#253485 Avvikende tårefilm hos glaukompasienter - Lokalbehandling versus kirurgisk intervensjon

Application Info

Søknadsid:	253485
Utlysning:	Prosjektsøknad
Søker:	Kjell Gunnar Gundersen
Prosjektleder:	Kjell Gunnar Gundersen

MEDISINSK OG HELSEFAGLIG FORSKNINGSPROSJEKT

Jeg har lest instruksjonene i feltet over og fyller ut søknaden på norsk

Ja

1 GENERELLE OPPLYSNINGER

1.1 Utsatt offentlighet

1.1 Søkes det om utsatt offentlighet?

Nei

1.2 Tidsramme for prosjektet

1.2.1 Prosjektstart - estimert start for prosjektet: det tidspunkt hvor rekrutteringen starter, eller det tidspunkt hvor du vil be om utlevering av data fra register eller humant biologisk materiale fra en biobank.	01.06.2021
1.2.2 Prosjektslutt - tidspunkt hvor du planlegger at publisering av resultater i prosjektet skal være overstått.	31.05.2022

1.3 Prosjekttittel

1.3.1 Norsk tittel	Avvikende tårefilm hos glaukompasienter - Lokalbehandling versus kirurgisk intervensjon

1.3.2 Vitenskapelig tittel

Ocular Surface and glaucoma. A contralateral study of IOP reducing eyedrops versus surgical intervention on Ocular Surface

1.4 Prosjektleder

Registrerte opplysninger om prosjektleder

ID	14412
Fornavn	Kjell Gunnar
Etternavn	Gundersen
Epost	kg@ifocus.no
Telefon	4791648707

1.5 Forskningsansvarlig institusjon

1.5.1 Hvilken norsk forskningsinstitusjon er prosjektleder knyttet til i prosjektet (Koordinerende institusjon)?	IFocus Øyeklinikk AS

1.6 Samarbeidende institusjoner

Institusjon	Universitetet i Sørøst-Norge
Kontaktperson	Per Lunmark
Stilling	Amanuensis
E-post	per.lundmark@usn.no

1.7 Prosjektmedarbeidere

Navn	Andrea Mihovilovic
Akademisk grad	Mastergrad
Stilling	Optometrist
Institusjon	IFocus Øyeklinikk AS
Prosjektrolle	Prosjektoptiker og masterkandidat

1.8 Initiativtaker

1.8.1 Hvem er initiativtaker til prosjektet?	Prosjektleder og/eller forskningsansvarlig institusjon (bidragsforskning)

1.9 Utdanningsprosjekt

1.9.1 Er prosjektet del av en utdanning?

Ja

1.9.1.1 Studium/fag	Mastergrad innen optometri
1.9.1.2 Studienivå	Master

1.10 Utprøving av medisinsk utstyr

1.10.1 Omfatter studien utprøving av medisinsk utstyr?

Nei

1.11 Samarbeid med utlandet

1.11.1 Har prosjektet noen form for samarbeid med utlandet?

Ja

1.11.1.1 Hvilket samarbeid?

- Annet samarbeid?

1.11.1.1.4 Annet samarbeid med utlandet - hvilke land?
USA

1.11.1.1.5 Annet samarbeid med utlandet - beskriv

Studien mottar økonomisk støtte fra Glaukos,
229 Avenida Fabricante, San Clemente, CA 92672
tel 949-481-0172 fax 949.367.9984
www.glaukos.com

1.12 Andre prosjekter med betydning for vurderingen

1.12.1 Har REK behandlet framleggingsvurdering, annet prosjekt eller generell biobank som kan være relevant for vurderingen av dette prosjektet?

Ja

1.12.1.1 Hvilke?

Prosjektnummer	Prosjektnavn	Relevans
64847	Prevalensstudie av avvikende tårefilmkvalitet hos grå stær pasienter	Tårekvalitetsstudie - OSD
65988	Avvikende tårefilmkvalitet - Betydning for optimal refraktiv presisjon ved operative behandling av grå stær	Tårekvalitetsstudie - OSD
140664	Metabolomikk av tåreprøver	Tårekvalitetsstudie - OSD

1.12.2 Er det andre opplysninger REK bør kjenne til som kan ha betydning ved behandlingen av søknaden?

Nei

2 PROSJEKTOPPLYSNINGER OG METODE

Oppsummering av forskningsprosjektet

2.1 Prosjektbeskrivelse

Formålet er å vurdere behandlingen av høy intraokulært trykk (IOP) i pasienter med glaukom. Pasienter skal få behandling med IOP-redserende øyedråper i et øye og kirurgi i det andre. Prosjektet skal vise hvilken behandling passer beste til enkelt pasienter med spesifikk egenskaper og overalt suksess.

Studiemetode/-design

2.2.1 Metode for analysering av data

- Kvantitative analysemetoder
- Kvalitative analysemetoder

2.2.2 Prosjekttype

- Klinisk behandlingsstudie (HODs definisjon)

Klinisk behandlingsstudie

- Annen klinisk intervensjonsstudie (deltakerne er pasienter)

2.2.2.5 Redegjør og begrunn planlagt informasjon og oppfølging av pasientene etter gjennomført studie

Studiedeltagere rekrutteres fra pasienter som behandles med en eller flere medikament for å redusere øyetrykket (IOP) i begge øyne. Studiedeltagere skal etter inklusjon gjennomgå en grundig klinisk og laboratoriebasert diagnostikk for avvikende tårefilmkvalitet. Etter at deltagernes tårefilmstatus er dokumentert skal et øye randomiseres til fortsatt medikamentell behandling med lokale øyedråper, mens det andre randomiseres til implantasjon av iStent Inject, Det skal implanteres to iStent inject i hvert studieøye etter fastlagt operativ protokoll, enten i forbindelse med en grå stær operasjon, eller som frittstående behandling. iStent inject er godkjent for operativ behandling av høyt øyetrykk og er vel dokumentert (Ref. J Cataract Refract Surg 2021; 47:385-399).
Studiedeltagerne vil deretter bli fulgt med studiebesøk etter fastlagt protokoll for å observere IOP og tårestatus i studieøynene. Etter siste studiebesøk vil pasientene fortsatt følges opp i regi av klinikkens glaukomkontroll.

3 FORSKNINGSDATA

Innsamling av data

3.1 Skal det samles inn nye data i prosjektet?

Ja

3.1.1 Metode for innsamling

- Kliniske undersøkelser
  Tonometry, synsfelt, synsstyrke og refraksjon, pachymeti, ophthalmoskopi, bildetaging av synasnevrehodet ved hjelp av Scanning laser oftalmoskopi (Optomap) og Optical coherence tomography (OCT)
- Spørreskjema
  Pasienter skal fylle inn et spørreskjema for å vurdere endringer i subjektiv øyestatus (OSDI), synskvalitet (NEI) og smerte

3.1.1.1.1 Er spørreskjema validert?

Ja

Tidligere registrerte opplysninger

3.2 Skal det forskes på tidligere registrerte opplysninger?

Nei

3.2.9 Skal det hentes opplysninger fra utenlandske registre?

Nei

Humant biologisk materiale

3.4 Skal det forskes på humant biologisk materiale?

Ja

3.4.1 Skal det forskes på allerede innsamlet humant biologisk materiale?

Nei

3.4.2 Skal det forskes på nytt humant biologisk materiale?

Ja

3.4.2.1 Velg hvilken type humant biologisk materiale

- annet materiale
  Prøver fra pasientens tårevæske, jmf tilgrensede tidligere prosjekt.

3.4.2.2 Skal materialet destrueres senest to måneder etter prøvetaking?

Nei

3.4.2.3 Skal materialet lagres i en spesifikk forskningsbiobank knyttet til prosjektet?

Ja

3.4.2.4 Skal materialet lagres i en allerede godkjent generell forskningsbiobank?

Nei

3.4.3 Skal det gjøres genetiske undersøkelser av biologisk materiale?

Nei

Stråling

3.5 Ioniserende stråling

Nei

Begrunnelsen for valg av data og metode i prosjektet

3.6 Redegjør for den faglige og vitenskapelige begrunnelsen for valg av data og metode

Kliniske tester vil gi data for analyse av endringer i intraokulært trykk og synskvalitet. Spørreskjemaet vil gi informasjon for analyser av kvalitativ endring i pasientens oppfatning av forbedringer i tårefilmstatus og i smertenivået. Den kontralaterale utformingen av studien vil tillate direkte sammenligning av resultatene ved bruk av disse to behandlingene.

4 STUDIEPOPULASJON OG SAMTYKKE

Studiepopulasjon (forskningsdeltakere/utvalg)

4.1 Hvem skal inkluderes i studien?

- Pasienter/klienter
  Pasienter som er diagnostisert som åpen vinkel glaukom, og som idag står på trykkreduserende behandling med lokale øyedråper i begge øyne.

4.2 Beskriv inklusjons- og eksklusjonskriterier

Inklusjons og eksklusjonskriterier iht vedlagt protokoll. Vi skal rekruttere pasienter som behandles med IOP reduserende øyedråper i begge øyne og som er eligible for grå stær operasjon

4.3 Hvor mange forskningsdeltakere er planlagt inkludert totalt?	30
4.3.1 Hvor mange forskningsdeltakere er planlagt inkludert i Norge?	30

4.3.2 Begrunn antallet. Dersom det er relevant, redegjør også for styrkeberegning med statistiske analysemetoder

All statistical tests of hypotheses will employ a level of significance of alpha=0.05. Odds ratios with 95% confidence intervals may also be used.
The sample size calculation is based on hyperosmolarity as the primary outcome measure, using an alpha of 0.05 and a power of 0.8. (Epitropoulos et al., 2015) provide normative data for normal and hyperosmolar eyes of subjects presenting for cataract surgery.

4.4 Beskriv rekrutterings prosedyre

Potensielle studiedeltagere vil bli identifisert og rekruttert fra iFocus sitt elektroniske journalsystem. Studieleder vil forespørre om studiedeltagelse. Kandidatene vil få minimum 1 ukes betenkningstid, i de fleste tilfelle 1 måned. Potensielle studiedeltagere svarer til studieleder eller studiemedarbeider.

4.5 Er prosjektet del av samisk helseforskning og/eller forskning på samisk humant biologisk materiale?

Nei

Samtykke

4.6.2 Vil det bli innhentet samtykke for voksne?

Ja

4.6.2.1 For hvilke voksne skal samtykke innhentes?

Alle studiedeltagere vil bli forelagt informasjonsskriv om studien som må underskrives før inkludering

4.6.2.2 For hvilke tester og opplysninger skal samtykke innhentes?

Samtykke omfatter alle kliniske og laboratoriemessige tester og data som skal samles inn i regi av den vedlagte protokollen

4.6.2.3 For hvilket biologisk materiale vil samtykke innhentes?

Prøver fra pasientens tårevæske

4.7 Er samtykke allerede innhentet?

Nei

4.8 Søkes det om fritak fra kravet om å innhente samtykke?

Nei

5 INFORMASJONSSIKKERHET, DATAFLYT OG DELTAKERNES RETTIGHETER

Behandling av personopplysningene i prosjektperioden

5.1 Behandles det personidentifiserbare opplysninger direkte identifiserbare med 11-sifret personnummer eller navn, adresse og/eller fødselsdato i hele prosjektperioden?

Nei

5.2 Behandles data indirekte identifiserbare ved bruk av koblingsnøkkel?

Ja

5.2.1 Beskriv hvordan koblingsnøkkel vil bli oppbevart og hvem som vil ha tilgang

Koblingsnøkkel som kan reidentifisere avidentifiserte data skal oppbevares i eget rom , i eget låst skap. Nøkkel disponeres kun av studieleder og studiemedarbeider (optometrist og masterkandidat)

5.3 Kan personidentifiserbare opplysninger være systematisk reidentifiserbare ved kombinasjon av variabler?

Nei

5.4 Skal helseopplysninger overføres til andre land?

Nei

5.5 Skal helseopplysninger overføres fra utlandet?

Nei

Biologisk materiale

5.6 Skal biologisk materiale behandles avidentifisert med koblingnøkkel?

Ja

5.6.1 Beskriv hvordan koblingnøkkelen vil bli oppbevart og hvem som vil ha tilgang

Koblingsnøkkel som kan reidentifisere avidentifiserte data skal oppbevares i eget rom , i eget låst skap. Nøkkel disponeres kun av studieleder og studiemedarbeider (optometrist og masterkandidat)

5.7 Benyttes biologisk materiale direkte identifiserbart med 11-sifret personnummer eller navn, adresse og/eller fødselsdato i hele perioden?

Nei

5.8 Benyttes anonymisert biologisk materiale?

Nei

5.9 Skal humant biologisk materiale overføres til utlandet?

Nei

5.10 Skal biologisk materiale overføres fra utlandet?

Nei

Ivaretakelse av deltakernes rettigheter i prosjektperioden

5.11 Hvordan ivaretas deltakernes rettigheter i form av krav til innsyn, retting og sletting av datamateriale, og med tanke på destruksjon av humant biologisk materiale?

Studiedeltagere vil ha innsyn i egne data under studien. Studiedeltagere kan uansett tidspunkt be om retting eller sletting av data knyttet til studien. Unntaket er om data inngår i allerede publiserte vitenskapelige artikler.

5.12 Vil deltakerne få løpende informasjon?

Ja

5.13 Hvem skal deltakerne kontakte for å fremme krav om innsyn, retting, sletting og destruksjon av biologisk materiale?

Prosjektleder Kjell Gunnar Gundersen, eller prosjektmedarbeider Andrea Mihovilovic

Håndtering av data/materiale ved prosjektslutt

5.14 Når et forskningsprosjekt er avsluttet (senest ved godkjent sluttdato) skal en eventuell koblingnøkkel oppbevares i fem år (15 år ved legemiddelstudier), men kun for kontrollhensyn. Deretter skal en eventuell kodenøkkel slettes og data makuleres eller anonymiseres. Planlegges det å fravike denne regelen?

Nei

5.15 Når et forskningsprosjekt er avsluttet (senest ved godkjent sluttdato) er hovedregelen at biologisk materiale i en prosjektspesifikk biobank skal destrueres. Planlegges det å fravike denne regelen?

Nei

Datadeling

5.16 Planlegges det noen form for datadeling etter prosjektslutt?

Nei

6 AVVEINING AV NYTTE OG RISIKO

Angi forutsigbar nytte eller fordeler nå eller i fremtiden

6.1 For den enkelte deltaker/pasient

Epidemiologiske data indikerer at avvikende tårefilmkvalitet kan påvises i 30-60% av alle pasienter henvist til øyelege, og den varierende prevalensen knytter seg til blant annet til ulike cohorter. Mange av disse pasientene er klart underdiagnostisert.

Glaukompasienter representerer en cohort med stor risiko for avvikende tårefilm basert på ulikerisikofaktorer.
Individ rekruttert til denne studien vil gjennomgå en meget grundig utredning av sin tårestatus. Utredningen kan avdekke uheldige og potensielt toksiske effekter av deres etablerte lokalbehandling med øyedråper. Deltagelse i studien kan således avdekke behov for ulike typer intervensjon som igjen kan bedre status for den enkelte. her kan det ligge en betydelig individuell gevinst.

6.2 For gruppen

Glaukom rammer >2% av befolkningen over 50 år og er dermed en hyppig øyesykdom. Optimal behandling av denne store pasientgruppen representerer en stor utfordring, men også et stort potensiale for å bedre status for gruppen som helhet. Økt kunnskap knyttet til forekomst og grad av avvikende tårefilmkvalitet i denne gruppen kan representere en viktig faktor for optimal behandling. Negativ compliance (bevisst eller ubevisst sabotasje av medisineringen) representerer et betydelig problem i alle typer kronisk sykdom og avvikende tårefilmkvalitet kan per see gi økte plager knyttet til behandlingen. Dette kan igjen øke tendensen til negativ compliance.

6.3 Nå eller i fremtiden for samfunnet eller vitenskapen

Hvis vi kan vise at operativ intervensjon i form av iStentimplantasjon kan eliminere eller redusere behovet for lokalbehandling med øyedråper kan dette gi en betydelig helsegevinst for sykdomsgruppen direkte og indirekte fo samfunnet og vitenskapen. Alle tiltak som kan redusere effekten av negativ compliance vil gi en klar samfunnsgevinst. Selv om den operative behandlingen har en spesifikk kostnad knyttet til selve intervensjonen, kan både kostnader til medisinering og konsekvensen av uheldig og irreversibel sykdomsutvikling kunne reduseres betydelig.

Angi mulig risiko/ulempe nå eller i fremtiden

6.4 For den enkelte deltaker/pasient

Potensiell risiko for pasientene kan hovedsaklig knyttes til to element. A) Den praktiske belastningen knyttet til en grundig undersøkelse og flere studiebesøk. B) Potensielle komplikasjoner knyttet til den operative behandlingen. Ingen operative inngrep er uten potensielle bivirkninger eller komplikasjoner, men både grå stær operasjon og iStentimplantasjon (i en eller to seanser) har en kjent og veldokumentert lav risikoprofil (Se vedlegg "Review-artikkel iStent". Klinikken har lang og grundig erfaring knyttet til inngrepene, og vi vil følge etablerte operasjonsprotokoller basert på internasjonal faglig konsensus.

6.5 For gruppen

Potensielle ulemper for gruppen vil være et resultat av summen av individuelle ulemper, se 6.4.

6.6 For samfunnet eller vitenskapen

For samfunnet og vitenskapen er det få potensielle ulemper. Selv om studien ikke vil vise hva vi forventer, er dette en begrenset cohort og vi vurderer derfor den samfunnsmessige risikoen som minimal. For vitenskapen vil selv et "negativt" funn ha en en egen verdi.

Tiltak for å redusere eller begrense risiko og ulempe

6.7 Redegjør for tiltak

1. Innsamling av data vil bli begrenset til et minimum iht protokoll og vil bli behandlet med tung vekt på pasientsikkerhet
2. Vi vil følge etablert internasjonal faglig standard knyttet til alle operative inngrep. Studiepasienter vil bli fulgt opp iht protokoll og denne protokollen er klart mer omfattende enn vanlig klinisk rutine.
3. Studiedeltagere vil bli fulgt opp både i og etter studien iht faglig etablerte retningslinjer
4. Klinikken utfører årlig nesten 2000 intraokulære inngrep og har solide rutiner for beredskap
5. Vi vil ila studien kontinuerlig utføre interimanalyser. Skulle disse vise resultat som indikerer en skadelig effekt for den enkelte studiedeltager, vil studien bli avbrutt umiddelbart. Alle studiedeltagere vi da fortsette kliniske kontroller i klinikken uten opphold.

Forsvarlighet

6.8 Gi en samlet vurdering av prosjektets forsvarlighet for å begrunne at nytten står i et rimelig forhold til den risiko/ulempe som pasienter/deltakere utsettes for

Klinikken har lang og tung erfaring i utredning og behandling av pasienter med glaukom. Vi har i tillegg en omfattende forskningsaktivitet knyttet til avvikende tårekvalitet. Prosjektet er initiert for å sikre ny og viktig kunnskap knyttet til kombinasjonen av glaukom og avvikende tårefilmkvalitet.
Summen av klinisk og forskningsbasert kunnskap sikrer etter vårt syn at prosjektet kan gjennomføres forsvarlig og i takt med faglige retningslinjer. Vi oppfatter at relasjonen mellom risiko og gevinst er vel ivaretatt på individuell så vel som samfunnsmessig basis.

7 FORSIKRING, FINANSIERING OG PUBLISERING

Forsikring for forskningsdeltakere

7.1 Forsikring for forskningsdeltakere

- Pasientskadeloven

Interesser

7.2 Finansieringskilder

Vi vil motta studiestøtte i form av iStent implantat og støtte til analyse og publikasjon av studien fra Glaukos Corp, USA

7.3 Godtgjørelse til institusjon

Institusjonen mottar ingen godtgjørelse utover 7.2.

7.4 Honorar til prosjektleder/-medarbeidere

Prosjektleder/medarbeider mottar ingen godtgjørelse utover 7.2.

7.5 Eventuelle interessekonflikter for prosjektleder/-medarbeidere

Ingen

Publisering

7.6 Er det restriksjoner med hensyn til offentliggjøring og publisering av resultatene fra prosjektet?

Nei

7.7 Redegjør for hvordan resultatene skal gjøres offentlig tilgjengelig

Studien er planlagt for vitenskapelig publikasjon i internasjonalt fagfelle vurdert tidsskrift

Kompensasjon til deltakere

7.8 Planlegges det å gi kompensasjon til pasienter/deltakere?

Nei

8 VEDLEGG

8.1 CV for prosjektleder/ansvarshavende	1 vedlegg (CV KGG 2021.pdf)
8.2 Forskningsprotokoll	1 vedlegg (20210226 Gundersen OSD contra-eye study .pdf)
8.6 Spørreskjema	2 vedlegg (OSDI-Norsk.pdf, Speed 2 -Norsk.pdf)
8.9 Forespørsel om deltakelse til voksne	1 vedlegg (Pasientsamtykke OSD -Glaukom.pdf)
8.11 Andre nødvendige vedlegg	1 vedlegg (Vitenskapelige referanser.pdf)

9 ANSVARSERKLÆRING

Jeg er kjent med

Ja

Jeg erklærer at prosjektet vil bli gjennomført i henhold til gjeldende lover, forskrifter og retningslinjer

Ja

Jeg erklærer at prosjektet vil bli gjennomført i samsvar med opplysninger gitt i denne søknaden

Ja

Jeg erklærer at prosjektet vil bli gjennomført i samsvar med eventuelle vilkår for godkjenning, gitt av REK

Ja

Kjell Gunnar Gundersen, 181058-46327

Flathauggaten 26 • 5523 Haugesund, • Telefon: +47 91648707 • E-post: kg@ifocus.no

Education:

Cand Med Bonn/Oslo 1984

MD Oslo 1986

Specialist in Ophthalmology and Ophthalmic Surgery 1991

PhD, Lunds Universitet, Sweden 1999

Thesis: "Computerised three-dimensional analysis of optic nerve head topography in normal and glaucomatous eyes"

Professional experience:

Haukeland University Hospital	Specialist in ophthalmology	1986-1991
Malmø Universitetsjukehus	PhD degree	1992-1999
Privatsykehuset Haugesund AS	Private Eye Surgeon	1996-2015
IFocus Eye Clinic AS	Private Eye Surgeon	2016-

Surgical qualifications:

Intraocular surgery since 1998 - >40.000 intraocular surgeries, > 5000 MFIOL

Refractive surgery since 2001 - >10.000 surgeries including laser refractive, ICL and RLE

Science and publication:

Teaching ophthalmic surgery at University of south East Norway (USN) since 2015

>25 scientific articles in peer review journals (PubMed)

>200 scientific presentations at international congresses

Mentor for 1 PhD project ending in 2020 – "Biometry in post LASIK patients"

Mentor for 3 PhD projects starting in 2020 planned to be finished in 2023

"Ocular Surface Disorder (OSD) and surgical precision"

Mentor for 1 PhD project to be starting in 2021 – "Utilizing Artificial Intelligence in Ocular Surface Disorder (OSD)"

Conculting:

Consultant for Alcon, 1stQ, Glaukos, Centricity, ORA and Staar Surgical AG

List of publications on Pubmed:

Clinical Results After Precision Pulse Capsulotomy.
Gundersen KG, Potvin R.Clin Ophthalmol. 2020 Dec 29;14:4533-4540. doi: 10.2147/OPTH.S293819. eCollection 2020.PMID: 33402816
Treatment of Open-Angle Glaucoma and Ocular Hypertension with Preservative-Free Tafluprost/Timolol Fixed-Dose Combination Therapy: The VISIONARY Study.
Oddone F, Tanga L, Kóthy P, Holló G; VISIONARY Study Group.Adv Ther. 2020 Apr;37(4):1436-1451. doi: 10.1007/s12325-020-01239-8. Epub 2020 Feb 18.PMID: 32072493 **Free PMC article.**
Rotational stability and visual performance 3 months after bilateral implantation of a new toric extended range of vision intraocular lens.
Gundersen KG. Clin Ophthalmol. 2018 Jul 18;12:1269-1278. doi: 10.2147/OPTH.S173120. eCollection 2018.PMID: 30050279 **Free PMC article.**
Retreatments after multifocal intraocular lens implantation: an analysis.
Gundersen KG, Makari S, Ostenstad S, Potvin R.Clin Ophthalmol. 2016 Mar 1;10:365-71. doi: 10.2147/OPTH.S100840. eCollection 2016.PMID: 27041983 **Free PMC article.**
A review of results after implantation of a secondary intraocular lens to correct residual refractive error after cataract surgery.
Gundersen KG, Potvin R.Clin Ophthalmol. 2017 Oct 3;11:1791-1796. doi: 10.2147/OPTH.S144675. eCollection 2017.PMID: 29042749 **Free PMC article.**
Trifocal intraocular lenses: a comparison of the visual performance and quality of vision provided by two different lens designs.
Gundersen KG, Potvin R.Clin Ophthalmol. 2017 Jun 8;11:1081-1087. doi: 10.2147/OPTH.S136164. eCollection 2017.PMID: 28652693 **Free PMC article.**
Comparative visual performance with monofocal and multifocal intraocular lenses.
Gundersen KG, Potvin R.Clin Ophthalmol. 2013;7:1979-85. doi: 10.2147/OPTH.S52922. Epub 2013 Oct 7.PMID: 24143064 **Free PMC article.**
Refractive and Visual Outcomes After Implantation of a Secondary Toric Sulcus Intraocular Lenses.
Gundersen KG, Potvin R.Clin Ophthalmol. 2020 May 18;14:1337-1342. doi: 10.2147/OPTH.S255725. eCollection 2020.PMID: 32546940 **Free PMC article.**
Prevalence of Signs and Symptoms of Dry Eye Disease 5 to 15 After Refractive Surgery.
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Protocol

Ocular Surface and glaucoma. A randomized study of IOP reducing eyedrops versus surgical intervention

1. TITLE PAGE

Protocol Number:	KGG – V 1.1
IRB / ERC:	REK, Regional Ethics Committitee
Sponsor:	Glaukos iFocus Eyeclinic, Haugesund, Norway
Candidate:	Andrea Mihovilovic, optometrist and master student at Ifocus øyeklinikk, Haugesund. Norway
Principal Investigator:	Kjell Gunnar Gundersen, MD, PhD Ifocus øyeklinikk, Haugesund. Norway

2. GENERAL INFORMATION

Objective	The primary objective is to study the effect of surgical intervention and discontinuation of IOP reducing eydrops on Ocular Surface Disease (OSD) in glaucoma patients.
Sample size	30 subjects (60 eyes)
Study Population	Glaucoma patients on IOP reducing eydrops.
Number of sites	One site in Haugesund, Norway.
Study Design	This is a prospective randomized interventional study
Masking	None
Variables	**Subjective tear film assessment:** OSDI questionnaire Speed II questionnaire **Objective tear film assessment:** Tear osmolarity (primary) Schirmer 1 without anesthesia Bulbar redness Tear Menicus Height Non-invasive tear break up time (NIBUT) OSI index Ocular Surface Staining (OSS) Cochet Bonet Aestiometer Meiboscore, quality, expressibility Visual acuity and refraction Biometry variables from Lensstar Biometry variables from Anterion **Tear Sample analysis** Metabolomics = Proteomics & Lipoproteomics

3. TABLE OF CONTENTS

4. INTRODUCTION

Open angle glaucoma is a chronic eye disease which potentially needs medical treatment over many years. IOP reducing eye drop medication is the most common treatment modality in open angle glaucoma. Both the drug itself, but especially the preseratives used to avoid contamination of the drugs, may have an toxix effect on the ocular surface/tear film (Ref).

Such a toxic effect might harm the ocular surface per see, but also potentially increase compliance challenges, eg. patients stop using their medication due to discomfort etc.

Successful surgical intervention has the potential of controlling IOP without any medication needed. If so, such eyes will not be exposed to the potential toxicity of any IOP reducing eydrops/drugs. Surgical intervention may therefore represent a better treatment option since compliance problems can be eliminated. Existing OSD might also show normalization over time when the potentially toxi drug treatment is discontinued.

5. OBJECTIVES AND SIGNIFICANCE

The primary objectives of this study is A) to determine the prevalence of Ocular Surface Disorder in patients on ocular glaucoma medication and B) study the impact of surgical intervention with cataract surgery and iStent implantation. Such intervention may eliminate the need of ocular medication and thus initiate a normalization of the Ocular Surface over time.

Identification and monitoring of OSD during this study will be performed both at the baseline study visit and after surgical intervention - collecting subjective, objective and tear sample analysis data utilizing advanced metabolomic analyses.

The results of the study will be published, so that findings can be used by other clinicians to utilize new and objective data in their clinical decision making prosesses.

6. SUBJECTS

6.1. Subject Population

Men or women on IOP lowering eyedrop treatment for mild to moderate glaucoma

6.2. Inclusion Criteria

Subjects are eligible for the study if they meet the following criteria:

Note: Ocular criteria must be met in **BOTH** eyes.

- Signed informed consent
- Willingness and ability to attend to all study visits
- No rheumatoid disease or other systemic disease involving the corneal surface.
- Glaucoma diagnosis based on visual field and topographic analysis of the optic disc based on European guidelines for glaucoma diagnosis and staging of disease
- Visual fields with a MD loss of maximal 5dB
- Clinically significant cataract eligible for cataract surgery

6.3. Exclusion Criteria

If any of the following exclusion criteria are applicable to the subject or either eye, the subject should not be enrolled in the study.

- Manifest corneal disease or scarring
- Lid deformities
- Corneal ectasia
- Rheumatoid disease or other systemic disease involving the corneal surface
- Recent intra or extra-ocular surgery
- Previous refractive prosedures (LASIK, LASEK, radial keratotomy
- Previous corneal transplant, DSAEK, lamellar keratoplastyor similar prosedures
- Diabetic retinopathy
- Subjects who have an acute or chronic disease or illness that would confound the results of this investigation (*e.g.*, imunocompromised, connective tissue disease, clinically significant atopic disease, diabetes, and any other such disease or illness)
- Pregnancy

Note: This above list of exclusion criteria is not all inclusive. The investigator will use medical judgment to exclude patients that have disease/conditions that may compromise study results, and patients that are not ideal participants.

7. STUDY DESIGN

7.1. Study Design

This is a prospective randomized contralateral-eye study. After a pre-screening based on patients' electronic medical journal, patients meeting the inclusion criteria will be invited to an informative visit where the study will be explained and the subjects asked to sign an informed consent document.

Subjects intested in and willing to be included in the present study will be invited to a Baseline visit for an extensive clinical examination. This examination will include a subjective OSDI and Speed II questionnaire. Objective evaluation will include tear osmolarity, non-invasive tear break up time (NIBUT),Schirmer 1, Ocular surface staining (OSS) and collect tear sample for later analysis of inflammation markers (if desired by the Investigator).

After this Baseline visit is finished, one eye (either right or left, selected at random) of each patient will be randomized to either of the following two groups. The contralateral eye will be assigned to the other group; thus, each patient will have one eye in the surgery group and one eye in the control group. The two groups are:

A) Surgical treatment of their cataract combined with implantation of at least two iStent inject stents
or
B) Continued medical treatment without any planned surgical invention during the study follow-up period

Group A) will be invited to a preoperative visit for biometric calculation of IOL power, followed by surgical intervention and postoperative visits at Day 2, Week 1, Month 1,3 and 6 after surgery. Month 6 visit will be the final visit in this study. Clinical data and tear film samples (if desired by the Investigator) will be collected at all visits for group A.

After the Baseline visit, Group B will return for a final study visit 6 months later to collect a full range of subjective and objective OSD parameters together with a final tear sample (if desired) for a final metabolomic analysis. Tear samples will be placed into storage so that maetabolomic analysis could be undertaken in the future if desired (i.e., no analysis as part of the current protocol).

7.2. Methods Used to Minimize Bias

We will recruit patients from our clinic population who have bilateral cataract and mild to moderate glaucoma who are eligible for stent-cataract surgery in both eyes. One eye of each patient will be randomized to surgery, and the other eye will be assigned to the

control group for the period of the study. The process of randomization and the contralateral-eye study design will minimize bias, as the preoperative demographics of the two groups will be identical (i.e. both eyes of the same patients).

All data collection will be completed through provided Case Report Forms (CRFs) or computer files generated by automated test equipment. All site personnel involved in the study will be trained with regard to conducting study-specific procedures.

Variables

- Tear osmolarity (primary), measured with the Tear Lab system continuous: mMol/l
- Schirmer 1, measure the tear volume and stimulated tear reflex tear flow: 0-35 mm
- OSDI questionnaire, continuous: index (0-100)
- Speed II questionnaire, continuous: index (0-64)
- Objective non-invasive tear break-up time, continuous, seconds before first tear break-up
- Ocular Surface Staining (OSS), graded 0-5 (Oford scale)

7.3. Study feasibility and time frame

iFocus Eyeclinic has put together a well-rounded and motivated research group focusing on Ocular Surface Disease (OSD) and other eye co-morbidities which provides many advantages:

1. A dedicated, broad research group with significant knowledge of both DED other eye co-morbidities as well as the emerging field of metabolomics.
2. A state of the art OSD, glaucoma, cataract and research facility at iFocus eyeclinic.
3. Access to a huge patient population at the same facility.

Dr. Kjell Gunnar Gundersen is the founder and owner of iFocus øyeklinikk AS. He completed his PhD at the University of Lund in 1999 but has continued with extensive research after. He has considerable experience in the field of cataract surgery with over 25 publications and numerous presentations at international meetings.

Katja B. Prestø Elgstøen has masters in chemistry as well as a PhD in medical biochemistry from University of Oslo in 2010. She is the head of development at Section for Inborn Errors of Metabolism, Dept. Medical Biochemistry, Oslo University Hospital and has significant experience in the field of metabolomics.

Together with her colleagues she has developed and implemented a state of the art metabolomics platform suitable for studying thousands of metabolites (the metabolome), both knowns and unknowns, in body fluids such as whole blood (dried blood spots), urine, plasma/serum, bile, and tear fluid.

Furthermore, iFocus has at present three ongoing PhD programs within OSD research. The PhD-candidates are Per Graae Jensen, Dr.Christian Nilsen and Dr.Morten Gundersen. All three candidates will contribute to the present study as well, even if it falls slightly out of the main cource of their own projects. Thus, collectively, we believe that the team has all that is required to fulfill this study.

8. STUDY PROCEDURE

8.1. Patient recruitment

We will recruit patients on treatmant for mild to moderate glaucoma scheduled for cataract. The recruitment goal is 30 subjects with bilateral disease (60 eyes).

8.2. Visits and Examinations

All subjects will invited to a baseline visit. All measures will be done consecutively. The recruitment goal is 30 subjects with bilateral disease (60 eyes).

Patient recruitment and study visit plan							
Pre-screening based on Patient EMR recordings	Baseline exami-nation All eyes	Rando mization	Preoperative biometry	Surgical intervention	W 5	M 3	M 6
		Surgical intervention	X	X	X	X	X
		Continued medical treatment					X

8.2.1. <u>Study Visit Testing</u>

At the start of the visit, eligibility will be confirmed and the subject information and consent form will be provided to the subjects. Subjects who are qualified and agree to participate will be assigned a Subject ID. Subject numbers will be assigned sequentially in the order of enrollment.

The study exam will include the tests in the following order described below:

- Tear Lab system

    - Osmolarity
- OSDI -questionnaire
- Speed II- questionnaire
- Auto Refractor
    - Refraction and visual acuity
- Oculus Keratograph 5M
    - NIKBUT
- Schirmer 1 test without anesthetic
    - Calibrated strip collected, marked with Subject ID and stored in a ultrafreezer
- Slit Lamp- examination
    - Corneal staining with Fluorescein.
    - Staining graded according to Oxford Scheme

Measurements should be made as described in section 8.3 below.

8.2.2. Preoperative biometry

8.2.2.1. Standard preoperative biometry will be performed to decide the patients IOL choice

8.2.3. Surgical intervention

8.2.3.1. Standard small incision phaco cataract surgery will be performed including implantation of the chosen intraocular lens (IOL)

8.2.3.2. After IOL implantation, two iStent Inject will be implanted in the inferior part of the patients trabecular meshwork in accordance to a standar protocol of iStent implantation

8.2.4. Postoperative controls

8.2.4.1. Postoperative controls will be performed at day 2, Week 5, Month 3 & 6.

8.3. Study Methods and Measurements

Study examination procedures are described below.

8.3.1. Osmolarity

Tear Lab
Precision (CV)≈1.5%,Standard Deviation (Stdev) 5.0 mOsms/L,
Accuracy r2=0.95, Range 275-400 mMol/L(TearLab™ Osmolarity System · Clinical Utility Guide)
Range normal eyes: 270 to 315 mOsm/L [122–137], with an overall average of 300 mOsm/L(Willcox et al., 2017)
Patient should not have used therapeutic or diagnostic drops last 2hours.
Sample is taken by letting the test card touch the lower temporal tear meniscus.

8.3.2. OSDI – questionnaire

Values 0-100**,** Normal value <13(Wolffsohn et al., 2017)
The questionnaire should be administered with only a general explanation. The patient should understand that we presume the use of spectacles when needed
We will avoid interpreting survey questions for subjects. That is, avoid re-phrasing questions if a subject asks, "What does this mean?"

8.3.3. Speed II- questionnaire

Values 0-64, Normal value <5 (Starr et al. 2018)
The test is administred by the subject without help from a technician.
The subject is asked to fill out the forms to the best of their ability

8.3.4. Auto refractor, Refraction and visual acuity

Huvitz Keratometer HRK-9000A
Range sph.-30,0D - +25,0 Dcyl ±12 , step 0,12/0,25 D, axis 0-180 dgr step.
Record refraction and corrected visual acuity(own spectacles or AR refraction)

8.3.5. NIBUT

Oculus Keratograph 5M, OCULUS, Inc.
Non-Invasic Keratograph Break-up time, automatic detection
Seconds to first break up.
Device is aligned and patient is instructed to blink twice. After the second blink, measurement will automatically begin. Instruct and motivate the patient to keep his/her eyes open without blinking. Measurement is automatically terminated if the patient blinks, moves strongly, or the tear film significantly breaks up.

8.3.6. Schirmer 1 test

Performed without anesthetic. Calibrated strips of a non-toxic filter paper are used. The free end of the strip is placed within the temporal part of the lower lid without anaesthesia and both eyes are gently closed for 5 minutes.
At the end of the test the paper strips are removed from each lower eyelid and the amount of the wetting of the paper is measured in milimeter. Schirmer scores fir >10 mm are considered as normal. The diagnostic cut-off for OSD is ≤ 5.0 mm in 5 minutes (Afonso et. al, 1999)
Strips is stored in a plastic container filled with BSS

8.3.7. Slit lamp examination
Routine slit lamp examination of the anterior segment.
Evaluation of corneal staining based on Oxford schema which is used to estimate surface damage in dry eye.(Brons Evans Smith, 2003)
Description: Surface damage to the exposed eye, assessed by staining, is graded against standard charts.
Grading Schema: Staining is represented by punctate dots on a series of panels. Staining ranges from 0-5 for each panel.
Conduct of test: A quantified 5 µl of 2% Fluorescein sodium is instilled into each conjunctival sac with a micro-pipette (using a sterile tip).
The observation is done with slit lamp with a yellow filter, corneal fluorescein staining is graded from 0-5

8.3.8. Tear sample collection

If desired by the Investigator, tear samples will be collected from all subjects at the baseline and Month 6 visit. In addition, tear samples will be collected at Week 5 and month 3 for patients undergoing surgical intervention. All tear samples will be placed into storage so that maetabolomic analysis could be undertaken in the future if desired (i.e., no analysis as part of the current protocol).

9. ANALYSIS PLAN

9.1. Analysis Data Sets

Analyses will be performed based on data from those subjects who complete all testing in the study visit.

9.2. Statistical Methodology

A summary of the data will be prepared for all subjects.

For variables measured on a continuous scale, these summaries will include the sample size, as well as the mean, standard deviation, median, minimum, and maximum. For variables measured on a categorical scale, summaries will provide the number and percentage of subjects who provided each score.

Preliminary considerations of the data will include the investigation as to whether any transformation (*e.g.*, logarithmic) should be applied prior to the statistical analyses. For categorical data, the sparseness of the data across categories will be considered, and the combination of categories prior to statistical analysis will be applied where deemed appropriate.

For variables measured on a continuous scale, the statistical significance of between-treatment differences will be investigated using an Analysis of Variance (ANOVA) with appropriate post-hoc testing. For variables measured on an ordinal categorical scale, the Kruskal-Wallis signed-rank test will be employed.

Questionnaire data will be analyzed using current standards.

9.3. General Statistical Considerations

The statistical analyses will be performed using SPSS version 24. All statistical tests of hypotheses will employ a level of significance of alpha=0.05. Odds ratios with 95% confidence intervals may also be used.

10. SAMPLE SIZE JUSTIFICATION

The sample size calculation is based on hyperosmolarity as the primary outcome measure, using an alpha of 0.05 and a power of 0.8. (Epitropoulos et al., 2015) provide normative data for normal and hyperosmolar eyes of subjects presenting for cataract surgery.

11. QUALITY COMPLAINTS AND ADVERSE EVENTS

As a dual arm partly interventional partly non-interventional study, quality complaints and adverse events has to be addressed as follows:

12. GCP, ICH and ETHICAL CONSIDERATIONS

Both the cataract and iStent procedures are invasive and may represent risk of significant discomfort for the patient. Patients undergoing surgical interventions will be followed tightly based on established clinical guidlines for patients safety with postoperative visits day 2, Week 1, Month 1,3 and 6 after surgery.

If suspicion of any disease arises, patient will be referred to general practitioner or appropriate specialist. The subject will sign an informed consent. Participation is voluntarily, and the subjects can withdraw at any time.

Personal data are protected according to Norwegian laws.

This study will be conducted in compliance with Good Clinical Practices (GCPs), including International Harmonization (ICH) Guidelines, and in general, consistent with the 1996 version of the Declaration of Helsinki. In addition, all applicable local, state and federal requirements will be adhered to.
This study is to be conducted in accordance with Institutional Review Board regulations. The investigator will obtain appropriate IRB/ethics committee approval prior to initiating the study.

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Other references:

TearLab™ Osmolarity System · Clinical Utility Guide

Keratograph 5M. Instruction manual

Måling av symptomer på tørre øyne

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

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

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

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

I bil/rom med aircondition?	4	3	2	1	0

Oppsummering

Finn først ut av pasientens samlede score ved å summere svarene for hvert av de 12 spørsmålene og noter det her:_____Noter deretter hvor mange relevante spørsmål
pasienten har besvart: _____

En samlet score for de besvarte spørsmålene på færre enn 15 betyr at pasienten er uten symptom på tørre øyne.

Du kan videre bestemme graden av symptomer i nedenstående skjema og følge utviklingen over tid og resultatene av eventuell behandling. Finn ut og marker det punktet i tabellen som beskriver pasientens to verdier og avles på fargeskalaen:

		Pasientes samlede symptom og score									
		5	10	15	20	25	30	35	40	45	48
Antall besvarte spørsmål	12	10,4	20,8	31,1	41,7	52,1	62,5	72,9	83,3	93,8	100
	11	11,4	22,7	34,1	45,5	56,8	68,2	79,5	90,9	100	
	10	12,5	25	37,5	50	62,5	75	87,5	100		
	9	13,9	27,8	41,7	55,6	69,4	83,3	97,2			
	8	15,6	31,3	46,9	62,5	78,1	93,8	100			
	7	17,9	35,7	53,6	71,4	89,3	100				
	6	20,8	41,7	62,5	83,3	100					
	5	25	50	75	100						
	4	31,3	62,5	93,8							
	3	41,7	83,3								
	2	62,5									
	1										

Fargeskalen på de enkelte boksene viser graden av tørre øyne:			
Normal	Mild	Moderat	Svært
	(Teksten er modifisert, basert på OSDI, copyright Allergan Inc)		

SPØRRESKJEMA TØRRE ØYNE - SPEED II

Tørre øyne er en vanlig tilstand som kan gi alvorlige plager og kan være årsaken til store feilkilder ved operasjon av grå stær. Ta deg derfor tid til så godt som mulig å svare på spørreskjemaet.

Navn:_____

Dato: _____

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

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

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

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

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

---

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

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

Har du varierende syn? ☐ Aldri ☐ Noen ganger ☐ Ofte ☐ Alltid

Om ja, hjelper det å blunke eller dryppe med dråper? ☐ Ja ☐ Nei

Har du Blefaritt (betennelse på øyelokkskanten)? ☐ Ja ☐ Nei

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

Har du på øyelokket hatt disse symptomer i det siste? ☐ Rødt ☐ Puss/flass ☐ irritasjon

Bruker du kontaktlinser? ☐ Ja ☐ Nei

Hvis ja, når brukte du de sist? _____

Hvis ja, er det mer ubehag hvis du bruker de? ☐ Ja ☐ Nei

Har du kløe i øynene ? ? ☐ Aldri ☐ Noen ganger ☐ Ofte ☐ Alltid

Hvis ja, har du kjent allergi eller kjent øyebetennelse? ☐ Ja ☐ Nei

Er dine øyeplager like på begge øyne? ☐ Ja ☐ Nei

Om nei, på hvilket øye har du mest plager? ☐ Høyre ☐ Venstre

Har du noe imot å bruke bruke briller eller kontaktlinser? ☐ Ja ☐ Nei

Hvis ja, er du villig til å betale ekstra for å bli kvitt dine brillereller kontaktlinser? ☐ Ja ☐ Nei

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKT

TÅREFILMSTATUS

HOS PASIENTER SOM BEHANDLES MED ØYEDRÅPER FOR GRØNN STÆR

Dette er et spørsmål til deg om å delta i et forskningsprosjekt for å studere tårefilmen hos pasienter som behandles med trykkreduserende øyedråper for grønn stær (glaukom)

HVA INNEBÆRER PROSJEKTET?

Nyere forskning har vist oss at øyets tårefilm kan endres som et resultat av lokale øyedråper. Eventuelle uheldige effekter kan knyttes både til dråpenes konservering og selve den aktive substansen i øyedråpene.

Vi kjenner til at jo bedre tårefilmen er, desto bedre er øyet beskyttet mot uheldige bivirkninger av behandlingen. Den planlagte studien er planlagt i to faser:

A) Kartlegge tårefilmstatus hos pasienter som behandles med øyedråper for grønn stær i begge øyne.

B) Velge et øye (randomisere) for operativ behandling der vi implanterer en mikroventil i øyet (iStent inject) for å redusere øyetrykket, mens det andre øyet fortsetter med medikamentell behandling.

Ved studiestart/forundersøkelsen, vil vi innhente og registrere noen opplysninger om deg. I tillegg til avidentifiserte opplysninger om alder og kjønn vil vi samle inn følgende: A) Data fra to spørreskjema (OSDI og Speed 2) B) Objektive data fra diverse øyeinstrumenter og C) en biokjemisk analyse av din tårefilm.

Det vil bli utført i alt 5 klinikkbesøk i regi av studien.

I. Oppstartsbesøk med utredning av tårestatus. Ved dette besøket vil vi velge hvilket øye som skal opereres
II. Operasjon
III. Kontroll etter 5 uker, 3 og 6 måneder

Prosjektansvarlig er Dr. Med. Kjell Gunnar Gundersen og Ifocus øyeklinikk har behandlingsansvar.

Forventet prosjektslutt: Mai 2022

MULIGE FORDELER OG ULEMPER

Trykkreduserende dråper er den vanligste behandlingen for grønn stær. Vi vet imidlertid at behandlingen kan gi ulike lokale bivirkninger og slike bivirkninger kan ofte relateres til avvikende tårekvalitet. Slike bivirkninger kan påvirke pasientenes vilje og evne til å gjennomføre behandlingen i tråd med etablerte retningslinjer. Manglende gjennomføring av behandlingen kan øke risikoen for skader knyttet til sykdommen.

Denne studien kan gi oss bedre innsikt i hvordan tårefilmen påvirkes av din dråpebehandling. Videre ønsker vi å studere om slike effekter forsvinner når behandlingen kan avsluttes etter vellykket operativ behandling med innsetting av iStent for å redusere øyetrykket.

Bedre tårefilm og mindre behov for øyedråper vil representere en klar fordel for deg som pasient. Dine mulige ulemper er dels knyttet til å møte til flere grundige studiebesøk og dels ulemper knyttet til den operative behandlingen.

Vår klinikk har lang erfaring med slik operativ behandling og vil følge vedtatte retningslinjer for inngrepet. Som studiedeltager vil du bli fulgt opp grundig og samvittighetsfullt i studieperioden og i fremtiden etter studiet er avsluttet.

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

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i prosjektet. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke. Dette vil ikke få konsekvenser for deg.

Dersom du trekker deg fra prosjektet, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom du senere ønsker å trekke deg eller har spørsmål om prosjektet, kan du kontakte prosjektansvarlig Kjell Gunnar Gundersen, mailadresse: kg@ifocus.no Ifocus øyeklinikk AS, Telefon 52808900.

HVA SKJER MED INFORMASJONEN OM DEG?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Du har rett til innsyn i hvilke opplysninger som er registrert om deg og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Denne koden oppbevares innelåst og kun prosjektleder og doktorand har tilgang til denne koden.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om deg blir behandlet på en sikker måte. Informasjon om deg vil bli anonymisert eller slettet senest fem år etter prosjektslutt. Lagring og sletting av data følger retningslinjene til Regional komite for medisinsk og helsefaglig forskningsetikk (REK)

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Tåreprøver vil samles inn ved Ifocus øyeklinikk. Prøvene vil bli fryst ned og oppbevares som en del av en spesifikk forskningsbiobank for senere analyse ved spesialiserte miljø innen analytisk kjemi ved Oslo Universitetssykehus (OUS). OUS er databehandler i prosjektet.

Biobanken opphører etter prosjektslutt. Tåreprøvene vil bli destruert ved biobankens prosjektslutt i 2023.

Navnet på biobanken er «Biobank for tårefilmanalyser i PhD studien Haugesund» og ansvarshavende er Dr. Med Kjell Gunnar Gundersen.

FORSIKRING

Som pasient og studiedeltager hos oss er du dekket av Norsk Pasientskadeerstatning (NPE)

ØKONOMI

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

Prosjektet dekker ekstraordinære utgifter dersom det ikke dekkes av pasientreiser

GODKJENNING

Prosjektet forutsetter godkjenning av Regional komite for medisinsk og helsefaglig forskningsetikk
Forskningspesifikk biobank er godkjent av REK søknad (#95774)

SAMTYKKE TIL DELTAKELSE I PROSJEKTET

JEG ER VILLIG TIL Å DELTA I PROSJEKTET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato	Signatur
	Rolle i prosjektet

REVIEW/UPDATE

iStent inject: comprehensive review

Wesam Shamseldin Shalaby, MD, Jing Jia, BA, L. Jay Katz, MD, Daniel Lee, MD

Microinvasive glaucoma surgeries (MIGSs) are new surgical procedures for treatment of glaucoma. They aim to safely and effectively reduce intraocular pressure (IOP) with minimal trauma to the eye and less complications. The first-generation iStent is the first approved ab interno MIGS implant for management of open-angle glaucoma. It works by allowing aqueous humor to drain directly from the anterior chamber into Schlemm canal bypassing the trabecular meshwork, the major site of outflow resistance. The second-generation iStent inject is the smallest available trabecular device that occupies less than 0.5 mm. It is designed to facilitate the surgical technique and allow simultaneous implantation of 2 stents, aiming for more IOP reduction. This review examines publications about the iStent inject, focusing on the device's efficacy, safety, and comparison with the first generation iStent. Both devices were found to be a safe and effective tool in management of open-angle glaucoma.

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Glaucoma is a leading cause of irreversible blindness worldwide and is the second most common cause of bilateral blindness after cataract.[1,2] The current estimate on the number of people affected by glaucoma in 2020 is 76.0 million and is expected to increase to 111.8 million in 2040.[3] Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterized by death of retinal ganglion cells and degeneration of their axons,[4] and it accounts for two-thirds of all glaucomas.[5] Elevated intraocular pressure (IOP) is one of the major risk factors for development and progression of POAG, and its reduction is considered the only intervention proved to slow progression of the disease.[6] IOP reduction is currently achieved by topical hypotensive medications, laser therapy, or incisional surgical procedures including trabeculectomy and glaucoma drainage devices. However, compliance and tolerability are poor in the case of medications, whereas serious complications and failure are common with incisional surgeries.[7,8] Recently, a new class of procedures termed microinvasive glaucoma surgeries (MIGSs) have emerged to provide safer and effective IOP reduction. Generally, MIGS have an ab interno approach with minimal conjunctival or scleral manipulation, yielding an improved safety profile and rapid recovery compared with traditional incisional glaucoma procedures.[9]

Trabecular microbypass stents are one of the most widely used MIGS devices, and they work by improving conventional trabecular outflow through the Schlemm canal, bypassing the trabecular meshwork, which is considered the major site of aqueous outflow resistance in open-angle glaucoma (OAG).[10] The iStent (Glaukos Corp.) is the first trabecular microbypass stent to be approved in the United States. It is a heparin-coated, nonferromagnetic titanium stent with the dimensions of 1 mm in length and 0.3 mm in height, making it the smallest implantable medical device ever approved for use in humans by the U.S. Food and Drug Administration, at the time of approval. Several studies have proved the efficacy and safety of iStent either as a solo procedure or combined with phacoemulsification.[11–16] Further studies comparing the effect of single vs multiple stent implantation have reported an incrementally increasing therapeutic efficacy with each additional stent.[17–19] With this in mind, the second-generation iStent inject (Glaukos Corp.) was developed, allowing the implantation of 2 stents and was approved by the U.S. Food and Drug Administration in 2018.

The first-generation iStent was approved in 2012, and associated studies have been reviewed.[20,21] In this article, we review the second-generation iStent inject studies published from 2012 to March 2020. A PubMed search for "iStent inject" revealed 38 articles. Each of these full-text articles was reviewed. Secondary searches for "trabecular microbypass" and "micro incisional glaucoma surgery" or "MIGS" identified additional relevant articles.

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Randomized controlled trials and relevant case series were included in this review in addition to laboratory investigation studies and meta analyses.

The device features a modified injector loaded with 2 stents, allowing surgeons to place both stents with a single entry into the eye. Moreover, the head of the device imbedded in the Schlemm canal has 4 side outlets in addition to the central one, and this theoretically may allow multidirectional aqueous outflow.[22] The device is also designed to have easier surgical technique compared with the first generation, with its smaller size, absence of the snorkel, and easier positioning with no required sideways sliding. Its symmetrical configuration allows implantation in either the left or right eye (Figure 1).

DESIGN

The iStent inject contains 2 preloaded heparin-coated biocompatible implant-grade titanium stents. The stent has a single piece design with a 230 μm by 360 μm diameter and height. The central inlet and outlet lumen has a diameter of 80 μm, and the head has 4 side outlets of 50 μm each (Figure 2). The iStent inject stent is composed of 3 parts: the flange, which faces the anterior chamber; the head, which resides in the Schlemm canal; and the thorax, which is retained by the trabecular meshwork (Figure 2). Two preloaded intraocular stents are provided in the injector (Figure 3). Each stent is designed to carry the entire amount of aqueous humor produced by the human eye (~2.5 μL/min) with minimal resistance.[22] The ab interno multiple stent placement is designed to increase access to more collector channels and create arcs of flow up to 6 clock hours.

SURGICAL TECHNIQUE

Although individual techniques may slightly vary, the implantation of the iStent inject device is generally as follows. Intracameral ophthalmic viscosurgical device is introduced through a corneal incision to deepen and maintain the anterior chamber. The injector is advanced through a temporal clear corneal incision, while the nasal angle and device are visualized through direct gonioscopy. The sleeve of the injector is retracted, revealing the trocar and microinsertion tube. The trocar is penetrated through the trabecular meshwork, and the delivery button is depressed to implant the first stent. The trocar is placed 2-3 clock hours away, and the second stent is delivered. After confirmation of proper stent placement and seating, ophthalmic viscosurgical device is removed.

The timing of iStent implantation before or after phacoemulsification may vary based on surgeon preference and patient factors. Surgeons may choose to implant the stent prior to cataract surgery to ensure stent implantation before any potential complications of phacoemulsification and take the advantage of a clearer corneal view and higher scleral rigidity facilitating the implantation. On the other hand, implantation may be performed following phacoemulsification to provide wider angle for implantation and avoid accidental tear of the anterior lens capsule.

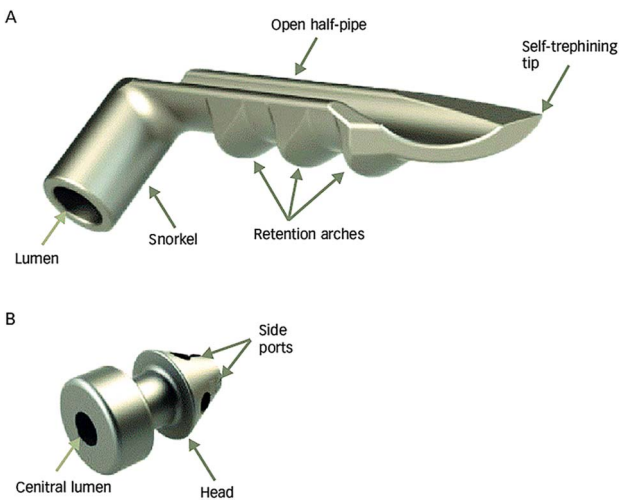

Figure 1. Design difference between iStent (*A*) and iStent inject (*B*). Image courtesy of Glaukos Corp; reprinted with permission.

EFFICACY

Many studies have been conducted to evaluate the efficacy of the iStent inject either combined with phacoemulsification or as a standalone procedure (Tables 1 and 2). Fewer studies have compared the iStent inject with other MIGS procedures (Table 3).

iSTENT INJECT WITH CATARACT SURGERY

Prospective Studies

In 2019, Samuelson et al. published the 2-year results of the pivotal trial of the iStent inject.[22] The study was a prospective, randomized, comparative, multicenter investigation conducted in the United States, in which a total of 505 eyes from 41 sites were randomized in a 3:1 fashion to undergo either implantation of the iStent inject after uneventful cataract surgery (iStent inject group) or cataract surgery alone (control group). The study is considered the largest randomized clinical trial on iStent inject up to date. Eligibility criteria included patients with visually significant age-related cataract with mild to moderate POAG, preoperative IOP ≤24 mm Hg on 1 to 3 medications, and unmedicated diurnal IOP (DIOP) after medication washout 21 to 36 mm Hg. Patients were followed through 2 years postoperatively with annual washout of ocular hypotensive medication. At 24 months, 75.8% of treatment eyes vs 61.9% of control eyes experienced ≥20% reduction from baseline in unmedicated DIOP (P = .005), and mean reduction in unmedicated DIOP from baseline was greater in treatment eyes (7.0 ± 4.0 mm Hg) than in control eyes (5.4 ± 3.7 mm Hg) (P < .001). Of the responders, 84% of treatment eyes and 67% of control eyes were not receiving ocular hypotensive medication at 23 months. Furthermore, 63.2% of treatment eyes vs 50.0% of control eyes had month 24 medication-free DIOP ≤18 mm Hg (difference 13.2%). The study concluded that clinically and statistically

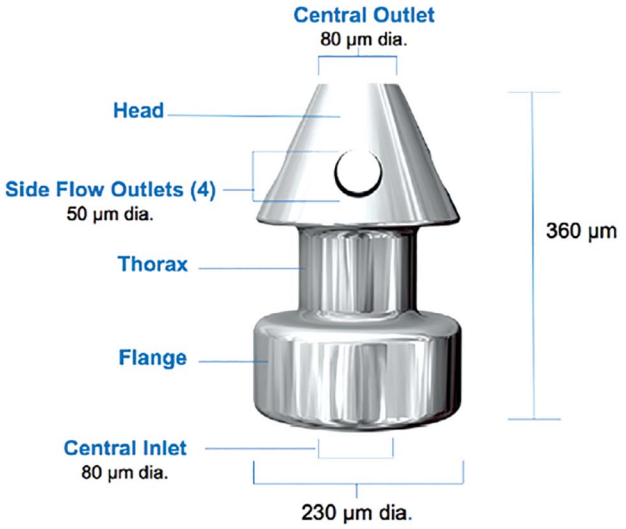

Figure 2. Parts and dimensions of the iStent inject. Image courtesy of Glaukos Corp; reprinted with permission.

greater reduction in IOP without medication was achieved after iStent inject implantation with cataract surgery vs cataract surgery alone, with excellent safety through 2 years.

Another 2019 prospective randomized study conducted by Best et al.[23] investigated the outcomes of iStent inject with cataract surgery in eyes with mild to moderate POAG.[23] The study included 65 eyes from 56 patients: 31 underwent a combined cataract surgery with iStent inject, and 34 eyes underwent standard cataract surgery alone. The longest follow-up time was 38 months, with a mean follow-up time of 14 months. IOP reduction with combined surgery was 5.9 mm Hg or 23.5%, compared with 2.1 mm Hg or 9.5% ($P < .001$) in cataract surgery alone. The number of glaucoma medications was reduced from 2.8 preoperatively to 1.5 at month 4 postoperatively in the iStent group, whereas in cataract surgery alone, it was reduced from 2.6 to 2.1 ($P < .001$); these numbers remained constant through the follow-up period in both groups. The study concluded that combined phacoemulsification with iStent inject was shown to be an effective and safe treatment method for reduction of IOP, and the burden of topical antiglaucoma medications with the extent of IOP reduction depended on the level of the preoperative pressure.

Two prospective noncomparative, nonrandomized case series evaluating the long-term efficacy of iStent inject combined with phacoemulsification demonstrated outcomes similar to previous studies.[24,25] One study with up to 5-year follow-up included 20 patients with POAG, pseudoexfoliation glaucoma (PXG), or ocular hypertension (OHT) who underwent uneventful cataract surgery with iStent inject. In 7 patients, only 1 stent was visible. The mean follow-up period was 47.4 ± 18.46 months. Mean baseline medicated IOP was 19.95 ± 3.71 mm Hg and after washout was 26 ± 3.11 mm Hg. At the end of follow-up, mean IOP was 16.25 ± 1.99 mm Hg, with a difference of 9.74 ± 3.14 mm Hg from preoperative unmedicated IOP, representing a significant decrease of 36.92% ($P < .001$). The mean IOP drop relative to preoperative medicated IOP was 3.7 ± 3.7 mm Hg, representing a 16.49% decrease ($P < .001$). The majority of patients reduced their medication burden during the course of follow-up. Before surgery, the mean number of glaucoma medications was 1.3 ± 0.66. At the end of follow-up, the mean number of medications decreased to 0.75 ± 0.79, representing a significant mean reduction in glaucoma medications of 0.5 ± 0.89 ($P = .017$). At the end of follow-up, 45% of the patients were medication free, and all patients showed good visual outcomes with no serious adverse events recorded, suggesting that iStent inject with phacoemulsification could be a long-term safe and effective treatment option for patients with both cataract and mild to moderate OAG or OHT.[24]

A more recent prospective case series conducted by Hengerer et al., with 3-year follow-up, included 81 eyes in 55 consecutive patients with a wider range of glaucoma types including POAG, PXG, pigmentary glaucoma (PG), neovascular glaucoma (NVG), or appositional angle-closure glaucoma (ACG), defined as a Shaffer grade of 2, with an open angle in the area of stent implantation.[25] At baseline, 32% of the eyes had undergone prior glaucoma surgery. In all eyes that were followed up for 36 months (n = 41), mean IOP decreased to 14.3 ± 1.7 mm Hg vs 22.6 ± 6.2 mm Hg preoperatively (37% reduction), and mean medication burden reduced to 0.8 ± 0.9 vs 2.5 ± 1.1 medications preoperatively (68% reduction). A ≥20% IOP reduction was achieved in 78% of eyes, with 100% of eyes reaching IOP ≤18 mm Hg and 71% reaching ≤15 mm Hg. Medication burden also decreased; at 36 months, 54% of eyes (n = 22) were medication free compared with 1% (n = 1) preoperatively; conversely, 2% of eyes (n = 1) were on ≥3 medications compared with 56% of eyes (n = 45) preoperatively. At 36 months, 92.7% of the eyes had decreased the number of medications from their preoperative regimens. The most striking in this study is that outcomes were observed in a clinically heterogeneous patient population with a considerable preoperative medication burden and prevalence of prior glaucoma surgery. This diversity could

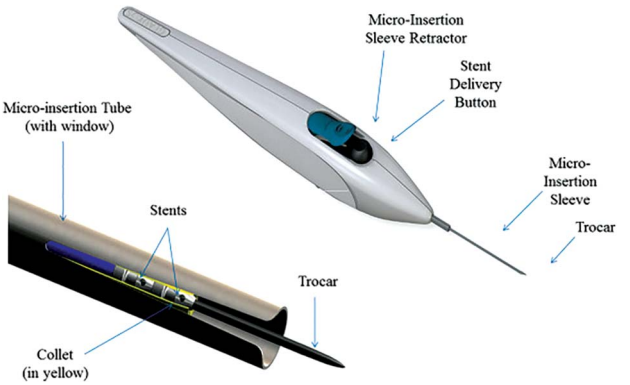

Figure 3. iStent inject delivery system. Image courtesy of Glaukos Corp; reprinted with permission.

Table 1. Summary of iStent inject combined with phacoemulsification studies.

Author/Year	Site	Design	Center	Eyes, n	Glaucoma Type
Samuelson et al./2019[22]	U.S.	RCT	Multicenter	505	POAG
Best et al./2019[23]	Germany	RCT	Single center	65	POAG
Arriola-Villalobos et al./2016[24]	Spain	PCS		20	POAG, PXG, OHT
Hengerer et al./2018[25]	Germany	PCS	Single center	81 (41 completed follow-up)	POAG, PXG, PG, NVG, ACG
Alnawaiseh et al./2018[26]	Germany	PCC	Single center	48	OAG
Clement et al./2019[27]	Australia	RCS	Multicenter	290 (165 completed follow-up)	POAG, OHT, ACG, PXG, NTG
Salimi et al./2019[28]	Canada	RCS	Single center	118	POAG, ACG, NTG, PXG, PG
Neuhann et al./2020[29]	Germany	RCS	Single center	164	POAG, PXG, NTG, OHT
Neuhann et al./2020[29]	Germany	RCS	Single center	88	POAG, PXG, NTG, OHT
Ioannidis et al./2020[30]	Australia, Switz.	RCS	Multicenter	106	POAG

ACG = angle-closure glaucoma; IOP = intraocular pressure; meds = medications; NTG = normotensive glaucoma; NVG = neovascular glaucoma; OAG = open-angle glaucoma; OHT = ocular hypertension; PCC = prospective case control; PCS = prospective case series, PG = pigmentary glaucoma; postop = postoperatively; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; RCS = retrospective case series; RCT = randomized control trial

make the data more representative of real-life clinical populations with stronger evidence of iStent inject efficacy.

An interesting prospective comparative study that was conducted by Alnawaiseh et al. evaluated the IOP and, additionally, the flow density measured by optical coherence tomography angiography (OCTA) after iStent inject implantation combined with cataract surgery.[26] A total of 48 eyes of 48 patients underwent either cataract surgery alone (cataract group, n = 24) or cataract surgery with implantation of 2 iStent inject devices (iStent group, n = 24). IOP and flow density data before and after surgery were extracted and analyzed. OCTA images were obtained using the AngioVue OCTA system (RTVue XR Avanti with AngioVue; OptoVue Inc.). Macular imaging was performed using 3.0 × 3.0 mm scans, whereas images over the optic nerve head (ONH) were performed with 4.5 × 4.5 mm scans. The flow density data were evaluated in the superficial and deep retinal layers of the macula and the radial peripapillary capillary layer of the ONH. In the iStent group, the mean postoperative IOP was 13.2 ± 2.3 vs 18.2 ± 3.3 mm Hg preoperatively ($P < .001$). The IOP in the cataract group also improved significantly with a mean postoperative value of 15.1 ± 2.7 mm Hg compared with 17.1 ± 2.4 mm Hg preoperatively ($P = .003$). However, the macular (superficial: $P = .002$; deep: $P = .034$) and ONH ($P = .011$) flow density improved significantly after surgery in the iStent group only with no statistically significant differences in the cataract group. These results suggest that flow density measured by OCTA can be a useful tool to evaluate the short-term success of therapy besides the IOP reduction.

Retrospective Studies

The largest retrospective study reported on iStent inject combined with phacoemulsification was a multicenter, multisurgeon study conducted in Australia including 290 eyes with mild to advanced glaucoma of different types, with the predominant diagnosis being POAG (69.7%). The other diagnoses included OHT (10.9%), appositional ACG or ACG suspects (6.7%), PXG (4.8%), and normotensive glaucoma (NTG) (4.2%). One-third of eyes (55/165) had undergone prior glaucoma intervention (1 trabeculectomy and 45 laser trabeculoplasty or laser peripheral iridotomy), and ~88% had mild to moderate disease. At 12 months, only 165 eyes had completed postoperative follow-up. The mean IOP reduced significantly from 18.27 ± 5.41 mm Hg preoperatively to 14.04 ± 2.98 mm Hg at 12 months (23.2% reduction, $P < .001$). All but 7 eyes (95.8% or 158/165) achieved month 12 IOP of ≤18 mm Hg. The 7 remaining eyes, while not meeting the ≤18 mm Hg cutoff, were able to reduce medications considerably (elimination of 1-2 medications vs preoperative). The postoperative number of glaucoma medications decreased to 0.47 ± 0.95 vs 1.65 ± 1.28 preoperatively (71.5% reduction). In addition, 76.4% of eyes (126/165) were medication free (vs 29/165 or 17.6% preoperatively; $P < .001$).[27]

A similar large retrospective case series was conducted by Salimi et al. in Canada evaluating the outcomes of iStent inject with phacoemulsification at 1 year with different glaucoma types and any severity.[28] The study included 118 eyes from 71 patients. Diagnoses consisted of POAG (n = 64), primary ACG (n = 23), NTG (n = 16), PXG (n = 10), and PG (n = 5). Disease severity did not differ across different glaucoma subtypes ($P = .169$). The majority of the eyes (81%) had mild or moderate glaucoma, whereas 19% had severe disease. Half of the eyes had no prior glaucoma intervention, 1.7% had prior incisional glaucoma surgery, 28% had previous selective laser trabeculoplasty (SLT), and 20% had previous laser peripheral iridotomy, corresponding to all primary ACG eyes (n = 23) as well as a PXG eyes with narrow angles. At month 12, both IOP and medication burden showed significant reduction that had been maintained throughout follow-up. Mean IOP reduced by 17.8%, from 17.00 ± 3.83 mm Hg to 13.97 ± 2.65 ($P < .001$). Approximately 93% of eyes achieved IOP ≤18 mm Hg at month 12 (vs 69% preoperatively). Mean medication

Table 1. Continued

Glaucoma Severity	Previous Glaucoma Surgery	Follow-up (mo)	Washout	IOP Reduction (mm Hg)	Medication Reduction, n
Mild to moderate	No	24	Yes	7.0	
Mild to moderate	No	14 (longest 38)	No	5.9	1.3
Mild to moderate	No	47.4	Yes	9.74	0.5
Any with progression	Yes (32%)	36	No	8.3	1.7
Uncontrolled on meds	No	Early postop	No	5.0	
Mild to severe	Yes (0.6%)	12	No	4.23	1.18
Mild to severe	Yes (1.7%)	12	No	3.03	1.28
	Yes (5%)	12	No	5.1	1.7
		24	No	5.4	1.7
Mild to moderate	No	1	No		

burden decreased by 56%, from 2.31 ± 1.33 to 1.03 ± 1.10 medications ($P < .001$). At month 12, 47% of the eyes were medication free compared with 4% preoperatively. Moreover, the study added a linear regression model to identify predictors of postoperative IOP improvement. The model showed that greater baseline preoperative IOP ($P < .001$) and thinner corneas ($P = .042$) were associated with a larger postoperative IOP reduction. A second model was created to identify predictors of postoperative medication reduction, which showed that a higher number of glaucoma medications at baseline were associated with a greater reduction in medication burden postoperatively ($P < .001$). Differences in age, sex, type, and severity of glaucoma and in prior history of glaucoma surgery did not account for the amount of IOP or medication reduction in either model. The study concluded that iStent inject implantation with phacoemulsification is a safe, consistently efficacious, and tissue-preserving glaucoma treatment option for patients with cataract and various types of mild to severe glaucoma.

Neuhann et al. reported the 12- and 24-month results of iStent inject implantation combined with cataract surgery in single article published in 2020.[29] In a retrospective case series, 164 eyes of 109 patients with POAG (n = 84), PXG (n = 42), NTG (n = 18), and OHT (n = 20) were included in the 12-month cohort. Of these eyes, 88 eyes (46 with POAG, 19 with PXG, 10 with NTG, and 13 with OHT) completed the 24-month follow-up. At month 12, IOP was reduced by 25.5% (from 20.0 ± 5.5 mm Hg to 14.9 ± 2.0 mm Hg; $P < .001$), and the number of glaucoma medications was reduced by 85.0% (from 2.0 ± 1.0 to 0.3 ± 0.8 medications; $P < .001$). At month 24, IOP was reduced by 26.6% (from 20.3 ± 6.1 mm Hg to 14.9 ± 1.9 mm Hg; $P < .001$), and the number of medications was reduced by 81.0% (from 2.1 ± 1.1 to 0.4 ± 0.8 medications; $P < .001$). After 12 months, 96.3% of eyes had an IOP ≤18 mm Hg, with 81.1% of eyes free of any medication, compared with 1.8% at baseline. After 24 months, 98.9% of eyes had an IOP ≤18 mm Hg, with 72.7% free of medications compared with 1.1% at baseline. The authors concluded that insertion of the iStent inject with cataract surgery effectively provides a sustained IOP reduction with a markedly improved medication burden up to 24 months postoperatively.

A new retrospective study was conducted to primarily evaluate the refractive outcomes of iStent inject implantation combined with femtosecond laser–assisted cataract surgery rather than its IOP reduction power. The cohort included 106 eyes from 89 patients with mild to moderate POAG requiring additional IOP reduction on the advice of the principal surgeon. The refractive outcomes were analyzed at week 4 postoperatively. The mean absolute difference from spherical equivalent target refraction was 0.36 ± 0.25 diopter (D), with 73.9% of eyes were within ± 0.5 D of the refractive target and 98.9% of eyes were within ±1.00 D. Also, 73.8% of eyes had 0.5 D or less residual refractive astigmatism following the procedure. More than 95% of eyes were able to reach 20/40 uncorrected vision following surgeries. Regarding efficacy, almost 60% of patients maintained or reduced their preoperative IOP value (16.16 ± 5.29 mm Hg) at the final visit, and 83.6% of patients reduced their medication usage following surgery. Although the study lacks the control group, its results indicate that the iStent inject is refractively neutral with the excellent refractive outcomes achieved in the study.[30]

iSTENT INJECT STANDALONE

Prospective Studies

The largest prospective randomized trial on iStent inject as a standalone procedure was a multicenter study conducted in Europe in 2014 and was designed to compare outcomes of iStent inject vs medical therapy in patients with OAG not controlled on 1 medication. Patients using 1 ocular hypotensive medication who, in the opinion of the investigator, required additional IOP lowering, were screened for the trial and were washed out of their current glaucoma medication in the study eye prior to randomization. Of 192 eyes (phakic or pseudophakic), 94 were randomized to surgery with implantation of the iStent inject and 98 to receive medical therapy consisting of a fixed combination of latanoprost/timolol. After 12 months, 94.7% of eyes in the iStent inject group reported unmedicated IOP reduction ≥20% vs baseline unmedicated IOP, and 91.8% of eyes in the medical therapy group reported an IOP

Table 2. Summary of iStent inject standalone studies.

Author/Year	Site	Design	Center	Eyes, n	Glaucoma Type	Glaucoma Severity
Fea et al./2014[31]	Europe	RCT	Multicenter	192	POAG, PXG, PG	Uncontrolled on 1 med
Voskanyan et al./2014[32]	Europe	PCS	Multicenter	112 (88 analyzed)	POAG, PXG, PG	Uncontrolled on 2 meds
Berdahl et al./2017[33]	Armenia	PCS	Single center	53	OAG	Uncontrolled on 2 meds
Lindstrom et al./2016[34]	Armenia	PCS	Single center	57	POAG	Uncontrolled on 1 med
Lindstrom et al./2020[35]	Armenia	PCS	Single center	57	POAG	Uncontrolled on 1 med
Hengerer et al./2019[36]	Germany	PCS	Single center	44 (33 completed follow-up)	POAG, PXG, ACG, NVG	Any with progression
Klamann et al./2015[37]	Germany	PCS	Single center	35	POAG, PXG, PG	Moderate
Davids et al./2018[38]	Germany	RCS	Single center	22 (16 completed follow-up)	POAG, PXG, SC	Failed trabeculectomy
Macher et al./2018[39]	Germany	RCS	Single center	42	POAG, PXG, PG	Failed filtration surgery

ACG = angle-closure glaucoma; IOP = intraocular pressure; med/s = medication/s; mf = multiple failures; NVG = neovascular glaucoma; OAG = open-angle glaucoma; PCS = prospective case series, PG = pigmentary glaucoma; pm = primary failure; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; RCS = retrospective case series; RCT = randomized control trial; SC = secondary glaucoma

reduction ≥20% vs baseline unmedicated IOP. An IOP ≤18 mm Hg was reported in 92.6% of eyes in the iStent inject group and 89.8% of eyes in the medical therapy group. At month 12, mean IOP in the iStent inject group was 13.0 mm Hg vs baseline medicated IOP 21.1 mm Hg and unmedicated IOP 25.2 mm Hg (12.2 mm Hg reduction). For eyes in the medical therapy group, mean IOP at month 12 was 13.2 mm Hg vs baseline medicated IOP 20.7 mm Hg and unmedicated IOP 24.8 mm Hg (11.6 mm Hg reduction). These data show that the use of the iStent inject is at least as effective as 2 medications, with the clinical benefit of reducing medication burden and assuring continuous treatment with full compliance to implant and high safety profile. This study was designed in recognition of the European Glaucoma Society guidelines that specify addition of a second medication in POAG prior to surgery. The results suggested that surgery with the iStent inject can be a valid alternative to a second medication. A significantly higher proportion of iStent inject eyes vs medication eyes achieved month 12 IOP reduction ≥50% vs baseline unmedicated IOP, making the device a preferable alternative to chronic use of multiple medications in patients with OAG.[31]

Another European, multicenter prospective case series was conducted nearly at the same time to evaluate iStent inject standalone in patients with OAG on at least 2 topical ocular hypotensive medications who required additional IOP lowering to control glaucoma progression. A total of 112 phakic or pseudophakic patients with OAG (including POAG, PXG, and PG) were included, and washed out of medications to evaluate baseline unmedicated IOP. By month 12, only 88 eyes were available for analysis of efficacy end points. Mean IOP at the 6-month visit was 16.8 ± 4.1 mm Hg. At this visit, 24.4% were administered medication for additional IOP control. By the 12-month visit, mean IOP was 15.7 ± 3.7 mm Hg in all 88 patients, representing a 10.2 mm Hg or 39.7% decrease from baseline unmedicated IOP 26.3 mm Hg. The primary end point, IOP ≤18 mm Hg after 12 months without medications, was achieved by 66% of patients. The secondary end point, IOP ≤18 mm Hg after 12 months regardless of medications, was achieved by 81% of patients. Regarding medications, 86.9% of patients had reduced their medication burden at month 12, including 15.2% with reduction of 1 medication and 71.7% with reduction of 2 or more (53.5% reduced by 2, 17.2% reduced by 3, and 1% reduced by 4 medications). The study concluded that implantation of the iStent inject as a solo procedure in OAG has a favorable benefit/risk profile with ability to provide a clinically significant IOP reduction with high safety.[32]

With similar inclusion criteria, Berdahl et al. published a prospective case series completed in Armenia evaluating the efficacy of iStent inject standalone in patients with OAG uncontrolled on 2 medications, with the addition of postoperative topical travoprost 1 day after surgery in all cases.[33] The study included 53 eyes, mostly phakic (51 eyes), that were washed out of medications at baseline and after 12 months. Originally, the efficacy end point was planned to be after 12 months, but at the time of manuscript submission, all patients have completed 18-month follow-up. At month 18, medicated IOP was 12.9 ± 2.1 mm Hg compared with preoperative medicated IOP of 19.7 ± 1.5 and unmedicated IOP of 24.9 ± 1.1. At month 13 after washout, unmedicated IOP decreased to 16.6 ± 1.4 mm Hg vs 24.9 ± 1.1 mm Hg preoperative unmedicated IOP. Furthermore, medication burden was halved to 1 medication through 18 months, except for 1 patient who was placed on 1 additional medication for IOP of 18 mm Hg at month 18. In conclusion, this study provided meaningful data about the substantial decrease in medicated IOP, which appeared to reflect the combined effects of increased trabecular and uveoscleral outflow via 2 proven modalities, trabecular stents and prostaglandins, respectively. More importantly, this reduction occurred while also decreasing medication burden by 50%. In addition, the 1-year medication washout offered an informative estimation of the independent performance of the iStent inject.

The third prospective case series was also completed in Armenia and included 57 phakic eyes with POAG

Table 2. Continued

Previous Glaucoma Surgery	Follow-up (mo)	Washout	IOP Reduction (mm Hg)	Medication Reduction, n
No	12	Yes	12.2	
No	12	Yes	10.2	1 in 15.2%, 2 or more in 71.7%
No	18	Yes	12	1
No	18	Yes	10	1 in 98%
No	48	Yes	11.2	1 in 95%
Yes (50%)	36	No	10.7	2.43
No	6	No	7/POAG, 8.42/PXG	1.31/POAG, 1.29/PXG
Yes (100%)	12	No	7.0	0.35
Yes (100%)	12	No	13.1/pf, 9.8/mf	0.7

uncontrolled on 1 medication. The patients underwent medication washout and then implantation of the iStent inject as a solo procedure and were followed for 18 months. At month 12, 100% of eyes had achieved an IOP reduction ≥20% without medications vs preoperative unmedicated IOP (100% had IOP ≤18 mm Hg and 67% had IOP ≤15 mm Hg), and 75% had IOP reduction ≥20% vs preoperative medicated IOP. At month 18, mean unmedicated IOP had decreased by 41% vs preoperative unmedicated IOP (14.4 ± 2.1 mm Hg vs 24.4 ± 1.3 mm Hg preoperatively) and had decreased by 27% vs preoperative medicated IOP (19.5 ± 1.5 preoperatively). One patient was placed on a medication at month 18 for optic nerve findings (IOP was 17.7 mm Hg), but all the remaining patients remained off medications.[34] In 2020, the authors published the 4-year outcomes of this cohort.[35] At month 48, all patients were available for follow-up (n = 57), 95% of eyes achieved an IOP reduction of ≥20% without medication vs preoperative unmedicated IOP, and 81% of eyes still had an IOP reduction of ≥20% vs preoperative medicated IOP. Mean 48-month unmedicated IOP decreased by 46% to 13.2 ± 1.6 mm Hg vs 24.4 ± 1.3 mm Hg preoperatively ($P < .0001$), with 95% of medication-free eyes having IOP ≤18 mm Hg and 82% having IOP ≤15 mm Hg. Only 2 more patients were placed on medications at months 30 and 32 (total = 3), the later underwent trabeculectomy. All the remaining patients remained free of medications. These results confirmed the previous short-term outcomes and proved the long-term efficacy of the iStent inject as a stand-alone procedure in lowering IOP down to ≤15 mm Hg in cases with OAG uncontrolled on 1 medication.

Another long-term prospective case series for iStent inject as a solo procedure with a 36-month follow-up period was published in 2019.[36] A total of 44 consecutive eyes of 31 patients were evaluated in this cohort, with glaucoma diagnoses including POAG (n = 38), PXG (n = 4), appositional ACG (n = 1), and NVG (n = 1). Preoperative ocular parameters reflected a substantial disease burden. Mean medicated IOP was 25.3 ± 6.0 mm Hg on a mean of 2.98 ± 0.88 medications, with 75% (33/44) of eyes on 3–5 glaucoma medications and no eyes were medication free. Half of the eyes (22/44) had undergone a total of 35 glaucoma interventions prior to iStent inject implantation. At month 36 postoperatively, mean IOP reduced by 42% to 14.6 ± 2.0 mm Hg ($P < .0001$), with 87.9% of eyes (29/33) decreasing IOP by ≥20% vs preoperatively. Nearly all eyes (97.0% or 32/33) achieved month 36 IOP ≤18 mm Hg vs 9.1% (4/44) preoperatively ($P < .0001$), and 70.0% of eyes (23/33) achieved month 36 IOP ≤15 mm Hg vs 2.3% (1/44) preoperatively ($P < .0001$). The mean number of medications decreased by 82% to 0.55 ± 0.79 ($P < .0001$). At month 36, 61% of eyes (20/33) became medication free (vs 0% preoperatively) and only 3.0% (1/33) on 3 medications vs 75% (33/44) on 3–5 medications preoperatively. Compared with the previously published outcomes of the same surgeon's stent-cataract experience, in which IOP was reduced by 37% and medications were reduced by 68%, the IOP and medication reduction in this standalone cohort were slightly higher (42% and 82% reduction, respectively).[25] Possible reasons for this difference include the higher preoperative IOP in the standalone cohort, as this is known to produce greater postoperative IOP reduction or this difference may just reflect the surgeon's learning curve.[28]

Retrospective Studies

Klamann et al. reported a retrospective study evaluating iStent inject standalone in phakic open-angle glaucoma.[37] The study included 35 eyes of 35 consecutive patients including POAG (n = 17), PXG (n = 15), and PG (n = 3), all were of moderate disease severity with no previous glaucoma intervention. According to visual field and disc cupping, target IOP was determined to be lower than 16 mm Hg in all cases. Subgroup analysis was performed and showed a mean IOP reduction of 33% in the POAG group ($P < .001$) and 35% in the PXG group ($P < .001$) after 6 months. The number of preoperative medications was 2.19 ± 0.91 in the POAG group and 2.33 ± 1.23 in the PXG group. A significant decrease was present during the whole follow-up period in both groups, resulting in 0.88 ± 0.62 in the POAG group ($P < .001$) and 1.04 ± 0.30 in the PXG group ($P < .001$) after 6 months. Comparing POAG and PXG, the IOP was significantly lower in POAG at 3- and 6-month visits postoperatively, but there was no difference in the number of medications at any follow-up visits between the 2 groups. In the PG group, IOP before surgery was 28.31 ± 3.21, and the number of medications was 3.66 ±

Table 3. Summary of iStent inject vs other MIGS studies.

Author/Year	Site	Design	Center	Eyes, n	Glaucoma Type	Glaucoma Severity
Hooshmand et al./2019[41]	Australia	PCCS	Multicenter	245	POAG	Mild to moderate
Manning/2019[42]	Australia	RCCS	Single center	137	POAG, PXG, OHT, ACG	Mild to moderate
Guedes et al./2019[44]	Brazil	RCCS	Single center	73	POAG, PXG, PG	Mild to severe
Guedes et al./2019[43]	Brazil	RCCS	Single center	58	POAG, PXG, PG	Mild to severe
Gonnermann et al./2017[45]	Germany	RCCS	Single center	54	POAG, PXG	Moderate with progression
Pantalon et al./2020[46]		RCCS	Single center	109	POAG, PXG, PG, OHT	Mild to moderate

ACG = angle-closure glaucoma; ECP = endocyclophotocoagulation; IOP = intraocular pressure; OAG = open-angle glaucoma; OHT = ocular hypertension; PCCS = prospective comparative case series, PG = pigmentary glaucoma; Phaco = phacoemulsification; POAG = primary open-angle glaucoma; PXG = pseudoexfoliation glaucoma; RCCS = retrospective comparative case series

0.57. One day after surgery, IOP decreased significantly to 12.33 mm Hg ± 4.93, with the same number of medications. However, between 2 and 4 weeks postoperatively, IOP was raised above 30 mm Hg. To exclude steroid response, topical steroids were stopped, but IOP did not decrease after 1 week. To exclude stent blockage by pigment, Nd: YAG laser of the visible stent opening was performed. However, no response was detected after 5 days in all patients, and a trabeculectomy was subsequently scheduled. With the addition of subgroup analysis, the study concluded that iStent inject implantation has the ability to significantly reduce IOP and medication burden in POAG and PXG, but in phakic PG, limitations may exist and necessitate further investigation with a larger sample size.

Another retrospective study with different design was reported. The study was restricted to only patients with uncontrolled IOP after failed trabeculectomy, also iStent inject was implanted either alone, in most cases, or in combination with cataract surgery. A total of 22 eyes from 21 patients were included. A vast majority of the patients had an advanced POAG (n = 18 or 81.8%). The remaining cases were PXG (n = 3 or 13.7%) and secondary glaucoma (n = 1 or 4.5%). The iStent inject implantation was combined with a cataract surgery in 5 eyes (22.7%) of 6 phakic eyes (27.3%) in the study, whereas 16 eyes (72.7%) were pseudophakic from the start. In 3 eyes (13.6%), a preoperative SLT was documented. The results showed a significant IOP decrease from 22.5 ± 4.6 preoperatively to 15.5 ± 3.4 mm Hg at month 12 ($P = .012$). The glaucoma medications were reduced from 2.6 ± 1.2 preoperatively to 2.25 ± 1.5 after 12 months, but this difference was insignificant ($P > .05$). There was no significant difference between POAG and PXG. The combination of the iStent inject implantation with cataract surgery did not have an additive effect on the outcome as well as the previous SLT. The time that has passed since the trabeculectomy was performed (mean = 9.6 ± 8.1 years; range: 1–35 years) did not have an influence on the outcome. The study reported that 6 eyes (27.3%) dropped out of the study because the IOP did not reach the target pressure with need to subsequent intervention: re-trabeculectomy in 3 cases, cyclophotocoagulation (CPC) in 2 cases, and ab interno trabeculotomy in 1 case. The author suggested that implantation of the iStent inject might be a reasonable alternative procedure after a failed trabeculectomy. This must be taken into consideration in cases of drug intolerance and a low target pressure as an indication for surgery.[38]

Similar idea was seen in the retrospective study reported by Macher et al., as they included patients with advanced OAG who had been using at least 2 IOP-lowering medications for at least 6 months after previous filtration surgery but still required additional IOP lowering.[39] A total of 42 eyes from 42 patients with POAG, PXG, and PG were included. Eleven eyes (26%) had combined cataract surgery, and 33 eyes (74%) were pseudophakic. Eighteen eyes (43%) had filtration surgery once, 15 eyes (36%) twice, 7 eyes (17%) 3 times, and 2 eyes (4%) 4 times. After 12 months, the IOP of primary failures was lowered from 23.8 ± 3.9 mm Hg preoperatively to 15.2 ± 2.7 mm Hg postoperatively and in the other patients from 26.1 ± 5.7 mm Hg to 16.3 ± 3.3 mm Hg. The number of medications decreased from 2.7 ± 0.9 to 2.0 ± 1.1. Fifteen eyes (36%) required additional surgery within 6 months in the form of filtering bleb revision, a drainage device, or CPC. This study showed that iStent inject implantation in eyes with advanced OAG and previous filtration surgery resulted in safe and successful IOP reduction to less than 18 mm Hg by two-thirds of the patients.

iSTENT INJECT WITH CATARACT SURGERY VS iSTENT STANDALONE META-ANALYSIS

A meta-analysis evaluating the efficacy and safety of the iStent and iStent inject for OAG was published in 2018. Of the 1767 eyes included, the vast majority (1398%, 79.1%) received a first-generation iStent, whereas 369 eyes (20.9%) received an iStent inject. For the second-generation iStent inject, the author compared the combined stent implantation with phacoemulsification vs standalone implantation and concluded that the iStent inject alone has greater IOP and medication reduction than the combined procedure. Studies reporting on the iStent inject alone had a significantly greater IOP reduction ($P < .001$) compared with studies reporting on the phaco-iStent. Postoperatively, the phaco-iStent cohort had a significantly higher IOP relative to the iStent inject alone ($P < .001$). There was a significantly greater reduction in medication classes ($P < .001$)

Table 3. Continued

Previous Glaucoma Surgery	Follow-up (mo)	Washout	Comparison	Phaco
No	12	No	iStent inject vs iStent	Yes
Yes (22%)	12	No	iStent inject vs iStent	Yes
No	6	No	iStent inject vs iStent	Yes
No	12	No	iStent inject vs iStent	Yes
No	12	No	iStent inject vs trabectome	Yes
No	12	No	iStent inject + ECP vs iStent inject	Yes

and a lower number of postoperative medication classes (P = .03) following the iStent alone relative to the phaco-iStent.[40]

iSTENT INJECT VS OTHER MIGS

Relatively fewer studies have compared the outcomes of the iStent inject with other trabecular MIGS procedures, mainly with the older first-generation iStent.[41–45] In a prospective comparative case series in Australia, the effect of a single iStent was compared with a double iStent inject combined with cataract surgery in POAG. A total of 245 eyes from 148 patients with mild to moderate POAG were consecutively recruited from 2 centers in Australia. There were 145 eyes in the iStent group and 100 eyes in the iStent inject group. The mean preoperative IOP was identical in both groups (18.9 mm Hg). The mean preoperative number of topical agents was 1.7 in the iStent group and 1.6 in the iStent inject group. At month 12, 56.0% of the iStent eyes vs 51.3% of the iStent inject eyes had achieved primary success (IOP ≤18 mm Hg with no medications), and 63.1% vs 57.7% had achieved secondary success (IOP ≤18 mm Hg with reduced medication number). The mean postoperative IOP was 16.6 mm Hg in the iStent and 16.9 mm Hg in the iStent inject, with no significant difference between the 2 groups. The mean number of glaucoma medications reduced from 1.7 to 0.6 in the iStent eyes and from 1.6 to 0.7 in the iStent inject eyes. By month 12, 63.8% iStent and 66.7% iStent inject eyes had recommenced topical glaucoma therapy, with a mean time to initiate therapy of 12 months for iStent and 7 months for iStent inject. These results suggested that both trabecular stents combined with cataract surgery are effective in reducing IOP and medication burden, with no statistically significant difference between the 2 groups, although the iStent inject required earlier recommencement of medications for optimal IOP control.[41]

Two other retrospective case series compared iStent vs iStent inject combined with cataract surgery.[42,43] The larger is a single-center study conducted by Manning et al., again in Australia.[42] The study included all consecutive eyes implanted with either iStent or iStent inject combined with cataract surgery and performed by a single surgeon. A total of 137 consecutive eyes with mild to moderate glaucoma and cataract and 12 months of follow-up were included. The iStent group (n = 67) included predominantly eyes with POAG and PXG, and the iStent inject group (n = 70) included mostly eyes with POAG, OHT, and ACG (with open-angle configuration in the area of stent implantation). Over 73% of eyes in both groups had early glaucoma, and approximately 22% of eyes had undergone prior glaucoma surgical or laser procedures. At month 12, mean IOP decreased from 18.4 ± 4.2 mm Hg to 14.2 ± 2.5 mm Hg in iStent eyes (P < .0001) and from 20.4 ± 5.6 mm Hg to 14.4 ± 2.1 mm Hg in iStent inject eyes (P < .0001). The IOP reduction was significantly greater for iStent inject eyes than for iStent eyes (6.0 mm Hg vs 4.2 mm Hg reduction, P = .034). Both groups had high proportions of patients achieving the IOP effectiveness end points (IOP ≤18 mm Hg), but with greater proportions with iStent inject (95.7%) than iStent (92.5%). Regarding medication usage, mean medication burden at month 12 decreased from 1.8 ± 0.7 medications to 0.3 ± 0.5 in iStent eyes (84.0% reduction, P ≤ .0001) and from 1.3 ± 0.9 medications to 0.1 ± 0.3 in iStent inject eyes (94.7% reduction, P ≤ .0001). The percentage of eyes on 2 or more medications decreased significantly in both groups, from 68.7% to 4.5% in the iStent group (P ≤ .0001) and from 41.4% to 0% in the iStent inject group (P ≤ .0001). A significantly higher proportion of iStent inject eyes than iStent eyes were medication free after 12 months (92.9% vs 76.1% in the 2 groups, respectively; P = .0068). In conclusion, outcomes through 12 months showed clinically and statistically significant reduction in IOP and medications in both groups, with greater efficacy in the iStent inject eyes.

The second, single-center retrospective study, conducted in Brazil, with inclusion of 58 consecutive eyes POAG (72.4%), PXG, and PG showed a similar conclusion in favor of the iStent inject. Any disease severity was allowed with majority of cases were mild to moderate stage (96.6%). All eyes underwent uncomplicated phacoemulsification, followed by implantation of either the iStent (n = 35) or the iStent inject (n = 23), and followed for 12 months. In iStent eyes, mean IOP reduced from 16.1 ± 3.6 mm Hg at baseline to 15.4 ± 2.4 mm Hg at month 12 (P = .201). In iStent inject eyes, mean IOP reduced from 16.2 ± 3.1 mm Hg at baseline to 13.1 ± 2.2 mm Hg at month 12 (P < .001). Mean IOP reduction was significantly greater in iStent inject eyes (19.1%) than in iStent eyes (4.3%) (P ≤ .001), although baseline IOP was similar in the 2 groups (P = .882). Regarding medications, at baseline, the iStent and iStent inject groups had nearly similar mean number of medications (1.8 vs 1.7, respectively, P = .565). At month 12, iStent inject eyes

Table 4. Summary of iStent inject studies assessing aqueous outflow facility and stent position.

Author/Year	Site	Design	Center	Eyes, n	Glaucoma Type
Bahler et al./2012[47]	U.S.	PLI, ex vivo	Single center	14	Cultured AS, no glaucoma
Hunter et al./2014[48]	U.S.	PLI, ex vivo	Single center		Human pseudophakic globes, no glaucoma
Gillmann et al./2018[49]	Switzerland	CR, in vivo	Single center	1	POAG
Gillmann et al./2019[50]	Switzerland	PCCS, in vivo	Single center	38	POAG, PXG
Huang et al./2019[51]	Armenia	PCCS, in vivo	Single center	15	POAG, PXG
Huang et al./2016[52]	U.S.	PLI, ex vivo	Single center	11	Human globes, no glaucoma

3D Micro CT = 3D microcomputed tomography; AA = aqueous angiography; AS = anterior segment; AS-OCT = anterior segment optical coherence tomography; CFD = computational fluid dynamics; CR = case report; MIGS = microinvasive glaucoma surgery; PCCS = prospective comparative case series; Phaco = phacoemulsification; PLI = prospective laboratory investigation; POAG = primary open-angle glaucoma; PXG, pseudoexfoliation glaucoma; SC = Schlemm canal; SEM = scanning electron microscopy

reduced medication burden by 94.1% ($P < .0001$), and iStent eyes decreased their medication burden by 72.2% ($P < .0001$). Medication reduction was significantly greater in iStent inject eyes than in iStent eyes ($P = .023$). In addition, iStent inject eyes had a significantly lower mean number of medications than iStent eyes after 12 months (0.1 ± 0.2 medications vs 0.5 ± 0.8 medications, respectively, $P = .021$), with 71.4% of iStent eyes vs 95.7% of iStent inject eyes becoming medication free ($P = .021$). The reduction in the number of medications vs baseline was statistically significant ($P < .001$) for both groups.[43] The authors published the intermediate 6 months results of their study in a separate cohort, as more patients were available for follow-up at that time point.[44] After 6 months, 73 eyes were analyzed in the study: 38 with the iStent and 35 with the iStent inject, with more than 90% of eyes in both groups had early glaucoma. The 6-month results were comparable to the 12-month results. The IOP was reduced from 16.5 ± 3.9 to 13.9 ± 2.3 mm Hg in the iStent group ($P < .001$) and from 17.3 ± 3.0 to 12.7 ± 1.8 mm Hg in the iStent inject group ($P < .001$). Although 6-month IOP reduction in the iStent group was higher compared with the 12-month reduction, yet IOP reduction was still significantly greater in the iStent inject eyes than in the iStent eyes (26.6 vs 15.8%) ($P = .005$). Significantly more eyes receiving the iStent inject compared with the iStent achieved an IOP ≤18 mm Hg at 6 months (100 vs 86.8%) ($P = .033$). The mean medication number was reduced from 1.8 to 0.4 in iStent eyes (77.8%, $P < .001$) and from 2.3 to 0.4 in iStent inject eyes (82.6%, $P < .001$). Two eyes in the iStent group required additional glaucoma surgery (one of them was included in the 12-month cohort), whereas no secondary surgeries were needed in the iStent inject group at both time points. In conclusion, both cohorts showed greater efficacy and fewer adverse events in the iStent inject group compared with the iStent group.

Gonnermann et al. published a retrospective case series in 2017 comparing 2 different modalities of trabecular MIGS combined with cataract surgery[45]: Trabectome in 1 eye vs iStent inject in the contralateral eye of the same patient. This intraindividual eye comparison study included 54 eyes of 27 patients with moderate OAG including POAG (n = 19) and PXG (n = 8) with IOP above target and glaucoma progression on maximally tolerated medical therapy. At month 12, IOP decreased by 30% in the Trabectome group ($P < .001$) and 34% in the iStent inject group ($P < .001$). A significant decrease in postoperative IOP during the whole follow-up period was evident in both groups; however, there was no statistically significant difference between the 2 groups ($P > .05$). The number of glaucoma medications decreased significantly in both groups at month 12 ($P < .05$), from 2.08 ± 1.12 to 1.44 ± 1.29 in the Trabectome group and from 2.04 ± 0.89 to 1.28 ± 1.17 in the iStent inject group. The number of topical medications was significantly higher in the Trabectome group in comparison to the iStent group only at 6 weeks postsurgery. This difference is due to the postoperative use of pilocarpine 1% eyedrops after Trabectome surgery, which was tapered down over 6 weeks. Pilocarpine was not used after iStent inject implantation. So, in conclusion, combined surgery using both procedures, iStent inject and Trabectome, has the ability to significantly lower the postoperative IOP in OAG, with no statistically significant difference between the 2 procedures.

An interesting retrospective study compared the outcomes of combined iStent inject, phacoemulsification, and endocyclophotocoagulation (ECP) vs phacoemulsification-iStent inject alone. The ICE2 (2 iStents-cataract extraction-ECP) group included 63 eyes, and the phaco-iStent group included 46 eyes. The study included eyes with mild to moderate OAG (POAG, PXG, and PG) as well as OHT. In both groups, there was a significant IOP and medication reduction both at 6 and 12 months compared with baseline. At month 12, there was a 35% IOP reduction from baseline medicated IOP (13.05 ± 2.28 mm Hg vs 19.97 ± 4.31 mm Hg preoperatively, $P < .001$) in the ICE2 group, whereas in the phaco-iStent group, IOP was reduced by 21% (14.09 ± 1.86 mm Hg vs 17.63 ± 3.86 mm Hg, $P < .001$). Such percent IOP reduction in the ICE2 group was significantly more prominent than the phaco-iStent group ($P = .03$). Also, final IOP was lower in the ICE2 group than the phaco-iStent group (13.05 ± 2.18 mm Hg vs 14.09 ± 1.86 mm Hg, $P = .01$). Similar results were found regarding the final number of glaucoma medications (1.24 ± 1.05 in the ICE2 group vs 1.39 ± 1.03 in the phaco-iStent group, $P = .01$). For the

Table 4. Continued

Glaucoma Severity	Previous Glaucoma Surgery	Follow-up (mo)	Washout	Imaging	Phaco
No glaucoma	No	72 h	No	SEM, 3D Micro CT	AS/no lens
No glaucoma	No		No	CFD	Pseudophakic globes
Moderate	No	6	No	AS-OCT	Yes
Mild to moderate	No	3	No	AS-OCT	Yes
	No	3	Yes	AA	Yes
No glaucoma	No		No	AA	No

ICE2 group, the number of medications was reduced by 45% ($P < .001$). In the phaco-iStent group, there was a final 33% reduction of medication from baseline, but significantly inferior to the ICE2 group ($P = .04$). The authors concluded that the ICE2 procedure offers better results in IOP and medication reduction at 12 months than phacoemulsification-iStent alone with favorable safety profile in both groups. This study highlights the additive effect of 2 different MIGS procedures compared with the use of only 1 modality.[46]

ASSESSMENT OF AQUEOUS OUTFLOW FACILITY AND STENT POSITION

The position of the iStent inject in the Schlemm canal and aqueous outflow through the stent were assessed in several studies either in vitro or in vivo using different modalities (Table 4).

Laboratory investigations using normal human donor eyes have been performed to detect the influence of the iStent inject on aqueous outflow, in addition to IOP reduction.[47,48] One of the earliest iStent inject studies published in 2012 was designed to prospectively evaluate aqueous outflow facility in the cultured human anterior segment. Seven pairs of normal human eyes (no glaucoma or topical medications) were bisected at the equator; the iris, lens, ciliary body, and vitreous were then removed. The remaining anterior segment was clamped in a modified Petri dish perfused with Dulbecco's Modified Eagle media. Pressure was recorded with an automated computerized system. Once baseline pressure was established, anterior segments were removed from culture, an iStent inject was inserted through the uveal trabecular meshwork into the Schlemm canal from the posterior side using a specially designed injector, then anterior segments were returned to culture and pressure was monitored for 72 hours. Seven anterior segments received 1 stent, and 2 of them received a second stent approximately 24 hours after the first one. Seven fellow control anterior segments were removed from culture, underwent similar manipulations, and were placed back in culture without an iStent inject. Morphology of the trabecular meshwork and Schlemm canal was assessed by scanning electron microscopy (SEM) and 3-dimensional micro-computed tomography (3D micro-CT). Results of 1 iStent inject insertion after 6 hours showed increased outflow facility from 0.16 ± 0.05 to 0.38 ± 0.23 μL L/min/mm Hg (127%, $P < .03$, n = 7), with concurrent pressure reduction from 16.7 ± 5.4 to 8.6 ± 4.4 mm Hg. Addition of a second iStent inject significantly increased outflow facility to 0.78 ± 0.66 μL/min/mm Hg (n = 2) compared with 1 stent. In contrast, the fellow control anterior segments had minimal change in pressure and outflow facility. SEM was used in 4 samples and showed the iStent inject flange compressed against the uveal region of the trabecular meshwork, the thorax securely inserted within the trabecular meshwork, and the head located in the lumen of the Schlemm canal with dilation of the Schlemm canal around the iStent inject head. The 3D micro-CT confirmed the proper placement of iStent inject in the trabecular meshwork and alignment with the Schlemm canal. Being an ex vivo model, the human anterior segment culture studies have some limitations. In 5 of the 7 segments, 1 iStent inject reduced the pressure to nearly the base level, rendering a pressure too low to accurately assess the addition of the additional stent. Also, the pressure values obtained may not represent the exact pressure reduction obtained in vivo in the absence of an episcleral venous pressure and absence of inflammation and fibrosis in the normal healing process.[47]

As a complementary study, Hunter et al. conducted another prospective laboratory investigation in 2014 to evaluate aqueous outflow and pressure reduction after implantation of the iStent or iStent inject in a whole human eye perfusion model, instead of using a cultured human anterior segment model.[48] Numerical modeling, including computational fluid dynamics, was used to evaluate the flow through the stents. The results showed that a single stent reduced IOP by 6.0 mm Hg from baseline and the addition of a second stent further reduced IOP by 2.9 mm Hg, achieving a total IOP reduction of 8.9 mm Hg. Computational modeling showed that simulated flow through the iStent or iStent inject is smooth and laminar at physiological flow rates. These results show that both iStent and iStent inject therapies are potentially titratable, providing clinicians with the opportunity to achieve lower target IOPs by implanting additional stents.

Gillmann et al., in 2018, reported the first in vivo description of a trabecular bypass device visualized using anterior segment OCT (AS-OCT).[49] In a case report, a patient with POAG underwent successful cataract surgery combined with iStent inject implantation. At 6 months, the patient was medication free vs 2 medications preoperatively besides 1 mm Hg IOP reduction. Under AS-OCT (Spectralis OCT, Heidelberg Engineering AG, Germany), the stent appears as a 300 μm long hyperreflective hollow device within the trabecular meshwork; approximately a

third of it protruded into the anterior chamber. A second AS-OCT section 500 μm beside the stent shows a markedly dilated Schlemm canal, with a major diameter of 390 μm, which represents 220% increase in the canal diameter compared with the observed mean (122 μm). These findings confirm that the iStent inject has dual action: not only does it maintain an outflow pathway through the trabecular meshwork, but it can also achieve significant dilation of the Schlemm canal similarly to what has been observed in canaloplasty techniques. In 2019, the same authors published a prospective comparative case series to evaluate iStent inject implantation using AS-OCT with addition of IOP correlation. A total of 25 eyes with mild to moderate OAG were enrolled and underwent iStent inject implantation combined with cataract surgery, with 13 nonoperated fellow eyes served as control. The results showed that 92% of devices were visible on AS-OCT vs 88% visible on gonioscopic examination. The mean major diameter of the Schlemm canal was 308.7 ± 197.4 μm vs 126.9 ± 60.3 μm in control eyes (P = .03). Device protrusion and larger Schlemm canal diameters were associated with lower postoperative IOP (P = .005 and P = .04, respectively). Of note, this study revealed a significant portion of injected stents not visible within the Schlemm canal. Despite the apparent extraluminal positioning of the device heads, filtration still appeared to occur as evidenced by the observation of Schlemm canal dilation.[50]

Huang et al. used a different technology to assess the function rather than the position of trabecular stents with imaging of aqueous humor outflow (AHO) patterns.[51] In a prospective comparative case series, sequential aqueous angiography was used intraoperatively to compare angiographic AHO patterns before and after iStent inject implantation with a tracer injected intracameral and imaged by an angiographic camera. The study included 14 eyes with OAG (phacoemulsification + iStent inject) and 1 nonglaucomatous control eye (phacoemulsification alone). Indocyanine green (ICG) aqueous angiography established initial baseline nasal angiography, the routine surgery was performed, and subsequent fluorescein (FL) aqueous angiography was used to query alterations. At baseline, all eyes showed segmental angiographic AHO patterns. Focused on the nasal angle, initially low ICG signal regions showed transient or persistent improved FL angiographic signal (11.2-fold, P = .014), whereas eyes with initially high ICG signal showed faster development of FL angiographic patterns (3.1-fold; P = .02). Regarding the control eye, ICG and FL showed similar angiographic signals pre- and postcataract surgery. This study was designed to replicate prior experimental design in postmortem human eyes, and similar results were obtained.[52]

SAFETY

The hallmark about the iStent inject, like the first-generation iStent and trabecular MIGS in general, is its excellent safety profile. All randomized clinical trials and case series of the iStent inject, either combined with phacoemulsification or as a standalone procedure, reported absence of serious postoperative adverse events like hypotony, flat anterior chamber, suprachoroidal hemorrhage or effusion, cyclodialysis, corneal decompensation, endophthalmitis, and atrophy. The majority of cases showed a postoperative visual acuity of 20/40 or better, with stable visual field, cup-to-disc ratio, and central corneal thickness. Most of the intraoperative and postoperative adverse events were mild and were successfully managed. Based on the safety outcomes reported in the literature, patients undergoing combined cataract-iStent inject surgery can reasonably expect that stent implantation will not diminish the visual benefits anticipated from cataract surgery. They can thereby address both issues (glaucoma and cataract) in a single safe operation.

The most common intraoperative adverse event was blood reflux from the Schlemm canal, which is considered a sign of correct position and patency of the stent. Gonnermann et al. reported blood reflux in 100% of cases, and Davids et al. and Klamann et al. reported it in about 91% of their cases.[37,38,45] Best et al. reported 1 case of severe blood reflux that was managed with irrigation/aspiration before the second stent implantation.[23] The subsequent early postoperative microhyphema was also one of the most common adverse events. It occurred in 3.9% of patients as reported by Samuelson et al. and in 5% of patients as reported by Salimi et al.[22,28] Clement et al. and Hengerer et al. reported only 1 case of hyphema. In all cases, hyphema was resolved spontaneously in the first week postoperatively.[27,36]

The 2 stents were successfully implanted in all cases in most studies. Failure to implant the second stent was reported in 4 studies, with 2 or 3 eyes in each one.[22,24,27,42] Early postoperative complications, rather than the microhyphema, included temporary corneal edema,[25,27,28] IOP spikes,[23,28,31] and iritis.[22,27,28,36] All these complications were transient and resolved with medications.

Stent-related complications included stent malposition, stent obstruction, peripheral anterior synechiae (PAS), and invisible stent. Samuelson et al. reported implantation of the 2 stents in the same location, with one of them in the ciliary body.[22] Clement et al. reported 1 case of intermittent stent-iris touch that resulted in no sequelae and 1 case with incomplete visualization of the second stent.[27] Voskanyan et al. reported also 1 case of stent malposition and 13 cases of only 1 visible stent.[32] Arriola-Villalobos et al. reported 4 eyes with only 1 visible stent.[24] Stent obstruction occurred in 24 cases (only 3 treated with YAG laser) in the study conducted by Samuelson et al. and in 6 cases (3 cases resolved without lase treatment) as reported by Voskanyan et al., whereas Fea et al. reported only 1 case (treated with YAG laser).[22,31,32] PAS was also reported by Samuelson et al. in 1.8% of eyes and by Voskanyan et al. in only 1 eye that was treated with YAG laser.[22,32]

Most cases achieved significant IOP and medication reduction in all studies. However, additional glaucoma interventions were required in some cases for more IOP

reduction. In the study conducted by Samuelson et al., 1.6% (6 eyes) in the iStent inject group vs 3.4% (4 eyes) in the control group required additional intervention.[22] Of the 6 eyes in the iStent inject group, 2 were treated with SLT, and 4 required trabeculectomy/Express shunt. Hengerer et al. reported that 3 cases required additional intervention, with the Xen implant in 1 case and CPC in 2 eyes.[25] Clement et al. reported that 3 cases required further surgery in the form of deep sclerectomy, second stent implantation, and SLT followed by trabeculectomy, but all of them were recurrent cases with previous glaucoma surgery before the iStent inject implantation.[27] Salimi et al. reported that 5 cases required SLT, but no incisional surgery.[28] Neuhann et al. reported that only 1 case required trabeculectomy in the 24-month cohort.[29] Voskanyan et al. reported that 6 cases, of 10 with high IOP, required additional surgery including trabeculectomy, deep sclerectomy, and goniotrephination.[32] Lindstrom et al. reported that 1 case with persistent IOP elevation after adding medications at month 32 underwent trabeculectomy.[35] Hengerer et al. reported that 2 cases required further intervention with CPC or Xen implant.[36] Of interest, in the study conducted by Klamann et al., the 3 cases with pigmentary glaucoma included in the study were the only resistant cases that required further intervention for persistent IOP elevation despite steroid withdrawal and relief of any potential stent obstruction by YAG laser.[37] The 3 cases eventually underwent trabeculectomy. The authors recommended further studies evaluating the iStent inject in pigmentary glaucoma with a larger sample size.

In the studies evaluating the iStent inject as a standalone procedure, there were special complications related to the lens status. Progression of cataract was observed in 3 studies with 1 or 2 eyes in each one.[32,34–36]

Comparative studies have shown comparable adverse events in the iStent inject and iStent. Hooshmand et al. reported a slightly higher rate of early postoperative hyphema and corneal edema with the iStent than the iStent inject.[41] However, he reported 1 case of delayed spontaneous nontraumatic hyphema in the iStent inject group that was conservatively managed. Manning et al. reported the same safety profile with the iStent and iStent inject.[42] Guedes et al. reported 1 case of stent obstruction treated with YAG laser, and 2 cases required additional IOP-lowering surgery with deep sclerectomy in the iStent group, with no additional intervention in the iStent inject group.[43,44] In the study comparing iStent inject vs ab interno trabeculectomy, Gonnermann et al. reported similar adverse events with need for trabeculectomy in 2 eyes in each group.[45]

These diverse clinical studies demonstrate favorable safety of the iStent inject, both in standalone implantation procedures and in conjunction with cataract surgery. The risks associated with stent implantation are shown to be largely similar to cataract surgery alone, which has a well-known superb safety profile and is the most widely performed surgery worldwide. The iStent inject is composed of biocompatible titanium and has truly microscale dimensions (occupying < 0.5 mm total for both iStent inject stents in the trabecular meshwork); these characteristics may contribute to the very low rates of inflammation and inflammatory sequelae such as PAS as well as the infrequent incidence of secondary surgeries.

ECONOMIC ANALYSIS

Two published studies examined the cost-effectiveness of the iStent inject compared with antiglaucoma medications alone.[53,54] A cost-utility analysis was conducted using efficacy and safety results of the iStent inject pivotal randomized clinical trial from the Canadian healthcare perspective.[22,53] iStent inject implantation during cataract surgery appeared to be cost-effective for reducing IOP in patients with mild to moderate OAG vs cataract surgery alone. Compared with cataract surgery alone, iStent inject + cataract surgery had a 99% probability of being more effective (+0.023 QALYs [95% CI, 0.004 to 0.044]) and a 73.7% probability of being cost saving (net cost, −C$389.00 [95% CI, −C$1712.00 to $850.70]). In Patel's study, the value of 2 stents (2 iStents or iStent inject) implanted as a stand-alone procedure compared with medications only in patients without visually significant cataract was calculated from the Canadian public payer's perspective.[54] The cost-utility results based on a 15-year time horizon showed that 2 stents dominated medical therapy and provided better effectiveness (additional 0.068 QALYs) at lower total costs (−$CAN2908.30). Cost savings were driven predominantly by lower medication costs with 2 stents vs medication only. Economic analyses of the iStent inject demonstrated the cost-effectiveness of this device. Each MIGS device is associated with a unique safety and efficacy profile and so is also associated with unique resource utilization. Therefore, results supporting the cost-effectiveness of one MIGS device cannot be generalized to others.

CONCLUSION

The iStent inject has been shown in numerous publications to be a safe and effective procedure in treatment of different types of open-angle glaucoma either as a stand-alone procedure or combined with cataract surgery. It was also suggested to be superior to the first-generation iStent. As evidenced in these clinical studies, the iStent inject embodies the 5 key criteria of MIGS procedures, including high safety, minimal tissue disruption, swift recovery, at least modest effectiveness, and ab interno approach.[9] In a recent survey of the American Glaucoma Society, 76% of surgeons who choose to perform MIGS procedures preferred to use the iStent.[55] Within the MIGS category, the iStent inject is noteworthy as the smallest available device, minimizing tissue disruption within the angle. Preservation of ocular tissue may potentially allow for future more invasive angle-based procedures if needed. The clinical literature broadly indicates comparable safety of iStent inject implantation to cataract surgery alone. Adverse events are generally uncommon, mild, and readily corrected. This positive benefit-to-risk assessment customarily is

considered applicable to patients with more mild or moderate glaucoma that does not yet warrant the risks of filtering surgery. In addition, our review of the recent literature reveals that the indications of iStent inject use have been expanded to severe and recurrent forms of glaucoma as well. Future studies should add more information and comparisons to other trabecular MIGS.

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