Maximising endothelial protection, improving patient outcomes:

Selecting the right OVDs for modern cataract surgery

The phaco/OVD dilemma

Among the global ophthalmic surgical community, endothelial protection has long been recognised as essential to favourable patient outcomes of cataract surgery.

Through the use of Ophthalmic Viscosurgical Devices (OVDs), surgeons are able to achieve good levels of endothelial protection. Most modern OVDs perform well in their primary functions of maintaining the anterior chamber and protecting the endothelium, due to the manufacturers' selection of each OVD's viscosity and cohesion-dispersion properties that contribute positively to modern phaco techniques.

Phacoemulsification subjects the eye to heat, pressure and turbulence. Despite recent attempts by manufacturers to increase the efficiency and reduce the power of phaco equipment, there is still a need to further improve patient outcomes. Another avenue to reduce the risk of endothelial damage caused by phaco is through protection against the phaco-created unstable free radical molecules.

Rayner has explored products with improved free radical scavenging as well as increased dispersive properties to reduce endothelial cell loss. As leading ophthalmic surgeon Dr Steve Arshinoff, MD, FRCSC, comments:

> *"During the turbulence of phacoemulsification and irrigation/aspiration, the enhanced retention of dispersive OVDs gives additional protection of the endothelial surface with the presence of a barrier layer of OVD".*[1]

Given that in many countries there is no funding for pre or post-surgical endothelial cell counts, which would enable surgeons to assess the effect their surgeries have on the endothelium, it is critical that surgeons are able to distinguish among OVDs – to understand their contrasting properties and attributes. When a company, or a surgeon wants to change an OVD, it must be understood that some OVDs are better suited to certain surgical methods than others. However, careful OVD modification by the manufacturer can ensure that through subtle changes surgeons can adapt their techniques to a newer, similarly viscous, but more dispersive OVD, and thereby provide greater endothelial protection and, in turn, enhanced patient outcomes, while facilitating surgical techniques.

1. Function and fragility: the corneal endothelium

Corneal endothelial health is critical to sustain corneal structure and clarity, without which the patient's vision becomes impaired.

Over time, endothelial cell density diminishes significantly, decreasing from 7,500 cells per mm^2 at birth to an average of 2,500-2,700 cells per mm^2 in older adults. After the age of 20, the normal rate of endothelial cell loss is approximately 0.5% per year – a process of reduction that is often accelerated by corneal disease, inflammation and surgical trauma. Damaged endothelial cells lack the capacity for self-repair, and when they die the remaining cells expand laterally and migrate, as needed, to cover the inner corneal surface. As they do so, they become less regular in size and shape and, over time, less able to support the fluid regulation function so vital to corneal clarity.

Heat, turbulence and free radical energy: the trauma of phacoemulsification

Cataract surgery is the single most common cause of endothelial cell loss. In standard phacoemulsification patients can lose up to 12% of endothelial cells, while in phakic / AC IOL implantations up to 20% can be lost.[2] As the tip of the phaco probe heats up during surgery, it can cause endothelial cell damage through mechanical turbulence, thermal and oxidative stress mechanisms.

Ultrasound energy used in phaco creates cavitation, which leads to the formulation of micro-bubbles in the aqueous environment. Once formed, around 75% of these bubbles implode, generating powerful shockwaves that radiate out from the tip of the phaco probe. Critically, the breaking of these micro-bubbles creates reactive free radicals, the most common of which is the hydroxyl radical, that cause profound and lasting damage to the corneal endothelium.

The link between cavitation and free radicals is well established.[3] Once formed, free radicals attack the nearest stable molecules and appropriate their electrons, in turn creating further molecular instability and triggering a chain reaction. This process can quickly escalate and cascade, resulting in widespread damage to the surrounding endothelial cells.

Clinical evidence has confirmed the impact of phacoemulsification on the endothelium, showing that free radicals are formed and may be a significant contributory factor in the development and severity of postoperative corneal oedema.[4] Indeed, in one study, routine uncomplicated phacoemulsification surgery demonstrated a 9% endothelial cell loss one year postoperatively.[5] Furthermore, a large study of 200 routine cataract procedures found an average of 18.41 % cell loss following phacoemulsification.[6]

2. Close scrutiny: the importance of checking endothelial health

In an ideal world, the specific measures undertaken during surgery to minimise endothelial cell loss should be informed by pre and postoperative assessment of the patient's endothelial cell counts.

Preoperative endothelial cell counts give the surgeon an opportunity to forewarn specific patients of potential for operative endothelial damage should their results prove marginal. This risk is particularly high among older patients and those with Fuchs' dystrophy or glaucoma.[7] Testing enables informed decisions about how surgery might be modified for these cases; for example, planning a better OVD strategy.

The case for postoperative endothelial assessment is also strong. One study shows that at one-to-five days after cataract extraction, a variable decrease in endothelial cell density is noted depending upon surgical trauma.[8] Postoperative endothelial cell density has been shown to decrease at an average rate of 2.5% per year for at least 10 years, which is five times the un-operated rate of decline.[8] Subtle decrease in the acuity of a pseudophake may be a sign of progressive endothelial cell loss and early corneal oedema, and not always early posterior capsular opacification.

Best practice versus budgetary constraints

However, pre and postsurgical endothelial cell counts represent an aspirational best practice scenario that in reality can be very hard to implement. As Dr Steve Arshinoff observes:

"The best practice is to do endothelial cell counts before and after surgery, say a few months later, and to monitor your surgical technique to see if you can improve what you're doing to decrease the loss of endothelial cells. The problem is that in many jurisdictions there is simply no funding for such testing, as everyone wants to pay as little as they can for cataract surgery. So in most places, people don't test endothelial cell health before or after surgery, beyond performing simple corneal pachymetry, if that."

3. Vital protection: the role of OVDs

Given the importance of the endothelium and its vulnerability to damage, the protection of this specialised corneal layer during surgery is paramount. OVDs currently offer the best form of defence against endothelial cell loss, and have come a long way since Sir Harold Ridley's first intraocular lens (IOL) implant in 1949 without any OVD. As is well documented, in the early days of intraocular lens implantation:

"Surgeons used air, balanced salt solution, and the patient's plasma in cataract surgery to maintain space and to attempt to minimise contact of surgical instruments and the IOL with the corneal endothelium during intraocular lens implantation. Unfortunately, these substances lack sufficient viscosity and elasticity to prevent their escaping from large surgical wounds, often resulting in collapse of the anterior chamber at inopportune times."[9]

Over the years, advances in ophthalmic science and research have led to important innovations in surgical methods and materials. Such innovations include the invention of the foldable lens, the development of phacoemulsification, and the use of OVDs to alleviate the risk of anterior chamber collapse and tissue damage from surgical procedures.

These developments have led to the creation of a range of high-performing OVDs that fulfil three key surgical functions:

- **Intraoperative endothelial protection.**
- **Anterior chamber and capsular bag space maintenance.**
- **Ease of removal.**

As we look to the future, we find that we can also look beyond the rheological properties of OVDs to enhance their performance. Enhanced free radical scavenging can provide additional endothelial protection. Of course, the NaHa substance used in many OVDs is itself a natural free radical scavenger. However, additional chemical scavenging can enhance protection against the damage caused by modern phaco techniques.

The problem, as Dr Arshinoff observes, is that "there is decreased attention altogether for everything to do with OVDs". From surgeon training through to corporate marketing, OVDs are often positioned as secondary to other more expensive devices, despite their primary role in facilitating surgery and making it safer.

4. Ophteis® FR Pro

In the current surgical landscape, discernment among OVDs is critical to the improvement of patient outcomes. Of those OVDs that are reasonably available, Rayner's Ophteis® FR Pro with Sorbitol is unique in offering the benefit of free radical scavenging that can make a palpable difference to endothelial protection.

Launched in April 2016, Ophteis® FR Pro with sorbitol is an innovative and viscous OVD designed to exceed core OVD requirements and enhance endothelial protection during surgery. In addition to a 2% NaHa, FR Pro contains 4% sorbitol, which is a known free radical scavenger that lends two additional free radical scavenging molecules to every NaHa chain.

Sorbitol is a naturally occurring sugar alcohol that is found in certain fruits like pears and plums and in aqueous humour, where it acts as a key corneal nutrient. It is a small, stable non-reactive molecule, which makes it a perfect free radical scavenger. Within FR Pro, it binds to NaHa chains and adds a vital layer of chemical protection to the OVD. As Dr Arshinoff remarks:

"Of the OVDs that are available, FR Pro is the first in the world to take this approach. Does it offer an advantage? Well, it offers an advantage in that you have two mechanisms now – not just the physical presence of the OVD but the chemical presence of an item, a molecule, that will scavenge to get rid of free radicals, so it offers more protection. And of course, the more corneal protection you have, the better."

Other key product benefits of FR Pro include:

- **Coating properties and more dispersive rheology** ensure that FR Pro is retained longer than similar viscous cohesive OVDs on the endothelium during phacoemulsification.
- **Creation of volume and space:** Classified as a viscous cohesive, FR Pro balances the benefits of slightly reduced cohesion (compared to other viscous cohesive OVDs) with excellent space creation due to zero-shear viscosity.
- **Clarity:** Its higher refractive index compared to aqueous BSS, added to its viscous cohesive nature yield excellent visualisation through FR Pro.
- **Ease of removal:** Its cohesive nature allows for more efficient removal of FR Pro compared to more dispersive OVDs.

Dr Arshinoff again:

"Sorbitol makes this a more dispersive OVD, so it should stay in the eye longer than other OVDs during phaco surgery, assuming everything else is the same. Plus, for as long as the Sorbitol is there it will also scavenge free radicals, yielding a second or dual effect to remove free radicals and thereby protect the cornea. So it's an advantage."

The presence of Sorbitol also serves to stabilise the hyaluronic acid chain, which means FR Pro can be stored outside of a fridge. Whereas some other hyaluronate based OVDs have to be refrigerated to prevent the breakdown of hyaluronic acid molecules, FR Pro is stable at room temperature. So, if a package of FR Pro is deposited in a hospital receiving area over a weekend, or spends a long time in unrefrigerated transit, the product itself will not spoil.

Clinical and in vitro laboratory trials

In addition to expert endorsement, FR Pro has undergone several studies and trials since launch in 2016. Rayner conducted a product trial with 73 ophthalmic surgeons who compared the performance of FR Pro to their usual OVD. The results from the surgeons that responded showed that:

- 78% of surgeons who tried Ophteis FR Pro said they would recommend it
- 50% said it offered endothelial protection better than their existing product:
  – Cumulatively, 97% said "same" or "better"
- Furthermore, 96% said that "it creates and maintains a deep anterior chamber to [their] clinical satisfaction for the entire duration of the procedure" in the same way or better than their existing OVD
- And 44.2% said they saw an improvement in "visibly clearer corneas postoperatively"
  – 98% said "same" or "better" [10]

In addition, in 2016 the University of Brighton, in collaboration with Dr Steve Arshinoff, carried out an in vitro laboratory study. Investigating cell viability, the study compared the cellular protection provided by FR Pro and other leading OVDs from free radical damage under phaco conditions. The results showed that during a three-second phaco exposure study, FR Pro showed greater overall average cell viability (28.4%) compared to the three tested market-leading OVDs (Figures 1 & 2).[11]

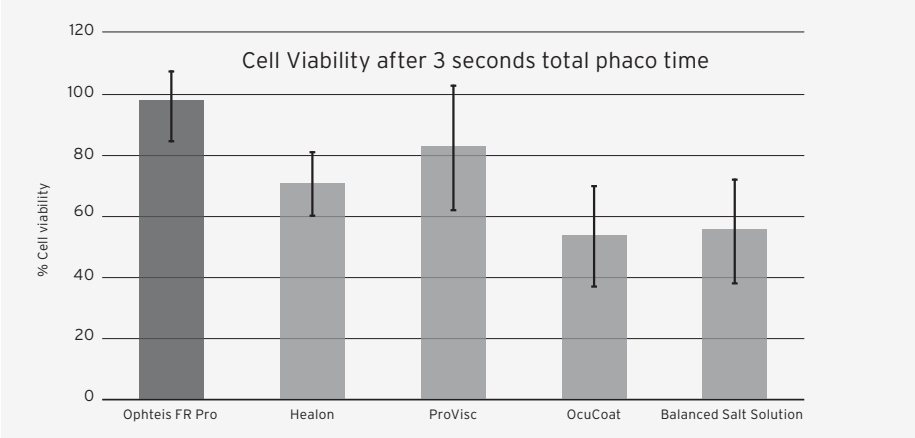

Figure 1.
3T3 Cellular viability post 3 sec ultrasound time: 3t3 Cells were exposed to 3 second total ultrasound time at 60% power in linier chop mode. Cell viability was quantified using MTS assay. FR Pro provided the greatest level of cell protection significantly greater than Healon, OcuCoat and BSS.

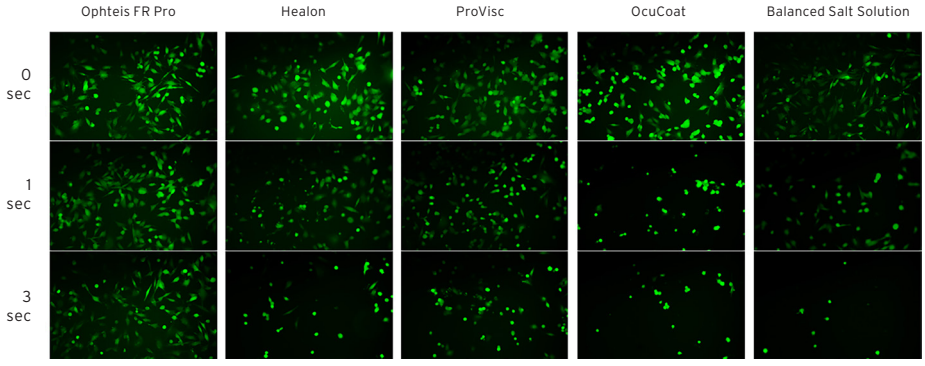

Figure 2.
3T3 Cellular viability post 0, 1 & 3 sec ultrasound time: Cell viability and morphology where visually assessed using Calcein-AM staining. The results closely match that of the MTS assay supporting the quantitative analysis findings. FR Pro provided the best level of cellular morphological protection following all exposures, with typical healthy spread fibroblastic form. While all other OVDs presented with spherical or reduced morphology.

Conclusion

Ophteis® FR Pro with Sorbitol is the first of a new type of OVD characterized by being a viscous-cohesive with increased OVD dispersion as well as enhanced free radical scavenging action, which together offer enhanced protection to the corneal endothelium.

Of course, surgeons who have spent years perfecting their techniques may be resistant to any slight change in their methods or materials. But the changes in technique are subtle, while the long-term benefits are significant. And as Dr Arshinoff concludes:

"Surgeons want good results for their patients. This is a reasonably simple way of achieving better outcomes for patients."

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