Ocular surface complications in primary open-angle glaucoma

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

Project protocol, 04.09.2021.

Introduction:

Glaucoma is a chronic progressive optic neuropathy characterized by retinal ganglion cell death and optic nerve fiber layer loss that can cause progressive deterioration of the peripheral vision, and if left untreated, can lead to severe visual impairment and even blindness (Weinreb, Aung, & Medeiros, 2014). Elevated intraocular pressure (IOP) is the most consistent risk factor for developing glaucoma, and lowering it is the only recognized treatment method (Boland et al., 2013). Topical IOP-lowering eye drops are often used as the first line of treatment to reduce the intraocular pressure and prevent damage to the optic nerve; however, recent research indicates an association between topical treatment and ocular surface disease (OSD) (Zhang, Vadoothker, Munir, & Saeedi, 2019).

The prevalence of OSD in patients with glaucoma varies from 22% to 78%, depending on the specific test used (Baudouin et al., 2013; Fechtner et al., 2010; Leung, Medeiros, & Weinreb, 2008). Research agrees that glaucoma and ocular surface disease co-exist, and OSD often worsens with age, duration of the treatment, and a number of topical IOP lowering eye drops with and without preservatives (Baudouin et al., 2013; Stewart, Stewart, & Nelson, 2011). Dryness, fatigue, burning, variable visual acuity, and photophobia are the most common symptoms of OSD and can affect a patient's ability to work and quality of life (Leung et al., 2008; Zhang et al., 2019). Schwartz et all. demonstrated that 23 to 59% of patients are not adherent to prescribed therapy with topical IOP lowering medication, but it is unclear whether this is related to OSD (Schwartz & Quigley, 2008). A study by Boso et all. that investigated the impact of the OSD treatment in glaucoma patients (Boso, Gasperi, Fernandes, Costa, & Alves, 2020) showed that short-term treatment could improve signs and symptoms of OSD. A better understanding of the cause-effect relationship between OSD and glaucoma treatment with IOP-lowering eye drops may help individualize treatment options for patients in agreement with personalized medicine.

Signs and symptoms of OSD are often non-specific to the ocular surface and caused by allergic, pro-inflammatory, or toxic conditions (Stewart et al., 2011). Ocular surface toxicity, especially to benzalkonium chloride (BAK) preservative, has been established and thoroughly discussed in the literature, which is why preservative-free treatment options are increasingly advocated, especially in patients already presenting with OSD (Stewart et al., 2011; Zhang et al., 2019). Performing a comprehensive tear film assessment in glaucoma patients may be beneficial and lead to a better understanding of the disease. To the best of our knowledge, no studies performed a full ocular surface assessment in glaucoma patients on topical treatment with IOP-lowering eye drops.

Research objectives and significance:

The main objective of the study is to investigate signs and symptoms of ocular surface disease in patients on topical glaucoma medications.

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

1. What is the occurrence of signs and symptoms 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 signs and symptoms of OSD in patients with POAG related to added preservatives in the IOP-lowering eye drops?
3. Is the occurrence of signs and symptoms of OSD in patients with POAG modified by the active pharmacological substance in the IOP-lowering eye drops?

4. Is the occurrence of signs and symptoms 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 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.
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 symptoms of OSD, defined as OSDI index ≥ 13 or SPEED II values >5, 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 signs of OSD, defined as hyperosmolarity, reduced NIKBUT, ocular surface staining, or reduced Schirmer 1 test 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 symptoms of OSD, defined as OSDI index ≥ 13 or SPEED II values >5, 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 signs of OSD, defined as hyperosmolarity, reduced NIKBUT, ocular surface staining, or reduced Schirmer 1 test 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 symptoms of OSD, defined as OSDI index ≥ 13 or SPEED II values >5, 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 is to investigate a relationship between compliance and signs and symptoms of the 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 signs of OSD, defined as hyperosmolarity, reduced NIKBUT, ocular surface staining, or reduced Schirmer 1 test, 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 symptoms of OSD, defined as OSDI index ≥ 13 or SPEED II values >5, 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 signs of OSD, defined as hyperosmolarity, reduced NIKBUT, ocular surface staining, or reduced Schirmer 1 test, 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 symptoms of OSD, defined as OSDI index ≥ 13 or SPEED II values >5, 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.

The results are expected to improve the understanding of the connection between glaucoma treatment with IOP-lowering eye drops and ocular surface disease. Acknowledgment of the problem may help to individualize treatment options for patients in agreement with personalized medicine. This could consequentially lead to the general improvement of patient life quality and treatment compliance that could also positively affect glaucoma treatment outcomes.

Study design:

This is a cross-sectional study with six months prospective data collection.

Study sample:

The target population is patients on topical treatment for POAG.

Study population:

This study is a sub-study of an "Ocular Surface and glaucoma. A randomized study of IOP reducing eye drops versus surgical intervention" study (REK no. 253485). Invited to participate in the study are men and women between 50 and 75 years of age with early POAG, diagnosed in agreement with the European guidelines for glaucoma diagnoses and staging of the disease, with MD loss of less than 5 dB on visual fields and with a clinically significant cataract eligible for surgery, who come for a routine glaucoma follow-up examination and a presurgical assessment for cataract extraction at the ophthalmology practice of Ifocus Øyeklinikk in Haugesund, Norway, in the period between August 2021 and February 2022.

Exclusion criteria:

- Recent changes (<3 months) in the treatment with topical IOP-lowering medications (i.e., active pharmacological substance, dosage, preservatives) based on the patient medical journals.
- Use of more than one IOP-lowering eyedrops with different active pharmacological substances based on the patient medical journals.
- Self-reported OSD comorbidity defined as an autoimmune or inflammatory disease, such as Sjogren's syndrome or Rheumatoid Arthritis (RA), or any other systemic disease that can directly affect the ocular surface.
- Conditions that may confound the results of the study:
    - Self-reported acute or chronic diseases such as connective tissue disease, clinically significant atopic disease, diabetes type 1 and 2, immunocompromised, or any other such condition.
    - Manifest corneal disease, dystrophy, or scaring based on the clinical exam.
    - Corneal ectasia based on the clinical exam.
    - Lid deformities based on the clinical exam.

- Recent intra- or extra-ocular surgery based on the patient medical journals.
- Previous refractive procedures like LASIK, LASEK, or radial keratotomy based on the patient medical journals.
- A previous corneal transplant, DSAEK, lamellar keratoplasty, or similar procedure based on the patient medical journals.

Recruitment:

Recruitment of subjects will take place in the ophthalmologic practice of Ifocus Øyeklinikk in Haugesund, Norway. This study is a sub-study of an "Ocular Surface and glaucoma. A randomized study of IOP reducing eye drops versus surgical intervention" study (REK no. 253485), and the participants in this study will be recruited from subjects that have given their consent to participate in the main study. Patients who come for follow-up glaucoma controls with visual field examination in our clinic and meet all criteria for inclusion will be invited to participate in the study. Eligible patients will be given oral and written information about the study together with a consent form (Appendix 1). The recruited patients' names will be replaced with unique randomized three-digit ID numbers to ensure the anonymity of the participants. The key list that links patients' names with ID numbers will be deleted five years after the completion of the study. The aim is to recruit 30 subjects (60 eyes), which is a feasible number of subjects to perform a full ocular surface assessment on in the chosen timeframe of six months.

Variables:

Outcome variables:

OSD-related disability (The Ocular Surface Disease Index (OSDI)) is defined as an impairment caused by OSD that makes it more difficult for an individual to perform daily activities. Operationally, it is defined as the self-reported frequency of ocular symptoms (3 items), visual function (6 items), and environmental triggers (3 items) measured by means of The Ocular Surface Disease Index (Schiffman, Christianson, Jacobsen, Hirsch, & Reis, 2000), which is a validated questionnaire that has been proven to accurately differentiate between normal, mild to moderate, and severe dry eye disease. It measures the frequency of symptoms with one week recall period. The OSDI is registered in whole numbers on a numerical scale from 0 (0=no disability) to 100 (100=complete disability).

Nature of the symptoms of the OSD (Standard Patient Evaluation of Eye Dryness II (SPEED II)) is defined as characteristics of the symptoms related to OSD such as type, frequency, and severity. Operationally, it is defined as a self-reported type (dryness, grittiness or scratchiness; soreness or irritation; burning or watering; eye fatigue), frequency (0=never, 1=sometimes, 2=often or 3=constant), and severity (0=no problem, 1=tolerable, 2=uncomfortable, 3= bothersome, 4=intolerable) of the symptoms of OSD measured by means of The Standard Patient Evaluation of Eye Dryness questioner (Ngo et al., 2013) which has been validated to accurately detect dry eye disease. The SPEED II is registered in whole numbers on a numerical scale of 0 to 64 (most symptoms).

Tear film osmolarity is defined as the concentration of a solution expressed as the total number of solute particles of salt per volume tear and represents the balance between the rate of tear production and tear loss from the eye. Operationally, tear film osmolarity is defined as tear film osmolarity measured in one 50 µL tear sample collected from the temporal part of the lower eyelid margin by means of The TearLab Osmolarity System (TearLab Corporations). Tear film osmolarity is registered in whole numbers with the unit mOsm/L on a numerical scale for the right and the left eye.

Non-invasive Keratograph tear break-up time (NIKBUT) is defined as the time passed before the appearance of a first dry spot on the cornea after a complete blink. Operationally, NIKBUT is defined as

the time from a blink to the disruption, or the disturbance of the pattern of reflected Placedo rings in the tear film using an Oculus Keratograph 5M (OCULUS, Inc). 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 measurement, and both will be registered. NIKBUT-first and NIKBUT-average are measured in seconds and registered with two decimals on a numerical scale for the right and the left eye.

Bulbar redness or conjunctival hyperemia is defined as vasodilatation of the conjunctival blood vessels. Vasodilatation is associated with many ocular conditions, inflammation, and irritation. Operationally, bulbar redness or conjunctival hyperemia is defined as bulbar and limbal redness measured objectively with Oculus Keratograph 5M (OCULUS, Inc). R-Scan is an integrated software that detects the blood vessels in the conjunctiva and evaluates the degree of redness. Bulbar and limbal redness is measured in 0.1 steps on a numerical scale from 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 for the right and the left eye.

Tear Meniscus Height is defined as the volume of tear fluid that is accumulated along the lid margins in an open eye. Operationally, it is defined as the height of the tear prism on the lower eyelid margin in line with the pupil center measured objectively from a single photograph taken with Oculus Keratograph 5M (OCULUS, Inc) that has an integrated ruler and various magnification options. It is measured in millimeters and registered with two decimals on a numerical scale for the right and the left eye.

Tear production (Schirmer 1 test) is defined as the rate of physiological production of tears secreted by all lacrimal glands in the eye. Operationally, tear production is defined as the amount of wetting that can be observed on a standardized strip of non-toxic filter paper (TearFlo^{TM}) applied to the temporal part of the lower eyelid of both eyes for 5 minutes. The Schirmer test is a diagnostic test that is performed without anesthesia. It supposedly measures both basal and reflex tear production. Wetting is measured in whole numbers of millimeters and registered on a numerical scale for the right and the left eye.

Ocular surface staining (OSS) or superficial punctate staining is an inflammation marker presented as fine, scattered, punctate corneal epithelial loss or damage. Operationally, OSS is defined as a punctate staining pattern on the ocular surface that can be observed with slit-lamp biomicroscopy when the tear film is tinted with fluorescein sodium (MINIMS® Fluorescein Sodium 2%, Bausch&Lomb) and using a yellow filter (HUVITZ Microscope Slit-lamp HS-7000) and cobalt blue light. Evaluation of corneal staining is based on the Oxford schema (Bron, Evans, & Smith, 2003), which is used to estimate surface damage in dry eyes. Staining is subjectively assessed and graded in 0.5 steps on an ordinal scale using a clinical grading scale that ranges from 0 (absent) to 5 (severe) for the right and the left eye.

Meibum quality is defined as the degree of viscosity of the oil secreted from the Meibomian glands. Operationally, meibum quality is defined as the subjective assessment of the content of the meibomian glands by applying moderate digital pressure on each of the eight glands of the central third of the lower lid with a flat, perpendicular surface like index finger or Q-tip for 10 seconds. Properties of the expressed content of the glands are evaluated and registered in whole numbers on the ordinal scale from 0 to 3 (0=clear meibum; 1=cloudy meibum; 2=cloudy with debris (granular); 3=thick, like toothpaste) for each of the eight glands (Nichols et al., 2011) for the right and the left eye.

Meibum expressibility is defined as a combination of the viscosity and the integrity of the channels and orifices that make up for expressibility. Operationally meibum expressibility is defined as an ability to express the content of the meibomian glands in five central glands in the lower eyelid by applying moderate digital pressure on the glands. Evaluation of the meibum expressibility is performed simultaneously with an evaluation of the Meibum quality. Expressibility is recorded in whole numbers on

the ordinal scale from 0 to 3 (0=all glands expressible, 1=3-4 expressible, 2= 1-2 expressible, 3=non expressible) (Nichols et al., 2011).

Corneal sensitivity is defined as the ability of the cornea to sense a variety of stimuli. Operationally, it is defined as the threshold for corneal surface to sense the touch of a fine nylon filament (0,12 mm) applied to the corneal apex by means of a Cochet-Bonnet Aesthesiometer (Luneau Technology Group). The length of the nylon filament can be adjusted (from 60 mm (highest sensitivity) to 5 mm (lowest sensitivity)). It is measured in millimeters and registered with one decimal on a numerical scale for the right and the left eye.

Meibomian gland dropout is defined as partial or total loss of acinar tissue of the meibomian glands and its function in the upper and lower eyelid. Operationally, meibomian gland dropout is defined as changes in the morphological appearance in the meibomian glands of the upper and the lower eyelid evaluated by means of infrared trans-illumination of the lids using an Oculus Keratograph 5M (OCULUS, Inc). Gland tissues are made visible using Meibo-Scan software and classified on the Meiboscale grading scale from a photograph taken with Oculus Keratograph 5M (Pult & Riede-Pult, 2013). It is registered in whole numbers on an ordinal scale that ranges from 0 to 4 (0=0% loss; 1=≤25%; 2=26%-50%; 3=51%-75%; 4=>75%) for the right and the left eye.

Predictor variables:

Preservative is defined as a substance or a chemical that is added to pharmaceutical drugs and other products to prevent decomposition by microbial growth or by undesirable chemical changes. Operationally, a preservative is defined as any of the following substances in the specification of the prescribed eye drops during the period of three months before inclusion into the study: Benzalkonium chloride, Polyquaternium-1, and Boric acid. The preservative is registered on a dichotomous scale where preservative=1 and no preservative=0.

Active pharmacological substance is an ingredient used in a finished pharmaceutical product, intended to provide pharmacological activity or to otherwise have a direct effect in the diagnosis, cure, treatment, or prevention of disease. Operationally, the active pharmacological substance is defined as any of the following substances in the specification of the prescribed eye drops during the period of 3 months before inclusion into the study: prostaglandin analogs, beta-blocker, carbohydrase inhibitor, or alfa-2-agonist. The active pharmacological substance used by the patients will be known from the patient history and will be noted on a nominal scale (1= prostaglandin analogs, 2=beta-blocker, 3=carbohydrase inhibitor, 4= alfa-2-agonist).

The duration of the treatment is defined as the period in which the patient has been treated with the same pharmacological substance. Operationally, it is defined as information about the duration of the treatment collected from the medical records and registered on a numerical scale with the whole number of months of use.

Self-reported compliance is defined as an act complying or adhering to requirements (prescribed treatment). Operationally, it is defined as self-reported adherence to taking drops in agreement with the prescription measured by means of a simple interview question of how often one may skip a dose (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). It will be registered on an ordinal scale.

Other variables:

Age will be registered as the whole number of years on a numerical scale.

Sex will be registered as female=1 and male=0 on a dichotomous scale.

Methods:

Recruitment:

Recruitment of the subjects will take place in the private ophthalmology clinic, Ifocus Øyeklinikk in Haugesund, Norway, in the period from August 2021 to February 2022. This study is a sub-study of an "Ocular Surface and glaucoma. A randomized study of IOP reducing eye drops versus surgical intervention" study (REK no. 253485), and the participants in this study will be recruited from subjects that have given their consent to participate in the main study. Recruitment methods, therefore, will apply for both studies and will be performed simultaneously. Patients that meet inclusion and exclusion criteria on the routine glaucoma controls in our clinic will be invited to participate in the main study and in the described sub-study. Patients who show interest in participating in the study will be contacted via telephone and offered an appointment. On the day of the first (for the main study) and only study (for a sub-study) appointment, the subjects will be given oral and written information about the studies. Those who sign the consent form for the described study (Appendix 1) in addition to the consent form for the main study, are regarded as recruited into the study. Thereafter, a complete data collection/ocular surface assessment for this study will be performed in addition to several clinical tests required for the main study. Patients will be instructed during the telephone call to abstain from taking therapeutic or diagnostic drugs at least two hours before the set appointment. The original signed consent form will be maintained by the investigator as a permanent part of the subject's medical record. A signed copy will be provided to the subject. The recruited patient names will be replaced with unique randomized three-digit ID numbers to ensure the anonymity of the participants. A decoding list with names will be kept separated from data collection sheets. The key list that links patients' names with ID numbers will be deleted five years after the completion of the study.

Measurements:

Subjects included in this study will undergo a comprehensive tear film evaluation on both eyes. All examinations will be performed by an experienced observer (A.M.) in the fixed order from the least to the most invasive one. Firstly, **OSD-related disability (OSDI)** (Appendix 2), and **The nature of the symptoms (SPEED II)** (Appendix 3) will be examined by means of questionnaires. The patient will be given approximately 5 minutes to complete the questioners. The examiner will be in the room with the patient and will provide only a general explanation. The examiner will avoid interpreting or rephrasing the questions. The OSDI questioner has shown good specificity (0.83) and moderate sensitivity (0.60) when differentiating between dry eye disease patients and healthy patients (Schiffman et al., 2000). The sensitivity and specificity for the SPEED II questioner are 0.90 and 0.80 (Ngo et al., 2013). Thereafter, clinical examinations will be performed on the right eye followed by the left eye in this order: **Tear film osmolarity, Non-invasive Keratograph tear break-up time (NIKBUT), Bulbar redness, Tear Meniscus Height, Tear production (Schirmer 1 test), Ocular surface staining (OSS), Meibum quality, Meibum expressibility, Corneal sensitivity, Meibomian gland dropout. Tear film osmolarity** will be measured with The TearLab Osmolarity System by TearLab Corporation that has a precision (CV) of 1,5% with a standard deviation (Stdev) of 5.0 mOsm/L and accuracy of r2=0,95. Tear collection will be performed at the lateral (temporal) extent of the eyelid, and the test card should touch the lower temporal tear meniscus. **Non-invasive Keratograph tear break-up time (NIKBUT), Bulbar redness, and Tear Meniscus Height (TMH)** will be measured with The Oculus Keratograph 5M by OCULUS, Inc. The patient will be instructed to place head correctly in the chinrest, and when the Keratograph is aligned with the patient's face, the patient will be instructed to blink twice. After the second blink, the measurement of the NIKBUT will automatically begin. The patient will be encouraged to keep their eyes open as long as possible without blinking. The

measurement is automatically stopped by the device if the patient moves or blinks. Bulbar redness will be measured and graded automatically and objectively by taking a picture with the Oculus Keratograph 5M. Similarly, Tear Meniscus Height (TMH) will be measured objectively from the picture taken with Oculus Keratograph 5M that has an integrated ruler and various magnification options. Following, Schirmer 1 test will be performed without anesthetics. The free end of the non-toxic calibrated filter paper will be placed in the temporal part of the lower eyelid of both eyes, and the patient will be asked to hold the eyes gently closed for 5 minutes. At the end of the 5-minute interval, the paper strips will be removed from each lower eyelid, and the amount of wetting of the paper will be noted. Slit-lamp examination of the anterior segment will be performed in order to evaluate Ocular surface staining (OSS). A quantified 5 µl of 2% Fluorescein sodium will be instilled into each conjunctival sac with a micro-pipette (using a sterile tip), and then observation will be done with a slit-lamp using a yellow filter and cobalt blue light. Meibum quality and Meibum expressibility will be also evaluated during the slit lamp exam. Meibum quality will be assessed in each of the eight glands of the central third of the lower lid by applying pressure on the eyelid with a Q-tip. It will be 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 will be assessed in the five central glands in the lower lid by applying pressure on the lid with a Q-tip. It will be 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). Cochet – Bonnet Aesthesiometer will be used to measure corneal sensitivity. Fine nylon filament, the length of which can be adjusted (60 mm to 5 mm), will be used to apply different intensities of stimuli on the corneal surface. The shortest length of the filament that the patient reacts will be noted. Meibomian gland dropout (Meibography) will be measured by taking infrared photos of the upper and lower eyelid with Oculus Keratograph 5M with minimal discomfort to the patient. Gland tissues will be made visible by everting the upper and lower eyelids with a Q-tip and using Meibo-Scan. The degree of Meibomian dropout will be scored and noted for all four eyelids. Finally, Self-reported compliance will be examined by means of simple interview question of how often one may skip a dose (Appendix 4). Information's about age, gender, duration of the treatment, the active pharmacological substance, and the preservatives in the topical IOP-lowering medication will be collected from the patient journals.

Analyses:

The results of the comprehensive tear film evaluation will be 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. will be stored in a separate database called Oculus Patient Data Management. Once measurements are performed, data related to the study will be transferred from the patient journal to a data registration form (Appendix 4). The names of the patients will be replaced with ID numbers. All data will be transferred to and organized in a database (Excel, Microsoft Inc.). To identify empty cells or unrealistic values, an algorithm in Excel will flag the cells in question. A quality-assured version of the database will constitute the basis for statistical analyses. For variables measured on a numerical scale, these summaries will include the sample size, as well as the mean, standard deviation, median, minimum, and maximum. For variables measured on a categorical scale, summaries will provide the number and percentage of subjects who provided each score. Preliminary considerations of the data will include the investigation as to whether any transformation (i.e., logarithmic) should be applied prior to the statistical analyses. For categorical data, the sparseness of the data across categories will be considered, and the combination of categories prior to statistical analysis will be applied where deemed appropriate. For variables measured on a continuous scale, the statistical significance of the difference

between groups will be investigated using an Analysis of Variance (ANOVA) with appropriate post-hoc testing. For variables measured on an ordinal categorical scale, the Kruskal-Wallis signed-rank test will be employed. Questionnaire data will be analyzed using current standards. The statistical analyses will be performed using SPSS version 24. All statistical tests of hypotheses will employ a level of significance of alpha=0.05. Odds ratios with 95% confidence intervals may also be used.

Project management and organization:

Principal investigator: Per Olof Lundmark
Project manager: Andrea Mihovilovic

Resources, equipment, and physical facilities:

All equipment is available in the ophthalmic practice Ifocus Øyeklinikk in Haugesund, Norway, where the study will take place:

- The TearLab Osmolality System by TearLab Corporations.
- The Oculus Keratograph 5M by OCULUS, Inc.
- TearFlo™ calibrated strips of non-toxic filter paper.
- MINIMS® Fluorescein Sodium 2%, Bausch&Lomb, and micro-pipettes.
- HUVITZ Microscope Slit-lamp HS-7000.
- Chrocet-Bonnet Aesthesiometer by Luneau Technology Group.
- Computer with Microsoft Office Word, Microsoft Office Excel, and SPSS.

Budget and financial plan:

Post		Debit	Credit
1	Ophthalmic instruments		
2	Single-use examination equipment (TearLab test cards, Schirmer 1 test filter paper, Fluorescein dye)		6600
3	Office supplies, poster, and binding		2000
5	Sponsorship from Ifocus Øyeklinikk	8600	
6	**Balance**	**8600 NOK**	**8600 NOK**

All expenses regarding equipment, office supplies, and publishing will be sponsored by the ophthalmologic practice Ifocus Øyeklinikk in Haugesund, Norway, where the study will take place.

Project plan:

	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr
Planning and preparation												
Recruitment and data collection												
Analysis												
Report and publishing												

Dissemination:

This is a Master thesis project, and it will be orally presented. The results from the study will be submitted to optometric or ophthalmologic journals such as Clinical Ophthalmology.

Ethical considerations and privacy protection:

This study is a sub-study of an "Ocular Surface and glaucoma. A randomized study of IOP reducing eye drops versus surgical intervention" study that obtained approval from The Regional committees for medical and health research ethics (REK no. 253485). Nearly all of the procedures in this study are non-invasive and will not cause major discomfort to the patient. Minimally invasive procedures like the Schirmer 1 test or assessment of the corneal sensitivity, Meibum quality, and expressibility can cause minor discomfort but are not associated with the risk of ocular injury. If a suspicion of eye pathology arises from the patient's history or the clinical examinations, the patient will be referred to an appropriate specialist. All eligible and motivated subjects are going to sign an informed consent before any data collection. Participation in the study is voluntary, and the subjects can withdraw the consent at any time without any explanation. This will not affect patients' further follow-up in the clinic. The original signed consent form will be maintained by the investigator as a permanent part of the subject's medical record. A signed copy will be provided to the subject. The recruited patient names will be replaced with unique randomized three-digit ID numbers to ensure the anonymity of the participants. A decoding list with names will be kept separated from data collection sheets. The key list that links patients' names with ID numbers will be deleted five years after the completion of the study. Personal data collected during the study will be protected according to Norwegian laws. The study will be registered at the Norwegian Centre for Research Data (NSD).

References:

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