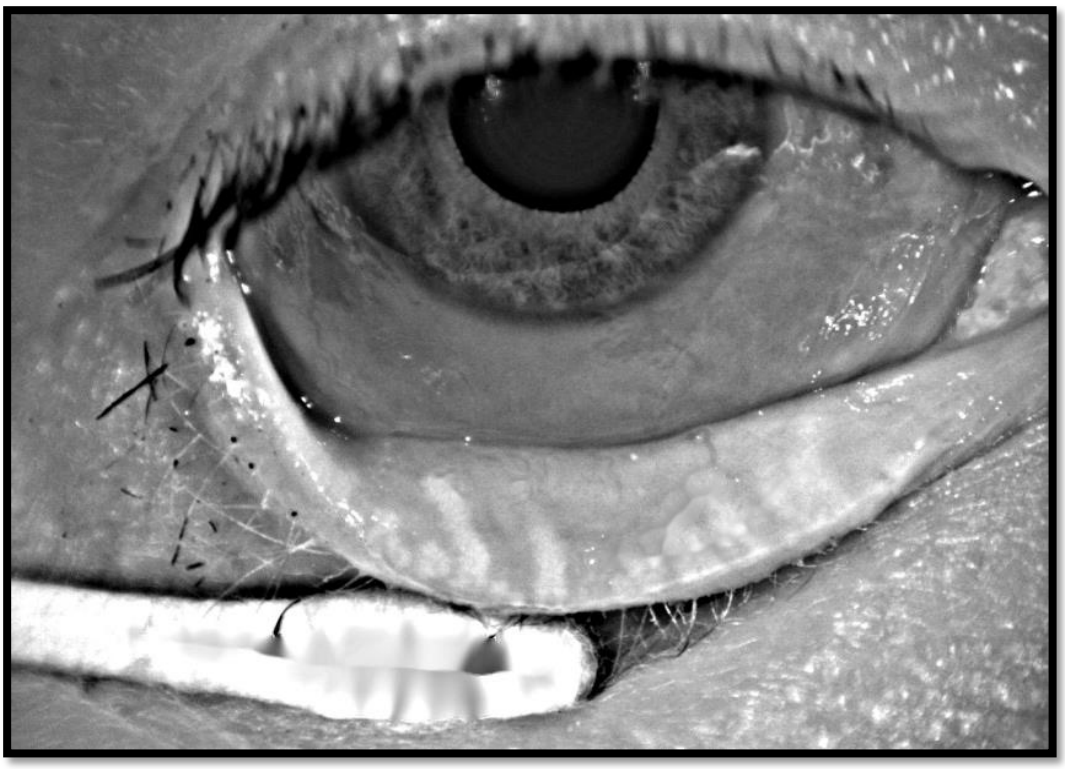
Twenty-two (71%) of study participants exhibited positive ocular surface staining in at least one of the eyes. The highest percentage of subjects (45%) had Grade 1 (minimal) positive OSS (in at least one of the eyes), and 26% of the subjects exhibited Grade 2 (mild) staining. This is in agreement with a study done by Ramli et al. that reported some degree of staining in 63% of the subjects, whereas positive ocular surface staining was reported in 22% of subjects by Leung et al. (Leung et al., 2008; Ramli et al., 2015). Leung et al.'s results might be explained with different grading criteria by not regarding minimal staining (Grade 1) as a positive OSD finding as we did in this study. Moreover, Rossi et al. reported that the number of eye drops and the number of installations per day are independent risk factors for the development of OSS (Rossi et al., 2013).

Meibomian glands play a critical role in maintaining ocular surface homeostasis by secreting meibum, which contains components of the lipid layer of the tear film (Asiedu & Abu, 2019; Wolffsohn et al., 2017). Any changes in the meibomian gland morphological structure or glandular secretion can result in alteration of the tear film, increased evaporation of tears resulting in hyperosmolarity, activation of inflammatory mechanisms, symptoms, and signs of ocular surface disease (Bron & Tiffany, 2004; Knop, Knop, Millar, Obata, & Sullivan, 2011). In this study, all subjects were exhibiting meibomian dropout, 31% classified as Grade 1, 21% as Grade 2, 21% as Grade 3, and 24% classified as Grade 4. We also observed a decreased meibum quality in 58% of study subjects, whereas no more than 13% of eyes were found to have all glands expressible. This is in agreement with several studies, like the one done by Arita et al. or Cho et al., that found a high occurrence of meibomian gland dropout and reduced meibum quality and expressibility in topically treated glaucoma patients (Arita et al., 2012b; Cho et al., 2018; Uzunosmanoglu, Mocan, Kocabeyoglu, Karakaya, & Irkec, 2016). Mocan et

al. reported a higher prevalence of MGD in patients treated with PGA monotherapy (92%) compared to those receiving non-PGA therapy (58.3%) (p=0.02) (Mocan et al., 2016). Moreover, Arita et al. found that meibomian gland duct distortion is associated with allergic conjunctivitis, which led them to believe that meibomian gland loss in topically treated glaucoma patients might be caused by chronic subclinical inflammatory and allergic reactions resulting in lid margin abnormalities, causing the stagnation of meibum followed by the keratinization of orifices in the meibomian glands (Arita et al., 2012b). Furthermore, recent studies have shown that IOP-lowering eye drops can have a devastating effect on meibomian glands, causing permanent glandular dropout and low secretion expressibility. We also observed a decreased meibum quality in 58% of study subjects, whereas no more than 13% of eyes were found to have all glands expressible. However, there was no significant correlation between MGD markers and active substance or duration of the treatment. This is surprising, as one would expect age-related condition such as MGD to progress with the duration of the treatment; however, it agrees with a study done by Arita et al., where they speculated that such changes might not have been detected if the alterations of the meibomian glands had begun within a year of the treatment initiation (Arita et al., 2012a).



Picture 4 Meibomian glands of a glaucoma patient treated with a single unpreserved IOP-lowering agent



Picture 5 Severe meibomian gland drop out of a glaucoma patient treated with a single unpreserved IOP-lowering agent

To the best of our knowledge, this is the first study where all participants were treated with an unpreserved active ingredient that allowed us to examine the effect of only an active ingredient on the ocular surface. When evaluating active substances as an independent risk factor for the development of the OSD, we found that participants treated with prostaglandin analogs had significantly longer NIKBUT compared to patients treated with beta-blockers (p=0.004). When comparing the occurrence of the symptoms, we did not find a significant difference. In the past PGAs have been connected to higher prevalence and severity of obstructive MGD, but this study failed to correlate them, even though we observed a high general occurrence of MGD in both groups (Arita et al., 2012a; Mocan et al., 2016). However, there has been mounting evidence that switching from treatment with preserved to unpreserved active ingredients can dramatically improve OSD symptoms and signs (Henry, Peace, Stewart, & Stewart, 2008; Rosin & Bell, 2013).

Finally, it's important to keep in mind that all of the participants had early POAG; whereas the severity of glaucoma advances, clinicians should expect possible worsening of OSD symptoms and signs and be aware of this when planning further treatment (Baudouin et al., 2012).

Our secondary objective was to explore the relationship between ocular surface disease symptoms and signs and patient self-reported compliance to prescribed topical IOP-lowering treatment as it has been hypothesized that OSD is a significant barrier to adherence and persistence to treatment. Interestingly, we found that compliance was not greatly affected, with 94% of the participants reporting missing a single dose less than once or twice a month. Although cost-effective and straightforward, self-reporting often leads to overestimating compliance due to recall bias and fear of judgment, so the reader should take these results "with a grain of salt". A study of self-reported compliance that used similar criteria as the present study, performed in Canada that included 500 patients in 10 centers, found an overall non-compliance of 27.9%, where the most common reasons for not administering medication was "forgetfulness" and "being away from drops" (Kholdebarin et al., 2008). In the USA, adherence was estimated to be 70%, similar to hypertension pills, and slight side effects like stinging or burning upon installation were surprisingly correlated to better adherence. By contrast, bulbar redness was associated with decreased adherence and medicine discontinuation (Quigley, Friedman, & Hahn, 2007). Moreover, Wolfram et al. found that men were more likely to be non-adherent, whereas age, social status, fear of blindness, and disease severity were not directly related to nonadherence levels (Wolfram et al., 2019). We found no association between compliance and OSD symptoms or signs. Lemij et al. reported that, all things considered, 89% of study participants were satisfied with prescribed treatment regardless of receiving preserved agents (Lemij et al., 2015). Improvement in adherence is seen with a duration of treatment and a once-daily fix combination (Kastelan et al., 2013). Patients in Norway are at an advantage, having access to a strong public healthcare system, where preservative-free medications have been prescribed more frequently in recent years, especially to those suffering from OSD.

Finally, as the first line of treatment, the unpreserved active agent is almost always superior to the preserved ones. Emphasis should be on reducing exposure to BAK, as its devastating effect on the ocular surface (OS) is well-documented through literature; however, it may not be enough to sustain homeostasis. As this study has demonstrated, unpreserved agents may delay the occurrence of OSD symptoms; however, signs are surprisingly a common occurrence in population that use unpreserved topical agents. We would argue that the occurrence of OSD in topically treated patients is not a matter of "if" and more of "when". New treatment methods, like selective laser trabeculoplasty (SLT), have a double benefit, delaying treatment with topical agents and, in such, preventing the development of OSD, as well as

reducing medication non-compliance (X. Zhang et al., 2019). As a primary treatment of POAG, Conlon et al. (2017). reported that SLT alone could be cost-effective over six years, assuming that SLT is repeated every 2 to 3 years. New laser modalities, like micropulse diode laser trabeculoplasty (MDLT), titanium sapphire laser trabeculoplasty (TSLT), and pattern scan laser trabeculoplasty (PLT), are currently under investigation, but preliminary data is encouraging (Conlon et al., 2017). Nevertheless, how laser trabeculoplasty affects ocular surface homeostasis is not known yet. Minimally invasive glaucoma surgery (MIGS) can also be a good option for the patients that require cataract surgery, as the procedure can be performed without additional risks, and it has a high safety profile, good ability to lower IOP, causes minimal trauma, and has quick recovery time (Quigley et al., 2007). IStent Inject by Glaukos Corporation is one of the widely used MIGS devices, and Schweitzer et al. had recently reported a dramatic improvement in ocular surface health three months post-surgical implantation of such device and discontinuation of topical treatment (Schweitzer et al., 2020). Similar improvement was observed by Romano et al., where successful trabeculectomy of one eye showed better ocular surface homeostasis than a topically treated fellow eye (Romano, De Ruvo, Fogagnolo, Farci, & Rossetti, 2022). In the absence of better treatment options, when a physician has to prescribe preserved topical treatment, a study done by Boso et al. found that short-term OSD treatment can improve symptoms, IOP control, avoid discontinuation of the medicine, and prevent poor compliance (Boso et al., 2020). The combination of a heated eye mask and intense pulse light (IPL) treatment might be used to treat MGD (Arita, Fukuoka, & Morishige, 2019; Tashbayev, Yazdani, Arita, Fineide, & Utheim, 2020). The topical use of 20% autologous serum for toxic corneal epitheliopathy has proven effective (Yoon et al., 2020). New forms of medication delivery are also being researched, such as bimatoprost ocular insert, latanoprost, travoprost punctal plugs, latanoprost-eluting contact lenses, and bimatoprost and travoprost intraocular implants (X. Zhang et al., 2019).

This study has a few limitations, including a small sample without a control. A cross-sectional study design can make it hard to determine the "cause-effect" relationship between variables and, therefore, unable to reveal a true mechanism behind OSD in glaucoma patients. Moreover, the status of meibomian glands before initiation of the treatment was unknown, and a longitudinal study design might have been more appropriate to investigate the effect of topical IOP-lowering medications on the morphology of meibomian glands. Another limitation of the study is that we did not account for the possible changes in treatment over the disease course, which could have led to the effect of the last (current) medication being overestimated. The

principal investigator being unmasked and some of the examinations being subjective opened a possibility for bias in the form of underestimation, overestimation, and misclassification. Since all eligible subjects were recruited from a single private practice, selection bias might have caused us to overestimate the occurrence of the OSD symptoms and signs by recruiting patients that may not be representative of a general Norwegian POAG population. Lastly, compliance with the treatment might have been better investigated by accessing the subject's pharmacy logs. Despite its various limitation, this study has proven that the occurrence of OSD symptoms and signs is still alarmingly high, despite all subjects being treated with unpreserved agents, leaving us with a conclusion that BAK might not be a "whole story". Future studies, performing such a comprehensive tear-film evaluation on more POAG patients using a single unpreserved topical agent may be necessary to confirm the contents of the study; however, a case-control or longitudinal study design might be more appropriate in order to reveal the true mechanism behind OSD in glaucoma patients. Also, further research is needed on the effects of mentioned new modalities on the ocular surface.

Conclusion

To the best of our knowledge, this is the first study where all subjects were currently treated with an unpreserved active ingredient that allowed us to examine the effect of a single active ingredient on the ocular surface. This study observed a high occurrence of OSD signs in POAG patients under treatment with unpreserved prostaglandin analogs and beta-blockers, whereas the frequency of symptoms (OSDI) was reported in considerably fewer participants. The relationship between treatment compliance and severity of OSD symptoms and signs remains inconclusive. Further studies are warranted.

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List of tables, figures, and pictures

Annexes

Annex 1: Consent form

IFOCUS ØYEKLINIKK

OSDAM-PROTOCOL-APPEND1-040921

FØRESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT

TÅREFILM STATUS

HOS PASIENTER SOM BEHANDLES MED ØYEDRÅPER FOR GRØNN STÆR

Dette er en forespørsel til deg om å delta i et forskningsprosjekt for å studere tårefilmen hos pasienter som behandles med trykkreduserende øyedråper for grønn stær (glaukom). I dette skrivet vil vi gi deg informasjon om målene for prosjektet og hva deltakelsen vil innebære for deg.

HVA INNEBÆRER PROSJEKTET?

Det er kjent at øyedråper som brukes i behandlingen av grønn stær kan gi problemer med tørre øyne for noen. Slike bivirkninger kan påvirke viljen og evnen til å utføre behandlingen slik den er foreskrevet av øyelegen. Unnlatelse av å fullføre behandlingen kan øke risikoen for skader relatert til sykdommen.

Vi kjenner til at jo bedre tårefilmen er, desto bedre er øyet beskyttet mot uheldige effekter av øyedråpene. Målet med denne studien er å undersøke forekomsten av tørrhet og øyeirritasjon hos pasienter som daglig bruker trykkreduserende øyedråper for grønn stær. Vi håper at en bedre forståelse av problemet kan føre til bedre behandlingsalternativer i fremtiden.

Denne studien er en del av en mastergradsoppgave ved Universitetet i Sørøst-Norge og er en del av et overordnet forskningsprosjekt ved Ifocus Øyeklinikk.

For å gjennomføre studien må vi gjøre en grundig tårefilmevaluering. Dette er en tilleggsundersøkelse som varer omtrent en time. Alle undersøkelser vil bli utført av en erfaren kliniker. Spørreskjemaer vil bli brukt for å undersøke symptomer og funksjonsbesvær som kan være relatert til tørt øye. Kvaliteten på tårefilmen vil bli undersøkt direkte og indirekte med anerkjente kliniske metoder for vurdering av saltheten i tårefilmen (osmoloratitet), stabiliteten av tårefilmen og volumet, tåreproduksjon og tårekvalitet. Hornhinnen vil bli undersøkt for spor av uttørkning og nedsatt følsomhet. Øyelokkets kjertler som er viktige for tårekvaliteten vil også bli undersøkt. I tillegg vil det innhentes opplysninger om behandlingen med trykksenkende øyedråper, eks typen av dråper, dosering, konserveringsmidler og behandlingstid.

Side 1/4

MULIGE FORDELER OG ULEMPER

Det er ingen direkte fordeler eller ulemper forent med deltakelse i prosjektet.

Som deltaker i studien er du forsikret gjennom Norsk Pasientskadeerstatning (NPE).

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Hvis du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst, og uten å oppgi noen grunn trekke ditt samtykke. Det vil ikke ha noen negative konsekvenser for deg eller din behandling hvis du ikke vil delta eller senere velger å trekke deg.

Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Dersom du senere ønsker å trekke deg eller har spørsmål til prosjektet, kan du kontakte prosjektmedarbeider Andrea Mihovilovic eller prosjektleder Kjell Gunnar Gundersen (se kontaktinformasjon på side 3).

HVA SKJER MED INFORMASJONEN OM DEG?

Opplysningene som registreres om deg skal kun brukes slik som beskrevet under formålet med prosjektet. Eventuelle utvidelser i bruk og oppbevaringstid kan kun skje etter godkjenning fra REK og andre relevante myndigheter. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert. Du har også rett til å få innsyn i sikkerhetstiltakene ved behandling av opplysningene. Du kan klage på behandlingen av dine opplysninger til Datatilsynet og institusjonen sitt personvernombud.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun prosjektmedarbeider Andrea Mihovilovic og prosjektleder Kjell Gunnar Gundersen som har tilgang til denne listen.

Opplysningene om deg planlegges brukt til til 31 mai 2022. Opplysningene om deg vil deretter bli oppbevart i fem år etter prosjektslutt av kontrollhensyn.

FORSIKRING

Som deltaker i studien er du forsikret gjennom Norsk Pasientskadeerstatning (NPE).

ØKONOMI

Det ytes ingen kompensasjon for tapt arbeidstid eller reise til og fra studiedeltagelse.

Prosjektet dekker ekstraordinære utgifter dersom det ikke dekkes av pasientreiser.

GODKJENNINGER

Regional komité for medisinsk og helsefaglig forskningsetikk har gjort en forskningsetisk vurdering og godkjent prosjektet. REK no. 273850.

Etter ny personopplysningslov har behandlingsansvarlig institusjon Universitetet i Sørøst-Norge et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

På oppdrag fra Universitetet i Sørøst-Norge har NSD – Norsk senter for forskningsdata AS vurdert at behandlingen av personopplysninger i dette prosjektet er i samsvar med personvernregelverket. Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet eller ønsker å trekke deg fra deltakelse, kan du kontakte:

- Prosjektmedarbeider Andrea Mihovilovic, mailadresse: andrea@ifocus.no, telefon: 52808900,
- Prosjektansvarlig Kjell Gunnar Gundersen, mailadresse: kg@ifocus.no, Ifocus Øyeklinikk AS, telefon: 52808900
- Prosjektansvarlig Per O. Lundmark, mailadresse: per.lundmark@usn.no, telefon: 31 00 89 37.

Dersom du har spørsmål om personvernet i prosjektet kan du ta kontakt med personvernombudet ved Universitetet i Sørøst-Norge er Paal Are Solberg, mailadresse: paal.a.solberg@usn.no, telefon: 35 57 50 53/918 60 041.

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER BRUKES SLIK DET ER BESKREVET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Rolle i prosjektet

Annex 2: OSDI questioneer

Måling av symptomer på tørre øyne

Dette er en måling av dine symptomer på tørre øyne. Overvei nøye for hvert av de 12 spørsmålene i hvilken grad de passer for dine opplevelser i løpet av **den siste uken.** Sett deretter en sirkel rundt det tallet som passer best til hvert spørsmål.

Har du opplevet følgende symptomer den siste uken?	Hele tiden	Det meste av tiden	Halvparten av tiden	Noen ganger	Aldri
Grus eller følelse av fremmedlegeme?	4	3	2	1	0
Smerte eller irritasjon i øynene?	4	3	2	1	0
Lysømfindtlighet?	4	3	2	1	0
Tåkesyn?	4	3	2	1	0
Dårlig syn?	4	3	2	1	0

Har øyeproblemer medført begensning av følgende aktiviteter den siste uken?	Hele tiden	Det meste av tiden	Halvparten av tiden	Noen ganger	Aldri
Lesing?	4	3	2	1	0
Bilkjøring i mørket?	4	3	2	1	0
Arbeid ved PC?	4	3	2	1	0
Se på TV?	4	3	2	1	0

Har du merket ubehag i øynene ved følgende den siste uken?	Hele tiden	Det meste av tiden	Halvparten av tiden	Noen ganger	Aldri
Når det blåser?	4	3	2	1	0
I lokaler med tørr luft?	4	3	2	1	0
I bil/rom med aircondition?	4	3	2	1	0

Annex 3: SPEED II questioneer

IFOCUS

SPØRRESKJEMA TØRRE ØYNE - SPEED II

Navn:_____ Dato:_____

1. Beskriv **hyppigheten** av symptomene dine ved å krysse av i tabellen nedenfor

	0	1	2	3
Symptomer	Aldri	Noen ganger	Ofte	Alltid / Konstant
Tørrhet eller ruskfølelse				
Sårhet eller irritasjon				
Rennende øyne				
Trøtthet i øynene				

2. Beskriv **alvorlighetsgraden** av symptomene dine ved hjelp av listen nedenfor

	0	1	2	3	4
Symptomer	Ikke noe problem	Lette plager	Moderate plager	Alvorlig	Uutholdelig
Tørrhet eller ruskfølelse					
Sårhet eller irritasjon					
Rennende øyne					
Trøtthet					

3. Kryss av hvis du har opplevet symptomene ovenfor ☐ I dag ☐ Siste 3 dager ☐ siste 3 mnd

Bruker du kontaktlinser? ☐ Ja ☐ Nei

Benytter du deg av øyendråper og/eller salver ☐ Ja ☐ Nei

Om ja, hvilke dråper/salver bruker du og hvor ofte?

_____

Når brukte du sist dråper/salver? _____

Har du varierende syn som bedres ved blunking? ☐ Aldri ☐ Noen ganger ☐ Ofte

Har du Blefaritt? ☐ Ja ☐ Nei Har du blitt behandlet for «Sti på øyet» ☐ Ja ☐ Nei

Har du hatt disse symptomer i det siste? ☐ Røde/irriterte øyelokk ☐ Puss/flass på øyelokk

Annex 4: Data registration form

DATA COLLECTION REGISTRATION FORM: OCULAR SURFACE AND GLAUCOMA

Study subject ID: _____

Signed consent from: ☐

Age: _____ Sex: _____

Active pharmacological substance: 1= prostaglandin analogs / 2=beta-blocker/ 3=carbohydrase inhibitor/ 4= alfa-2-agonist

Duration of the treatment: _____

Preservative: YES / NO

Self-reported compliance:

0=less than once or twice a month / 1=once or twice a month / 2=approximately once a week / 3 = more than once a week

Test:

	Def	Score
OSDI	≥ 13; 1-100	
Speed II	> 5; 0-28	

Tear film osmolarity (TearLab)	Def	OD	OS	Air temperature/humidity
	≥ 308 m0sm/L			

	Def	OD	OS	Air temperature/humidity
NIKBUT (first)	< 10 sec			
NIKBUT (average)	< 10 sec			
Bulbar redness	Grade 1 - 4			
TMH	< 0,2 mm			

Schirmer 1 test	Def	OD	OS	Air temperature/humidity
	< 10 mm			

Ocular surface staining	Def	OD	OS
	Oxford grading; 0-5		

Cormeal sensitivity (Cochet-Bonnet)	Def	OD	OS
	60 mm to 5 mm		

Meibom	Def	OD	OS
Meiboscore	Grade 0 = 0%, no loss; Grade 1 = ≤25% loss; Grade 2 = 26%-50% loss; Grade 3 = 51%-75% loss; Grade 4 = >75% loss.		
Meibum quality	Grade 0 = clear; Grade 1 = cloudy; Grade 2 = granular; Grade 3 = white, toothpaste.		
Meibum expresibility	Grade 0 = all expressible, Grade 1 = 3-4 expressible, Grade 2 = 1-2 expressible, Grade 3 = non expressible		