

Ocular Surface Changes and Glaucoma: A Prospective Contralateral Study of IOP-Reducing Eyedrops versus iStent Inject Surgery

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Purpose: To compare ocular surface outcomes between interventional glaucoma treatment with trabecular micro-bypass stent implantation and continued topical intraocular pressure-lowering therapy.

Patients and Methods: A prospective, single-center, contralateral-eye study of patients with bilateral, mild-to-moderate open-angle glaucoma undergoing implantation of the iStent inject in the study eye, while the fellow eye (control eye) continued topical medications. Just over half the eyes in both groups underwent phacoemulsification. Ocular surface parameters were evaluated using objective tests and validated symptom questionnaires at baseline and at 1, 3, and 6 months.

Results: Fifty-six eyes were included, 28 in each group. At 6 months, medication use reduced significantly in study eyes (from 1.9 ± 1.0 preoperatively to 0.4 ± 0.6 ; $p < 0.001$), but not in control eyes (from 1.5 ± 0.9 to 1.4 ± 0.8 ; $p = 0.168$). Study eyes demonstrated significant improvements in keratograph bulbar redness score (2.4 ± 0.6 to 2.0 ± 0.4 ; $p = 0.003$), and Oxford ocular surface staining (OSS) score (1.6 ± 1.2 to 0.7 ± 1.0 ; $p < 0.001$) while control eyes did not; improvements in bulbar redness and OSS scores were significantly greater in study eyes ($p = 0.005$ and $p = 0.045$, respectively). Patient-reported symptoms improved significantly: OSDI (Ocular Surface Disease Index) scores decreased from 18.4 ± 16.4 to 9.3 ± 8.9 ($p = 0.007$) and SPEED (Standard Patient Evaluation of Eye Dryness) II scores decreased from 8.0 ± 7.8 to 4.5 ± 4.1 ($p = 0.005$).

Conclusion: Interventional glaucoma treatment with trabecular micro-bypass stent implantation significantly reduced medication burden, which was associated with improved signs and symptoms of ocular surface disease at 6 months. Compared to fellow eyes on topical therapy, stent-treated eyes showed better outcomes in selected ocular surface parameters, supporting the benefits of an interventional approach.

Keywords: ocular surface disease, glaucoma medications, iStent inject, dry eye disease, MIGS

Introduction

Despite advances in glaucoma treatment, topical medical therapy remains the established first-line treatment, effective in reducing intraocular pressure (IOP) and preventing progression to irreversible blindness.¹ However, laser trabeculoplasty techniques—such as selective laser trabeculoplasty (SLT) and micropulse laser trabeculoplasty (MP-LT)—are increasingly being adopted as primary interventions for early or moderate glaucoma, as they effectively lower intraocular pressure while reducing the long-term burden and ocular surface toxicity associated with chronic topical therapy.^{2,3} Nevertheless, for many patients, the burden of lifelong topical therapy and complex multi-drug regimens remains considerable, often leading to poor treatment adherence, increased cost of care, and impaired quality of life (QoL).⁴ Another significant drawback is the risk of ocular surface toxicity.

Ocular surface disease (OSD) is widespread in glaucoma patients, showing a prevalence of 48–59% in various studies.^{5,6} Benzalkonium chloride, a common preservative in glaucoma medications, is known to cause corneal and conjunctival toxicity in patients on long-term topical glaucoma therapy. BAK can disrupt the corneal epithelium, reduce goblet cell density, and induce inflammation, thereby exacerbating ocular surface disease and potentially compromising



surgical outcomes.⁷ Recent developments include the introduction of preservative-free formulations and alternative, less cytotoxic preservatives such as Polyquad[®], potassium sorbate, and Purite[®], which are associated with a lower risk of ocular surface toxicity. Although clinical evidence remains limited, these agents represent a useful strategy to minimize preservative-related ocular surface injury when preservative-free options are not available or affordable.⁸ In addition, the IOP-lowering active agents themselves can also be associated with ocular surface toxicity: prostaglandin analogs can cause conjunctival hyperemia and meibomian gland dysfunction, while beta-blockers can impair tear production, cause corneal epithelial disruption, and induce inflammatory changes in the conjunctiva.⁹ Several studies have shown an association between OSD severity and the number of glaucoma medications used.^{10,11}

Ocular symptoms due to OSD, such as tearing, burning, or itching, can worsen adherence to glaucoma medications, increasing the risk of progressive glaucomatous vision loss.^{12,13} OSD in medically treated patients can also negatively affect QoL due to the ocular discomfort and associated visual disturbances, such as blurred vision, night vision difficulties, and trouble with near vision and reading.^{14,15} Additionally, increased subclinical conjunctival inflammation can increase the likelihood of failure of filtration surgery.¹⁶ Due to these significant drawbacks, glaucoma treatment aims to not only reduce IOP but also medication dependence.

Although filtration surgery such as trabeculectomy can achieve freedom from medications, it carries the risk of sight-threatening complications.¹⁷ Additionally, trabeculectomy itself has been associated with development of OSD in some studies.^{18,19} In comparison, minimally invasive glaucoma surgery (MIGS) has a more favorable safety profile, with proven efficacy in reducing IOP and medication use, making them an ideal alternative to invasive surgeries in mild to moderate glaucoma.²⁰ However, the impact of MIGS on the ocular surface, either through medication reduction or through the surgical process itself, has yet to be established.

Interventional Glaucoma (IG) is a contemporary treatment paradigm that emphasizes early procedural intervention to reduce dependence on topical IOP-lowering medications.⁴ Within this framework, trabecular micro-bypass stents such as the iStent and iStent inject (Glaukos Corporation, Laguna Hills, CA) are commonly used MIGS devices. These biocompatible titanium implants create direct channels for aqueous outflow through the trabecular meshwork and have been shown to effectively decrease IOP and medication use in open-angle glaucoma (OAG).^{21,22} However, limited data are available on the impact of iStent surgery on ocular surface health.^{23,24} This study evaluated the effect of iStent inject implantation, with or without cataract surgery, on ocular surface parameters over six months, comparing outcomes to those of fellow eyes managed with ongoing topical therapy.

Patients and Methods

Study Design and Participants

This prospective nonrandomized contralateral-eye study recruited patients with bilateral glaucoma at a private eye clinic in Haugesund, Norway, from March 2022 to December 2023. The study complied with the tenets of the Declaration of Helsinki and Good Clinical Practice (GCP) and was approved by the Regional Committee for Medical and Health Research Ethics in Norway (reference number 2021/253,485). All participants provided written informed consent.

Inclusion criteria were age above 18 years, a diagnosis of bilateral OAG, visual field (VF) mean deviation better than -12 dB, and stable, well-controlled glaucoma on topical medications. Stability was defined as no progression on Standard Automated Perimetry (SAP) using the Zeiss Humphrey 24-2 program, with no worsening detected across three consecutive VF tests performed within six-months.

Exclusion criteria were manifest corneal pathology or scarring, eyelid deformities, intra- or extra-ocular surgery in the preceding six months, pregnancy, and any acute or chronic illness that could confound the study outcomes (eg, autoimmune disorders, connective tissue disease, clinically significant atopy, diabetes).

The eye with higher IOP and/or worse VF damage was designated as the study eye and received iStent inject implantation. The fellow eye continued glaucoma medications and served as the control. Study and control eyes with visually significant cataract underwent phacoemulsification in addition to stent implantation or pharmacotherapy, respectively.

Preoperative and Postoperative Assessments

All patients underwent standard ophthalmological examination, including refraction and visual acuity measurements, at baseline, 1-month, 3-month, and 6-month visits. At each visit, OSD was evaluated using a battery of objective and subjective assessments, with a 3-minute break between tests for standardization of measurements. Temperature and humidity in the examination room were noted for the baseline and 6-month visits to account for the influence of environmental conditions.²⁵

Patients were asked to discontinue any eyedrops two hours prior to OSD testing. Tests were performed in the following order:

1. Tear osmolarity was measured using the TearLab Osmolarity system (Tearlab Corp, California, USA) with the test card touching the lower temporal tear meniscus. Values ≥ 308 mOsm/L or inter-eye difference > 8 mOsm/L were defined as OSD.²⁶ Osmolarity was graded from 0–3: 0 (< 308 mOsm/L), 1 (308–315 mOsm/L), 2 (316–335 mOsm/L), and 3 (≥ 336 mOsm/L).
2. OSD symptoms were measured using two validated questionnaires:
 - i. The Ocular Surface Disease Index (OSDI) questionnaire measures visual disability due to ocular symptoms. Symptoms are scored from 0 (none of the time) to 4 (all of the time), with total scores ranging from 0–100; a score of ≥ 13 was considered as cut-off for OSD.²⁶ Scores were graded from 0–3 based on standard cutoffs for no, mild, moderate, and severe OSD: 0 (0–12), 1 (13–22), 2 (23–32), and 3 (> 33).²⁷
 - ii. The American Society of Cataract and Refractive Surgery (ASCRS)-modified Preoperative OSD SPEED II questionnaire is comprised of the original SPEED (Standard Patient Evaluation of Eye Dryness) questionnaire, which evaluates symptom frequency and severity, with additional questions designed to screen a preoperative population.²⁸ Total scores range from 0–28, with values ≥ 4 considered as OSD. Scores were graded from 0 (< 4) to 1 (4–28).
3. Bulbar conjunctival redness was measured using the Keratograph 5M (OculusOptikgeräte GmbH, Wetzlar, Germany). The software calculated redness scores (percentage area ratio between blood vessels and the rest of the analyzed area) from 0.0 to 4.0.²⁹ Higher scores represent greater hyperemia.
4. Tear meniscus height (TMH) and non-invasive keratograph tear break-up time (NIK BUT) were measured using the Keratograph 5M. NIK BUT was automatically measured by the device as time (seconds) from the last blink to the first tear film break-up (NIK BUT 1st) and average of all breakups (NIK BUT average) occurring in the measurement period set by the software (up to 24.98 s).³⁰ NIK BUT < 10 seconds was considered OSD²⁶ and given a score of 1, while NIK BUT measurements of 10–24 seconds were given a score of 0. TMH (millimeters) was measured at the central lower eyelid and a value ≤ 0.2 mm was considered OSD.
5. Tear film thickness (TFT) was measured with the Lipiview II Interferometer (TearScience Inc., Morrisville, NC), with 75 nm used as cut-off for OSD.
6. Tear production was measured with the Schirmer's I test (without anesthetic). Wetting of the Schirmer paper strips (TearFlo, MDT, Krakow, Poland) by ≤ 5.0 mm in 5 minutes was considered as cut-off for OSD.
7. Corneal sensitivity was measured in the center of the cornea with the Cochet–Bonnet esthesiometer (Aesthesiometer 12/100 mm; Luneau SAS, Pruney-Le-Gillon, France). On a grading scale of 0–6 mm, a grade of ≤ 5 was considered abnormal.
8. Ocular surface staining (OSS) was measured using the Oxford grading scheme (grades 0–5)³¹ after instillation of 5 μ L of 2% fluorescein sodium into the inferior fornix with a sterile-tip micro-pipette. Severity grades ≥ 2 were considered as OSD.
9. Meibomian gland dropout was examined using the Keratograph 5M and meiboscore was calculated on a 0–3 scale: 0 (no dropout), 1 ($< 1/3$ of glands lost), 2 ($1/3 - 2/3$ glands lost) and 3 ($> 2/3$ glands lost).³²
10. Meibum produced by the 5 central glands in the lower eyelid was assessed under the slit lamp by gently rolling a cotton swab towards the eyelid margin. Meibum expressibility was graded from 0–3: 0 (all glands expressible), 1 (3–4 glands were expressible), 2 (1–2 glands were expressible), and 3 (no glands were expressible). Meibum quality was graded from 0–3: 0 (clear fluid), 1 (cloudy meibum), 2 (granular meibum) and 3 (thick, toothpaste-like meibum).³³

TFT, corneal sensitivity, meiboscore, meibum characteristics, and ocular symptoms (OSDI and SPEED II scores) were evaluated at baseline and 6-month visits. All other OSD tests were performed at every visit. A diagnosis of OSD was made as per the Tear Film & Ocular Surface Society Dry Eye (TFOS/DEWS) II criteria: OSDI \geq 13 and at least one positive result for markers of homeostasis (osmolarity, OSS, NIKBUT).²⁶

Additionally, patients selected for cataract surgery underwent standard biometric evaluation for intraocular lens (IOL) power calculation.

Anti-Glaucoma Topical Medication

Patients were on prostaglandin analog monotherapy or fixed-combination therapy at baseline. When additional IOP lowering was required, a second agent (eg, carbonic anhydrase inhibitors, beta blocker or alpha-agonists) was prescribed at the discretion of the treating physician. Variability existed in the specific brands used within each medication class due to differences in prior prescriptions and pharmacy availability. Both preservative-free and BAK-containing formulations were represented. No medication washout or changes to topical therapy were performed during the study, except when IOP exceeded 20 mmHg, in which case escalation was recorded.

Adherence was assessed at each follow-up visit through patient self-report of missed doses within the previous week and cross-checked with pharmacy dispensing records when available.

Surgical Intervention

Study eyes underwent surgery with the iStent inject, comprised of 2 second-generation stents. The preloaded injector was inserted through a corneal incision and the first stent was implanted in the inferior nasal trabecular meshwork as described in the literature.^{21,22} The second stent was implanted 2–3 clock hours away from the first.

In eyes undergoing cataract surgery, standard small-incision phacoemulsification was performed, followed by iStent inject implantation.

Sample Size Calculation

The sample size calculation was based on hyperosmolarity as the primary outcome measure, with reference to normative data reported by Epitropoulos et al.³⁴ Using an alpha level of 0.05 and a power of 0.80, the estimated sample size was determined to be sufficient to detect clinically meaningful differences in tear osmolarity between groups.

Statistical Analysis

Statistical analyses were performed using SPSS version 24 (IBM SPSS, NY, USA). Primary outcomes were ocular surface parameters, while IOP and medications were secondary outcomes. Continuous variables were summarized using descriptive statistics. Baseline and 6-month data, as well as comparisons between the study and control eyes, were analyzed using the Wilcoxon signed-rank test. P value < 0.05 was considered statistically significant.

The study was designed and conducted independently by the investigators. Statistical analysis and medical writing support were provided by an independent writing agency funded by the study sponsor. The authors had full access to all study data, were responsible for data interpretation, and retained final authority over manuscript preparation and submission.

Results

Demographics

Thirty-two patients were enrolled. Four patients were excluded from the study: one due to panuveitis, one due to previous trabeculectomy, one for missing the follow-up visit, and one withdrew from the study. Fifty-six eyes of 28 patients (14 male and 14 female; mean age: 74.0 \pm 6.4 years) were included in the study. At baseline, patients were treated one of the following prostaglandin analogs or fixed combinations: tafluprost 0.15 mg/mL (3/28; 10.7%), bimatoprost 0.3 mg/mL (3/28; 10.7%), latanoprost 50 μ g/mL (6/28; 21.4%), timolol/bimatoprost 5 mg/0.3 mg per mL (5/28; 17.9%), or timolol/tafluprost 5 mg/0.15 mg per mL (11/28; 39.3%). Tafluprost formulations used in this cohort were preservative-free, whereas most other agents contained benzalkonium chloride (BAK) as the preservative.

Regarding concomitant phacoemulsification, 16 study eyes (57%) underwent stent + phacoemulsification and 12 (43%) underwent standalone stent implantation. Out of 28 control eyes that continued glaucoma medications, 15 (54%) underwent phacoemulsification.

IOP and Medications

IOP was significantly higher in the study eyes at baseline and 6 months postoperatively ($p < 0.001$), consistent with the selection of the worse eye for stent implantation (Figure 1). At 6 months, mean IOP reduced significantly in both study (20.5 ± 4.7 to 17.7 ± 4.3 mmHg, $p = 0.003$) and control groups (15.9 ± 3.7 to 14.3 ± 3.1 mmHg, $p = 0.019$), with comparable reductions between groups ($p = 0.125$).

Medication usage was comparable between groups at baseline ($p = 0.054$) and lower in the study group at 6 months ($p < 0.001$) (Figure 1). Medication burden was significantly reduced from baseline in study eyes (1.93 ± 1.0 to 0.43 ± 0.6 , $p < 0.001$) but not in control eyes (1.54 ± 0.9 to 1.36 ± 0.8 , $p = 0.168$), with greater reduction in study eyes ($p < 0.001$).

Ocular Surface Outcomes

Tables 1, 2, and Figure 2 show ocular surface outcomes in study and control eyes. Baseline ocular surface parameters were similar between groups: tear osmolarity, NIKBUT, NIKBUT-first, tear lab grading, tear film thickness (TFT), corneal staining score, Schirmer I, corneal sensitivity, and meiboscore values showed no statistically significant differences between study and control eyes (Tables 1 and 2, all $p > 0.05$).

No significant changes from baseline to 6 months were observed in either group for tear osmolarity, tear meniscus height (TMH), TFT, Schirmer I test, meiboscore, meibum expressibility, or corneal sensitivity (Table 1). NIKBUT remained stable in the control group, while the study group showed transient reductions at months 3 and 6, although the overall baseline-to-6-month change was not statistically significant. Between-group comparisons at 6 months also revealed no differences in these parameters, except that the study group demonstrated a greater change in tear osmolarity ($p = 0.045$) and higher Cochet–Bonnet esthesiometry values ($p = 0.013$), indicating better corneal sensitivity.

Meibum quality worsened slightly in both study and control eyes ($p = 0.032$ and $p = 0.015$, respectively). NIKBUT 1st was significantly reduced (worsened) from baseline in study eyes ($p = 0.006$), but reductions from baseline were comparable between study and control eyes (-2.74 ± 7.6 seconds versus -3.66 ± 8.3 seconds, respectively; $p = 0.940$) (Table 2). Room temperature and humidity were comparable between baseline and 6-month visits ($23.6 \pm 0.7^\circ\text{C}$ versus $23.9 \pm 0.8^\circ\text{C}$, $p = 0.213$ and $33.3 \pm 10.2\%$ versus $34.9 \pm 8.9\%$, $p = 0.718$, respectively).

Bulbar conjunctival redness and Oxford ocular surface staining (OSS) scores improved significantly from baseline in the study eyes ($p = 0.003$ and $p < 0.001$, respectively), but not in the control eyes ($p = 0.406$ and $p = 0.216$, respectively)

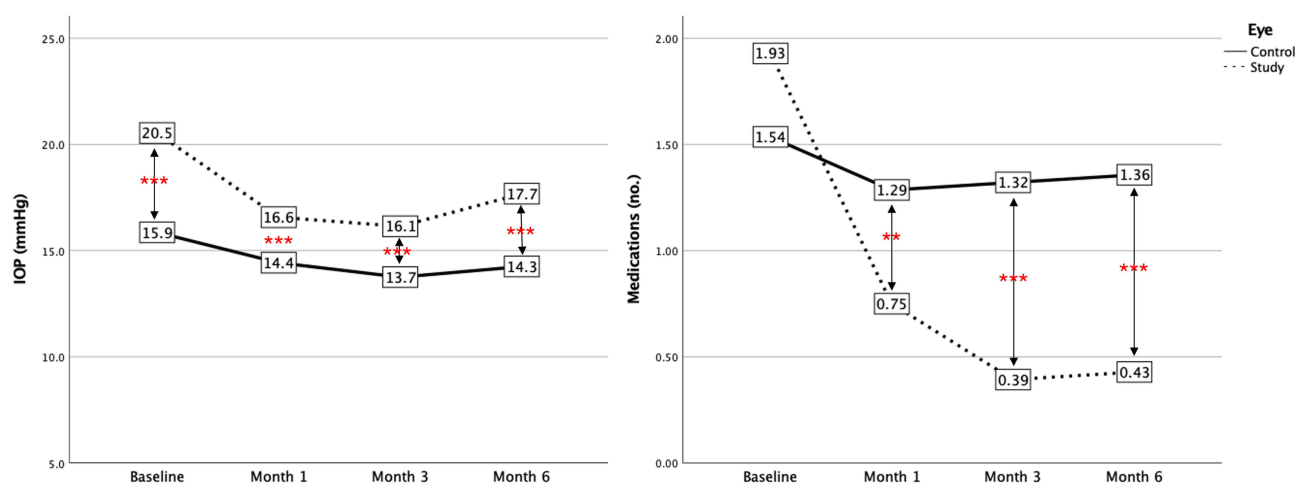


Figure 1 Line graphs showing intraocular pressure and medication usage of eyes in the control and study groups. Asterisks at a timepoint indicate statistically significant difference between the groups: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table I Ocular Surface Metric Outcomes of Study vs Control Group Showing No Significant Change from Baseline to 6 Months. P values Between Baseline and 6 Months, and P values Between Groups Were Calculated Using Wilcoxon Signed-Rank Test

OCULAR SURFACE METRICS	Baseline	Month 1	Month 3	Month 6	Change	P value [†]
Osmo						
Control group (n=28)	299.6±11.5	299.7±7.6 (n=26)	298.9±10.7	301.0±11.7 (n=27)	1.33±16.9 (n=27)	0.767
Study group (n=28)	302.3±12.8	301.3±14.4 (n=27)	301.2±13.5	298.7±1.26 (n=27)	-4.11±15.7 (n=27)	0.435
P value bet. groups	0.232	0.647	0.799	0.382	0.045*	
Tear Lab Grading						
Control group (n=27)	0.33±0.7	NA	NA	0.33±0.7	-0.04±0.9 (n=26)	0.714
Study group (n=28)	0.50±0.8	NA	NA	0.39±0.8	-0.11±1.2	0.716
P value bet. groups	0.301	-	-	0.943	0.296	
NIK BUT average						
Control group (n=28)	15.2±5.7	13.4±5.0 (n=27)	14.6±4.4	15.9±3.9 (n=26)	0.26±5.4 (n=26)	0.788
Study group (n=28)	14.1±5.9	13.2±4.9	12.2±3.9	12.8±4.1	-1.30±7.2	0.274
P value bet. groups	0.354	0.679	0.006*	0.002*	0.062	
NIK BUT grading						
Control group (n=28)	0.21±0.4	NA	NA	0.08±0.3 (n=26)	-0.12±0.4 (n=26)	0.233
Study group (n=28)	0.29±0.5	NA	NA	0.21±0.4	-0.07±0.6	0.565
P value bet. groups	0.424	-	-	0.129	0.588	
TMH						
Control group (n=28)	0.25±0.1	0.27±0.2 (n=26)	0.30±0.2 (n=27)	0.25±0.2 (n=26)	0.00±0.2 (n=26)	0.989
Study group (n=28)	0.30±0.2	0.25±0.1 (n=27)	0.32±0.3 (n=27)	0.26±0.1	-0.04±0.2	0.624
P value bet. groups	0.040*	0.409	0.936	0.241	0.619	
TFT						
Control group (n=28)	74.4±19.0	NA	NA	75.3±22.3 (n=26)	-0.73±21.7 (n=26)	0.958
Study group (n=28)	73.8±22.9	NA	NA	77.7±23.5 (n=27)	2.56±25.2 (n=27)	0.420
P value bet. groups	0.697	-	-	0.322	0.360	
Schirmer I						
Control group (n=28)	11.5±8.6 (n=27)	13.5±10.4 (n=26)	14.5±10.1	14.8±10.6 (n=27)	3.31±8.6 (n=26)	0.069
Study group (n=28)	12.1±9.2 (n=27)	16.1±11.1 (n=27)	15.4±9.6	14.3±9.5	1.93±7.3 (n=27)	0.219
P value bet. groups	0.702	0.272	0.670	0.371	0.770	
Cochet Bonnet						
Control group (n=28)	5.48±0.8	NA	NA	5.38±0.8	-0.11±0.5	0.316
Study group (n=28)	5.30±0.9	NA	NA	5.46±0.6	0.16±0.7	0.241
P value bet. groups	0.082	-	-	0.436	0.013*	
Meiboscore						
Control group (n=28)	1.20±0.9	NA	NA	1.30±0.8	0.11±0.4	0.209
Study group (n=28)	1.09±0.8	NA	NA	1.25±0.7	0.16±0.4	0.063
P value bet. groups	0.224	-	-	0.676	0.536	
Express						
Control group (n=28)	1.48±0.8	NA	NA	1.61±0.7	0.13±0.6	0.307
Study group (n=28)	1.48±0.8	NA	NA	1.59±0.8	0.11±0.5	0.326
P value bet. groups	0.887	-	-	0.829	0.958	

Notes: *Statistically significant. †P value between baseline and month 6.

Abbreviations: Osmo, Osmolarity; NIK BUT, Non-Invasive Keratograph Break-Up Time; TMH, Tear Meniscus Height; TFT, Tear Film Thickness; Express, Expressibility.

Table 2 Ocular Surface Metric Outcomes of Study vs Control Group Showing Significant Change from Baseline to 6 Months. P values Between Baseline and 6 Months, and P values Between Groups Were Calculated Using Wilcoxon Signed-Rank Test

OCULAR SURFACE METRICS	Baseline	Month 1	Month 3	Month 6	Change	P value [†]
Quality						
Control group (n=28)	1.13±0.6	NA	NA	1.39±0.6	0.27±0.5	0.015*
Study group (n=28)	1.13±0.6	NA	NA	1.36±0.6	0.23±0.5	0.032*
P value bet. groups	1.000	–	–	0.346	0.346	
NIK BUT 1st						
Control group (n=28)	11.0±7.1	6.61±4.8 (n=27)	7.18±5.1	7.90±5.3 (n=26)	-3.66±8.3 (n=26)	0.067
Study group (n=28)	8.53±6.7	6.57±5.1	5.40±3.1	5.89±4.5 (n=26)	-2.74±7.6	0.006*
P value bet. groups	0.119	0.611	0.198	0.018*	0.940	
Bulbar Red						
Control group (n=28)	2.23±0.5	2.19±0.6 (n=26)	2.29±0.4	2.25±0.4 (n=26)	-0.02±0.6 (n=26)	0.406
Study group (n=28)	2.39±0.6	2.27±0.4 (n=27)	2.22±0.5	2.00±0.4 (n=26)	-0.38±0.7	0.003*
P value bet. groups	0.138	0.211	0.448	0.014*	≤0.001*	
OSS Cornea						
Control group (n=28)	1.43±1.2	1.13±1.0 (n=26)	0.94±1.1 (n=27)	1.25±1.3	-0.18±1.2	0.216
Study group (n=28)	1.57±1.2	0.94±1.1 (n=27)	0.48±0.7 (n=27)	0.68±1.0	-0.89±1.1	<0.001*
P value bet. groups	0.522	0.528	0.016*	0.042*	0.010*	

Notes: *Statistically significant. †P value between baseline and month 6.

Abbreviations: NIKBUT, Non-Invasive Keratograph Break-Up Time; BulbarRed, Bulbar redness; OSS, Ocular Surface Staining.

(Table 2). Study eyes showed significantly greater improvements in bulbar redness scores (-0.38±0.7 versus -0.02±0.6, p=0.001) and OSS scores (-0.89±1.1 versus -0.18±1.2, p=0.010).

Considering the results per patient (as opposed to study eye versus control eye), OSDI and SPEED scores were significantly improved from baseline to 6 months (p=0.007 and 0.005, respectively). Mean OSDI score reduced from 18.4±16.4 at baseline to 9.3±8.9 at 6 months (-9.1±14.9), while SPEED score reduced from 8.0±7.8 to 4.5±4.1 (-3.6±6.6). Inter-eye difference in osmolarity showed no significant change from baseline (7.82±7.4 to 11.1±9.5; p=0.055).

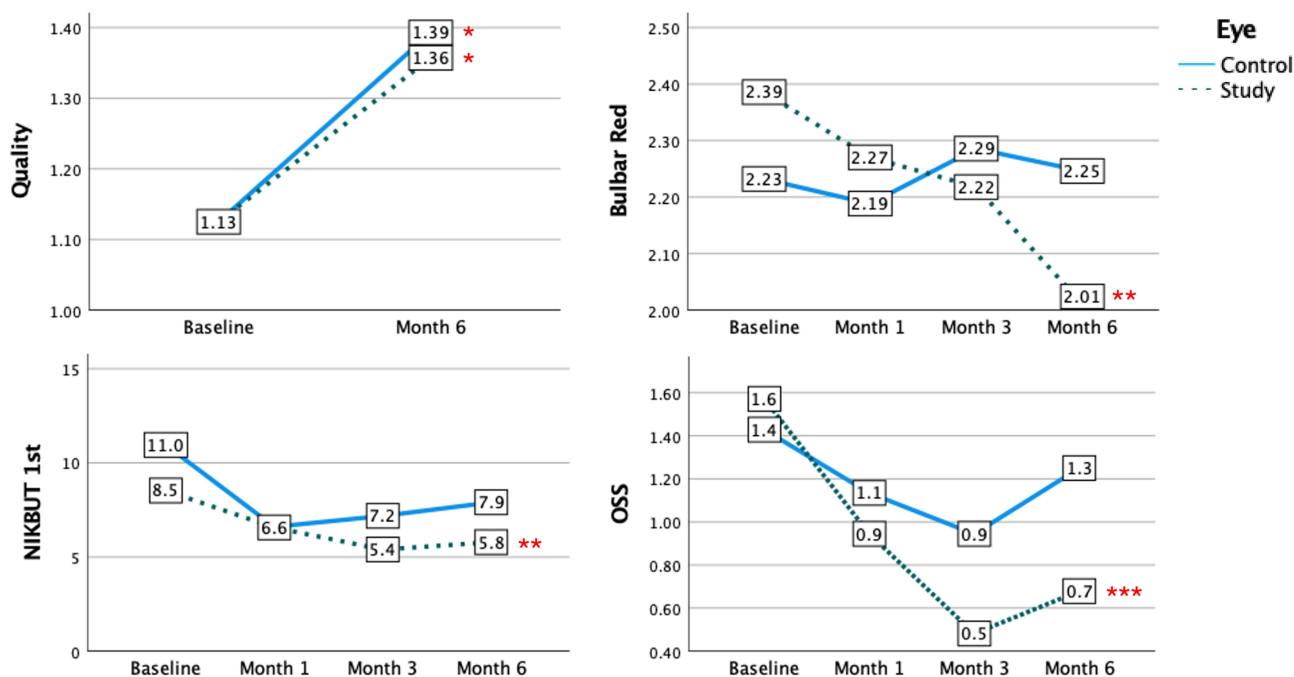


Figure 2 Ocular surface metric outcomes of eyes in the control and study groups showing significant change from baseline. Asterisks at a timepoint indicate statistical difference between baseline and Month 6. *p<0.05, **p<0.01, ***p<0.001.

Subgroup Analysis without Cataract Surgery (iStent-Only vs Medications-Only)

In the subgroup analysis excluding all eyes that underwent cataract surgery, most ocular surface parameters showed no significant differences between the iStent-only and medications-only groups at baseline or month 6 (Table 3). Tear osmolarity, tear meniscus height, tear film thickness, meiboscore, meibum quality, and meibum expressibility remained comparable between groups across all time points.

Table 3 Ocular Surface Metrics Outcomes of Eyes Grouped by Procedure (iStent Group vs No Procedure Group, Excluding Eyes That Underwent Cataract Surgery. P values Were Calculated Using the Wilcoxon Signed-Rank Test

OCULAR SURFACE METRICS	Baseline	Month 6	Change
Osmo	n=11	n=11	n=11
iStent	300.4±10.4	299.3±14.8	-1.1±17.9
Meds only	300.2±10.9	295.5±9.1	-4.6±15.9
P value bet. groups	0.606	0.407	0.878
Tear Lab Grading	n=11	n=11	n=11
iStent	0.36±0.7	0.36±0.8	0.00±1.2
Meds only	0.36±0.7	0.09±0.3	-0.27±0.8
P value bet. groups	1.000	0.371	0.850
NIK BUT 1st	n=12	n=11	n=11
iStent	9.0±6.0	5.7±3.0	-3.7±4.7
Meds only	8.9±5.8	9.2±6.9	-0.2±6.0
P value bet. groups	0.838	0.032*	0.175
NIK BUT average	n=12	n=11	n=11
iStent	15.1±5.2	13.3±3.7	-2.5±5.1
Meds only	14.8±5.9	16.5±4.5	1.2±6.0
P value bet. groups	0.790	0.005*	0.032*
NIK BUT grading	n=12	n=11	n=11
iStent	0.25±0.5	0.18±0.4	0.00±0.6
Meds only	0.25±0.5	0.09±0.3	-0.09±0.5
P value bet. groups	1.000	0.773	0.850
Bulbar Red	n=12	n=11	n=11
iStent	2.34±0.6	2.02±0.4	-0.38±0.4
Meds only	2.13±0.6	2.33±0.5	0.15±0.3
P value bet. groups	0.349	0.066	0.006*
TMH	n=12	n=11	n=11
iStent	0.30±0.2	0.25±0.1	-0.06±0.1
Meds only	0.25±0.1	0.28±0.2	0.04±0.3
P value bet. groups	0.126	0.563	0.083
TFT	n=12	n=11	n=11
iStent	68.0±19.6	76.4±20.8	7.2±21.2
Meds only	72.7±19.5	78.7±22.6	4.1±19.6
P value bet. groups	0.066	0.636	0.541
Schirmer I	n=12	n=11	n=11
iStent	14.0±9.2	15.0±12.0	1.0±6.3
Meds only	15.5±10.0	12.2±10.5	-2.2±7.2
P value bet. groups	0.574	0.108	0.024*
OSS Cornea	n=12	n=12	n=12
iStent	1.63±1.5	0.83±1.0	-0.79±1.2
Meds only	1.42±1.6	1.13±1.3	-0.29±0.9
P value bet. groups	0.784	0.495	0.102

(Continued)

Table 3 (Continued).

OCULAR SURFACE METRICS	Baseline	Month 6	Change
Cochet Bonnet	n=12	n=12	n=12
iStent	5.33±0.7	5.38±0.6	0.04±0.5
Meds only	5.54±0.7	5.21±0.9	-0.33±0.4
P value bet. groups	0.269	0.387	0.032*
Meiboscore	n=12	n=12	n=12
iStent	1.17±0.8	1.38±0.8	0.21±0.3
Meds only	1.33±0.8	1.42±0.8	0.08±0.3
P value bet. groups	0.174	1.000	0.345
Quality	n=12	n=12	n=12
iStent	1.29±0.6	1.42±0.6	0.13±0.4
Meds only	1.29±0.6	1.42±0.6	0.13±0.4
P value bet. groups	1.000	1.000	1.000
Express	n=12	n=12	n=12
iStent	1.42±0.9	1.58±0.9	0.17±0.7
Meds only	1.46±0.8	1.46±0.8	0.00±0.4
P value bet. groups	0.890	0.345	0.203

Note: *Statistically significant.

Abbreviations: Osmo, Osmolarity; NIKBUT, Non-Invasive Keratograph Break-Up Time; TMH, Tear Meniscus Height; TFT, Tear Film Thickness; Express, Expressibility; BulbarRed, Bulbar redness; OSS, Ocular Surface Staining.

However, several NIKBUT parameters demonstrated significant between-group differences at month 6. The medications-only group maintained higher NIKBUT average values compared with the iStent group (16.5 ± 4.5 vs 13.3 ± 3.7 ; $p = 0.005$), with a corresponding difference in change from baseline ($p = 0.032$). NIKBUT-1st was also significantly higher in the medications-only group at month 6 ($p = 0.032$).

Bulbar hyperemia diverged between groups, showing a greater reduction in the iStent group while increasing slightly in the medications group, yielding a significant difference in change from baseline ($p = 0.006$). Schirmer I test also showed a significantly different change pattern, with an increase in the iStent group and a decrease in the medications group ($p = 0.024$). Corneal sensitivity demonstrated a small but statistically significant between-group difference in change from baseline, favoring the iStent group ($p = 0.032$).

Safety

Corrected distance visual acuity (CDVA) improved from baseline to 6 months in both groups (Figure 3), with statistically significant improvement in the study eyes (0.04 ± 0.09 to -0.01 ± 0.08 logMAR; $p=0.003$) but not in control eyes (0.02 ± 0.09 to 0.00 ± 0.07 logMAR; $p=0.055$). Study eyes showed greater improvement in CDVA, although differences between groups were not statistically significant ($p=0.089$). No intraoperative or postoperative complications related to stent implantation or cataract surgery were noted.

Discussion

Following trabecular micro-bypass with the iStent inject, study eyes experienced a 79% reduction in glaucoma medication use (-1.5 ± 0.8 from a baseline of 1.9 ± 1.0) and a 13.95% IOP reduction, from 20.5 ± 4.7 to 17.7 ± 4.3 mmHg at 6 months. This was associated with statistically significant improvements in both objective and subjective ocular surface parameters, including bulbar redness, OSS, OSDI, and SPEED II scores. Notably, bulbar redness and OSS improved more in the study eyes than in the control eyes, supporting the contribution of reduced medication burden to enhanced ocular surface health. No adverse events were observed, and stent implantation did not compromise visual outcomes following cataract surgery.

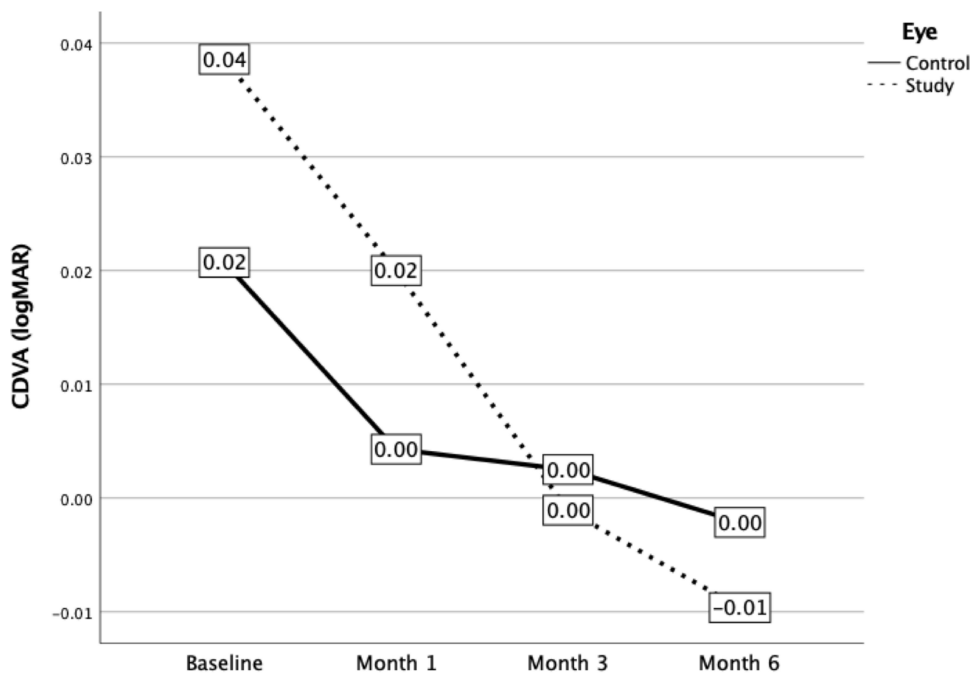


Figure 3 Line graphs showing visual outcomes of eyes in the control and study groups.

In contrast, the fellow control eyes that continued anti-glaucoma medications showed a modest IOP reduction from 15.9 ± 3.7 to 14.3 ± 3.1 mmHg (10%), despite not receiving an iStent. This improvement is likely multifactorial. A proportion of control eyes also underwent phacoemulsification, which can lower IOP by approximately 1–3 mmHg.^{35,36} Additionally, better overall adherence following surgery in the study eye may have indirectly influenced IOP control in the fellow eye. Together, these factors likely explain the modest yet statistically significant IOP decrease observed in the control eyes in this contralateral-eye study.

Although the study eye was defined by higher IOP or worse visual field, baseline measures of ocular surface disease were comparable between groups; therefore, selection of the study eye did not produce a detectable baseline OSD imbalance that could account for the greater OSD improvement observed after surgery.

Previous studies have found OSDI and OSS to be significantly correlated with number of medications used.^{6,37} Consistent with the literature, we found OSS to be significantly improved at 6 months in the study eyes, with improvements noticed from the first month, showing that ocular health was rapidly restored following medication reduction. OSDI was significantly improved despite unilateral intervention. Mean OSDI score improved from mild OSD (score of 18.4 ± 16.4) to normal (score of 9.3 ± 8.9). Notably, this improvement (-9.1 ± 14.9) was more than the minimal clinically important difference (MCID) defined for OSDI, which ranges from 4.5 to 7.3 for mild OSD, and 7.0 to 9.9 for all OSD grades.²⁷ Additionally, improvements were observed in both objective and subjective OSD measures, which is significant when compared to previous literature showing low correlations between signs and symptoms of OSD.^{33,38,39} In our study, osmolarity did not show significant changes from baseline in either group, but this may be attributed to the baseline osmolarity in both groups being well below the cutoff for OSD (302.3 ± 12.8 and 299.6 ± 11.5 mOsm/L in study and control groups, respectively).

Compared to the broad evidence base on the IOP- and medication-lowering efficacy of the iStent devices, the assessment of ocular surface changes following trabecular micro-bypass has been limited. Samuelson et al found patient-reported QoL outcomes to be significantly improved over 24 months following iStent inject implantation with cataract surgery, with responders (patients that showed minimally important differences) found to be more likely to be medication-free than non-responders.⁴⁰ Jones et al observed significantly improved glaucoma-specific and general health QoL, OSDI, tear break-up time (TBUT), and corneal staining at 4 months following iStent + phacoemulsification, with or without adjunctive endocyclophotocoagulation.²⁴ Schweitzer et al found OSDI, ocular staining, and fluorescein TBUT to

be significantly improved 3 months after iStent or iStent inject implantation with concomitant cataract surgery.²³ Following reduction in medication burden by 60% from 1.5 ± 0.9 to 0.6 ± 0.8 medications, OSDI score reduced by 56% from 39.8 ± 21.9 to 16.4 ± 14.8 , and Oxford ocular staining score showed a 71% reduction from 1.4 ± 1.0 to 0.4 ± 0.5 ($p < 0.0001$). Similarly, in the current study, mean OSDI score was reduced by 49% at 6 months (18.4 ± 16.4 to 9.3 ± 8.9 ; $p = 0.007$) and mean OSS score reduced by 56% in the study group (1.6 ± 1.2 to 0.7 ± 1.0) ($p < 0.001$). This was associated with medication reduction by 79% (1.9 ± 1.0 to 0.4 ± 0.6 ; $p < 0.001$).

Contrary to Schweitzer et al and Jones et al, the current study found NIKBUT 1st to be significantly worsened from baseline to 6-month timepoints in the study eyes, despite non-significant differences in room temperature, humidity, and TFT between visits. The unexpected worsening of NIKBUT 1st in the study eyes may reflect a transient postoperative effect rather than a paradoxical deterioration. Corneal incisions, postoperative inflammation, and topical medications may transiently destabilize the tear film. In our series, NIKBUT 1st decreased markedly at 1 month but showed gradual improvement at 3 and 6 months, although values remained below baseline at the 6-month follow-up. This trend suggests that tear-film stability begins to recover after surgery but may require a longer period to fully normalize once postoperative factors resolve and topical medication burden is reduced. However, average NIKBUT measurement did not show a significant change from baseline ($p = 0.274$). It must be noted that NIKBUT values show high between-visit variability due to various factors including keratograph precision and intrinsic variability in the tear film.^{41,42} The standard deviations of TBUT observed in the current study were greater than that noted by Schweitzer et al,²³ which could also have contributed to increased variability of results, as keratograph measurements have been found to show lower repeatability at higher values.⁴¹

It must be noted that cataract surgery itself can also induce OSD due to factors including damage to corneal nerves, ocular surface drying/repeated irrigation, phototoxicity, and perioperative medications.^{43,44} Thus, it is possible that ocular surface parameters in the current study could have been confounded by concomitant phacoemulsification. However, a similar proportion of patients underwent phacoemulsification in the study and control groups (57% and 54%, respectively), and we can assume that confounding factors were comparably distributed between both groups. To address the potential confounding effect of phacoemulsification, we performed a subgroup analysis restricted to eyes that underwent iStent implantation alone compared with eyes that remained on topical therapy. After removing all eyes that had cataract surgery, most ocular surface parameters remained comparable between groups, indicating that the primary findings were not driven by phacoemulsification. Tear film stability indices (NIKBUT) remained higher in the medications-only group, whereas the iStent-only group demonstrated more favorable changes in bulbar hyperemia, Schirmer I, and corneal sensitivity. These patterns mirror the trends observed in the full cohort, supporting the conclusion that the differential effects observed between groups are attributable to the treatment modality rather than cataract surgery.

The current study allows the ocular surface-related changes following MIGS to be compared to traditional filtering surgery results reported in the scientific literature. Trabeculectomy can reduce ocular inflammation and improve ocular surface parameters by reducing medication dependence.^{45–47} However, the surgery itself may also worsen OSD: the filtering bleb can impair tear film distribution,¹⁹ while antimetabolite usage can cause limbal stem cell deficiency, and conjunctival trauma can impair ocular surface homeostasis.⁴⁸ In comparison, iStent inject surgery preserves ocular tissue with a high safety profile demonstrated in previous studies as well as the current study. Our findings provide additional evidence that iStent inject implantation, with or without concomitant cataract surgery, does not impair ocular surface health, but rather improves it. As glaucoma patients have a higher risk of OSD, it is vital to consider the ocular surface benefits of a procedure in addition to its IOP- and medication-lowering efficacy during the decision-making process.

This study contributes some of the first evidence on the impact of MIGS on the ocular surface. The strengths of the study include its prospective design, which reduces selection bias. The contralateral-eye design was also valuable in removing bias due to inter-individual anatomic or physiological differences. Additionally, OSD was evaluated with a comprehensive slate of both objective and subjective measures, with the subjective parameters measured by widely used validated questionnaires (OSDI and SPEED II).

The limitations of this study include a relatively small sample size from a single-center population in Norway, limiting the generalizability of results to other ethnicities. Examiners were unmasked to the study groups, which could have introduced some bias. Additionally, a history of lubricant eyedrop use was not an exclusion criterion, which could

have underestimated OSD severity in patients using such drops. A further limitation is the heterogeneity of preservative exposure across brands of topical therapy prior to enrolment. While the primary focus was on drug class and medication burden, different preservative formulations may have contributed variably to ocular surface disease. In addition, although we assessed self-reported adherence and logged any medication modifications, recall bias and unrecorded changes cannot be entirely excluded. Further studies with longer durations of follow-up are required to investigate the longer-term effects and the durability of iStent inject implantation on the ocular surface and possible late changes.

Conclusion

In summary, this study evaluated the impact of an interventional glaucoma approach—specifically, trabecular microbypass stent implantation—on ocular surface parameters in patients with open-angle glaucoma. At 6 months post-operatively, marked reduction in medication burden and achievement of IOP control were accompanied by significant improvements in both signs and symptoms of ocular surface disease. Objective improvements, in particular, reductions in bulbar conjunctival redness and Oxford ocular surface staining scores, occurred in parallel with decreased medication use. Similarly, subjective assessments such as the OSDI and SPEED II scores showed clinically meaningful improvements. While these results support the potential of interventional glaucoma strategies to alleviate ocular surface toxicity associated with long-term topical pharmacotherapy, the findings should be interpreted with caution given the modest sample size, single-center design, and short follow-up period. Future multicenter studies with larger cohorts and longer follow-up are warranted to confirm these results and further explore the long-term ocular surface effects of MIGS.

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Disclosure

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