Endothelial cell loss associated with minimally invasive glaucoma surgery

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Purpose of review
Minimally invasive glaucoma surgery (MIGS) represents a safer, albeit moderately effective surgical option for intraocular pressure control. However, the CyPass Micro-Stent (Alcon Laboratories) was withdrawn from the market in 2018 as the COMPASS-XT study demonstrated greater cornea endothelial cell (CEC) loss in patients who received the CyPass Micro-Stent with phacoemulsification compared with phacoemulsification alone. This led to the increased attention on MIGS-associated CEC loss and thus, this review will summarise the recent, available evidence on MIGS-associated CEC loss.

Recent findings
Prospective clinical trials and retrospective observational studies published between 2011 and 2021 reported a wide range of 12 month CEC loss from 'insignificant', and up to 14.6%, for phacoemulsification combined with various MIGS procedures. Recent clinical trials over the same time period reported CEC loss of 12.8–15.2% associated with phacoemulsification alone.

Summary
Apart from the CyPass Micro-Stent clinical trial, no other studies on combined phacoemulsification with MIGS that is 'phaco-plus' procedures have reported a higher short-term CEC loss compared with phacoemulsification alone. However, studies that specifically examine postprocedural CEC loss following phacoemulsification compared to 'phaco-plus' procedures over a longer follow-up period are required.

Keywords
Cornea, Glaucoma, Cornea Endothelial Cells, Phacoemulsification, Minimally invasive glaucoma surgery

INTRODUCTION

Minimally invasive glaucoma surgery (MIGS) has been positioned as a moderately effective intraocular pressure (IOP) control solution with a better safety profile. MIGS is traditionally defined by minimal disruption of normal anatomy, efficacious at lowering IOP and rapid postprocedure recovery [1]. They can be classified based on their anatomical intervention site: Schlemm's canal, suprachoroidal and subconjunctival MIGS. Schlemm's canal MIGS are designed to bypass or remove the trabecular meshwork, the site of greatest aqueous outflow resistance, to allow direct drainage through the Schlemm's canal. Suprachoroidal MIGS enable direct access to the suprachoroidal space via stent placement, increasing uveoscleral outflow. Subconjunctival MIGS allow direct access to the subconjunctival space via an ab-interno small incision approach [2].

The cornea endothelium comprises a monolayer of corneal endothelial cells (CEC) interdigitated with apical tight junctions. CEC have active transporters that create an ionic gradient to counteract the passive diffusion of water within the stroma, keeping an optimal level of corneal hydration to maintain visual clarity [3]. However, CECs are arrested in the G1 phase of the cell cycle and do not regenerate [4]. On average, humans are born with approximately 4000 CEC/mm^2 which gradually declines to 2500 CEC/mm^2 by adulthood [5] and 2000 CEC/mm^2 by old age. Although the rate of CEC loss over a lifetime is nonlinear, the average annual CEC loss is estimated to be 0.6% [6]. This CEC loss can be accelerated by diabetes mellitus,

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KEY POINTS

- MIGS may provide a safer surgical option, with a moderate effect on intraocular pressure control.
- Recent studies (published 2011–2021) reported 12-month CEC loss that ranged from 'insignificant', up to 14.6% for phacoemulsification combined with various MIGS procedures.
- Apart from the CyPass Micro-Stent clinical trial, no other studies on combined phacoemulsification with MIGS have reported a higher CEC loss compared with phacoemulsification alone – however, more long-term studies are required.

concomitant ocular conditions, genetic conditions such as cornea endothelial dystrophies, and previous surgical procedures including phacoemulsification and glaucoma surgeries [7,8].

Although iatrogenic CEC loss have been frequently studied, interstudy comparisons can be difficult due to the wide disparity of surgical methods, surgeon experience and patient factors. Nonetheless, the reported CEC loss associated with routine phacoemulsification ranges 6.3–17.0% at 6 months; while combined phacoemulsification and trabeculectomy surgeries can range from 23.2 to 42.6% at 12 months and 8.5 to 12.3% at 12 months following glaucoma shunt surgeries (Table 1). Phacoemulsification-associated CEC loss varies widely depending on the study duration, use of femtosecond laser, the performing surgeon, type of viscoelastic and anatomical features like the anterior chamber depth and cataract density [9–11]. Trabeculectomy-associated CEC loss varies depending on the study duration, use of adjunctive antiproliferative agents, experience of the performing surgeon and concomitant cataract surgery [12–17]. Finally, glaucoma shunt associated CEC loss varies depending on the study duration, type of implant, implant positioning, skill of the performing surgeon and concomitant cataract surgery (Table 1) [13,14,18,19].

As CEC loss can result in corneal decompensation and potential visual impairment, when the 5-year results of the COMPASS-XT trial highlighted a significantly greater CEC loss associated with the CyPass Micro-Stent (Alcon Laboratories, Fort Worth, Texas, USA) combined with phacoemulsification compared with phacoemulsification alone, the United States Food and Drug Administration (FDA) withdrew the device from the market [20]. Due to the subsequent interest in MIGS-associated CEC loss, we conducted a literature review of the PubMed and PubMed Central databases between 2011 and 2021 on FDA-approved MIGS. The search terms 'minimally invasive glaucoma surgery' or 'MIGS' and 'endothelial cell' were used. Further search was done for each MIGS options including 'Trabectome', 'Kahook Dual Blade', 'iStent', 'iStent Inject', 'Hydrus', 'CyPass', 'Xen Gel Stent', 'InnFocus Microshunt', 'Preserflo Microshunt' and 'endothelial cell'. Any prospective clinical trial or retrospective observational study evaluating MIGS-associated CEC loss were included. We summarized and present the most recent literature on MIGS-associated CEC loss for this review (Table 2).

SCHLEMM'S CANAL MINIMALLY INVASIVE GLAUCOMA SURGERY

Trabectome

The Trabectome (NeoMedix Inc, Tustin, California, USA) is an ab-interno electrocautery device which ablates between 90 and 120° of trabecular meshwork and the inner wall of the Schlemms' canal to provide direct aqueous access to the collector channels. FDA approval was obtained in 2004.

In a retrospective observational study of 159 Trabectome-treated eyes, no significant CEC loss was noted after 36 months, even when combined with phacoemulsification surgery [21]. No significant CEC loss was noted after 12 months in a separate prospective, interventional study evaluating 80 Trabectome-treated eyes [22]. As the Trabectome does not require long-term device implantation, the risk of long-term CEC loss may be reduced.

Kahook dual blade

The Kahook Dual Blade (KDB) (New World Medical Inc, Rancho Cucamong, California, USA) is a single-use goniotomy blade which is used ab-interno to almost completely remove the trabecular meshwork. This facilitates aqueous outflow into the Schlemm's canal. In a post-hoc analysis of 42 eyes from a randomized controlled trial (RCT), the iStent and phacoemulsification (iStent-Phaco) was associated with a significantly greater CEC loss compared with KDB and phacoemulsification (KDB-Phaco) (−9.0 vs. −3.4%) [23]. A separate, 12-month RCT involving 42 eyes showed significantly greater CEC loss associated with phacoemulsification as compared with KDB-phaco (25.2 vs. 11.8%). However, the difference may be due to the phacoemulsification being performed by two surgeons using different nucleus fragmentation techniques (horizontal chop vs. stop and chop) [24]. As the KDB also does not require any long-term implants, it may explain the lower long-term CEC loss reported above.

Table 1. Corneal endothelial cell loss associated with phacoemulsification, trabeculectomy, glaucoma tube implants (Ahmed and Baerveldt)

Study name	Type of study	Clinical trial ID	Procedure	Study duration	Findings
Phacoemulsification					
Comparison of refractive predictability and endothelial cell loss in femtosecond laser-assisted cataract surgery and conventional phaco surgery: prospective randomized trial with 6 months of follow-up (Krarup *et al.*, 2019) [1]	RCT 192 eyes	Not provided	FLACS Phacoemulsification	6 months	FLACS (−13.6% over study duration) Phacoemulsification (−17.03% over study duration) Difference between 2 groups is statistically significant
Comparative evaluation of femtosecond laser-assisted cataract surgery and conventional phacoemulsification in eyes with a shallow anterior chamber (Vasavada *et al.*, 2019) [2]	RCT 182 eyes	NCT 03587909	FLACS Phacoemulsification	6 months	FLACS (−7.6% over study duration) Phacoemulsification (−8.2% over study duration) Difference between 2 groups is not statistically significant
Differences in energy and corneal endothelium between femtosecond laser-assisted and conventional cataract surgeries: prospective, intraindividual, RCT (Bascaran *et al.*, 2018) [3]	RCT 200 eyes	ISRCTN 24007865	FLACS Phacoemulsification	6 months	FLACS (−6.4% over study duration) Phacoemulsification (−6.33% over study duration) Difference between 2 groups is not statistically significant
Trabeculectomy					
Corneal endothelial cell loss after trabeculectomy and phacoemulsification in one or two steps: a prospective study (Soro-Martinez *et al.*, 2021) [4]	2 prospective cohort studies included 1 Double-arm, randomized 40 eyes 1 Single-arm, randomized 20 eyes	Not provided	Double-arm study Trabeculectomy and phacoemulsification in one procedure (Phaco-trab) Trabeculectomy and phacoemulsification 3 months after Single-arm study Phacoemulsification	Double-arm 12 months Single-arm 1 month	Double arm study Phaco-trab (−31.6% over study duration) Trabeculectomy and phacoemulsification 3 months after (−42.6% over study duration) Single-arm study Phacoemulsification (−17.9% over study duration)
Effect of trabeculectomy on corneal endothelial cell loss (Hirooka *et al.*, 2020) [5]	Prospective observational study 117 eyes	Not provided	Trabeculectomy	24 months	Trabeculectomy (−6.3% over study duration)
Changes in corneal endothelial cell after Ahmed glaucoma valve implantation and trabeculectomy: 1-year follow-up (Kim *et al.*, 2016) [6]	Prospective observational study 68 eyes	Not provided	AGV Trabeculectomy	12 months	AGV (−12.3% over study duration) Trabeculectomy (−3.2% over study duration) Difference between 2 groups is statistically significant
Trabeculectomy vs. EX-PRESS shunt vs. Ahmed valve implant: short-term effects on corneal endothelial cells (Casini *et al.*, 2015) [7]	Prospective, interventional, case series 128 eyes	Not provided	Trabeculectomy AGV EX-PRESS Implant	3 months	Trabeculectomy (−4.2% over study duration) AGV (−3.5% over study duration) Both Trabeculectomy and AGV groups had statistically significant CEC loss EX-PRESS Implant (no change over study duration)

Table 1 (*Continued*)

Study name	Type of study	Clinical trial ID	Procedure	Study duration	Findings
Prospective randomized study comparing combined phaco-ExPress and phacotrabeculectomy in open angle glaucoma treatment: 12-month follow-up (Konopinska, 2015) [8]	Prospective, randomized trial 85 eyes	Not provided	Phaco-trab EX-PRESS Implant and phacoemulsification	12 months	Phaco-trab (−23.2% over study duration) EX-PRESS Implant and phacoemulsification (−37.4% over study duration) Difference between 2 groups is statistically significant
Effect of mitomycin-C augmented trabeculectomy on corneal endothelial cells (Zarei *et al.*, 2015) [9]	Case series 31 eyes	Not provided	Trabeculectomy Trabeculectomy with mitomycin C	3 months	Trabeculectomy (−4.6% over study duration) Trabeculectomy with MMC (−8.7% over study duration) Difference between 2 groups is statistically significant
Glaucoma tube implants (Ahmed and Baerveldt)					
Corneal endothelial cell changes and surgical results after Ahmed glaucoma valve implantation: ciliary sulcus vs. anterior chamber tube placement (Kim *et al.*, 2021) [10]	Retrospective, observational study 62 eyes	NA	Anterior chamber AGV Ciliary sulcus AGV	36 months	Anterior chamber AGV (−25.6% over study duration) Ciliary sulcus AGV (−7.1% over study duration) Difference between 2 groups is statistically significant
Prospective cohort study of corneal endothelial cell loss after Baerveldt glaucoma implantation (Iwasaki *et al.*, 2018) [11]	Prospective cohort study 59 eyes	UMN 000007812	acBGI ppBGI	12 months	For central CEC loss acBGI (−12.1% over study duration) ppBGI (no significant loss)
Changes in corneal endothelial cell after Ahmed glaucoma valve implantation and trabeculectomy: 1-year follow-up (Kim *et al.*, 2016) [6]	Prospective observational study 68 eyes	Not provided	AGV Trabeculectomy	12 months	AGV (−12.3% over study duration) Trabeculectomy (−3.2% over study duration) Difference between 2 groups is statistically significant
Trabeculectomy vs. EX-PRESS shunt vs. Ahmed valve implant: short-term effects on corneal endothelial cells (Casini *et al.*, 2015) [7]	Prospective, interventional, case series 128 eyes	Not provided	Trabeculectomy AGV EX-PRESS Implant	3 months	Trabeculectomy (−4.2% over study duration) AGV (−3.5% over study duration) Both Trabeculectomy and AGV groups had statistically significant CEC loss EX-PRESS Implant (no change over study duration)

AGV, Ahmed glaucoma valve; acBGI, anterior chamber Baerveldt glaucoma implant; CEC, Corneal endothelial cells; FLACS, femtosecond laser-assisted cataract surgery; MMC, Mitomycin-C; ppBGI, Pars plana Baeveldt glaucoma implant; RCT, randomized controlled trial.

Table 2. Corneal endothelial cell loss associated with minimally invasive glaucoma surgery

Study name	Type of study	Clinical trial ID	Procedure	Study duration	Findings
Schlemm's Canal MIGS					
Trabectome					
The influence of trabectome surgery on corneal endothelial cells (Kasahara *et al.*, 2019) [12]	Retrospective, observational study 159 eyes	NA	Phakic eyes Trabectome Trabectome with phacoemulsification Pseudophakic eyes Trabectome	36 months	No significant change noted for all groups over study duration
Evaluation of trabectome in open-angle glaucoma (Maeda *et al.*, 2013) [13]	Prospective, interventional study 80 eyes	Not provided	Trabectome	12 months	No significant change noted for all groups over study duration
KDB					
Twelve-month results of ab interno trabeculectomy with KDB: an interventional, randomized, controlled clinical study (Ventura-Abreu *et al.*, 2021) [14]	RCT 42 eyes	NCT 04202562	KDB with phacoemulsification (KDB-Phaco) Phacoemulsification	12 months	KDB-Phaco (11.8% over study duration) Phacoemulsification (25.2% over study duration) Difference between 2 groups is statistically significant
Corneal endothelial cell changes after phacoemulsification combined with excisional goniotomy with the KDB or iStent: a prospective fellow-eye comparison (Dorairaj *et al.*, 2020) [15]	Post-hoc follow-up of RCT 42 eyes	NCT 02784249	KDB-Phaco iStent with phacoemulsification (iStent-Phaco)	CEC loss measured at different timepoints Average: 18.2 months (12.5–28.7 months)	KDB-Phaco (−3.4% over study period iStent-Phaco (−9.0% over study period) Difference between 2 groups is statistically significant
iStent and iStent Inject					
Fellow-eye comparison between phaco-microhook ab-interno trabeculotomy and phaco-iStent trabecular micro-bypass stent (Takayanagi *et al.*, 2021) [16]	Retrospective, observational study 64 eyes	NA	Microhook ab-interno trabeculotomy and phacoemulsification (Microhook-Phaco) iStent-Phaco	12 months	Microhook-Phaco (−5.0% over study period) iStent-Phaco (−7.2% over study period) Difference between 2 groups is not statistically significant
Corneal endothelial cell changes after phacoemulsification combined with excisional goniotomy with the KDB or iStent: a prospective fellow-eye comparison (Dorairaj *et al.*, 2020) [15]	Post-hoc follow-up of RCT 42 eyes	NCT 02784249	KDB-Phaco iStent with phacoemulsification (iStent-Phaco)	CEC loss measured at different timepoints Average: 18.2 months (12.5–28.7 months)	KDB-Phaco (−3.4% over study period iStent-Phaco (−9.0% over study period) Difference between 2 groups is statistically significant
iStent trabecular micro-bypass stent implantation with cataract surgery in a Japanese glaucoma population (Nitta *et al.*, 2020) [17]	Retrospective, observational study 53 eyes	NA	iStent-Phaco	24 months	iStent-Phaco (−3.6% over study period)

Table 2 (*Continued*)

Study name	Type of study	Clinical trial ID	Procedure	Study duration	Findings
Safety and efficacy of two trabecular micro-bypass stents as the sole procedure in Japanese patients with medically uncontrolled primary open-angle glaucoma: a pilot case series (Shiba *et al.*, 2017) [18]	Nonrandomized clinical trial 10 eyes	UMIN 000004002	iStent (2 devices)	6 months	No significant change noted over study duration
Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract (Arriola-Villalobos *et al.*, 2013) [19]	Nonrandomized clinical trial 20 eyes	Not provided	iStent-Phaco	12 months	iStent-Phaco (−13.2% over study duration) Difference pre and postoperative is statistically significant
A prospective analysis of iStent inject microstent implantation: surgical outcomes, endothelial cell density, and device position at 12 months (Gillmann *et al.*, 2020) [20]	Nonrandomized clinical trial 54 eyes	NCT 03624699	iStent Inject (2 devices) with phacoemulsification (iStent Inject-Phaco) Phacoemulsification	12 months	iStent Inject-Phaco (−14.6% over study period) Phacoemulsification (−14.4% over study period)
Prospective, randomized, controlled pivotal trial of an ab interno implanted trabecular micro-bypass in primary open-angle glaucoma and cataract: two-year results (Samuelson *et al.*, 2019) [21]	RCT 505 eyes	NCT 00323284	iStent Inject-Phaco Phacoemulsification	24 months	iStent Inject-Phaco (−13.1% over study period) Phacoemulsification (−12.3% over study period)
Hydrus microstent					
Three-year findings of the HORIZON trial: a schlemm canal microstent for pressure reduction in primary open-angle glaucoma and cataract (Ahmed *et al.*, 2021) [22]	RCT 556 eyes	NCT 01539239	Hydrus microstent with phacoemulsification (hydrus-phaco) Phacoemulsification	36 months	Hydrus-phaco (−15.0% over study period) Phacoemulsification (−11.0% over study period) Difference between 2 groups is not statistically significant
Results from the United States cohort of the HORIZON trial of a schlemm canal microstent to reduce intraocular pressure in primary open-angle glaucoma (Jones *et al.*, 2019) [23]	RCT 331 eyes	NCT 01539239	Hydrus-phaco Phacoemulsification	24 months	Hydrus-phaco had slightly more CEC loss (101 cells/mm^2) than phacoemulsification group over study duration Difference between 2 groups is not statistically significant
A comparison of endothelial cell loss in combined cataract and MIGS (hydrus) procedure to phacoemulsification alone: 6-month results (Fea *et al.*, 2015) [24]	Retrospective, observational study 62 eyes	NA	Phakic patients Phacoemulsification Phakic patients with POAG Hydrus-phaco Phacoemulsification	6 months	Phakic patients Phacoemulsification (−9.1% over study duration) Phakic patients with POAG Hydrus-phaco (−11.7% over study duration) Phacoemulsification (−17.4% over study duration) Difference between hydrus-phaco and both phaco groups are not statistically significant

Table 2 (*Continued*)

Study name	Type of study	Clinical trial ID	Procedure	Study duration	Findings
Suprachoroidal MIGS					
CyPass microstent					
Corneal endothelial cell loss and morphometric changes 5 years after phacoemulsification with or without CyPass microstent (Lass *et al.*, 2019) [25]	3-year safety extension of RCT 282 eyes	NCT 02700984	CyPass microstent with phacoemulsification (CyPass-phaco) Phacoemulsification	60 months	CyPass-phaco (−20.4% over study period) Phacoemulsification (−10.1% over study period) Difference between 2 groups is statistically significant
Subconjunctival MIGS					
XEN Gel Stent					
XEN Gel Stent vs. trabeculectomy: Short-term effects on corneal endothelial cells (Olgun *et al.*, 2021) [26]	Nonrandomized clinical trial 80 eyes	Not provided	XEN Gel Stent (XEN) Trabeculectomy	3 months	XEN (−2.1% over study period) Trabeculectomy (−10.0% over study period) Difference between 2 groups is statistically significant
Endothelial cell density after XEN implant surgery: short-term data from the Italian XEN glaucoma treatment registry (XEN-GTR) (Oddone *et al.*, 2021) [27]	Prospective observational study 108 eyes	Not provided	XEN XEN with phacoemulsification (XEN-phaco) Phacoemulsification	6 months	XEN (−5.6% over study period) XEN-phaco (−11.3% over study period) Phacoemulsification (−13.0% over study period) Difference between XEN-phaco and XEN groups is statistically significant Difference between phacoemulsification and XEN group is statistically significant
Impact of Phacoemulsification Combined with XEN Gel Stent Implantation on Corneal Ednothelial Cell Density: 2-Year Results *(Gillmann et al. 2020)* [28]	Retrospective, observational 32 eyes	NCT 03151577	XEN-Phaco Phacoemulsification	24 months	XEN-Phaco (−14.3% over study period) Phacoemulsification (−14.5% over study period) Difference between 2 groups is not statistically significant
Anterior chamber XEN Gel Stent movements: the impact on corneal endothelial cell density (Gillmann *et al.*, 2019) [29]	Case study 1 eye	NA	Bilateral XEN Left XEN migration into anterior chamber with intermittent corneal contact	1 month	−2.1% over study period
Preserflo microshunt (previously InnFocus Microshunt)					
Ab-externo microshunt vs. trabeculectomy in primary open-angle glaucoma: one year results from a 2-year randomized, multicenter study (Baker *et al.*, 2021) [30]	RCT 527 eyes	NCT 01881425	Preserflo Microshunt with mitomycin C Trabeculectomy with Mitomycin C	12 months	Preserflo Microshunt (−5.2% over study period) Trabeculectomy (−6.9% over study period)

CEC, Corneal endothelial cells; KDB, Kahook Dual Blade; MIGS, minimally invasive glaucoma surgery; POAG, Primary open angle glaucoma; RCT, randomized controlled trial.

iStent and iStent inject

The iStent (Glaukos Corp, Laguna Hills, California, USA) is a titanium, microbypass implant which is surgically embedded through the trabecular meshwork into the Schlemm's canal, providing a direct passage for aqueous flow. There are currently two generations of devices – iStent and iStent Inject. The first-generation iStent obtained FDA approval in 2012.

Post-FDA approval, a single-arm trial of 20 eyes observed a significant 13.2% CEC loss over 12 months associated with iStent and phacoemulsification surgery (iStent-Phaco) [25]. In the previously mentioned RCT post-hoc analysis of 42 eyes, iStent-Phaco was associated with significantly greater CEC loss compared with the KDB-Phaco group (9.0 vs. 3.4%) [23]. CEC loss was measured at varying durations from surgery, with the average duration being 18.2 months. This suggests that implant-based MIGS may result in significantly greater CEC loss than nonimplant MIGS. Another retrospective study involving 64 eyes observed a 7.2% CEC loss over 12 months [26]. The longest retrospective study to date of 53 eyes also reported a CEC loss of 3.6% over 24 months in a Japanese population [27]. In another study, no significant CEC loss was noted 6 months after two iStent devices were implanted in 10 eyes [28]. These reports highly comparable CEC losses with phacoemulsification-associated CEC loss.

Approved by the FDA in 2018, the smaller, second-generation, IStent Inject is designed to function as two stents with two patent openings that sit in the Schlemm's canal. Better IOP control is achieved by improving the aqueous flow of the trabecular and episcleral venous system. A 24-month RCT comparing IStent Inject and phacoemulsification (IStent Inject-Phaco) with phacoemulsification alone observed a minimal difference in CEC loss (13.1 vs. 12.3%) [29]. Another nonrandomized clinical trial also observed similar CEC loss when comparing between phacoemulsification and the combination of phacoemulsification and two IStent Inject devices (14.4 vs. 14.6%). There was also no significant difference in CEC loss between well positioned devices and devices protruding in the anterior chamber [30]. In these studies, iStent Inject-associated CEC loss were similar to phacoemulsification-associated CEC loss.

Hydrus microstent

The Hydrus Microstent (Ivantis, Inc, Irvine, California, USA) is a 8 mm curved, long nitinol stent which sits in the Schlemm's canal. The device dilates the canal to counteract its collapse caused by raised IOP. FDA approval was obtained in 2018.

A retrospective study did not note any significant difference in CEC loss over 6 months when comparing the Hydrus Microstent insertion and phacoemulsification with phacoemulsification alone (11.7 vs. 17.4%) [31]. HORIZON, a long-term RCT involving 556 eyes was launched to compare the outcomes of the Hydrus Microstent and phacoemulsification with phacoemulsification alone. 36 months after implantation, it was noted the addition of the Hydrus Microstent resulted in an additional CEC loss of 2% immediately postoperatively (13 vs. 11%). However, this was not statistically significant. Subsequent CEC loss up to 36 months was not significantly different between the two treatment groups [32▪▪]. A subset analysis involving only the United States HORIZON cohort also found similar CEC loss over 24 months [33].

SUPRACHOROIDAL MINIMALLY INVASIVE GLAUCOMA SURGERY

CyPass microstent

The CyPass Microstent is a 6.35-mm long polyimide tube (Fig. 1). Inserted with a guidewire, it is passed through the anterior chamber to the suprachoroidal space via a controlled cyclodialysis. Despite initially obtaining FDA approval, the CyPass Microstent was required to provide an additional 3 years of postimplantation safety data. The COMPASS-XT trial, designed for this purpose, eventually uncovered a significant greater CEC loss associated with the

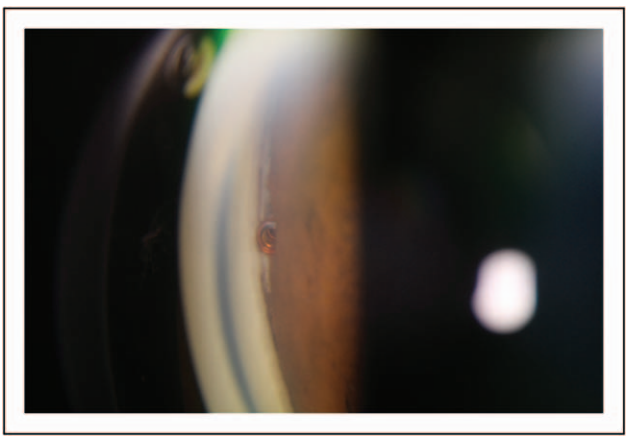

FIGURE 1. Gonioscopy photography of a well implanted CyPass microstent in a glaucomatous right eye. No cornea endothelial touch was observed. No significant difference was noted between the specular microscopy per-operatively (endothelial cell density: 2019 cells/mm^2; coefficient of variation: 25; hexegonality: 65%) and 3 years after surgery (endothelial cell density: 2192 cell/mm^2; coefficient of variation: 27; hexagonality: 72%).

CyPass Microstent and phacoemulsification (CyPass-Phaco) in comparison with phacoemulsification alone after 48 months (18.4 vs. 7.5%). By 60 months, this had increased to 20.4 and 10.1%, respectively. A market recall of the device was issued in 2018. Device position in the anterior chamber was also noted to affect CEC loss. Using the number of visible device rings as a gauge of implantation depth, devices with no rings showing, one ring showing and two or three rings showing had increasing annual CEC loss of 1.39, 2.74 and 6.96%, respectively [34▪▪]. Since the recall, the American Society of Cataract and Refractive Surgery has recommended CEC loss monitoring using a risk stratification based on the number of device rings visible [35]. If corneal decompensation has developed in implants with more than one ring visible, the repositioning or trimming of the implant should be considered [36,37].

SUBCONJUNCTIVAL MINIMALLY INVASIVE GLAUCOMA SURGERY

XEN Gel Stent

The XEN Gel Stent (Allergan INC, Dublin, Ireland), approved by the FDA in 2016, is made of porcine collagen-derived gelatin cross-linked with glutaraldehyde. It can be inserted ab intero or ab externo as a drainage shunt from the anterior chamber to the subconjunctival space through a scleral tunnel. A 24-month retrospective study of 32 eyes did not observe any significant difference in CEC loss when comparing the combined XEN Gel Stent with phacoemulsification procedure and phacoemulsification only (14.3 vs. 14.5%) [38]. A recent 6-month prospective study by the Italian XEN Glaucoma Treatment Registry (XEN-GTR) involving 108 eyes noted a CEC loss of 5.6% associated with the XEN Gel Stent. In comparison, the phacoemulsification arm had a significantly greater CEC loss (5.6 vs. 13.0%). No significant difference in CEC loss was observed between the XEN Gel Stent with phacoemulsification and phacoemulsification arms (11.3 vs. 13.0%) [39].

A separate nonrandomised clinical trial involving 80 eyes observed a significantly greater CEC loss associated with trabeculectomy as compared with the XEN Gel Stent after 3 months (10 vs. 2.1%) [40]. These studies suggest that the XEN Gel Stent is not associated with significantly higher CEC loss compared with phacoemulsification and trabeculectomy. However, longer duration studies are required. An interesting case study examined a migrated XEN Gel Stent with intermittent corneal contact. The patient experienced a 2.1% CEC loss over 1 month. This further suggests the importance of implant positioning even in MIGS devices [41].

PRESERFLO MICROSHUNT

The Preserflo Microshunt (Santen Pharmaceutical Co. Ltd, Osaka, Japan) (previously known as InnFocus Microshunt) is a 8.5-mm long tube made of a biocompatible, synthetic polymer that is implanted via an ab-externo approach (Fig. 2). It is designed to promote a more posterior aqueous flow to form an ideal bleb.

Innfocus was renamed as the Preserflo Microshunt after the acquisition by Santen in 2016. In the pivotal RCT involving 527 eyes, the device resulted in a 5.2% CEC loss compared with 6.9% in the trabeculectomy arm after 1 year. One patient with the Preserflo Microshunt developed a 9.4% CEC loss which was presumed to be due to the proximity to the cornea [42]. The device is currently being reviewed for FDA approval.

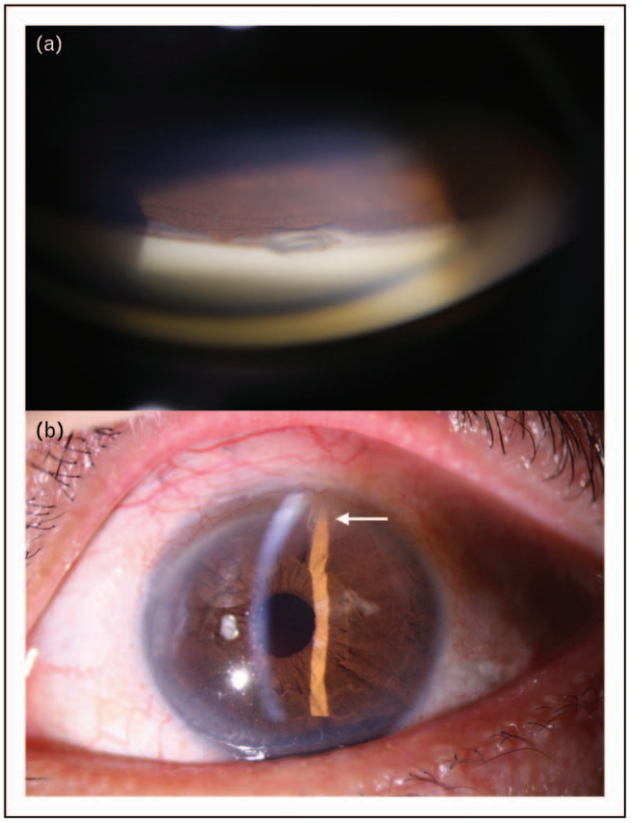

FIGURE 2. (a) Gonioscopy photography of a PRESERFLO Microshunt in a glaucomatous left eye. (b) Anterior segment photograph showing PRESERFLO Microshunt tip (white arrow) in the anterior chamber. Endothelial cell density reduced from baseline (endothelial cell density: 2119 cells/mm^2; coefficient of variation: 28; hrxagonality: 68%) till 3 years after surgery (endothelial cell density: 1018 cells/mm^2; coefficient of variation: 36; hexagonality: 70%).

DISCUSSION

Studies that have reported short-term CEC loss following MIGS procedures have been generally similar to phacoemulsification alone, while trabeculectomy and glaucoma tube shunts may be associated with a higher CEC loss postoperatively (Table 1). Despite these studies, direct comparisons between traditional glaucoma surgeries with MIGS procedures are currently lacking. A nonrandomised clinical trial of 80 eyes observed significantly higher CEC loss in trabeculectomy compared with the XEN Gel Stent (10.0 vs. 2.1%) [40]. However, trabeculectomy-associated CEC loss can vary widely depending on surgical technique and the use of adjunct antiproliferative agents [12,17]. A case series of 31 eyes noted significantly greater CEC loss after 3 months associated with the use of mitomycin C in trabeculectomy (8.7 vs. 4.6%) [17]. Significantly, in a clinical trial comparing phacoemulsification and trabeculectomy in a single procedure and trabeculectomy with phacoemulsification 3 months after, performing them separately resulted in greater CEC loss over 12 months [15]. Nonetheless, more head-to-head comparative studies of MIGS and traditional glaucoma surgeries with adequate follow-up are required.

CEC loss associated with the Ahmed (AGV; New World Medical, Rancho, Cucamonga, California, USA) and Baerveldt (Advanced Medical Optics, Inc, Santa Ana, California, USA) implants also vary depending on surgical technique and implant type. A prospective observational study of 68 eyes noted a significantly higher CEC loss associated with the Ahmed implant compared with trabeculectomy after 12 months (12.3 vs. 3.2%) [13], suggesting greater CEC loss in implant-based procedures. Implant positioning and its proximity to the corneal endothelial layer is a key factor for tube-associated CEC loss [43,44]. In a retrospective study of 62 eyes, anterior chamber Ahmed glaucoma valves resulted in significantly higher CEC loss after 36 months as compared with ciliary sulcus implantation (25.6 vs. 7.1%) [19]. Another cohort study also noted significantly higher CEC loss associated with anterior chamber Baerveldt tubes as compared with pars plana tubes after 12 months (12.1% vs. no significant loss) [18].

To date, the mechanisms of MIGS-associated CEC loss are not well understood. The post-hoc RCT analysis which observed a significantly higher CEC loss associated with iStent-phaco compared with KDB-Phaco (9.0 vs. 3.4%) suggest that implant-based MIGS procedures may have a higher risk of CEC loss. The COMPASS – XT trial also highlighted the effect of implant positioning on CEC loss. This is similar to the mechanisms involved in glaucoma tube associated CEC loss where location and proximity of tube opening to CEC play a crucial role. This may have important implications on future MIGS device designs and help identify current ones which are more likely to develop significant CEC loss. Moreover, longer duration studies are also required to study the effect of MIGS on CEC loss. In the COMPASS-XT trial, CEC loss associated with the CyPass Microstent and phacoemulsification procedure was only significantly greater 4 years after initial implantation. However, most studies on MIGS have not reported such long duration of follow-up. Future studies should also involve detailed CEC imaging and analysis of CEC parameters over a longer duration to allow for a better understanding and trend of CEC loss over time.

In summary, our review suggests that 12-month CEC loss associated with combined MIGS-phacoemulsification procedures can widely, with some reports of up to 14.6% (Table 2). Apart from the CyPass Microstent, no other studies on MIGS-phacoemulsification procedures have reported significantly greater CEC loss compared with phacoemulsification alone. Combined phacoemulsification and MIGS associated CEC loss were similar to reported phacoemulsification-associated CEC loss at 12 months postoperatively (range 12.8–15.2%). However, most studies are early and do not provide head-to-head comparison with traditional glaucoma surgeries. Future studies should address this and elucidate the mechanisms resulting in MIGS-associated CEC loss.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Saheb H, Ahmed II. Micro-invasive glaucoma surgery: current perspectives and future directions. Curr Opin Ophthalmol 2012; 23:96–104.
2. Pereira ICF, van de Wijdeven R, Wyss HM, *et al.* Conventional glaucoma implants and the new MIGS devices: a comprehensive review of current options and future directions. Eye 2021; 35:3202–3221.
3. Van den Bogerd B, Zakaria N, Adam B, *et al.* Corneal endothelial cells over the past decade: are we missing the mark(er)? Transl Vis Sci Technol 2019; 8:13.

4. Price MO, Mehta JS, Jurkunas UV, Price FW Jr. Corneal endothelial dysfunction: evolving understanding and treatment options. Prog Retin Eye Res 2021; 82:100904.
5. Jeang LJ, Margo CE, Espana EM. Diseases of the corneal endothelium. Exp Eye Res 2021; 205:108495.
6. Bourne WM, Nelson LR, Hodge DO. Central corneal endothelial cell changes over a ten-year period. Invest Ophthalmol Vis Sci 1997; 38:779–782.
7. Taşlı NG, Icel E, Karakurt Y, *et al.* The findings of corneal specular microscopy in patients with type-2 diabetes mellitus. BMC Ophthalmol 2020; 20:214.
8. Liu X, Zheng T, Zhao C, *et al.* Genetic mutations and molecular mechanisms of Fuchs endothelial corneal dystrophy. Eye Vis (Lond) 2021; 8:24.
9. Krarup T, Ejstrup R, Mortensen A, *et al.* Comparison of refractive predictability and endothelial cell loss in femtosecond laser-assisted cataract surgery and conventional phaco surgery: prospective randomised trial with 6 months of follow-up. BMJ Open Ophthalmol 2019; 4:e000233.
10. Vasavada VA, Vasavada S, Vasavada AR, *et al.* Comparative evaluation of femtosecond laser-assisted cataract surgery and conventional phacoemulsification in eyes with a shallow anterior chamber. J Cataract Refract Surg 2019; 45:547–552.
11. Bascaran L, Alberdi T, Martinez-Soroa I, *et al.* Differences in energy and corneal endothelium between femtosecond laser-assisted and conventional cataract surgeries: prospective, intraindividual, randomized controlled trial. Int J Ophthalmol 2018; 11:1308–1316.
12. Hirooka K, Nitta E, Ukegawa K, *et al.* Effect of trabeculectomy on corneal endothelial cell loss. Br J Ophthalmol 2020; 104:376–380.
13. Kim MS, Kim KN, Kim CS. Changes in corneal endothelial cell after Ahmed glaucoma valve implantation and trabeculectomy: 1-year follow-up. Korean J Ophthalmol 2016; 30:416–425.
14. Casini G, Loiudice P, Pellegrini M, *et al.* Trabeculectomy versus EX-PRESS shunt versus Ahmed valve implant: short-term effects on corneal endothelial cells. Am J Ophthalmol 2015; 160:1185–1190.e1.
15. Soro-Martínez MI, Miralles de Imperial-Ollero JA, Pastor-Montoro M, *et al.* Corneal endothelial cell loss after trabeculectomy and phacoemulsification in one or two steps: a prospective study. Eye (Lond) 2021; 35:2999–3006.
16. Konopińska J, Deniziak M, Saeed E, *et al.* Prospective randomized study comparing combined phaco-express and phacotrabeculectomy in open angle glaucoma treatment: 12-month follow-up. J Ophthalmol 2015; 2015:720109.
17. Zarei R, Zarei M, Fakhraie G, *et al.* Effect of mitomycin-C augmented trabeculectomy on corneal endothelial cells. J Ophthalmic Vis Res 2015; 10:257–262.
18. Iwasaki K, Arimura S, Takihara Y, *et al.* Prospective cohort study of corneal endothelial cell loss after Baerveldt glaucoma implantation. PLoS One 2018; 13:e0201342.
19. Kim JY, Lee JS, Lee T, *et al.* Corneal endothelial cell changes and surgical results after Ahmed glaucoma valve implantation: ciliary sulcus versus anterior chamber tube placement. Sci Rep 2021; 11:12986.
20. Novartis. Alcon announces voluntary global market withdrawal of CyPass Micro-Stent for surgical glaucoma 2018 [Available from: https://www.novartis.com/news/media-releases/alcon-announces-voluntary-global-market-withdrawal-cypass-micro-stent-surgical-glaucoma.
21. Kasahara M, Shoji N, Matsumura K. The influence of trabectome surgery on corneal endothelial cells. J Glaucoma 2019; 28:150–153.
22. Maeda M, Watanabe M, Ichikawa K. Evaluation of trabectome in open-angle glaucoma. J Glaucoma 2013; 22:205–208.
23. Dorairaj S, Balasubramani GK. Corneal endothelial cell changes after phacoemulsification combined with excisional goniotomy with the Kahook Dual Blade or iStent: a prospective fellow-eye comparison. Clin Ophthalmol 2020; 14:4047–4053.
24. Ventura-Abreu N, García-Feijoo J, Pazos M, *et al.* Twelve-month results of ab interno trabeculectomy with Kahook Dual Blade: an interventional, randomized, controlled clinical study. Graefes Arch Clin Exp Ophthalmol 2021; 259:2771–2781.
25. Arriola-Villalobos P, Martínez-de-la-Casa JM, Díaz-Valle D, *et al.* Mid-term evaluation of the new Glaukos iStent with phacoemulsification in coexistent open-angle glaucoma or ocular hypertension and cataract. Br J Ophthalmol 2013; 97:1250–1255.
26. Takayanagi Y, Ichioka S, Ishida A, Tsutsui A, Tanito M. Fellow-Eye Comparison between Phaco-Microhook Ab-Interno Trabeculotomy and Phaco-iStent Trabecular Micro-Bypass Stent. J Clin Med 2021; 10:2129.
27. Nitta K, Yamada Y, Morokado S, Sugiyama K. iStent trabecular micro-bypass stent implantation with cataract surgery in a Japanese glaucoma population. Clin Ophthalmol 2020; 14:3381–3391.
28. Shiba D, Hosoda S, Yaguchi S, *et al.* Safety and efficacy of two trabecular micro-bypass stents as the sole procedure in Japanese patients with medically uncontrolled primary open-angle glaucoma: a pilot case series. J Ophthalmol 2017; 2017:9605461.
29. Samuelson TW, Sarkisian SR Jr, Lubeck DM, *et al.* Prospective, randomized, controlled pivotal trial of an ab interno implanted trabecular micro-bypass in primary open-angle glaucoma and cataract: two-year results. Ophthalmology 2019; 126:811–821.
30. Gillmann K, Mansouri K, Ambresin A, *et al.* A prospective analysis of iStent inject microstent implantation: surgical outcomes, endothelial cell density, and device position at 12 months. J Glaucoma 2020; 29:639–647.
31. Fea AM, Consolandi G, Pignata G, *et al.* A comparison of endothelial cell loss in combined cataract and MIGS (Hydrus) procedure to phacoemulsification alone: 6-month results. J Ophthalmol 2015; 2015:769289.
32. ■■ Ahmed IIK, Rhee DJ, Jones J, *et al.* Three-year findings of the HORIZON trial: a Schlemm canal microstent for pressure reduction in primary open-angle glaucoma and cataract. Ophthalmology 2021; 128:857–865.

This is the longest minimally invasive glaucoma surgery (MIGS) trial assessing cornea endothelial cell loss in an implant-based MIGS.

33. Jones J, Koch DD, Vold S, *et al.* Results from the United States cohort of the HORIZON trial of a Schlemm canal microstent to reduce intraocular pressure in primary open-angle glaucoma. J Cataract Refract Surg 2019; 45:1305–1315.
34. ■■ Lass JH, Benetz BA, He J, *et al.* Corneal endothelial cell loss and morphometric changes 5 years after phacoemulsification with or without CyPass micro-stent. Am J Ophthalmol 2019; 208:211–218.

Results from this study led to the market withdrawal of CyPass Micro-stent.

35. Mah DRNRF. ASCRS CyPass withdrawal consensus statement 2018 [Available from: https://ascrs.org/news/ascrs-news/cypass-withdrawl.
36. Fili S, Seddig S, Vastardis I, *et al.* Explantation of the CyPass implant in a case series of patients with corneal decompensation. Ophthalmologe 2021; 118:42–49.
37. Medra A, Schwanengel M, Weber A, Brinkmann CK. Microsurgical trimming of the CyPass stent: surgical procedure of the neubrandenburg eye clinic (Video article). Ophthalmologe 2020; 117:1241–1246.
38. Gillmann K, Bravetti GE, Rao HL, *et al.* Impact of phacoemulsification combined with XEN gel stent implantation on corneal endothelial cell density: 2-year results. J Glaucoma 2020; 29:155–160.
39. Oddone F, Roberti G, Posarelli C, *et al.* Endothelial cell density after XEN implant surgery: short-term data from the Italian XEN glaucoma treatment registry (XEN-GTR). J Glaucoma 2021; 30:559–565.
40. Olgun A, Duzgun E, Yildiz AM, *et al.* XEN Gel Stent versus trabeculectomy: short-term effects on corneal endothelial cells. Eur J Ophthalmol 2021; 31:346–353.
41. Gillmann K, Bravetti GE, Mermoud A, Mansouri K. Anterior chamber XEN gel stent movements: the impact on corneal endothelial cell density. J Glaucoma 2019; 28:e93–e95.
42. Pillunat KR, Herber R, Haase MA, Jamke M, Jasper CS, Pillunat LE. PRESERFLO™ MicroShunt versus trabeculectomy: first results on efficacy and safety. Acta Ophthalmol 2021. doi: 10.1111/aos.14968. [Epub ahead of print]
43. Zhang Q, Liu Y, Thanapaisal S, *et al.* The effect of tube location on corneal endothelial cells in patients with Ahmed glaucoma valve. Ophthalmology 2021; 128:218–226.
44. Hau S, Bunce C, Barton K. Corneal endothelial cell loss after Baerveldt glaucoma implant surgery. Ophthalmol Glaucoma 2021; 4:20–31.