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QUALITATIVE AND QUANTITATIVE ANALYSIS OF THE IMPACT OF CATARACT SURGERY ON THE OCULAR SURFACE

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QUALITATIVE AND QUANTITATIVE ANALYSIS OF THE IMPACT OF CATARACT SURGERY ON THE OCULAR SURFACE

INTERNATIONAL DOCTORAL THESIS

Presented for the degree of Doctor of Philosophy (PhD)

by

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IMO, Instituto de microcirugía ocular
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UNIVERSIDAD AUTÓNOMA DE BARCELONA
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ANÁLISIS CUALITATIVO Y CUANTITATIVO DEL IMPACTO DE LA CIRUGÍA DE CATARATAS EN LA SUPERFICIE OCULAR

TESIS DOCTORAL INTERNACIONAL

Memoria para optar al grado de Doctor
presentada por

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Dr. José García Arumí, Catedrático de Oftalmología, del Departamento de Cirugía de la Universidad Autónoma de Barcelona (UAB), como director y tutor académico,

y

Dr. José Luís Güell Villanueva, Profesor de Córnea y Cirugía Refractiva del Instituto de Microcirugía Ocular (IMO) y de ESASO, como director,

Certifican

Que la presente memoria de Tesis titulada **"Análisis cualitativo y cuantitativo del impacto de la cirugía de cataratas en la superficie ocular"** ha sido realizada bajo nuestra dirección por la licenciada Dña. **Spyridoula Souki** en el Instituto de Microcirugía Ocular (IMO) en Barcelona, dentro del programa de doctorado en Cirugía y Ciencias Morfológicas, para optar al grado de Doctor por la Universidad Autónoma de Barcelona. Hacemos constar que la citada Tesis reúne todos los requisitos necesarios para su defensa y aprobación.

Y para que conste a los efectos oportunos, firmamos el presente certificado.

Barcelona, Mayo de 2020

José García Arumí
Catedrático de Oftalmología UAB

José Luís Güell Villanueva
Profesor de Córnea y Cirugía Refractiva IMO

"A small but always persistent discipline is a great force;
for a soft drop, falling persistently, hollows out hard rock."

St. Isaac the Syrian

To the most Holy Theotokos,

Mother of the Light,

For guiding me through and enlightening my path

Dedicated to Georgios

for his affection, love and encouragement

In grateful and blessed memory of

my mother Kalliope and father Theodore

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ABSTRACT

Purpose: To assess the effect of intracameral fixed combination of mydriatics and anaesthetic (ICMA) compared to standard mydriatic and anaesthetic eye drops on ocular surface.

Design: A phase IV, open-label, randomized clinical trial conducted in Instituto de Microcirugía Ocular (IMO, Barcelona,Spain).

Methods: 50 patients, aged 40 to 88 years, undergoing cataract surgery in both eyes were included in the study. ICMA (Fydrane®) was administered in one eye and the standard mydriatic/anaesthetic eye drops in the fellow eye. Before performing the cataract surgery in the first eye, subjects were randomized (1:1) to receive ICMA (with oxybuprocain chlorhydrate 0.4%+ tetracaine chlorhydrate 0.1%) or just eye drops (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%). Surgery of the fellow eye was performed within 7 days after the first surgery. All surgeries were performed by one single surgeon. Patients were evaluated before, immediately after, 1 day and 7 days after the surgery.

Results: Both groups presented similar preoperative data. The first postoperative day, the change from baseline in corneal and conjunctival surface staining was slightly less for ICMA, but not statistically significant. For the ICMA treated patients, corneal epithelial alterations were fewer the first postoperative day ($p<0.005$), conjunctival folliculo-papillary reaction was less frequent ($p=0.015$), ocular symptoms such as irritation/burning/stinging were less frequent and milder ($p=0.018$), length of procedure was shorter ($p<0.001$), and patient and investigator satisfaction were higher ($p<0.05$). Intraocular scattering and other postoperative changes generally favoured ICMA but were not statistically significant. Serious and related adverse events were not detected.

Conclusions: ICMA in routine cataract surgery reduced ocular surface damage by decreasing corneal epithelial and conjunctival toxicity with faster recovery of ocular surface integrity, compared to topical eye drops. ICMA shortened the procedure time, increased the intraoperative comfort, decreased the postoperative symptoms and improved patient and investigator satisfaction.

RESUMEN

Objetivo: Evaluar los efectos de la combinación fija intracameral de midriáticos y anestésico (ICMA) en comparación con el tratamiento estándar con gotas oftálmicas de midriáticos y anestésicos en la superficie ocular.

Diseño: un ensayo clínico de fase IV, abierto y aleatorizado, realizado en el Instituto de Microcirugía Ocular (IMO, Barcelona, España).

Métodos: 50 pacientes, de 40 a 88 años, sometidos a cirugía de catarata en ambos ojos fueron incluidos en el estudio. ICMA (Fydrane®) se administró en un ojo y los midriáticos/anestésicos tópicos en el otro. Antes de la cirugía en el primer ojo, se aleatorizó a los sujetos (1:1) a recibir el primer tratamiento: ICMA tras la instilación de clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1% o solo los colirios midriáticos y anestésicos (tropicamida 1%, fenilefrina 10% y clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%). La cirugía del segundo ojo se realizó dentro de los 7 días posteriores a la primera cirugía. Todas las cirugías fueron realizadas por un solo cirujano. Los pacientes fueron evaluados antes, inmediatamente después, 1 día y 7 días después de la cirugía.

Resultados: Ambos grupos presentaron datos preoperatorios similares. El primer día postoperatorio, la variación en la tinción de la superficie corneal y conjuntival, desde el momento basal, fue ligeramente menor para ICMA, pero no fue estadísticamente significativo. Para los pacientes tratados con ICMA, las alteraciones del epitelio corneal fueron menores el primer día postoperatorio ($p<0.005$), la reacción folículo-papilar conjuntival fue menos frecuente ($p=0.015$), los síntomas oculares como irritación/ardor/escozor fueron menos frecuentes y más leves ($p=0.018$), la duración del procedimiento fue más corta ($p<0.001$), y la satisfacción de los pacientes e investigadores fue mayor ($p<0.05$). La dispersión intraocular y otros cambios postoperatorios generalmente favorecieron a ICMA, pero no fueron estadísticamente significativos. No se detectaron eventos adversos graves ni relacionados con el tratamiento.

Conclusiones: El uso de ICMA en la cirugía de cataratas redujo el daño de la superficie ocular al disminuir la toxicidad conjuntival y del epitelio corneal con una recuperación más rápida de la integridad de la superficie ocular, en comparación con el tratamiento tópico. ICMA acortó el tiempo del procedimiento, aumentó la comodidad intraoperatoria, disminuyó los síntomas postoperatorios y mejoró la satisfacción de los pacientes e investigadores.

1. LIST OF ABBREVIATIONS

Abbreviations & Acronyms	Meaning
ADDE	Aqueous deficient dry eye
AE	Adverse event
BAK	Benzalkonium chloride
BCVA	Best corrected visual acuity
C	Control
CFS	Corneal fluorescein staining
C1	Cortical cataract grade 1
C2	Cortical cataract grade 2
DED	Dry eye disease
ECCE	Extracapsular cataract extraction
EDE	Evaporative dry eye
ICMA	Intracameral fixed combination of mydriatics and anaesthetic
IMO	Instituto de Microcirugía Ocular
ICCE	Intracapsular cataract extraction
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IEC	Independent ethics committee
IRB	Institutional Review Board
Lab	Laboratories
LGS	Lissamine green staining
LOCS III	Lens Opacities Classification System III
logMAR	Logarithm of the Minimum Angle of Resolution
MGD	Meibomian gland dysfunction
MIN	Minutes

Abbreviations & Acronyms	Meaning
NEI	National Eye Institute
NIBUT	Non-invasive break up time
N1	Nuclear cataract grade 1
N2	Nuclear cataract grade 2
OQAS	Optical Quality Analysis System
OSD	Ocular surface disorders
OSDI	Ocular Surface Disease Index
OSI	Objective Scatter Index
O/T	Oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%
Ox	Oxford schema
QoL	Quality of life
PAHO	Pan American Health Organization
PP	Per Protocol
PSF	Point spread function
SAE	Serious adverse event
SAP	Statistical analysis plan
SPK	Superficial Punctate keratitis
TBUT	Tear break-up time
T/P	Tropicamide/Phenylephrine
VB	Van Bijsterveld schema
VBUT	Vision break-up time
V0, V1, V2, V3	Visit 0, 1, 2, 3

2. SUMMARY

2.1 INTRODUCTION

Cataract surgery may compromise ocular surface and may induce or aggravate dry eye (1) (2) (3) (4) (5). Pupillary dilatation is commonly achieved by repeated administration of mydriatic agents. The use of intracameral mydriatics represents an alternative to traditional topical mydriatics in cataract surgery to avoid some of the associated disadvantages. The intracameral route of administering mydriatics reduces the need for preoperative eye drops and delivers minute doses of the drugs to the target organ to achieve the desired effect, thus minimizing potential systemic adverse effects (6) (7), avoiding prolonged preparation time, potential ocular surface contamination and mitigating corneal toxicity and ocular surface damage.

2.2 OBJECTIVES

2.2.1 Primary objective

To evaluate the effects of intracameral fixed combination of mydriatics-anaesthetic (ICMA), after oxybuprocain chlorhydrate 0.4% & tetracaine chlorhydrate 0.1% eye drops instillation, and the standard mydriatic-anaesthetic eye drops protocol (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% & tetracaine chlorhydrate 0.1%) on ocular surface.

2.2.2 Secondary objectives

1. To assess changes in best corrected visual acuity recovery.
2. To evaluate epithelial alterations.
3. To describe changes in conjunctival hyperaemia.
4. To assess changes in intraocular pressure.
5. To evaluate the point-spread function (PSF) by the objective scatter index (OSI) in the Optical Quality Analysis System (OQAS) HD Analyzer™.
6. To evaluate tear film stability, measured by vision break-up time (VBUT) in the OQAS HD Analyzer™

7. To determine changes in the Ocular Surface Disease Index (OSDI) questionnaire.
8. To describe ocular symptoms/signs experienced by patients.
9. To describe surgical procedure time-points.
10. To assess patients' perceptions on satisfaction with study treatments.
11. To determine satisfaction assessed by investigators.
12. To describe the safety profile of study treatments.

2.3 MATERIAL AND METHODS

This is a phase IV, open-label, prospective, randomized, clinical trial to evaluate the effects of intracameral fixed combination of mydriatics and anaesthetic (ICMA), (Fydrane®, Laboratoires Théa, France), after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops instillation and the standard mydriatic-anaesthetic eye drops protocol (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%) administered by topical route on ocular surface in subjects undergoing cataract surgery in both eyes.

The study was conducted in both eyes: ICMA and standard eye drops were administered before surgery, one in each eye. Before conducting the cataract surgery in the first eye, subjects were randomized (1:1) to receive the first treatment: ICMA, after instillation of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops, or just mydriatic-anaesthetic eye drops (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%). The remaining treatment was administered for the surgery of the fellow eye.

The study included a screening period of 7 days before conducting the surgery in the first eye (visit 0) and three additional visits per eye: 1) on the day of the surgery (visit 1), 2) 12-36 hours after surgery (visit 2) and 3) 7±1 days after surgery (visit 3).

2.4 STUDY POPULATION

A total of 50 patients, aged 40 to 88 years undergoing cataract surgery in both eyes, within the next 17 days were included in the study. No screening failures were detected. All patients received the study treatment and were analysed as *safety* population (N=50). Eligible patients were those who met all inclusion criteria and none of the exclusion criteria, and were analysed as *per protocol* population (N=46).

2.5 SELECTION CRITERIA

2.5.1 Inclusion criteria

1. Patients aged 40 to 88 years, scheduled to undergo bilateral cataract surgery within the next 17 days.
2. Pupil diameter ≥ 7 mm at selection visit after following the dilatation protocol.
3. Patient willing and able to provide written informed consent prior to any study-related procedure and to comply with all study requirements.

2.5.2 Exclusion criteria

1. Patient who have combined surgery; previous intraocular and/or corneal surgery; iatrogenic, traumatic or congenital cataract; pupillary abnormalities; iris synechiae; eye movement disorders; tear drainage system pathologies; history of inflammatory ocular disease; corneal disease; history of ocular traumatism, infection or inflammation within the last 3 months; pseudoexfoliation, exfoliative syndrome in any eye.
2. Clinically significant corneal endothelial dysfunction.
3. Patients with a cataract hardness in one of the eyes and/or grade ≥3 as per the Lens Opacities Classification System III (LOCS III) (8).
4. Patients suffering from asthma or heart failure.

5. The following concomitant medications were not allowed: systemic corticoid and immunosuppressive treatments within 3 months before surgery; systemic opioid and morphinic drugs within 7 days before surgery, topical ocular treatment with mydriatic and/or anaesthetic action within 7 days before surgery; other systemic analgesics (except paracetamol) within 7 days before surgery; topical treatment with anti-inflammatory and antibiotic action within 1 day before surgery (except for the preoperative treatment specified in this protocol); anxiolytics and hypnotics on the day of surgery (except for those used in the anaesthesia by protocol); adrenaline or any other agent with a mydriatic action in the intraocular irrigating solution.
6. Contact lenses were not allowed within 7 days before surgery
7. Any known ocular disorders affecting eye surface (i.e. staining grade >1 as per the Oxford schema).
8. Known hypersensitivity to the active substances (tropicamide, phenylephrine, lidocaine, oxybuprocain, tetracaine), any of their excipients, anaesthetics of the amide type or atropine derivatives.
9. Pregnancy or breastfeeding, in women of childbearing potential.

2.6 STUDY TREATMENT

1. ICMA and anaesthetic eye drops

- *Oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%*: 1-2 drops were instilled in the eye before performing the preoperative antiseptic procedure and the first incision
- *ICMA (intracameral fixed combination of mydriatics and anaesthetic)*: 0.2 ml in a slow intracameral injection were administered at the beginning of the surgical procedure.

2. Standard mydriatic and anaesthetic eye drops

Reference therapy was topical eye drops of tropicamide 1%, phenylephrine 10%, and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% following the standard protocol of administration established at the participating site.

2.7 STUDY ENDPOINTS

2.7.1 Safety

The primary study endpoint was the change in corneal/conjunctival surface staining measured as per the Oxford schema (corneal staining with fluorescein) and van Bijsterveld schema (conjunctival staining with lissamine green) with ICMA versus the standard eye drop protocol from baseline (visit 0) to 7 days post-surgery (visit 3). In addition, changes were assessed from baseline (visit 0) to just after surgery (visit 1) and from baseline (visit 0) to 12-36 hours post-surgery (visit 2) *.

The secondary endpoints safety-related include:

1. The change in best corrected visual acuity according to the Snellen test from baseline (visit 0) to 7 days after surgery (visit 3).
2. The percentage of patients with epithelial alterations evidenced by slit-lamp examination (i.e. none, mild, and significant) at 12-36 hours (visit 2) and 7 days post-surgery (visit 3).
3. The change in conjunctival hyperaemia as per MacMonnies photographic scale (0 to 5) from baseline (right before study treatment administration at visit 1) to 7 days post-surgery (visit 3). In addition, changes in conjunctival hyperaemia from baseline (right before study treatment administration at visit 1) to just after surgery (visit 1) and from baseline to 12-36 hours post-surgery (visit 2) were described*.
4. The change in intraocular pressure from baseline (visit 0) to 7 days post-surgery (visit 3).
5. Point-spread function (PSF) measured by the objective scatter index (OSI) in the Optical Quality Analysis System (OQAS) HD Analyzer™ 12-36 hours (visit 2) and 7 days post-surgery (visit 3).
6. Changes in the vision break-up time (VBUT) measured by OQAS HD Analyzer™ from baseline (visit 0) to 7 days post-surgery (visit 3). In addition, changes in VBUT from baseline to 12-36 hours (visit 2) and 7 days post-surgery (visit 3).

7. The change in the Ocular Surface Disease Index (OSDI) from baseline (visit 0) to 7 days post-surgery (visit 3).
8. Percentages of patients with ocular symptoms as perceived by patients and signs assessed by investigators according to ordinal scales ranging from 0 (absent/none) to 3 (severe) 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3).
9. Differences in preparation duration and surgery length, from first drop administration to first incision, from first incision to the end of surgery and from first drop administration to end of surgery.
10. The incidence of adverse events related to study treatments.

* Photographs were taken in every visit for the corneal/conjunctival staining and conjunctival hyperaemia assessment. They were codified, put in miscellaneous order and sent for evaluation to an assessor ophthalmologist of the institute, blinded to the trial treatment (blind ophthalmologist reader). The same slit-lamp biomicroscopy and photographic system was used in each case, under the same settings and clinic room illumination conditions. The blind ophthalmologist reader graded the photographs displayed on own monitor, using similar room illumination for the reading and without any time limitation.

2.7.2 Efficacy

The secondary endpoints efficacy-related include:

1. Patients' satisfaction with study treatments assessed on an ordinal scale ranging from 0 (very satisfactory) to 3 (unsatisfactory) just after surgery (visit 1).
2. Satisfaction assessed by the investigators according to an ordinal scale ranging from 0 (very satisfactory) to 3 (unsatisfactory) just after surgery (visit 1).

2.8 STATISTICAL METHODS

2.8.1 Justification of sample size calculation

It was needed to have an estimation of an expected mean change and standard deviation in staining scales from baseline to day 7 post-surgery. As no data could

be found to have such an estimation, no formal sample size calculation was carried out and the size of 50 patients was considered appropriate as an exploratory/pilot assessment.

2.8.2 Analysis populations

The following populations were defined for the study analyses:

- *Safety population:* all patients who received any of the study treatment (N=50)
- *Per protocol (PP) population:* included all patients meeting selection criteria (eligible patients) who received the study treatment and without any major protocol deviations (N=46).

The *safety* population set was used to analyse the primary study objective

2.8.3 Statistical methods

Once the trial was completed and all possible data discrepancies were resolved, the study database was closed and a detailed statistical analysis plan (SAP) was prepared to guide the analysis of the data and justify any change in the original plan.

An overall description was made of the variables included in the study. Absolute and relative frequency distributions of qualitative variables were presented, as well as the measures of central tendency and dispersion (mean, standard deviation, median, minimum and maximum) of quantitative variables. Ninety-five percent confidence intervals were presented for the results associated with the primary objective and the main secondary variables.

2.9 RESULTS

2.9.1 Demographic and clinical baseline characteristics

A total of 50 patients were included in the study at the *Instituto de Microcirugía Ocular* (IMO, Barcelona, Spain) and all of them received the study treatment (safety population). The mean age of the patients was 61.0±10.0 years and 27 of them (54%) were female. Eleven patients (22%) had ophthalmologic disorders

other than cataract, 15 patients (30%) had cardiovascular disorders, 7 patients (14%) had neurologic disorders, 4 patients (8%) had endocrine disorders and 3 patients (6%) had diabetes mellitus. Twenty six patients (52%) declared to suffer other disorders. The mean pupil dilatation (mm) recorded at screening visit (V0) were and 7.8±0.5 in the ICMA group and 7.9±0.5 in the control group (p=0.933).

Regarding the type of lens used at surgery, multifocal intraocular lenses were implanted in 54% of the cases in both groups. Monofocal lenses were implanted in 26% of the ICMA group versus 24% in the control group and toric lenses were implanted in 20% versus 22%, respectively. The differences between the groups were not considered significant (p=0.957).

Safety population (N=50) was used to perform safety analysis. Four patients were not considered for *PP* population (N=46) due to major protocol deviation, and they were not evaluated in efficacy analyses.

2.9.2 Safety and efficacy results

2.9.2.1 Primary objective

The mean values of corneal and conjunctival staining, assessed by Oxford (Ox) and van Bijsterveld (VB) schemas, were similar in both treatments, with a slightly faster recovery following ICMA administration compared to control treatment. Though the trend was not of statistical significance (Ox: Visit 0 (V0), p=not applicable, Visit 1 (V1), p=0.118, Visit 2 (V2), p=0.626 and Visit 3 (V3), p=0.975; VB: V0, p=0.299; V1, p=0.475; V2, p=0.493 and V3, p=0.878).

The comparison of grades of damage in ocular surface experimented in patients treated with ICMA and control treatment was not statistically significant: Ox: V0, p=not applicable; V1, p=0.162; V2, p=0.592; V3, p>0.999. VB: V0, p=0.297; V1, p=0.668; V2, p=0.515; V3, p=0.894.

The changes in Oxford and Van Bijsterveld schema were compared between treatments across study visits, and no statistically significant differences were found: V0-V1:Ox, ICMA-1.3±0.7 vs. control -1.4±0.7 (p=0.169); VB, ICMA -0.4±0.6 vs. control -0.4±0.6 (p=0.845). V0-V2: Ox, ICMA -0.2±0.4 vs. control -0.3±0.5

(p=0.455); VB, ICMA -0.1±0.6 vs. control -0.3±0.6 (p=0.130). V0-V3: Ox, ICMA 0.0±0.1 vs. control 0.0±0.2 (p=0.975); VB, ICMA 0.0±0.6 vs. control -0.1±0.6 (p=0.350).

2.9.2.2 Secondary objectives

1. Best corrected visual acuity was evaluated using Snellen chart in every case and measurements were reported in the decimal scale (Snellen). In the screening visit (V0) the mean BCVA was 0.8±0.2 in both groups. After surgery, the mean BCVA was 0.8±0.2 the first postoperative day and 0.9±0.2 one week after surgery, in both groups respectively. There were no significant differences between the two groups across visits (V0, p=0.969; V2, p=0.270; V3, p=0.689; Mann-Whitney test). LogMAR transformation was performed for the statistical analysis.
   Changes between visits were compared in both groups and no statistically significant differences were observed (logMAR): V0-V2: ICMA 0.0±0.2 vs. control 0.0±0.2 (p=0.552); V0-V3: ICMA 0.0±0.1 vs. control 0.0±0.2 (p=0.823); V2-V3: ICMA 0.0±0.1 vs. control 0.0±0.1 (p=0.508).

2. No epithelial alterations were found for any treatment group at visit 0 and visit 1 (before surgery). At visit 2 (12-36h after surgery), 8% of patients in ICMA group showed statistically significant fewer epithelial alterations in contrast to 30% of patients in control group (p=0.005). At visit 3, none of the patients treated with ICMA experienced epithelial alterations, but 8.7% of those treated with control treatment still presented epithelial alterations (p=0.056), that went further than the end of the study follow-up time.
   The percentage of patients with changes in epithelial alterations between visits (V0 to V2 and V0 to V3) were evaluated and compared between treatment groups: V0-V2, ICMA 8% and control 30%, (p=0.005); V0-V3, ICMA 0% and control 8.7%, (p=0.056).

3. The grades of conjunctival hyperaemia were evaluated using MacMonnies photographic scale and were compared between ICMA and control group. No

statistically significant differences were found: V1 (pre-surgery), p=0.300; V1 (post-surgery), p=0.312; V2, p=0.172 and V3, p=0.449.

The mean change in hyperaemia between visits were compared in paired analysis: V1(pre-surgery)-V1(post-surgery), ICMA -0.2±0.9 and control -0.3±0.8 (p=0.454); V1(pre-surgery)-V2: ICMA -0.5±0.7 and control -0.8±0.7 (p=0.102); V1(pre-surgery)-V3: ICMA -0.8±0.9 and control -0.9±0.9 (p=0.732).

The percentage of patients with grade 0 hyperaemia was compared before and after surgery showing no statistically significant differences: ICMA, V1(pre-surgery) 65.3% and V1(post-surgery) 54.3%, (p=0.301); control, V1(pre-surgery) 60% and V1(post-surgery) 43.5%, (p=0.152). When the percentage was compared between V1(pre-surgery) and V2, both groups showed significant differences (ICMA, 65.3% vs. 29.2%, p=0.001; control, 60% vs. 12%, p<0.001).

4. Intraocular pressure was measured at visit 0 (ICMA 14.5±3.1 vs. control 15.0±3.2; p=0.415) and at visit 3 (ICMA 9.5±3.1 vs. control 9.6±2.5; p=0.679). The mean change from V0 to V3 in ICMA group (5.1±3.0) and control group (5.7±3.1) were compared in paired analysis and the differences were not significant (p=0.382).

5. Objective scatter index (OSI), obtained by the double-pass point-spread function (PSF) image, was evaluated in visit 2 (ICMA 2.5±1.5 vs. control 2.8±1.5; p=0.273) and in visit 3 (ICMA 2.5±1.5 vs. control 2.9±1.5; p=0.237), and no statistically significant differences were found between treatment groups. The change between both visits was compared and no significant differences were found either (ICMA 0.0±1.8 vs. control 0.0±1.6; p=0.668). However, lower intraocular scattering is associated with better optical quality and is considered to be of clinical importance.

6. Vision break-up time (VBUT) of the tear film was measured with the OQAS across visits and compared between groups, and only at visit 0 a statistically significant difference in the percentage of patients presenting stable, moderate or unstable VBUT was found (p=0.033). Changes in tear film VBUT between visits were compared in both groups showing no significant differences (mean changes):

V0-V2: ICMA 0.2±1.2 vs. control 0.1±0.8, (p=0.864); V0-V3: ICMA 0.2±1.1 vs. control 0.1±0.8, (p=0.618); V2-V3: ICMA -0.1±0.8 vs. control -0.1±0.7, (p=0.944).

7. OSDI questionnaire was answered by patients at visit 0 (A: ICMA 3.1 vs. control 3.3, (p=0.867); B: ICMA 3.2 vs. control 3.2, (p=0.997); C: ICMA 1.5 vs. control 1.4, (p=0.826); Total: ICMA 16.9 vs. control 17.1, (p=0.952)) and visit 3 (A: ICMA 2.0 vs. control 2.7, (p=0.250); B: ICMA 1.1 vs. control 1.6, (p=0.610); C: ICMA 0.9 vs. control 1.1, (p=0.815); Total: ICMA 8.8 vs. control 11.9, (p=0.231)) and the scores compared between groups showed no statistically significant differences. Changes between visits were also evaluated and no significant differences were obtained (A: ICMA 0.8 vs. control 0.2, (p=0.641); B: ICMA 1.7 vs. control 1.3, (p=0.916); C: ICMA 0.6 vs. control 0.3, (p=0.666); Total: ICMA 6.3 vs. control 3.5, (p=0.689)).

8. Symptoms and objective signs were evaluated after surgery by patients and investigators respectively during the follow-up period (visit 2 and visit 3).

   At visit 2, evaluation of "irritation/burning/stinging" demonstrated a significant difference between patients treated with ICMA (6.1%) and patients in control group (26%) (p=0.018). In the rest of the symptoms declared by the patients (pain, p=0.185; photophobia, p=0.391; foreign body sensation, p=0.051 and other symptoms, p>0.999), the differences were not significant. At visit 3 there were no significant differences between compared groups (pain, p=0.615; irritation/ burning/stinging, p=0.482; photophobia, p=0.466; foreign body sensation, p=0.090 and other symptoms, p=0.837).

   At visit 2, investigators evaluated that patient in control group suffered significantly more conjunctival folliculo-papillary reaction (32%) than those in ICMA group (10.2%) (p=0.015). For the rest of the evaluated signs (palpebral oedema, p=0.407; chemosis, p=0.331; conjunctival hyperaemia, p=0.239; conjunctival discharge, p=0.495 and other signs, p=0.437) no significant differences were found. At visit 3, no statistically significant differences between groups were found for any of the evaluated signs (palpebral edema, p>0.999; chemosis, p>0.999; conjunctival hyperaemia, p=0.072; conjunctival discharge,

p=not applicable; conjunctival folliculo-papillary reaction, p=0.266 and other signs, p=0.203)

9. Surgery times (minutes) were recorded at three time-points: from first drop administration to first incision (ICMA 5.0±0.0min vs. control 29.7±1.5min, p<0.001), from first incision to end of surgery (ICMA 10.0±1.6 vs. control 9.5±1.4, p=0.143) and the total time from first drop administration to the end of surgery (ICMA 15.0±1.6 vs. control 39.2±1.9, p<0.001), showing a significantly shorter time in the ICMA group for preoperative preparation (from first drop administration to first incision) and for the whole procedure (from first drop to the end of surgery).

10. Patients' satisfaction focused on intraoperative comfort, was rated significantly higher in the ICMA treated patients. 98% of the ICMA group classified the treatment as "very satisfactory" versus 80% in the control group (p=0.008). Patients in the control group justified their satisfaction rate as "satisfactory" and "unsatisfactory" for having experienced some discomfort, pain and/or pressure during surgery.

11. Investigators' satisfaction was significantly higher in the ICMA treated patients, 98% versus 80% in the control group (p=0.008). Patients' cooperation during surgery increased in the ICMA treated group, due to the absence of intraoperative pain or discomfort, which made the procedure less technically challenging.

12. Adverse events (AE) were detected in 19 cases, and they were not serious nor related with the study treatment. The only AEs with an incidence ≥2% were corneal edema in 8% of the eyes and rotation of a toric lens in 2%. The rest of AEs had an incidence of 1% and were described as: wound leak, mild cystoid macular edema (CME), Descemet folds, corneal epithelial defect, superficial punctate keratitis (SPK) and unspecified blurred vision.

2.10 CONCLUSIONS

1. Corneal and conjunctival surface staining decreased faster following administration of ICMA compared to control treatment, although the trend was not of statistical significance.
2. Evaluation of BCVA recovery provided similar results for ICMA and standard eye drop treatment.
3. Significantly less corneal epithelial alterations and faster recovery of epithelial integrity were reported for the ICMA treated patients. In some cases of the standard eye drop group, epithelial alterations persisted further than 7 days.
4. Conjunctival hyperaemia increased along the study in both treatment groups, with the ICMA maintaining a higher percentage of patients without hyperaemia during the early postoperative visits, although without statistically significant differences between groups.
5. Changes in intraocular pressure, 7 days after surgery from the preoperative values, did not demonstrate significant differences between groups.
6. There were trends for less objective scatter index (OSI) measurements in ICMA treated eyes compared to standard eye drops. Even though there was no statistical difference, lower intraocular scatter is associated with better optical quality and is considered to be of clinical significance.
7. Postoperative tear film instability (VBUT) was observed with a tendency to gradual recovery at one week after surgery, in both groups. Changes before and 7 days after surgery, demonstrated no statistically significant differences between groups.
8. OSDI questionnaire demonstrated an overall improvement at the one week postoperative OSDI total scores in both groups, with slightly better results in the ICMA group, focusing the improvement in the visual symptoms. No significant changes in the preoperative and postoperative OSDI were detected between groups.

9. Ocular symptoms such as irritation, burning and stinging were experienced in a significant lower percentage of patients and with less severity in ICMA treated patients the first postoperative day compared to control group.
10. The percentage of patients who suffered conjunctival folliculo-papillary reaction was significantly lower in ICMA group the first postoperative day compared to control group.
11. Patient preparation and waiting time for surgery was significantly decreased by about 25 minutes in the ICMA cases, which was more comfortable and less stressful for the patient.
12. Patients and investigators reported significantly greater satisfaction when using ICMA than standard eye drop protocol. Patients felt more comfortable during surgery with the ICMA treatment.
13. Serious and related adverse events were not detected in this study. ICMA safety profile demonstrated to be similar to the standard eye drop protocol in the parameters evaluated.

3. RESUMEN

3.1 INTRODUCCIÓN

La cirugía de cataratas puede comprometer la superficie ocular e inducir o agravar el ojo seco (1) (2) (3) (4) (5). La dilatación pupilar se logra comúnmente mediante la administración repetida de colirios midriáticos. El uso de midriáticos intracamerales representa una buena alternativa a los midriáticos tópicos tradicionales, en la cirugía de cataratas, para evitar algunas de las desventajas asociadas. La ruta intracameral de administración de midriáticos reduce la necesidad de gotas oftálmicas preoperatorias y permite administrar dosis mínimas de los medicamentos al órgano objetivo para lograr el efecto deseado. Se minimizan así los posibles efectos adversos sistémicos (6) (7), evitando el tiempo de preparación prolongado, la contaminación potencial de la superficie ocular y mitigando la toxicidad corneal y el daño de la superficie ocular.

3.2 OBJETIVOS

3.2.1 Objetivo principal

Evaluar los efectos de la combinación fija intracameral de midriáticos y anestésico (ICMA), tras la instilación de un colirio anestésico (clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%), y del protocolo estándar de colirios midriáticos/anestésicos (tropicamida 1%, fenilefrina 10% y clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%) sobre la superficie ocular.

3.2.2 Objetivos secundarios

1. Evaluar los cambios en la recuperación de la agudeza visual mejor corregida.
2. Evaluar las alteraciones epiteliales.
3. Describir las variaciones de la hiperemia conjuntival.
4. Evaluar las variaciones de la presión intraocular.
5. Evaluar la función de dispersión del punto (PSF) mediante el índice de dispersión objetivo (OSI) en el sistema de análisis de calidad óptica (OQAS) HD Analyzer™.

6. Evaluar la estabilidad de la película lagrimal, medida por el tiempo de ruptura lagrimal visual (VBUT) en el OQAS HD Analyzer™
7. Determinar las variaciones en el cuestionario OSDI (Índice de enfermedad de la superficie ocular).
8. Describir los síntomas/signos oculares experimentados por los pacientes.
9. Describir los tiempos del procedimiento quirúrgico.
10. Evaluar las percepciones de los pacientes sobre la satisfacción con los tratamientos del estudio.
11. Determinar la satisfacción evaluada por los investigadores.
12. Describir el perfil de seguridad del tratamiento de estudio.

3.3 MATERIAL Y MÉTODOS

Ensayo clínico en fase IV, abierto y aleatorizado para evaluar los efectos de combinación fija intracameral de midriáticos y anestésico (ICMA) (Fydrane®, Laboratoires Théa, Francia), tras la instilación de un colirio de clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1% y del protocolo estándar de colirios midriáticos - anestésicos (tropicamida 1%, fenilefrina 10% y clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%) sobre la superficie ocular en sujetos sometidos a cirugía de cataratas bilateral.

El estudio se realizó en ambos ojos de los pacientes: Se administraron ICMA y los colirios estándar antes de la intervención, uno en cada ojo respectivamente. Antes de practicar la cirugía de cataratas en el primer ojo, se aleatorizó a los sujetos (1:1) a recibir el primer tratamiento: ICMA tras la instilación de clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1% o solo los colirios midriáticos-anestésicos (tropicamida 1%, fenilefrina 10% y clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%). El otro tratamiento se administró en la cirugía del ojo adelfo.

El estudio incluyó un período de selección de 7 días antes de realizar la cirugía en el primer ojo, visita de inclusión (V0), y tres visitas adicionales por ojo: primera

visita, el día de la intervención (V1); segunda visita, 12-36 horas después de la intervención (V2); y tercera visita, 7±1 días después de la intervención (V3).

3.4 POBLACIÓN DE ESTUDIO

Un total 50 pacientes, de 40 a 88 años que iban a someterse a cirugía de catarata en ambos ojos en los próximos 17 días, se incluyeron en el estudio. No se detectaron fallos de cribado. Todos los pacientes recibieron el tratamiento del estudio y fueron analizados como población *de seguridad* (N = 50). Los pacientes elegibles fueron aquellos que cumplieron con todos los criterios de inclusión y ninguno de los criterios de exclusión y se analizaron según la población *del protocolo* (N = 46).

3.5 CRITERIOS DE SELECCIÓN

3.5.1 Criterios de inclusión

1. Pacientes de entre 40 y 88 años, con cirugía bilateral de cataratas, programada en los 17 días siguientes.
2. Diámetro de la pupila ≥ 7 mm en la visita de selección después de aplicar el protocolo de dilatación.
3. Disposición y capacidad del paciente para otorgar su consentimiento informado por escrito antes de realizar cualquier procedimiento relacionado con el estudio y para cumplir todos los requisitos del estudio.

3.5.2 Criterios de exclusión

1. Pacientes que se han sometido a cirugía combinada, cirugía intraocular o corneal previa; pacientes que presentan cataratas iatrogénicas, traumáticas o congénitas, anomalías pupilares, sinéquias del iris, trastornos del movimiento ocular, enfermedades del sistema de drenaje lagrimal, antecedentes de enfermedad ocular inflamatoria, enfermedad corneal, antecedentes de traumatismo, infección o inflamación ocular en los 3 últimos meses, pseudoexfoliación o síndrome exfoliativo en uno de los ojos.

2. Disfunción endotelial corneal clínicamente significativa.
3. Pacientes con una dureza de la catarata en uno de los ojos de grado ≥ 3 según el Sistema de Clasificación de Opacidades del Cristalino III (LOCS III) (8).
4. Pacientes que padecen de asma bronquial o insuficiencia cardíaca.
5. No se permitió el uso de los siguientes medicamentos concomitantes: corticoides e inmunosupresores sistémicos en los 3 meses previos a la intervención, opiáceos y derivados de la morfina sistémicos en los 7 días previos a la intervención, tratamiento ocular tópico con acción midriática o anestésica en los 7 días previos a la intervención, otros analgésicos sistémicos (excepto paracetamol) en los 7 días previos a la intervención, tratamiento tópico con acción antiinflamatoria y antibiótica en el día previo a la intervención (excepto el tratamiento preoperatorio especificado en este protocolo), ansiolíticos e hipnóticos el día de la intervención (excepto los usados en la anestesia por protocolo) y adrenalina o cualquier otro fármaco con acción midriática en la solución de irrigación intraocular.
6. No se permitió el uso de lentes de contacto en los 7 días previos a la intervención.
7. Cualquier trastorno ocular conocido que afecte a la superficie ocular (es decir, grado de tinción > 1 según el esquema de Oxford).
8. Hipersensibilidad conocida a los principios activos (tropicamida, fenilefrina, lidocaína, oxibuprocaína o tetracaína) o a cualquiera de sus excipientes, a anestésicos de tipo amida o a derivados de la atropina.
9. Embarazo o lactancia materna en mujeres en edad fértil.

3.6 TRATAMIENTO DE INVESTIGACIÓN

1. **ICMA y colirio anestésico**

- *Clorhidrato de oxibuprocaína 0,4% + clorhidrato de tetracaína 0,1%*: instilación de 1-2 gotas en el ojo antes de aplicar el procedimiento antiséptico preoperatorio y de practicar la primera incisión.
- *ICMA (combinación fija intracameral de midriáticos y anestésico):* 0,2 ml administrados en inyección intracameral lenta al comienzo de la intervención quirúrgica.

2. **Tratamiento estándar con colirios midriáticos - anestésicos**

El tratamiento de referencia fue tópico con tropicamida 1%, fenilefrina 10% y oxibuprocaína 0,4% + tetracaína 0,1% siguiendo el protocolo de administración habitual establecido en el centro participante.

3.7 CRITERIOS DE EVALUACIÓN

3.7.1 Seguridad

El criterio de valoración principal del estudio fue la variación de la tinción de la superficie corneal/conjuntival medida según los esquemas de Oxford (tinción corneal con fluoresceína) y de van Bijsterveld (tinción conjuntival con verde de lisamina) con ICMA en comparación con el protocolo estándar de colirios, entre el momento basal (visita 0) y 7 días después de la intervención (visita 3). Además, se evaluaron las variaciones entre el momento basal (visita 0) e inmediatamente después de la intervención (visita 1) y entre el momento basal (visita 0) y 12-36 horas después de la intervención (visita 2)*****.

Los criterios de valoración secundarios relacionados con la seguridad fueron:

1. Variación de la agudeza visual mejor corregida (BCVA) según la prueba de Snellen entre el momento basal (visita 0) y 7 días después de la intervención (visita 3).

2. Porcentaje de pacientes con alteraciones epiteliales demostradas mediante exploración con lámpara de hendidura (es decir, ninguna, leves y significativas) 12-36 horas después (visita 2) y 7 días después de la intervención (visita 3)
3. Variación de la hiperemia conjuntival según la escala fotográfica de MacMonnies (0 a 5) entre el momento basal (inmediatamente antes de la administración del tratamiento del estudio en la visita 1) y 7 días después de la intervención (visita 3). Además, se describieron las variaciones de la hiperemia conjuntival entre el momento basal (inmediatamente antes de la administración del tratamiento del estudio en la visita 1) e inmediatamente después de la intervención (visita 1) y entre el momento basal y 12-36 horas después de la intervención (visita 2)*.
4. Variación de la presión intraocular entre el momento basal (visita 0) y 7 días después de la intervención (visita 3).
5. Función de dispersión del punto (PSF) medida mediante el índice de dispersión objetivo (OSI) en el sistema de análisis de calidad óptica (OQAS) HD Analyzer™ 12-36 horas después (visita 2) y 7 días después de la intervención (visita 3).
6. Variación en el tiempo de ruptura de la película lagrimal visual (VBUT) medido por OQAS HD Analyzer ™ desde el momento basal (visita 0) hasta 7 días después de la cirugía (visita 3). Además, los cambios en VBUT desde el momento basal hasta las 12-36 horas después de la cirugía (visita 2) y los 7 días posteriores a la cirugía (visita 3).
7. Variación del Índice de enfermedad de la superficie ocular (OSDI) entre el momento basal (visita 0) y 7 días después de la intervención (visita 3).
8. Porcentajes de pacientes con síntomas oculares percibidos por los pacientes y signos evaluados por los investigadores según escalas ordinales de 0 (ausentes/ninguno) a 3 (graves) 12-36 horas después (visita 2) y 7 días después de la intervención (visita 3).
9. Variaciones en la duración de la preparación y la cirugía, desde la administración de la primera gota hasta la primera incisión, desde la primera incisión hasta el final de la cirugía y desde la administración de la primera gota hasta el final de la cirugía.
10. Incidencia de acontecimientos adversos relacionados con los tratamientos del estudio.

* En cada visita del estudio se tomaron fotografías para la evaluación de la tinción corneal/conjuntival y la hiperemia conjuntival. Las fotografías se codificaron, se mezclaron y se enviaron a un investigador colaborador del Instituto, ciego al tratamiento del ensayo. Se utilizó el mismo sistema de biomicroscopía de lámpara de hendidura y de fotografía para cada caso, bajo las mismas condiciones de encuadre e iluminación de la consulta. El oftalmólogo evaluador ciego clasificó las fotografías, mostradas en su propio monitor, utilizando una iluminación similar de la sala para la evaluación y sin límite de tiempo.

3.7.2 Eficacia

Los criterios de valoración secundarios relacionados con la eficacia fueron:

1. Satisfacción de los pacientes con los tratamientos del estudio evaluada en una escala ordinal de 0 (muy satisfactorio) a 3 (insatisfactorio) inmediatamente después de la intervención (visita 1).
2. Satisfacción evaluada por los investigadores según una escala ordinal de 0 (muy satisfactorio) a 3 (insatisfactorio) inmediatamente después de la intervención (visita 1).

3.8 MÉTODOS ESTADÍSTICOS

3.8.1 Justificación del cálculo del tamaño de la muestra

Debía disponerse de una estimación de la variación media prevista, con la desviación estándar, entre el momento basal y 7 días después de la intervención en las escalas de tinción. Dado que no pudieron identificarse datos para realizar una estimación de este tipo, no se realizó un cálculo formal del tamaño de la muestra y se consideró apropiado un tamaño de 50 pacientes como evaluación exploratoria/piloto.

3.8.2 Poblaciones de análisis

Para los análisis del estudio se definieron las siguientes poblaciones:

- *Población de seguridad:* formada por todos los pacientes que recibieron cualquiera de los tratamientos del estudio (N=50).
- *Población por protocolo (PP):* formada por todos los pacientes que cumplieron los criterios de selección (pacientes elegibles) y recibieron el tratamiento del estudio sin desviaciones importantes del protocolo (N=46).

La población de *seguridad* se utilizó para analizar el objetivo principal del estudio

3.8.3 Métodos estadísticos

Una vez finalizado el ensayo y resueltas todas las posibles discrepancias en los datos, se cerró la base de datos del estudio y se preparó un plan de análisis estadístico (PAE) detallado, para orientar el análisis de los datos y justificar cualquier cambio en el plan original.

Se hizo una descripción general de las variables incluidas en el estudio. Se presentaron distribuciones de frecuencias absolutas y relativas de las variables cualitativas, así como las medidas de tendencia central y dispersión (media, desviación estándar, mediana, mínimo y máximo) de las variables cuantitativas. Se presentaron intervalos de confianza del 95% para los resultados asociados al objetivo principal y las principales variables secundarias.

3.9 RESULTADOS

3.9.1 Características demográficas y clínicas basales

En total, se incluyó a 50 pacientes en el estudio en el Instituto de Microcirugía Ocular (IMO, Barcelona, España) y todos ellos recibieron el tratamiento del estudio (población de seguridad). La edad media de los pacientes era de 61,0±10,0 años y 27 de ellos (54%) eran mujeres. Once pacientes (22%) tenían trastornos oftalmológicos distintos de cataratas, 15 (30%) trastornos cardiovasculares, 7 (14%) trastornos neurológicos, 4 (8%) trastornos endocrinos y 3 pacientes (6%) diabetes mellitus. Veintiséis pacientes (52%) declararon padecer

otras enfermedades. La dilatación pupilar media (mm) registrada en la visita de selección (V0) fue de 7,8±0,5 mm en el grupo de ICMA y 7,9±0,5 mm en el grupo control (p=0,933).

En cuanto al tipo de lente utilizada en la cirugía, se implantaron lentes intraoculares multifocales en el 54% de los casos en ambos grupos. Lentes monofocales se implantaron en el 26% del grupo ICMA frente al 24% en el grupo de control y lentes tóricas se implantaron en el 20% frente al 22%, respectivamente. Las diferencias entre los grupos no se consideraron significativas (p = 0,957).

La población de *seguridad* se utilizó para realizar el análisis de la seguridad (N=50). Cuatro pacientes quedaron excluidos de la población *por protocolo* (N=46) por una desviación mayor del protocolo y no fueron evaluados en los análisis de eficacia.

3.9.2 Resultados de seguridad y eficacia

3.9.2.1 Objetivo principal

Los valores medios de tinción corneal y conjuntival, evaluados por los esquemas de Oxford (Ox) y van Bijsterveld (VB), fueron similares en ambos tratamientos, con una recuperación ligeramente más rápida después de la administración de ICMA en comparación con el tratamiento de control. Aunque la tendencia no fue de significación estadística (Ox: Visita 0 (V0), p=no aplicable, Visita 1 (V1), p=0,118, Visita 2 (V2), p=0,626 y Visita 3 (V3), p=0,975; (VB: V0, p=0,299; V1, p=0,475; V2, p=0,493 y V3, p=0,878).

La comparación de los grados de lesión en la superficie ocular experimentada por los pacientes tratados con el ICMA y el tratamiento de control no fue estadísticamente significativa (Ox: V0, p=no aplicable; V1, p=0,162; V2, p=0,592; V3, p>0,999. VB: V0, p=0,297; V1, p=0,668; V2, p=0,515; V3, p=0,894).

Los cambios en los valores de los esquemas de Oxford y van Bijsterveld se compararon entre los productos en todas las visitas del estudio y no se observaron diferencias estadísticamente significativas: V0-V1: Ox, ICMA-1,3±0,7 y control

-1,4±0,7 (p=0,169); VB, ICMA -0,4±0,6 y control -0,4±0,6 (p=0,845). V0-V2: Ox, ICMA -0,2±0,4 y control -0,3±0,5 (p=0,455); VB, ICMA -0,1±0,6 y control -0,3±0,6 (p=0,130). V0-V3: Ox, ICMA 0,0±0,1 y control 0,0±0,2 (p=0,975); VB, ICMA 0,0±0,6 y control -0,1±0,6 (p=0,350).

3.9.2.2 Objetivos secundarios

1. La agudeza visual mejor corregida (BCVA) se evaluó mediante la prueba Snellen en los dos grupos y los datos obtenidos se presentaron según la escala decimal (Snellen). En la visita de selección (V0), la media de la BCVA fue de 0,8±0,2 en ambos grupos. Después de la cirugía, la media de la BCVA fue de 0,8±0,2 el primer día postoperatorio y 0,9±0,2 en una semana después de la cirugía, en ambos grupos respectivamente. No se observaron diferencias significativas entre los dos grupos entre las visitas (V0 p=0,969, V2 p=0,270, V3 p=0,689, prueba de Mann-Whitney). Se realizó transformación a logMAR para el análisis estadístico.

   Se compararon las variaciones entre las visitas en ambos grupos y no se observaron diferencias estadísticamente significativas (logMAR): V0-V2: ICMA 0,0±0,2 y control 0,0±0,2 (p=0,552); V0-V3: ICMA 0,0±0,1 y control 0,0±0,2 (p=0,823); V2-V3: ICMA 0,0±0,1 y control 0,0±0,1 (p=0,508).

2. No se observaron alteraciones epiteliales en ninguno de los grupos de tratamiento en las visitas 0 y 1 (antes de la intervención). En la visita 2 (12-36 h después de la intervención), el 8% de los pacientes del grupo del ICMA mostró alteraciones epiteliales, que fueron significativamente menores, en comparación con el 30% de los del grupo de control (p=0,005). En la visita 3, ninguno de los pacientes tratados con el ICMA presentó alteraciones epiteliales, mientras el 8,7% de los tratados con el producto de control presentaban alteraciones epiteliales (p=0,056), que persistieron tiempo más largo que el seguimiento del estudio.
   Se evaluó el porcentaje de pacientes con cambios entre las visitas (entre V0-V2 y entre V0-V3) y se comparó entre los grupos de tratamiento: V0-V2, ICMA 8% y control 30%, (p=0,005); V0-V3, ICMA 0% y control 8,7%, (p=0,056).

3. Los grados de hiperemia conjuntival se evaluaron usando la escala fotográfica de MacMonnies y se compararon entre los grupos ICMA y control. No se observaron

diferencias estadísticamente significativas: V1 (antes de la intervención), p=0,300; V1 (después de la intervención), p=0,312; V2, p=0,172; V3, p=0,449.

La variación media de la hiperemia entre las visitas se comparó entre grupos: V1(antes de la intervención)-V1(después de la intervención), ICMA -0,2±0,9 y control -0,3±0,8 (p=0,454); V1(antes de la intervención)-V2: ICMA -0,5±0,7 y control -0,8±0,7 (p=0,102); V1(antes de la intervención)-V3: ICMA=-0,8±0,9 y C=-0,9±0,9 (p=0,732).

Se comparó el porcentaje de pacientes con hiperemia de grado 0 antes y después de la intervención, sin observarse diferencias estadísticamente significativas: ICMA, V1 (antes de la intervención) 65,3% y V1 (después de la intervención) 54,3%, (p=0,301); control, V1 (antes de la intervención) 60% y V1 (después de la intervención) 43,5%, (p=0,152). Al comparar el porcentaje entre V1 (antes de la intervención) y V2, ambos grupos mostraron diferencias significativas (ICMA, 65,3% frente al 29,2%, p=0,001; control, 60% frente al 12%, p< 0,001).

4. La presión intraocular se midió en las visitas 0(ICMA 14,5±3,1 y control 15,0±3,2; p=0,415) y 3 (ICMA 9,5±3,1 y control 9,6±2,5; p=0,679). Se comparó la variación media entre las visitas 0 y 3 en el grupo del ICMA (5,1±3,0) y de control (5,7±3,1) y las diferencias no fueron significativas (p=0,382).
5. El índice de dispersión objetivo (OSI), obtenido por la imagen de la función de dispersión del punto (PSF) de doble paso, se evaluó en las visitas 2 (ICMA 2,5±1,5 y control 2,8±1,5; p=0,273) y 3 (ICMA 2,5±1,5 y control 2,9±1,5; p=0,237), sin observarse diferencias estadísticamente significativas entre los grupos de tratamiento. Se comparó la variación entre ambas visitas y tampoco se constataron diferencias significativas (ICMA 0,0±1,8 y control 0,0±1,6; p=0,668). Sin embargo, dispersión intraocular más baja implica mejor calidad óptica y se considera de importancia clínica.
6. El tiempo de ruptura de la película lagrimal visual (VBUT) se midió con OQAS en todas las visitas y se comparó entre los grupos, y tan solo en la visita 0 se observó una diferencia estadísticamente significativa en el porcentaje de pacientes que presentaban VBUT estable, moderadamente estable o inestable (p=0,033). Las variaciones entre las visitas se compararon en ambos grupos y no

se observaron diferencias significativas: V0-V2, ICMA 0,2±1,2 y control 0,1±0,8, p=0,864; V0-V3, ICMA 0,2±1,1 y control 0,1±0,8, p=0,618; V2-V3, ICMA -0,1±0,8 y control -0,1±0,7, p=0,944.

7. El cuestionario OSDI fue contestado por los pacientes en las visitas 0 (A: ICMA 3,1 y control 3,3, p=0,867; B: ICMA 3,2 y control 3,2, p=0,997; C: ICMA 1,5 y control 1,4, p=0,826; Total: ICMA 16,9 y control 17,1, p=0,952) y 3 (A: ICMA 2,0 y control 2,7, p=0,250; B: ICMA 1,1 y control 1,6, p=0,610; C: ICMA 0,9 y control 1,1, p=0,815; Total: ICMA 8,8 y control 11,9, p=0,231) y las puntuaciones comparadas entre los grupos no mostraron diferencias estadísticamente significativas. También se evaluaron las variaciones entre las visitas y no se obtuvieron diferencias significativas (A: ICMA 0,8 y control 0,2, p=0,641; B: ICMA 1,7 y control 1,3, p=0,916; C: ICMA 0,6 y control 0,3, p=0,666; Total: ICMA 6,3 y control 3,5, p=0,689).

8. Los síntomas y signos objetivos fueron evaluados por los pacientes y los investigadores, respectivamente, en el período de seguimiento después de la intervención (visitas 2 y 3).

   En la visita 2, la evaluación de la "irritación/quemazón/escozor" reveló una diferencia significativa entre los pacientes tratados con ICMA (6,1%) y los del grupo de control (26%), (p=0,018). En el resto de los síntomas declarados por los pacientes (dolor, p=0,185; fotofobia, p=0,391; sensación de cuerpo extraño, p=0,051 y otros síntomas, p>0,999), las diferencias no fueron significativas. En la visita 3 no hubo diferencias significativas entre los grupos comparados (dolor, p=0,615; irritación/quemazón/escozor, p=0,482; fotofobia, p=0,466; sensación de cuerpo extraño, p=0,090 y otros síntomas, p=0,837).

   En la visita 2, los investigadores evaluaron que los pacientes del grupo de control sufrieron significativamente más reacción folículo-papilar conjuntival (32%) que los del grupo del ICMA (10,2%), (p=0,015). En el resto de signos evaluados (edema palpebral, p=0,407; quemosis, p=0,331; hiperemia conjuntival, p=0,239; secreción conjuntival, p=0,495 y otros signos, p=0,437) no se apreciaron diferencias significativas. En la visita 3 no se observaron diferencias estadísticamente significativas entre los grupos en ninguno de los signos evaluados (edema palpebral, p>0,999; quemosis, p>0,999; hiperemia conjuntival,

p=0,072; secreción conjuntival, p=no aplicable; reacción folículo-papilar, p=0,266 y otros signos, p=0,203).

9. Se registraron los tiempos quirúrgicos (minutos) en tres momentos: entre la administración de la primera gota y la primera incisión (ICMA 5.0±0.0min vs. control 29.7±1.5min, p<0,001), entre la primera incisión y el final de la intervención (ICMA 10.0±1.6min vs. control 9.5±1.4min, p=0,143) y el tiempo total transcurrido entre la administración de la primera gota y el final de la intervención (ICMA 15.0±1.6min vs. control 39.2±1.9min, p<0,001). En el grupo de ICMA se constató un tiempo significativamente menor de preparación preoperatoria (entre la administración de la primera gota y la primera incisión) y del procedimiento completo (entre la administración de la primera gota y el final de la intervención).
10. La satisfacción de los pacientes, fue centrada en la comodidad intraoperatoria y calificada significativamente más alta en los pacientes tratados con ICMA. El 98% del grupo ICMA clasificó el tratamiento como "muy satisfactorio" frente al 80% en el grupo control (p=0,008). Los pacientes en el grupo de control justificaron su satisfacción como "satisfactoria" e "insatisfactoria" por haber experimentado algunas molestias, dolor y/o presión durante la cirugía.
11. La satisfacción de los investigadores fue significativamente mayor en el grupo tratado con ICMA, 98% frente al 80% en el grupo control (p=0,008). La cooperación de los pacientes durante la cirugía aumentó en el grupo tratado con ICMA. Eso fue debido a la ausencia de dolor o molestias intraoperatorias, por lo que el procedimiento fue técnicamente menos complejo.
12. Acontecimientos adversos (AA) se detectaron en un total de 19 casos y no fueron graves ni se consideraron relacionados con los tratamientos del estudio. Los únicos AA con una incidencia ≥ 2% fueron el edema corneal en el 8% de los ojos y la rotación de lente tórica en el 2%. El resto de los AA fueron del 1% y se describen a continuación: filtración de la herida, edema macular cistoideo leve (CME), pliegues de Descemet, defecto epitelial corneal, queratitis punteada superficial (SPK) y visión borrosa no especificada.

3.10 CONCLUSIONES

1. La tinción de la superficie corneal y conjuntival disminuyó más rápidamente después de la administración de ICMA en comparación con el tratamiento control, aunque la tendencia no fue estadísticamente significativa.
2. La evaluación de la recuperación de la BCVA proporcionó resultados similares para ICMA y para el tratamiento estándar de colirios.
3. Se notificaron significativamente menos alteraciones epiteliales corneales y una recuperación más rápida de la integridad epitelial para el grupo ICMA. Las alteraciones epiteliales persistieron más de 7 días en algunos casos con el protocolo estándar de gotas de midriáticos y anestésicos.
4. La hiperemia conjuntival aumentó a lo largo del estudio en ambos grupos de tratamiento y el ICMA mantuvo un mayor porcentaje de pacientes sin hiperemia durante las primeras visitas postoperatorias, aunque sin diferencias estadísticamente significativas entre los grupos.
5. La variación en la presión intraocular, 7 días después de la cirugía comparada con los valores preoperatorios, no demostraron diferencias significativas entre los grupos.
6. Se ha registrado una tendencia a mediciones menores del índice de dispersión objetivo (OSI) en los ojos tratados con ICMA en comparación con el tratamiento estándar. Aunque no se observó diferencia estadísticamente significativa, menor dispersión intraocular se asocia a mejor calidad óptica y se considera de relevancia clínica.
7. Se observó inestabilidad de película lagrimal (VBUT) en el postoperatorio con tendencia a la recuperación gradual una semana después de la cirugía, en ambos grupos. Los cambios antes y 7 días después de la cirugía no demostraron diferencias estadísticamente significativas entre los grupos.
8. El cuestionario OSDI demostró una mejora general en los puntajes totales de los OSDI postoperatorios a la semana en ambos grupos, con resultados ligeramente mejores en el grupo ICMA, enfocando la mejora en los síntomas visuales. No se

detectaron cambios significativos entre el OSDI preoperatorio y postoperatorio comparando los grupos.

9. Los pacientes tratados con ICMA experimentaron síntomas oculares tales como irritación, quemazón y escozor en un significativamente menor porcentaje y con menor intensidad el primer día después de la cirugía frente a los pacientes tratados con el tratamiento control.
10. El porcentaje de pacientes que sufrieron reacción folículo-papilar el primer día postoperatorio fue significativamente menor en el grupo ICMA frente al grupo control.
11. La preparación y el tiempo de espera de los pacientes para la cirugía se disminuyeron significativamente unos 25 minutos cuando se utilizó ICMA, lo que fue más cómodo y causó menos estrés en los pacientes.
12. Los pacientes y los investigadores refirieron una mayor satisfacción con el uso de ICMA que con el protocolo estándar de colirios midriáticos y anestésicos. Los pacientes sintieron mayor comodidad durante la cirugía con la administración de ICMA.
13. En este estudio no se detectaron acontecimientos adversos graves ni relacionados con el tratamiento. El perfil de seguridad de ICMA fue similar al del protocolo estándar de colirios en los parámetros evaluados.

4. INTRODUCTION

4.1 CATARACT SURGERY

Current cataract surgery with clear corneal micro-incisions has been recognized as one of the most promising surgical procedures. However, postoperative ocular discomfort has been reported in most patients due to dry eye (3) (9) (10) (11). The changes in tear film stability due to reduced corneal sensitivity (12) (13) (14) and loss of conjunctival cells via topical medication with preservatives (3) (15) and anaesthetics (16) (17) and the increase of inflammatory factors (18) are all involved in the onset of cataract surgery-induced dry eye (19) (20).

4.1.1 Prevalence and incidence

Cataract is a leading cause of visual impairment globally, accounting for 33% of blindness worldwide (21). Global prevalence of cataract in adults, over 50 years of age, was estimated at 47.8% (22). Crude prevalence of cataract in European adults was calculated at 19.3% (23). Cataract is affecting more than 24.4 million Americans (24). With the aging of the US population, this number rose by 20% from 2000 to 2010, and is projected to increase to 38.7 million by 2030 (25). The rate of cataract surgery has also increased over the past several decades. Cataract surgery, nowadays, is the second most commonly undertaken ocular surgical procedure after intravitreal injections (26). The majority of cataract surgery is performed in older patients, a group with a higher incidence of dry eye. Ocular surface disease is one of the most common ocular conditions in the elderly and an important cause of ophthalmologist visiting (27) (28) (29).

4.1.2 Cataract surgery and ocular surface

Several studies have demonstrated that cataract surgery may induce or aggravate dry eye (1) (2) (3) (4) (5). Dry eye symptoms increase after uncomplicated phacoemulsification with a duration of about 3 months (1) (3) (20) (30), although the duration of the symptoms, evaluated by the OSDI questionnaire may improve at 1 month after surgery (2) (9) (10) and also after using non-preserved medications, artificial tears or topical cyclosporine A

postoperatively (1). Most studies observe increased ocular surface staining and tear film instability, with shorter TBUT, after cataract surgery with recovery to preoperative levels around 3 months or longer (1) (3) (9). Intraocular scattering (OSI) decreases after cataract surgery reaching best optical quality around 3 months postoperatively (31) (32) (33), even though the values remain slightly higher than those in a study of a population of similar age but with healthy eyes (34), indicating that once the cataract is eliminated and the refractive defect is resolved, these eyes continue to present more scattering than a healthy eye of a subject of the same age. Probably, there is an association with ocular surface disease. After cataract surgery changes in Schirmer I score can be observed (13) (35). Likewise, changes in tear volume or tear meniscus height have been found with recovery to preoperative levels at 2-3 months after surgery (1) (3) (9) (20). Ocular symptoms and tear film stability are generally worsened over a more prolonged postoperative period in diabetic patients, who are more susceptible to dry eye after cataract surgery compared to non-diabetics (19) (36) (37).

4.1.3 Risk factors for ocular surface disorders

Cataract surgery was identified as a risk factor for dry eye disease (DED) (1) (2) (3) (4) (5). Large epidemiologic studies confirm that female sex and older age increase the risk for DED (38). An association was found between older age and an increase in positive dry eye signs (39) (40) (41). Race is likely to be a confounding factor in the prevalence estimates of abnormal tear function. Using the same diagnostic criteria and similar age range, Asians have a higher prevalence of tear instability and ocular surface staining than Caucasians. A relationship between sex and objective signs of dry eye remains controversial (38).

Several studies reported perioperative risk factors for ocular surface disorders (OSD) in cataract surgery. These factors include preservatives in eye drops (42), topical anaesthetics (16) (17), topical mydriatics (43) (44) (45), cleansing of the conjunctival sac and lids with povidone iodine (4) (46), forceful opening with

eyelid speculum (47), light and heat from the operating microscope (41) (48) and topical non-steroidal anti-inflammatory drugs (49).

4.1.4 Pathophysiology

There are many elements of cataract surgery that can contribute to the pathophysiology of postoperative dry eye. These multifactorial pathophysiological mechanisms include the use of topical anaesthetics, mydriatics and exposure desiccation, possible light toxicity from the operating microscope, corneal nerve transection, elevation of inflammatory factors, conjunctival goblet cell loss, and meibomian gland dysfunction (MGD) (11).

- **Corneal nerve transection**

Cornea has the highest density of sensory nerve endings in the human body. Corneal incisions created during phacoemulsification can cause partial denervation of cornea. The surgical trauma is associated with the production of oxygen-free radicals, proteolytic enzymes, prostaglandins, leukotrienes and cytokines. These inflammatory mediators, released intra and postoperatively, may also alter the physiology of the corneal nerves resulting in reduced corneal sensitivity with subsequent decrease in blinking and reduction in tear production, thus leading to increased epithelial permeability, decreased epithelial metabolic activity, impaired epithelial wound healing and loss of cytoskeletal structures (1) (10) (41) (50) (51) (52) (53). Neural growth factor is released to regenerate the subepithelial corneal axon and is completed approximately within 1 month. The healing of the nerves may explain why dry eye signs and symptoms are prominent early after surgery and improve thereafter (52). With time corneal sensitivity can recover to preoperative levels (12). Grooved and longer incisions were associated with worse dry eye signs and symptoms, and with longer recovery time to return to baseline (30); while there appeared to be little impact of incision location or shape (5). Corneal denervation caused by intracapsular (ICCE) or extracapsular surgery (ECCE) could last up to 2 years (54) in

comparison with 3 months with phacoemulsification (30). Some studies have shown that corneal sensation dropped centrally and temporally with temporal incision, but returned to baseline within 1 month with a 2.8mm incision (30) and within 3 months with a 4.1mm incision (12), and similar temporal changes were found in the TBUT (19). Small corneal incisions also leave enough of the corneal sensory nerve distribution intact, thereby having minimal effect on tear secretion and blinking (30).

- **Conjunctival goblet cell loss**

Conjunctival goblet cells produce the mucinous component of the tear film. Mucins are important in converting the hydrophobic corneal surface to a hydrophilic surface by attachment to glycocalyx on the corneal microvilli, thereby allowing the tear film to adhere to the corneal surface. A decrease in goblet cells compromises the integrity of the tear film and can lead to evaporative dry eye. A marked decrease in conjunctival goblet cell density was observed following uncomplicated cataract surgery and conjunctival goblet cell density had not returned to baseline even 3 months postoperatively (3) (30) (41). The degree of goblet cell loss and associated conjunctival cell squamous metaplasia was related to operating room time (9) (30) and the length of exposure to the operating microscope light (2) (19) (41). Some *in vitro* studies suggest that certain inflammatory mediators, IL-13 and leukotrienes, may actually promote goblet cell differentiation and secretion (55) (56).

- **Elevation of inflammatory factors**

Ocular surface irritation during cataract surgery may induce an inflammatory response, resulting in the recruitment of neutrophils and macrophages, and production of chemical mediators, such as free radicals, proteolytic enzymes and cyclooxygenase (18) (57). These inflammatory mediators can irritate and damage ocular surface structures, thus inducing changes in the tear film.

Moreover, topical anaesthetics, pre- and postoperative preservative-containing eye drops have been suggested to contribute to the inflammatory reaction (15). Animal models have shown that preservatives can elevate inflammatory markers and worsen dry eye parameters (58) (59).

There have been a number of studies promoting the use of preservative-free medications (53) (60). One of them compared preservative-free and preserved combinations of sodium hyaluronate 0.1% and fluorometholone 0.1% in cataract surgery patients with preexisting dry eye syndrome. Although both groups experienced improvements in all the dry eye and inflammatory parameters, the preservative-free group had significantly greater improvements (61). It is possible that the inflammatory and toxic properties of the preservatives offset the benefit of topical steroids and lubricants. Because of this, clinicians have been encouraged to prescribe preservative-free drops, especially if frequency of use exceeds four times daily (62). Efforts to establish appropriate therapeutic strategies taking into consideration the effect of these concomitant pathological changes may contribute to better clinical outcomes after cataract surgery.

4.2 ROLE OF PRESERVATIVES ON OCULAR SURFACE

Increasing attention has been directed to the relationship between the repeated use of topical therapies and ocular surface disorders (OSD). Chronic exposure of the ocular surface to preservatives is now well recognized to induce toxicity and adverse changes to the ocular surface (63) (64) (65) (66).

The Pharmacopoeia recommends that eye drops must contain an antimicrobial agent (preservative) to avoid or to limit microbial proliferation after the bottle is opened. Eye drops are contaminated essentially by the hands when handling the bottle or by contact of the tip touching the eyelids, lashes, conjunctiva or tears. There is also a risk of cross-transmission when the same eye drops are shared by several patients, especially in a hospital environment.

Preservatives used in ophthalmic preparations belong to a variety of chemical families, including mercury derivatives, alcohols, parabens, EDTA, and

chlorhexidine, but quaternary ammonium compounds, due to their low allergenic effects and apparently good safety profiles, have progressively become the major preservatives in use today (15) (19).

- **Benzalkonium chloride (BAK)**

The most commonly used preservative in ophthalmic preparations is benzalkonium chloride (BAK). BAK is a nitrogenous cationic surface-acting agent belonging to the quaternary ammonium group. BAK is commonly used at concentrations ranging from 0.004 to 0.025%. BAK may cause or aggravate ocular surface disease through various mechanisms, such as its toxic and proinflammatory effects, as well as its detergent properties, which have been well demonstrated in numerous experimental and clinical investigations (15) (19). Several *in vitro* and *in vivo* studies demonstrate that BAK can induce corneal and conjunctival epithelial cell apoptosis, damage the corneal nerves, delay corneal wound healing, interfere with tear film stability and cause loss of goblet cells (67) (68) (69). BAK has cytotoxic effects on several structures of the eye, with a threshold of toxicity found at about 0.005%, below the concentration used in most eye drops (15).

In an *in vitro* study, a BAK concentration in excess of 0.005% significantly impaired lipid spreading and compromised the morphology of the tear lipid layer (70). Goblet cells produce soluble mucins and contribute to tear film stability and immune defenses. After exposure to a BAK concentration of 0.01% for 5 to 15 minutes a mucous layer alteration was observed by transmission electron microscopy, whereas prolonged exposure for 60 minutes to BAK 0.01% destroyed the mucous layer, causing tear film instability (71). Increased tear osmolarity was also observed in patients receiving preserved eye drops compared to those who received unpreserved topical medication (72). Following the loss of its protective properties, the impaired tear film not only results in dry eye symptoms and corneal damage, but also may convey cytotoxic inflammatory mediators throughout the ocular surface. Hence, increased corneal epithelial permeability has been shown in dry eye with additional impairment when using artificial tears

containing BAK compared to non-preserved eye drops (73). Tear film alterations may therefore stimulate a series of biological changes in the ocular surface, leading to subsequent neurogenic inflammation and further impairment of the tear film, creating a vicious cycle (19) (74). BAK causes disruption of the tight junctions of the corneal epithelium, an effect that has led to BAK being considered an enhancer of drug penetration into the anterior chamber (15). The cytotoxic effects of BAK have been shown to be increased experimentally when cells are previously subjected to a hyperosmotic stress mimicking dry eye *in vitro*. Therefore, BAK can cause some level of toxicity in normal eyes, which can be compensated by tissue defenses, but causes a much greater level in dry eyes, consistent with clinical findings. However, as BAK may progressively cause tear instability and hence hyperosmolarity, this compound is likely to change the conditions of its own tolerance and result in increasing toxicity levels (75). Other studies demonstrated BAK higher expression of inflammatory markers with the release of cytokines or increased expression of receptors to chemokines and cytokines (19) (76) (77) (78).

- **Oxidative preservatives**

To avoid issues with long-term exposure to preservatives, variants of preservatives designed to have a lower impact on the ocular surface have been developed, including oxidative preservatives (sodium chlorite; Purite® and OcuPure™ and sodium perborate; GenAqua™), polyquaternium-1 (Polyquad®) and Sof-Zia™. Sodium chlorite degrades to chloride ions and water upon exposure to UV light after instillation and sodium perborate is converted to water and oxygen on contact with the tear film. Some reports suggest that even these so-called “disappearing preservatives” can show some negative effects on the ocular surface (79). Therefore, preservative-free drops may be a better choice for patients who have pre-existing ocular surface conditions and/or need frequent instillation of eye drops. Preservative-free eye drops have shown greater effectiveness than preserved drops in decreasing inflammation on the ocular

surface and increasing the antioxidant contents in tears of patients with dry eye (80) (81).

4.3 ANAESTHESIA IN CATARACT SURGERY

In the history of modern cataract surgery, there has been a gradual move towards a more localized therapy with a more rapid passage of the patient through the surgical process.

In the case of anaesthesia that has meant moving from general anaesthesia to local anaesthesia, such as peribulbar and subtenon, to eye drops and more recently to intracameral anaesthesia (82) (83) (84) (85). Such approaches yield the obvious benefit of delivering the agent directly to where it is needed to achieve the desired effect with minimal systemic toxicity while leaving other ocular structures unaffected (86).

Topical anaesthesia became feasible after the development of small sutureless incisions, providing more rapid postoperative visual recovery without diplopia or ptosis (84). However, as topical anaesthesia can be difficult in cases such as highly anxious patients or more complicated surgeries, intracameral anaesthesia was introduced in cataract surgery (83). This technique was shown to be effective and safe (85), without diffusion in posterior segment (87). Nowadays, topical and intracameral drug administration are preferred methods for anaesthesia in cataract surgery (88). However, increased experience with topical anesthesia has shown that certain parts of the cataract surgery are associated with patient discomfort. These include iris manipulation, globe expansion as the phaco-emulsification handpiece or irrigation-aspiration handpiece is inserted into the eye, and intraocular lens insertion. Some patients also experience discomfort from the operating microscope light (89). This fact headed investigations toward improving patient comfort during cataract surgery. In 1995, Gills et al. proposed anterior chamber irrigation with 1% unpreserved lidocaine during the cataract surgery, in an attempt to increase patient comfort while undergoing cataract surgery under topical anesthesia (82) (83). In 1999, Crandall et al. reported increased patient cooperation during cataract surgery and reduced discomfort

during tissue manipulation when 1% preservative-free lidocaine was irrigated into the anterior chamber after the initial paracentesis (89). A meta-analysis on five randomized controlled trials showed lower intraoperative pain perception in patients using intracameral lidocaine and no significant difference in adverse events, corneal toxicity or need for supplemental anaesthesia (84). Intracameral combined lidocaine seems to be safer and more effective than using 1% lidocaine eye drops, which seems to be too acidic (pH as low as 6) (90). Although some surgeons would rather use a product containing a topical anaesthesia in combination with viscoelastic, it may also cause a greater loss of corneal endothelial cells due to its permanent contact during the surgery (91).

4.4 MYDRIASIS IN CATARACT SURGERY

Mydriasis is a physiological phenomenon controlled by the iris, composed of two antagonistic muscles controlling its opening, and allowing the eye to adapt to the surrounding light intensity. The pupil dilate under the action of the radial dilator smooth muscle, when there is poor light and this is the mydriasis. Conversely, when the light intensity is high, the pupil contracts under the action of the circular sphincter muscle and this is the miosis. The diameter of the pupil can vary from 0.5mm to 13mm. Physiologically, these two phenomena are governed by the autonomic nervous system (92). The radial dilator muscle is innervated by the sympathetic system, whereas the sphincter muscle is innervated by the parasympathetic system (93).

4.4.1 Impact of topical mydriatics on ocular surface

Cataract surgery requires a maximally dilated pupil to implant the intraocular lens. The size used for capsulorhexis is usually 5 mm; thus, obtaining a pupil size of 5.5 mm is the minimum required for cataract surgery. Traditionally, the main strategy surgeons use to achieve preoperative mydriasis, consists in the combination of two topical mydriatic agents, parasympatholytics (tropicamide,

cyclopentolate), and sympathomimetics (phenylephrine) (94) (95). Additionally, topical anaesthesia is used to provide patient comfort during the procedure.

The bioavailability of topical eye drops has always been suboptimal. The administration of drugs at the ocular surface, for local action by conventional eye drops, often leads to low ocular bioavailability (5–10%) because of eye blinking and naso-lacrimal drainage (96), resulting in high absorption at the systemic level (50–90%) and potentially leading to severe side effects (97) (98) (99). Only about 20% of a drop is retained in the cul-de-sac because of a limited raise in the volume of the lacrimal fluid. The rapid turnover of the fluid in the tear reservoir of 16% per minute also reduces the amount of the drug (100). Moreover, topical eye drops must permeate through a complex physiological corneal matrix, permeating through a lipid-rich hydrophobic epithelium, a hydrophilic stroma and another hydrophobic barrier at the corneal endothelium. Corneal permeability studies have shown that lipid solubility of a drug molecule is more important than water solubility to facilitate penetration. Topical medication prolong the time to pupil dilation because of the poor bioavailability (101). The rapid elimination of the administered eye drops often results in a short duration of the therapeutic effect, therefore requiring frequent administrations. To reach a sufficient mydriasis during surgery, many eye drops of each mydriatic agent are required with a ten minutes interval between each drop to obtain an effective mydriasis within 30 to 45 min. This leads to a prolonged stay of the patients in the preparation room, contamination of the ocular surface, epithelial toxicity due to the topical formulas and discomfort due to the frequent instillation of drops.

Mydriatics, cycloplegics (tropicamide, phenylephrine, cyclopentolate), topical anaesthetics (tetracaine) and excipients have been considered as causing dry eye disease (DED) (102), but specific data on the active compounds are mostly lacking as ophthalmic preparations are most often tested in preserved formulations, which may hinder interpretation of the role of the drug, preservatives and excipients, independently (19).

Topical drugs may act at the level of the ocular surface through various mechanisms, exerting allergic, toxic and/or immuno-inflammatory effects or by

chemical interaction with the lacrimal film, either by disrupting the lipid layer through detergent tensio-active effects, by reducing aqueous secretion, or by damaging: goblet cells, the conjunctival and corneal epithelia, corneal nerves through neurotoxic effects or even eyelids at the skin or meibomian gland level (19).

Tropicamide is a medication that is almost routinely used in ophthalmic examination to provide temporary mydriasis for fundus examination and prior to cataract surgery. Tropicamide is an acetylcholine receptor blocker drug, which has short acting cycloplegic and mydriatic effect. It is available in 0.5% and 1% ophthalmic solutions. Its maximum effect is achieved in about 20–25 minutes (min) and lasts about 20 min, with complete recovery being in 4 to 6 hours (103).

Phenylephrine, a selective alpha1-adrenergic receptor agonist of the phenethyl-amine class, is used primarily as a decongestant for mydriasis prior to cataract surgery (104) (105) (106) (107). It has been reported that topical administration of phenylephrine eye drops can cause abnormal cell morphology and pathogenic symptom of corneal epithelium, which gives rise to more attention for clinical safety (43). Unfortunately, phenylephrine abuse often causes unexpected side effects on the cornea such as increase of corneal thickness (108), spherical aberration (109), and resulting in acute angle-closure glaucoma (110). The cytotoxic effect of phenylephrine to the cornea and the underlying cytotoxic mechanisms have been investigated using *in vitro* model of human corneas and *in vivo* models of animal corneas (44) (45). Phenylephrine concentrations of 10% to 1.25% induce necroptosis and 0.625% induce apoptosis in *in vitro* cultured human corneal epithelial cells. Phenylephrine 10% induced destruction of the corneal epithelia and apoptosis of corneal epithelial cells in rabbit corneas *in vivo* (45). Phenylephrine, at concentrations above 1/128 of its clinical therapeutic dosage, has dose- and time-dependent cytotoxicity to human corneal stromal cells *in vitro*, and its cytotoxicity are most probably realized by inducing cell apoptosis which is also proven by cat keratocytes *in vivo*. Moreover, the pro-apoptotic effect of phenylephrine is achieved via a Bcl-2 family proteins-mediated mitochondrion-dependent pathway (44).

Common excipients in ophthalmic formulations (solutions, ointments, suspensions, and emulsions) could also contribute to dry eye symptoms. Additionally, the chemical properties of the formulation, such as iso/hypotonicity and pH, may also impact upon the tear film and local tolerance upon instillation (19).

4.4.2 Solid insert of tropicamide and phenylephrine

An insoluble ophthalmic insert releasing phenylephrine and tropicamide is currently available (Mydriasert®). The insert is an osmotic tablet, placed in the lower conjunctival bag by a trained medical staff. Its use entails holding the patient in the preparation room 1-1.5 hours before surgery, as it must remain for a minimum of 30-45 minutes in the conjunctival bag to induce a sufficient mydriasis and it can cause some discomfort for the patient (111). Nurses should be trained in the appropriate handling of the insert to avoid its loss, though patients can yet lose it without noticing (112) (113). In addition, after topical mydriatics, some eyes may exhibit insufficient dilation at the beginning of surgery, pupil dilation may decrease during its early phase or pupils may contract.

4.4.3 Intracameral mydriatics and anaesthetics

Intracameral injection of mydriatics and lidocaine for cataract surgery improves the bioavailability of the drugs, provides almost instantaneous mydriasis without adverse events (7) (95) (114) (115).

In 2003, Cionni et al described a surgical technique using intracameral lidocaine hydrochloride 1% to induce mydriasis, avoiding all preoperative dilating eye drops in cataract surgery (116). The same year, Lundberg with Behndig and, a year later, Behndig with Eriksson compared intracameral mydriatics and anaesthesia (preservative-free mixture of cyclopentolate 0.1%, phenylephrine 1.5% and lidocaine hydrochloride 1%) versus topical mydriatics (cyclopentolate 1%, phenylephrine 10%) combined with intracameral lidocaine hydrochloride 1%.

They found that intracameral mydriatics were a rapid, effective and safe alternative to topical mydriatics in phacoemulsification, without increasing the operation time or the complication rates (95) (114). In 2008, Lundberg and Behndig, concluded that the use of cyclopentolate does not increase mydriatic efficacy; therefore, it can be safely removed from the intracameral cocktail (117). Those were the first steps to a series of studies reporting the safety and efficacy of intracameral mydriatics and anaesthetics with short and long-term results (118) (119) (120).

Similarly, epinephrine and adrenaline have been used for intracameral mydriasis. Some surgeons irrigate the anterior chamber with epinephrine or adrenaline to induce or maintain mydriasis (121) (122), while others use intracameral injection of mydriatics to re-dilate pupils (123) (124) (125) (126). After the intracameral injection of mydriatics, the onset of mydriasis is almost instantaneous, pupils do not contract intraoperatively and visual acuity improves after surgery (95) (7).

Several studies have reported that systemic exposure to intracameral mydriatics and anaesthetics is lower and cardiovascular effects are less frequent (7) (6) (127) (128) (118). Changes in blood pressure and pulse are minimal and do not differ from those expected in patients whose pupils were dilated in the conventional manner (6). The intracameral route of administering mydriatics delivers minute doses of the drugs to the target organ to achieve the desired effect, thus minimizing potential cardiovascular effects (7) (6). Indeed, intracameral injections of substances with potential cardiovascular side-effects, such as epinephrine, have been shown to cause little or no cardiovascular side-effects (127) and intracameral injections of lidocaine 1% rendered no detectable blood levels (128). As the systemic absorption rate of intracameral administered substances is likely to be limited by the aqueous humour turnover rate (129) and the washing performed within one minute after injection, the risk of systemic side-effects may generally be lower after intracameral than after topical administration. A study comparing topical mydriasis, ophthalmic insert and intracameral mydriasis showed that from the cardiovascular point of view, intracameral mydriasis was the safest (118).

Another primary advantage of intracameral medication is the ease of delivery. Multiple applications of topical drops are unnecessary when medication is delivered into the anterior chamber. This has the additional advantage of eliminating toxicity from topical medications, especially those with preservatives such as benzalkonium chloride (BAK), since intracameral medications are mostly preservative free. One more possible advantage is enhanced efficacy as the theoretically higher dose is at the site where the medication's action will take place. The use of intracameral regimens combining mydriatics and anaesthetics may therefore avoid some disadvantages associated with topical regimens and entail potential benefits such as less irritation of cornea, faster recovery of visual acuity due to quicker undilate and increased patient comfort.

Nevertheless, the combinations of intracameral mydriatics and anaesthetics used, had to be prepared ad hoc in the operating room and there were not commercialized medication, approved by the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Moreover, these "homemade cocktails" could lead to dilution errors, inadequate concentration or dose of the medication and accidental use of medications containing preservatives, which could cause toxic anterior segment syndrome (130) (131) (132).

The launch of Fydrane® meant that we can now apply this principle to anaesthesia and mydriasis with a commercially manufactured product. Although Fydrane has proved to be effective and safe in phase II and III clinical trials, its effects on ocular surface warrant further assessment in phase IV trials.

4.4.4 Intracameral fixed combination of mydriatics-anaesthetic

Fydrane® (Laboratoires Théa) is the first commercially available intracameral mydriatic and anaesthetic injectable solution licensed for use during cataract surgery. It is comprised of an intracameral standardized combination of two synthetic mydriatic agents, an anticholinergic (tropicamide 0.02%) and an alpha sympathomimetic (phenylephrine 0.31%), and an anaesthetic (lidocaine 1%) (133). The efficacy and safety of this intracameral fixed combination of mydriatics and anaesthetic (ICMA) was demonstrated in a phase III international

multicenter clinical trial (134). In this issue, Chiambaretta et al. evaluated the pupil dilation dynamics with the ICMA (tropicamide 0.02%, phenylephrine 0.31%, and lidocaine 1%) and demonstrated that pupil dilation with this combination is prompt, adequate (mean pupil size larger than 7.0 mm), and sustained during all the steps of cataract surgery (115) (131).

The intracameral route of administering mydriatics delivers minute doses of the drugs to the target organ to achieve the desired effect, thus minimizing adverse effects. Intracameral administration reduces the need for preoperative eye drops, mitigating corneal toxicity and ocular surface damage.

4.5 OCULAR SURFACE

The ocular surface is one of the most complex and unique tissues in the body. The ocular surface must remain stable to not only provide protection to the structures of the eye against microbes, trauma, and toxins, but to maintain the comfort of the eye and provide a refractive surface that allows for good-quality vision. The ocular surface is the interface between the functioning eye and our environment. This surface provides anatomic, physiologic, and immunologic protection and comprises the palpebral and bulbar conjunctiva, the cornea, the corneoscleral junction called limbus and the tear film. The cornea and the overlying tear film are responsible for refraction and transmission of light into the eye. However, the limbus and the conjunctiva maintain the clarity and functions of the cornea by providing necessary support. The ocular surface not only provides an unusually efficient mechanical barrier to the entry of microorganisms into the eyes, but nutrition and metabolic interactions with the underlying stromal tissue as well. While the anatomical areas of the ocular surface have a continuous multilayered surface epithelial layer in common, significant morphological and functional differences exist between the structures (135).

The term *ocular surface* stresses the interdependence of the corneal and conjunctival epithelia in maintaining the health of the external eye. Initially, the ocular surface was considered as an anatomical classification based solely on the physical continuity of the stratified nonkeratinizing epithelium of the

conjunctiva, limbus, and cornea. More recently, clinical and research insights have offered compelling evidence of important functional relationships with in this anatomical entity. This rethinking of the ocular surface as a functional unit has stimulated a complete reorganization of the current approach to the management of ocular surface disease (136).

Creation of an unstable ocular surface from trauma, surgery or disease can compromise the integrity of any one of these protective functions and can lead to various forms of corneal and conjunctival dysfunction, broadly ranging from a mild corneal abrasion to severe stem cell loss, decreased vision, and ultimate blindness in the most severe disease. The health and function of all these structures is imperative for a stable ocular surface (135).

4.5.1 Ocular surface disorders

Ocular surface disorders include a variety of conditions. One of the most common conditions and challenges encountered in practice after cataract surgery include dry eye disease (DED) (1) (2) (3) (38) (137).

4.5.1.1 Dry eye disease

There has been much controversy over the past 20 years regarding the appropriate definition for dry eye. The National Eye Institute (NEI) definition stated: Dry eye is a disorder of the tear film due to tear deficiency or excessive tear evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of discomfort (138). The TFOS DEWS II developed a new definition: Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles (137) (139).

The prevalence of dry eye syndrome (DED), with and without symptoms, ranges from 5 to 50% (38). There is increased prevalence of DED with age, in post-menopausal women and patients with autoimmune diseases (29) (51).

In DED, reduced tear secretion leaves the corneal epithelium exposed to adverse environmental conditions that may result in inflammation of the ocular surface and peripheral nerve damage. DED is associated with morphological abnormalities in nerve terminals, such as increased tortuosity, reflectivity and beading while changes in nerve density are not consistent. An increased density of inflammatory cells in DED has been reported (140).

The TFOS DEWS II report maintain an etiological classification of two primary categories of dry eye - aqueous deficient dry eye (ADDE) and evaporative dry eye (EDE) (137). EDE is the most prevalent form of dry eye disease (141) (142). Lemp et al. found 86% of dry eye patients in their cohort were classified to have an element of evaporative dry eye. Additionally, ADDE and EDE are not mutually exclusive. 36% of patients in the same study had a combination of ADDE and EDE (mixed dry eye disease) (141). ADDE describes conditions affecting lacrimal gland function. EDE is recognized to include both ocular surface-related and lid-related causes (137).

- **Aqueous deficient dry eye (ADDE)**

ADDE arises from a reduction in lacrimal gland secretion and results in tear film hyperosmolarity. The tear film evaporates at a normal rate however, it is evaporating from a reduced aqueous pool (143). This leads to an imbalance of electrolytes in the tear film, causing hyperosmolarity and initiating a cascade of inflammatory events. ADDE is further sub-classified into Sjögren's syndrome dry eye and non-Sjögren's syndrome dry eye. The non-Sjögren's syndrome dry eye refers to lacrimal dysfunction (lacrimal deficiency, lacrimal gland ducts obstruction, reflex hyposecretion and systemic drugs), in the absence of systemic autoimmune features of Sjögren's syndrome dry eye (137) (143).

- **Evaporative dry eye (EDE)**

Evaporative dry eye (EDE) is caused by excessive tear evaporation from the ocular surface in the presence of normal lacrimal secretion. EDE arises from intrinsic and extrinsic factors. Ocular surface disorders, topical drugs preservatives, contact lens wear and vitamin A deficiency contribute to the extrinsic factors of EDE. Meibomian oil deficiency, lid aperture disorders, low blink rate and drug action contribute to the intrinsic influences of EDE. However, intrinsic and extrinsic causes are not mutually exclusive (137) (143).

4.5.2 Ocular surface disorders impact on quality of life

Patients may experience ocular surface disorders (OSD) and dry eye symptoms during months after cataract surgery. Quality of life (Qof) can adversely be impacted by untreated or undertreated dry eye (144). Often, daily activities that require optimal visual clarity, like reading, computer use, professional work, night driving, sewing, and watching television are significantly hampered (145) (146). Individuals with dry eye are three times more likely to report difficulties, than those without dry eye (144).

The use of visual displays has risen enormously, not only among workers but also in the general population, due to the widespread use of home computers, tablets and mobile devices (38). It has been hypothesized that during visual display use, a diminished blink frequency rate and incomplete blinking contribute to accelerated tear evaporation, leading to tear film instability, mild epithelial damage and dry eye symptoms (38) (147) (148). Large cross-sectional studies have demonstrated a high prevalence of dry eye symptoms among visual display workers, predominantly young adults (149) (150) (151).

Apart from affecting the visual function perception and visual performance, OSD can cause symptoms such as pain and irritation. That way can affect not only ocular but also general health and well-being. Pain associated with OSD can have psychological and physical impacts, while blurred vision may impose restrictions in daily life activities such as reading, driving, watching television,

and operating smart-phones (152) (153) (154) (155). Utility assessments suggest that patients with mild and severe DED experience a reduction in QoL at a level similar to that experienced by patients with mild psoriasis and moderate-to-severe angina, respectively (38) (156).

Dry eye represents the most common reason for seeking medical eye care and thus it represents a significant cost burden due to direct and indirect health costs and reduced work productivity (157). It has been estimated the economic impact of dry eye is staggering given that 7-10 million Americans purchased over $100 million in artificial tear formulations based on 15 year-old data (158). In addition, these figures do not include costs for visits to eye care professionals and the health and productivity of the individual (158). The total annual cost for the management of DED was estimated to be $3.84 billion in the United States (159)

The cost of DED treatment and the chronicity/intractability of DED symptoms affect the social life of an individual. Collectively, all these factors affect QoL and have an impact on public health.

4.5.3 Ocular surface disorders impact on quality of vision

With the development of new techniques and equipment, cataract surgery is considered a therapeutic procedure for extracting an opaque lens as well as a refractive procedure. After cataract surgery, patients may experience dry eye. Although visual acuity remains the gold standard for estimating optical function, the measurement of visual acuity alone is not sufficient to explain the optical condition objectively and precisely (160) (161). The optical quality of the retinal image results from light passing through the ocular structures. The precorneal film is the first structure that influences the optical light path, and optical quality of the eye surface depends largely on its properties (162). The visual acuity can be normal according to standard measurements, however, instability of the tear film introduces higher-order aberrations and scattering in the optical system that result in a decrease in visual quality (163). Tear film instability and corneal surface irregularities due to epithelial desiccation, resulting in changes in

optical quality, can be visualized and quantified using a range of techniques (38) (144) (164).

Patients with OSD often report vision-related difficulties during daily activities, resulting in a decreased QoL and these changes are often related to depression and anxiety (165).

4.5.4 Ocular surface disorder indicators

A variety of clinical and diagnostic criteria are used by clinicians to diagnose dry eye. The leading challenge with interpreting major dry eye epidemiological studies is that various tests and criteria are used to classify dry eye. The constant technological revolution that underlies in ophthalmology, has brought with it a multitude of instruments and software capable of analyzing ocular surface disorder (OSD) indicators. A series of diagnostic tests and cut-offs values can be used as a dry eye screening tool (166).

- **Ocular Surface Staining**

The use of diagnostic dyes on the ocular surface aids the assessment of ocular surface integrity that often becomes compromised after cataract surgery. Ocular surface superficial punctate staining remains a popular diagnostic test to assess dry eye status, because of its strong association with the disease and tear film integrity (167) (168) (169) (170). Ocular surface staining aids not only with diagnosis but allows the clinician to determine disease severity and efficacy of treatment and interventions (171). Several vital dyes have been used to quantify ocular surface staining. Among these include sodium fluorescein and lissamine green (166) (171) (172) (173).

Several mechanisms have been proposed to elucidate ocular surface staining including loss of tight junction integrity between adjacent epithelial cells (174) and epithelial cell damage (175). In the latter, epithelial cell damage has been associated with ocular surface disease and several etiologies have been proposed

for such damage (176). One proposed cause may involve inflammatory mediator release into the tear film from other damaged ocular surface cells (177) or from products produced from lipid degradation by lipase-producing commensal microbes (178). Tear film evaporation may play a role in ocular surface damage (179). Despite these proposed mechanisms, other studies provided evidence that neither tight junction integrity nor epithelial cell damage play a role in ocular surface staining (180) (181) (182). It is still accepted in the scientific community, however, that ocular surface staining is the most likely the result of tight junction damage.

Corneal and conjunctival staining have been shown to be informative markers of disease severity in severe dry eye disease (DED), however, staining of the ocular surface in mild/moderate DED showed poor correlation with disease severity (183). Therefore, observing staining of the cornea and conjunctiva is considered an important aspect in the clinical analysis of severe DED. For consistent recording of staining severity of the ocular surface, there are various grading systems. Among the scales used to determine staining severity include the Oxford and van Bijsterveld schema, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) schema, and the National Eye Institute (NEI)/Industry Workshop guidelines (138) (171) (172) (173). In the present study, the Oxford schema (171) is used to quantify corneal punctate staining and the Van Bijsterveld schema (172) to quantify the conjunctival staining (see section 8.11). The scoring system is illustrated in figures 3 & 5 (section 8.11). To assess corneal staining, sodium fluorescein is the dye of choice while lissamine green is used to visualize punctate staining of the conjunctiva (171).

Fluorescein has a peak excitation wavelength of 495 nm, whereas the commonly used cobalt blue light filters of slit lamp biomicroscopes have a peak of around 450 nm. The fluorescence peak is around 515 nm within the pH range of the tear film. The yellow barrier filter required for optimum observation should band pass at around 500 nm for enhancing contrast and further increasing sensitivity of the fluorescein staining (166) (184) (185).

The volume of diagnostic dye administered can influence the determination of ocular surface damage. A large, uncontrolled dose of fluorescein can over-saturate the epithelium, masking true staining because of fluorescein quenching; conversely, the visibility of staining with lissamine green is highly dose-dependent (171). A solution of 2% fluorescein and 1% lissamine green has been found to be optimal in terms of comfort and staining efficacy (186). Sequential staining and/or using more than one paper strip will increase the likelihood of observing ocular surface damage (184) (186) (187). In our study, we used 2 µL of 2% sterile fluorescein instilled into the conjunctival sac and the upper eyelid was lifted slightly to grade the whole cornea surface. After recovery from fluorescein, a 25 µL of 1% lissamine green was instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down, so that the dye could diffuse to superior, inferior, temporal and nasal conjunctiva.

Areas of punctate staining are indicated by the presence of small dot-like areas of stain when viewed under at least 10x magnification. Other ocular surface pathologies like ulcerations, abrasions, and sub epithelial infiltrative events have larger, deeper, and more irregular staining patterns and can easily be differentiated from punctate staining. Although fluorescein and lissamine green can be used to assess conjunctival and corneal staining, respectively, it is often much more difficult because of visibility issues (171).

- **Conjunctival hyperaemia**

The most common clinical sign that is suggestive of ocular surface inflammation is conjunctival hyperaemia (188) (189) (190). This is a consistent sign of conjunctival vascular dilation and reactive change to pathological stimuli. Ocular redness can be easily detected with standard slit lamp biomicroscopic examination. Ocular discomfort and other symptoms may accompany conjunctival hyperaemia (166). Furthermore, it can result in a cosmetic issue.

Several clinical methods have been described to classify conjunctival hyperaemia. These range from a simple binary scale (redness vs. non-redness), to the

comparison of ocular surface photographs with reference images (191). The most widely used image-based classification scales are the McMonnies scale (192), the Efron scale (193), the validated bulbar redness scale (VBR) (194) and the Institute for Eye Research Scale (IER) (195). The Efron scale is based on artistic illustrations rather than photographic images (193). The McMonnies scale was the first photographic classification scale introduced to measure bulbar redness in contact lens wearers, and has demonstrated sufficient diagnostic discriminative capacity to detect significant differences between hard and soft contact lens wearers (192). In our study, we used the McMonnies photographic scale to assess the conjunctival hyperaemia.

- **Ocular symptoms**

Several symptoms are reported by patients after cataract surgery related to ocular surface disorders (OSD). Although the relationship between symptoms and signs of OSD is not linear and varies across individuals and types of OSD (196), the ability to accurately quantify ocular surface symptoms is an important screening tool that can assist in establishing the medical necessity for additional OSD evaluation. It is also critical for monitoring the progression of the condition and response to treatments.

Symptoms of dry eye often vary throughout the day, usually worsening in the evening (197) (198) (199). Reported symptoms include: Ache, blurry (fluctuating) vision, burning, dryness, discomfort (irritation), foreign body sensation, grittiness, itching, ocular fatigue, pain, photophobia, conjunctival redness, scratchiness, soreness, sticky tears, stinging, swollen/red eyelids and watery eyes (200).

It is therefore recommended that a validated symptom questionnaire be administered at the beginning of the patient interaction (166).

- **Symptom Questionnaires**

In the clinical setting, clinicians often rely on case history to diagnose and characterize ocular surface disorders (OSD) (201) (202). The development of methods to assess OSD in detail enables clinicians to understand the magnitude of the effects of OSD on quality of life (QoL). To enhance standardization, symptoms are typically gathered through the use of questionnaire tools. There are a variety of questionnaires available that either measure ocular surface discomfort or vision symptoms associated with OSD, the impact of OSD on everyday function, or health-related quality of life. These questionnaires widely range from a few items that take less than a minute to answer to extensive multi-item questionnaires that cover topics from the types of symptoms experienced to the environmental situation where symptoms are at their worst (202) (199) (203) (204). In addition, dry eye questionnaires have demonstrated their usefulness as an important tool in monitoring dry eye disease progression and in clinical trials evaluating the effectiveness of investigative dry eye therapies (38) (205).

- **Ocular Surface Disease Index (OSDI)**

One of the available measurement tools to measure ocular surface disease severity is the Ocular Surface Disease Index (OSDI) questionnaire, a currently validated dry eye specific questionnaire (38) (146) (154) (152) (153) (166). The OSDI is among the most frequent symptom-based questionnaires used to assess and monitor the dry eye status in randomized clinical trials and epidemiologic studies (203). The 12 OSDI questions consist of three different subscales and provides a quick assessment of ocular symptoms (photophobia, foreign body sensation, pain, blurred or poor vision), types of vision-related functions and limitations (problems with reading, driving at night, working on a computer, or watching TV), and environmental triggers (wind, low humidity) that may exacerbate those symptoms during a one week recall period. Each answer is scored on the basis of symptom frequency using a five-point scale where 0

indicates no problem and 4 indicates a significant problem. In scoring the OSDI, the following formula is used.

$$OSDI\ Total\ score = D \times 25 / E$$

D = sum of scores for all questions answered
E = total number of questions answered

The scoring range for the OSDI is from 0-100. Higher scores indicate greater disability. It has been established in the literature that any values above 12 is considered indicative of dry eye with scores falling in the range of 13-22, 23-32, and 33-100 indicating mild, moderate, and severe dry eye, respectively (203).

- **Objective scatter index (OSI)**

Studies using the wavefront sensor aberrometer showed image aberrations in normal subjects (206) (207) and in patients with dry eye (164) (208) (209) between blinks, but ignored the scattering effect, and, thus, may have overestimated optical quality in these patients (210). Recent studies investigated the optical aberrations and scattering induced by the optical system and tear film during the interblink period (211) (212) using a double-pass method, showing good reproducibility (213) (214).

The Optical Quality Analysis System HD Analyzer™ (OQAS, Visiometrics, Terrassa, Spain) was designed for use in clinical practice to objectively determine the optical quality, including intraocular scattering of the human eye using a double-pass technique (215). Using the double-pass system, many authors evaluated ocular optical performance after a variety of ophthalmological surgical procedures (216) (217) (218). The double-pass system also allows the evaluation of the quality and stability of the tear film in detecting mild symptoms of dry eye (211). The OQAS provides data on the objective scatter index (OSI), a parameter that offers objective quantification of intraocular scattering. The double-pass technique is based on recording images from a point source of infrared light after reflection on the retina and a double pass through ocular media. The size and shape of the light spot are quantified by measuring the point spread function (PSF) (210) (215). In the OQAS, the central area selected is a circle of a radius of

11 minute of an arc, while the peripheral zone is a ring set between 12 and 20 minutes of arc (219). In healthy young eyes, the OSI value is lower than 0.5 (220). A higher OSI indicates a higher influence of intraocular scattering (210). Even though OSI high values are strongly associated with cataract classification and severity (221), measurements after cataract surgery offer information about intraocular scattering and consequently quality of vision in pseudophakic eyes (31) (32) (33) (222).

- **Tear film stability**

The importance of a stable tear film for retinal imaging is well known (223), and many approaches are used to study its influence on visual function. Tear film instability is one of the core mechanisms of dry eye (137). There have been described many ways of evaluating tear film stability (166) (224).

- **Tear break up time (TBUT)**

Tear break up time (TBUT) is a clinical procedure used to evaluate tear film stability. This particular diagnostic test is commonly used to evaluate evaporative dry eye and is defined as the elapsed time from the end of a complete blink to the appearance of the first break in the tear film after fluorescein instillation (225) or by observation of tear film distortion (166) (226). Tear film break up within the blink interval is a cause of visual degradation and its character and time course have been studied (227). The effect of precorneal tear film break up on vision is due to variations in film thickness, rupture of the film and, in dry eye, exposed epithelial irregularities at the site of break up and the presence of light scattering and epithelial opacities (143). In most healthy individuals, the tear film is extremely stable and values reported for TBUT are well beyond the normal blink interval (228). However, tear break up in the blink interval does occur in some healthy individuals. In mild cases of evaporative dry eye, the tear volume does not always decrease, and only shortening of the tear break up time (TBUT) indicates a tear abnormality (229). In a clinical setting,

there are many borderline cases that fall between evaporative dry eyes and healthy eyes, in which short TBUT is found without dry eye symptoms, ocular surface damage, or tear deficiency (230). In eyes with short TBUT, the tear film might begin to break up rapidly before the next blink during a period of suppressed blinking despite adequate tear volume on the ocular surface, which may result in symptoms of blurred vision, ocular fatigue, and discomfort. It has been reported that the shortness of TBUT has a large impact on vision (231) (232).

Tear film instability, initiated by a loss of ocular surface wettability, such as occurs in xerophthalmia and chronic topical preservative use, can be an independent starting point for tear hyperosmolarity and ocular surface-related evaporative dry eye (143).

- **Fluorescein break up time**

Fluorescein is fairly soluble in the aqueous and lipid layers (233). It may be instilled either by a micropipette or more commonly impregnated strips in varying volumes and concentrations (234). Fluorescein reduces the stability of the tear film and, therefore, this procedure has been described in the literature as being inaccurate and poorly reproducible (166) (225) (235). Since controlling the volume instilled with strips may be difficult, the use of narrow strips (1mm) and dry sterile applicators have been proposed (235) (236) (237).

A significant downfall of the measurement of fluorescein TBUT is its dependence on subjective assessment by the observer and attempts have consequently been made to automate the measurement (238).

- **Vision break up time (VBUT)**

Since tear film stability can be affected by fluorescein, temperature, humidity and air circulation, non-invasive break up time (NIBUT) measurements have become more popular in both clinical practice and research. Vision break up time (VBUT), measured with the Optical Quality Analysis System (OQAS), estimates

the tear film stability by recording the time taken for an image of a regular pattern projected onto the cornea surface to distort or break up following a full blink. This technique minimizes reflex tearing and other variables related to repeatability issues encountered with fluorescein TBUT. VBUT allows to essentially see an automated tear break up time without having to instill fluorescein or other drops into the eye, which could change the entire tear dynamics. Thus, the measurement of the tear break up time is made without perturbing the tear film (219). The VBUT is calculated as the time elapsed in seconds from 0 seconds to the time at which the subject's vision quality index has dropped below a defined threshold. Depending on how low the vision quality index falls, within 10 seconds of a blink, the program categorizes the break up time measurement as stable, moderately stable and unstable (239).

5. THESIS JUSTIFICATION

JUSTIFICATION

The ocular surface is formed by the conjunctiva (palpebral, bulbar and fornix), the cornea (epithelium, underlying stroma and endothelium), the sclerocorneal limbus (anatomical transition zone between the conjunctiva and the cornea) and the tear film. All these structures behave like a true functional unit so that a significant alteration in one of them often ends up affecting the rest.

Tear film, conjunctiva and cornea alterations represent a very important part in the pathology of the ocular surface. Recently, there has been a breakthrough in the knowledge of the physiopathology and therapeutics of ocular surface disease, and this has allowed improving the state of conjunctiva and cornea in ocular surgery. However, it still represents a real therapeutic challenge.

Ocular surface integrity can be compromised after cataract surgery, although integrity is required so as to achieve postoperative optical quality. The precorneal tear film and the cornea provide the first refractive element of the eye that focuses an image of the visual world upon the retina. Maintaining a healthy ocular surface is essential for achieving faster the best visual outcome after cataract surgery. Furthermore, corneal and conjunctival alterations can cause ocular symptoms and discomfort in the postoperative period.

Pupillary dilatation is commonly achieved by repeated administration of mydriatic/ cycloplegic agents. The use of mydriatic topical eye drops as preoperative option implies repeated applications until the pupil reaches the appropriate size to begin the intervention. Several studies have determined that that topical mydriatics, anaesthetics, excipients and preservatives have been considered as causing ocular surface damage. Furthermore, the preparation procedure with the repeated instillation of eye drops is usually long, 1 to 1.5 hour holding the patients in the preparation room and creating an uncomfortable and stressful ambient.

The intracameral fixed combination of mydriatics and anaesthetic delivers minute doses of the drugs directly to the target organ to achieve the desired effect, thus minimizing ocular and systemic adverse effects. Intracameral

administration route reduces the need for preoperative eye drops, improving preoperative medication tolerability and patient comfort, decreasing intraoperative/ postoperative symptoms, and mitigating corneal toxicity and ocular surface damage.

Prevention of ocular surface damage in cataract surgery is beneficial not only in patients with established ocular surface disease, but also in those with previously healthy ocular surface. Identifying these issues and taking measures, can build a high value of postoperative satisfaction for patients and surgeons.

6. HYPOTHESIS AND OBJECTIVES

6.1 HYPOTHESIS

Each of the objectives of this research project is marked by a well-defined conceptual hypothesis. Overall, the main hypothesis of the study is that intracameral fixed combination of mydriatics and anaesthetic (ICMA) administered after the first incision during cataract surgery, have a positive impact on ocular surface. Our hypothesis postulates that repeated administration of topical mydriatic agents, so as to achieve pupillary dilatation, build unfavourable preoperatory conditions, due to contamination of the ocular surface, corneal epithelial toxicity and conjunctival damage by the presence of preservatives in the eye drops and patient discomfort due to the frequent instillation of topical formulas and prolonged preparation time in the clinic. The intracameral route of administering mydriatics and anaesthetics delivers minute doses of the drugs to the target organ to achieve the desired effect, thus minimizing adverse effects. Intracameral administration reduces the need for preoperative eye drops, mitigating corneal toxicity and ocular surface damage.

6.2 STUDY OBJECTIVES

Primary Objective

The primary objective of the study was to evaluate the effects of intracameral fixed combination of mydriatics and anaesthetic (ICMA) after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye-drop instillation and the standard mydriatic-anaesthetic eye-drop protocol (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%) on ocular surface.

Secondary objectives

The secondary objectives of the study were:

1. To assess changes in best corrected visual acuity recovery.
2. To evaluate epithelial alterations.
3. To describe changes in conjunctival hyperaemia.
4. To assess changes in intraocular pressure.
5. To evaluate the point-spread function (PSF) by the objective scatter index (OSI) in the Optical Quality Analysis System (OQAS) HD Analyzer™.
6. To evaluate tear film stability, measured by vision break-up time (VBUT) in the OQAS HD Analyzer™
7. To determine changes in the Ocular Surface Disease Index (OSDI) questionnaire.
8. To describe ocular symptoms/signs experienced by patients.
9. To describe surgical procedure time-points
10. To assess patients' perceptions on satisfaction with study treatments.
11. To determine satisfaction assessed by investigators.
12. To describe the safety profile of study treatments.

7. ETHICAL CONSIDERATIONS

7. ETHICAL CONSIDERATIONS

7.1 Regulatory and ethical compliance

- **Institutional Review Board / Independent Ethics Committee**

Prior to the conduct of this study and in compliance with Royal Decree 1090/2015, the protocol and informed consent from along with the pertinent documentation were submitted to the reference Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of the medical centre (Instituto de Microcirugía Ocular, Barcelona) for evaluation and subsequent report. The study was initiated, once written approval was obtained from the IRB/IEC.

- **Ethical conduct of the study**

This clinical trial was conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki on medical research in human subjects (60th WMA General Assembly, Fortaleza, Brazil; October 2013), and in accordance with applicable regulatory requirements, in particular the 1996 ICH Harmonized Tripartite Guidelines for Good Clinical Practice (Royal Decree 1090/2015 regulating clinical trials with medicinal products in Spain, Ethics Committees of medicines research and the Spanish Clinical Trials Register) and incorporating the specific provisions for application in Spain of Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use.

By signing the protocol, the investigators agreed to adhere to the instructions and procedures described in the protocol and therefore to comply with the principles of good clinical practice on which it is based.

Informed consent for participation in the study was freely granted before performing any study-specific procedure.

7.2 Patient information and informed consent

Each subject who was asked to participate in the study was given a written document called “Patient Information Sheet”, which contained the necessary relevant information about the nature of the study, the objectives, the procedures, the potential benefits and risks for the patient, and gave the patient the sufficient time to read, understand and decide if he/she wished to participate in the trial. Explanations and clarifications considered by the patients were provided after having read the study information. The investigators obtained the participants' written consent before performing any study-specific procedure and provided guarantee to protect the patients' data. In addition, this document stated the voluntary nature of participation of the patient in the study and indicated in a clear and unequivocal manner, that he/she was free to refuse to participate in the study and that he/she could withdraw his/her consent at any time for any reason without penalty or refusal of the best treatment as the investigators' discretion. The investigators kept the signed informed consent in the study file and it was documented in the patients' medical records. A copy of this inform consent was released to the participants.

8. MATERIAL AND METHODS

8. MATERIAL AND METHODS

8.1 STUDY DESIGN

This is a phase IV, open-label, prospective, randomized, clinical trial to evaluate the effects of intracameral mydriatics and anaesthetics (ICMA), (Fydrane®, Laboratoires Théa), after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops instillation (Colircusi Anestésico Doble, Novartis) and the standard mydriatic - anaesthetic eye drops protocol (tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%) administered by topical route on ocular surface in subjects undergoing cataract surgery in both eyes.

This study initiated in June 2018 and was completed in April 2019, at Instituto de Microcirugía Ocular (IMO, Barcelona, Spain). 50 eligible patients, aged 40 to 88 years old, who met all selection criteria, scheduled to undergo phacoemulsification with foldable intraocular lens (IOL) implantation under topical anaesthesia in both eyes were included in the study. ICMA was administered in one eye and the standard mydriatic - anaesthetic eye drops protocol (control treatment) in the fellow eye.

Three periods were distinguished in the study:

- A **screening period** of 7 days before performing cataract surgery in the first eye (Visit 0, day -7 to day 0). In the inclusion visit, ophthalmologic procedures were carried out in both eyes to assess patients' best corrected visual acuity (BCVA), epithelial alterations, corneal/conjunctival staining, intraocular pressure and record patients' subjective ocular complaints by answering the OSDI questionnaire. In addition, it was decided whether the first surgery would be conducted in the right or left eye, based upon dominance or patients' preferences. At the end of visit 0, the study treatment was randomly assigned 1:1 to receive in the first surgical procedure: ICMA with anaesthetic drops (oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%) or just mydriatic - anaesthetic eye drops (tropicamide 1%, phenylephrine 10%, and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%). The remaining treatment was administered in the surgery of the fellow eye (Figure 1).

- **Treatment administration and surgery** (visit 1). The day of surgery, patients were evaluated in the slit lamp and photographs were taken to assess hyperaemia before surgery and before any study treatment administration. ICMA with anaesthetic drops or just mydriatic - anaesthetic eye drops were administered, according to the treatment assignment, and data relevant to the surgical procedure were recorded, as surgery time-point and type of intraocular lens. Just after surgery, photographs were taken, once again, to assess postoperative hyperaemia, corneal/conjunctival staining and data were collected about patients' comfort during surgery and patients/ investigators satisfaction with the treatment.

- **Follow-up period:** two follow-up visits were conducted, 12-36h after surgery (visit 2) and 7±1 days after surgery (visit 3). In the follow-up visits, ophthalmologic procedures were carried out to assess BCVA, epithelial alterations, corneal/conjunctival staining, hyperaemia, intraocular pressure, objective scatter index (OSI), vision break-up time (VBUT), ocular symptoms and signs, and subjective ocular complaints were recorded by answering the OSDI questionnaire. In patients who withdrew study before visit 3 (early termination), a study visit was conducted to identify reasons for study termination and to collect data related to the last study visit. In cases of informed consent withdrawal, no data were collected.

  After the first eye surgical intervention, the second eye surgery was conducted in a period no longer than 10 days; and visits 1, 2 and 3 were repeated for the second eye.

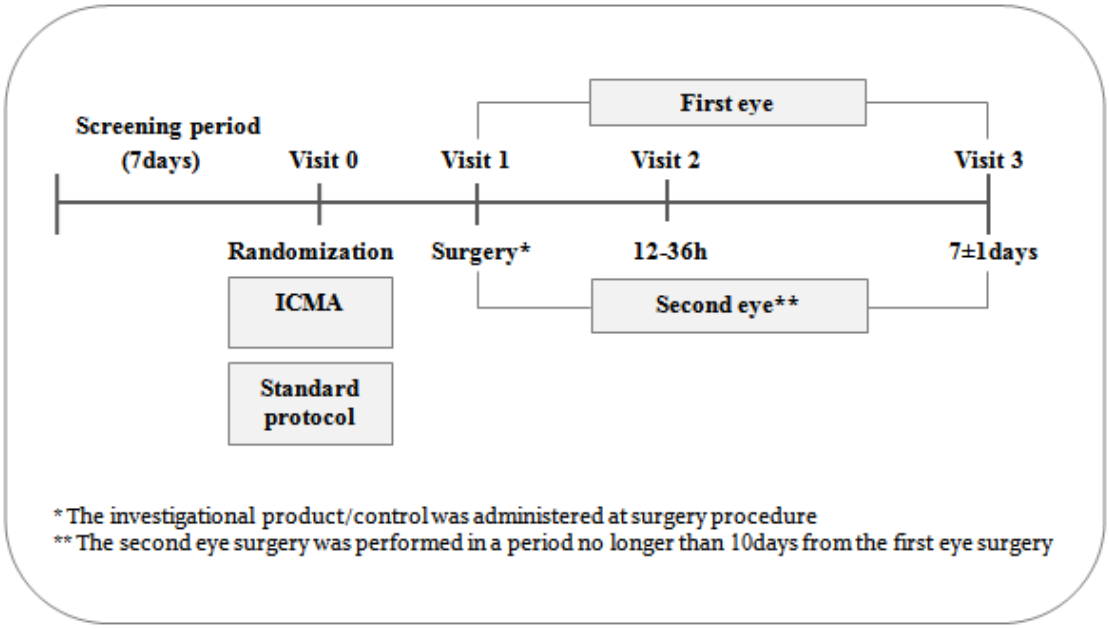


Figure 1. An overall description of the study design and visits

8.2 SURGICAL PROCEDURE

50 eligible patients, aged 40 to 88 years, scheduled to undergo phaco-emulsification in both eyes, with foldable intraocular lens (IOL) implantation, under topical anaesthesia with clear self-sealing corneal incisions. All cataract surgeries were performed by one single surgeon (JL.G.) under the same microscope (Leica Proveo 8 with a LED light source, using 58% in principal light and 44% in reflex). Patients received, after random assignation, one treatment in each eye at the surgery day.

A preoperative conditioning was carried out before ICMA/ control treatment administration. Patients received eye drops of norfloxacin (Chibroxin®, Laboratoires Théa) on the eye that was going to be operated, 3 times per day during 3 days before surgery.

Those eyes randomized to take ICMA, received treatment as follows: one or two drops of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% were administered, by instillation in the eye, before performing the preoperative antiseptic procedure, 5 minutes and 1 minute before the first incision. Then, at the beginning of the surgical procedure, 0.2 ml of ICMA (Fydrane) were

administered in a slow intracameral injection in the anterior chamber just after the first corneal incision (Figure 2).

Control treatment involved applying topical eye drops of mydriatics and anaesthetics in those eyes randomized to receive standard protocol. One-two drops of tropicamide 1% (Colircusi Tropicamida®, Alcon Cusí, Barcelona, Spain) and phenylephrine 10% (Colircusi Fenilefrina®, Alcon Cusí) (T/P) were administered 3 times with an interval of 10 minutes, beginning 30 minutes before the surgery, so as to obtain pupillary dilation. Topical anaesthesia was achieved by instilling eye drops of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% (Colircusi Anestésico Doble, Alcon Cusí) (O/T) during the preparation, following the routine practice of the institute (Figure 2).

Povidone-iodine 5%, or chlorhexidine 5% if contraindicated, was applied to the periocular area for obtaining preoperative antisepsis. Clear self-sealing corneal incisions were created. Phacoemulsification was performed using CENTURION® Vision System (Alcon Laboratories, USA), and a foldable monofocal, multifocal or toric IOL was implanted in the capsular bag. The incisions were closed with stromal hydration using balanced salt solution (BSS). BSS was irrigated to hydrate the corneal surface as soon as it was necessary for a good visibility during the surgery. At the end of the surgery, intracameral cefuroxime (1mg) was administered for endophthalmitis prophylaxis. No dose modification of the study treatments was applicable in this study.

After surgery, patients followed the same topical medication on the operated eye: 1-2 drops of dexamethasone (Dexafree®, Lab. Théa) and 1-2 drops of norfloxacin (Chibroxin®, Lab. Théa) three times per day; 1-2 drops of timolol (Timabak®, Lab. Théa) twice a day for 3 weeks after surgery. No other medications or lubricant eye drops were used during the study follow-up time, that ended at 7 ± 1 days after surgery.

8.3 STUDY PERIODS AND DURATION

The study initiated in June 2018 and was completed in April 2019. A screening period of 7 days before conducting the first surgery was provided in each case (visit 0).

A total of 50 patients undergoing cataract surgery in both eyes were included in the study. After signing the informed consent and before conducting the cataract surgery of the first eye, subjects were randomized (1:1) to receive the first treatment: ICMA with topical anaesthesia (O/T) or standard eye drops of mydriatics and anaesthetics (T/P and O/T); the remaining treatment was administered in the surgery of the fellow eye, which was conducted no later than 10 days after the first surgery.

Besides screening visit (visit 0), three additional visits were conducted per eye: A) on the day of the surgery, before and just after surgery (visit 1), B) 12-36 hours after surgery (visit 2) and C) 7 ±1 days after surgery (visit 3).

8.4 STUDY TREATMENTS

The study treatments were as follows:

1. **Intracameral Mydriatics and Anaesthetic (ICMA) + anaesthetic drops**

- The oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% (O/T) topical anaesthesia was of a single-use sterile eye drops. 1-2 drops of O/T were instilled twice in the eye, before performing the preoperative antiseptic procedure and before the first incision (-5 min and -1min before the first incision).
- ICMA: At the beginning of the surgical procedure, 0.2ml of tropicamide 0.2mg/ml, phenylephrine 3.1mg/ml and lidocaine chlorhydrate 10mg/ml (Fydrane) were administered in a slow intracameral injection in the anterior chamber just after the first corneal incision (Figure 2). Each ml of solution for injection contains tropicamide 0.2mg, phenylephrine 3.1mg and lidocaine 10mg. One dose of 0.2ml contains tropicamide 0.04mg, phenylephrine 0.62mg and lidocaine 2mg (240).

Before administering ICMA, the unopened blister was inspected to ensure that it was intact. The solution was also visually inspected and was only used if it was clear, slightly brownish-yellow and practically free from visible particles. After breaking the ampoule containing the product, the 5-micron filter sterile needle provided was assembled onto the sterile syringe. The 5-micron filter sterile needle protector was removed and at least 0.2 ml of the solution for injection was withdraw from the ampoule into the syringe. Then, the needle was disconnected from the syringe and the syringe was assembled with an appropriate anterior chamber cannula. The air was carefully expelled from the syringe, 0.2 mg were adjusted and the 0.2 ml syringe volume was slowly injected into the anterior chamber of the eye, as only one injection. The remaining solutions was discarded.

2. Standard mydriatic and anaesthetic eye drops

In the cases where the administration of control treatment was assigned, the preparation initiated 30 minutes before surgery and the standard procedure of topical mydriatics and anaesthetics according to the routine practice of the institute was followed:

- Tropicamide 1%, phenylephrine 10% (T/P), topical form administration: 1-2 drops of T/P were instilled in 3 intervals of 10 minutes (30 minutes, 20 minutes and 10 minutes before surgery)
- Oxybuprocain chlorhydrate 0.4% and tetracaine chlorhydrate 0.1% (O/T), topical anaesthesia, was of a single-use sterile eye drops. 1-2 drops of O/T were instilled in the eye during the mydriatic process, before performing the preoperative antiseptic procedure and the first incision, following the routine practice of the institute (Figure 2).

3. Other treatment

- **Preoperative antibiotic prophylaxis**

  One-two drops of norfloxacin (Chibroxin®) were administered 3 times per day on the eye that was going to be operated during 3 days before surgery.

- **Preoperative antisepsis**

  Povidone-iodine 10% was applied on the periocular area and povidone-iodine 5% drops was instilled into the conjunctival sac and onto the cornea 3 minutes before surgery. Where povidone-iodine was contra-indicated (e.g. allergy and hyper-thyroidism), aqueous chlorhexidine 0.05% was used.

- **Ocular hydration during surgery**

  Three drops of balanced salt solution were administered on the eye every 30 seconds during surgery.

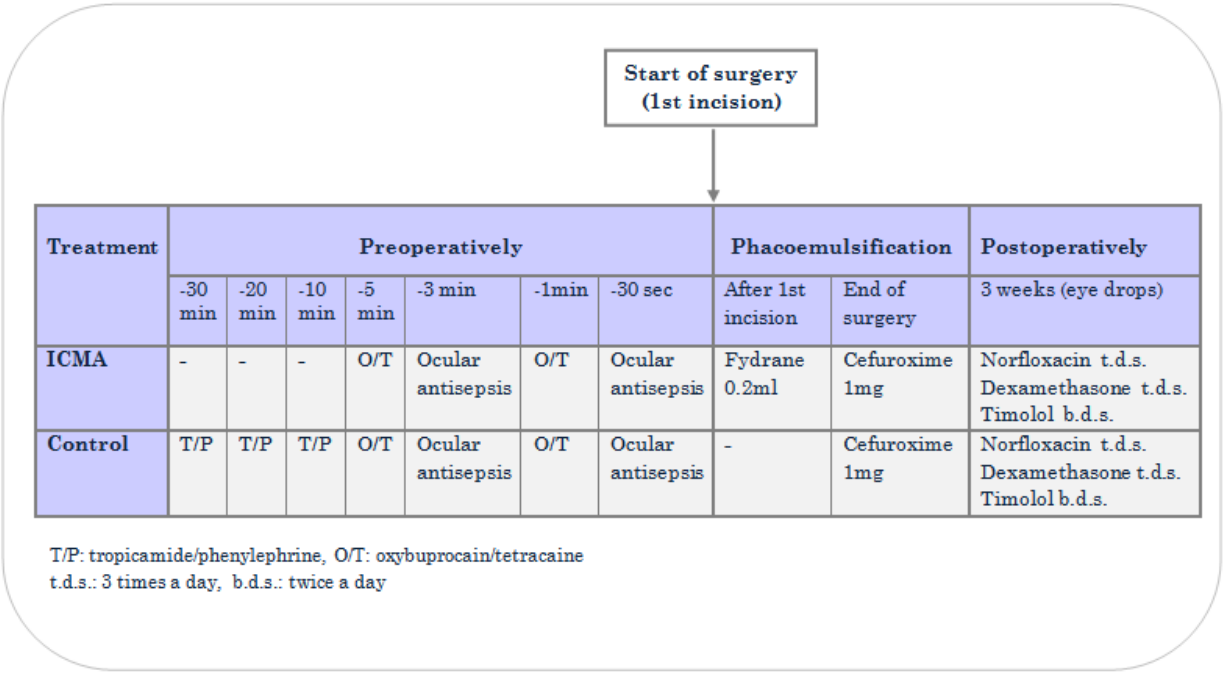
- **Intraoperative antibiotic prophylaxis**

  Intracameral cefuroxime (1mg) was administered on the operated eye for endophthalmitis prophylaxis at the end of every surgery. In case of allergy in penicillin, intracameral vancomycin was administered instead.

- **Postoperative treatment**

  One-two drops of dexamethasone (Dexafree®) and one-two drops of norfloxacin (Chibroxin®) were administered 3 times per day on the operated eye for 3 weeks after surgery. One-two drops of timolol (Timabak®) was administered twice a day on the operated eye for 3 weeks after surgery (Figure 2). Patients completed the postoperative treatment during 3 weeks after surgery, following the routine practice of the institute. Though, the study follow-up time was completed at 1 week after surgery, and no further data about postoperative treatment were collected.

  The administration of the study treatment were only applied on the day of the cataract surgeries. No dose modification of study treatments were applicable in the study.



Treatment	Preoperatively							Phacoemulsification		Postoperatively
	-30 min	-20 min	-10 min	-5 min	-3 min	-1min	-30 sec	After 1st incision	End of surgery	3 weeks (eye drops)
ICMA	-	-	-	O/T	Ocular antisepsis	O/T	Ocular antisepsis	Fydrane 0.2ml	Cefuroxime 1mg	Norfloxacin t.d.s. Dexamethasone t.d.s. Timolol b.d.s.
Control	T/P	T/P	T/P	O/T	Ocular antisepsis	O/T	Ocular antisepsis	-	Cefuroxime 1mg	Norfloxacin t.d.s. Dexamethasone t.d.s. Timolol b.d.s.

T/P: tropicamide/phenylephrine, O/T: oxybuprocain/tetracaine
t.d.s.: 3 times a day, b.d.s.: twice a day

Figure 2. Study treatment administration protocol for intracameral administration of a fixed combination of mydriatics and anaesthetic (Fydrane) in one eye and standard mydriatic and anaesthetic eye drops in the fellow eye.

8.5 STUDY POPULATION

A total of 50 patients, aged 40 to 88 years undergoing cataract surgery in both eyes, within the next 17 days, who met all inclusion criteria and none of the exclusion criteria (eligible patients), were included in the study. No screening failures were detected, and all patients (N=50) received the study treatment. They were administered both ICMA and control treatment, one in each eye, to provide anaesthesia and mydriatic effect before surgery. Subjects division into groups was done regarding number of eyes instead of number of patients.

8.6 RANDOMIZATION

Method of assigning patients to treatment groups: At the end of the screening visit, it was decided whether the first surgery would be conducted in the right or left eye, in accordance with ocular dominance or patients' preferences. Once the eye to have the first procedure was specified, patients were randomized (1:1) to receive the first treatment: ICMA (Fydrane) with oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops or topical treatment with tropicamide 1%, phenylephrine 10%, oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops. The remaining treatment was administered before the surgery of the second eye respectively.

The randomization lists were created using the EPIDAT (Pan American Health Organization [PAHO] and Consellería de Sanidade de la Xunta de Galicia; version 4.0) statistical software and a permuted block design with a computer random number generator.

8.7 SELECTION & WITHDRAWAL CRITERIA

Inclusion criteria

Patients were included in the study if all of the following criteria were met:

1. Male or female, aged 40 to 88 years, scheduled to undergo bilateral cataract surgery within the next 17 days (under topical anaesthesia, using clear corneal self-sealing incisions to perform phacoemulsification with foldable intraocular lens implantation).
2. Pupil diameter ≥7 mm at selection visit after the following dilatation protocol: One drop of tropicamide 1% and one drop of phenylephrine 10%, with a maximum of 3 combined instillations at 10-minute intervals (i.e. time 0 minutes, time 0+10 minutes, and time 0+20 minutes), if necessary.
3. Patient willing and able to provide written informed consent prior to any study-related procedure and to comply with all study requirements.

Exclusion criteria

Patients were excluded for participating in this study, if one or more of the following criteria were met:

1. Patient who presented, in any eye, ocular history of:
   - combined surgery
   - previous intraocular and/or corneal surgery
   - iatrogenic, traumatic or congenital cataract
   - pupillary abnormalities (e.g. irregular)
   - iris synechiae
   - eye movement disorders (e.g. nystagmus)
   - dacryocystitis and all other pathologies of tear drainage system
   - inflammatory ocular disease (e.g. iritis, uveitis, herpetic keratitis)

- corneal epithelial, stromal or endothelial residual or evolutionary disease (including corneal ulceration and superficial punctate keratitis)
- ocular traumatism, infection or inflammation within the last 3 months
- pseudoexfoliation, exfoliative syndrome

2. Clinically significant corneal endothelial dysfunction.
3. Patients with a cataract hardness in one of the eyes and/or grade ≥3 as per the Lens Opacities Classification System III (LOCS III) (8).
4. Patients suffering from asthma or heart failure.
5. The following concomitant medications were not allowed:
   - Systemic corticoid and immunosuppressive treatments within 3 months before surgery.
   - Systemic opioids and morphinic drugs within 7 days before surgery.
   - Topical ocular treatment with mydriatic and/or anaesthetic action within 7 days before surgery.
   - Other systemic analgesics (except paracetamol) within 7 days before surgery.
   - Topical treatment with anti-inflammatory and antibiotic action within 1 day before surgery (except for the preoperative treatment specified in this protocol)
   - Anxiolytics and hypnotics on the day of surgery (excluding the standard used for the surgery).
   - Adrenaline or any other agent with a mydriatic action in the intraocular irrigating solution.
6. Contact lenses were not allowed within 7 days before surgery
7. Any known ocular disorders affecting eye surface (i.e. staining grade >1 as per the Oxford schema).
8. Known hypersensitivity to the active substances (tropicamide, phenylephrine, lidocaine, or oxybuprocain), any of their excipients, anaesthetics of the amide type or atropine derivatives.

9. Pregnancy or breastfeeding, in women of childbearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile).

Withdrawal criteria

Patients were informed that they could withdraw from the clinical trial whenever they wished and for any reason, without this affecting their subsequent medical care in any way.

We could also withdraw patients from the trial when any of the following circumstances occurred:

- Withdrawal of patient consent (at the patient's request, refusal to receive treatment, and/or another reason).
- Development of an unacceptable adverse event.
- Administration of any prohibited medication.
- Concomitant disease/condition that, in our opinion, made it necessary to withdraw the patient.
- Major protocol violations.
- Systematic noncompliance with the study protocol, including the scheduled visits, without any evidence of actions to try to remedy it.
- Patient lost to follow-up.
- Administrative reasons.

In case of premature withdrawal for reasons others than the withdrawal of informed consent, the last study visit was performed whenever possible, identifying the reason for study termination. In the case of patients who withdrew their consent, no more data were collected from the time of their withdrawal and they were followed according to the standard clinical practice of the Institute.

Patients who withdrew from the trial for any reason were not replaced and could not be included again in the study.

8.8 STUDY ENDPOINTS

Primary endpoint

The primary endpoint was the change in corneal/conjunctival surface staining measured as per the Oxford schema (corneal staining with fluorescein) and van Bijsterveld schema (conjunctival staining with lissamine green) with ICMA versus the standard eye-drop protocol from baseline (visit 0) to 7 days post-surgery (visit 3). In addition, changes from baseline (visit 0) to just after surgery (visit 1) and from baseline (visit 0) to 12-36 hours post-surgery (visit 2) were assessed.

Secondary endpoints

Secondary endpoints included:

1. The change in best corrected visual acuity according to the Snellen test from baseline (visit 0) to 7 days post-surgery (visit 3).
2. The percentage of patients with epithelial alterations evidenced by slit-lamp examination (i.e. none, mild, and significant), 12-36 hours post-surgery (visit 2) and 7 days after surgery (visit 3).
3. The change in conjunctival hyperaemia as per MacMonnies photographic scale (0 to 5) from baseline (right before study treatment administration at visit 1) to 7 days post-surgery (visit 3). In addition, changes in conjunctival hyperaemia from baseline (right before study treatment administration at visit 1) to just after surgery (visit 1) and from baseline (right before study treatment administration at visit 1) to 12-36 hours post-surgery (visit 2) were described.
4. The change in intraocular pressure from baseline (visit 0) to 7 days after surgery (visit 3).
5. Point-spread function (PSF) measured by the objective scatter index (OSI) in the Optical Quality Analysis System (OQAS) HD Analyzer™ 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3).

6. Changes in the vision break-up time (VBUT) measured by OQAS HD Analyzer™ from baseline (visit 0) to 7 days post-surgery (visit 3). In addition, changes in VBUT from baseline to 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3).
7. The change in the Ocular Surface Disease Index (OSDI) from baseline (visit 0) to 7 days post-surgery (visit 3).
8. Percentages of patients with ocular symptoms as perceived by patients and signs assessed by investigators according to ordinal scales ranging from 0 (absent/ none) to 3 (severe) 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3).
9. Differences in preparation duration and surgery length, from first drop administration to first incision, from first incision to the end of surgery and from first drop administration to end of surgery.
10. Patients' satisfaction with study treatments assessed on an ordinal scale ranging from 0 (very satisfactory) to 3 (unsatisfactory) just after surgery (visit 1).
11. Satisfaction assessed by the investigators according to an ordinal scale ranging from 0 (very satisfactory) to 3 (unsatisfactory) just after surgery (visit 1).
12. The incidence of adverse events related to study treatments.

8.9 STUDY VISITS AND PROCEDURES

8.9.1 VISIT 0 - SCREENING VISIT

Eligible patients were provided with all the information needed to decide whether they wanted to participate in the clinical trial and give their informed consent. Patients' informed consent was obtained before conducting any of the study-specific procedures. Selection criteria were revised and eligibility of patients were confirmed according to the pertinent assessments (conducted within 7 days prior to first cataract surgery). Procedures conducted as per routine clinical practice were not considered as study-specific; however, they were used to confirm the eligibility of patients provided that they were conducted within the above-mentioned timelines. Once patients gave their informed consent to participate in the study and we confirmed that they met all selection criteria, patients were considered as included. In this visit, we also decided whether the first surgery would be conducted in the right or in the left eye, based upon dominance or patients' preferences. Then, the study treatment, to be administered for the surgery of the first eye, was randomly assigned: ICMA with topical anaesthetic eye drops of O/T or standard mydriatic/anaesthetic eye drops (T/P and O/T); the remaining treatment was administered in the surgery of the fellow eye, which was conducted no later than 10 days of the first surgery.

The procedures conducted and data collected in the screening visit are detailed bellow:

- **Patient information** on the trial and **informed consent** to participate
- **Selection criteria:** Revision of inclusion and exclusion criteria. This included the assessment of pupil dilatation, for which the following dilatation protocol was followed: 1 drop of tropicamide 1% + 1 drop of phenylephrine 10%, with a maximum of 3 combined instillations at 10-minute intervals (i.e. time 0 minutes, time 0 + 10 minutes, and time 0 + 20 minutes), if necessary. Afterwards, patients were examined under the same slit lamp biomicroscopy and bilateral pupil size was measured with a light meter. If pupil size was less than 7.00 mm in one or

both eyes, the patient was excluded from the study, as one of the inclusion criteria was pupil size ≥ 7.0mm

- **Adverse events** reported after obtaining the informed consent, but before the administration of the study treatment. If the result of a safety parameter was considered as an adverse event, the adverse event form was also filled in.
- **Demographics:** date of birth, sex, and race/ethnicity.
- **Medical/ophthalmologic history:**
  - *Previous or current diseases:* data available on relevant previous diseases or those present at screening.
  - *Concomitant treatments:* data on concomitant treatments at screening or those interrupted in the past 3 months.

➢ **Urine pregnancy test (for women of childbearing potential):**

It was conducted locally, at the laboratory of the participating site. According to the Clinical Trial Facilitation Group, a woman is considered of childbearing potential when she is fertile, following menarche and until becoming postmenopausal unless permanently sterile (241). Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Women of childbearing potential were only included after a negative highly sensitive urine pregnancy test (241).

➢ **Ophthalmologic procedures/data:**

- ***Best-corrected visual acuity:*** The Snellen test was used to assess visual acuity. The patient was positioned 6 metres from the Snellen chart, in a well-lit area and seated, if possible; if 6 metres were not available, a reduced chart was used at 3 metres or a mirror was positioned at 3 metres and used with a chart with reversed letters. An optometrist covered the patient's left eye and ask the patient to start at the top of the chart and read the letters out, to the smallest size he/she could manage. It was repeated by occluding the patient's right eye. The optometrist recorded the level of acuity achieved for each eye as

a fraction, with the distance test that was performed at on the top and the size of the letters managed on the bottom; if a reduced chart was used, it was recorded as if it was performed at 6 metres. If the patient was unable to see the largest letter on the chart, the optometrist moved it towards the patient, one metre at a time, until the patient could manage to see it or until the optometrist was at 1 metre distance; it was recorded in the same way as above, the distance the test was performed at on the top and the size of the letters managed on the bottom. If the patient was still unable to read the letter at 1 metre, the optometrist would hold up several fingers at about 1/2 to 1/3 metre to see if the patient could see the movement; if the patient saw it, this was recorded as "counts fingers vision". If the patient was unable to count the optometrist's fingers, optometrist would move his/her hand across the patient's visual field at about 1/2 to 1/3 metre to see if the patient could see the movement; if the patient could see it, this was recorded as "hand movements vision". If the patient was unable to see hand movements, the optometrist would see if the patient was aware of a pen torch; this would be "perception of light vision" and if the patient was unable to make out the pen torch, the vision would be recorded as "no perception of light". The test was performed with and without glasses (i.e. those normally worn for driving and/or watching television) and it also needed to be recorded. If the patient's visual acuity was below 6/9 and/or the patient did not have their distance prescription available, then a pinhole was used: the pinhole occlude was placed in front of the right eye with the total occlusion side covering the left eye, the patient was asked to start at the top of the chart and read the letters out to the smallest size he/she could manage, it was repeated for the left eye, and the optometrist recorded both the level of vision achieved and the use of a pinhole in the notes.

- ***Slit-lamp examination:*** It was performed to assess epithelial alterations in each eye. These alterations were graded as none, mild or significant.
- ***Corneal/conjunctival staining:***

  Corneal staining. Fluorescein was used for corneal staining. In every eye, 2µL of 2% sterile fluorescein was instilled into the conjunctival sac and the

upper eyelid was lifted slightly to grade the whole cornea surface. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone. Since fluorescein diffuses rapidly into tissues, punctuate staining blurs after a short period. Therefore, it was essential to take photographs rapidly for staining assessment.

Conjunctival staining. Lissamine green was used for conjunctival staining. After recovery from fluorescein, a 25 µL of 1% lissamine green was instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. Photographs were also taken for this staining assessment.

Corneal and conjunctival staining were conducted in both eyes. One platform with slit-lamp bio-microscopy, photographic system and imaging software (Imaging Module 900, EyeSuite™, Haag-Streit, UK) was used in every case, under the same settings, magnification and clinic room illumination. An assessor ophthalmologist of the institute, blinded to the trial treatment (blind ophthalmologist reader), was entitled to evaluate staining according to the photographs taken. All photographs were codified and placed in random order before being delivered. The blind ophthalmologist reader graded the photographs displayed on own monitor, using similar room illumination for the reading and without any time limitation.

Corneal staining with fluorescein was graded as per the Oxford schema and conjunctival staining with lissamine green was graded as per the van Bijsterveld schema.

- ***Intraocular pressure:*** It was measured by applanation tonometry. A drop of topical anaesthetic was used as the probe would make contact with the cornea. A calibrated applanation tonometer was used and intraocular pressure was measured in millimetres of mercury (mmHg).
- ***Vision Break up time:*** The vision break-up time (VBUT) of the tear film was measured with the Optical Quality Analysis System (OQAS, HD Analyzer™).
- ***Intraocular Surface Disease Index (OSDI):*** Patients were asked the 12 questions of the OSDI questionnaire and the answers were recorded for each

eye. Then, the boxes A, B, C, D, and E of the questionnaires were filled according to the instructions beside each.

- ***Patient diary to record adherence to pre/post-surgery treatment:*** Patients were provided with a diary to record adherence to pre- and postoperative treatments and were instructed how to do so.

- **Randomization**: Randomization of patients included in the study (i.e. patients who gave their informed consent to participate and met all selection criteria) was performed at the end of this visit.

- **STUDY VISITS FOR EACH EYE**

Once the patient was selected to participate in the study and the screening visit was completed, three following visits were conducted for each eye. A) On the day of the surgery (visit 1), B) 12-36 hours after surgery (visit 2) and C) 7±1 days after surgery (visit 3).

8.9.2 VISIT 1 – DAY OF SURGERY

This visit was conducted on the day of surgery and included procedures divided in two parts: before surgery (before any eye drop), and just after surgery.

8.9.2.1 Before surgery

The procedures conducted and data collected before surgery (before any eye drop instillation) are detailed bellow:

- **Adverse events:** recording of any adverse event evidenced from the previous study visit. If the result of a safety parameter was considered as an adverse event, the adverse event form was also filled in.
- **Ophthalmologic procedures/data** on the eye where the surgery would be performed:
  - ***Slit-lamp examination:*** It was performed to assess epithelial alterations in the eye. These alterations were graded as none, mild or significant.
  - ***Hyperaemia assessment:*** Photographs were taken. A blind ophthalmologist reader from the institute was entitled to evaluate them. This ophthalmologist assessed conjunctival hyperaemia as per the MacMonnies photographic scale.
  - ***Study treatment administration:*** the study treatments were administered as described in study design.
- **Concomitant treatments:** modifications of concomitant treatments from the previous study visit.

8.9.2.2 Just after surgery

The procedures conducted and data collected just after surgery are detailed bellow:

- **Adverse events:** recording of any adverse event that occurred during the surgery. If the result of a safety parameter was considered as an adverse event, the adverse event form was also filled in.
- **Ophthalmologic procedures/data** on the eye where the surgery was conducted:
  - ***Hyperaemia assessment:*** photographs were taken. A blind ophthalmologist reader from the institute was entitled to evaluate them. This ophthalmologist graded conjunctival hyperaemia as per the MacMonnies photographic scale.
  - ***Corneal/conjunctival staining:***

    Corneal staining: Fluorescein was used for corneal staining. 2 µL of 2% sterile fluorescein was instilled into the conjunctival sac and the upper eyelid was lifted slightly to grade the whole cornea surface. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone. Since fluorescein diffuses rapidly into tissues, punctuate staining blurs after a short period. It was therefore essential to take photographs rapidly for staining assessment.

    Conjunctival staining: Lissamine green was used for conjunctival staining. After recovery from fluorescein, a 25 µL of 1% lissamine green was instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. Photographs were also taken for this staining assessment. The blind ophthalmologist reader was entitled to assess corneal and conjunctival staining according to the photographs taken.

    Corneal staining with fluorescein was graded as per the Oxford schema and conjunctival staining with lissamine green was graded as per the van Bijsterveld schema.

- ***Type of intraocular lens:*** the type of lens was at discretion of the surgeon and the data were collected on the intraocular lens used during the cataract surgery (e.g. monofocal lens, multifocal lens, toric lens).
- ***Surgery time-point recording:*** first drop, first incision, and end of surgery.
- ***Patient's satisfaction:*** satisfaction with the treatment received in the eye was assessed by asking the patient about intraoperative comfort.
- ***Satisfaction assessed by the investigators:*** satisfaction with the treatment received in the eye was assessed according to the investigators' consideration of the study product.

8.9.3 VISIT 2 – THE FIRST POSTOPERATIVE DAY

This visit was conducted 12 to 36 hours after surgery.

The procedures conducted and data collected are detailed bellow:

- **Adverse events:** recording of any adverse event evidenced from the previous study visit. If the result of a safety parameter was considered as an adverse event, the adverse event form was also filled in.

- **Ophthalmologic procedures/data** on the eye where the surgery was conducted:

  - ***Best-corrected visual acuity:*** The Snellen test was used to assess visual acuity. The patient was positioned 6 metres from the Snellen chart, in a well-lit area and seated, if possible; if 6 metres were not available, a reduced chart was used at 3 metres or a mirror was positioned at 3 metres and used with a chart with reversed letters. The optometrist covered the patient's eye and asked the patient to start at the top of the chart and read the letters out, to the smallest size he/she could manage. The optometrist recorded the level of acuity achieved as a fraction, with the distance test that was performed at on the top and the size of the letters managed on the bottom; if a reduced chart was used, it was recorded as if it was performed at 6 metres. If the patient was unable to see the largest letter on the chart, the optometrist moved it towards the patient, one metre at a time, until the patient could manage to see it or until the optometrist was at 1 metre; it was recorded in the same way as above, the distance the test was performed at on the top and the size of the letters managed on the bottom. If the patient was still unable to read the letter at 1 metre, the optometrist would hold up several fingers at about 1/2 to 1/3 metre to see if the patient can see the movement; if the patient saw it, this was recorded as “counts fingers vision”. If the patient was unable to count the optometrist's fingers, optometrist moved his/her hand across the patient's visual field at about 1/2 to 1/3 metre to see if the patient could see the movement; if the patient saw it, this was recorded as “hand movements vision”. If the patient was unable to see hand movements, the optometrist

observed if the patient was aware of a pen torch; this would be "perception of light vision" and if the patient was unable to make out the pen torch, the vision was recorded as "no perception of light". The test was performed with and without glasses (i.e. those normally worn for driving and/or watching television) and it also was recorded. If the patient's visual acuity was below 6/9 and/or the patient did not have their distance prescription available, then a pinhole was used: the pinhole occlude was placed in front of the eye with the total occlusion side covering the fellow eye, the patient was asked to start at the top of the chart and read the letters out to the smallest size he/she could manage, and the optometrist recorded both the level of vision achieved and the use of a pinhole in the notes.

- ***Slit-lamp examination:*** it was performed to assess epithelial alterations in the eye. These alterations were graded as none, mild or significant.
- ***Hyperaemia assessment:*** photographs were taken. A blind ophthalmologist reader from the institute was entitled to evaluate them. This ophthalmologist assessed conjunctival hyperaemia as per the MacMonnies photographic scale.
- ***Corneal/conjunctival staining:***

  Corneal staining: Fluorescein was used for corneal staining. 2 µL of 2% sterile fluorescein were instilled into the conjunctival sac and the upper eyelid was lifted slightly to grade the whole cornea surface. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone. Since fluorescein diffuses rapidly into tissues, punctuate staining blurs after a short period. It was therefore essential to take photographs rapidly for staining assessment.

  Conjunctival staining: Lissamine green was used for conjunctival staining. After recovery from fluorescein, a 25 µL of 1% lissamine green was instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. Photographs were also taken for this staining assessment. A blind ophthalmologist reader from the institute was entitled to assess corneal and conjunctival staining according to the photographs taken.

Corneal staining with fluorescein was graded as per the Oxford schema and conjunctival staining with lissamine green was graded as per the van Bijsterveld schema.

- ***Point-spread function:*** an Optical Quality Analysis System (OQAS) HD Analyzer™ was used to assess the point-spread function (PSF) by the objective scatter index (OSI).
- ***Vision Break up time:*** The vision break-up time (VBUT) of the tear film was measured with the Optical Quality Analysis System (OQAS, HD Analyzer™).
- ***Ocular symptoms/signs:*** patient's perception on ocular symptoms and investigator's assessment of ocular objective signs were determined.

- **Concomitant treatments:** modifications of concomitant treatments from the previous study visit.

8.9.4 VISIT 3 – 7±1 DAYS AFTER SURGERY

This visit was conducted 7±1 days after surgery. In patients who withdrew from the study before these 7±1 days after surgery, a study visit was also conducted identifying the reason for study termination and carrying out the assessments and collection of data related to the last study visit (early termination). In cases of informed consent withdrawal, we tried to complete and notify the observations carried out just before such a withdrawal; no data was collected after informed consent withdrawal and patients received follow up as per routine clinical practice.

The procedures conducted and data collected are detailed bellow:

- **Adverse events:** recording of any adverse event evidenced from the previous study visit. If the result of a safety parameter was considered as an adverse event, the adverse event form was also filled in.

- **Ophthalmologic procedures/data** on the eye where the surgery was conducted:

  - ***Best-corrected visual acuity:*** The Snellen test was used to assess visual acuity. The patient was positioned 6 metres from the Snellen chart, in a well-lit area and seated, if possible; if 6 metres were not available, a reduced chart was used at 3 metres or a mirror was positioned at 3 metres and used with a chart with reversed letters. The optometrist covered the patient's eye and asked the patient to start at the top of the chart and read the letters out, to the smallest size he/she could manage. The optometrist recorded the level of acuity achieved as a fraction, with the distance test that was performed at on the top and the size of the letters managed on the bottom; if a reduced chart was used, it was recorded as if it was performed at 6 metres. If the patient was unable to see the largest letter on the chart, the optometrist moved it towards the patient, one metre at a time, until the patient could manage to see it or until the optometrist was at 1 metre; it was recorded in the same way as above, the distance the test was performed at on the top and the size of the letters managed on the bottom. If the patient was still unable to read the letter at 1

metre, the optometrist would hold up several fingers at about 1/2 to 1/3 metre to see if the patient can see the movement; if the patient saw it, this was recorded as “counts fingers vision”. If the patient was unable to count the optometrist's fingers, optometrist moved his/her hand across the patient's visual field at about 1/2 to 1/3 metre to see if the patient could see the movement; if the patient saw it, this was recorded as “hand movements vision”. If the patient was unable to see hand movements, the optometrist observed if the patient was aware of a pen torch; this would be “perception of light vision” and if the patient was unable to make out the pen torch, the vision was recorded as “no perception of light”. The test was performed with and without glasses (i.e. those normally worn for driving and/or watching television) and it also was recorded. If the patient's visual acuity was below 6/9 and/or the patient did not have their distance prescription available, then a pinhole was used: the pinhole occlude was placed in front of the eye with the total occlusion side covering the fellow eye, the patient was asked to start at the top of the chart and read the letters out to the smallest size he/she could manage, and the optometrist recorded both the level of vision achieved and the use of a pinhole in the notes.

- ***Slit-lamp examination:*** it was performed to assess epithelial alterations in the eye. These alterations were graded as none, mild or significant.
- ***Hyperaemia assessment:*** photographs were taken. A blind ophthalmologist reader from the institute was entitled to evaluate them. This ophthalmologist assessed conjunctival hyperaemia as per the MacMonnies photographic scale.
- ***Corneal/conjunctival staining:***

  Corneal staining: Fluorescein was used for corneal staining. 2 µL of 2% sterile fluorescein were instilled into the conjunctival sac and the upper eyelid was lifted slightly to grade the whole cornea surface. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone. Since fluorescein diffuses rapidly into tissues, punctuate staining blurs after a short period. It was therefore essential to take photographs rapidly for staining assessment.

Conjunctival staining: Lissamine green was used for conjunctival staining. After recovery from fluorescein, a 25 µL of 1% lissamine green was instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. Photographs were also taken for this staining assessment. A blind ophthalmologist reader from the institute was entitled to assess corneal and conjunctival staining according to the photographs taken.

Corneal staining with fluorescein was graded as per the Oxford schema and conjunctival staining with lissamine green was graded as per the van Bijsterveld schema.

- ***Intraocular pressure:*** it was measured by applanation tonometry. A drop of topical anaesthetic was used as the probe made contact with the cornea. A calibrated applanation tonometer was used and intraocular pressure was measured in millimetres of mercury (mmHg).
- ***Point-spread function:*** an Optical Quality Analysis System (OQAS) HD Analyzer™ was used to assess the point-spread function (PSF) by the objective scatter index (OSI).
- ***Vision Break up time:*** The vision break-up time (VBUT) of the tear film was measured with the Optical Quality Analysis System (OQAS, HD Analyzer™).
- ***Intraocular surface Disease Index (OSDI):*** Patients were asked the 12 questions of the OSDI questionnaire and the answers were recorded. Then, the boxes A, B, C, D, and E of the questionnaires were filled according to the instructions beside each.
- ***Ocular symptoms/signs:*** patient's perception on ocular symptoms and investigator's assessment of ocular objective signs were determined.
- ***Patients diary to record adherence to pre-/postoperative treatment***: we collected the diaries returned by the patients.

- **Concomitant treatments:** The patient had to inform about modifications of concomitant medications and/or non-drug therapies that he/she was receiving from the screening visit until the last visit. All these medications/ therapies were recorded, including the active ingredient, indication, route of administration, dose, and start/end date.

- **Permitted concomitant medications**

Any concomitant medication that patients needed were permitted, except those described in exclusion criteria.

- **Prohibited concomitant medications**

As per exclusion criteria, the following concomitant medications and treatments were not allowed:

- Systemic corticoid and immunosuppressive treatments within 3 months before surgery.
- Systemic opioids and morphinic drugs within 7 days before surgery.
- Topical ocular treatment with mydriatic and/or anaesthetic action within 7 days before surgery.
- Other systemic analgesics (except paracetamol) within 7 days before surgery.
- Topical treatment with anti-inflammatory and antibiotic action within 1 day before surgery (except for the preoperative treatment specified in this protocol).
- Anxiolytics and hypnotics on the day of surgery (excluding the standard used for the surgery).
- Adrenaline or any other agent with a mydriatic action in the intraocular irrigating solution.

The following medications were also prohibited throughout the study:

- Administration of any investigational product other than the study treatments.

8.10 EFFICACY ASSESSMENTS

The efficacy assessments included in this study are:

- **Patients' satisfaction with study treatments**: The following question were asked to patients to assess their satisfaction with the treatment received in each eye just after surgery (visit 1):

  "How do you judge your ocular comfort during cataract surgery?"

  The patient satisfaction was graded by the patient according to the following scale:

  (0) = Very satisfactory

  (1) = Satisfactory

  (2) = Not very satisfactory

  (3) = Unsatisfactory

- **Investigators' rating of satisfaction:** Just after surgery the investigators answered the following question (visit 1):

  "How do you consider the study product satisfaction?"

  The satisfaction was graded by the investigator according to the following scale:

  (0) = Very satisfactory

  (1) = Satisfactory

  (2) = Not very satisfactory

  (3) = Unsatisfactory

Their analysis of the efficacy assessments were conducted in the "per protocol" population.

8.11 SAFETY ASSESSMENTS

8.11.1 PRIMARY SAFETY ASSESSMENT

The primary safety assessment of the study is the change in corneal/conjunctival surface staining measured as per the Oxford schema (corneal staining with fluorescein) and van Bijsterveld schema (conjunctival staining with lissamine green) with ICMA versus the standard eye-drop protocol from baseline (visit 0) to 7 days post-surgery (visit 3). In addition, changes from baseline (visit 0) to just after surgery (visit 1) and from baseline (visit 0) to 12-36 hours post-surgery (visit 2) were assessed.

- **Corneal staining**

It assesses damage of ocular surface by staining the cornea with fluorescein dye. 2 µL of 2% sterile fluorescein were instilled into the conjunctival sac. The upper eyelid was lifted slightly to grade the whole cornea surface. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone. Since fluorescein diffuses rapidly into tissues, punctuate staining blurs after a short period. It was therefore essential to take photographs rapidly for staining assessment.

A blind ophthalmologist reader from the institute was entitled to evaluate the photographs and sent a report with the result of the evaluation to the investigator.

Corneal staining with fluorescein was graded according to Oxford schema (171) (242). Staining was represented by punctuate dots on a series of panels (A to E) and staining ranges from 0 to 5 for each panel (Figure 3 & 4).

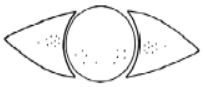
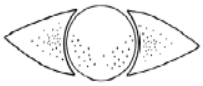
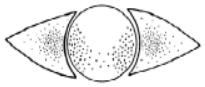
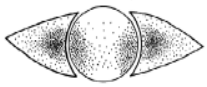
PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Figure 3. Grading staining: Oxford schema (242)

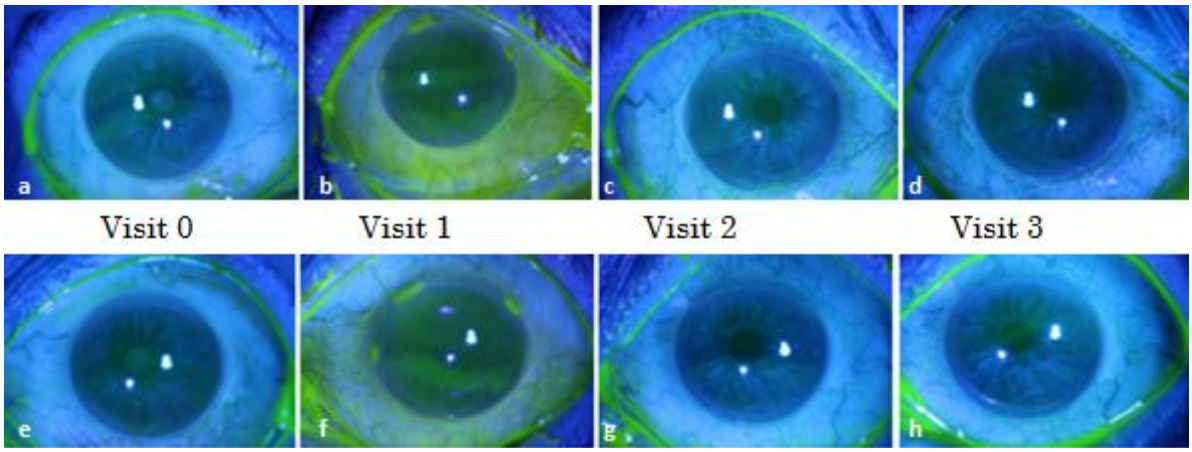


Figure 4. This is an example of a patient's follow up during the study. Both eyes (right eye a-d, left eye e-h), were examined with corneal fluorescein staining and photo documented during each visit (V0, before surgery (a,e); V1, after surgery (b,f); V2, 12-36h after surgery (c,g); V3, 7 days after surgery (d,h)).

- **Conjunctival staining**

It assesses damage of ocular surface by staining the conjunctiva with lissamine green dye. 25 µL of 1% lissamine green were instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. The subject looked nasally to grade the temporal zone and temporally to grade the nasal zone and photographs were taken for staining assessment. An assessor blind ophthalmologist reader from the institute was entitled to evaluate the

photographs and sent a report with the result of the evaluation to the investigator.

Conjunctival staining with lissamine green was graded according to van Bijsterveld schema (172) (243). Intensity was scored in 2 exposed conjunctival zones and cornea. Each zone was scored from 0 to 3; the maximum score was 9 (Figure 5 & 6).

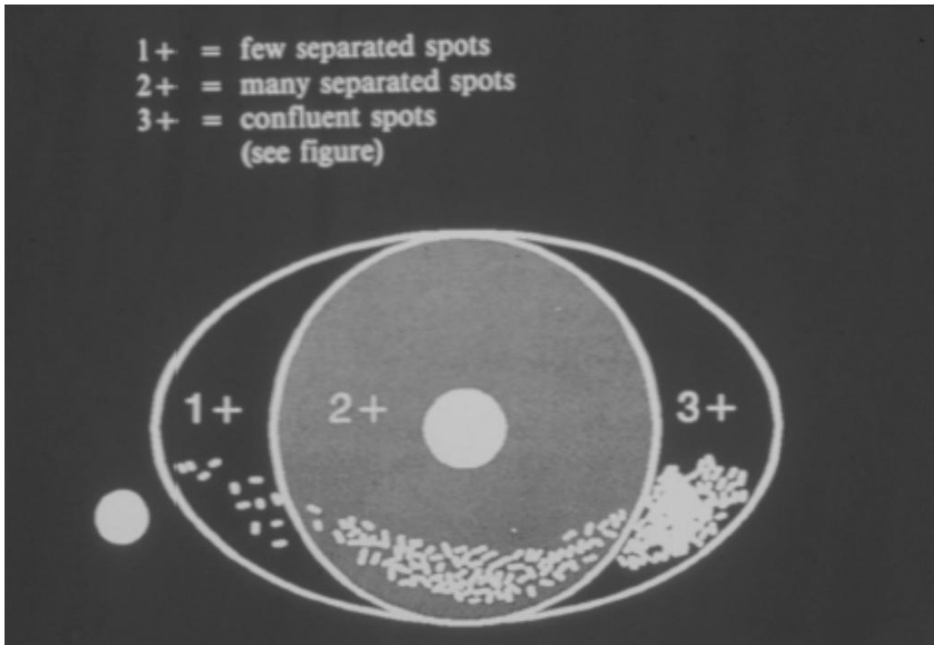


Figure 5. Grading staining: van Bijsterveld schema (243)

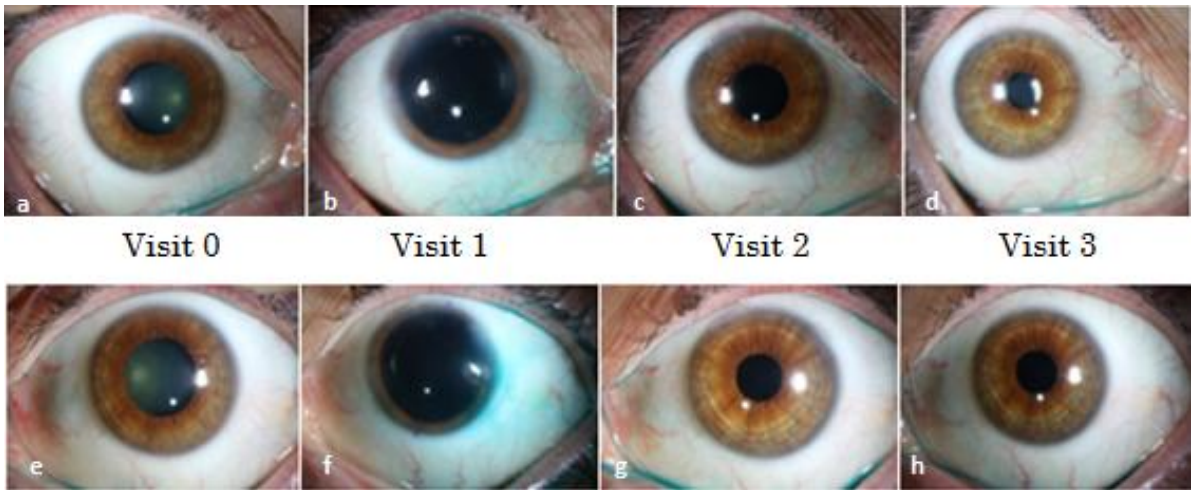


Figure 6. This is an example of a patient's follow up during the study. Conjunctiva was examined in both eyes (right eye a-d, left eye e-h) with lissamine green staining and were photo documented during each visit (V0, before surgery (a,e); V1, after surgery (b,f); V2, 12-36h after surgery (c,g); V3, 7 days after surgery (d,h)).

8.11.2 SECONDARY SAFETY ASSESSMENTS

Secondary safety assessments include:

- **Best corrected visual acuity assessment**

The change in best corrected visual acuity from baseline (visit 0) to 7 days post-surgery (visit 3) were assessed according to the Snellen test, which is a common method of measuring visual acuity by using eye charts. Snellen developed charts using optotypes (alpha numeric capitals) on a 5x5 grid, on which the line thickness is one unit and the letter width and height are five units. The normal Snellen chart is printed with eleven lines of block letters. The first line consists of one very large letter which may be one of several letters (e.g. E, H or N). Subsequent rows have increasing numbers of letters that decrease in size. A person taking the test covers one eye and reads aloud the letters of each row, beginning at the top. The smallest row that can be read accurately indicates the visual acuity in that specific eye.

The Snellen chart is placed at a standard distance of 6 metres and normal acuity is designated as "6/6"; other acuities are expressed as ratios with a numerator of 6. Some clinics do not have 6-metre eye lanes available and either a half-size chart subtending the same angles at 3 metres or a reversed chart projected and viewed by a mirror is used to achieve the correct size letters.

- **Slit-lamp examination**

A slit-lamp examination was conducted to evaluate epithelial alterations 12-36 hours (visit 2) and 7 days post-surgery (visit 3), which was graded as follows:

- None: no alterations
- Mild: mild changes from normal that are clinically insignificant
- Significant: significant changes that may require clinical intervention

- **Hyperaemia assessment**

Changes in hyperaemia from baseline (right before study treatment administration at visit 1) to 7 days post-surgery (visit 3) were described. In addition, changes in conjunctival hyperaemia from baseline (right before study treatment administration at visit 1) to just after surgery (visit 1) and from baseline (right before study treatment administration at visit 1) to 12-36 hours post-surgery (visit 2) were described.

To assess conjunctival hyperaemia, photographs were taken and an assessor blind ophthalmologist reader from the institute was entitled to evaluate them and sent a report with the result of the evaluation. This ophthalmologist assessed conjunctival hyperaemia as per the MacMonnies photographic scale, which included six levels of conjunctival hyperaemia ranging from grade 0 (none) to grade 5 (severe) (192) (244) (245) (Figure 7 & 8).

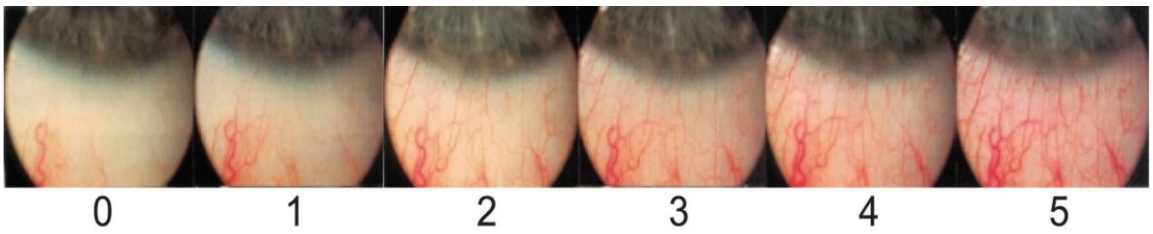


Figure 7. Conjunctival hyperaemia as per the MacMonnies photographic scale

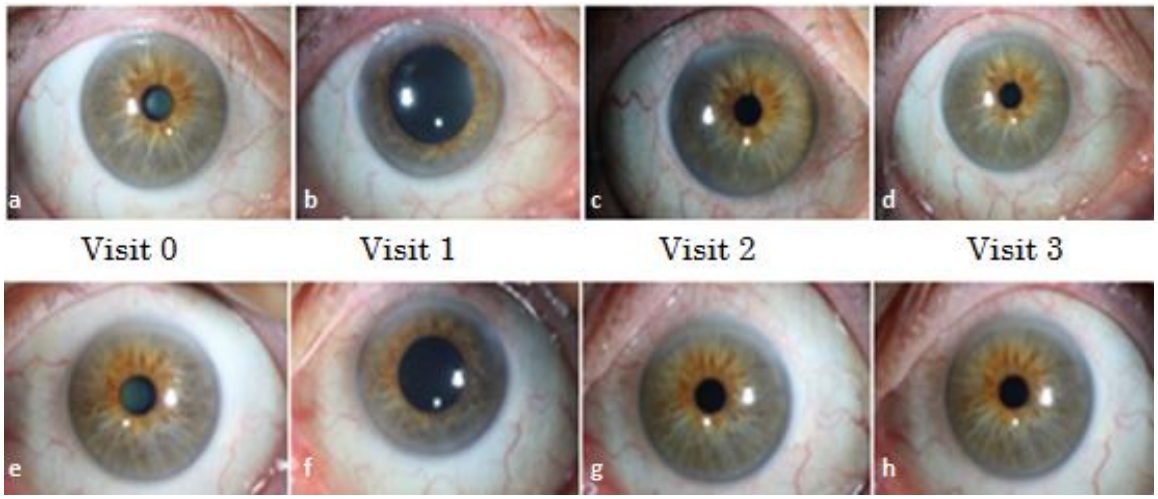


Figure 8. This is an example of a patient's follow up during the study. Conjunctival hyperaemia was examined in both eyes (right eye, a-d; left eye, e-h) and photo documented during each visit (V0, before surgery (a,e); V1, after surgery (b,f); V2, 12-36h after surgery (c,g); V3, 7 days after surgery (d,h)).

- **Intraocular pressure measurement**

  Changes in intraocular pressure from baseline (visit 0) to 7 days post-surgery (visit 3) were assessed by applanation tonometry, which measured the amount of force needed to temporarily flatten a part of the cornea.

  The test involved using a tiny flat-tipped cone that gently comes into contact with the cornea and thus measures the pressure (mmHg) inside the eye.

- **Objective Scatter Index (OSI)**

  The point-spread function (PSF) by the objective scatter index (OSI) in the Optical Quality Analysis System HD Analyzer™ (OQAS, Visiometrics, Spain) was recorded 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3). The OQAS was developed to perform an objective evaluation of optical vision quality and scatter through a double-pass technique that is based on recording images from a point source after reflection in the retina and a double pass through ocular media. The point source of light is obtained after centration of an infrared signal that records the retinal image (213) (215) (246). A personal computer was used to grab and process the retinal images. The sequences for acquisition and treatment of the images were automated and optimized in the OQAS to obtain the measurements in the least possible time. The OQAS measured the retinal point-spread function and gave the OSI as an objective measure calculated from the brightness of the point-spread function. The procedure was conducted following the manufacturer's instructions.

  The OSI parameter can be affected by uncorrected refractive errors (defocus and astigmatism) (219). Hence, all patients had a refractive examination and all measurements were performed with best-corrected sphere and cylinder to avoid these artifacts. The OSI is an objective evaluation of the scattering degree caused by the loss of transparency of one or more of the ocular structures, such as corneal opacities or cataract. Normal OSI values are less than 0.5 for a young person with a healthy eye (220). An OSI score of less than 2 corresponds to the absence of cataract, whereas a score between 2 and 4 corresponds to an early-stage cataract, and greater than 4 to a mature cataract, , (221) (219) (247). OSI

value of 3.2 is an optimum cutoff to discriminate between surgical cataracts and non surgical cataracts (248). Postoperative OSI normal values in pseudophakic eyes are considered to be below 2, as eyes without cataract. The higher the OSI value, the higher the level of intraocular scattering indicating degradation of the quality of the patient's vision (210) (Figure 9).

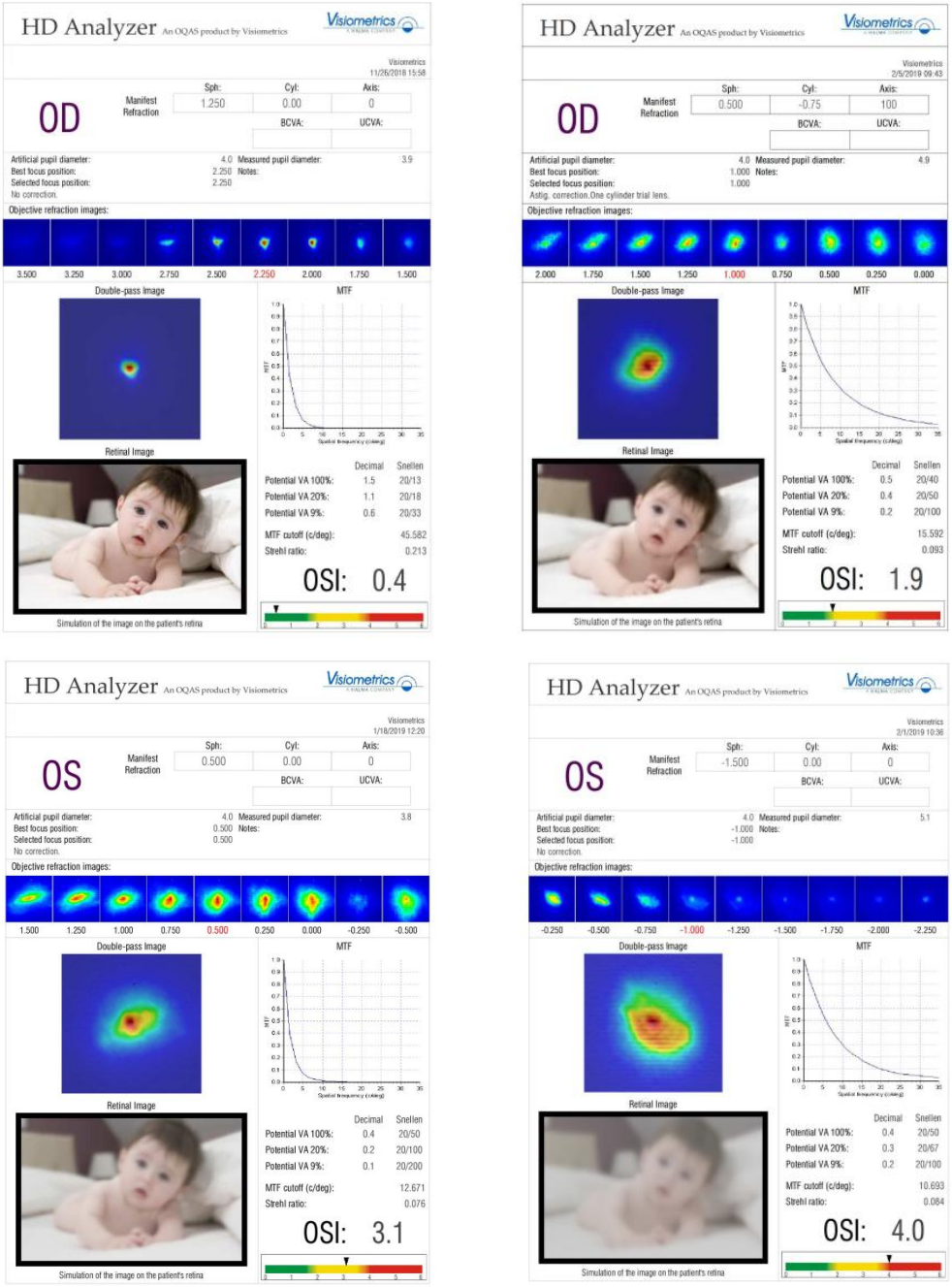


Figure 9. The OQAS determines the objective scatter index (OSI) by analyzing retinal image quality. Double-pass images are clearly deteriorated by the increasing levels of scatter and, equally, the higher the OSI value, the higher the level of intraocular scattering, indicating degradation of the quality of the patient's vision.

- **Vision Break up time**

The vision break-up time (VBUT) of the tear film was measured with the Optical Quality Analysis System (OQAS, HD Analyzer™). The VBUT was estimated as the time elapsed in seconds from 0 seconds to the time at which the subject's vision quality index dropped below a defined threshold. The visual function of the tear film (VBUT) was classified in a three value score: stable, moderately stable (moderate) and unstable vision, depending on how low the vision quality index fell within 10 seconds of a blink (Figure 10). The VBUT was measured before surgery (visit 0), one day after surgery (visit 2) and one week after surgery (visit 3).

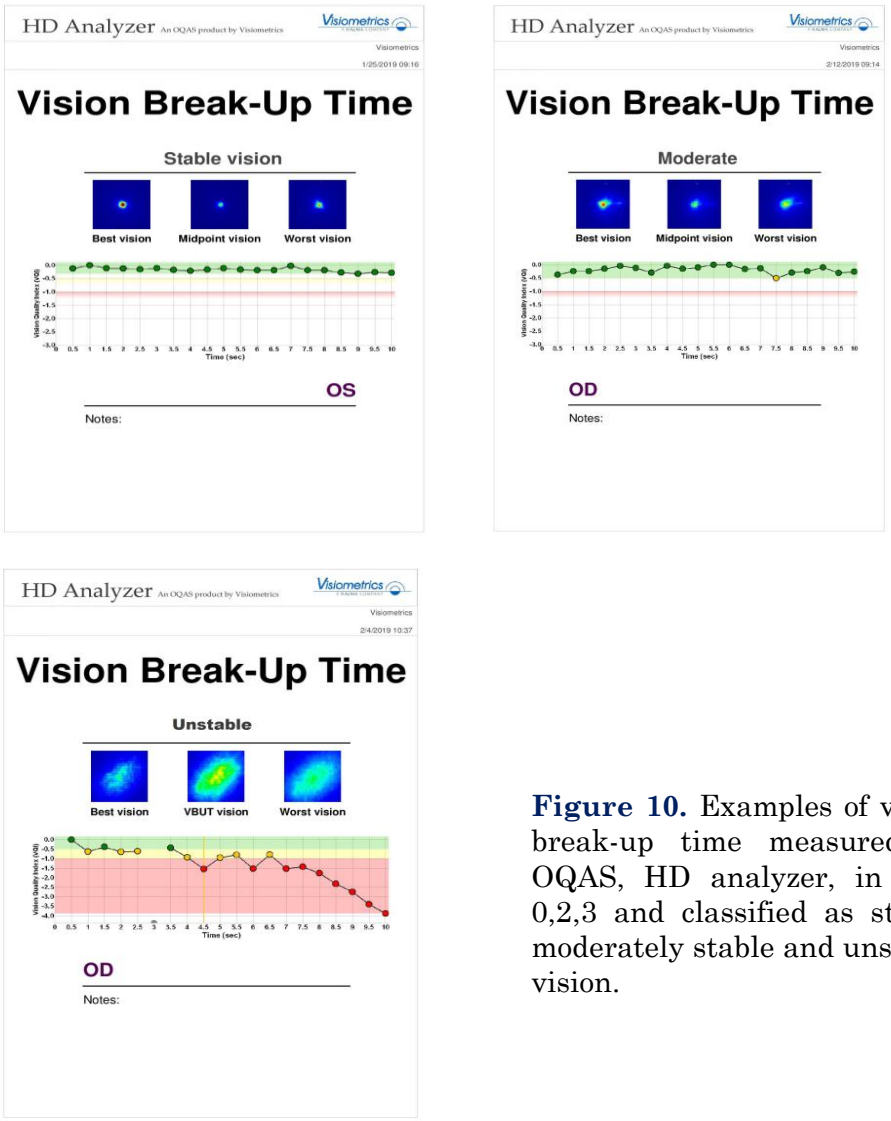


Figure 10. Examples of vision break-up time measured by OQAS, HD analyzer, in visit 0,2,3 and classified as stable, moderately stable and unstable vision.

- **Ocular Surface Disease Index (OSDI)**

The OSDI is a valid instrument for measuring dry eye, effect on vision-related function and environmental triggers (203). It is assessed on a scale of 0 to 100, with higher scores representing greater disability (Figure 11). Changes in the OSDI from baseline (visit 0) to 7 days post-surgery (visit 3) were determined.

Ocular Surface Disease Index© (OSDI©)

Ask your patients the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

Have you experienced any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light? . .	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

Have problems with your eyes limited you in performing any of the following *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

Have your eyes felt uncomfortable in any of the following situations *during the last week*?	All of the time	Most of the time	Half of the time	Some of the time	None of the time	N/A
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned? . . .	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

Add subtotals A, B, and C to obtain D
(D = sum of scores for all questions answered) (D)

Total number of questions answered
(do not include questions answered N/A) (E)

Figure 11. Ocular surface disease index questionnaire

- **Ocular symptoms/signs**

The description of ocular symptoms and signs 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3) were carried out by using the following questions and ordinal scales:

- Question asked to the patient regarding ocular symptoms:

How do you judge your ocular discomfort regarding the following symptoms	*The ocular symptoms were be graded by the patie according to the following scale*			
	Absent	**Mild**	**Moderate**	**Severe**
Pain	0	1	2	3
Irritation/burning/stinging	0	1	2	3
Photophobia	0	1	2	3
Foreign body sensation	0	1	2	3
Other symptoms	0	1	2	3

- Investigators' assessment of ocular objective signs:

Ocular objective signs	*The ocular objective signs were assessed by the investigator and scored as followed*			
	None	**Mild**	**Moderate**	**Severe**
Palpebral edema	0	1	2	3
Chemosis	0	1	2	3
Conjunctival hyperaemia	0	1	2	3
Conjunctival discharge	0	1	2	3
Folliculo-papillary reaction	0	1	2	3
Other sings	0	1	2	3

- **Surgery time-points recording**

  During the day of surgery (visit 1), preoperative preparation and surgical procedure times were recorded. Time necessary from first drop administration to first incision, first incision to end of surgery and first drop administration to end of surgery were registered in every case, so as to analyze the results and compare the differences between the treatment groups.

- **Safety profile**

  All adverse events reported over the medical interview or evidenced on any of the study assessments were collected from the moment of patient's signature of informed consent to the last study visit (visit 3).
  Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and their severity was graded. Analysis of safety assessments were conducted in the safety population.

8.11.3 ADVERSE EVENTS

- **Adverse events**

  Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which did not necessarily have a causal relationship with this treatment. Therefore, an adverse event could be any of the following:

  - Any unfavourable and unintended sign, symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not considered related to this medicinal product.
  - Any new disease or exacerbation of an existing disease (worsening in the nature, frequency or severity of a known disease).
  - Recurrence of an intermittent medical condition (e.g. headache) not present in the screening visit.

- Any worsening of a laboratory value or other clinical test associated with symptoms, or that resulted in a change in the study treatment or concomitant treatment, or discontinuation of the study treatment.
- Adverse events related to protocol-required interventions, including those occurring before administration of the study treatment.

Adverse events were collected and recorded in the medical history of every participant. These adverse events, both serious and non-serious, were described and graded, recording the start and end dates, the outcome and possible causal relationship to the study drugs, the maximum intensity achieved and the seriousness. If action was taken with regard to the study medication, it was also recorded.

Serious Adverse Events

A serious adverse event (SAE) is any adverse event that at any dose could fulfill at least one of the following criteria:

- It is medically significant when it could jeopardize the patient or could require medical/surgical intervention to prevent one of the outcomes listed below.
- Requires patient hospitalization or prolongation of existing hospitalization (elective hospitalizations or those for social reasons would be excluded).
- Results in persistent or significant disability/incapacity (i.e. the adverse event resulted in a substantial change in the patient's ability to lead a normal life).
- It is life-threatening. The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it did not refer to an event which could hypothetically have caused a death had it been more severe.
- It is fatal, i.e. results in death. The cause would be specified.
- Congenital anomaly/birth defect in neonate/infant born to a mother exposed to study drug.

- Suspected transmission of infectious agents via a medicinal product would also be considered as a SAE.

  The terms “severe” and “serious” are not synonymous. Severity refers only to the intensity of an adverse event, regardless of whether it fulfilled the seriousness criteria listed above.

  Medical and scientific judgment would be exercised in deciding whether other situations, such as important medical events that could not be immediately life-threatening or result in death or hospitalization but could jeopardize the patient or could require intervention to prevent one of the seriousness criteria listed above. These situations were also considered serious.

- **Adverse reaction**

  Any reaction to a medicinal product which was noxious and unintended and which occurred at doses normally used in humans for the prophylaxis, diagnosis or treatment of disease or for the restoration, correction or modification of physiological functions. This term also included all adverse clinical consequences derived from dependence, abuse and improper use of medicinal products, including those caused by use under non-authorized conditions and medication errors.

- **Serious adverse reaction**

  Any adverse reaction that may result in death, or is a life-threatening situation, or require hospitalization or prolongation of hospitalization, permanent or significant disability or incapacity, or a congenital anomaly/birth defect may be considered a serious adverse drug reaction. Suspected adverse reactions considered medically important would be also treated as serious, even if they would not fulfill the above criteria, such as those that jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed above. Likewise all suspected transmissions of an infectious agent via a medicinal product would be treated as serious.

- **Unexpected adverse event**

An adverse event the nature, severity or frequency of which was not consistent with the known product safety information.

- **Pre-existing medical conditions worsening during the study**

A pre-existing medical condition was one that was present at the screening visit of the trial. Pre-existing medical conditions that worsen (in frequency, severity or nature of the condition) during the study were recorded as adverse events. If they met any of the seriousness criteria, they would also be reported as a SAE by means of the appropriate form.

- **Assessment of severity**

The severity of adverse events was classified as follows:

1. Mild (grade 1): adverse events overall transient that did not interfere with usual activities of patients.
2. Moderate (grade 2): adverse events that caused a restriction in conducting daily activities of patients, but without making them impossible.
3. Severe (grade 3): adverse events that caused unbearable discomfort or pain that made impossible to conduct usual activities of patients.

- **Assessment of causality**

We used our knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to decide whether the adverse event was considered related to the study drug, indicating “yes" or "no" as appropriate.

The following guidelines were taken into consideration:

- Temporal relationship of the onset of the event to initiation of treatment with the study drug.

- Course of the event, considering in particular the effects of dose reduction, discontinuation of the study drug or reintroduction of the study drug (if applicable).
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non treatment-related factors that were known to be associated with the occurrence of the event.

In all adverse events, the causal relationship of the event to each of the study drugs were established according to the following categories:

-Related: The temporal relationship of the adverse event to the study medication made the causal relationship possible. It was not reasonably attributed to any other cause; other drugs, therapeutic interventions or underlying disorders did not provide an adequate explanation for the observed adverse event.

-Not related: The temporal relationship of the adverse event to the study medication made the causal relationship unlikely, or the adverse event was satisfactorily explained by other drugs, therapeutic interventions or underlying disorders.

Important: When the causal relationship could not be determined, the adverse event was considered to be related to the study medication.

Follow-up of patients after an adverse event

Adverse events were followed up until the last study visit.

The resolution of adverse events was documented in the patient's medical history. SAEs follow-up was demanded until the event was considered stable or resolved, the baseline or better grade was restored, regardless of whether the patient had completed the study or the patient withdrew his/her consent.

8.12 STATISTICAL METHODS AND DATA ANALYSIS

8.12.1 Sample size calculation

The sample size was based on calculating the number of patients who would be included in the study to make it possible to obtain sufficient data to achieve the primary objective. The secondary objectives were fulfilled according to the sample size determined for the primary objective.

The primary objective of the study was to evaluate the effects of ICMA (after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% instillation) and the standard mydriatic-anaesthetic eye drop protocol (tropicamide 1%, phenylephrine 10%, oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%) on ocular surface.

To assess this objective, the primary study endpoint was the change in corneal/conjunctival surface staining measured as per the Oxford schema (corneal staining with fluorescein) and van Bijsterveld schema (conjunctival staining with lissamine green) with ICMA versus the standard eye drop protocol from baseline (visit 0) to 7 days post-surgery (visit 3).

For the sample size calculation, it was needed to have an estimation of an expected mean change and standard deviation in staining scales from baseline to day 7 post-surgery. As no data could be found to have such an estimation, no formal sample size calculation was carried out and the size of 50 patients was considered appropriate as an exploratory/pilot assessment.

8.12.2 Overall statistical considerations

A general description is given below on the main aspects that were considered when making the statistical analysis for this trial. Once the trial was completed and all possible data discrepancies were resolved, the study database was closed and proceeded to statistical analysis. A detailed statistical analysis plan was prepared to guide the analysis of the data and justify any change from the original plan.

An overall description was made of the variables included in the study. Absolute and relative frequency distributions of qualitative variables are presented, as well as the measures of central tendency and dispersion (mean, standard deviation, median, minimum and maximum) of quantitative variables. Ninety-five percent confidence intervals are presented for the results associated with the primary objective and the main secondary variables.

Erroneous or missing data were not imputed and were left as lost. When an inferential analysis was required, parametric tests were used for continuous variables and non-parametric tests for ordinal, categorical or non-parametric variables. The hypothesis tests used were two-sided and with a significance level of 0.05. For variables not fitting a normal (or parametric) distribution, the Mann-Whitney test (for unpaired data) and the Wilcoxon test (paired data) were used.
In the analysis of contingency tables as well as for the comparison of proportions and/or frequency distributions between groups, the chi-square test or Fischer's exact test were used, as appropriate.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software.

8.12.3 Statistical analysis populations

At the time of closing the database there were 50 patients included in the study. No screening failures were detected, and all patients (N=50) received the study treatment.

The following analysis populations were considered:

- ***Per protocol population*:** Eligible patients, all patients meeting selection criteria (all the inclusion criteria and none of the exclusion criteria described in the protocol) who received the study treatments and without any major protocol deviations (N=46).

  Four patients were not included in per protocol population for presenting protocol deviations. All 4 discontinued the follow-up and missed the visit 3 of the second eye (study withdrawal).

- ***Safety population*:** All patients who received any of the study treatments (N=50).

The analysis, shown in this thesis, has been performed on the safety population, and the following analysis groups were considered:

- **ICMA group:** treated with intracameral fixed combination of mydriatics and anaesthetic (Fydrane) after instillation of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye drops (N=50 eyes).
- **Control group:** treated with eye drops of tropicamide 1%, phenylephrine 10% and oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% (N=50 eyes).

Global population is considered as ICMA and control group. The study patient disposition is summarized in the Figure 12.

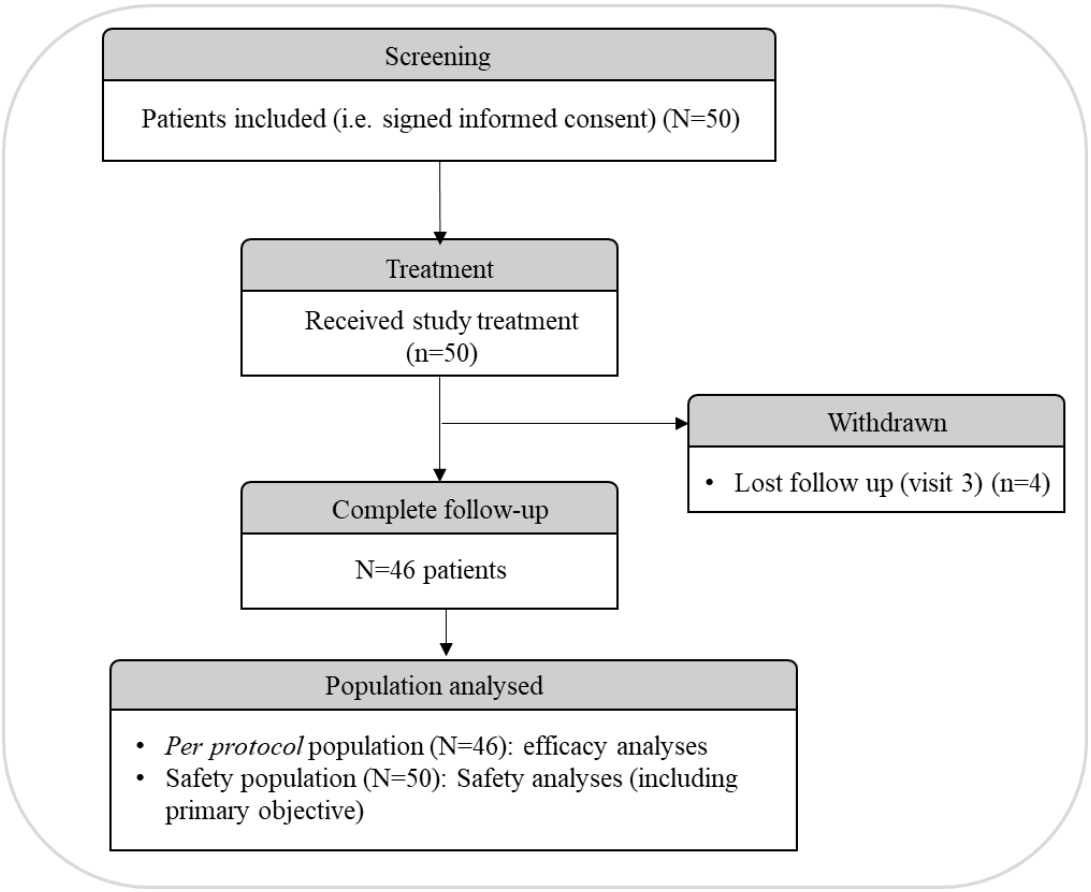


Figure 12. Study population disposition

8.12.4 Analysis of study objectives

Primary objective

The primary objective of the study was "*to evaluate the effects of ICMA (after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% instillation) and the standard mydriatic-anaesthetic eye-drop protocol (tropicamide 1%, phenylephrine 10%, oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1%,) on ocular surface*".

For the analysis of the primary study objective the "safety" population was used. A descriptive analysis of changes in corneal/conjunctival surface staining from baseline (visit 0) to 7 days post-surgery (visit 3) were performed for each eye, including the calculation of measurements of central tendency and dispersion of grades/scores as per the Oxford and van Bijsterveld schemas. Changes in

staining were compared between eyes using t-tests. In addition, changes from baseline (visit 0) to just after surgery (visit 1) and from baseline (visit 0) to 12-36 hours post-surgery (visit 2) were described and compared between eyes using t-tests.

Secondary objectives

The following statistical analyses were proposed to address the secondary study objectives:

- "*To assess changes in best corrected visual acuity recovery*"

The analysis was conducted in the "safety" population. A descriptive analysis of changes in best corrected visual acuity from baseline (visit 0) to 7 days post-surgery (visit 3) were performed for each eye, including the calculation of measurements of central tendency and dispersion of results on Snellen tests. Change was defined as final value minus initial value. If the calculation resulted positive, the change was recorded as favourable. Changes in visual acuity were compared between eyes using t-tests. To interpret the results, decimal acuity was transformed in logMAR decimal scale (Table 1). The logarithm applied for the transformation was logMAR = log10(1/quotient).

Conversion of Snellen acuity values into Decimal and logMAR		
DECIMAL	**SNELLEN (20 feet)**	**logMAR**
0.05	20/400	1.3
0.063	20/320	1.2
0.08	20/250	1.1
0.10	20/200	1.0
0.12	20/160	0.9
0.16	20/125	0.8
0.20	20/100	0.7
0.25	20/80	0.6
0.32	20/63	0.5
0.40	20/50	0.4
0.50	20/40	0.3
0.63	20/32	0.2
0.80	20/25	0.1
1.00	20/20	0.0
1.25	20/16	-0.1
logMAR, logarithm of the minimum angle of resolution		

Table 1. Snellen acuity conversion into decimal and logMAR.

- *"To evaluate epithelial alterations"*

  The analysis was conducted in the "safety" population. A descriptive analysis of epithelial alterations evidenced 12-36 hours (visit 2) and 7±1 days after surgery were performed for each eye, including the absolute frequency and percentage of eyes with no alteration, mild alterations and significant alterations. Epithelial alterations were compared between eyes using chi-square tests.

- *"To describe changes in conjunctival hyperaemia"*

  The analysis was conducted in the "safety" population. A descriptive analysis of changes in conjunctival hyperaemia was conducted from baseline (right before study treatment administration at visit 1) to 7 days post-surgery (visit 3) and was performed for each eye, including the measurements of central tendency and dispersion of scores on the MacMonnies photographic scale. Changes in conjunctival hyperaemia were compared between eyes using t-tests.

  In addition, changes in conjunctival hyperaemia from baseline (right before study treatment administration at visit 1) to just after surgery (visit 1) and from baseline (right before study treatment administration at visit 1) to 12-36 hours post-surgery (visit 2) were described and compared between eyes using t-tests.

- *"To assess changes in intraocular pressure"*

  The analysis was conducted in the "safety" population. A descriptive analysis of changes in intraocular pressure from baseline (visit 0) to 7 days post-surgery (visit 3) was performed for each eye, including the measurements of central tendency and dispersion. Changes in intraocular pressure were compared between eyes using t-tests.

- *"To evaluate the point-spread function (PSF) by the objective scatter index (OSI) in the Optical Quality Analysis System (OQAS) HD Analyzer™"*

  The analysis was conducted in the "safety" population. A descriptive analysis of OSIs evidenced 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3) was performed for each eye. OSIs were compared between eyes using t-tests.

- *"To assess changes in vision break-up time (VBUT)"*

  The statistical analysis was performed in the global population. For the descriptive and comparative analysis of the VBUT, the Chi-squared and the Mann-Whitney test were used respectively

- *"To determine changes in the Ocular Surface Disease Index (OSDI) questionnaire"*

  The analysis was conducted in the "safety" population. A descriptive analysis of changes in OSDI scores from baseline (visit 0) to 7 days post-surgery (visit 3) was performed for each eye, including the measurements of central tendency and dispersion. Changes in OSDI scores were compared between eyes using t-tests.

- *"To describe ocular symptoms/signs experienced by* patients*"*

  The analysis was conducted in the "safety" population. A descriptive analysis of symptoms/signs experienced 12-36 hours post-surgery (visit 2) and 7 days post-surgery (visit 3) was performed for each eye, including the absolute frequency and percentage in each category of the ordinal scales used. Symptoms/sings were compared between eyes using chi-square tests (when the magnitude of frequencies was enough for the analysis to be conducted).

- *"To describe surgical procedure time-points"*

  The analysis was conducted in the "safety" population. A descriptive analysis of the procedure duration was performed from first drop administration to first incision, from first incision to the end of surgery and from first drop administration to end of surgery. Surgery times were compared between eyes using the Mann-Whitney test.

- *"To assess patients' perceptions on satisfaction with study treatments"*

  The analysis was conducted in the "per protocol" population. A descriptive analysis of satisfaction perceived just after surgery (visit 1) for each eye, including the absolute frequency and percentage in each category of the satisfaction ordinal scale. Satisfaction was compared between eyes using chi-square tests.

- *"To determine satisfaction assessed by investigators":*

  The analysis was conducted in the "per protocol" population. A descriptive analysis of satisfaction perceived by investigators just after surgery (visit 1) was performed for each eye, including the absolute frequency and percentage in each category of the satisfaction ordinal scale. Satisfaction was compared between eyes using chi-square tests.

- *"To describe the safety profile of study treatments"*

  The analysis was conducted in the "safety" population. A descriptive analysis of adverse events related to study treatments evidenced throughout the study was performed. The safety profile of study treatments was compared using chi-square tests (when the number of events is enough for the analysis to be conducted).

9. RESULTS

9.1 VISIT 0 - SCREENING VISIT

Demographics

A total of 50 patients, 23 males (46%) and 27 females (54%), undergoing cataract surgery in both eyes, were included in the study. The mean age of the patients was of 61±10 years, with younger patient 40 years and older 78 years. The age was calculated on the date that the patient signed the informed consent. 98% of the patients were Caucasians (n=49) and 2% Arab (n=1) (Table 2).

Ophthalmologic history

Eleven patients (22%) indicated ophthalmologic disorders other than cataract. Between the pathologies mentioned were amblyopia (4%), high myopia (8%), high hyperopia (4%), exophoria (2%), posterior vitreous detachment (2%) and epiretinal membrane (2%) (Table 2).

Medical history

In each case a detailed medical anamnesis was taken and any medical disorder and/or procedure was described. Out of 50 patients, 15 (30%) referred having cardiovascular diseases (hypertension, hypercholesterolemia), 7 (14%) neurologic disorders (migraine, epilepsy, multiple sclerosis), 4 (8%) endocrine disorders (hyper and hypothyroidism), 3 (6%) Diabetes mellitus and 26 (52%) referred to have other health problems (12 articular/vertebral pathology, 18 common surgical procedures (apendicectomy (5), inguinal hernia surgery (5), varicectomy (3), amydgalectomy (3), hysterectomy (2)), cancer surgery (prostate/breast/ intestinal) (3) and anxiety disorders (2) (Table 2).

Concomitant medications

Patients informed about any concomitant medications and/or non-drug therapies that they were receiving at screening visit and their changes until last study visit. Any concomitant medication that patients needed were permitted, except

those described in the exclusion criteria. All these medications/therapies were recorded (Table 3).

Table 2. Demographic and clinical baseline characteristics

Demographic characteristics	**N=50 (%)**
Age (years), mean ± SD	61.0 ± 10.0
Sex, n (%)	
Male	23 (46.0)
Female	27 (54.0)
Race/Ethnicity, n (%)	
Caucasian	49 (98.0)
Arab	1 (2.0)
Ophthalmologic history	
Ophthalmologic disorder other than cataract, n (%)	11 (22.0)
Amblyopia	2 (4.0)
High myopia	4 (8.0)
High hyperopia	2 (4.0)
Exophoria	1 (2.0)
Posterior vitreous detachment	1 (2.0)
Epiretinal membrane	1 (2.0)
Other medical history	
Cardiovascular disease, n (%)	15 (30.0)
Arterial hypertension	6 (12.0)
Hypercholesterolemia	9 (18.0)
Other	2 (4.0)
Neurologic disorder, n (%)	7 (14.0)
Migraine	3 (6.0)
Multiple Sclerosis	1 (2.0)
Other	3 (6.0)
Endocrine disorder, n (%)	4 (8.0)
Hyperthyroidism	2 (4.0)
Hypothyroidism	2 (4.0)
Diabetes mellitus, n (%)	3 (6.0)
Other pathologies, n (%)	26 (52.0)

Table 3. Concomitant medications

Medication	Number of patients (%)
Atorvastatin 10mg	3 (6)
Aspirin 100mg	2 (4)
Calcium 500mg	2 (4)
Enalapril 20mg	2 (4)
Bisoprolol 5mg	1 (2)
Valsartan 80mg	2 (4)
Losartan 50mg/Hydrochlorotiazide 12.5mg	1 (2)
Eucreas (Vildagliptin 50mg/Metformin 850mg)	2 (4)
Metformin 850mg	1 (2)
Levothyroxine 50mg	3 (6)
Paracetamol 500mg	2 (4)
Simvastatin 20mg	2 (4)

Lenses opacities classification

This analysis was performed in the safety population. Lenses opacities were quite similar between the eyes of each patient and consequently between the two study groups. Cortical cataract grade 1 (C1) was present in 3 eyes (6%), cortical and nuclear cataract grade 1 (C1N1) in 2 eyes (4%) and cortical grade 2 (C2) in 14 eyes (28%) in each group respectively. In the ICMA group cortical cataract grade 2 and nuclear cataract grade 1 (C2N1) was present in 8 eyes (16%) and cortical/nuclear cataract grade 2 (C2N2) was present in 23 eyes (46%), while in the control group it was 7 (14%) and 24 eyes (48%) respectively (Table 4).

Table 4. Lenses opacities classification

LOC III	ICMA group N(%)	Control group N (%)
C1	3 (6.0)	3 (6.0)
C1N1	2 (4.0)	2 (4.0)
C2	14 (28.0)	14 (28.0)
C2N1	8 (16.0)	7 (14.0)
C2N2	23 (46.0)	24 (48.0)

ICMA= intracameral mydriatics and anaesthetic

Pupil dilatation

In the screening visit (V0), pharmacological mydriasis was achieved by tropicamide 1% drops and phenylephrine 10% drops, with a maximum of 3 combined instillations at 10-minute intervals if needed. Bilateral pupil size was measured with a light meter in all 50 patients, as one of the inclusion criteria was pupil size ≥ 7.0mm. If pupil size was less than 7.00 mm in one or both eyes, the patient was excluded from the study (Figure 13).

The mean pupil size after pharmacological mydriasis was 7.8±0.5 mm in the ICMA group (n=50 eyes) and 7.9±0.5 mm in the control group (n=50 eyes), with smaller pupil of 7.00 mm and bigger pupil of 9.00 mm. The pupil size after pharmacological mydriasis was similar in both groups with no statistical significant difference (p=0.933, Mann-Whitney U test) (Table 6).

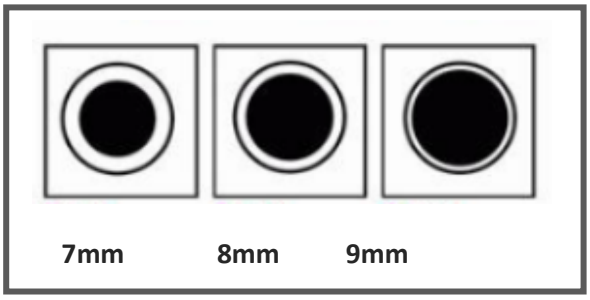


Figure 13. Grading pupil size after pharmacological mydriasis. To accurately evaluate pupil size, the light meter of a slit-lamp was used in all cases.

Visit 0 - Best corrected visual acuity

Best-corrected visual acuity (BCVA) was measured using the Snellen test. Patients were positioned 6 metres from the Snellen chart, in a well-lit area and seated. Optometrist covered the patient's left eye and asked the patient to start at the top of the chart and read the letters out loud, to the smallest size he/she could manage. The procedure was repeated by occluding the patient's right eye. The visual acuity achieved for each eye was recorded.

In the screening visit, the BCVA was similar in both groups (N=50). The mean BCVA was 0.8±0.2 (Snellen decimal) in both ICMA and control group, while the lower BCVA was 0.3 in the ICMA group versus 0.2 in the control group and the

higher was 1.0 in both groups. There were no statistical differences between the groups (p=0.969, Mann-Whitney test) (Table 5)

Table 5. Best corrected visual acuity before surgery

BCVA - Visit 0 (N=50)			
	ICMA group	**Control group**	
Snellen Decimal, (mean ± SD)	0.8 ± 0.2	0.8 ± 0.2	p-value = 0.969
logMAR, (mean ± SD)	0.1 ± 0.1	0.1 ± 0.2	p-value = 0.969

Visit 0 - Slit-lamp examination (V0)

All 50 patients were examined by slit-lamp biomicroscopy during the screening visit (visit 0). There were no corneal epithelial alterations detected, in any of the participants' eyes neither other corneal/conjunctival disorders . The epithelial alterations classification was established as none, mild and significant.

Visit 0- Corneal/conjunctival staining

The ocular surface was examined by impregnating cornea with fluorescein dye and conjunctiva with lissamine green dye. A specialized technician photo documented the ocular surface to assess corneal and conjunctival staining. All photographs were taken under one platform, using the same slit-lamp with a digital camera imaging module and software, applying a standard technique for all patients and the same background room light conditions. The photographs were codified and sent to the blind ophthalmologist reader for evaluation. The descriptive statistic is shown below for this continuous variable of corneal and conjunctival staining.

Oxford schema

Fluorescein eye stain test score: In the screening visit (V0), all patients were examined and photo documented with corneal fluorescein staining (CFS) (Figure 14). The photographs were evaluated by the assessor ophthalmologist, blinded to

the trial treatment. The CFS pattern was classified as per Oxford schema. Patients included in the study presented absence of corneal fluorescein staining pattern in both eyes (Oxford schema grade 0) during the inclusion visit (Table 6).

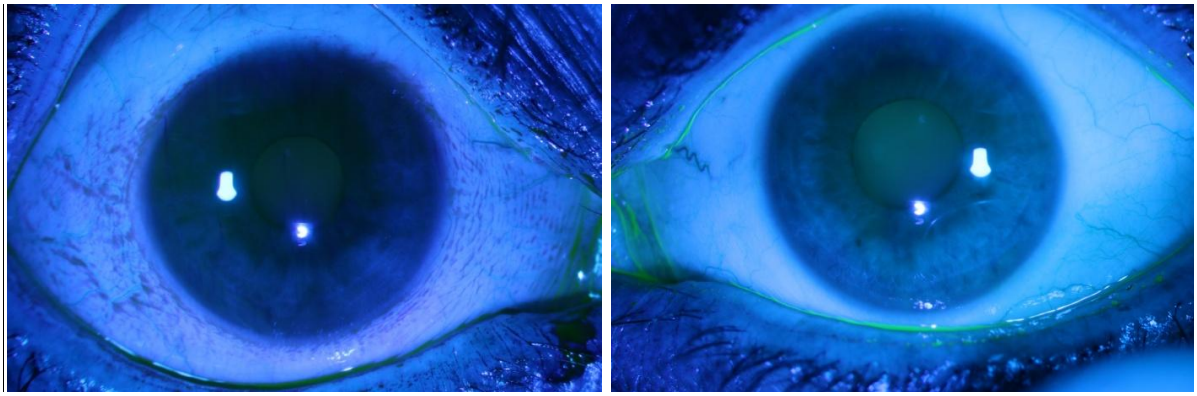


Figure 14. Preoperative photographs under cobalt blue light; examination with corneal fluorescein staining. Oxford schema graded 0 in both eyes of all patients during screening visit.

van Bijsterveld schema

Lissamine green eye staining test score: A lissamine green impregnated strip was placed in the upper conjunctival sac of the eye. Staining was recorded in the temporal bulbar conjunctiva, nasal bulbar conjunctiva, and cornea. Each graded on a scale of 0–3 points, with 0 being no stain, 1 indicating few separated spots of staining, 2 indicating many separated spots of staining, and 3 indicating confluent staining. The total score was from 0 to 9 points. All patients were examined and photo documented with lissamine green staining (LGS) during the inclusion visit (Figure 15). The photographs were evaluated by the blind ophthalmologist reader, just as in the corneal fluorescein staining case. The conjunctival LGS pattern was classified as per van Bijsterveld schema. In the screening visit, the mean grade observed for LGS was 0.2±0.4 in the ICMA group and 0.1±0.4 in the control group (p=0.299, Mann-Whitney test) (Table 6).

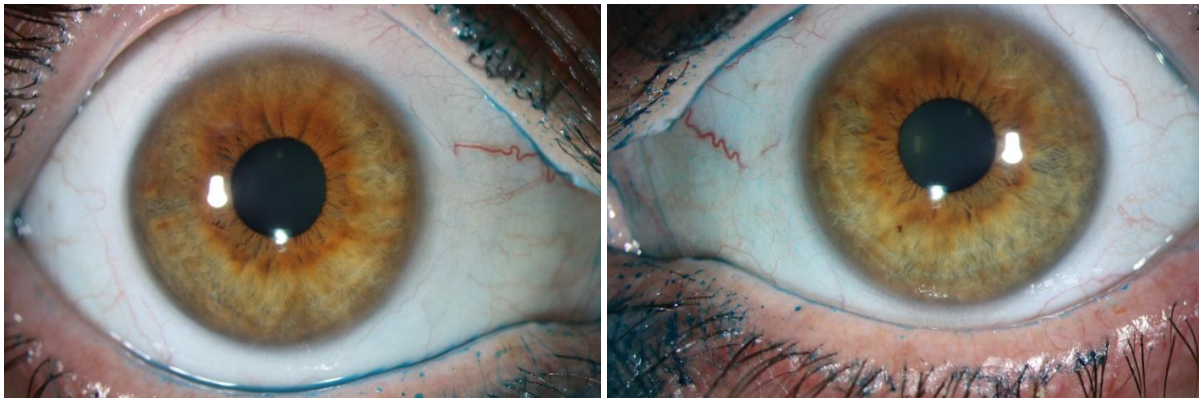


Figure 15. Preoperative photographs under lissamine green staining (visit 0). Score was graded as per van Bijsterveld schema by the assessor ophthalmologist, blinded to the trial treatment.

Visit 0- Intraocular pressure

During screening visit, intraocular pressure (IOP) was evaluated by applanation tonometry. Patients included in the study presented a range of normal values. The mean IOP was 14.5±3.1 mmHg in the ICMA group versus 15.0±3.2 mmHg in the control group, with lowest IOP 10mmHg in both groups and highest IOP 20mmHg in the ICMA group and 21mmHg in the control group. There were no statistical differences between the groups (p= 0.415, T- test) (Table 6).

Visit 0- Ocular Surface Disease Index (OSDI)

During the screening visit, all participants completed the Ocular Surface Disease Index (OSDI) questionnaire(n=50). For the descriptive statistic analysis of the continuous variables of OSDI total score (12-item questionnaire) and the 3 subscales, the Mann-Whitney test was used. The mean OSDI total score was 16.9±21.6 in the ICMA group and 17.1±21.9 in the control group. There were no statistical differences between the 2 groups (p=0.952, Mann-Whitney test) before surgery.

The OSDI total score was calculated as follows:

$$OSDI\ Total\ score = D \times 25 / E$$

D = sum of scores for all questions answered
E = total number of questions answered

There were 3 OSDI subscales in the questionnaire, interpreted as: a) ocular symptoms for answers 1 to 5 (A score), b) vision-related function for answer 6 to 9 (B score) and c) environmental triggers for answer 10 to 12 (C score). For the descriptive statistic analysis of the OSDI subscales Mann-Whitney test was used. The mean OSDI A score (ocular symptoms) was 3.1±4.0 in the ICMA group versus 3.3±4.3 in the control group (p=0.867). The mean OSDI B score (vision-related function) was 3.2±4.8 in both groups (p=0.997) and the mean OSDI C score (environmental triggers) was 1.5±2.7 in the ICMA group versus 1.4±2.7 in the control group (p=0.826). There were no statistical differences between the groups in the OSDI subscales (Mann-Whitney test) (Table 6).

In the table 6 below are summarized the results of the ophthalmological procedures during the screening visit (visit 0).

Table 6. Screening visit procedures results. Comparison between groups.

Ophthalmologic procedures	**ICMA**	**Control**	***p* value**	**N**
Pupil dilatation (mm), mean±SD	7.8±0.5	7.9±0.5	0.933	50
Best-corrected visual acuity, mean±SD				
logMAR	0.1±0.1	0.1±0.2	0.969	50
Decimal	0.8±0.2	0.8±0.2	0.969	50
Slit-lamp: presence of epithelial alterations, N (%)	0 (0.0)	0 (0.0)	-	50
Corneal Staining (Oxford schema), mean±SD	0.0±0.0	0.0±0.0	-	49
Conjunctival staining (Bijsterveld schema),mean±SD	0.2±0.4	0.1±0.4	0.299	49
Intraocular pressure (mmHg), mean±SD	14.5±3.1	15.0±3.2	0.415	50
Intraocular Surface Disease Index (OSDI),mean±SD				
A	3.1±4.0	3.3±4.3	0.867	50
B	3.2±4.8	3.2±4.8	0.997	50
C	1.5±2.7	1.4±2.7	0.826	50
Total	16.9±21.6	17.1±21.9	0.952	50

9.2 VISIT 1 - DAY OF SURGERY

9.2.1 Before surgery

Visit 1. Slit-lamp examination

All patients were evaluated by slit-lamp biomicroscopy, just after arriving in the institute and before any instillation of eye drops, to make sure that they presented no epithelial alterations, as this would be an exclusion criteria. 100% of the eyes in both groups presented a healthy cornea with no epithelial alterations before surgery.

Visit 1. Hyperaemia assessment

In the immediate preoperative time, before any drop instillation, a specialized technician photo documented the ocular surface for the conjunctival hyperaemia assessment. All photographs were taken under the same slit-lamp with a digital camera imaging module and software applying a standard technique for all patients and the same background room light conditions (Figure 16). The photographs were codified and sent to the blind ophthalmologist reader for evaluation.

MacMonnies photographic scale was used to classify the conjunctival hyperaemia grade (grade 0 (none), grade 1, grade 2, grade 3, grade 4, grade 5 (severe)). For the descriptive statistic analysis of the categorical variables of hyperaemia the Fisher's Exact test was used. 32 eyes (65.3%) of the ICMA group and 30 eyes (60%) of the control group presented no hyperaemia (grade 0) just before surgery, while 15 eyes (30.6%) and 20 eyes (40%) respectively presented grade 1 of hyperaemia (p=0.300), (Table 7).

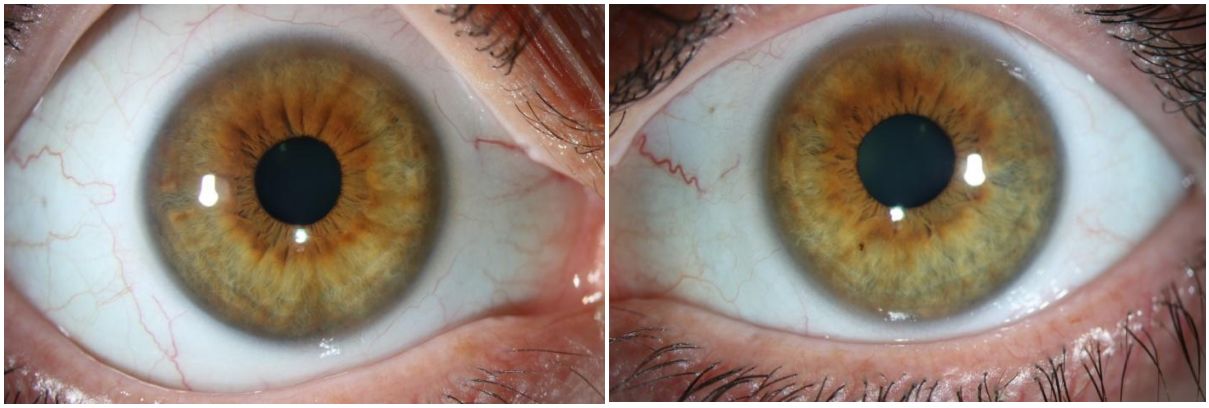


Figure 16. All patients were examined in slit-lamp the day of surgery. 50 patients with healthy eyes were included in the study. Photographs were taken before surgery to photo document conjunctival hyperaemia in all cases.

Table 7. Hyperaemia assessment before surgery

Visit 1 (before surgery)	MacMonnies photographic scale grade						Total	
	Grade 0 (none)		Grade 1		Grade 2		N	%
	N	%	N	%	N	%		
ICMA	32	65.3	15	30.6	2	4.1	49	100.0
Control	30	60.0	20	40.0	0	0.0	50	100.0
Total	62	62.6	35	35.4	2	2.0	99	100.0
p-value	0.300							

Visit 1. Study treatment administration

During the surgery preparation, the study protocol was carried out in every case without any protocol deviation and all patients received the treatment accurately since it was administered by the surgeon at the surgical procedure.

In the ICMA group, 1-2 drops of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% were instilled at 5 minutes and 1 minute before the beginning of the surgical procedure (first incision). Then, at the beginning of the surgical procedure, 0.2 ml of ICMA were administered in a slow intracameral injection in the anterior chamber just after the first corneal incision.

In the control group, 1-2 drops of tropicamide 1% and phenylephrine 10% were instilled 3 times with intervals of 10 minutes, starting at 30 minutes before surgery (-30 minutes, -20 minutes, -10 minutes) and eye drops of oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% were instilled before surgery, as the normal routine of the centre.

At the end of the phacoemulsification, 46 patients received intracameral administration of cefuroxime in the surgical procedure of both eyes, while 4 patients received vancomycin for having history of penicillin allergy.

The postoperative treatment prescribed included norfloxacin (Chibroxin®) eye drops and dexamethasone (Dexafree®) drops 3 times a day and timolol (Timabak®) drops twice a day during 3 weeks (n=50 in both groups).

9.2.2 Just after surgery

Visit 1. Hyperaemia assessment

The day of the surgery, just after the surgical procedure was completed and during the first postoperative hour, a specialized technician photo documented the ocular surface for the conjunctival hyperaemia, corneal and conjunctival staining assessment.

Once more, all photographs were taken under the same slit-lamp with a digital camera imaging module using a standard technique for all patients and the same background room light conditions. The photographs were codified and sent to the blind ophthalmologist reader for evaluation. MacMonnies photographic scale was used to classify the conjunctival hyperaemia grade (grade 0 (none), grade 1, grade 2, grade 3, grade 4, grade 5 (severe)).

For the descriptive statistic analysis, of the categorical variables of the conjunctival hyperaemia, the Fisher's Exact test was used. 25 eyes (54.3%) of the ICMA group and 20 eyes (43.5%) of the control group presented no hyperaemia (grade 0) just after surgery, while 17 eyes (37%) and 19 eyes (41.3%) presented grade 1 of hyperaemia and 3 eyes (6.5%) and 7 eyes (15.2%) presented grade 2 respectively (p=0.312), as seen in the table 8.

Four patients asked not to have the postoperative photographic session, but were willing to keep with the study follow-up (n=46 in both groups).

Table 8. Hyperaemia assessment immediately after surgery

Visit 1 after surgery	MacMonnies photographic scale grade								Total	
	Grade 0 (none)		Grade 1		Grade 2		Grade 3		N	%
	N	%	N	%	N	%	N	%		
ICMA	25	54.3	17	37.0	3	6.5	1	2.2	46	100
Control	20	43.5	19	41.3	7	15.2	0	0.0	46	100
Total	45	48.9	36	39.1	10	10.9	1	1.1	92	100
p-value	0.312									

Visit 1. Corneal/conjunctival staining

Oxford schema

Just after surgery, patients were examined and photo documented with corneal fluorescein staining (CFS). The photographs were evaluated by the assessor ophthalmologist, blind to the trial treatment. The CFS pattern was classified as per Oxford schema.

Five patients asked not to have the postoperative eye staining immediately after surgery, but were willing to keep with the rest of the study protocol (n=45 in both groups).

For the descriptive statistic analysis of the continuous variable of the corneal fluorescein staining (grade 0, grade 1, grade 2, grade 3, grade 4, grade 5), the Mann-Whitney test was used.

The mean CFS score was 1.3±0.7 in the ICMA group versus 1.4±0.7 in the control group, with minimum grade 0 in ICMA group versus grade 1 in the control group and maximum grade 4.0 in both groups. There were no significant differences between the two groups (p=0.118).

van Bijsterveld schema

Forty-five out of 50 patients were photo documented likewise with lissamine green staining (LGS) in the first postoperative hour. The photographs were evaluated by the blind ophthalmologist reader, just as in the corneal fluorescein staining case. The conjunctival LGS pattern was classified as per van Bijsterveld schema. For the descriptive statistic analysis of this continuous variable, the Mann-Whitney test was used.

The mean LGS was 0.7±0.7 in the ICMA group versus 0.6±0.7 in the control group, with minimum grade 0 in both groups and maximum grade 2 in both groups. There were no significant differences between the two groups (p= 0.475).

Visit 1. Type of intraocular lens

All 50 patients underwent uneventful phacoemulsification in both eyes with intraocular lens implantation into the capsular sac. The type of lens used at surgery was up to patients/surgeon's preference. It was recorded in all cases, showing a prevalence in multifocal lenses with an implantation of 54% of the cases in both groups (n=27 eyes, in each group). Monofocal lenses were inserted in 26% of the ICMA group (n=13 eyes) and 24% of the control group (n=12 eyes). Toric lenses were implanted in 20% (n=10 eyes) and 22% (n=11 eyes) respectively. The differences between groups were not considered significant (p=0.957, Fisher's Exact test) (Figure 17)

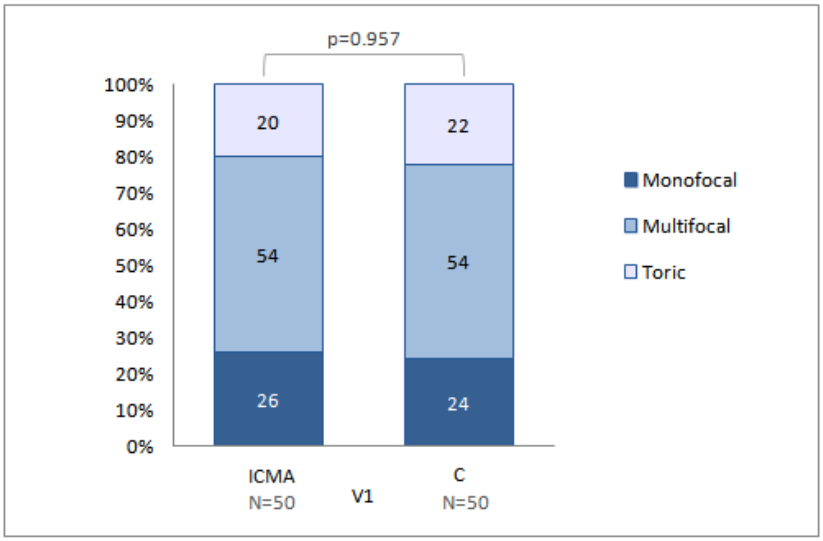


Figure 17. Intraocular lens implanted in each group

9.3 VISIT 2 - FIRST POSTOPERATIVE DAY

Visit 2. Best corrected visual acuity

The first postoperative day, 12-36 hours after surgery, BCVA was evaluated with Snellen test in all patients (n=50). For the descriptive statistic analysis of the continuous variable of BCVA, the Mann-Whitney test was used. The mean BCVA was 08±0.2 in both groups (decimal acuity). There were no significant differences between the two groups (p=0.270).

Visit 2. Slit-lamp examination

The first postoperative day, all patients were examined in the slit-lamp. The epithelial alterations were classified as none, mild and significant. Four eyes (8%) in the ICMA group and 15 eyes (30%) in the control group presented mild epithelial alterations. For the descriptive statistic analysis of the categorical variable of epithelial alterations, the Chi-squared test was used. There were observed statistical differences between the two groups (p=0.005, Chi-squared test).

Visit 2. Hyperaemia assessment

12-36 hours after surgery, all patients attended the follow up visit. Forty-eight out of 50 eyes in the ICMA group and 50 eyes in the control group were photo documented (Figure 18). The hyperaemia assessment as per MacMonnies photographic scale was evaluated by the blind ophthalmologist reader. For the descriptive statistical analysis of this categorical variable, the Fisher's Exact test was used.

No hyperaemia (grade 0) was observed in 14 eyes (29.2%) in the ICMA group versus 6 (12%) eyes in the control group. Grade 1 was registered in 24 eyes (50%) versus 31 eyes (62%). Grade 2 was present in 9 eyes (18.8%) versus 12 eyes (24%) respectively. Grade 3 was observed only in 1 eye (2%) in both groups (p=0.172).

Visit 2. Corneal/conjunctival staining

The first postoperative day, forty eight out of 50 eyes in the ICMA group and 50 eyes in the control group were photo documented with corneal fluorescein staining (CFS) and conjunctival lissamine green staining (LGS) (Figure 18). The photographs were evaluated by the assessor ophthalmologist, blind to the trial treatment.

Oxford schema

The CFS pattern was classified as per Oxford schema. For the descriptive statistic analysis of the continuous variable of the corneal fluorescein staining, the Mann-Whitney test was used. The mean CFS score was 0.2±0.4 in the ICMA group versus 0.3±0.5 in the control group, with minimum grade 0 in both groups and maximum grade 1.0 in the ICMA group and 2.0 in the control group. There were no significant differences between the two groups (p=0.626).

van Bijsterveld schema

The conjunctival LGS pattern was classified as per van Bijsterveld schema. For the descriptive statistic analysis of this continuous variable, the Mann-Whitney test was used. The mean LGS was 0.3±0.5 in the ICMA group versus 0.4±0.6 in the control group, with minimum grade 0 in both groups and maximum grade 2 in both groups. There were no significant differences between the two groups (p=0.493).

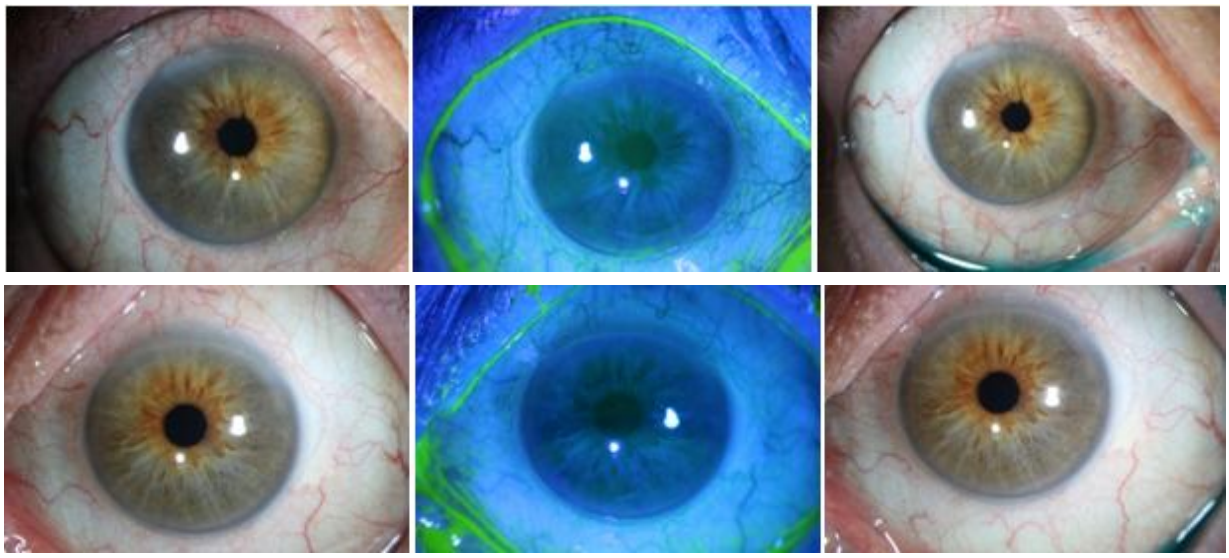


Figure 18. Photographs were taken in the postoperative visits. Hyperaemia classified as per MacMonnies photographic scale, CFS by Oxford schema and LGS by van Bijsterveld schema were evaluated by the assessor ophthalmologist blinded to the treatment.

Visit 2. Ocular symptoms/signs

Ocular symptoms

At visit 2, patients were asked to judge their postoperative ocular discomfort regarding the following symptoms and specify the grade in each item: pain, irritation/burning/stinging, photophobia, foreign body sensation and other symptoms. These items were classified with scores from 0 to 3, with 0 having absent symptoms, 1 mild, 2 moderate and 3 severe. Patients' judgment over the symptoms were analysed with the Fisher's Exact test (Table 9).

During the first 12-36 hours, 85.7% of the patients in the ICMA group denied experiencing any pain and 14.3% referred a mild grade. In the control group 74% referred absence of pain, while 20% presented mild and 6% severe pain (p=0.185). Photophobia was mentioned by 63.3% in the ICMA group and 52% in the control group (p=0.391). Foreign body sensation was experienced by 36.7% of the ICMA group versus 62% in the control group (p=0.051). Symptoms such as irritation, burning, stinging were present in 6.1% in the ICMA group (mild grade), versus 26% in the control group (16% mild, 2% moderate and 8% severe grade), demonstrating a significant difference between groups (p=0.018). In the rest of

the symptoms declared by the patients, the differences between groups were not significant.

Table 9. Ocular symptoms the first postoperative day

Ocular symptoms						
12-36h after surgery		**Percentage of patients (%)**		**Number of patients**		
		ICMA	**C**	**ICMA**	**C**	
Pain	Absent	85.7	74.0	42	37	
	Mild	14.3	20.0	7	10	p=0.185
	Moderate	0.0	0.0	0	0	
	Severe	0.0	6.0	0	3	
Irritation/burning/ stinging	Absent	93.9*	74.0	46	37	
	Mild	6.1	16.0	3	8	*p=0.018
	Moderate	0.0	2.0	0	1	
	Severe	0.0	8.0	0	4	
Photophobia	Absent	63.3	52.0	31	26	
	Mild	32.7	36.0	16	18	p=0.391
	Moderate	4.1	10.0	2	5	
	Severe	0.0	2.0	0	1	
Foreign body sensation	Absent	63.3	38.0	31	19	
	Mild	32.7	48.0	16	24	p=0.051
	Moderate	2.0	8.0	1	4	
	Severe	2.0	6.0	1	3	
Other	Absent	91.8	90.0	45	45	
	Mild	6.1	6.0	3	3	p>0.999
	Moderate	2.0	2.0	1	1	
	Severe	0.0	2.0	0	1	

ICMA N=49, C N=50

Ocular signs

At the first postoperative day, visit 2, ocular objective signs were evaluated and classified, each one of them, from grade 0 to 3, with 0 absent signs, 1 mild, 2 moderate and 3 severe signs. The assessment was about palpebral edema, chemosis, conjunctival hyperaemia, conjunctival discharge, conjunctival folliculo-papillary reaction and other objective signs. The assessments over the ocular signs were analysed with the Fisher's Exact test (Table 10). During the first 12-36 hours, 6.1% of the patients in the ICMA group presented palpebral edema

versus 14% in the control group (p=0.407). Chemosis was present in 4.1% in the ICMA group versus 10% in the control group (p=0.331). Conjunctival hyperaemia was observed in 12.2% of the ICMA group versus 24% in the control group (p=0.239). Conjunctival discharge was absent in 100% of the ICMA group versus 96% of the control group (p=0.495). Conjunctival folliculo-papillary reaction was reported in 10.2% in the ICMA group versus 32% in the control group, demonstrating a significant difference between groups (p=0.015). In the rest of signs observed, the differences between groups were not significant.

Table 10. Ocular signs the first postoperative day

Ocular signs						
12-36h after surgery		**Percentage of patients (%)**		**Number of patients**		
		ICMA	**C**	**ICMA**	**C**	
Palpebral edema	None	93.9	86.0	46	43	
	Mild	6.1	8.0	3	4	p=0.407
	Moderate	0.0	4.0	0	2	
	Severe	0.0	2.0	0	1	
Chemosis	None	95.9	90.0	47	45	
	Mild	4.1	4.0	2	2	p=0.331
	Moderate	0.0	6.0	0	3	
Conjunctival hyperaemia	None	87.8	76.0	43	38	
	Mild	10.2	16.0	5	8	p=0.239
	Moderate	2.0	8.0	1	4	
Conjunctival discharge	None	100	96.0	49	48	
	Mild	0	4.0	0	2	p=0.495
Folliculo-papillary reaction	None	89.8*	68.0	44	34	
	Mild	10.2	28.0	5	14	*p=0.015
	Moderate	0.0	4.0	0	2	
Other	None	85.7	86.0	42	43	
	Mild	10.2	14.0	5	7	p=0.437
	Moderate	4.1	0.0	2	0	

ICMA N=49, C N=50

9.4 Visit 3 - 7±1 DAYS AFTER SURGERY

Seven days (±1) after surgery all patients were invited to complete the study follow-up. 47 eyes in the ICMA group and 46 eyes in the control group carried out the follow-up within the required dates and ended the study as planned in the protocol. Reasons for patients' early withdrawal was working agenda or long distance. Those patients had a posterior postoperative follow-up, but were excluded from the study for not fulfilling the protocol dates.

Visit 3. Best corrected visual acuity

At 1 week time after surgery, 7±1 days, BCVA was evaluated with Snellen test in all patients (n=47 eyes, ICMA //n=46 eyes, control). For the descriptive statistic analysis of the continuous variable of BCVA, the Mann-Whitney test was used.

The mean BCVA was 0.9±0.2 in both groups (decimal acuity), with lower BCVA 0.3 in the ICMA group versus 0.5 in the control group, and higher 1.0 in both groups. There were no significant differences between the two groups (p= 0.689).

Visit 3. Slit-lamp examination

One week after surgery, 47 eyes (100%) in the ICMA group had no epithelial alterations versus 42 eyes (91.3%) in the control group (n=46, control). Four eyes (8.7%) in the control group presented mild epithelial alterations at the end of the study follow-up time (Figure 19). For the descriptive statistic analysis of the categorical variable of epithelial alterations, the Fisher's Exact test was used. 7±1 days after surgery, there were observed no statistical differences between the two groups (p=0.056, Fisher's Exact test).

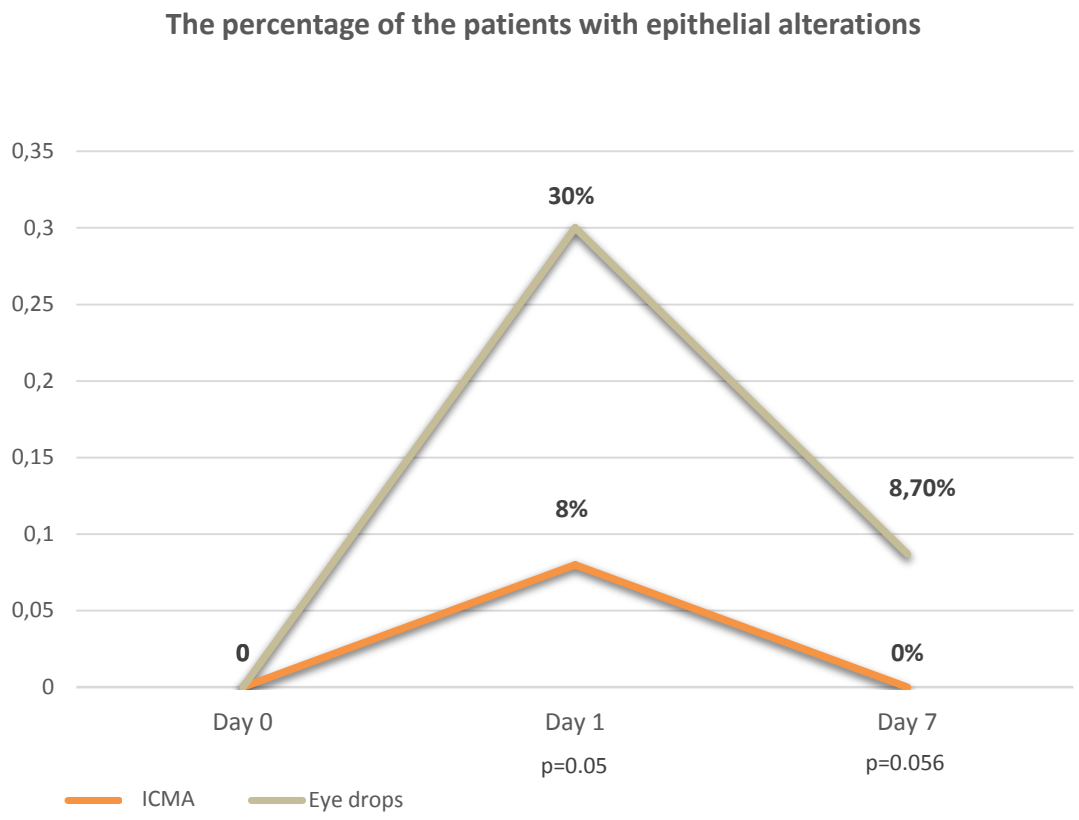


Figure 19. Epithelial alterations by slit-lamp examination

Visit 3. Hyperaemia assessment

One week after surgery, a total of 92 eyes were photo documented, 47 eyes in the ICMA group and 45 eyes in the control group. The hyperaemia assessment as per MacMonnies photographic scale was evaluated by the blind ophthalmologist reader. For the descriptive statistical analysis of this categorical variable, the Fisher's Exact test was used.

No hyperaemia (grade 0) was observed in 12 eyes (25.5%) in the ICMA group versus 9 (20%) eyes in the control group. Grade 1 was registered in 20 eyes (42.6%) versus 21 eyes (46.7%); grade 2 was present in 12 eyes (25.5%) versus 9 eyes (20%); grade 3 was observed in 2 eyes (4.3%) versus 6 eyes (13.3%); grade 4 was registered in one eye (2.1%) versus 0 eyes respectively (p=0.449, Fisher's Exact).

Visit 3. Corneal/conjunctival staining

Oxford staining schema

The CFS pattern was classified as per Oxford schema (grade 0, grade I, grade II, grade III, grade IV, grade V). For the descriptive statistic analysis of the continuous variable of the CFS, the Mann-Whitney test was used.

Seven days after surgery, the mean CFS score was 0.0±0.1 in both groups, with minimum grade 0 and maximum grade 1.0 in both groups. There were no significant differences between the two groups (p=0.975).

van Bijsterveld schema

The conjunctival LGS pattern was classified as per van Bijsterveld schema. For the descriptive statistic analysis of this continuous variable, the Mann-Whitney test was used.

The mean LGS was 0.2±0.4 in the ICMA group versus 0.2±0.5 in the control group, with minimum grade 0 in both groups and maximum grade 1 in the ICMA group and grade 2 in the control group. There were no significant differences between the two groups (p= 0.878).

Visit 3. Ocular symptoms/signs

Ocular symptoms

At visit 3, a week after surgery, patients were asked to judge their postoperative ocular discomfort regarding the following symptoms and specify the grade in each item: pain, irritation/burning/stinging, photophobia, foreign body sensation and other symptoms. These items were classified with scores from 0 to 3, with 0 having absent symptoms, 1 mild, 2 moderate and 3 severe. Patients' judgment over the symptoms were analysed with the Fisher's Exact test, for 47 eyes in the ICMA group and 46 eyes in the control group (Table 11). One week after surgery, 95.7% of the patients in the ICMA group versus 93.5% of the control group denied suffering any pain (p=0.615). Symptoms such as irritation, burning, stinging

were present in 8.5% in the ICMA group, versus 17.4% in the control group (p=0.482). Photophobia was mentioned by 25.6% in the ICMA group versus 37% in the control group (p=0.466). Foreign body sensation was experienced by 27.6% of the ICMA group versus 45.7% in the control group (p=0.090). A week after surgery, there were no statistically significant differences in the symptoms declared by the patients, between the groups.

Table 11. Ocular symptoms one week after surgery

Ocular symptoms						
Day 7 after surgery		**Percentage of patients (%)**		**Number of patients**		
		ICMA	**C**	**ICMA**	**C**	
Pain	Absent	95.7	93.5	45	43	
	Mild	2.1	2.2	1	1	p=0.615
	Moderate	0.0	4.3	0	2	
	Severe	2.1	0.0	1	0	
Irritation/burning/ stinging	Absent	91.5	82.6	43	38	
	Mild	6.4	10.9	3	5	p=0.482
	Moderate	2.1	4.3	1	2	
	Severe	0.0	2.2	0	1	
Photophobia	Absent	74.5	63.0	35	29	
	Mild	21.3	28.3	10	13	P=0.466
	Moderate	4.3	8.7	2	4	
	Severe	0.0	0.0	0	0	
Foreign body sensation	Absent	72.3	54.3	34	25	
	Mild	25.5	34.8	12	16	p=0.090
	Moderate	0.0	8.7	0	4	
	Severe	2.1	2.2	1	1	
Other	Absent	93.5	89.1	43	41	
	Mild	4.3	8.7	2	4	p=0.837
	Moderate	0.0	0.0	0	0	
	Severe	2.2	2.2	1	1	

ICMA (N=47), C= control (N=46)

Ocular signs

At one week time, visit 3, we evaluated the following ocular objective signs and classified each one of them from 0 to 3, with 0 absent signs, 1 mild, 2 moderate

and 3 severe signs. Our assessment was about palpebral edema, chemosis, conjunctival hyperaemia, conjunctival discharge, conjunctival folliculo-papillary reaction and other objective signs. Our assessments over the ocular signs were analysed with the Fisher's Exact test, for 47 eyes in the ICMA group and 46 eyes in the control group (Table 12). One week after surgery, 2.1% of the patients in the ICMA group versus 2.2% in the control group presented palpebral edema (p>0.999). Chemosis suffered 2.1% of the ICMA group and none of the control group (p>0.999). Conjunctival hyperaemia was observed in 19.1% of the ICMA group versus 26.1% in the control group (p=0.072). Conjunctival discharge was absent in 100% of the cases in both groups. Conjunctival folliculo-papillary reaction was reported in 8.5% in the ICMA group versus 17.4% in the control group (p=0.266). There were no statistically significant differences in the ocular signs observed between the groups at 1 week after surgery.

Table 12. Ocular signs one week after surgery

Ocular signs						
Day 7 after surgery		**Percentage of patients (%)**		**Number of patients**		
		ICMA	**C**	**ICMA**	**C**	
Palpebral edema	None	97.9	97.8	46	45	
	Mild	2.1	2.2	1	1	p>0.999
	Moderate	0.0	0.0	0	0	
	Severe	0.0	0.0	0	0	
Chemosis	None	97.9	100.0	46	46	
	Mild	2.1	0.0	1	0	p>0.999
	Moderate	0.0	0.0	0	0	
Conjunctival hyperaemia	None	80.9	73.9	38	34	
	Mild	19.1	15.2	9	7	p=0.072
	Moderate	0.0	10.9	0	5	
Conjunctival discharge	None	100.0	100.0	47	46	—
	Mild	0.0	0.0	0	0	
Folliculo-papillary reaction	None	91.5	82.6	43	38	
	Mild	8.5	10.9	4	5	p=0.266
	Moderate	0.0	6.5	0	3	
Other	None	97.9	91.3	46	42	
	Mild	2.1	8.7	1	4	p=0.203
	Moderate					

ICMA (N=47), C= control (N=46)

Visit 3. Intraocular pressure

During the postoperative visit one week after surgery, all patients were examined and IOP was evaluated by applanation tonometry. The mean IOP was 9.5±3.1 in the ICMA group versus 9.6±2.5 in the control group, with lower 4.0mmHg versus 5.0mmHg and higher 18.0mmHg versus 17.0mmHg respectively (p=0.679, Mann-Whitney test).

Visit 3. Intraocular Surface Disease Index (OSDI)

The mean OSDI total score, 7 days after surgery, was 8.8±8.7 in the ICMA group (n=47 eyes) and 11.9±14.4 in the control group (n=46 eyes). There were no statistical differences between the 2 groups (p=0.231, Mann-Whitney test).

The OSDI total score was calculated as follows:

$$OSDI\ Total\ score = D \times 25 / E$$

D= sum of scores for all questions answered

E= total number of questions answered

There were 3 OSDI subscales in the questionnaire, interpreted as: a) ocular symptoms for answers 1 to 5 (A score), b) vision-related function for answer 6 to 9 (B score) and c) environmental triggers for answer 10 to 12 (C score). For the descriptive statistic analysis of the OSDI subscales Mann-Whitney test was used.

The mean OSDI A score (ocular symptoms) was 2.0±1.9 in the ICMA group versus 2.7±3.3 in the control group, with minimum 0.0 in both groups and maximum 7.0 in the ICMA group versus 19.0 in the control group (p=0.250). The mean OSDI B score (vision-related function) was 1.1±1.4 in the ICMA group and 1.6±2.8 in the control group, with minimum 0.0 in both groups and maximum 7.0 in the ICMA versus 15.0 in the control group (p=0.610). The mean OSDI C score (environmental triggers) was 0.9±1.7 in the ICMA group versus 1.1±2.1 in the control group, with minimum 0.0 and maximum 9.0 in both groups (p=0.815). There were no statistical differences between the groups in the OSDI subscales (Mann-Whitney test).

9.5 SAFETY AND EFFICACY EVALUATION

9.5.1 Primary objective

The primary objective of the study was to evaluate the effects of ICMA (after oxybuprocain chlorhydrate 0.4% + tetracaine chlorhydrate 0.1% eye-drop instillation) and the standard mydriatic-anaesthetic eye drop protocol (tropicamide 1%, phenylephrine 10%, oxybuprocain chlorhydrate 0.4% +tetracaine chlorhydrate 0.1%) on ocular surface. Statistical analyses were performed in safety population (N=50) to evaluate primary endpoint.

9.5.1.1 Corneal and conjunctival staining

Corneal and conjunctival staining were assessed by Oxford and van Bijsterveld schemas respectively. The descriptive analysis of the corneal and conjunctival surface staining were performed in every case, in the screening visit (V0), just after surgery (V1), the first postoperative day visit (V2) and 7 days after surgery (V3). There were observed no statistical differences in the staining values according to the Oxford and van Bijsterveld schemas between ICMA and control group in any visit (Table 13).

Changes in staining were defined as initial value minus final value. If the calculation was positive, the change was favourable. The Mann-Whitney test was used for the comparison of changes in corneal/conjunctival staining between groups.

Table 11. Corneal/conjunctival staining values across visits. Comparison between groups

	Visit 0 (V0)			Visit 1 (V1)			Visit 2 (V2)			Visit 3 (V3)		
	Mean±SD	N	*p*	Mean±SD	N	*p*	Mean±SD	N	p	Mean±SD	N	*p*
Oxford Schema												
ICMA	0.0±0.0	49	-	1.3±0.7	45	0.118	0.2±0.4	48	0.626	0.0±0.1	47	0.975
Control	0.0±0.0	49		1.4±0.7	45		0.3±0.5	50		0.0±0.1	45	
Van Bijsterveld schema												
ICMA	0.2±0.4	49	0.299	0.7±0.7	45	0.475	0.3±0.5	48	0.493	0.2±0.4	47	0.878
Control	0.1±0.4	49		0.6±0.7	45		0.4±0.6	50		0.2±0.5	45	

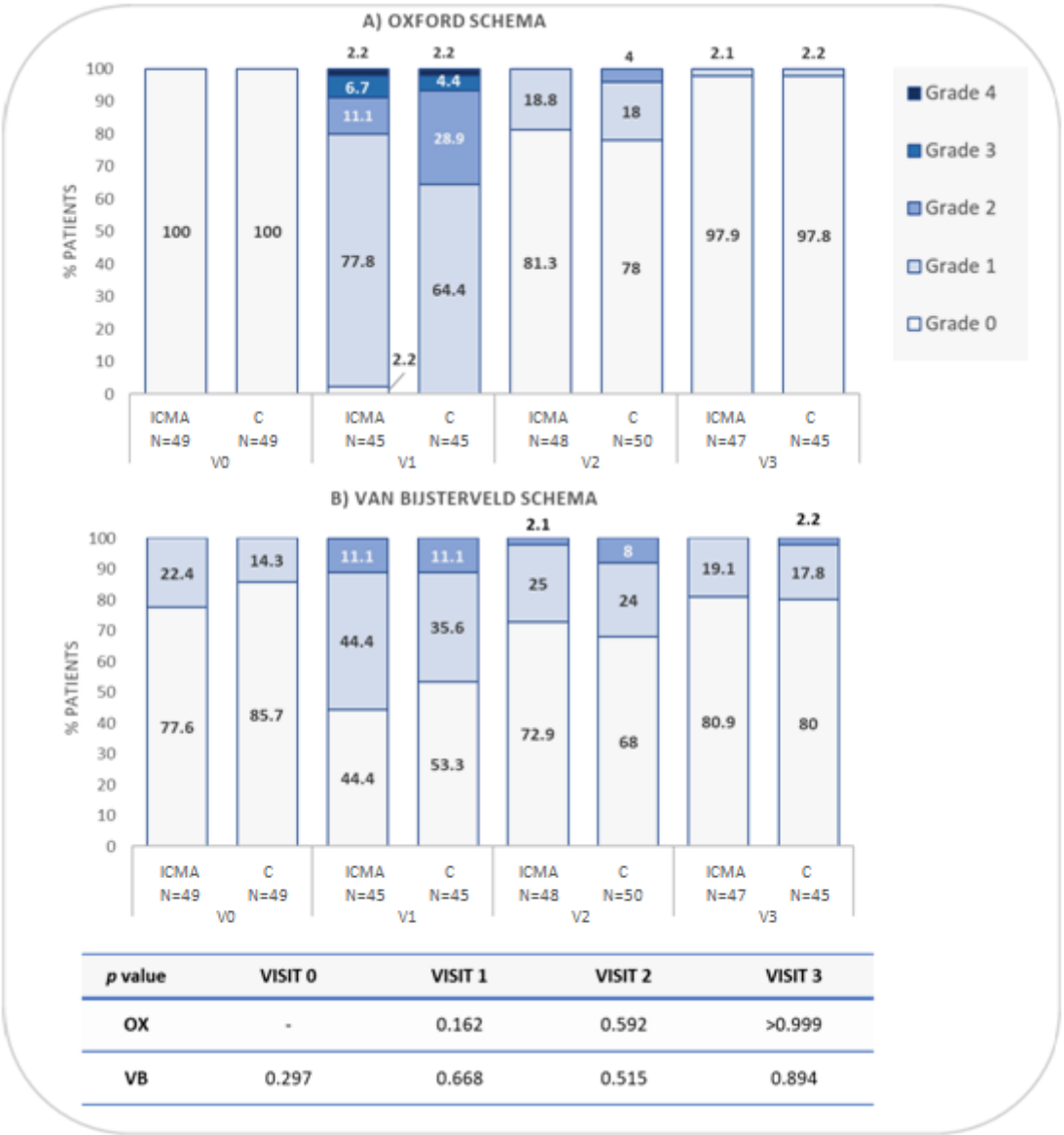
The grade of damage in ocular surface (severity increases from grade 0 to grade 5) according Oxford and Van Bijsterveld schemas was compared between ICMA and control group.

Corneal fluorescein staining (CFS) test was used to evaluate corneal damage in all 50 patients undergoing cataract surgery in both eyes, receiving treatment with ICMA in one eye and the standard mydriatic and anaesthetic eye drops in the fellow eye. Before surgery, CFS grade 0 was noted in all cases. Immediately after surgery, 97.8% of the ICMA group and 100% of the control group suffered some grade of CFS, mostly grade 1 (77.8% and 64.4% respectively) and the rest of the patients presented grade 2 to 4 (p=0.162). 12-36 hours after surgery, 18.8% of the ICMA treated patients presented CFS grade 1, while 22% of the control group presented CFS grade 1 and 2 (p=0.592). At one week after surgery, 2.1% of the ICMA and 2.2% of the control group presented CFS grade 1 respectively (p>0.999). The comparison of grades of damage experimented between groups was not statistically significant (Figure 20A).

To evaluate the conjunctival damage we used lissamine green staining (LGS) test. Before surgery, 22.4% of the ICMA group and 14.3% of the control group presented LGS grade 1 (p=0.297). Immediately after surgery, 55.5% of the ICMA group and 46.7% of the control group presented LGS, mainly grade 1 (44.4% and 35.6% respectively) and fewer patients grade 2 (11.1% in both groups), (p=0.668). At the visit 2, 12-36 hours after surgery, 27.1% of ICMA group and 32% of the control group presented LGS grade 1 and 2 (p=0.515). One week after surgery,

19.1% of the ICMA group presented LGS grade 1 and 20% of the control group presented LGS grade 1 and 2 (p=0.894). The comparison of grades of damage experimented in patients treated with ICMA and control product was not statistically significant (Figure 20B).

Figure 20. Comparison of ocular surface damage between groups.



p value	VISIT 0	VISIT 1	VISIT 2	VISIT 3
OX	-	0.162	0.592	>0.999
VB	0.297	0.668	0.515	0.894

ICMA= intracameral mydriatics-anaesthetic, C= control, OX= Oxford Schema
VB= van Bijsterveld Schema, N=number of patients, V=Visit.

Furthermore, corneal and conjunctival staining changes from screening visit (V0) to the rest of the visits (V1, V2 and V3) were recorded in both groups and

compared, showing no significant differences for any of the paired analysis (Tables 14, 15 & 16),(Figures 21 & 22).

Table 12. Comparison of corneal/conjunctival staining changes (visit 0 to visit 1) between groups

Mean change V0 vs. V1	mean±SD	*p* value
Oxford schema		
ICMA	-1.3±0.7	0.169
Control	-1.4±0.7	
Van Bijsterveld schema		
ICMA	-0.4±0.6	0.845
Control	-0.4±0.6	

ICMA, Control (N=44)

Table 13. Comparison of corneal/conjunctival staining changes (visit 0 to visit 2) between groups

Mean change V0 vs. V2	mean±SD	*p* value
Oxford schema		
ICMA	-0.2±0.4	0.455
Control	-0.3±0.5	
Van Bijsterveld schema		
ICMA	-0.1±0.6	0.130
Control	-0.3±0.6	

ICMA (N=47), control (N=49)

Table 14. Comparison of corneal/conjunctival staining changes (visit 0 to visit 3) between groups

Mean change V0 vs. V3	mean±SD	*p* value
Oxford schema		
ICMA	0.0±0.1	0.975
Control	0.0±0.2	
Van Bijsterveld schema		
ICMA	0.0±0.6	0.350
Control	-0.1±0.6	

ICMA (N=46), control (N=44)

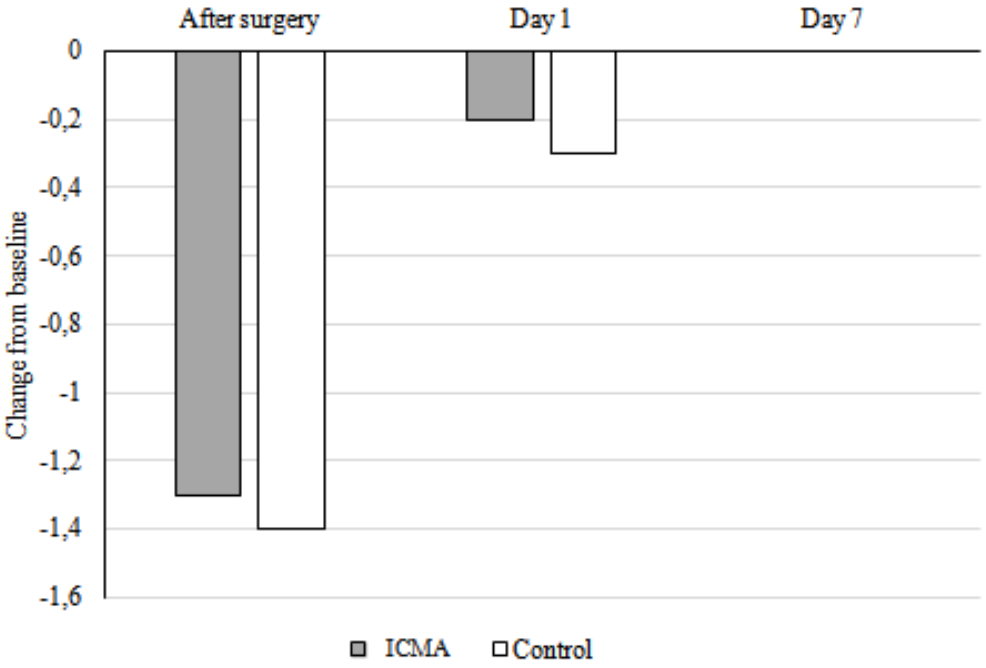


Figure 21. Changes from baseline (V0) in corneal surface staining measured as per the Oxford schema (corneal fluorescein staining)

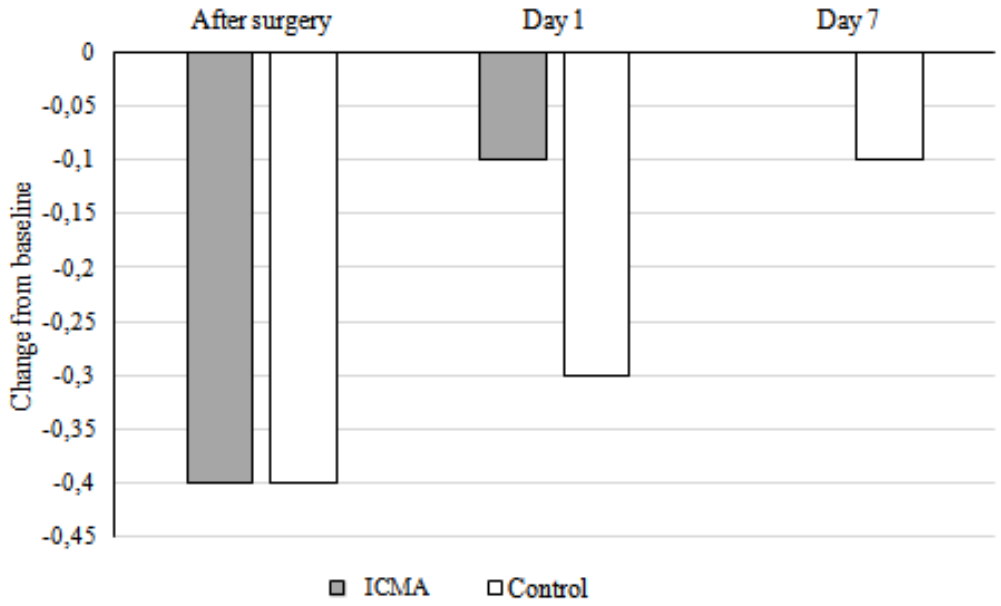


Figure 22. Changes from baseline (V0) in conjunctival surface staining measured as per the van Bijsterveld schema (lissamine green staining)

9.5.2 SECONDARY OBJECTIVES

➢ Secondary objective No.1

9.5.2.1 Best-corrected visual acuity

To assess changes in best corrected visual acuity recovery (visit 0 versus visit 3). Change was defined as final value minus initial value. If the calculation resulted positive, the change was recorded as favourable.

The descriptive analysis of changes in best corrected visual acuity was performed in the safety population. The Snellen chart was used to assess best corrected visual acuity in both groups. The optometrists scored the level of vision acuity achieved with glasses in the decimal scale (Snellen optotype) and data were collected at visit 0, visit 2 and visit 3. To interpret the results, decimal acuity was transformed in logMAR decimal scale (Table 17). The algorithm applied for the transformation was logMAR = log10(1/quotient).

Table 15. BCVA (Snellen test results) across visits

	V0			V2			V3		
	Mean±SD	**N**	***p***	**Mean±SD**	**N**	***p***	**Mean±SD**	**N**	***p***
LogMAR									
ICMA	0.1±0.1	50	0.969	0.1±0.2	50	0.270	0.1±0.1	47	0.689
Control	0.1±0.2	50		0.1±0.1	50		0.1±0.1	46	
Decimal									
ICMA	0.8±0.2	50	0.969	0.8±0.2	50	0.270	0.9±0.2	47	0.689
Control	0.8±0.2	50		0.8±0.2	50		0.9±0.2	46	

Paired analyses were performed to evaluate changes between visit 0 to visit 2 (Table 18), visit 0 to visit 3 (Table 19) and visit 2 to visit 3 (Table 20) in each group, using the Mann-Whitney test. The comparative analysis performed between groups, did not show any significant differences in the score change.

Table 16. Changes in Snellen test results from V0 to V2: comparison between groups.

V0 to V2	Mean change	*p* value
LogMAR		
ICMA	0.0±0.2	0.552
Control	0.0±0.2	
Decimal		
ICMA	0.0±0.2	0.510
Control	0.0±0.3	

ICMA, Control: N=50

Table 17. Changes in Snellen test results from V0 to V3: comparison between groups.

V0 to V3	Mean change	*p* value
LogMAR		
ICMA	0.0±0.1	0.823
Control	0.0±0.2	
Decimal		
ICMA	-0.1±0.2	0.766
Control	-0.1±0.2	

ICMA, N=47; control, N=46

Table 8. Changes in Snellen test results from V2 to V3: comparison between groups.

V2 to V3	Mean change	*p* value
LogMAR		
ICMA	0.0±0.1	0.508
Control	0.0±0.1	
Decimal		
ICMA	-0.1±0.2	0.508
Control	-0.1±0.1	

ICMA, N=47; Control, N=46

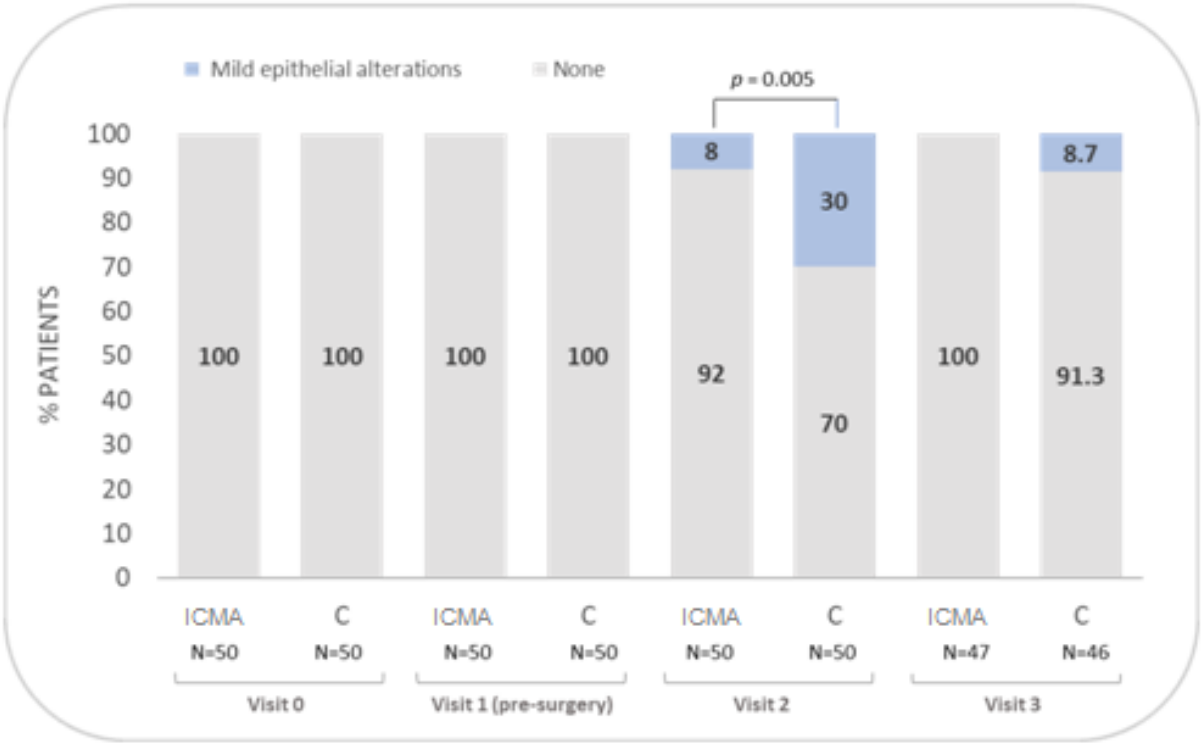
➢ Secondary objective No.2

9.5.2.2 Epithelial alterations

Epithelial alterations were evaluated by slit-lamp examination in the safety population (global population), and they were clinically classified as none, mild or significant. In visit 2, 12-36 hours after surgery, as shown in Figure 23, the paired analysis between groups demonstrates a statistically significant difference in epithelial alteration between ICMA and control (p=0.005, Chi-squared test). Only 8% of patients showed mild epithelial alterations when treated with ICMA in contrast to 30% of patients in the control group.

In visit 3, 7±1 days after surgery, no ICMA treated patient presented epithelial alterations, while some patients of the control group experienced persisting epithelial alterations, that went further than the end of the study follow-up time. This percentage of patients (8.7%) was not considered of statistical significance, but it was of clinical importance according to physician criteria (p=0.056).

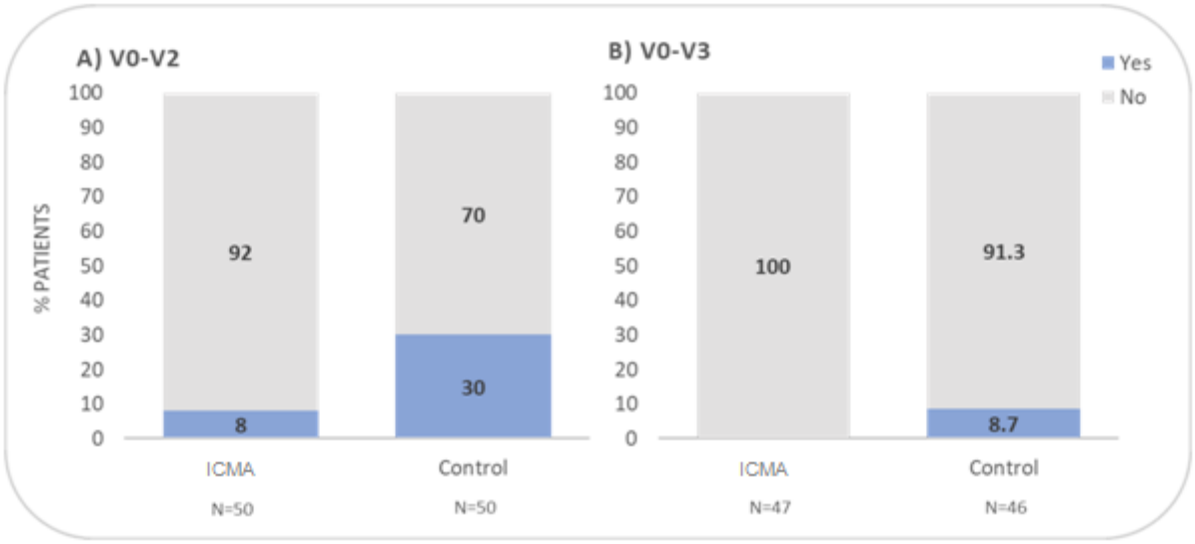
Figure 23. Differences in epithelial alterations between groups



ICMA: intracameral combination of mydriatics & anaesthetic, C: control

Changes in epithelial alterations between screening visit (V0) and postoperative visits 2 and 3 (V2, V3) were analysed. Patients in control group experienced significantly more changes between visit 0 and visit 2 than those randomized to ICMA group (p=0.005, Chi-squared), (Figure 24A). ICMA treated patients experienced a faster recovery of the corneal epithelium. However, the differences between visit 0 and visit 3 were not statistically significant (p=0.056, Fisher's Exact test), (Figure 24B).

Figure 24. Percentage of patients experiencing changes in epithelial alterations between visits.



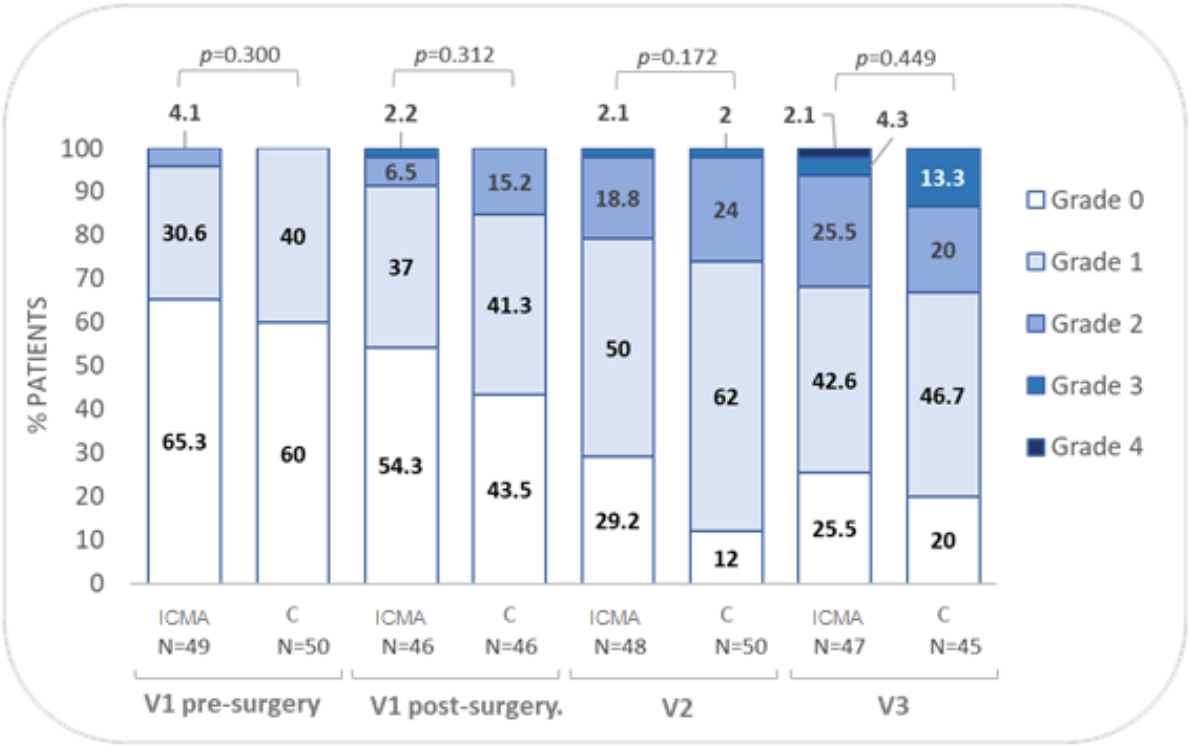
➢ Secondary objective No.3

9.5.2.3 Conjunctival hyperaemia

Conjunctival hyperaemia was evaluated using the MacMonnies photographic scale, and data were collected before and immediately after surgery (visit 1), 12-36h (visit 2) and one week after surgery (visit 3). The analysis was performed to the safety population. Change was defined as initial value minus final value. If the calculation was positive, the change was favourable. The grades of hyperaemia were compared between ICMA and control group, without statistically significant differences (Figure 25). The mean change in hyperaemia between visits were compared in paired analysis: the mean change in data collected at visit 1 (pre-surgery) was compared with visit 1 (post-surgery), visit 2

and visit 3. No statistically significant differences were described (Mann-Whitney test) (Table 21).

Figure 25. Comparison of grades of hyperaemia between groups



ICMA=: intracameral mydriatics and anaesthetic; C= control; V1= visit 1; V2= visit 2; V3= visit 3

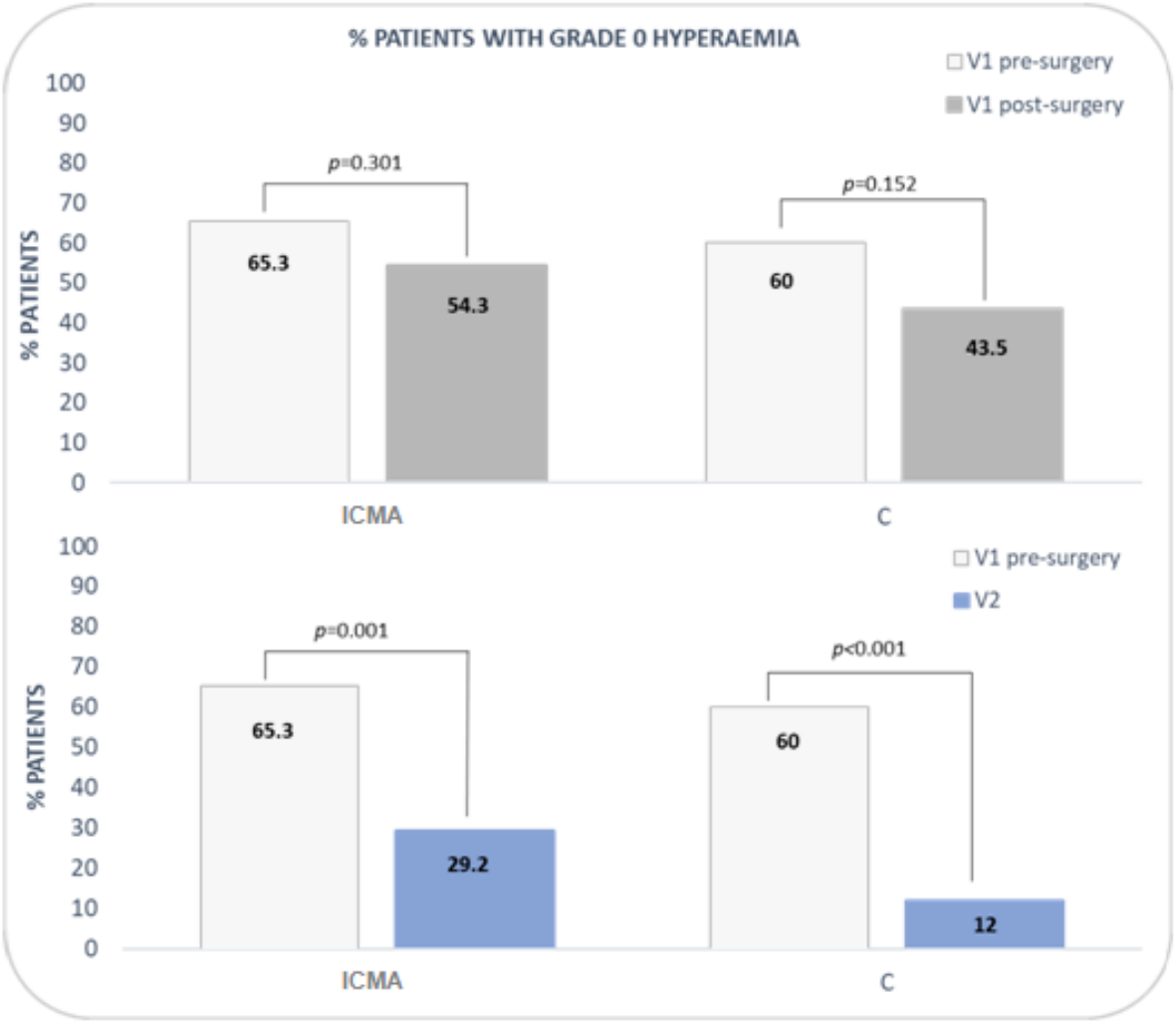
Table 21. Comparison of conjunctival hyperaemia between visits

	Number of patients (N)	Mean change	*p* value
V1 (pre-surgery) to V1 (post-surgery)			
ICMA	45	-0.2±0.9	0.454
Control	46	-0.3±0.8	
V1 (pre-surgery) to V2			
ICMA	47	-0.5±0.7	0.102
Control	50	-0.8±0.7	
V1 (pre-surgery) to V3			
ICMA	46	-0.8±0.9	0.732
Control	45	-0.9±0.9	

V1= visit 1; V2= visit 2; V3= visit 3

The percentage of patients presenting grade 0 hyperaemia before and after surgery were compared in paired analysis, as shown in Figure 26. There was no difference between pre-surgery and immediately after surgery hyperaemia (visit 1). 65.3% of the patients in the ICMA group presented grade 0 hyperaemia before surgery and 54.3% of them after surgery (p=0.301). 60% of the patients in the control group presented grade 0 hyperaemia before surgery and 43.5% after surgery (p=0.152). However, when comparing the percentage of patients experiencing grade 0 hyperaemia in visit 1 pre-surgery compared to visit 2, the differences were statistically significant in both groups; ICMA, 65.3% versus 29,2% (p=0.001) and control, 60% versus 12% (p<0.001), respectively.

Figure26. Comparison of percentage of patients with grade 0 hyperaemia between visits



ICMA= intracameral mydriatics and anaesthetic group; C= Control group.

➢ Secondary objective No.4

9.5.2.4 Intraocular pressure

Intraocular pressure was measured by applanation tonometry in both ICMA and control group for visit 0 and visit 3 (Table 22). The analysis was performed to the safety population (global population). Change was defined as initial value minus final value. If the calculation was positive, the change was favourable. Differences between groups were not significant in any of the visits.

Table 9. Differences in intraocular pressure across visits

IOP	Number of patients	Mean ± SD	*p* value
Visit 0 (screening)			
ICMA	50	14.5±3.1	0.415
Control	50	15.0±3.2	
Visit 3			
ICMA	47	9.5±3.1	0.679
Control	45	9.6±2.5	

The change in intraocular pressure between visits V0 to V3 was compared in both groups. The mean change from V0 to V3 in ICMA group (5.1±3.0) and control group (5.7±3.1) were compared in paired analysis and the differences were not significant (p=0.382, T-test).

➢ Secondary objective No.5

9.5.2.5 Objective scatter index (OSI)

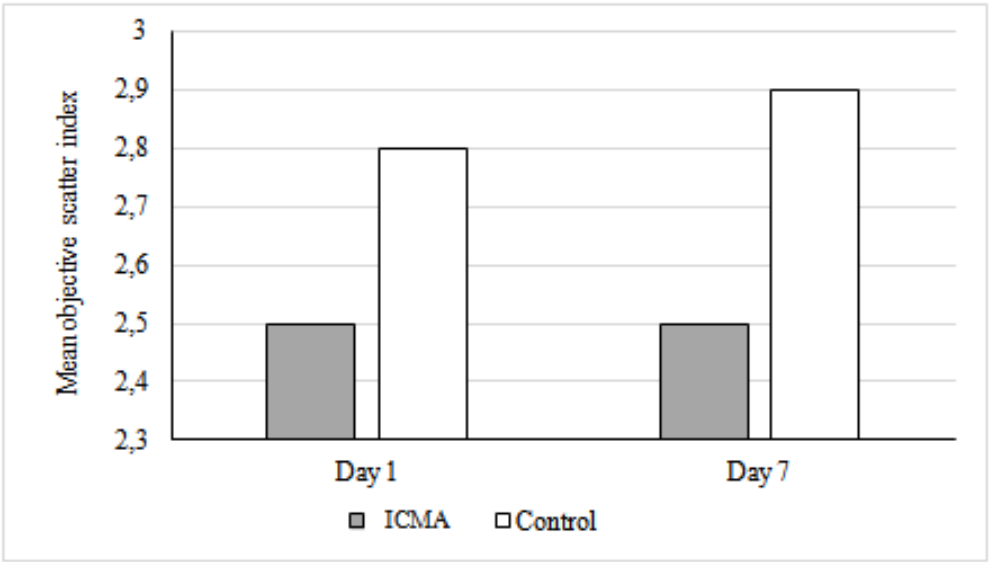
OSI, obtained from the double-pass point-spread function (PSF) image (OQAS, HD Analyzer™, Visiometrics, Spain), was measured at visit 2 and 3, aiming to perform an objective evaluation of optical vision quality. OSI results were compared between ICMA and control group in each visit (V2 and V3), and the changes from V2 to V3 were also compared between groups. This analysis was effectuated in the safety population. For the descriptive and comparative analysis of OSI, the Mann-Whitney test was used. Although, none of the comparison

performed showed statistically significant differences (Table 23), lower intraocular scattering in ICMA group (Figure 27) involved clinically better optical quality (Figure 28).

Table 23. OSI values in both treatment groups.

OSI	Number of patients	Mean ± SD	*p* value
Visit 2 (V2)			
ICMA	46	2.5±1.5	0.273
Control	47	2.8±1.5	
Visit 3 (V3)			
ICMA	45	2.5±1.5	0.237
Control	44	2.9±1.5	
Change V2 to V3			
ICMA	46	0.0±1.8	0.668
Control	45	0.0±1.6	

Figure 27. Point spread function (PSF) assessed by the Objective Scatter Index



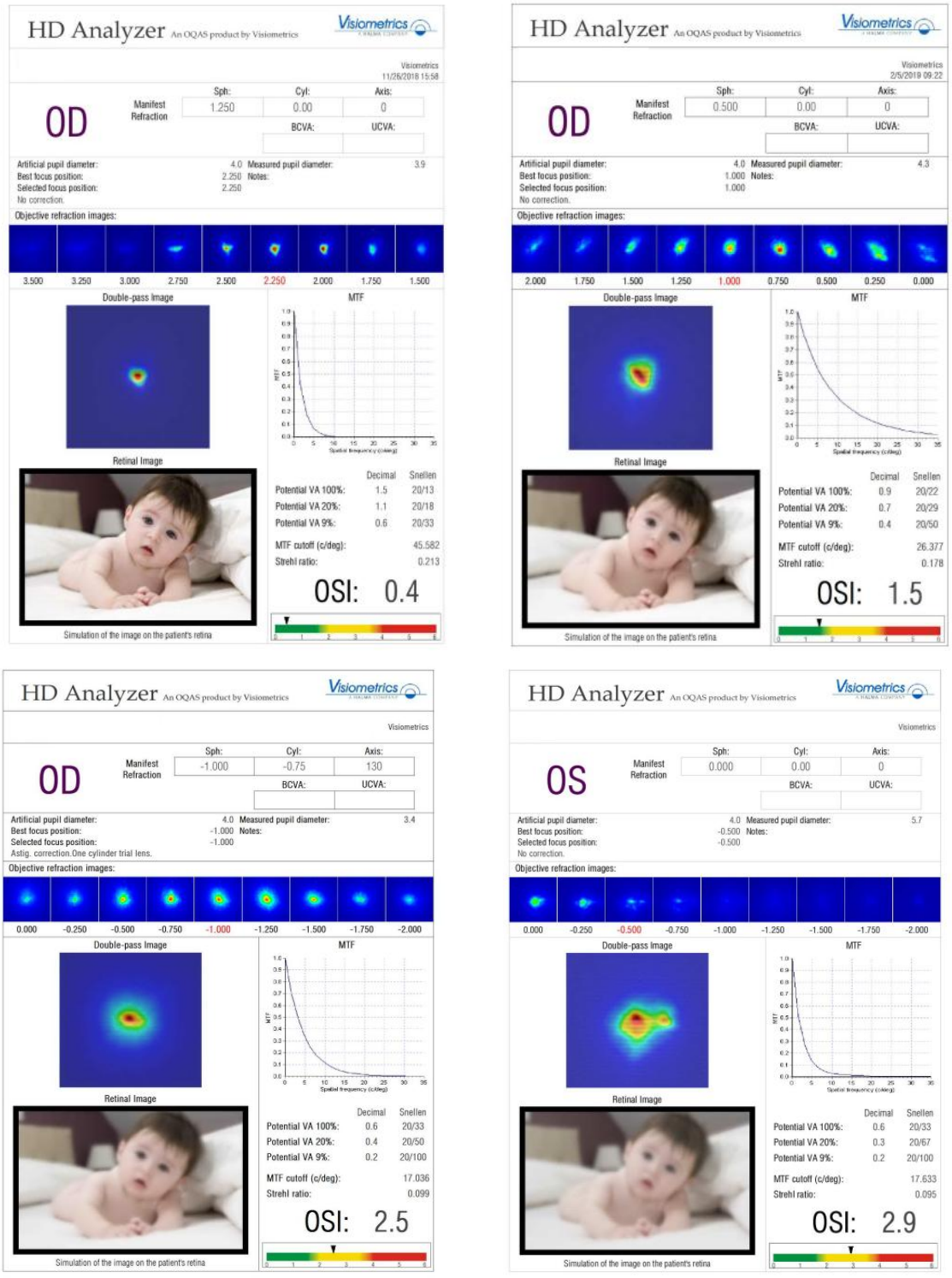


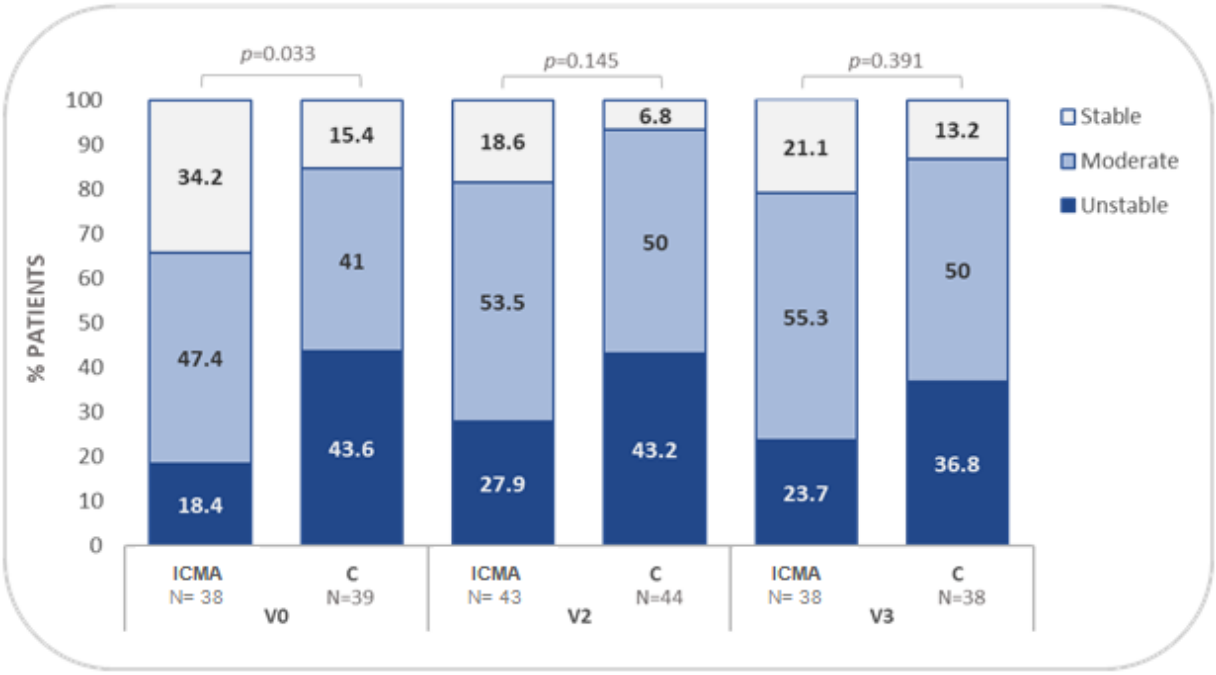
Figure 28. Images of OSI, where intraocular scatter of 0.4 (normal value), 1.5, 2.5 and 2.9 are observed. The difference in the retinal image can be identified as a simulation of the image on the patients' retina is demonstrated by OQAS HD Analyzer. Clinically, there is slightly better visual quality in OSI of 2.5 versus 2.9.

➢ Secondary objective No.6

9.5.2.6 Vision break-up time (VBUT)

Tear film vision break-up time (VBUT) was measured with the Optical Quality Analysis System (OQAS, HD Analyzer™). The VBUT was estimated as the time elapsed in seconds from 0 seconds to the time at which the subject's vision quality index dropped below a defined threshold. The VBUT was classified in a three value score: stable, moderately stable (moderate) and unstable. The VBUT was measured before surgery (visit 0), one day after surgery (visit 2) and one week after surgery (visit 3). The statistical analysis was performed in the global population. For the descriptive and comparative analysis of the VBUT, the Chi-squared and the Mann-Whitney test were used respectively. The percentage of patients graded as presenting stable, moderate or unstable VBUT in ICMA and control group were compared for each visit, showing statistically differences at visit 0 (V0). At the screening visit, stable VBUT was present in 34.2% of the cases in ICMA group versus 15.4% in control group; moderately stable VBUT was present in 47.4% of the cases versus 41.0% and unstable 18.4% versus 43.6% respectively (p=0.033). Measurements of VBUT were taken in 38 eyes in ICMA group and 39 eyes in control group. The first postoperative day, stable VBUT was observed in 18.6% of the ICMA versus 6.8% of the control group; moderately stable VBUT was observed in 53.5% versus 50.0% and unstable in 27.9% versus 43.2% respectively (p=0.145). Measurements were taken in 43 eyes of the ICMA group and 44 eyes of the control group. One week after surgery, at visit 3, stable VBUT was registered in 21.1% of the ICMA versus 13.2% of the control group; moderately stable was observed 55.3% versus 50.0% and unstable VBUT in 23.7% versus 36.8% respectively (p=0.391). Measurements were taken in 38 eyes in each group (Figure 29). Changes between visits were evaluated and compared in paired analysis (Table 24). The differences in VBUT between groups in each visit and changes observed between visits demonstrated no statistical significance.

Figure 29. Tear film vision break-up time across visits



ICMA=intracameral mydriatics and anaesthetic, C= Control, V=Visit

Table 24. Changes in tear film vision break-up time between visits.

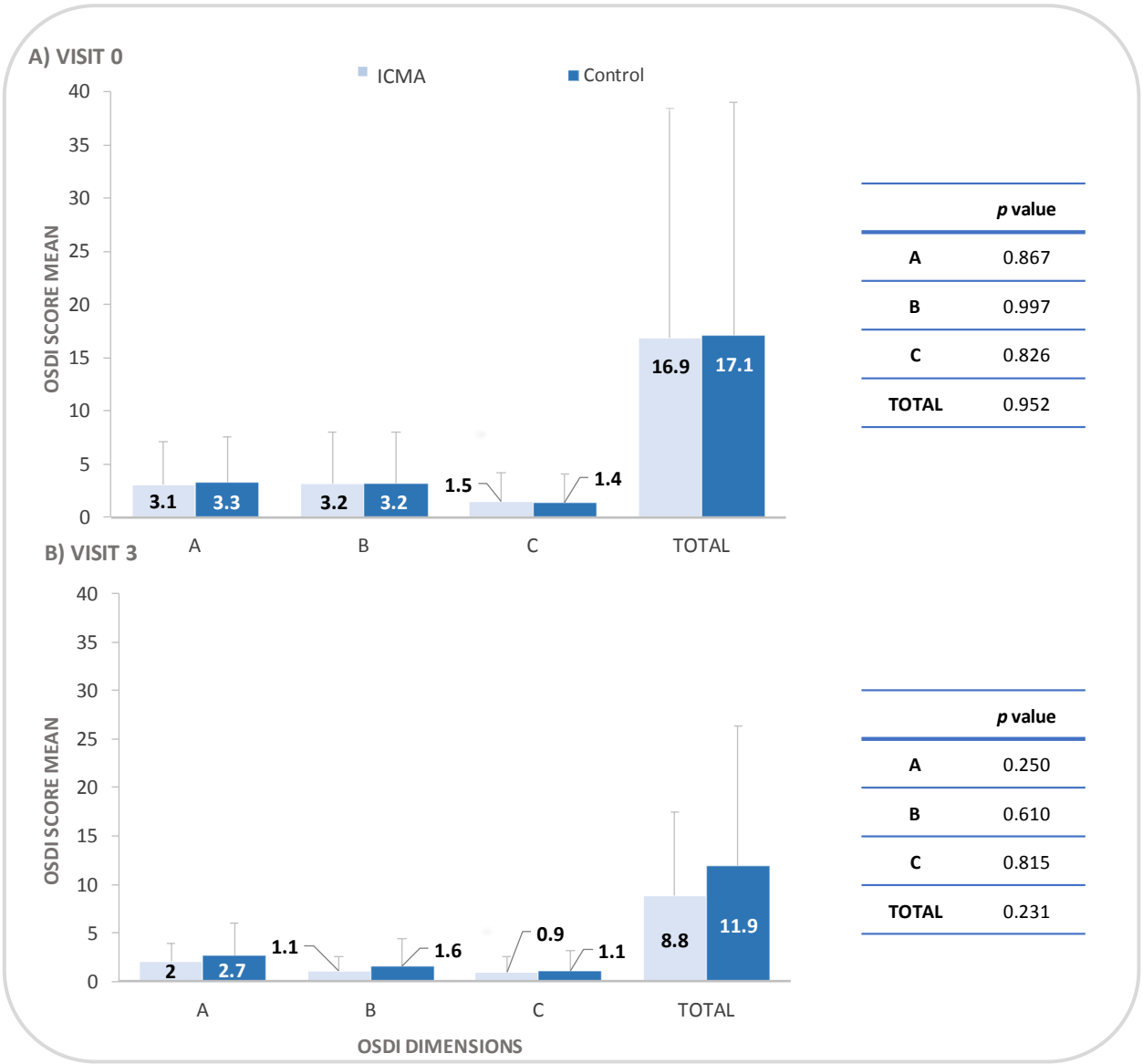
	Number of patients	Mean change	*p* value
Visit 0 to Visit 2 (V0-V2)			
ICMA	34	0.2±1.2	0.864
Control	35	0.1±0.8	
Visit 0 to Visit 3 (V0-V3)			
ICMA	31	0.2±1.1	0.618
Control	31	0.1±0.8	
Visit 2 to Visit 3 (V2-V3)			
ICMA	32	-0.1±0.8	0.944
Control	34	-0.1±0.7	

➢ Secondary objective No.7

9.5.2.7 Ocular Surface Disease Index (OSDI)

OSDI questionnaire was completed by patients in ICMA and control group, in visit 0 and visit 3. Results of A, B, C dimensions and total scores were compared between groups in each visit, and no statistically significant differences were found (Figure 30A & 30B). The analysis was performed in the safety population using the Mann-Whitney test. The change was defined as initial value minus last value. If the calculation was positive, the change was favourable.

Figure 30. OSDI questionnaire scores in V0 and V3



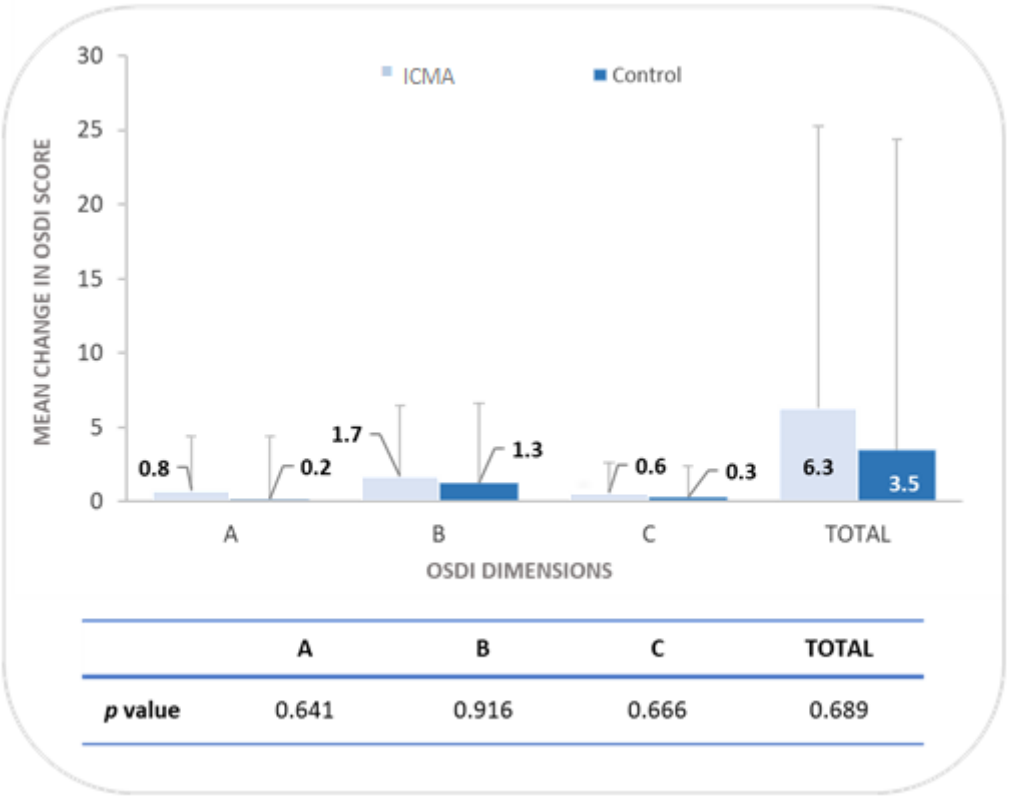
	p value
A	0.867
B	0.997
C	0.826
TOTAL	0.952

	p value
A	0.250
B	0.610
C	0.815
TOTAL	0.231

V0: N=50 patients in both groups. V3: ICMA: N=47 , Control: N=46

The mean OSDI change between visit 0 and visit 3 was evaluated in both treatment groups, demonstrating a lower change in control group, nonetheless it was not statistically significant. The mean change in OSDI total score from visit 0 to visit 3 was 6.3±19.0 in ICMA group and 3.5±20.9 in the control group (p=0.689). The mean change OSDI A score (ocular symptoms) was 0.8±3.6 in the ICMA group versus 0.2±4.2 in the control group (p=0.641). The mean change OSDI B score (vision-related function) was 1.7±4.8 in the ICMA group versus 1.3±5.3 in the control group (p=0.916) and the mean change OSDI C score (environmental triggers) was 0.6±2.0 in the ICMA group versus 0.3±2.1 in the control group (p=0.666) (Figure 31). For the analysis of the changes in OSDI total score and subscales the Mann-Whitney test was used.

Figure 31. Mean change in OSDI score from V0 to V3



	A	B	C	TOTAL
p value	0.641	0.916	0.666	0.689

ICMA group, N=47; Control group, N=46

➢ Secondary objective No.8

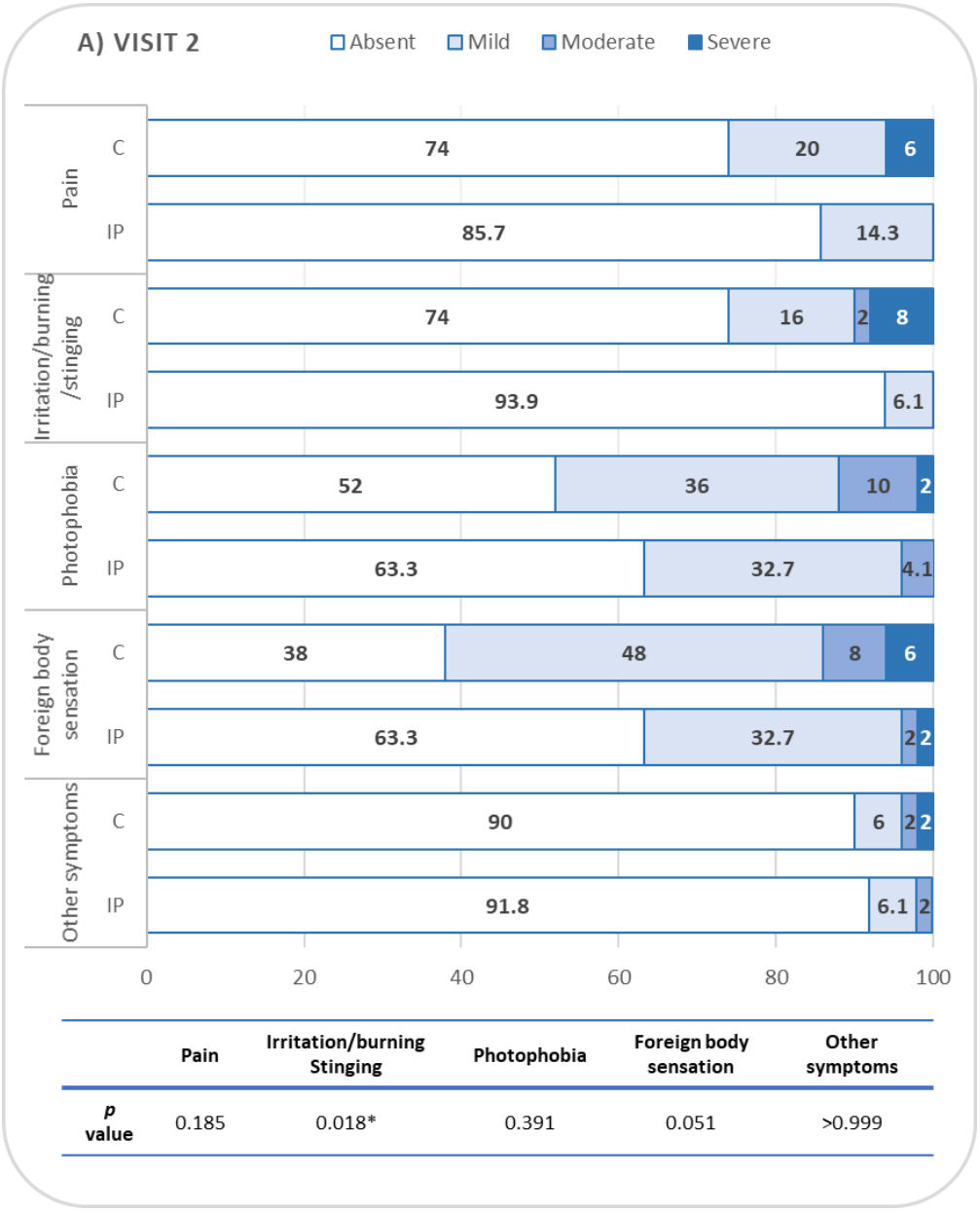
9.5.2.8 Ocular symptoms/signs

Ocular symptoms were measured at visit 2 and visit 3 after surgery and classified by severity (absent, mild, moderate or severe). The presence of symptoms and their severity were compared between groups (Figure 32A and 32B). This analysis was carried out in the global population.

At visit 2, evaluation of "irritation/burning/stinging" demonstrated a significant difference between patients treated with ICMA (6.1%) and patients in control group (26%) (p=0.018). Foreign body sensation was experienced in 62% of the patients in the control group versus 36.7% of the ICMA group, although the trend was not of statistical significance (p=0.051). Symptoms such as pain, photophobia and other declared by the patients, did not demonstrate statistically significant differences between the groups (Figure 32A).

At visit 3, high percentage of patients were asymptomatics. 95.7% of the ICMA versus 93.5% of the control group denied suffering any pain. Symptoms such as irritation/burning/stinging were present in 8.5% of the ICMA group, versus 17.4% of the control group and foreign body sensation was experienced by 27.6% of the ICMA versus 45.7% of the control group. None of the symptoms described were present in a proportion great enough to consider it significantly different in the comparison of treatment groups (Figure 32B).

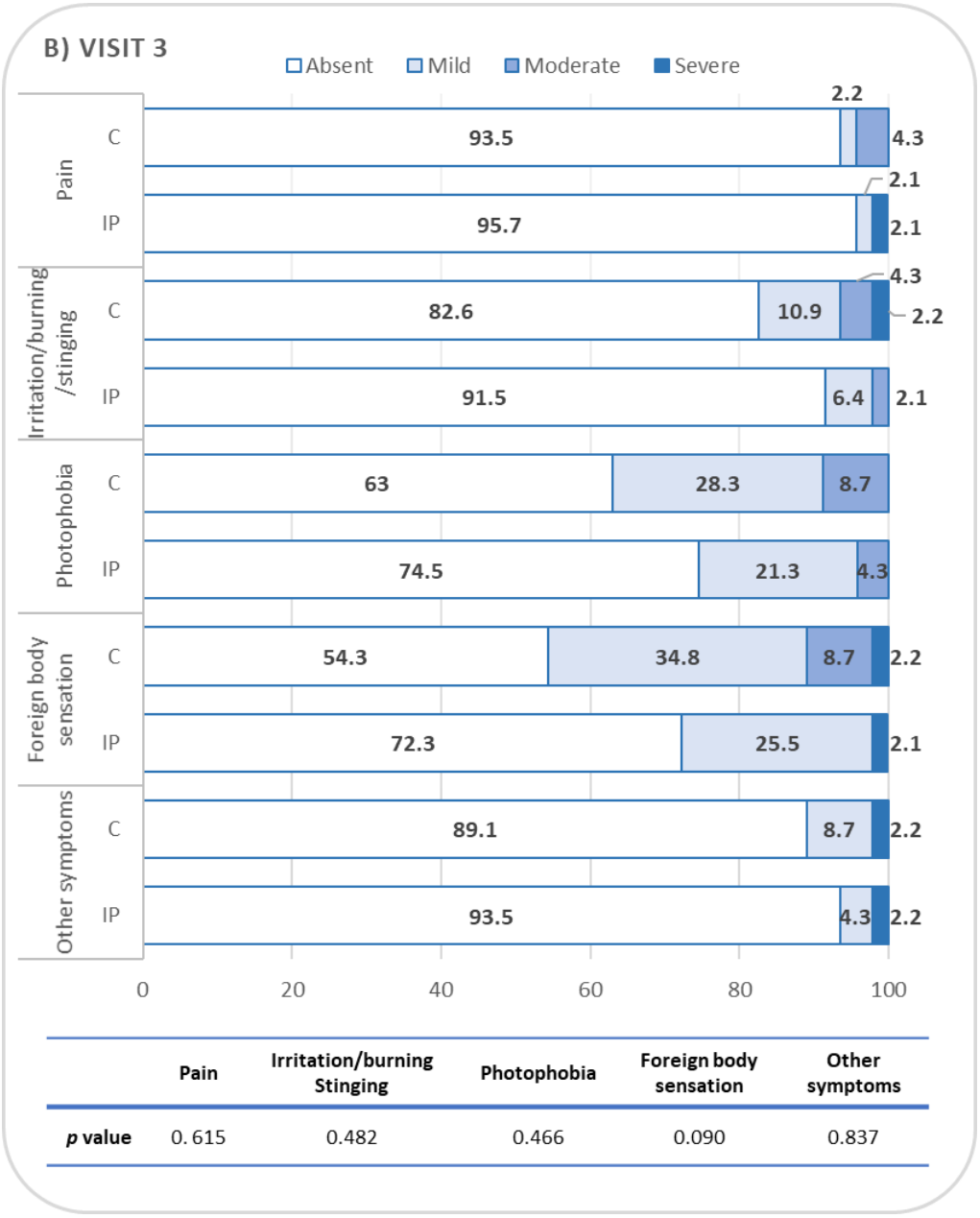
Figure 32A. Symptoms presented by patients at visit 2



	Pain	Irritation/burning Stinging	Photophobia	Foreign body sensation	Other symptoms
p value	0.185	0.018*	0.391	0.051	>0.999

IP= Investigational product (ICMA), N=49 patients; C= Control, N=50 patients

Figure 32B. Symptoms presented by patients at visit 3.



	Pain	Irritation/burning Stinging	Photophobia	Foreign body sensation	Other symptoms
p value	0. 615	0.482	0.466	0.090	0.837

IP=Investigational product (ICMA), N=47 patients; C=Control, N=46 patients

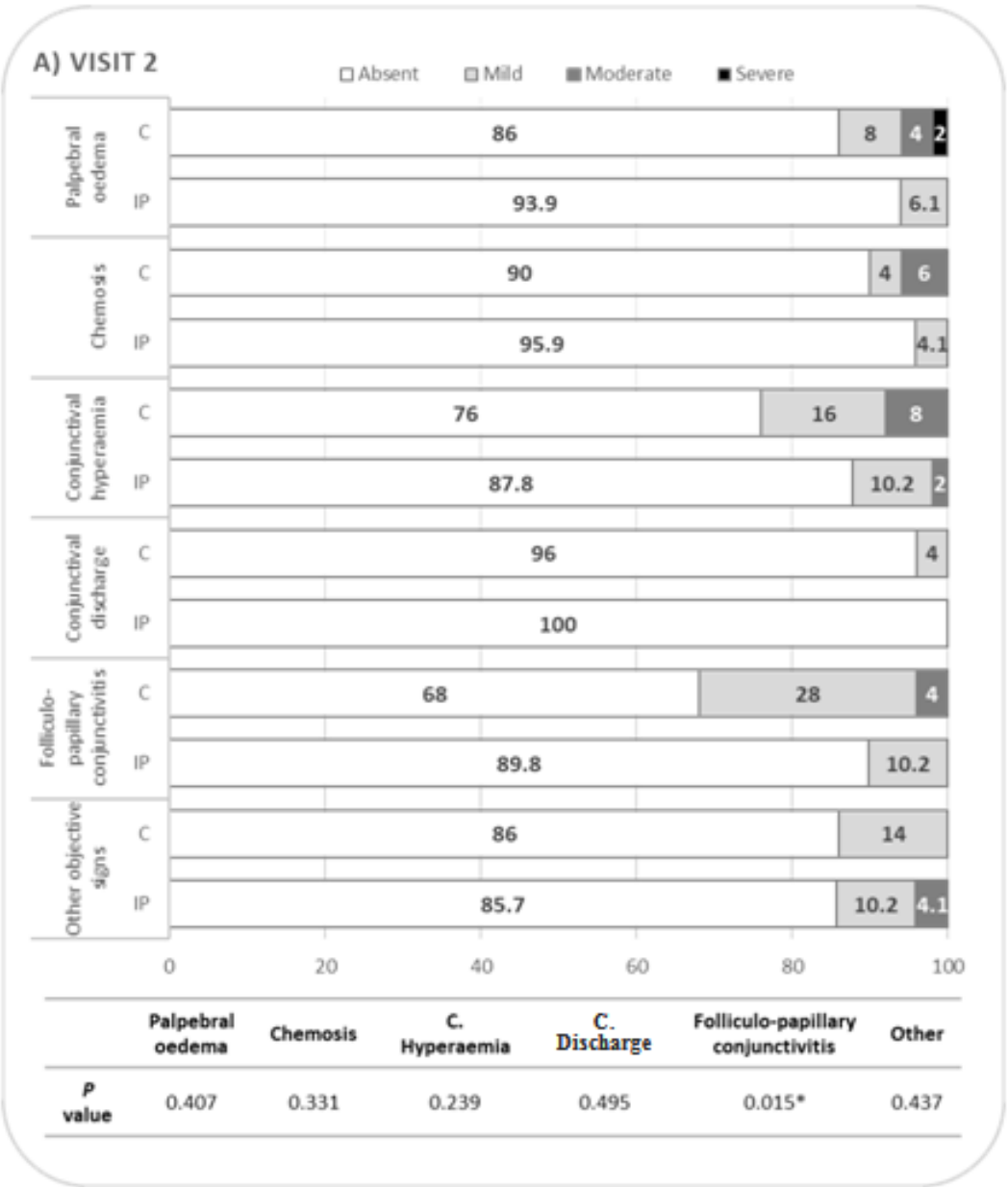
During slit-lamp examination, evaluation was made over palpebral edema, chemosis, conjunctival hyperaemia, conjunctival discharge, conjunctival folliculo-papillary reaction and other objective signs. The severity of the signs experimented by patients in both visits were assessed and classified as absent, mild, moderate or severe.

At first postoperative day, visit 2, conjunctival folliculo-papillary reaction demonstrated a significant difference between groups, 10.2% in the ICMA group

versus 32% in the control group (p=0.015). In the rest of signs observed in visit 2, the differences between groups were not significant (Figure 33A).

At visit 3, one week after surgery, high percentage of ocular signs decreased, persisting mainly conjunctival hyperaemia and folliculo-papillary reaction, although without statistically significant differences between the groups. The rest of signs described tended to cease without differences in the comparison of the two groups (Figure 33B.)

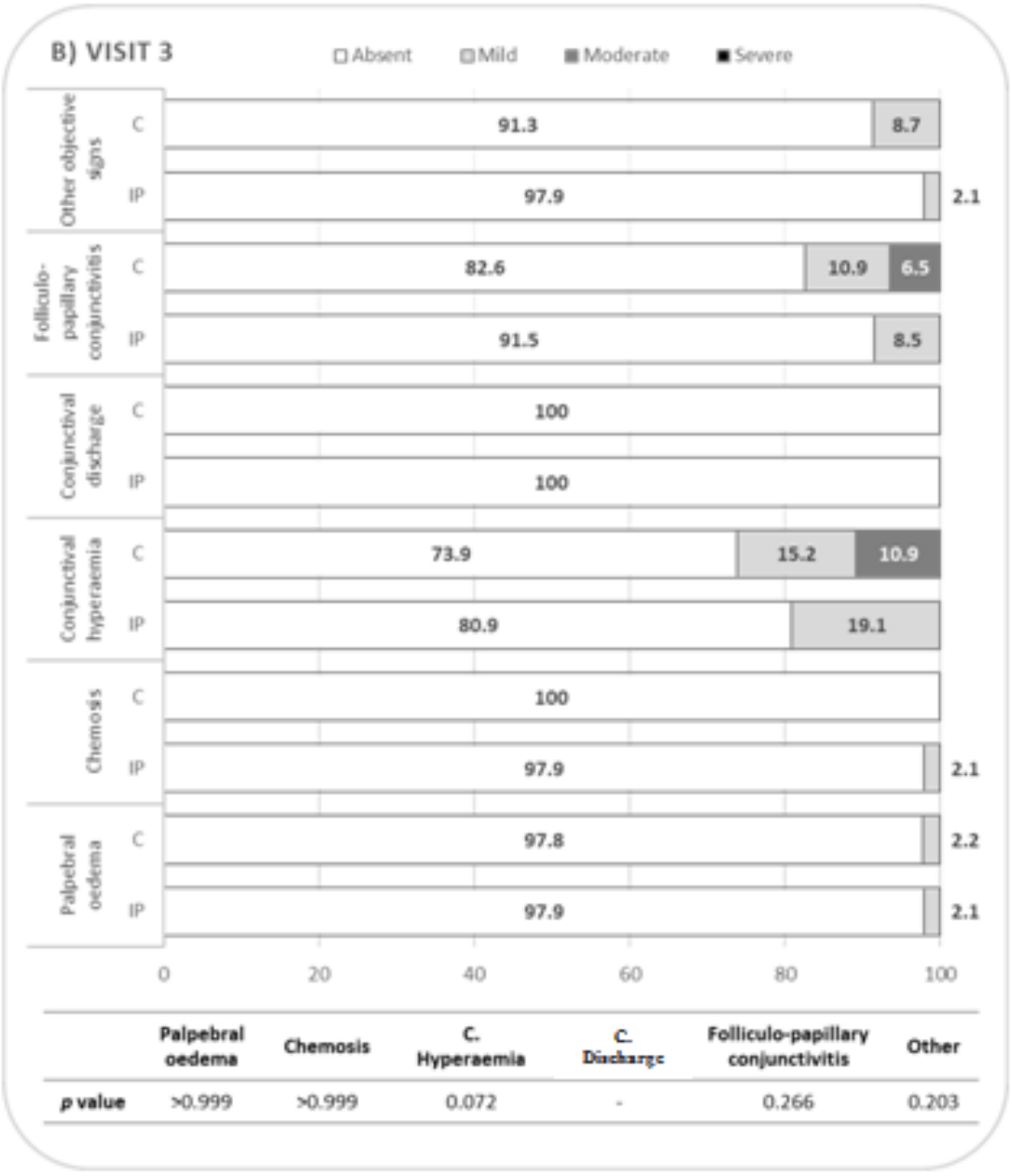
Figure 33A. Ocular signs evaluated at visit 2



	Palpebral oedema	Chemosis	C. Hyperaemia	C. Discharge	Follicular-papillary conjunctivitis	Other
P value	0.407	0.331	0.239	0.495	0.015*	0.437

IP= Investigational product (ICMA), N=49 patients; C= Control, N=50 patients

Figure 33B. Ocular signs evaluated at visit 3



	Palpebral oedema	Chemosis	C. Hyperaemia	C. Discharge	Follicular-papillary conjunctivitis	Other
p value	>0.999	>0.999	0.072	-	0.266	0.203

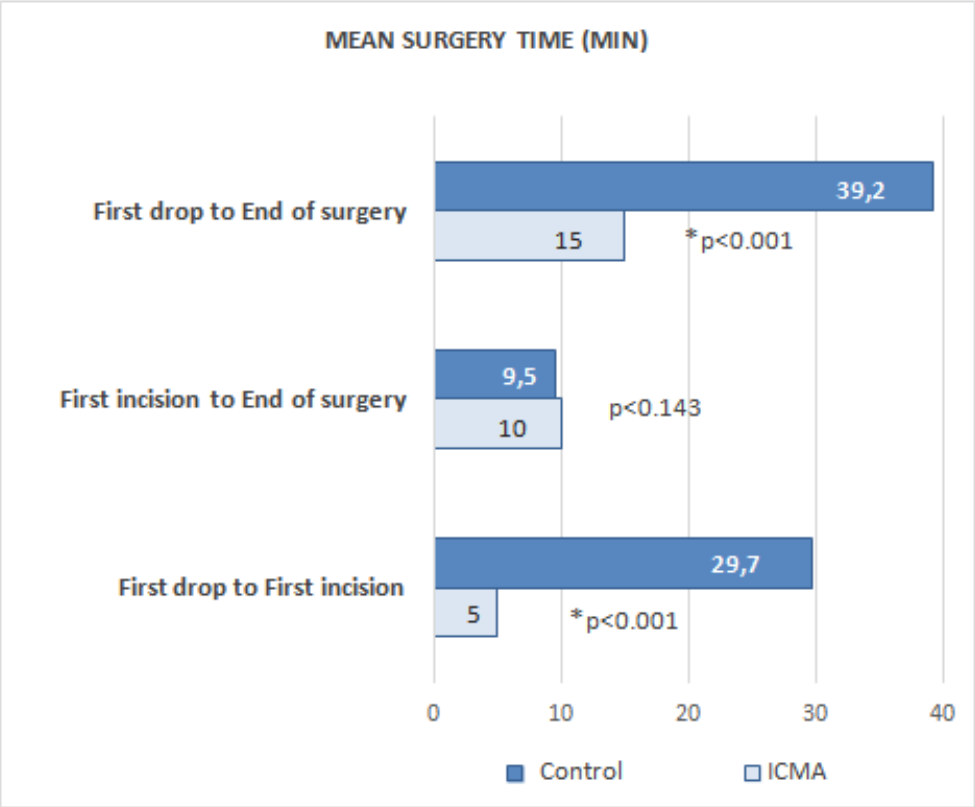
IP=Investigational product (ICMA), N=47 patients; C=Control, N=46 patients

➢ Secondary objective No.9

9.5.2.9 Surgery times

Regarding surgery time, the mean surgery duration (first incision to end of surgery) was quite similar in both groups, 10.0±1.6 minutes in the ICMA group versus 9.5±1.4 minutes in the control group (p=0.143). Patients treated with ICMA needed less time from treatment administration to beginning and end of surgery respectively, compared to the control group. There were statistically significant differences, between ICMA and control group, in the mean time from first drop administration to first incision (start of surgery), 5.0±0.0 minutes versus 29.7±1.5 minutes (p<0.001) and from first drop administration to the end of surgery, 15.0±1.6 minutes versus 39.2±1.9 minutes (p<0.001) (Figure 34). This analysis was performed in the global population and the Mann-Whitney test was used for the statistical analysis.

Figure 34. Preparation and surgical procedure duration



- **Secondary objective No.10**

9.5.2.10 Patient satisfaction

Monitoring patient satisfaction and examining its determinants is of value to improve cataract surgery care. At visit 1, just after surgery, patient satisfaction in response to the question "How do you judge your ocular comfort during cataract surgery?" was graded on a four-value scale (from 0 "very satisfactory", 1 "satisfactory", 2 "not very satisfactory" and 3 "unsatisfactory"). Patient satisfaction were measured by analyzing *per protocol* population. The Fisher's Exact test was used for the descriptive and comparative analysis.

The ICMA treatment was classified as "very satisfactory" by the 98% of patients (N=50), whilst the standard eye drop protocol was considered very satisfactory by 80% of them (N=50). The differences shown in satisfaction regarding ICMA and control treatment is considered statistically significant (p=0.008). One patient considered the standard eye drop protocol as "unsatisfactory" (Figure 35A).

Examining the causes of lower patient satisfaction in the standard eye drops mydriatics and anaesthetics group, patients justified their satisfaction rate as "satisfactory" and "unsatisfactory" for having experienced some discomfort, pain and/or pressure during surgery. These patients emphasized experiencing an unpleasant pressure during the IOL implantation.

- **Secondary objective No.11**

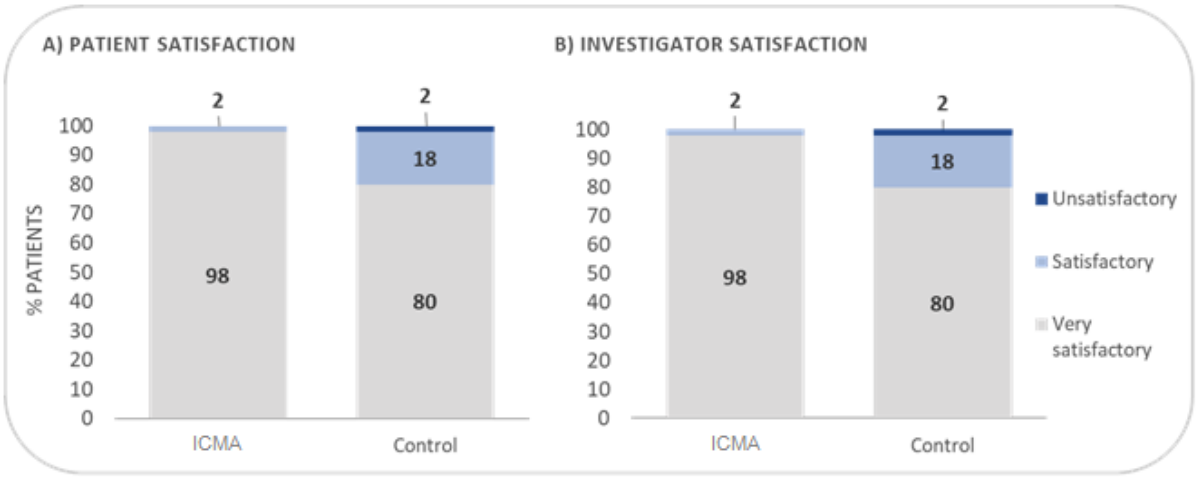
9.5.2.11 Investigator satisfaction

Once the surgery was over, our rating of satisfaction was determined in response to the question "How do you consider the study product satisfaction?", using a four-values scale (from 0 "very satisfactory", 1 "satisfactory", 2 "not very satisfactory" and 3 "unsatisfactory"). Our satisfaction was measured by analyzing *per protocol* population. The Fisher's Exact test was used for the descriptive and comparative analysis. We rated as "very satisfactory" the 98% of the cases (n=49) receiving the ICMA treatment versus the 80% (n=40) of those receiving the standard eye drops treatment. In one case the standard eye drops was considered

as “unsatisfactory”. The differences in satisfaction between ICMA and control treatment were considered statistically significant (p=0.008) (Figure 35B).

There was a satisfactory mydriasis in both groups and no complications nor mayor incidences took place during phacoemulsification. For that reason, the most significant predictor of our satisfaction was intraoperative pain and patients' comfort during surgery. All patients were educated before surgery so as to notify any kind of discomfort/pain, as monitoring intraoperative pain is part of our routine practice in the institute. 20% of the patients (n=10), receiving the standard mydriatic-anaesthetic eye drops, complained during surgery of feeling some kind of discomfort, pain or pressure, mostly during the IOL implantation. No patient complained in the ICMA group for experiencing pain, or pressure with surgical maneuvers and especially during IOL implantation, which increased patients' cooperation during surgery and made the procedure less technically challenging.

Figure 35. Patients and investigators satisfaction per group



➢ Secondary objective No. 12

9.5.2.12 Adverse events

All patients included in the study at the screening visit, randomly received the study treatment, intracameral mydriatics and anaesthetic (ICMA) in one eye and standard mydriatic-anaesthetic eye drops in the fellow eye.

Safety profile analysis was conducted in the "safety" population. A descriptive analysis of adverse events evidenced throughout the study was performed. A total of 19 adverse events (AE) were detected in the study population. Adverse events related to the study treatment were not detected. Serious adverse events (SAE) or other significant adverse event, ocular or systemic, were not registered. Preoperative and intraoperative AEs did not occur in any group of treatment and AEs were exclusively observed in the postoperative period. The only AEs with an incidence ≥ 2% were corneal edema in 8% of the eyes and rotation of a toric lens in 2%. The rest of AEs presented an incidence of 1% and were described as wound leak, mild cystoid macular edema (CME), Descemet folds, corneal epithelial defect, superficial punctate keratitis (SPK) and unspecified blurred vision. The first postoperative day, a mild-moderate corneal edema was observed in 8 cases. Following the postoperative treatment and without any further measures taken, complete recovery was noted at visit 3, one week after surgery, in all cases. Corneal epithelial defect and wound leak was observed in one case respectively (1%), at the immediate postoperative slit-lamp examination (visit 1- just after surgery), and were resolved in 24 hours with a contact lens bandage. 2 out 100 eyes had a rotated toric lens and an intraocular lens (IOL) repositioning was considered necessary so as to correct the refractive error. Descemet folds, present in one eye ,were resolved by retiring postoperative timolol eye drops. Mild cystoid macular edema appeared in one eye and unspecific blurred vision was registered in the fellow eye of the same patient, at visit 3 after surgery, and were ongoing on the end of the study follow-up.

10. DISCUSSION

10. DISCUSSION

Ophthalmic surgery may have the potential to temporarily induce or worsen dry eye conditions, typically during the short post-operative period (1) (2) (3) (4) (5) (9) (249). Cataract surgery might lead to disruption of homeostasis of the ocular surface due to the eyelid speculum, the surgical incisions, the prolonged surgical time and the light exposure from the operating microscope. The preoperative medication, such as the standard eye-drop mydriatics, anaesthetics and the intraoperative agents used, may also have an effect on the ocular surface, which is "stressed" under the conditions of surgery, possibly contributing to the signs and symptoms of dry eye.

The multifactorial etiology of dry eye is still not fully understood (250). Ocular surface integrity can be compromised after cataract surgery. In the setting of patients undergoing cataract surgery, it is critical to minimize ocular surface toxicity, improve the preoperatory medication tolerability and patient comfort, decrease intra- and postoperative symptoms and achieve a faster visual recuperation, with the highest refractive visual outcomes. Identifying these issues and taking measures, can build a high value of postoperative satisfaction for patients and surgeons.

In this phase IV, randomized, open-label, single-centre study the effects of the injectable solution of intracameral fixed combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% (ICMA, Fydrane®) were compared to standard topical mydriatics and anaesthetics, in cataract surgery.

Data collected at inclusion showed that 54% of the patient were female, and their mean age was 61.0±10 years. For these patients, the mean pupil dilatation achieved at screening visit was 7.8±0.5 mm (ICMA group) and 7.9±0.5 mm (control group).

The most frequent pathologies reported among patients were cardiovascular pathologies in 30%. Diabetes mellitus was reported in 6% of the patients.

10.1 Corneal/conjunctival staining

We used corneal fluorescein staining (CFS) and lissamine green staining (LGS) tests to evaluate ocular surface damage in 50 patients undergoing cataract surgery in both eyes, who received treatment with ICMA in one eye and the standard mydriatic and anaesthetic eye drops in the fellow eye. In regard to the results obtained and evaluated by Oxford (Ox) (V0, p=not applicable, V1, p=0.118, V2, p=0.626 and V3, p=0.975) and van Bijsterveld (VB) (V0, p=0.299; V1, p=0.475; V2, p=0.493 and V3, p=0.878) schemas, we observed that the mean values of corneal and conjunctival staining were similar in both treatments, with a slightly faster recovery following administration of ICMA compared to control treatment. Though the trend was not of statistical significance. Before surgery, CFS grade 0 was noted in all cases. Immediately after surgery, 97.8% of the ICMA group and 100% of the control group presented some grade of CFS, mostly grade 1 (77.8% and 64.4% respectively) and some patients presented grade 2 to 4 (p=0.162). 12-36 hours after surgery, 18.8% of the ICMA group presented CFS grade 1 and 22% of the control group presented CFS grade 1 and 2 (p=0.592). At one week after surgery, 2.1% of the ICMA group and 2.2% of the control group presented CFS grade 1 respectively (p>0.999). There were no statistically significant differences between the groups in the grade of corneal affectation for each visit evaluated.

So as to evaluate the conjunctival damage we used lissamine green staining (LGS). Before surgery, 22.4% of the ICMA group and 14.3% of the control group presented LGS grade 1 (p=0.297). Immediately after surgery, 55.5% of the ICMA group and 46.7% of the control group presented LGS, mainly grade 1 (44.4% and 35.6% respectively) and less of them grade 2 (11.1% in both groups), (p=0.668). At the visit 2, 12-36 hours after surgery, 27.1% of ICMA group and 32% of the control group presented LGS grade 1 and 2 (p=0.515). One week after surgery, 19.1% of the ICMA group presented LGS grade 1 and 20% of the control group presented LGS grade 1 and 2 (p=0.894). There were no statistically significant differences between the groups in the grade of conjunctival affectation for each visit evaluated.

Furthermore, the changes in corneal/conjunctival staining between visits, from visit 0 to visit 1 (Ox: p=0.169; VB: p=0.845), visit 0 to visit 2 (Ox: p=0.455; VB: p=0.130) and visit 0 to visit 3 (Ox: p=0.975, VB: p=0.350), were not of statistical significance. As a conclusion, it could not be demonstrated a significant difference in changes neither in grades of corneal/ conjunctival damage between visits with the use of intracameral injection of mydriatics and anaesthetic drugs compared to standard eye-drop protocol.

In previous studies it is reflected that after phacoemulsification with the standard treatment, great number of patients present different staining pattern at 24 hours, 1-2 weeks postoperatively and decreases at 4-6 weeks after surgery (2) (3) (9) (10). Li et al. observed that 20% of the eyes, after an uneventful phacoemulsification and intraocular lens (IOL) implantation carried out by one surgeon, presented some grade of corneal and conjunctival fluorescein staining as per Oxford and van Bijsterveld schema (grade I-IV) at 1 week time after surgery, with score significantly increasing and peaking at 1 month postoperatively and decreasing gradually thereafter. Moreover, they observed that patients whose cornea and conjunctiva fluorescein staining was positive at 1 week still had positive results 3 months after surgery. Li et al. had used Mydrin® eye drops (phenylephrine and tropicamide) 3 times over half an hour to dilate the pupil before cataract surgery (3). Compared to our study, these results agree with our conjunctival lissamine green staining as per van Bijsterveld score results. However, in our study, only 2% presented mild grade of corneal fluorescein staining as per Oxford schema in one week in both groups.

Fan et al. conducted corneal fluorescein staining in 90 eyes undergoing cataract surgery (grade 0 before surgery) and reported significant increase in postoperative corneal fluorescein staining at 1, 3, 7 days after surgery; staining was observed basically in the main and lateral incision, with complete recovery of the corneal epithelium without obvious staining at 1 month after surgery. Fan et al. did not find any significant differences at the corneal fluorescein staining compared to the time exposed to preoperatory 0.05% povidone-iodine irrigation (groups of 30 seconds, 1 minute and 2 minutes exposure) (4).

García Zamora et al. used corneal fluorescein staining (CSF), graded as per National Eye Institute/ Industry (NEI) - recommended guidelines staining grid with a score of 0 to 3 (0=normal, 1=mild, 2=moderate and 3=severe) assigned to each of five corneal regions (nasal, central, temporal, inferior and superior) with a maximum total score of 15 (138), to study 55 healthy eyes that underwent standard phacoemulsification with topical mydriasis (drops of tropicamide 1%, phenylephrine 10%), anaesthesia (oxybuprocain chlorhydrate 0.4% +tetracaine chlorhydrate 0.1%) and intracameral lidocaine 1%. 76.3% of the patients presented superficial punctate keratitis (SPK), located predominately in the central area of the cornea in 40% during the first 24 hours and 32.7% of patients one week after surgery. At one month postoperative examination, 21.8% of those patients still presenting some grade of SPK, showed predominance on the inferior quadrant of the cornea. NEI-scale corneal staining from 0 baseline score changed into 2.12±1.74 at 24 hours ($p<0.001$), 1.07±1.11 ($p<0.001$) at 1 week and 0.49±0.76 ($p<0.001$) at 1 month (10). Theses postoperative CFS scores were higher compared to both our study groups.

Kohli et al. reported that 6 weeks after uncomplicated phacoemulsification surgery in previously healthy eyes with standard eye drop mydriasis, 22% of the patients showed significant corneal fluorescein staining (grade >3) and 30% of the patients presented some grade of lissamine green staining (2). These findings present a great clinical difference compared to our results, despite the fact that both studies have participants with similar demographic data (age, sex). The difference could be due to various factors: a) surgery time. Kohli et al. reported effective phacoemulsification time 20.43±8.89 min, as the time noted from the phacoemulsification machine; b) the duration of exposure to the light of the microscope calculated from the start to the end of surgery was 28.66±6.69, which is prolonged over twice as long as our surgery time (first incision to end of surgery), 10.0±1.6 min (ICMA group) and 9.5 ±1.4 min (control group); c) the type of light exposure. Kohli et al. declared that all patients were operated under the same microscope i.e. S7 OPMI VISU 160 (Carl Zeiss Meditec AG, Jena, Germany) with a halogen light source (12 V, 100 W) (2), while our patients were all

operated under Leica Proveo 8 with a LED light source using 58% in principal light and 44% in reflex.

10.2 Best corrected visual acuity

It is considered that intracameral injections may hasten best corrected visual acuity recovery due to quicker reversion of pupil dilation. Nonetheless, the results obtained, in our study, for ICMA group showed no difference in the mean change of the BCVA from baseline to the first postoperative day, with mean BCVA (decimal) 0.8±0.2 in both groups, and one week after surgery with mean BCVA 0.9±0.2 in both groups (V0-V2, p=0.510; V0-V3, p=0.766; V2-V3, p=0.508). Behndig and Eriksson evaluated the use of intracameral mydriatics and anaesthetics (preservative-free mixture of cyclopentolate 0.1%, phenylephrine 1.5% and lidocaine hydrochloride 1%) versus topical mydriatics (cyclopentolate 1%, phenylephrine 10%) combined with intracameral lidocaine hydrochloride 1% in phacoemulsification and found BCVA significantly better in intracameral mydriasis group (mean BCVA 0.66±0.28 (decimal)) at day 1 compared to the eye drops group (mean BCVA 0.51±0.29), (p<0.001) (114), while Lundberg and Behndig in a similar study reported no significant differences in both groups at 1 month after surgery (mean change in BCVA (logMAR) 0.50±0.26 in the intracameral mydriatics versus 0.65±0.53 in the topical mydriatics (p=0.17)) (95). Schulz et al. evaluated intracameral Mydrane® versus topical mydriatics (cyclopentolate 1%, phenylephrine 2.5%) in 120 eyes undergoing cataract surgery and reported no statistical differences in the postoperative BCVA measured at routine follow-up 3-4 weeks after surgery (mean BCVA (logMAR) 0.08±0.15 versus 0.09±0.16 respectively, p=0.59) (251). Ajay et al. observed no statistically significant changes in mean BCVA the first postoperative day in patients undergoing manual small incision cataract surgery with topical eye drops (tropicamide 0.8%, phenylephrine 5% and flurbiprofen 0.03%) compared to intracameral anesthetic and mydriatics (lidocaine 0.5% and epinephrine 0.001%) (252). García Zamora et al. determined statistically significant lower visual

acuity in the SPK group than the non SPK group at 1 day (p=0.007), 1 week (p=0.006), and 1 month (p=0.004) after surgery (10).

The patients of our study experienced a faster visual recovery in the first postoperative day and one week after surgery in both eyes, compared to previous clinical trials, most of which measure BCVA one month postoperatively, without significant changes between groups. Further clinical experience is needed to determine the extent by which the intracameral regimen may impact faster visual recovery.

10.3 Epithelial alterations

Epithelial lesions such as superficial punctate keratitis and epithelial defects may be seen on the ocular surface after most of the ocular surgeries (9) (10) (27) (249) (253). Corneal sensory nerves originate from the ophthalmic division of the trigeminal ganglion, traveling in the nasociliary nerve and its long ciliary nerve branches, and ultimate branching into nerve fibers that penetrate the cornea around the limbus centripetally, between the basal epithelium and Bowman's layer, forming the sub-basal nerve plexus that supplies the overlying corneal epithelium, and achieve a homogeneous distribution over the entire cornea (10) (1) (50). In normal conditions, corneal nerves stimulate lacrimal gland for tear production and secretion by sending afferent stimuli to brain stem and parasymphathetic and symphathetic signals (254) (255). Corneal nerves not only induce tear production, but also stimulate the blinking and tear reflex. Intact corneal innervation is important, as damage of this circuit can cause dry eye. Corneal incisions created during phacoemulsification can cause partial denervation of cornea resulting in decreased blinking and reduction in tear production thus leading to increased epithelial permeability, decreased epithelial metabolic activity and impaired epithelial wound healing (1) (10) (50) (51). Inflammatory mediators released intra and postoperatively due to corneal incisions may also alter the physiology of the corneal nerves and reduce corneal sensitivity and result in tear film instability (52) (53). Neural growth factor is

released to regenerate the subepithelial corneal axon and is completed approximately within 1 month. The healing of the nerves may explain why dry eye signs and symptoms are prominent early after surgery and improve thereafter (52).

Some of the safety results in our study, have demonstrated certain advantage in the use of intracameral fixed combination of mydriatics and anaesthetic (ICMA) as an alternative of topical eye-drops with less epithelial damage and faster restoration of corneal epithelial surface. The incidence rate of epithelial alterations was significantly lower in the ICMA group (8%) compared to the control group (30%) (p=0.005) at 24 hours after surgery. The ICMA group presented smooth epithelium at the one week postoperative examination, while 8.7% of the control group presented some grade of epitheliopathy at 7 days after surgery. Corneal epithelial defect was observed in one case of the control group (1%) at the immediate postoperative slit-lamp examination (just after surgery), which was resolved with a contact lens bandage. Persistence of epithelial alterations further than one week time present in the standard eye drop mydriatics and anaesthetics group agrees with the results of previous studies, that described high incidence of epithelial alterations present at 24 hours after phacoemulsification, ongoing at 1 week and decreasing at 1 month after surgeru (4) (10). García Zamora et al. evaluated the short-term changes in ocular surface of 55 healthy eyes that underwent standard uneventful phacoemulsification with topical mydriasis (eye drops of tropicamide 1%, phenylephrine 10%), anaesthesia (eye drops of tetracaine chlorhydrate 0.1% and oxybuprocain chlorhydrate 0.4%) and intracameral lidocaine 1%; They observed postoperative high incidence of superficial punctate keratitis (SPK). 76.3% of the eyes presented SPK the first postoperative day, 53,8% one week and 33.3% one month after surgery (10). Fan et al. investigated the ocular surface damage in 90 eyes undergoing cataract surgery, with topical mydriatics and use of 0.05% Povidone-Iodine in the operative field, before the first incision, during 30sec/1min/2min (divided into 3 groups), and observed SPK in the main and lateral incision of the corneal surgery and in the lower corneal epithelium 24 hours after surgery. SPK was significantly reduced at 3 days after surgery, but still obvious at 1 week

postoperatively. Complete epithelium recovery was noted at 1 month after surgery (4).

10.4 Conjunctival hyperaemia

The presence of conjunctival hyperaemia increased along the study in both treatment groups with no statistically significant differences between them (V1 preoperative, p=0.300; V1 postoperative, p=0.312; V2, p=0.172 and V3, p=0.172). Additionally, the differences between changes in conjunctival hyperaemia across visits were neither significant (V1 preoperative to V1 postoperative, p=0.454; V1 preoperative to V2, p=0.102; V1 preoperative to V3, p=0.732). Nonetheless, the reduction in the percentage of patients with grade 0 hyperaemia over the visits was significant for both treatments (ICMA, p=0.001 and Control, p<0.001), proving once again the similarities in their safety profile. Behndig et al. compared conjunctival injection in eyes undergoing cataract surgery, that received intracameral mydriatics and anaesthetics versus topical mydriatics and reported insignificant differences between the 2 groups at the first postoperative day (p=0.57) (114). Labetoulle et al. in the international phase III, prospective, randomized study of 555 eyes undergoing phacoemulsification with intraocular lens implantation, comparing intracameral standardized ophthalmic combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1% (Mydrane®) versus topical eye drops of tropicamide 0.5% and phenylephrine 10%, observed mild ocular hyperaemia without significant differences between the groups (134).

10.5 Intraocular pressure

Changes in intraocular pressure, 7 days after surgery from baseline, did not demonstrate a significant difference when intracameral injections were administered, suggesting that the use of ICMA had a similar safety profile to the standard protocol for preoperative anaesthesia and mydriasis (V0, p=0.415; V3, *p*=0.679; V0-V3, *p*=0.382). Patients in our study received postoperative treatment with timolol 0.5% drops. One week after surgery, the mean IOP value was

9.5±3.1 in the ICMA group versus 9.6±2.5 in the control group. No postoperative moderate or high IOP spike was registered in any group. Our results agree with previous studies comparison between intracameral mydriasis and standard mydriatic eye drops (95) (114). Behndig et al reported IOP values after phacoemulsification to be 15.6±2.7 mmHg in the intracameral mydriatics group versus 16.1±4.0 mmHg in the topical mydriatics group (p=0.13) at the first postoperative day (114). Alwitry et al. in a study of 510 eyes undergoing cataract surgery with topical mydriatics (cyclopentolate 1% and phenylephrine 2.5%) recorded mean IOP value to be 15.3±7.7 mmHg the first postoperative day, with 3% of healthy eyes, without ocular hypertension nor glaucoma, having IOP >30mmHg (256). Tranos et al. focused on IOP in the early postoperative period in 141 eyes after uneventful phacoemulsification surgery with topical mydriatics, finding that moderate IOP spikes (<40mmHg, mean IOP value 19.44±7.04mmHg at 24 hours after surgery), were not associated with any significant morbidity and tended to resolve spontaneously in normal eyes (IOP ≤ 21mmHg at 3 weeks postoperatively) (257).

10.6 Objective scatter index (OSI)

The OSI, a parameter that offers objective quantification of intraocular scattering, was calculated using the Optical Quality Analysis System (OQAS) HD Analyzer™. In healthy younger eyes, the OSI value is lower than 0.5 (220). A higher OSI indicates a higher influence of intraocular scattering (210). OSI scores were not measured preoperatively as they are strongly associated with cataract classification and severity (221). The mean postoperative OSI was 2.5±1.5 in the ICMA group and 2.9±1.5 in the control group, 7 days after surgery. The comparison between ICMA and control group in each visit (V2: ICMA, 2.5±1.5; Control, 2.8±1.5; p=0.273; V3: ICMA, 2.5±1.5; C, 2.9±1.5; p=0.237) and the changes in OSI from the first postoperative day to 7 days after surgery showed no statistically significant differences between the groups (V2 to V3, p=0.668). However, OQAS HD analyzer through simulation of the image on the patients' retina showed that lower intraocular scattering in ICMA group involved clinically better optical

quality. In previous studies, significant differences were observed between the preoperative and postoperative OSI, but no statistical differences were reported between the postoperative visits (222). The OSI values in our study (>2.0) could be due to early postoperative measurements, as others studies, with standard mydriatic eye drops, reported postoperative OSI at 1-3 months after surgery and mean values below 2 were described. Jiménez et al. calculated in their series of cataract surgery the OSI value of 1.36±0.22 at 1 month postoperative (222). Debois et al., in a study of cataract surgery with toric IOL implantation, observed OSI value of 1.76±0.64 at 6 months after surgery (31). Xiao et al. in cataract surgery with toric IOL implantation reported OSI value 1.80±0.84 at 3 months after surgery (32). Lee et al. in uneventful cataract surgery with implantation of aspheric IOL reported OSI value 1.38±0.73 at 3 months postoperatively (33). These values are slightly higher than those in a study of a population of similar age but with healthy eyes (1.11±0.50) (34), indicating that once the cataract is eliminated and the refractive defect is resolved, these eyes continue to present more scattering than a healthy eye of a subject of the same age.

10.7 Vision break-up time (VBUT)

Tear film stability was determined for each eye with vision break-up time (VBUT), before surgery, 1 and 7 days postoperatively using the Optical Quality Analysis System (Visiometrics SL, HD Analyzer™). At the screening visit, there were statistical differences between the 2 groups, with the ICMA group presenting more stable and moderately stable VBUT compared to the control group. The first day after phacoemulsification increased tear film VBUT instability was observed in both groups. A tendency to recovery to preoperatory levels was registered at 7 days after surgery in both groups. However, the changes registered between the 2 groups, during the visits, demonstrated no statistically significant differences. In our knowledge, there are no studies with VBUT measurements by OQAS after cataract surgery to contrast our findings. However, previous studies reported shorter tear film break up-time (TBUT) after fluorescein instillation the first postoperative week with slow recovery at 1-3

months after surgery (3) (4). Fan et al. investigated the ocular surface damage in 90 eyes undergoing cataract surgery, with topical mydriatics and found significant shorter TBUT at 1, 3 and 7 days after cataract surgery compared to 3 days preoperatively; observing gradual recovery to the preoperative level at 1 and 3 months postoperatively (4). Li et al., in a study of uneventful phaco-emulsification and IOL implantation, carried out by one surgeon, with the use of Mydrin® eye drops (phenylephrine and tropicamide), observed slightly shorter TBUT at one week after surgery, with significantly decreasing peak at 1 month postoperatively and a trend to improvement at 3 months after surgery, but still with significant difference compared to the preoperative level (3).

10.8 Ocular surface disease index (OSDI)

OSDI questionnaire was used to evaluate items such as ocular symptoms (foreign-body sensation, pain, etc), effect on vision-related functions, difficulty in accomplishing activities of daily life and response to environmental conditions such as wind. OSDI questionnaire scores reported by patients indicated no differences between treatments, in any of the visits (V0: A-score, p=0.867; B-score, p=0.997; C-score, p=0.826 and Total-score, p=0.952. V3: A-score, p=0.250, B-score, p=0.610, C-score, p=0.815 and Total-score, p=0.231). The differences in changes between preoperative OSDI (V0) and one week postoperative OSDI (V3) were neither significant in both groups (V0 to V3: A-score, p=0.641; B-score, p=0.916; C-score, p=0.666 and Total-score, p=0.689). However, there was an improvement of clinical importance in the overall OSDI scores at 1 week after surgery, in both groups, standing out the improvement in the vision-related function (B-score) in the ICMA group.

Li et al. reported, after uneventful phacoemulsification in healthy eyes with the use of Mydrin® eye drops (tropicamide/phenylephrine) for pupillary dilatation, no statistical differences between preoperative and at 1 week postoperative OSDI total score in their series. Compared to before surgery most functional indices were significantly improved after cataract surgery, which agrees with our findings; however, many patients complained about ocular symptoms such as dry

eye (3). Similar studies of healthy eyes that underwent cataract surgery, after pharmacological dilatation with standard eye drops (tropicamide/ phenylephrine), showed a statistically significant aggravation in OSDI total score result at 1 week after surgery compared to the preoperative OSDI. In fact, improvement in the OSDI scores were described at 1 month after surgery (2) (9) (10), with no statistical differences between the preoperative and 1 month postoperative OSDI scores at one study (10) and statistical differences in the others (2) (9). Dry eye is a multifactorial disorder still not fully understood (250). Further studies evaluating the changes in OSDI, in eyes undergoing cataract surgery with the use of intracameral mydriatic/anaesthetic agents, are needed to determine improvement in ocular symptoms, vision-related function and environmental triggers compared to standard eye drop mydriatics and anaesthetics.

10.9 Ocular symptoms and signs

Symptoms in the early postoperative period such as irritation, burning and stinging were less severe and significantly lower when administrating ICMA instead of standard eye drops (p=0.018). Foreign body sensation was experienced in almost the double of cases in control group compared to ICMA (62% vs. 36.7%), which did not reach a statistical difference (p=0.051), but it is of clinical importance. Regarding ocular pain, photophobia or other subjective symptoms during the postoperative period, there were no differences between ICMA and control group. The results of our study are similar with the multicentric study of Mydrane® efficacy, phase III, where the follow up at one month showed statistically significant fewer patients who reported irritation/burning/stinging in the Mydrane group (134). In another study, Lundberg et al. observed no difference in pain experienced between intracameral and topical mydriatics (95). Kasetsuwan et al. reported that, signs and symptoms of dry eye occurred as early as 7 days post-phacoemulsification and the severity pattern improved over time (9). Sharma et al. related that different intracameral anaesthetics (Ropivacaine and Lidocaine) were both equally effective in providing analgesia during phacoemulsification with no statistically significant differences seen on

comparing painful surgical steps and postoperative inflammation (258). As a curiosity, we mention that Shi et al. in a review and meta-analysis and Liu et al. compared the perceived pain among patients undergoing bilateral cataract surgery and reported higher pain score for the second surgery than the first surgery both immediately after surgery and on the first postoperative day, when the second surgery underwent before an interval of 2 weeks (259) (260). Additionally, Liu et al. compared the perceived estimated operative duration among patients undergoing bilateral cataract surgery and reported longer operative duration for the second eye surgery, when it took place in an interval of less than 2 weeks after the first surgery (260). In our study, even though the second surgery took place in less than 10 days after the first surgery, we found no statistical differences in the perceived pain.

Toxic conjunctivitis has been described as a clinical picture of conjunctival papillary initial reaction, follicular subsequent reaction, watery discharge and often eyelid dermatitis and inferior punctate erosions (261) (262) (263). It is believed that ocular surface toxicity can be related to the repeated administration of topical mydriatic and anaesthetic agents. This is usually aimed at excluding corneal alterations, though in this instance we carefully examined conjunctiva so as to recognize conjunctival toxicity. We observed that standard eye drop mydriatics and anaesthetics caused significantly higher percentage of acute upper and lower tarsal conjunctival folliculo-papillary reaction compared to ICMA treatment the first postoperative day ($p=0.015$). However, examination at one week after surgery did not reveal significant differences in folliculo-papillary reaction between groups. Regarding other evaluated signs, there were no significant eyelid changes, chemosis, hyperaemia or discharge involved in both groups. Conjunctival toxicity is rarely considered, usually underdiagnosed and there are relatively few publications in the field. Previous studies have determined that topical mydriatics, anaesthetics, excipients and preservatives have been considered as causing ocular surface damage (19) (264) (265). Some studies reported ocular surface disorders after phacoemulsification, observing alterations in Schirmer Test, tear break-up time (BUT), impression cytology, lissamine green/fluorescein staining patterns, OSDI scores, and confirming

corneal disorders, tear film instability, even serious squamous metaplasia or decreased mean globet cell density in the epithelial layer of the globe conjunctiva (3) (9) (10). However, when trying to compare with previous studies about conjunctival clinical signs (conjunctival hyperaemia, chemosis, discharge, folliculo-papillary reaction) after cataract surgery, there are relatively few publications in the field. Nylon sutures for wound sealing in cataract surgery were reported to induce conjunctival reaction and giant papillary conjunctivitis as a traumatic process (266). In our study, the incisions were closed by stromal hydration using balanced salt solution and no sutures were considered necessary.

Clinical examination with a focus on these conjunctival characteristic features, in the early postoperative period, is fast, simple and useful so as to recognize conjunctival damage that may induce ocular symptoms such as irritation, burning, stinging and foreign body sensation.

10.10 Duration of preoperative workup and surgery

Intracameral administration of mydriatics and anaesthetic has demonstrated to reduce the time needed for preoperative conditioning and, as a result, the total time required to carry out the cataract surgery. These outcomes were previously described by other authors (95) (134). ICMA injection just after the first incision resulted in a significant reduction in preoperative preparation without increasing the duration of the surgery. We recorded significantly shorter time from the first drop administration to first incision in the ICMA group, 5.0±0.0 minutes, compared to the standard eye drops of mydriatics/anaesthetics, 29.7±1.5 minutes ($p<0.001$). Additionally, preparation time and phacoemulsification (from the first drop administration to the end of surgery) were significantly shorter in the ICMA group, 15.0±1.6 minutes, compared to the control group, 39.2±1.9 minutes ($p<0.001$). The surgical time recorded between first incision to the end of surgery was similar in ICMA and control group, 10.0±1.6 versus 9.5±1.4 respectively, without significant differences. Therefore, the duration of the entire procedure (from the first drop to the end of the surgery) decreased by about 25 minutes in the ICMA compared to the control group. The decrease in total preparation and

surgical time may result in a considerable benefit for the patients, as it can save them the discomfort of intensive topical mydriatics, burning, stinging and glare preoperatively, leading to a less stressful experience for patients in the ICMA group. The outcomes of our study agree with previous studies of intracameral administration of ICMA. Labetoulle M. et al. observed that the time between the first instillation of drops and the end of surgery was significantly shorter in the Mydrane group that spent 23.3±7.0 minutes in the preoperative and surgical rooms, versus the standard eye drops treated group (tropicamide 0.5%, phenylephrine 10%) that spent 49±11.3 minutes ($p<0.001$). Labetoulle M et al. reported that 1.5 minute was dictated in the protocol as waiting time after Mydrane injection in order to achieve pupillary dilation, reason for what time between first incision and the end of surgery was statistically significantly longer in Mydrane group than in the standard mydriatic eye drops group. However, it was highlighted that the time to perform the phacoemulsification (between capsulorhexis and end of surgery) was similar between groups (134). In our study, there was no need to wait more than few seconds after the injection of ICMA, until obtaining a satisfactory pupillary dilation and continuing the procedure.

10.11 Safety of intracameral mydriatics and anaesthetic

Intracameral fixed combination of mydriatics and anaesthetic (Fydrane®) contains two kind of mydriatics, a parasympatholytic (tropicamide 0.02%) and a sympathomimetic (phenylephrine 0.31%). Tropicamide use is associated with reduced cardiovascular risk (267) and faster recovery compared to other parasympatholytic agents, as cyclopentolate. Phenylephrine concentration is relatively low in the ICMA, which could mitigate any cardiac or systemic event. The lower concentration of components in the ICMA, compared to the topical mydriatics, should ensure greater safety and lower side effects.

A total of 19 adverse events (AE) were detected in the study population during the follow-up time. There were classified as not serious and not related with the intracameral treatment. There were no hemodynamically adverse events

reported intraoperatively in both groups. No hospitalization was required. In addition, there were no systemic AEs nor disorders noted during the postoperative visits. There were no serious adverse events (SAE) resulting in permanent visual loss in both groups.

Adverse events were observed only in the postoperative period and included corneal edema (8%), rotated toric lens with intraocular lens repositioning (2%), and the rest of AEs were of 1%, like mild cystoid macular edema, unspecified blurred vision, Descemet Folds, corneal epithelial defect and corneal wound leak. These last two were resolved by placing a contact lens bandage. No evidence of association of these adverse events as a consequence of the received treatment was proved. Intraoperative adverse events, related or not with the treatment, were not observed in both groups. In similar studies, comparing standard eye drops protocol versus intracameral treatment, adverse intraoperative events included iris prolapse, capsular tears with or without vitreous loss, retained lens fragments, lens fragments in the vitreous, wound leak with the need for corneal suturing, and the placement of a sulcus fixated lens (83) (89) (125) (268) (269) (270). Despite this fact, no significant association between intraoperative adverse events and either the intracameral treatment or the control group was identified in these studies (84). Rosenberg et al. observed a higher incidence of complications when mydriatic-assist devices (Mayugin ring or iris hooks) were used and appreciated a lower incidence of complications when intracameral mydriatic treatment was used (125).

10.11.1 Corneal edema

The incidence of corneal edema in our series was of 8% the first preoperative day with complete recovery at one week after surgery. Alwitry A et al. found 12% of central corneal edema in 61 out of 510 eyes the first postoperative day after phacoemulsification, in a study that all patients received preoperative mydriasis with eye drops of cyclopentolate 1% and phenylephrine 2.5% (256). Some studies have suggested that intracameral lidocaine can produce significant endothelial cell loss and corneal edema in a rabbit model. However, these effects appear to be

associated only with higher concentrations of anaesthetic, and the effects are transitory (86) (271) (272). Individual studies have independently found that the use of intracameral anaesthesia does not produce any measurable ocular toxicity. Carino et al measured postoperative corneal pachymetry 1 month after cataract surgery, without statistically significant differences between intracameral and topical treatment (85). Crandall et al (89) measured corneal edema using a subjective 4-point scale and found that grade 1 corneal edema, defined in the study as edema confined to the corneal wound site, was more prevalent in the intracameral lidocaine group. In addition, endothelial cell counts were measured in a subset of patients at 3 months after surgery. Martin et al (269) measured postoperative flare at 10 days and recorded endothelial cell counts in a subset of 93 patients with measurements taken at 69 days postoperatively at the earliest. Corneal pachymetry, endothelial cell counts and anterior chamber activity were measured in an attempt to identify intraocular toxicity. Yet, no statistically significant differences between intracameral treatment and control groups were found (85) (89) (269).

10.11.2 Macular Edema

Clinically meaningful macular edema was registered in one case (1%) of a non-diabetic patient. The adverse event appeared one week after surgery and was still ongoing after the study follow-up end. The prevalence rate of clinical macular edema in our study agrees with other studies of routine cataract surgery. Longo et al. reported 0.8%, 5 out of 644 eyes (273) and Anastasilakis et al. 3.8%, 4 out of 106 eyes developed macular edema after uncomplicated cataract surgery (274). Other studies relate macular edema with increased volume of intracameral cefuroxime (275). However, in our study there was no protocol deviation concerning the cefuroxime dose.

10.11.3 Wound leakage

In our study corneal wound leakage was noted in one eye (1%), during the visit 1, immediately after surgery. The case was self-limited with the use of a contact lens bandage during 24 hours. The incidence rate of wound leakage was similar to previous studies. Alwitry et al. described a 0.8% rate, 4 out of 510 eyes, after phacoemulsification, with 2 eyes requiring suturing in theatre and 2 settling with conservative management consisting of a short period of bandage contact lens use (256). Ipek et al. reported slower wound closing rate and reduced cell viability by 20%, in light exposed cells after 10 minutes of microscope light exposure with halogen bulb, in an *in-vitro* scratch assay performed on porcine conjunctival fibroblasts. These results suggest that light exposure might be one of the contributory factors for wound leakage (253).

Taking into account the absence of serious and related adverse events, intraoperative and postoperative, we may conclude that ICMA safety profile has not demonstrated differences with the current standard eye-drop protocol.

10.12 Efficacy of intracameral mydriatics and anaesthetic

Efficacy of intracameral fixed combination of mydriatics and anaesthetic (ICMA) administration before cataract surgery was measured in terms of patients and investigators satisfaction. Monitoring patient satisfaction and examining its determinants is of value to improve cataract surgery care.

Results obtained, in our study, support that patients considered ICMA as a significantly more satisfactory option for preoperative procedure and intraoperative comfort than topical mydriatic eye-drops (p=0.008). 20% of patients in the control group declared suffering pain, discomfort and/or pressure with surgical maneuvers, mainly during IOL insertion, while no patient complained about pain or pressure sensation during surgery in the ICMA group. 98% of the patients in the ICMA group classified the treatment as “very satisfactory” and only one patient (2%) as “satisfactory”.

A significantly higher level of surgeon/investigators satisfaction was reported in the ICMA group compared to control group (p=0.008). There was an adequate mydriasis in both groups and no complications nor mayor incidences took place during phacoemulsification. For that reason, the most significant predictor of our satisfaction was intraoperative pain and patients' comfort during surgery. Our experience with the administration of ICMA showed that patients' cooperation increased during surgery, compared to the control group, as no patient referred pain nor was bothered by surgical maneuvers, even during the IOL implantation.

Patient satisfaction with intracameral injection has been assessed in several studies providing different results about this preoperative option. Ezra DG et al. carried out a meta-analysis of five randomized clinical trials evaluating intraoperative pain/discomfort and patient satisfaction with topical anaesthesia alone compared with topical anaesthesia and adjunctive intracameral anaesthesia for phacoemulsification. The meta-analysis revealed that additional intracameral 1% lidocaine significantly decreased patient perception of intraoperative pain, increased patient cooperation and decreased the degree to which patients were bothered by surgical maneuvers. In terms of postoperative pain, the data derived from the meta-analysis did not identify any benefit of intracameral 1% lidocaine (84). Only one study of the meta-analysis, published by Carino et al., recorded patient satisfaction independently and demonstrated that patients showed no differences in their satisfaction regarding intracameral and topical administration or just topical (84) (85). In another study, Lundberg et al. observed less discomfort y less glare during the surgical procedure in the intracameral mydriatics than in the topical mydriatics group (95). When satisfaction was measured regarding patient anxiety before the surgery (measurement of heart rate, arterial pressure etc) and satisfaction questionnaire (ISAS, Iowa, Satisfaction with Anaesthesia Scale) it demonstrated that patient were satisfied with intracameral lidocaine injection (119). Regarding surgeons satisfaction, Carino et al found a significantly higher level of surgeon's satisfaction with the lidocaine group (84) (85).

Investigators' satisfaction agree with previous studies satisfaction records and as well with the patients' satisfaction results, showing a higher grade of satisfaction and preference to the ICMA. Even though phacoemulsification was uneventful in both groups, the procedure was less technically challenging, observing increased patient cooperation, during the surgical procedure in the ICMA group.

11. CONCLUSIONS

11.1 Safety conclusions

1. The damage in ocular surface evaluated by corneal and conjunctival staining, according to Oxford and van Bijsterveld schemas, decreased faster following administration of intracameral fixed combination of mydriatics and anaesthetic (ICMA) compared to standard eye drop mydriatics and anaesthetics, although the trend was not of statistical significance.

2. Evaluation of best corrected visual acuity (BCVA) recovery after cataract surgery provided similar results for intracameral fixed combination of mydriatics and anaesthetic and standard eye drop treatment.

3. The percentage of patients experiencing epithelial alterations after surgery was significantly lower in patients that received ICMA treatment. Additionally, faster restoration of corneal epithelial surface was achieved with a smooth homogeneous epithelium without any alterations at one week after surgery, while some patients that received standard mydriatic/anaesthetic eye drops suffered some grade of epitheliopathy that was ongoing at the end of the study follow-up, further than 7 days after surgery.

4. Conjunctival hyperaemia increased along the study in both treatment groups, with the ICMA maintaining a higher percentage of patients without hyperaemia during the early postoperative visits, although without statistically significant differences between groups.

5. Changes in intraocular pressure, from the preoperative values to 7 days after surgery, did not demonstrate a significant difference when intracameral injection was administered, suggesting that the use of ICMA had a similar safety profile to the standard protocol for preoperative mydriasis and anaesthesia.

6. The evaluation of optical quality by the objective scatter index (OSI) revealed lower intraocular scattering in the ICMA group compared to standard eye drop mydriatics and anaesthetics. Although the trend was not of statistical

significance, lower intraocular scatter is associated with better optical quality and is considered of clinical significance.

7. Tear film instability (VBUT) was determined, the first postoperative day, in both groups. A tendency to gradual recovery to preoperatory values was observed at one week after surgery. Changes in tear film stability, before and 7 days after surgery, demonstrated no statistically significant differences between groups.

8. Subjective ocular complaints scored with OSDI questionnaire demonstrated an overall improvement at the one week postoperative OSDI total scores in both groups, with slightly better results in the ICMA group, focusing the improvement in the visual symptoms (B-score). Nevertheless, changes in the preoperative and postoperative OSDI questionnaire between groups showed no statistical differences.

9. Ocular symptoms such as irritation, burning and stinging were experienced in a significantly lower percentage of patients and with less severity in ICMA-treated patients, the first postoperative day, demonstrating a statistically significant difference versus the standard eye drops group. The incidence of foreign body sensation suffered, the first postoperative day, was almost twice as high among patients treated with standard eye drops, even though the trend was not significant. Regarding ocular pain, photophobia or other subjective symptoms during the postoperative period, there were no further differences recorded between groups.

10. Standard eye drop mydriatics and anaesthetics caused significantly higher percentage of conjunctival folliculo-papillary reaction compared to ICMA, the first postoperative day. Examination at one week after surgery did not support any significant differences between groups. Neither was proved any difference in other ocular signs.

11. ICMA administration, just after the first incision, resulted in a significant reduction of the preoperative preparation, without increasing the duration of the surgery. The length of the entire procedure (from the first drop to the end of the surgery) significantly decreased by about 25 minutes in the ICMA treated patients compared to the standard eye drops, which shortened the procedure by 2-3 times. This markedly reduced preparation time may result in a considerable benefit for the patients, as it can omit the discomfort of intensive topical mydriatics preoperatively, leading to a less stressful experience for the ICMA treated patients.

12. The absence of serious and related to the treatment adverse events (AE), intraoperative and postoperative out to one week, indicates that the intracameral administration of fixed combination of mydriatics and anaesthetic did not demonstrate any differences in the safety profile compared to the current standard topical eye drops.

11.2 Efficacy conclusions

1. Efficacy of ICMA administration in cataract surgery was measured in terms of patients and investigators satisfaction. Monitoring patient satisfaction and examining its determinants is of value to improve cataract surgery care. Satisfaction score with the ICMA rated significantly higher the quality of the patients' comfort during cataract surgery compared to the control group. The causes of lower patient satisfaction with the standard mydriatic and anaesthetic eye drops could be focused onto intraoperative discomfort, pain and/or pressure suffered during surgical maneuvers and mainly the IOL implantation.

2. A significantly higher level of surgeon/investigators satisfaction was reported in the ICMA treated patients. Our experience with ICMA administration showed that patients' cooperation increased during surgery, making the procedure less technically challenging.

11.3 Overall conclusions

Certain advantages in the use of intracameral fixed combination of mydriatics and anaesthetic (Fydrane®), as an alternative to standard topical eye drops, have been demonstrated by safety and efficacy results in our study.

Fydrane usage in routine cataract surgery reduced ocular surface damage by decreasing corneal epithelial and conjunctival toxicity with faster recovery of ocular surface integrity and lower intraocular scattering, compared to the use of standard topical eye drops. Additionally, Fydrane shortened and facilitated the preoperative and surgical procedure; increased the intraoperative comfort, decreased the postoperative symptoms and was preferred by both patients and investigators.

12. CONCLUSIONES

12.1 Conclusiones de seguridad

1. El daño en la superficie ocular evaluado mediante la tinción corneal y conjuntival, de acuerdo con los esquemas de Oxford y van Bijsterveld, disminuyó más rápido después de la administración de la combinación fija intracameral de midriáticos y anestésico (ICMA) en comparación con el tratamiento estándar con gotas oftálmicas de midriáticos y anestésicos, aunque la tendencia no ha sido de significación estadística.

2. La evaluación de la recuperación de la agudeza visual mejor corregida (BCVA) después de la cirugía de cataratas proporcionó resultados similares para el tratamiento con ICMA y el estándar con gotas de midriáticos y anestésicos.

3. El porcentaje de pacientes que experimentaron alteraciones epiteliales después de la cirugía fue significativamente menor en los pacientes tratados con ICMA. Además, se logró una restauración más rápida de la superficie del epitelio corneal con un epitelio homogéneo, liso, sin alteraciones en una semana después de la cirugía; mientras que algunos pacientes que recibieron el tratamiento estándar con gotas oftálmicas midriáticas y anestésicas sufrieron algún grado de epiteliopatía, que seguía en curso al finalizar el seguimiento del estudio, más de 7 días después de la cirugía.

4. La hiperemia conjuntival aumentó a lo largo del estudio en ambos grupos de tratamiento, con el grupo ICMA manteniendo un mayor porcentaje de pacientes sin hiperemia durante las visitas postoperatorias, aunque sin diferencias estadísticamente significativas entre los grupos.

5. Los cambios en la presión intraocular, desde el preoperatorio a los 7 días después de la cirugía, no demostraron diferencias significativas cuando se administró la inyección intracameral, lo que sugiere que el uso de ICMA tenía un perfil de seguridad similar al protocolo estándar para midriasis y anestesia preoperatoria.

6. La evaluación de la calidad óptica por el índice de dispersión objetivo (OSI) reveló una menor dispersión intraocular en el grupo ICMA en comparación con el tratamiento estándar de gotas de midriáticos y anestésicos. Aunque la tendencia

no ha sido de significación estadística, menor dispersión intraocular se asocia con mejor calidad óptica y se considera de relevancia clínica.

7. Se observó inestabilidad de la película lagrimal (VBUT) el primer día postoperatorio en ambos grupos, con tendencia a la recuperación gradual a los valores preoperatorios una semana después de la cirugía. Los cambios en la estabilidad de la película lagrimal, antes y 7 días después de la cirugía, no demostraron diferencias estadísticamente significativas entre los grupos.

8. Las quejas oculares subjetivas, puntuadas con el cuestionario OSDI, demostraron una mejoría general en las puntuaciones totales de los OSDI postoperatorios a la semana de la cirugía en ambos grupos, con resultados ligeramente mejores en el grupo ICMA, centrando la mejora en los síntomas visuales (puntuación B). Sin embargo, no se detectaron cambios significativos entre el cuestionario OSDI preoperatorio y postoperatorio comparando los dos grupos.

9. Los síntomas oculares como irritación, ardor y escozor se experimentaron en un porcentaje de pacientes menor y con menos gravedad en aquellos tratados con ICMA el primer día postoperatorio, lo que ha demostrado una diferencia estadísticamente significativa en comparación con el grupo de tratamiento estándar con gotas de midriáticos y anestésicos. La incidencia de la sensación de cuerpo extraño, sufrida el primer día postoperatorio, fue casi el doble entre los pacientes tratados con el tratamiento estándar, aunque la tendencia no fue significativa. Con respecto al dolor ocular, la fotofobia y otros síntomas subjetivos, durante el postoperatorio, no se registraron más diferencias entre los grupos.

10. El tratamiento estándar con gotas de midriáticos y anestésicos causó un porcentaje significativamente mayor de reacción folículo-papilar conjuntival en comparación con el tratamiento ICMA el primer día postoperatorio. El examen a la semana después de la cirugía no confirmó diferencias significativas entre los grupos. Tampoco se demostraron diferencias en otros signos oculares.

11. La administración de ICMA, justo después de la primera incisión, resultó en reducción significativa de la preparación preoperatoria, sin aumentar la duración de la cirugía. La duración de todo el procedimiento (desde la administración de la

primera gota hasta el final de la cirugía) disminuyó significativamente unos 25 minutos en los pacientes tratados con ICMA en comparación con el tratamiento estándar, lo que acortó el procedimiento entre 2 y 3 veces. Este tiempo de preparación notablemente reducido puede resultar en un beneficio considerable para los pacientes, ya que puede omitir la incomodidad de la intensiva administración de midriáticos tópicos preoperatoriamente, y llevar a una experiencia menos estresante para los pacientes tratados con ICMA.

12. La ausencia de eventos adversos graves relacionados con el tratamiento, intraoperatorios y postoperatorios hasta una semana después de la cirugía, indica que la administración de ICMA no demostró diferencias en el perfil de seguridad en comparación con el actual protocolo estándar con gotas de midriáticos y anestésicos.

12.2 Conclusiones de eficacia

1. La eficacia de la administración de ICMA en la cirugía de cataratas se midió en términos de satisfacción de los pacientes e investigadores. Monitorear la satisfacción de los pacientes y examinar los determinantes de satisfacción es valioso para mejorar la atención de la cirugía de cataratas. Los pacientes declararon sentirse más cómodos durante la cirugía cuando fueron tratados con ICMA. La satisfacción de los pacientes fue calificada significativamente más alta con el ICMA en comparación con el tratamiento control. Las causas de menor satisfacción de los pacientes con el tratamiento estándar con midriáticos y anestésicos tópicos podrían centrarse en la incomodidad intraoperatoria, el dolor y/o la presión sufrida durante las maniobras quirúrgicas y principalmente durante la implantación de la lente intraocular (LIO).

2. La satisfacción de los investigadores/cirujano fue significativamente mayor con el tratamiento de ICMA. Nuestra experiencia con la inyección de ICMA demostró que la cooperación de los pacientes aumentó durante la cirugía, lo que hizo que el procedimiento fuera técnicamente menos complejo.

12.3 Conclusiones generales

En conclusión, ciertas ventajas en el uso de la combinación fija intracameral de midriáticos y anestésico (Fydrane®), como alternativa al tratamiento tópico estándar con gotas de midriáticos y anestésicos, han sido demostradas por los resultados de seguridad y eficacia en nuestro estudio.

El uso de Fydrane en la cirugía de cataratas redujo el daño de la superficie ocular al disminuir la toxicidad de la conjuntiva y del epitelio corneal con una recuperación más rápida de la integridad de la superficie ocular y con menos dispersión intraocular, en comparación con el uso del tratamiento tópico estándar. Además, Fydrane acortó y facilitó el procedimiento preoperatorio y quirúrgico; aumentó la comodidad intraoperatoria, disminuyó los síntomas postoperatorios y fue preferido tanto por los pacientes como por los investigadores.

13. REFERENCES

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