Review Article

# Corneal endothelial protection during manual small-incision cataract surgery: A narrative review

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Cataract causes bilateral blindness in 20 million people globally, the vast majority of whom live in developing countries. Manual small-incision cataract surgery (MSICS) has emerged as an efficient and economical alternative to phacoemulsification, giving comparable results in terms of final visual gain. One of the important determinants of postoperative visual gain is the status of the corneal endothelium. Multiple factors such as corneal distortion, irrigation solution turbulence, mechanical trauma by instruments, nuclear fragments, intraocular lens contact, and free oxygen radicals, all have been implicated in causing corneal damage during cataract surgery. MSICS with posterior chamber intraocular lens implantation has been reported to cause an endothelial cell loss of 15.83%, which is comparable with other modes of cataract surgery like extracapsular cataract extraction and phacoemulsification. Thorough preoperative assessment of endothelial status and taking necessary steps for endothelial protection during surgery can decrease the endothelial cell loss and overall burden of pseudophakic bullous keratopathy. In addition to surgical techniques, the type of irrigating solutions, ocular viscoelastic devices, intracameral dyes, and drugs all affect the endothelial cell status. This review presents a summary of available literature on the protection of endothelial cells during different steps of MSICS. This is especially relevant for developing countries where large-scale MSICS cataract surgeries are performed to decrease the cataract blindness burden.

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Preventable vision loss due to cataract and refractive error continue to cause most cases of blindness and moderate or severe vision impairment in adults aged 50 years and older, posing an important threat to the socio-economic development of the country.[1] Cataract is estimated to cause bilateral blindness in 20 million people worldwide and the situation is graver in developing countries where it is responsible for 50–90% of all blindness.[2] Important limitations in the treatment of cataract blindness in the developing world are related to cost restrictions, lack of population awareness, and shortage of trained personnel. Manual small-incision cataract surgery (MSICS) is emerging as the preferred technique for cataract surgery in the developing world as it is significantly faster, less expensive, and technologically less demanding than phacoemulsification (PE).[3] Although the recent literature reports both these techniques as relatively cornea-safe procedures, bullous keratopathy continues to be a well-known complication of cataract surgery occurring in about 1 to 2% of cases and is the most common indication for penetrating keratoplasty and regraft.[4] Multiple factors like corneal distortion, irrigation solution turbulence, mechanical trauma by instruments, nuclear fragments, intraocular lens (IOL) contact, and free oxygen radicals, all have been implicated in causing corneal damage during cataract surgery.[5] Given the scarcity of corneal tissue for grafting (only one cornea for every 70 needed) and the risks of keratoplasty, it is critical to ensure endothelial safety during cataract surgery.[6] This review aims at presenting an overview of the available literature on MSICS related to endothelial protection.

## Preoperative assessment and the role of specular microscopy

The status of endothelial cells (ECs) acts as an important indicator of overall corneal health. At birth, normal corneal EC density ranges between 4000 and 5000 (cells/mm$^2$), and it declines with age at a rate of 0.3–0.6% per year, with an approximate value of 2000–3000 cells/mm$^2$ in a normal adult eye.[7] In the Indian population, the EC density has been estimated to be 2527 ± 337 cells/mm$^2$.[8] It is essential to identify cases with low EC density before surgery because the corneal endothelium remains in a state of transition with a progressive decline in cell density for a long postoperative period.[9] MSICS with posterior chamber IOL implantation has been reported to cause an EC loss of 15.83% at 1 month of follow-up, which is comparable with other modes of cataract surgery like extracapsular cataract extraction (ECCE) and PE.[10] In the case-control study published by Hayashi *et al.*,[11] the

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change in corneal thickness and EC loss after 3 months of PE or ECCE surgery was not significantly different in the group with a low EC density (500 to 1000 cells/mm$^2$) from control eyes with a normal EC density, but there is often a reluctance to risk cataract surgery in cases with preoperative EC density less than 1000 cells/mm$^2$.[12] Preferably, all cases of cataract should undergo preoperative specular microscopic evaluation; however, it is crucial in those with corneal pathology, long-term contact lens wearers, ocular inflammation, raised intraocular pressure, small pupils, dense nuclear sclerosis, one-eyed patients, history of bullous keratopathy in the other eye, a previous corneal graft, planned anterior chamber IOL implantation, and short axial length of the eye.

### Entry wound construction

One of the major advancements in cataract surgery is the decrease in the size of the entry wound. In MSICS, typically a 5.5–7.5 mm long (depending on nuclear density), 1/3$^{rd}$ to ½ thickness scleral tunnel is created 1.0–1.5 mm behind the limbus. There is very limited literature available on the size of the external incision and EC loss in MSICS. A superior scleral placed, self-sealing 5.5 mm incision has been documented to produce lesser EC damage than a superior 5.5 mm clear corneal incision sealed with suture. Although this study was in reference to PE, in the scleral tunnel group, postoperative EC damage at the 12 o'clock position was significantly lower than that of the clear corneal group as it was placed more posteriorly and induced less direct and indirect endothelial trauma.[13]

The site of incision in MSICS can be superior, temporal, or superior-temporal. The primary objective of shifting the incision site is to lessen postoperative astigmatism in anticipation of the need for additional surgery and to facilitate exposure to the surgical field. How different incision site affects EC loss has not been studied for MSICS alone. Pote *et al*.[14] compared the EC loss between temporal MSICS and trabeculectomy with MSICS through a superior incision. The reported EC loss between these two groups (14.1% and 12.8%, respectively, at the end of postoperative 3 months) was not significantly different. The surgical trauma and instrument manipulation often lead to localized corneal edema around the entry incision. Localized Descemet's membrane detachment at the site of the entry wound, a frequently encountered complication for beginner surgeons, often gets alleviated by using a sharp entry blade, careful instrument manipulation, and an increase in the surgical experience. Widely available steel blades need to be assessed for their sharpness and quality before their use. This is all the more important when practicing MSICS for large-volume surgeries.

### Capsular staining

Capsular staining can be a very useful adjunct in pediatric cataract, traumatic cataract, eyes with poor red reflexes as mature cataracts, corneal scarring, corneal edema, vitreous hemorrhage, asteroid hyalosis, and retinal diseases. Poor visualization in these scenarios can lead to capsular tear and extension toward or beyond the lens equator, causing complications like vitreous loss, nuclear drop, and IOL displacement.

Trypan blue (TB), the most frequent capsular stain used in cataract surgery has been found to be safe in terms of increased intraocular pressure, anterior chamber inflammation, corneal thickening, and endothelial damage.[15] Its commonly used commercial preparations are available in the concentrations of 0.1% and 0.06%, and both have been found to be endothelially safe in clinical studies.[16] Techniques of capsular staining include using the dye beneath air bubbles, beneath ocular viscoelastic devices (OVDs), beneath OVDs, and balanced salt solution (BSS), mixing with an OVD, direct intracameral one-step injection at the beginning of surgery.[15] Using the dye beneath air bubbles prevents dilution of the dye by the aqueous and helps in the spread of the dye over the anterior capsule, bordered by the pupillary rim of the iris, thus preventing a direct endothelial contact, but there is a potential risk of air-induced endothelial toxicity.[17,18] Use of TB with OVDs decreases the risk of air-induced endothelial damage but in developing countries like ours, where white cataracts are a common entity, economic constraints may make injection under an air bubble a more viable option than the viscoelastic–dye combination.[19] Laureano *et al*.[20] proposed the direct intracameral one-step injection of TB via paracentesis as an economical, endothelially safe alternative technique of capsular staining.

### Maintenance of the anterior chamber depth during surgery

The surgical manipulations of MSICS happen within the confined space of the anterior chamber (AC) which is lined anteriorly by the corneal endothelium. Microtrauma due to surgical instruments, a prolapsed nucleus in the AC, and continuous flow of irrigating solution, all affect corneal endothelial health. The eyes with shorter axial lengths and those with a shallower AC are theoretically more prone to EC damage. To the best of our search, we did not find any study linking loss of EC with different depths of the AC during MSICS. This question has been answered in detail for PE. Published clinical studies on the relationship between AC depth and EC loss during PE reveal that eyes with an AC depth of less than 2.5 mm have significantly higher EC losses and lower EC densities at 3 months after cataract surgery compared to the baseline.[21,22] It is vital to maintain an adequate depth of AC during surgery by using OVDs, AC maintainers, and proper tissue handling. Nayak *et al*.[23] reported that the use of an AC maintainer for continuous AC infusion without OVD use during PE did not significantly affect corneal swelling or endothelial cell loss in the immediate postoperative period up to 1 month. A similar clinical trial using an AC maintainer during MSICS through a 6 mm scleral incision and IOL implantation evaluated the EC loss at 3 weeks, 3 months, and 1 year of follow-up of surgery. There was a regional discrepancy in EC loss—mean central and superior endothelial cell loss—at 3 months postoperatively was 16% and 22%, respectively, and at 12 months postoperatively was 20% and 25%, respectively. This study recommends that MSICS using the AC maintainer is an effective and safe technique; however, to minimize endothelial cell loss, they suggested concurrent use of OVDs.[24]

### Role of OVDs

The different rheological properties (viscoelasticity, viscosity, and pseudoplasticity) of OVDs are used for different purposes during cataract surgery. The primary aim of OVDs is the protection of the corneal endothelium and to facilitate surgery. They are broadly divided into cohesive and dispersive types. Higher viscosity, pseudoplasticity, and cohesiveness are characteristics of cohesive OVDs, such as Healon (1% sodium hyaluronate), Healon GV (1.4% sodium hyaluronate by

Abbott Medical Optics, Santa Ana, CA), Provisc (1% sodium hyaluronate by Alcon, Ft. Worth, TX), and Amvisc (1% sodium hyaluronate by Bausch and Lomb). They provide good working space inside the AC, but they come out as a mass from AC leaving the corneal endothelium vulnerable to damage. As compared to cohesive OVDs, dispersive OVDs, such as OcuCoat (2% Hydroxypropyl methyl cellulose by Bausch and Lomb), Viscoat (chondroitin sulfate 4%–sodium hyaluronate 3% Alcon), and Healon Endocoat (3% sodium hyaluronate by Abbott Medical Optics), are less cohesive, less entangled, and do not easily exit the AC during surgery. As a result, dispersive OVDs are better able to coat and protect the corneal endothelium.[25] Viscoadaptive OVDs, for example, Healon 5 (sodium hyaluronate 2.3% by AMO/J and J), have the advantage of both cohesive and dispersive OVDs. They are highly retentive and maintain the AC shape at a low flow rate and coat the endothelium very well during a high flow rate.[26] The soft-shell technique utilizes the rheological characteristics of different OVDs together for improved chamber stability and endothelial protection. It involves a combination of a lower-viscosity dispersive OVD and a higher-viscosity cohesive OVD into an outer and inner shell, respectively, or a combination of the outer shell of a viscoadaptive OVD to coat the corneal endothelium and BSS to create a low-viscosity working space (ultimate soft-shell technique) or a combination of viscodispersive OVDs as the outer shell, a viscoadaptive OVD as the middle shell, and BSS or lidocaine–phenylephrine as the inner shell (tri-soft-shell technique). The tri-soft-shell technique has especially been recommended for cases of Fuchs endothelial dystrophy.[27]

A meta-analysis using mixed-treatment comparison analysis, published on the protective effect of different types of OVDs (viscoadaptive, very low viscosity dispersive, a super-viscous cohesive) on the corneal endothelium during cataract surgery, assessed 21 randomized controlled trials including 1769 patients. The outcome considered was a loss in EC density 3 months after surgery. They reported that viscoadaptives have an 80% chance of being the best treatment option and the soft-shell technique has an 18% chance.[28] The intracameral safety of the combination of lidocaine and OVDs is not yet conclusively established as the combination has been reported to cause a greater endothelial loss in comparison to OVDs.[29,30]

### Role of irrigating solutions

Commonly used irrigating solutions during cataract surgery are Ringer's lactate (RL) solution, BSS, and the third generation of irrigation solution known as BSS Plus, which included sodium bicarbonate, dextrose, and glutathione disulfide in addition to the fundamental components of BSS.[31] RL is slightly acidic (osmolality 260 mmol/l, pH – 6.4) than BSS Plus (osmolality 305 mmol/l, pH – 7.40) and aqueous (osmolality 304 mmol/l, pH – 7.38).

Vasavada *et al*.[32] compared the effect of irrigating solution RL and BSS on the corneal endothelium in patients undergoing PE. On the first postoperative day, the central corneal thickness was significantly higher in the group where RL was used but at the 3-month follow-up, no difference in EC density loss and change in the coefficient of variation was noticed between the two groups.

Another study has reported RL to be cornea-safe (EC density, CV, and central corneal thickness) as BSS Plus for atraumatic PE, but it showed a trend toward lower postoperative EC density for surgeries with longer PE time and higher irrigation volumes if RL was used.[31] Lesser EC loss was observed (15.4%) with BSS Plus compared to BSS (22.7%), according to Kline *et al*.'s[33] study comparing the two during ECCE surgery.

### Nucleus management

Nucleus delivery is one of the most crucial steps of MSICS in terms of EC loss. The density of nucleosclerosis alone has been identified as an independent predictor of EC density decrease.[34] The commonly used techniques of nucleus delivery in MSICS include Vectis/Sinskey-assisted expression, fish hook technique, phacofracture using a snare, Kansas tri-sectors or triangular tri-sectors, phacosandwich technique, viscoexpression, and Blumenthal technique. A prospective randomized interventional study by Sharma *et al*. compared the postoperative complications of 5 different nucleus delivery techniques of MSICS (phacosandwich, fishhook, irrigating Vectis, viscoexpression, and AC maintainer). The most common postoperative complication was striate keratopathy followed by transient postoperative corneal edema. Striate keratopathy at the incision site was significantly more in instrumental techniques. Transient corneal edema was significantly more in occurrence and severe in phacosandwich and fishhook groups when compared with other groups. However, on the seventh day after surgery, edema resolved in all groups and the outcome of corneal edema was comparable among groups. The least occurrence of corneal edema and striate keratopathy was seen in the anterior chamber maintainer group as the AC remains formed (and endothelium protected) during all steps of the surgery.[35,36] In their prospective, randomized study, Vajpayee *et al*.[37] reported significantly higher EC loss after 3 months of surgery in the phacofracture group (17.66 ± 3.65%) in comparison to the PE group (12.03 ± 3.06%), and they advocated the need for further modification and more experience with manual phacofracture technique to present it as a safe alternative to PE. A manual phacotrisection technique has also been reported to have a high incidence (54%) of transient corneal edema.[38] Overall, the nucleus extraction techniques involving phacofracture and more instrument manipulation cause more EC loss, whereas OVDs and hydroprocedure-assisted nucleus delivery are relatively endothelially safe.

### Role of the IOL

A greater magnitude of cell loss has been reported following an apparently uneventful IOL insertion than following simple cataract extraction. The chronic, low-grade, smoldering inflammation following cataract surgery causes damage to the ECs reflected by declining cell density as well as other morphologic alterations.[39] Experiment studies have shown that contact with acrylic lenses causes severe endothelial damage, and this can be minimized by OVD coating of IOL.[40] Hydroimplantation of IOL in cases of PE has been found to be a safe technique, but its endothelial safety needs to be analyzed during MSICS where the size of the incision is much larger than phacoemulsification.[41,42]

IOL material: One of the comparative studies published on the effect of IOL material and EC loss has reported that it does not differ significantly between groups with hydrophilic

acrylic foldable lens implantation versus those with polymethyl methacrylate (PMMA) IOLs or between PMMA versus those with polyhydroxethylmethacrylate lens implantation.[43,44] A similar study compared the EC loss after 3 months of cataract surgery and reported no significant difference in patients having silicone IOL, higher refractive index silicone IOL, PMMA IOL, and those who underwent only cataract surgery without IOL implantation.[45]

IOL position: It is always recommended to go for an in-the-bag IOL placement. The reported EC loss after AC IOL implantation (20%) following cataract surgery is much higher than that reported after posterior chamber IOL insertion (12%).[46] Surgical management of aphakia has undergone a paradigm shift with the availability of different types of IOLs like scleral fixated IOLs (SFIOLs) and iris fixated IOLs. A recent survey on "Preferred practice patterns in aphakia management in adults in India" has revealed that in cases of posterior capsular tear with adequate capsular support, a three-piece IOL in the ciliary sulcus was the most preferred. In cases without adequate capsular support, anterior segment surgeons prefer retro pupillary iris-claw IOLs in the primary cataract setting, whereas posterior segment surgeons and more experienced anterior segment surgeons preferred SFIOLs in this scenario.[47] A meta-analysis on various techniques of SFIOL involving 2624 eyes reported an overall mean EC loss of 8.95% at 16.77 ± 11.04 months. Glued SFIOLs in this series caused the lowest endothelial cell loss, whereas sutureless, glueless SFIOL was associated with the greatest endothelial cell loss.[48] Iris-claw IOLs can be placed in AC or as retropupillary fixated IOLs. The EC loss reported with this procedure is comparable to routine MSICS.[49,50] On comparison of these two techniques, a published meta-analysis has reported no significant difference in EC count with a standard mean difference of −0.011.[51]

### Role of intracameral drugs

Intracameral use of drugs requires consideration regarding their pH, chemical property, and osmolarity before they can be used safely. One of the largest interventional studies published by Haripriya *et al*.[52] evaluated the role of intracameral moxifloxacin in the prevention of endophthalmitis in 20,62,643 patients of cataract surgery. They reported it to be safe for intracameral use with no occurrence of toxic anterior segment syndrome (TASS) or corneal decompensation attributable to the antibiotic injection. The incidence of persistent corneal edema beyond 1 month of surgery was also not higher in the intracameral moxifloxacin group in comparison to the control group with no antibiotic prophylaxis. The endothelial safety of the intracameral dose of moxifloxacin, 250 µg, was compared with 500 µg by exposing the first eye of each patient to either 500 or 250 µg dose of moxifloxacin intracamerally and the second eye with the other dose. Both doses were well tolerated clinically and the EC density was comparable in both the study groups on day 30 and day 90 after surgery.[53]

Intracameral use of pilocarpine and adrenaline has been associated with the development of TASS.[54] AC reformation at the end of cataract surgery with a sterile solution of 1% pilocarpine nitrate in water has been associated with the development of dense corneal edema and cornea guttate changes.[55] Studies published on the use of intracameral pilocarpine in lower concentration (0.2% by Sethi *et al*.[56] and 0.13 mg/mL by Wutthiphan *et al*.[57]) and AC wash at the end of surgery have been reported to induce the desired miotic effect without compromising endothelial health. Intracameral 0.001% or 1:100,000 epinephrine hydrochloride has been reported to be a safe intraoperative mydriatic that can be used to manage pupillary constriction without causing any adverse effects on the corneal endothelium.[58-60]

Intracameral lidocaine is widely used for intraoperative anesthesia. In one of the clinical trials, intracameral unpreserved lidocaine 1% was used along with topical anesthesia, and this group of patients were compared with those undergoing surgery under peribulbar anesthesia. The rate of EC loss or cell morphology after 20 months ± 5.1 of surgery was not significantly different in these two groups. Other studies also have resonated with the endothelial safety of intracameral lidocaine.[61,62]

### Comparison of EC Loss between MSICS and other types of cataract surgery

A study comprising 186 cataractous eyes compared the EC loss at 6 weeks postoperatively after ECCE, MSICS, or PE with non-foldable IOL implantation. The mean EC loss was not significantly different in any of the groups; ECCE induced an EC loss of 4.72%; SICS, 4.21%; and PE, 5.41%.[63] Another randomized control trial compared the EC loss between two groups of patients, 100 patients in each group, undergoing either PE or MSICS. The specular analysis was performed by both manual and automated methods, preoperatively and after 6 weeks of surgery. There were no clinical or statistically significant differences in EC loss between PE and MSICS groups.[64] A similar study comparing the endothelial safety of these two procedures has reported that the central corneal thickness, coefficient of variation, and standard deviation were maintained after both of these procedures. Although there was an initial reduction in the EC number compared to the preoperative value in the MSICS group after 1 week of surgery, the function and morphology of EC were unaffected at 6 weeks of evaluation. This study presented MSICS as a safe option for phacoemulsification in the developing world.[65]

## Conclusion

A postoperative corneal complication of MSICS is one of its important limitations. Endothelially safe MSICS involves careful endothelial evaluation before surgery, selection of the best suitable OVDs, avoiding repeated use of disposable instruments, only necessary use of intracameral drugs, careful tissue handling, application of the correct technique with minimal instrument manipulation during nucleus delivery, and in-the-bag IOL implantation. Decreasing corneal complications can lead to early visual rehabilitation, and MSICS can play a very important role in decreasing the overall burden of avoidable blindness in developing countries.

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### Conflicts of interest

There are no conflicts of interest.

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