





BMJ Open Clinical efficacy of diquafosol sodium 3% versus hyaluronic acid 0.1% in patients with dry eye disease after cataract surgery: a protocol for a single-centre, randomised controlled trial

Maria Miura,^{1,2} Takenori Inomata ^{1,2,3,4} Shuko Nojiri,⁵ Jaemyoung Sung,¹ Masashi Nagao ^{5,6,7} Jun Shimazaki ⁸ Akie Midorikawa-Inomata,⁴ Yuichi Okumura,^{1,2,3} Kenta Fujio,^{1,2} Yasutsugu Akasaki,^{1,2} Mizu Kuwahara,^{1,2} Tianxiang Huang,^{1,2} Masahiro Nakamura,^{2,9} Masao Iwagami ^{10,11} Kunihiro Hirose,^{1,2} Keiichi Fujimoto,^{1,2} Akira Murakami^{1,2}

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For numbered affiliations see end of article.

Correspondence to

Dr Takenori Inomata;
tinoma@juntendo.ac.jp

ABSTRACT

Introduction The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to ageing populations. Dry eye disease (DED) is a frequent side effect of cataract surgery, contributing to lower postoperative patient satisfaction and suboptimal quality of vision. It is unclear which eye-drops commonly used in these patients should be recommended for postoperative DED treatment. This study aims to compare the efficacy of topical administration of diquafosol sodium 3% vs hyaluronic acid 0.1% eye-drops in patients with DED after cataract surgery.

Methods and analysis The study is designed as a single-blind randomised controlled trial. The participants will be randomly (1:1) allocated to either the diquafosol sodium 3% topical administration group (n=21) or the hyaluronic acid 0.1% topical administration group (n=21). Each group will receive its assigned eye-drop intervention over a 12-week period. The primary outcome will be measured using the total score of the Japanese version of the Ocular Surface Disease Index during the visit 5 weeks postoperatively. Both groups will be followed up after their respective eye-drop application for 12 weeks according to the intervention regimens. Secondary outcome measures including meibomian gland function assessment, tear film break-up time, keratoconjunctival staining score, maximum blink interval and tear secretion volume using Schirmer's test I will be assessed at 1, 5, 9, 13 and 25 weeks postoperatively.

Ethics and dissemination This study has been approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (Approved protocol V.7.0 dated 7 May 2021. Approval number: J20-018) and has been registered with the Japan Registry of Clinical Trials. Written informed consent will be collected from every patient prior to study participation. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Trial registration number jRCT1031210018.

Strengths and limitations of this study

- This study will compare the efficacy of topical administration of diquafosol sodium 3% vs hyaluronic acid 0.1% eye-drops in alleviating symptoms following cataract surgery in patients without preexisting dry eye disease (DED).
- The total number of participants will be 42 patients randomly allocated to the diquafosol sodium 3% (n=21) or the hyaluronic acid 0.1% administration group (n=21).
- Following the treatment over a 12-week period, the observation period from 13 to 24 weeks will be used to assess persistent eye-drop effects and DED recurrence.
- The primary outcome will be measured using the total score of the Japanese version of the Ocular Surface Disease Index during the visit 5 weeks postoperatively.
- The generalisability of the findings of this study remains unknown since diquafosol sodium 3% and hyaluronic acid 0.1% are currently available in limited countries.

INTRODUCTION

The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to ageing populations worldwide.¹ Cataract surgery is generally recognised as a safe, reproducible and effective procedure owing to improvements in surgical techniques and instruments.² Therefore, patients demand high postoperative quality of vision. Unfortunately, dry eye disease (DED) is a common disease, affecting approximately 5%–50% of the population worldwide,³ and a major cause of postoperative discomfort,⁴ with

recent studies revealing that cataract surgery is associated with the development and increased severity of dry eye symptoms.^{5–8} In addition, DED has been shown to impair the quality of vision and increase economic losses due to reduced concentration and decreased work productivity stemming from a variety of DED-related symptoms, such as ocular discomfort and decreased visual acuity.^{9 10}

Importantly, contributory factors usually associated with DED differ from those implied in the development of DED after cataract surgery, which include the following: application of preoperative prophylactic medications; irritation of the ocular surface; application of topical anaesthetics and antiseptics; intraoperative exposure to microscope light; corneal nerve transection; increased tear osmolarity; goblet cell loss; meibomian gland dysfunction and surgery-related inflammation.^{1 5 11–15} Moreover, numerous host factors including age, sex, presence of systemic diseases, administration of systemic medications and pre-existing DED or meibomian gland dysfunction are associated with the development of DED after cataract surgery.^{1 4 5 14 16–23} The clinical presentation of postoperative DED caused by these factors is also different from that usually seen in DED, therefore, requiring a specialised treatment strategy for DED after cataract surgery.

Although the importance of DED management after cataract surgery has been recognised and many options to treat DED after cataract surgery have been developed,^{1 18–20 24–34} the choice of treatment is left to the discretion of each physician, as no clear guidelines exist for the treatment of DED following cataract surgery. Diquafosol sodium 3% and hyaluronic acid 0.1% eye-drops are two widely used medications in patients with DED.³⁵ There have been previous efforts to compare the effects of these eye-drops after cataract surgery, and diquafosol sodium 3% produces significant improvement in the tear film break-up time (TFBUT) and meibomian gland function.^{20 24 36} However, these studies did not target the patients with newly developed DED after cataract surgery. This highlights the need to assess the efficacy of various eye-drop medications in patients who develop DED following cataract surgery.^{37 38}

To the best of our knowledge, no report has yet compared the efficacy of diquafosol sodium 3% and hyaluronic acid 0.1% for DED after cataract surgery in patients without preexisting DED. Therefore, this study's objective is to compare the efficacy of these eye-drops for DED after cataract surgery in such patients.

METHODS AND ANALYSIS

Objectives

The primary objective is to compare the efficacy of topical administrations of diquafosol sodium 3% vs hyaluronic acid 0.1% to alleviate dry eye symptoms (measured using the Japanese version of the Ocular Surface Disease Index (J-OSDI)) after cataract surgery in patients without preexisting DED, as a therapy in addition to standard treatment following this operation.

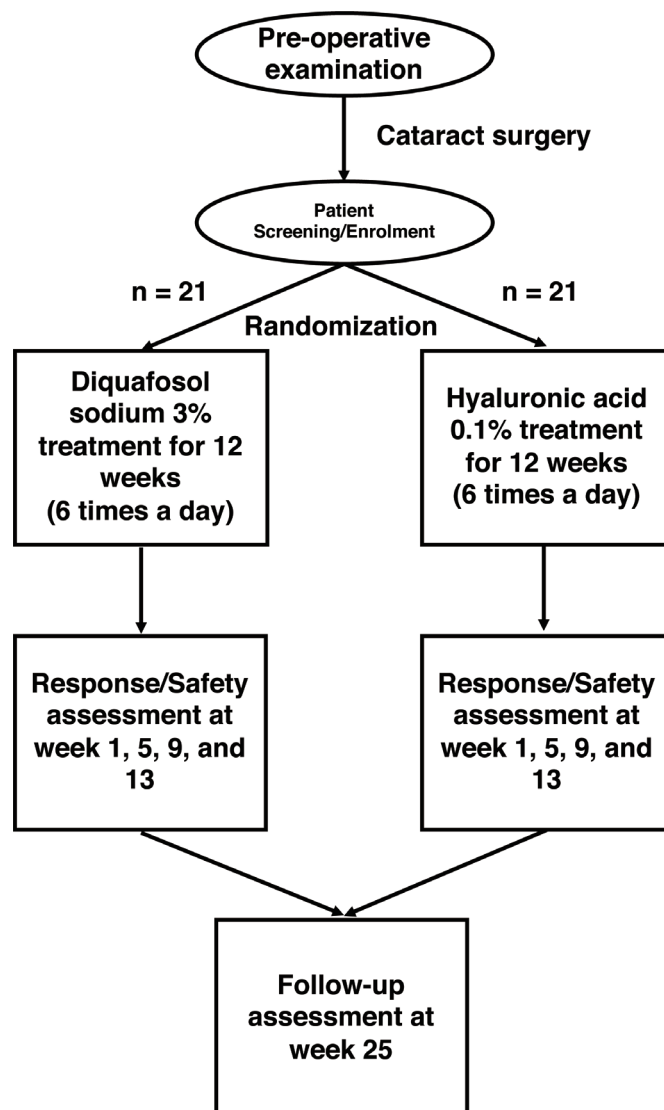


Figure 1 Study schema.

Study design

The study is designed as a prospective, single-blind, randomised, controlled trial. The total number of participants will be 42 patients randomly allocated to the diquafosol sodium 3% administration group (n=21) or the hyaluronic acid 0.1% administration group (n=21). Each group will receive the assigned treatment over a 12-week period. A subsequent 12-week observation period from 13 to 24 weeks will be used to check for persistent eye-drop effects and DED recurrence. The study design is depicted in [figure 1](#).

Study setting

This study will be conducted between 1 April 2021 and 30 November 2025. Participants will be recruited at the Department of Ophthalmology, Juntendo University Hospital.³⁹

Participant selection

This clinical trial will be conducted in a single centre, with the participant blinded to the treatment allocation.

Patients with DED after cataract surgery who attend the Department of Ophthalmology, Juntendo University Hospital, or are admitted there are eligible for inclusion in this study.

Inclusion criteria

1. Women who are 20 years of age or older at the time of providing informed consent.
2. Patients who have undergone cataract surgery in both eyes, with the second operation within 14 days after completion of the first.
3. Patients diagnosed with DED after cataract surgery (>13 points total score in the J-OSDI and TFBUT ≤ 5 s), according to the 2016 Asia Dry Eye Society criteria.⁴⁰
4. Patients who, after receiving a full explanation of their participation in the study and with a full understanding of the study, have given written consent to participate in the study of their own free will.
5. In case of inability to self-administer eye-drops, patients with a caregiver willing and able to assist in the administration of the assigned eye-drops as part of the study.

Exclusion criteria

1. Patients diagnosed with DED preoperatively.
2. Patients with active eye infections.
3. Venal keratoconjunctivitis patients.
4. Patients with recurrent corneal erosions.
5. Patients with hereditary corneal disease.
6. Patients with physical irritation of the cornea and conjunctiva due to eyelashes, tears, or conjunctivochalasis.
7. Patients who cannot or will not be able to discontinue eye-drops and medications listed as prohibited concomitant drugs (including all prescription and over-the-counter medications), beginning with the start of the screening test until the end of the administration of the study medication.
8. Patients who cannot discontinue the use of contact lenses in the inclusion period, between the start of the screening test and the last administration of the eye-drops.
9. Patients with a history of corneal refractive surgery.
10. Patients with punctal plugs or a history of surgical punctal occlusions.
11. Patients with hypersensitivity to components of the study drugs and reagents.
12. Patients using glaucoma eye-drops.
13. Patients with systemic diseases, such as diabetes mellitus, thyroid disease, autoimmune diseases and atopic dermatitis.
14. Patients whom the principal investigator deems unsuitable as a study participant.

Interventions

After enrolment in the study, participants will receive their corresponding study medication for the intervention period of 12 weeks after cataract surgery. The cataract surgery procedure entails an invasive corneal incision with a width of 2.4 mm. The conventional treatment is the

administration of gatifloxacin 0.3% ophthalmic solution four times a day, betamethasone sodium phosphate 0.1% four times a day, and bromfenac sodium 0.1% twice a day up to 1 month after cataract surgery.

Arm A

Diquafosol sodium 3% plus conventional treatment after cataract surgery.

The participants will use diquafosol sodium 3% eye-drops alongside conventional treatment after cataract surgery. Diquafosol sodium 3% is a P2Y2 receptor agonist that promotes tear fluid and mucin secretion.⁴¹ Diquafosol sodium 3% eye-drops will be administered six times a day.

Arm B

Hyaluronic acid 0.1% plus conventional treatment after cataract surgery.

The participants will use hyaluronic acid 0.1% eye-drops alongside conventional treatment after cataract surgery. Hyaluronic acid is a glycosaminoglycan disaccharide linear biopolymer composed of repeating alternating sequences of N-acetyl-glucosamine and glucuronate.⁴² Topical administration of hyaluronic acid 0.1% has been used to increase tear and mucin secretion on the ocular surface.⁴³ Hyaluronic acid 0.1% eye-drops will be administered six times a day.

Outcome assessments

The schedule for data collection and visits is shown in [table 1](#). Assessments will be performed following a predetermined sequence. After determining the subjective symptom score using the J-OSDI questionnaire, a physician will conduct a face-to-face medical examination and interview on lifestyle-related information. Following surgery, a wide range of ophthalmic examinations will be performed, including measurements of corrected vision, intraocular pressure, contrast sensitivity, corneal curvature radius, and corneal endothelial cell density. In-person slit-lamp microscopy and funduscopy examination by a physician will follow shortly after. The physician will continue with dry-eye-related ocular function tests and evaluate TFBUT, fluorescein staining score, maximum blink interval (MBI), and meibomian gland function. Subsequently, a trained nurse will measure the subject's tear production using Schirmer's test I. Patients will be provided with an individual patient diary that includes instructions for use, visit schedule, and how to use the eye-drops. Patients' reports include the number of times eye-drops were administered per day, reasons for not administering the eye-drops, any side effects and the use of new drugs other than the investigational drugs of this study.

Primary outcome

Japanese version of the Ocular Surface Disease Index

The primary outcome measure will be the scores of the OSDI, which is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision,

Table 1 Schedule for data collection and visits

	Preobservation period			Drug administration period (12 weeks)					Postadministration period (12 weeks)
	Before cataract surgery	Cataract surgery		After cataract surgery					
	0–3 months before cataract surgery	Week 0	Week 1	Week 5	Week 9	Week 13	Week 25		
Periods	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7		
Informed consent and eligibility screening	○								
Registration to the study			○						
Randomisation			○						
Participants' characteristics	○								
Lifestyle-related information	○		○	○	○	○	○	○	
Ophthalmic examinations									
Visual acuity	○		○	○	○	○	○	○	
Intraocular pressure	○		○	○	○	○	○	○	
Contrast sensitivity	○		○	○	○	○	○	○	
Keratometry	○		○	○	○	○	○	○	
Endothelial cell count measurement	○		○	○	○	○	○	○	
Slit-lamp microscopy	○		○	○	○	○	○	○	
Fundus examination	○		○	○	○	○	○	○	
Cataract surgery		○							
Postoperative eye-drops for cataract surgery		○	○	○	○	○	○	○	
Information about cataract surgery		○							
Subjective symptoms of dry eye (J-OSDI)	○		○	○	○	○	○	○	
Meibomian gland function assessment	○		○	○	○	○	○	○	
Dry eye examination									
Tear film break-up time	○		○	○	○	○	○	○	
Keratoconjunctival vital staining	○		○	○	○	○	○	○	
Maximum blink interval	○		○	○	○	○	○	○	
Tear secretion volume using Schirmer's test I	○		○	○	○	○	○	○	
Treatment: diquafosol sodium 3% or hyaluronic acid 0.1%, 6 times per day			○	○	○	○	○	*	
Adverse event collection			○	○	○	○	○	○	
Patient diary		○	○	○	○	○	○	○	

*During the follow-up period, the treatment will be administered when there is a recurrence of DED. DED, dry eye disease; J-OSDI, Japanese version of the Ocular Surface Disease Index.

ocular symptoms and any condition associated with DED.⁴⁴ The J-OSDI, the Japanese version of this index, has been validated and will be used for this study.⁴⁵ The patient will answer each question on a scale ranging from 0 to 4, with 0 indicating 'none of the time' and 4 indicating 'all of the time'. If a certain question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The J-OSDI total score is calculated according to the following formula.^{44 45}

$$J - OSDI \text{ total score} = \frac{(\text{Sum of scores for all questions answered}) \times 100}{(\text{Total number of questions answered}) \times 4}$$

The scale ranges from 0 to 100, with higher scores representing more severe cases of DED. This value will be checked during visits preoperatively and 1, 5, 9, 13 and 25 weeks postoperatively.

Secondary outcomes

Secondary outcomes will be largely categorised into five groups: (1) general characteristics and relevant medical history, (2) lifestyle factors, (3) ophthalmic examination, (4) surgical information and (5) ocular function tests.

Participants will provide characteristics including age, sex, diagnosis and relevant medical history regarding the use of contact lenses, increased intraocular pressure, ocular surgery, corneal disease, mental illness and hay fever. Information regarding lifestyle factors will contain self-reported headache, stiffness, screen time, sleep duration, exercise, smoking and sleeping pills. Examination results on corrected visual acuity, intraocular pressure, contrast sensitivity, keratometry, endothelial cell count measurement, slit-lamp microscopy and fundus examination will also be analysed. Various surgical information that pertains to the cataract surgery, including surgical procedure, surgery time, complications and information about the surgeon, will be collected for analysis.

Specific function test results on meibomian gland function and dry eye examinations will be collected and analysed as well, including TFBUT, keratoconjunctival vital staining (CFS), MBI, and tear secretion volume according to the Schirmer's test I.

Outcomes that pertain to repeatable examinations or function tests will be measured during the preoperative visit, as well as during postoperative visits in weeks 1, 5, 9, 13 and 25.

Meibomian gland function assessment

Meibomian gland function will be assessed by applying digital pressure onto the lower central eyelid, in conjunction with slit-lamp microscopy according to the standard method.⁴⁶ Abnormal findings around the orifices are considered positive when at least one of three findings (irregular lid margin, vascular engorgement, and anterior or posterior replacement of the mucocutaneous junction) is recognised. Findings indicating orifice obstruction will be judged positive when both findings indicating meibomian gland orifice obstruction (plugging, pouting and rigging, decreased meibomian secretion) are recognised.

Tear film break-up time

TFBUT will be measured using a fluorescein dye according to the standard method.⁴⁰ To minimise any effects of the test strip on tear volume and TFBUT, a small quantity of the dye will be administered with a wetted fluorescein strip. After the dye is instilled, the subject will be instructed to blink three times to ensure adequate mixing of the dye with the tears. The time interval between the last blink and the appearance of the first dark spot on the cornea will be measured with a stopwatch. The mean value of three measurements will be used. The cut-off value of TFBUT ≤ 5 s will be used to diagnose DED.⁴⁰

Keratoconjunctival vital staining

CFS will be graded according to the van Bijsterveld grading system,⁴⁷ dividing the ocular surface into three zones: nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea. Each zone will be evaluated on a scale of 0–3, with 0 indicating no staining and 3 indicating confluent staining. The maximum possible score is 9.

Maximum blink interval

MBI will be defined as the length of time that the participant can keep the eye open before blinking during each trial.⁴⁸ According to previous studies,^{48 49} using a stopwatch, MBI will be measured twice under a light microscope without light. MBI will be recorded as 30 s if it exceeds this value. The cut-off value of MBI ≤ 12.4 s will be used as a positive sign for DED.

Tear secretion volume using Schirmer's test I

Schirmer's test I will be performed without topical anaesthesia after the completion of all other examinations. Schirmer test strips (Ayumi Pharmaceutical Co., Tokyo, Japan) will be placed at the outer third of the temporal lower conjunctival fornix for 5 min. The strips will be removed, and the length of dampened filter paper (in mm) will be recorded.

Participant timeline and trial duration

The schedule for data collection and visits is shown in [table 1](#). After registration for this study, the assigned treatment intervention will be administered for 12 weeks. Furthermore, the effect of eye-drops and the recurrence of DED will be examined during the 12-week follow-up period 13–25 weeks after the surgery. During the follow-up period, the eye-drops will be administered when DED recurs.

Randomisation and allocation

Participants will be randomised to the diquafosol sodium 3% administration group or the hyaluronic acid 0.1% administration group. Randomisation will be performed by a member of the trial team on the day of the visit 1 week after cataract surgery. A web-based randomisation application will be used (<https://www.project-redcap.org/>). Allocation will be carried out using block randomisation and stratified according to age (allocation factor: age < 80 years or ≥ 80 years). A randomisation list for each

stratum will be prepared by an independent statistician and will be stored in the university data centre.

Masking

Study treatment assignment will be single masked. The study participants would be unable to identify the contents. Labels on the box containing the ampoules have a batch number, study reference number, participant ID, contact number, investigator name, site address, expiration date of the eye-drops, storage instructions and a statement informing the participant that the eye-drops are for clinical trial use only and are not to be ingested.

Compliance

The study is to be conducted using an intention-to-treat basis. The level of compliance with eye-drop use will be quantified based on the eye-drop use calendar. There is no minimum compliance criterion for eye-drop insertion that would cause the removal from the trial, but compliance will be controlled for in statistical analyses and used as a measure of acceptability of the treatment according to the secondary objectives. Evidence of overuse will also be discussed with participants, and they will be instructed on proper use and compliance.

Sample size and statistical analyses

The target number of cases is set at 42. The breakdown is as follows. First, a t-test for difference of means (power 0.8, significance level 5%, clinically valid difference in subjective symptom score 5.24,²⁴ SD of the comparison group 5.23²⁴) was used to determine a total of 34 cases in the two groups, with an additional 10% compensate since dry eye metrics often deviate from a normal distribution,⁵⁰ plus a 10% drop-out rate for withdrawal of consent.

The study population for the efficacy analysis will be the intention-to-treat analysis population, which includes all randomised patients. In addition, a per-protocol set will be defined and analysed to confirm the robustness of the study results.

The safety analysis will be conducted based on a safety analysis population that includes subjects who have received at least one dose of medication after randomisation.

In this study, the level of significance is set at 5% two sided, and the confidence coefficient is set at 95% unless otherwise specified. The study subject background will be tabulated by calculating the mean and SD for continuous variables and the frequency and percentage for categorical variables. If the continuous variables do not follow a normal distribution, the variables will be appropriately transformed by logarithmic transformation or other means and aggregated with the mean and SD, or the median and IQR will be used as descriptive statistics.

For the primary endpoint, between-group comparisons will be performed with baseline as a covariate and an analysis of covariance to calculate the adjusted mean, its 95% CI, and the p value. Within-group comparisons will be made employing a paired t-test. For safety, frequencies

and proportions will be calculated for each group and item, and between-group comparisons will be performed using Fisher's exact probability test or the χ^2 test.

Adverse events

Adverse events are unexpected signs, symptoms, or diseases encountered during the clinical trial, whether or not they are related to the treatment. Local, general and psychological adverse events may be observed. Local symptoms may include corneal epithelium disorder (filamentary keratitis, superficial keratitis, corneal erosion, etc), conjunctivitis, eye irritation, eye discharge, conjunctival hyperaemia, eye pain, eye itching, ocular foreign body sensation, visual discomfort, hyposphagma, abnormal sensation in the eye (feeling of dry eyes, strange sensation of the eye, sticky eye sensation), blurred vision, photophobia and lacrimation. If serious adverse events occur, these will be referred to the Juntendo Hospital Certified Review Board; experimental treatments will be stopped immediately, and appropriate treatments will be administered.

Participant withdrawal

Patients will be withdrawn from the study based on the following criteria:

1. When it is judged to be difficult to continue the research due to the occurrence of other diseases.
2. When the study participant becomes untraceable.
3. In the event of pregnancy or suspected pregnancy.
4. When participants or their guardians request to terminate their participation in the research.
5. When the participant's caregiver cannot guarantee cooperation in the research.
6. When the research study is discontinued.
7. When the principal investigator and subinvestigators determine that it is appropriate to discontinue the research for other reasons.

Data management

The principal investigator (Takenori Inomata) designated a person (Maria Miura, Juntendo University Faculty of Medicine, Department of Ophthalmology) to be in charge of the data management. This study uses Research Electronic Data Capture (REDCap) as a case report form and management tool to collect data. Following database lock, the locked data will be transferred to the person in charge of statistical analysis. Details are specified in the data management manual. After the research is completed, a data management report will be prepared on the implementation and status of the data management, followed by its submission to the principal investigator along with the locked research data.

Limitations

First, the design of this study raises some concerns about confounding effects regarding the postoperative use of three types of eye-drops: steroids, antibiotics and anti-inflammatory drugs. For example, steroid eye-drops can improve parameters associated with DED.⁵¹ In addition,

three of the postoperative eye-drops used in this study contain preservatives. Preservatives may have an adverse effect on postoperative DED.^{11 18 20} However, all patients in both groups will use the three postoperative eye-drops in the same way. Therefore, differences between the two study groups are likely to be caused primarily by the tested eye-drops for DED treatment. Second, the study based on this protocol will be a single-blind clinical trial and is not designed as a double-blind study, involving a risk of bias even when the researchers assess the study results as fairly as possible. Third, the sample size of this study is relatively small at 42, and the duration of eye-drop implementation is relatively short at 12 weeks. A double-blind study with larger sample size and a longer treatment period could further validate the results of this study. In addition, we would only include women as participants to decrease the drop-out rate due to DED not developing following cataract surgery. Therefore, this study may have selection bias and cannot compare the effects of the eye-drops on DED between the sexes. Finally, the generalisability of the findings of this study remains unknown since diquafosol sodium 3% and hyaluronic acid 0.1% are currently available in limited countries only.

ETHICS AND DISSEMINATION

Ethics

This study was approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (Approved protocol V.7.0 dated 7 May 2021. Approval number: J20-018). Each participant will provide written informed consent prior to participation in the study.

Dissemination plan

The results of the study will be disseminated regardless of the direction of the effect. Trial results will be disseminated to all potential beneficiaries of the study, including patients, caregivers, relatives, physicians, advisory boards and medical board members. This will take the form of publications in high-impact, open-access medical journals and presentations at national and international medical conferences.

Author affiliations

¹Department of Ophthalmology, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

²Department of Digital Medicine, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

³Department of Strategic Operating Room Management and Improvement, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

⁴Department of Hospital Administration, Juntendo University Graduate School of Medicine, Bunkyo-ku, Tokyo, Japan

⁵Medical Technology Innovation Center, Juntendo University, Bunkyo-ku, Tokyo, Japan

⁶Department of Orthopedic Surgery, Juntendo University Faculty of Medicine, Bunkyo-ku, Tokyo, Japan

⁷Department of Sports Science, Juntendo University Faculty of Health and Sports Science, Chiba, Japan

⁸Department of Ophthalmology, Tokyo Dental College Ichikawa General Hospital, Ichikawa, Chiba, Japan

⁹Precision Health, Department of Bioengineering, Graduate School of Engineering, The University of Tokyo, Bunkyo-ku, Tokyo, Japan

¹⁰Department of Health Services Research, University of Tsukuba, Tsukuba, Japan

¹¹Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

Twitter Takenori Inomata @eyetake

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ORCID iDs

Takenori Inomata <http://orcid.org/0000-0003-3435-1055>

Masashi Nagao <http://orcid.org/0000-0002-8909-4650>

Jun Shimazaki <http://orcid.org/0000-0002-0435-3095>

Masao Iwagami <http://orcid.org/0000-0001-7079-0640>

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