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# CORNEAL ENDOTHELIAL SAFETY & TOXICITY WITH INTRAOCULAR SURGICAL AGENTS

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Ophthalmic surgeons should not only be wary of all fluids, medications, and instrumentation introduced into the eye but also be aware of current safety procedures to avoid mishaps.

Toxicity to the endothelium has been linked to substances based on chemical composition (1,2), pH (3), and osmolality (4). **Toxic endothelial cell destruction syndrome**, a disease entity described by Breebaart et al. (5) and Nuyts et al. (6), has been characterized as having star-shaped Descemet folds, a twofold increase in corneal thickness, and a visual acuity of counting fingers occurring within a few postoperative days. The mechanism of corneal edema is related to the breakdown of the endothelial barrier function; therefore, steroids are minimally effective to ineffective on the repair process (5).

**Toxic anterior segment syndrome(TASS)** has links similar to toxic endothelial cell destruction syndrome (ie, pH, osmolality, antibiotics, residues from viscoelastics and detergents), but this disease entity is symptomatically different. Although both have corneal edema 1 to 2 days after surgery, the corneal edema of TASS is less pronounced. However, TASS has a marked increase in inflammation, increased leukocytes, and sometimes a hypopyon, making it more related to endophthalmitis at presentation. However, the corneal edema, timing, impairment of iris sphincter function, and increased intraocular pressure to a level between 40 to 70 mm Hg help to differentiate TASS from endophthalmitis. Management of TASS involves use of topical steroids every hour and nonsteroidal agents every 6 hours. Milder cases resolve within a few days to 1 to 3 weeks, but after 6 weeks, more dire consequences are likely. Severe disease can lead to permanent endothelial damage, profound cystoid macular edema, a permanently dilated pupil, and even permanent damage to the trabecular meshwork leading to resistant glaucoma that requires multiple surgeries (7,8).

## PRESERVATIVES

Benzalkonium chloride is highly toxic, and topical applications of 2% have been shown to cause necrosis

of the conjunctiva and cornea (9). However, endothelial damage with topical use is rare and has only been reported in one patient who required corneal transplantation because of frequent applications of 0.004% BAC for ocular surface disease (10). Intraocular use of 0.05% BAC causes irreversible endothelial necrosis, whereas 0.01% BAC causes reversible corneal edema in healthy rabbit eyes (11).

The threshold for physiologic and ultrastructural alterations of the endothelium is 0.0001% (12), and the highest safe intraocular concentration is 0.001% (13). These numbers were generated from rabbit experiments, and, therefore recommendation is to avoid preservatives for intraocular use in humans as much as possible, no matter what the concentration.

## INTRAOCULAR MEDICATIONS: ANTIBIOTICS

Recently, studies have been published regarding the safety and efficacy of intraocular antibiotics to help to prevent endophthalmitis. In the past, investigators have suggested the use of Gentamycin sulfate, vancomycin, or both for prophylaxis (14-16). However, concerns about vancomycin-resistant organism and aminoglycoside related macular toxicity have caused the need for better intraocular antibiotics options. Kramann et al. (17) studied the effects of prophylactic intracameral cefotaxime on the human corneal endothelium. Cefotaxime is a third-generation cephalosporin that has broad gram negative coverage and lesser but still useful activity against gram-positive organism. They found no significant endothelial damage in terms of cell density or morphology at 3 months follow up. No evidence of toxicity was found when 0.25% cefotaxime solution was instilled into the anterior chamber.

## INTRAOCULAR MEDICATIONS: ANESTHETICS

Intracameral anesthesia is thought to be superior to peribulbar anesthesia because it avoids the possibility of severe complications such as globe perforation, retinal vascular occlusion, retrobulbar hemorrhage, optic nerve injury, and brainstem anesthesia(18).

Heuermann et al. (19) compared peribulbar anesthesia with topical 2% lidocaine and intracameral preservative free 1% lidocaine and found intracameral lidocaine to be a safe alternative. They showed that there was no statistically significant endothelial cell loss or morphologic variation after phacoemulsification using either anesthetic protocol.

Based on the data published, intracameral methylparaben-free 1% lidocaine hydrochloride is not only a safe and easy alternative to retro/peribulbar anesthesia, but also the technique of choice for phacoemulsification (20).

#### **INTRAOCULAR MEDICATIONS: HYALURONIDASE**

Exogenously injected hyaluronidase has been reported to induce vitreous liquefaction and to increase aqueous outflow. It has been investigated as an intraocular pharmacological agent for multiple uses, including chemical vitreolysis, glaucoma therapy, refractive surgery, corneal scar therapy, and prevention of postoperative intraocular pressure elevation associated with the use of hyaluronic acid-containing viscoelastics (21-25).

Jumper et al. (26) reported a study that tried to determine whether toxicity to the cornea was related to the hyaluronidase itself, the impurities in the preparations sold commercially, or the accompanying vehicle. They concluded that surgeons should avoid less purified or preservative containing hyaluronidase preparations for intraocular use (26).

#### **INTRAOCULAR INDOCYANINE GREEN**

ICG has been used to stain both the internal limiting membrane in vitreoretinal surgery and the anterior capsule in cataract surgery. Holley et al. (27.) studied the effects of ICG on the human and rabbit corneal endothelium. They showed that human corneas exposed to ICG had no corneal endothelial ultrastructural damage by scanning and transmission electron microscopy. They did note one word of caution when using this product. ICG comes in the form of a 25-mg powder that needs to be dissolved in 0.5mL of aqueous solvent (distilled water) that is then diluted with 4.5mL BSS or BSS Plus. If the ICG is dissolved in distilled water alone or if the distilled water itself is injected into the anterior chamber, corneal edema will result (27.). Other than that, they found the dye to be safe for future intraocular surgeries.

#### **GLAUCOMA MEDICATIONS: MITOMYCIN C**

Mitomycin C can lead to the development of hypotony with a shallow chamber, hypotonic maculopathy, extended choroidal detachment, or a decrease in visual acuity related to progressive cataracts. Damage to the corneal endothelium may be induced owing to the iridocorneal contact resulting from a shallow to flat anterior chamber (28.). Smith et al. (29) correlated decreased corneal endothelial cell density to higher grades of anterior chamber flattening. The decrease in cell density was found to be much higher than would be expected by grade 2 shallow chambers without mitomycin use. It was therefore concluded that the use of mitomycin C was a key factor in worsening the corneal endothelial damage.

#### **STERILIZATION DETERGENTS**

A relatively new issue that will need to be addressed by ophthalmic surgeons and operating room personnel is enzymatic detergent - related toxicity to the corneal endothelium. Because ethylene oxide is now considered an occupational carcinogen and reproductive toxin by the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention (30,31), there has been a greater demand for better and safer alternatives. Enzymatic detergents are supposed to be an answer. However, if the instruments are not rinsed thoroughly, detergents thus entering the anterior chamber can be toxic to the endothelium. These detergents contain subtilisin, an exotoxin, and alpha amylase enzymes that are deactivated only if exposed to temperatures exceeding 140 C. However, most autoclaves in use today reach maximal temperatures of 120C to 130C. Parikh et al, (32) reported in vitro data showing a dose-related increase in corneal thickness in both humans and rabbits and corneal endothelial ultrastructural damage in both rabbits and humans. The importance of this information stems from the possibility of introducing active enzymes into the anterior chamber from instruments that are not cleaned properly. Without adequate rinsing, detergent and/or viscoelastic residue can build up in reusable instruments and can be irrigated in to the eye (32).

#### **OPHTHALMIC VISCOELASTIC DEVICES**

Kim et al. (33), using donor human eyes and rabbit eyes, compared Healon, Healon GV, and Viscoat with controls that received no viscoelastic to protect the

integrity of the endothelium. They found that Viscoat was the best viscoelastic for preventing endothelial damage. Additionally, they surmised that Viscoat must interact with the mucinous layer of the endothelium because the layer appeared thinned by transmission electron microscopy than controls, Healon 5, or Healon GV exposed eyes. They observed that Viscoat actually trapped air bubbles, which prevented them from making contact with the endothelium.

#### REFERENCES

1. Edelhauser HF, Van Horn DL, Schultz RO, et al.: Comparative toxicity of intraocular irrigating solutions on the corneal endothelium. *Am J Ophthalmol* 1976, 81:473 - 481.
2. Carter LM, Duncan G, Rennie GK: Effects of detergents on the ionic balance and permeability of isolated bovine cornea. *Exp Eye Res* 1973, 17:409-416.
3. Gonnering R, Edelhauser HF, Van Horn DL, et al.: The pH tolerance of rabbit and human corneal endothelium. *Invest Ophthalmol Vis Sci* 1979, 18:373-390
4. Edelhauser HF, Hanneken AM, Pederson HJ, et al.: Osmotic tolerance of rabbit and human corneal endothelium. *Arch Ophthalmol* 1981, 99:1281-1287.
5. Breebart AC, Nuyts RMMA, Pels E, et al.: Toxic endothelial destruction of the cornea after routine extracapsular cataract surgery. *Arch Ophthalmol* 1990, 108:1121-1125.
6. Nuyts RMMA, Edelhauser HF, Pels E, et al.: Toxic effects of detergent on the corneal endothelium. *Arch Ophthalmol* 1990, 108: 1158-1162.
7. Ronge LJ. Toxic anterior segment syndrome: why sterile isn't clean enough. *Eyenet* 2002, Nov/Dec:17-18. This article describes causes, identification, management, and prognosis of TASS.
8. Lipner M: Putting an end to endophthalmitis. *Eye world* 2003, Jan:20.
9. Swan KC : Reactivity of the ocular tissue to wetting agents . *Am J Ophthalmol* 1944,27: 1118-1122.
10. Lemp MA, Zimmerman LE: Toxic endothelial degeneration in ocular surface diseases treated with topical medications containing benzalkonium chloride, *Am J Ophthalmol* 1988, 10: 670-673.
11. Kohchi H, Goto M, Higashino I, et al.: Bullous keratopathy ; endothelial cell changes in experimental corneal edema (in Japanese). *Acta Soc Ophthalmol Jpn* 1980, 84:1244-1254.
12. Green K, Hull DS, Vaughn ED, et al.: Rabbit endothelial response to ophthalmic preservatives. *Arch Ophthalmol* 1977, 95: 2218-2221.
13. Britton B, Hervery R, Kasten K, et al.: Intraocular irritation evaluation of benzalkonium chlorides in rabbits. *Ophthalmic Surg* 1976,7:46-55.
14. Gill JP: Filters and antibiotics in irrigating solutions for cataract surgery (letter). *J Cataract Refract Surg* 1991, 17:385.
15. Peyman GA, Daun M: Prophylaxis of endophthalmitis. *Ophthalmic Surg* 1994,25:671-674.
16. Teichmann KD: Antibacterial concentrations (letter). *J Cataract Refract Surg* 1993,19:446.
17. Kramann C, Pitz S, Schwenn O, et al.: Effects of intraocular cefotaxime on the human corneal endothelium. *J Cataract Refract Surg* 2001, 27:250-255.
18. Anderson N , Nath R, Anderson J, et al.: Comparison of preservatives free bupivacaine vs lidocaine for intracameral anesthesia: a randomized clinical trial and in vitro analysis. *Am J Ophthalmol* 1999, 127:393-402.
19. Heurermann T, Hartmann C, Anders N: Long term endothelial cell loss after phacoemulsification : peribulbar anesthesia versus intracameral lidocaine 1%. *J Cataract Refract Surg* 2002,28:639-643.
20. Hejny C, Edelhauser HF: Surgical pharmacology: intraocular solutions and drugs used for cataract surgery. In *Phacoemulsification: Principles and Techniques*. Edited by Buratto L, Werner L, Zaini M, et al.: Thorofare, NJ: Slack, 2003, 2<sup>nd</sup> edition, chapter 12.219-246.

21. Grierson I, Lee WR, Abraham S: A light microscopic study of the effects of testicular hyaluronidase on the outflow system of a baboon (*Papio cynocephalus*). *Invest Ophthalmol Vis Sci* 1979, 18 :356-360.
22. Kupperman BD, Thomas EL, Graue F, et al. : Clearance of vitreous hemorrhage after intravitreal administration of hyaluronidase pre-clinical pharmacology and clinical outcomes (ARVO abst. 1814). *Invest Ophthalmol Vis Sci* 2000, 41:B60.
23. Turan S, Slem G, Baykal E, et al. : An experiment on the effect of hyaluronidase on the corneal refraction. *Ann Ophthalmol* 1972, 4:403-404.
24. Lambert RW, Wagstaff RE, Vu C, et al. : Resolution of human corneal scars by ACS-hyaluronidase (ARVO abst.3704). *Invest Ophthalmol Vis Sci* 2000, 41:B802.
25. Harooni M, Freilich JM, Abelson M, et al. : Efficacy of hyaluronidase in reducing increase on intraocular pressure related to the use of viscoelastics substances. *Arch Ophthalmol* 1998,116: 1218-1221.
26. Jumper JM, McCauley MB, Equi RA, et al. : Corneal toxicity of the intraocular hyaluronidase. *J Ocul Pharmacol Ther* 2002, 18:89-97.
27. Holley GP, Alam A, Kiri A, et al.: Effect on indocyanine green intraocular stain on human and rabbit corneal endothelial structure and viability. *J Cataract Refract Surg* 2002,28:1027-1033.
28. Fukuchi T, Hayakawa Y, Hara H, et al. : Corneal endothelial damage after trabeculectomy with mitomycin C in two patients with glaucoma with cornea guttata. *Cornea* 2002, 21:300-304.
- These are two cases reports of the toxic effects of mytomycin C on the corneal endothelium.
29. Smith DL, Skuta GL, Kincaid MC, et al.: The effects of glaucoma filtering surgery on corneal endothelial cell density. *Ophthalmic Surg* 1991, 22:251- 255.
30. National Institute for Occupational Safety and Health : Current Intelligence52: Ethylene Oxide Sterilizers in Health Care Facilities: Engineering Controls and Work Practices. Cincinnati, OH: US Department of Health and Human Services, Public Health Services, Centers for Diseases Control, National Institute for Occupational Safety and Health; 1989, (DHHS publications (NIOSH) 89-115.)
31. National Institute for Occupational Safety and Health: Current Intelligence 35:Ethylene Oxide (ETO): Evidence of Carcinogenicity. Cincinnati, OH:US Department of Health and Human Services, Public Health Services, Centers for Diseases Control, National Institute for Occupational Safety and Health;1981.(DHHS publications (NIOSH)81-130.)
32. Parikh CH, Dippy BD, Martin DF, et al.: Effects of enzymatic sterilization detergents of the corneal endothelium. *Arch Ophthalmol* 2002, 120:165-172.
33. Kim EK, Cristol SM, Kang SJ, et al.: Viscoelastic protection from endothelial damage by air bubbles. *J Cataract Refract Surg* 2002,28: 1047-1053.

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