### CATARACT SURGERY COMPLICATIONS

# Managing Residual Lens Material After Posterior Capsular Rupture

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## ABSTRACT

After posterior capsule rupture, removal of residual lens material is a challenging but important goal. Sequential, interdependent strategies to accomplish this include the Viscoat PAL, the Viscoat Trap, bimanual pars plana anterior vitrectomy, and bimanual irrigation–aspiration of cortex. Once brought into the anterior chamber, the nucleus can be removed either with phacoemulsification above a Sheet's glide, or by converting to a manual extracapsular cataract extraction approach.

## ■ HISTORICAL PERSPECTIVE

Retained nuclear fragments in the posterior segment greatly increase the risk of postoperative complications, and must usually be retrieved through a subsequent three-port vitrectomy.<sup>1–14</sup> Therefore, the early diagnosis and proper management of posterior capsule rupture is particularly critical while there is still nucleus present within the eye (Table 1). Once posterior rupture is recognized, the surgical goals are listed in Table 2.<sup>15</sup>

Currently, when attempting to manage residual lens material after posterior capsule rupture, most surgeons continue to work through the limbal cataract incision using the coaxial phaco and irrigation-aspiration (I-A) tips, and the vitrectomy handpiece. This paper will present the concepts of combining five interdependent strategies for preventing dropped or retained lens material in the face of a capsular defect (Table 3).

#### Technique

Phacoemulsification utilizes high irrigation inflow to maintain the anterior chamber. This inflow, along with the phaco tip and other instruments, are directed toward and approach the nucleus from above. This system is safe and effective because of the underlying support of the posterior capsule. However, once the posterior capsule ruptures, these identical surgical maneuvers and fluidic forces suddenly start working to our disadvantage. Fluctuations in chamber depth, and surgical maneuvers such as nuclear rotation, sculpting, and cracking, will now tend to expand the capsular defect. The downwardly directed infusion and instrumentation forces will now tend to push the remaining nucleus posteriorly.

# Strategy 1: Extracting the Nucleus—To Convert or Not?

Converting to Standard Extracapsular Cataract Extraction from Topical/Clear Cornea If posterior capsule rupture has occurred, and a large portion of the nucleus remains, converting to a manual, large-incision extracapsular cataract extraction (ECCE) technique is frequently the most prudent decision.<sup>11,15</sup> The decision of whether to continue phaco or not is influenced by the surgeon's individual experience and confidence level.<sup>16,17</sup> Regardless, a large or brunescent nucleus, the presence of other risk factors (e.g., small pupil), and poor remaining nuclear support all argue for this approach.<sup>17,18</sup> If vitreous prolapse or vitreous loss has already occurred, this will usually be the strategy of choice. Because the temporal clear corneal or scleral pocket incision is so shelved, it is generally better to construct a new limbal incision superiorly. The self-sealing temporal corneal or scleral incision can be abandoned and left unsutured. A curved Simcoe cannula (Katena) can be used through an inferior fornix conjunctival buttonhole to inject 2% lidocaine (Xylocaine) into the posterior sub-Tenon's space. Phaco Above a Sheet's Glide If there is no vitreous prolapse, and the nucleus is still well supported within the capsular bag, the option of continuing phacoemulsification can be considered.<sup>19</sup> This is a reasonable alternative if the capsular defect is small and localized, if the nucleus is soft, or if only a small amount of residual nucleus remains. The primary objective becomes extracting the remaining nucleus without aspirating vitreous. If the nucleus has not descended, and depending on its size and position, it may be possible bring it forward by injecting an ophthalmic viscodevice (OVD) behind it. One should also readjust the phaco machine parameters. Low-

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**TABLE 1.** Early signs of possible posterior capsule rupture

 or zonular dehiscence

- 1. Sudden deepening of the chamber, with momentary expansion of the pupil
- 2. Sudden, transitory appearance of a clear red reflex peripherally
- 3. Newly apparent inability to rotate a previously mobile nucleus
- 4. Excessive lateral mobility or displacement of the nucleus
- 5. Excessive tipping of one pole of the nucleus
- 6. Partial descent of the nucleus into a more posterior position or plane

ering the irrigating bottle height, and reducing the aspiration flow rate (e.g., to 20–22 mL/min) will slow the pace down. The vacuum should be decreased (e.g., 100–125 mm Hg) to eliminate any possibility of postocclusion surge.

An effort should be made to confine the use of phacoemulsification and aspiration to zones away from the problem area. One also should avoid sculpting or rotating the nucleus if possible. If a central capsular defect exists, Michelson's technique of using a trimmed Sheet's glide as an artificial posterior capsule should be considered—particularly if multiple small fragments of nucleus remain.<sup>19</sup> The phaco incision should first be slightly enlarged to accommodate the glide together with the phaco or I-A tip. The remaining nuclear fragments should be elevated with the OVD into the anterior chamber if possible.

After sliding the glide across the pupil and beneath the residual nucleus, the phaco tip can be used with the modified fluidic parameters discussed above. The glide will prevent small nuclear fragments from falling posteriorly, and will block vitreous from being aspirated as long as the tip is kept positioned directly over the glide. For this reason, one should not chase peripherally located fragments with the phaco tip. Instead, a second instrument can be used to manually position these pieces in front of the stationary phaco tip. This technique can be safely continued until vitreous is aspirated.

If one has experience with bimanual phaco, this technique may be particularly advantageous for this situation.

**TABLE 2.** Surgical goals after posterior capsule rupture (in descending order of importance)

- Avoid a dropped nucleus and extract all of the nucleus
- · Remove as much of the epinucleus and cortex as possible
- Perform a thorough anterior vitrectomy, avoiding retinal
- traction and vitreous incarceration in the incisionsPreserve an intact capsulorrhexis or as much residual capsular support as possible
- Securely implant a posterior or anterior chamber intraocular lens

## **TABLE 3.** Strategies for removing lens material after posterior capsule rupture

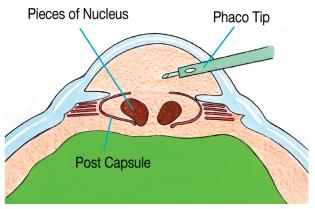
- 1. Phaco over Sheet's glide (or conversion to large incision, manual extraction)
- 2. Viscoat posterior assisted levitation of descending nucleus
- 3. Viscoat Trap (for retained material after vitreous loss)
- 4. Bimanual pars plana anterior vitrectomy
- 5. Bimanual I-A cortical cleanup

After inserting the Sheet's glide through the phaco incision, the irrigating chopper and bare phaco needle are inserted through separate, snug corneal paracentesis openings to minimize incisional leak. This, and the use of reduced flow fluidic parameters, will lessen the chance of vitreous prolapsing up to the incisions. In addition, the ability to dissociate the irrigation and aspiration instruments can help to reduce the chance of aspirating vitreous.

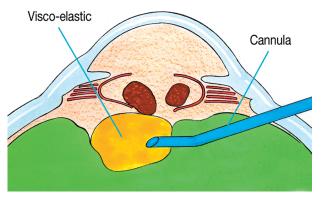
# Strategy 2: Rescuing a Partially Descended Nucleus—The Viscoat PAL

Early recognition of a posterior capsule or zonular rupture is usually the key to avoiding a dropped nucleus. This is because if the nucleus remains anterior to the posterior capsule defect, it is much easier to remove it using the techniques described above. As phaco continues, an unrecognized capsular defect can eventually expand enough to permit the nucleus to drop.

How far the nucleus initially descends through a capsular rent will depend upon the vitreous anatomy. If the vitreous is very liquefied, the nucleus may abruptly and rapidly sink down to the retina without antecedent vitreous prolapse. This may occur so rapidly that there is no time to respond. Alternatively, the nucleus may partially descend onto an intact hyaloid face. This slight posterior displacement may be very subtle. Finally, if the hyaloid face is ruptured, the nucleus may tip or partially descend until it is suspended and supported by formed vitreous. It



**FIGURE 1.** Nuclear fragments partially descended through a posterior capsule defect.



**FIGURE 2.** Viscoat posterior assisted levitation. After introducing the Viscoat cannula through the pars plana sclerotomy, dispersive OVD is immediately injected behind the nuclear fragments to provide supplemental support.

is in these situations where the nucleus has only partially descended that a rescue technique may be possible.

The worst tactic for recovering a partially descended nucleus is to try to chase and spear it with the phaco tip. Lacking the normal capsular barrier, the downwardly directed irrigation flow will flush more vitreous forward, expanding the rent and propelling the nucleus away. Attempting to phacoemulsify or aspirate the nucleus may ensnare vitreous into the phaco tip. Applying ultrasound or moving the phaco tip after massive vitreous incarceration into such a large diameter opening can easily create a giant retinal tear.<sup>5,11,20</sup>

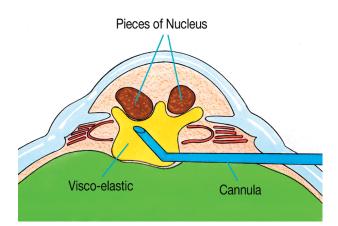
Clearly, the safer alternative is to elevate the nucleus into the pupillary plane or anterior chamber. However, there may be numerous obstacles to accomplishing this. First, the pupil or capsulorrhexis diameter may be very small. Indeed, these may have been the predisposing factors for a capsular complication in the first place. Too small a pupil or capsulorrhexis may impede elevation of the nucleus and can make it particularly difficult for a spatula or OVD cannula to maneuver behind it. Any vitreous that has prolapsed in front of the nucleus will further hinder attempts to inject OVD behind it. Continued vitreous loss or prolapse deprives the nucleus of much-needed remaining support.

Finally, even without a small pupil and vitreous loss, it may still be difficult to inject OVD behind a large, partially descended nucleus via a limbal incision. This is because any instrument inserted through the phaco wound is approaching the nucleus from too steep an angle. For this reason, Charles Kelman, MD popularized the posterior assisted levitation, or "PAL" technique in which a metal spatula, inserted through a pars plana sclerotomy, is used to levitate the nucleus into the anterior chamber from below.<sup>21</sup> Compared with the phaco incision, the pars plana sclerotomy provides a much better instrument angle for getting behind the lens. Richard Packard, MD, has suggested using Viscoat (Alcon, 3% sodium hyalvronate and 4% chondroitin sulfate) instead of a spatula to levitate the nucleus via a pars plana approach. He and this author reported their success using the Viscoat PAL technique in a series of 6 consecutive cases with partially descended nuclei.<sup>22</sup> A disposable microvitreoretinal (MVR) blade (Alcon, Fort Worth, TX) is used to make a pars plana stab incision located 3.5 mm behind the limbus. The Viscoat cannula is inserted far enough into the eye to be visualized and then advanced or aimed behind the nucleus. The first step is to inject a bolus of dispersive OVD behind the nucleus to immediately provide supplemental support. Periodic palpation of the globe confirms that overinflation has not occurred.

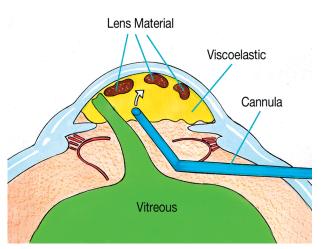
If the nucleus is subluxated laterally, directing OVD toward the region beneath it will often float the nucleus toward a more central position. This is preferable to using a metal spatula to reposition the nucleus because the tip, which cannot be visualized that far laterally, might accidentally contact the retina. One should not attempt to float the nucleus up using a massive injection of OVD alone. Unlike using liquid perfluorocarbon in a vitrectomized cavity, an excessive infusion of OVD may over-inflate the globe and cause vitreous expulsion through the sclerotomy or cataract incision.<sup>23</sup>

Instead, the cannula tip itself should be used at this point to prop and levitate the nucleus into the anterior chamber. Small aliquots of additional OVD can be injected to help in the levitation and maneuvering of the nucleus. The levitating force is sufficiently strong that the capsulorrhexis and pupil will stretch to accommodate a nucleus of greater diameter.

Because there is no aspiration involved, these PAL maneuvers should minimize iatrogenic vitreous traction. The ability to first support and reposition the nucleus by



**FIGURE 3.** Viscoat posterior assisted levitation. The nuclear fragments are carefully levitated into the anterior chamber with a combination of additional Viscoat injection, and manipulation with the cannula tip.



**FIGURE 4.** Viscoat Trap. After vitreous prolapse, the residual lens material is elevated toward the cornea prior to filling the anterior chamber with a dispersive OVD.

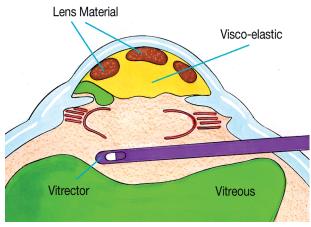
injecting dispersive OVD prior to definitive manual levitation reduces the chance of touching the retina with a metal spatula tip. This is a major advantage of the Viscoat PAL variation.

Once a fragment descends into the mid or posterior vitreous cavity, or lands on the retina, it is dangerous to blindly fish for it with the OVD cannula or vitrectomy instrument.<sup>24</sup> One should abandon the dropped nucleus and concentrate on removing the epinucleus and cortex, while preserving as much capsular support as possible. A thorough anterior vitrectomy must be performed prior to inserting the IOL. Because the vitreoretinal specialist will later use a 3-port fragmatome-vitrectomy approach to remove the retained nucleus, it is preferable to insert an IOL through the cataract incision at the time of the initial surgery if possible.

### Strategy 3: Managing Vitreous Loss and Residual Lens Material—The "Viscoat Trap"

As previously discussed, any residual nucleus or epinucleus delivered into the anterior chamber using the Viscoat PAL technique can be removed either by continuing phaco or by converting to a manual large-incision ECCE method. At some point during this sequence, vitreous may prolapse and be ensnared by the phaco or I-A tip. Because repeated vitreous aspiration and traction will risk causing a retinal tear, surgeons should stop to perform an anterior vitrectomy, with the goal being to later resume removing residual nuclear or cortical remnants.

The most common practice is to place a separate self-retaining irrigating cannula though a limbal paracentesis, and to insert the sleeveless vitrectomy probe through the phaco incision. However, there are multiple drawbacks to this approach. First, the phaco incision is too large for the probe diameter. This leaking incision



**FIGURE 5.** Bimanual pars plana anterior vitrectomy. The vitrectomy cutter tip is kept posterior to the plane of the anterior capsule where transpupillary bands can be severed without aspirating the Viscoat. The self-retaining limbal infusion cannula is not shown.

results in poor chamber fluidics and allows both irrigation fluid and vitreous to prolapse externally alongside the vitrector shaft. Second, performing the vitrectomy in the anterior chamber will tend to draw more posteriorly located vitreous forward. Finally, as more and more vitreous exits the eye through either the cutting instrument or the incision, the residual lens material that it is supporting will sink down toward the retina. It bears repeating that once the posterior capsule is open, it is the residual vitreous that is propping up and preventing the remaining nucleus and epinucleus from descending.

I propose a new strategy that I call the "Viscoat Trap" which, when combined with a pars plana anterior vitrectomy, can prevent this undesirable chain of events (Table 4). The first step is to use a dispersive OVD, such as Viscoat or Vitrax (3% sodium hyaluronate) (Advanced Medical Optics, Irvine, CA), to levitate any mobile lens fragments up toward the cornea. Next, one completely fills the anterior chamber with the OVD. Even though vitreous has prolapsed forward, injecting viscoelastic will not exert traction on the retina. The dispersive OVD will continue to support and trap the residual lens material in the anterior chamber once the vitreous is excised.

**TABLE 4.** Steps for the Viscoat Trap

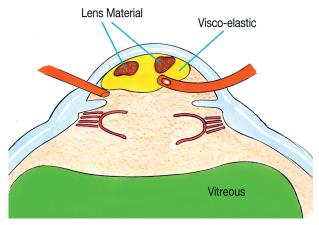
- 1. Levitate mobile lens material toward the cornea
- 2. Fill the anterior chamber with dispersive ophthalmic viscodevice
- 3. Create pars plana sclerotomy 3.5 mm behind the limbus (#19 microvitreo retinal blade)
- 4. Self-retaining limbal infusion cannula directed toward the pupil
- 5. Bimanual pars plana anterior vitrectomy with cutting tip kept behind the plane of the capsulorrhexis

### Strategy 4: Bimanual Pars Plana Anterior Vitrectomy

Unless it has already been created for a Viscoat PAL, a pars plana sclerotomy is made 3.5 mm posterior to the limbus, after making an overlying conjunctival peritomy. A disposable #19 MVR blade will create an adequately sized opening for most anterior vitrectomy cutters. A self-retaining irrigating cannula is placed through a limbal paracentesis, and angled toward the pupil. The sleeveless vitrectomy shaft is inserted through the pars plana sclerotomy until the tip can be visualized in the retropupillary space. If it does not pass through the incision easily, it is better to slightly enlarge the opening rather than to force the entry.

Utilizing a high cutting rate, a thorough anterior vitrectomy is performed while focusing posteriorly enough with the microscope to keep the tip under direct visualization. One should attempt to keep the vitrectomy tip behind the pupil at all times. While any transpupillary bands of vitreous will still be severed, this will avoid removing the dispersive OVD that fills the anterior chamber. When properly performed, one will see that the anteriorly trapped lens fragments remain completely immobilized as the vitrectomy is being carried out below. This is because two separate chambers have been formed by the OVD partition, such that the anterior chamber is isolated from the vitrectomized posterior chamber.

Use of a pars plana sclerotomy is an underutilized option for performing an anterior vitrectomy. A major advantage is that the opening is properly sized to avoid incisional leak and vitreous prolapse, and to provide a better fluidic seal. Unlike with a limbal incision, the vitrector need not transverse and invade the Viscoat Trap, and will not draw vitreous up into the anterior chamber. Performing the vitrectomy posterior to the pupil and the plane of the capsulorrhexis also decreases the



**FIGURE 6.** Bimanual irrigation-aspiration handpieces are used to evacuate the epinucleus and cortex after the vitreous prolapse has been addressed.

chance of inadvertently cutting either structure. If the latter is preserved, a foldable posterior chamber IOL may still be implanted in the ciliary sulcus.<sup>3–5,7–9,13,14,17</sup> The sclerotomy can be closed with an interrupted 8–0 Vicryl suture.

### **Strategy 5: Bimanual I-A for Cortex After Posterior Capsule Rupture**

After the limited vitrectomy, one can resume aspiration of the remaining cortex or epinucleus trapped in the Viscoat-filled anterior chamber. With a ruptured posterior capsule, and once the nucleus has been removed, epinuclear and cortical cleanup are best performed using separate, bimanual I-A handpieces through clear corneal paracentesis incisions. This is true regardless of whether vitreous loss or a vitrectomy has already occurred. Compared with coaxial I-A, this is a lower flow fluidic system. As with bimanual phaco incisions, these snug openings prevent incisional fluid leak and vitreous prolapse alongside the instruments. Lowering the I-A flow and vacuum settings slows things down and limits postocclusion surge. In combination, these factors reduce overall fluctuation in chamber depth.

The oppositely located bimanual incisions provide improved access to the subincisional area. Lacking an infusion sleeve, the aspirating tip can be advanced more easily out to the periphery. Immediately occluding the port with cortex blocks vitreous from entering. The ability to dissociate the irrigating and aspirating tips also facilitates positioning their openings as far from the capsular defect as possible. The irrigation flow should be directed toward the opposite angle rather than posteriorly. If the aspirating port becomes entangled with vitreous again, one simply repeats the Viscoat Trap maneuver followed by the pars plana anterior vitrectomy. Bimanual cortical I-A can then be resumed. In preparation for using this technique after posterior capsule rupture, it would be prudent for every anterior segment surgeon to practice using bimanual I-A instrumentation in routine, uncomplicated cases.

*Why Dispersive OVDs?* The Viscoat PAL and Trap are so named because of the need to employ a dispersive OVD. Although Vitrax is also a dispersive agent, the smaller gauge cannula of the Viscoat syringe makes it the preferred choice for the PAL technique. To effectively trap lens material, the OVD should be maximally retentive, so that it is less easily burped out of the eye through incisional manipulation. In addition, dispersive agents, such as Viscoat and Vitrax, better resist aspiration by a nearby I-A or vitrectomy port.

Finally, it is not practical to thoroughly aspirate the OVD from the vitreous cavity. The smaller molecular size and weight of dispersive agents makes a prolonged and protracted pressure spike less likely when they are not fully evacuated.<sup>25–27</sup> Because of the larger molecular weight, residual amounts of maximally cohesive OVDs, such as Healon 5 or Healon GV (Pharmacia Corporation, Peapack, NJ) will usually produce the most severe and most prolonged pressure spikes.

In conclusion, posterior capsule rupture while nucleus is still present is a precipitous and intimidating complication that tests a surgeon's ability to operate under pressure. It is incumbent upon all cataract surgeons to prepare for this scenario by understanding the management principles and mentally rehearsing the maneuvers in advance.

### REFERENCES

- Fastenberg DM, Schwartz PL, Shakin JL, et al. Management of dislocated nuclear fragments after phacoemulsification. *Am J Ophthalmol.* 1991;112:535–539.
- Blodi BA, Flynn HW Jr, Blodi CF, et al. Retained nuclei after cataract surgery. *Ophthalmology*. 1992;99:41–44.
- Gilliland GD, Hutton WL, Fuller DG. Retained intravitreal lens fragments after cataract surgery. *Ophthalmology*. 1992;99:1263– 1267.
- Kim LMW, Flynn HW Jr, Smiddy WE, et al. Retained intravitreal lens fragments after phacoemulsification. *Ophthalmology*. 1994; 101:1827–1832.
- Borne MJ, Tasman W, Regillo C, et al. Outcomes of vitrectomy for retained lens fragments. *Ophthalmology*. 1996;103:971–976.
- Kapusuta MA, Chen JC, Lam W-C. Outcomes of dropped nucleus during phacoemulsification. *Ophthalmology*. 1996;103:1184– 1187; discussion by Brucker AJ, 1187.
- Vilar NF, Flynn HW Jr, Smiddy WE, et al. Removal of retained lens fragments after phacoemulsification reverses secondary glaucoma and restores visual acuity. *Ophthalmology* 1997;104:787– 791; discussion by McDonald HR, 791–792.
- Margherio RR, Margherio AR, Pendergast SD, et al. Vitrectomy for retained lens fragments after phacoemulsification. *Ophthalmol*ogy. 1997;104:1426–1432.
- Stilma JS, van der Sluijs FA, van Meurs JC, et al. Occurrence of retained lens fragments after phacoemulsification in The Netherlands. J Cataract Refract Surg. 1997;23:1177–1182.
- Yeo LMW, Chartesis DG, Bunce C, et al. Retained intravitreal lens fragments after phacoemulsification: a clinicopathological correlation. *Br J Ophthalmol.* 1999;83:1135–1138.
- Lu H, Jiang YR, Grabow HB. Managing a dropped nucleus during the phacoemulsification learning curve. J Cataract Refract Surg. 1999;25:1311–1312.
- 12. Rossetti A, Doro D. Retained intravitreal lens fragments after phacoemulsification: Complications and visual outcome in vitrec-

tomized and nonvitrectomized eyes. J Cataract Refract Surg. 2002;28:310–315.

- Hansson LJ, Larsson J. Vitrectomy for retained lens fragments in the vitreous after phacoemulsification. J Cataract Refract Surg. 2002;28:1007–1011.
- Scott IU, Flynn HW Jr, Smiddy WE, et al. Clinical features and outcomes of pars plana vitrectomy in patients with retained lens fragments. *Ophthalmology*. 2003;110:1567–1572.
- Akura J, Hatta S, Kaneda S, et al. Management of posterior capsule rupture during phacoemulsification using the dry technique. *J Cataract Refract Surg.* 2000;27:982–989.
- Ah-Fat FG, Sharma MK, Majid MA, et al. Vitreous loss during conversion from conventional extracapsular cataract extraction to phacoemulsification. J Cataract Refract Surg. 1998;24:801–805.
- Aasuri MK, Kompella VB, Majji AB. Risk factors for and management of dropped nucleus during phacoemulsification. J Cataract Refract Surg. 2001;27:1428–1432.
- Guzek JP, Holm M, Cotter JB, et al. Risk factors for intraoperative complications in 1000 extracapsular cataract cases. *Ophthalmology*. 1987;94:461–466.
- Michelson MA. Use of a Sheets' glide as a pseudoposterior capsule in phacoemulsification complicated by posterior capsule rupture. *Eur J Implant Surg.* 1993;570–572.
- Moore JK, Scott IU, Flynn HW Jr, et al. Retinal detachment in eyes undergoing pars plana vitrectomy for removal of retained lens fragments. *Ophthalmology*. 2003;110:709–713.
- Rao SK, Chan WM, Leung AT, et al. Impending dropped nucleus during phacoemulsification [Letter]. J Cataract Refract Surg. 1999;25:1311–1312.
- Chang DF, Packard RB. Posterior assisted levitation for nucleus retrieval using Viscoat after posterior capsule rupture. J Cataract Refract Surg. 2003;29:1860–1865.
- Verma L, Gogoi M, Tewari HK, et al. Comparative study of vitrectomy for dropped nucleus with and without the use of perfluorocarbon liquid. Clinical, electrophysiological and visual field outcomes. *Acta Ophthalmol Scand.* 2001;79:354–358.
- Horiguchi M, Kojima Y, Shimada Y. Removal of lens material dropped into the vitreous cavity during cataract surgery using an optical fiber-free intravitreal surgery system. J Cataract Refract Surg. 2003;29:1256–1259.
- Burke S, Sugar J, Farber MD. Comparison of the effects of two viscoelastic agents, Healon and Viscoat, on postoperative intraocular pressure after penetrating keratoplasty. *Ophthalmic Surg.* 1990;21:821–826.
- Probst LE, Hakim OJ, Nichols BD. Phacoemulsification with aspirated or retained Viscoat. J Cataract Refract Surg. 1994;20:145– 149.
- Torngren L, Lundgren B, Madsen K. Intraocular pressure development in the rabbit eye after aqueous exchange with ophthalmic viscosurgical devices. J Cataract Refract Surg. 2000;26:1247– 1252.