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Posterior Capsular Opacification

A Problem Reduced but Not Yet Eradicated

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Posterior capsular opacification (PCO) is the most frequent complication of cataract surgery. Advances in surgical techniques, intraocular lens materials, and designs have reduced the PCO rate, but it is still a significant problem. The only effective treatment for PCO, Nd:YAG laser capsulotomy carries vision-related complications and risks and puts a significant financial burden on the health care system. This review contains current knowledge about the mechanisms of PCO development. Posterior capsular opacification is caused mainly by remnant lens epithelial cell proliferation and migration, epithelial-mesenchymal transition, collagen deposition, and lens fiber generation. All of these processes are influenced by cytokines, growth factors, and extracellular matrix proteins. We also describe advances and improvements in surgical techniques, intraocular lens materials, and the designs and use of therapeutic agents leading to safe, effective, and less expensive strategies to eradicate PCO.

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Cataract surgery is currently the most common and well-established ophthalmic surgical procedure in the world. This procedure involves the extracapsular extraction of the natural opaque lens fibers and implantation of an intraocular lens (IOL), which restores good vision.[1] However, posterior capsular opacification (PCO), which is also termed *secondary cataract*, is a common long-term complication of modern cataract surgery (**Figure 1**).[2-6] The first IOL implantation was performed by Sir Harold Ridley in 1950. Since that time, the technology has undergone a wide variety of improvements that reduced the incidence of PCO but did not eliminate it as a significant clinical problem. Decreased visual acuity induced by PCO is reported to occur in 20% to 40% of patients 2 to 5 years after surgery (Figure 1). Posterior capsular opacification development is age dependent, with a low incidence in older patients but high rates in young patients, especially children and infants.[2,7-9]

At present, the only effective treatment of PCO is Nd:YAG laser capsulotomy, which involves clearing the visual axis by creating a central opening in the opacified posterior capsule.[2,10] Although this procedure is easy and quick, there are complications, including retinal detachment, damage to the IOL, cystoid macular edema, an increase in intraocular pressure, iris hemorrhage, corneal edema, IOL subluxation, and exacerbation of localized endophthalmitis.[2,10,11] Changes induced by Nd:YAG capsulotomy have been shown to be affected by IOL material and design. Trinavarat et al[12] observed that silicone lenses were more easily damaged by laser capsulotomy than were acrylic or polymethyl methacrylate (PMMA) lenses. In addition, this treatment represents a considerable cost burden to national health care systems, and such laser treatment is not readily available in developing countries. Therefore, a better understanding of the pathogenic mechanism of PCO is highly desirable as a basis for improving the outcome of cataract surgery and eradicating PCO.

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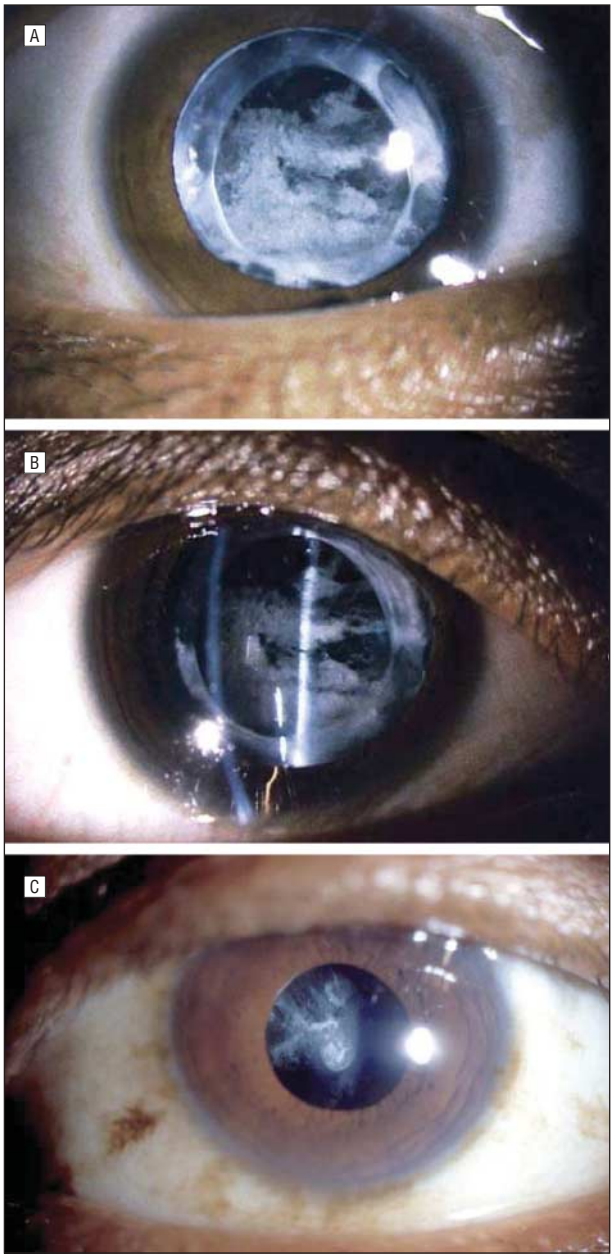

Figure 1. Representative slitlamp photographs of human eyes with posterior capsular opacification (PCO). A, Diffuse overall illumination and high magnification showing a large PCO blocking the visual axis. B, Optical sectioning and background illumination showing that the PCO is located on the central posterior lens capsule. C, Diffuse overall illumination and low magnification showing that the central visual axis is obscured.

Research laboratories worldwide attempting to eliminate the problem of PCO development are focusing on several strategies, including improving surgical techniques, IOL materials, IOL designs, use of therapeutic agents, and combination therapy (**Figure 2**). Recent improvements in surgical techniques and IOL materials and designs have served mainly to delay the onset of PCO rather than eliminate the problem.[13,14] The use of cytotoxic agents carries the risk of toxic effects on surrounding ocular tissues.

The aim of this review is to describe current knowledge about the mechanisms of PCO development and strategies to eliminate this sight-threatening problem.

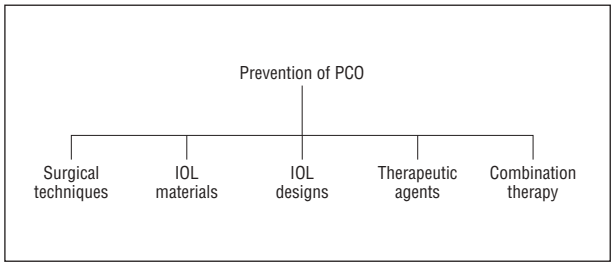

Figure 2. Schematic representation of current strategies toward finding a safe, effective, and less expensive way to eradicate posterior capsular opacification (PCO). IOL indicates intraocular lens.

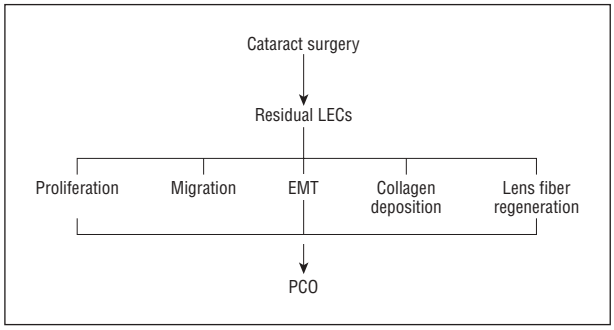

Figure 3. Schematic representation of the mechanism of posterior capsular opacification (PCO) development. Lens epithelial cells (LECs) left behind in the capsular bag after cataract surgery proliferate, migrate, convert from epithelial to mesenchymal cells (EMT), deposit collagen, and generate lens fibers, leading to PCO development.

MECHANISMS OF PCO DEVELOPMENT

Lens epithelial cells (LECs) left behind in the capsular bag after any type of extracapsular cataract surgery are mainly responsible for PCO development.[2] Proliferation, migration, epithelial-to-mesenchymal transition (EMT), collagen deposition, and lens fiber regeneration of LECs are the main causes of opacification (**Figure 3**). It appears that cataract surgery induces a wound-healing response in the lens, and leftover LECs proliferate and migrate across the posterior capsule and undergo lens fiber regeneration and EMT.[7,15,16] Clinically, there are 2 morphological types of PCO, the fibrosis type and the pearl type. Fibrosis-type PCO is caused by the proliferation and migration of LECs, which undergo EMT, resulting in fibrous metaplasia and leading to significant visual loss by producing folds and wrinkles in the posterior capsule.[7] Pearl-type PCO is caused by the LECs located at the equatorial lens region (lens bow) causing regeneration of crystallin-expressing lenticular fibers and forming Elschnig pearls and Soemmering ring, responsible for most cases of PCO-related visual loss.[2,17] The histological features of PCO are now well established, but to date the molecular mechanisms influencing leftover LEC behavior after cataract surgery are not completely clear. In vitro studies and animal models of PCO suggest that several cytokines and growth factors play a major role in the pathogenesis of PCO.[18,19]

Studies show that levels of several cytokines and growth factors increase in aqueous humor and influence the behavior of the remaining LECs after cataract surgery. These factors include transforming growth factor β (TGF-β), fibroblast growth factor 2 (FGF-2), hepatocyte growth fac-

tor, interleukins 1 and 6 (IL-1 and IL-6), and epithelial growth factor.[18,20] Wormstone et al[21] and Duncan et al[22] have studied LEC growth on human capsular bags in a protein-free medium, which has allowed the autocrine control by individual growth factors to be analyzed.

Transforming growth factor β plays a central role in the cell biology of PCO. It is a multifunctional growth factor with a wide range of opposing effects on cellular processes.[23] Transforming growth factor β induces EMT[24-27] and has been shown to suppress LEC proliferation.[26,28] A recent study showed that during PCO formation the TGFβ-activated pathway is influenced by SPARC (secreted protein, acidic, and rich in cysteine), which regulates matrix-cell interactions.[29] Members of the FGF family are known to play a critical role in establishing and maintaining normal lens structure and function. Proliferation, migration, and fiber differentiation of normal LECs have been shown to be affected by FGF-2 in vitro. Previous studies have shown that FGF-2 induces proliferation,[30,31] which may contribute to the development of PCO. Also, FGF-2 has been shown to counteract the TGF-β effect.[32] Hepatocyte growth factor is highly expressed in human capsular bag cultures in protein-free medium. Studies have shown that hepatocyte growth factor plays an important role in PCO development by inducing proliferation of LECs.[33,34] Interleukin 1 is synthesized by LECs in vitro[35] and stimulates LEC mitosis and collagen synthesis.[36] Interleukin 1 stimulates human LECs to produce prostaglandin-E_2, which contributes to increased inflammation after cataract surgery. In human vein endothelial cells, IL-1 induced IL-6 secretion,[37] suggesting that the action of IL-1 on LECs may be mediated by IL-6. Jiang et al[38] have shown that LEC migration is induced by epithelial growth factor, suggesting its role in PCO development.

Migration of human LECs plays an important role in the remodeling of the lens capsule[39,40] and is associated with matrix metalloproteinase activity in the lens.[41] Matrix metalloproteinases are a group of proteolytic enzymes, essential for cell migration and cell-mediated contraction after wound healing.[42] Changes in lens capsule structure during PCO development may include remodeling of the extracellular matrix by matrix metalloproteinases.

PREVENTION OF PCO

There are several urgent reasons to eradicate PCO. First, PCO remains the most common complication of cataract surgery.[43,44] Posterior capsular opacification is even more threatening in young adults and children, with a higher incidence, quicker onset, and greater amblyogenic effect. The rates of PCO in children ranged from 43.7% to 100%, probably because of the high proliferation of LECs. Recent advances in pediatric cataract surgery, such as posterior continuous curvilinear capsulorrhexis and anterior vitrectomy, have decreased PCO incidence.[2,44-52] Posterior capsular opacification in young children is always dense and may need to be removed with additional surgery, which carries more risks of potential complications.[45,46] In addition, Nd:YAG laser capsulotomy, the only currently available treatment of PCO, has several significant complications, and this procedure imposes a severe financial burden on the health care system. Therefore, investigators are constantly working to advance and improve the following areas to find a safe and effective way to eradicate PCO.

Surgical Techniques

Because PCO is predominantly caused by residual LECs in the capsular bag after cataract surgery,[2,19,53] several surgical techniques have been attempted for the removal of these LECs at the time of lens extraction. These techniques include aspiration of the anterior capsule using an extensive irrigation/aspiration system during cataract surgery,[54-61] pharmacological dispersion and aspiration of the anterior capsule,[62-65] and manual polishing of the anterior and/or posterior capsule.[58,66-68] These studies provided limited and conflicting information about the effect of residual LECs on long-term PCO development. One study showed that ultrasonic vacuuming during cataract surgery reduced the number of patients requiring laser capsulotomy.[54] Another study showed that capsule vacuuming reduced but did not eliminate PCO.[69] Khalifa[66] determined that vacuuming the posterior capsule had no effect on the long-term development of PCO. Therefore, vacuuming or polishing the capsule may delay the onset of PCO, but the long-term benefit is limited because PCO is mainly caused by germinative LECs in the equatorial region rather than the displaced metaplastic LECs already on the posterior capsule.[70] Also, equatorial capsule vacuuming has been found to be associated with additional surgery time and trauma and risk of capsule tears, damaging the capsular support of the IOL implant.[71,72] Davidson et al[73] suggested that near 100% removal of residual LECs at the time of cataract surgery may be necessary to prevent LEC proliferation on the posterior capsule and development of PCO. Hydrodissection-enhanced cortical cleanup after cataract surgery to remove retained/regenerative cortical material and cells has been shown to be important for PCO prevention.[14] Fine[74] modified this technique by cleaning the residual cortex in the presence of a posterior chamber IOL, which protected the posterior capsule from disruption. These studies demonstrated that hydrodissection is an effective, practical, and inexpensive method for cortex removal, but alone it does not completely eliminate LECs. The rare complications of this technique are posterior capsule rupture[75] and nuclear dislocation into the vitreous.[76] Peng et al[14] demonstrated the importance of the barrier effect of the IOL optic in preventing LEC growth and suggested that it can be a second line of defense when cortical cleanup is incomplete.

A sealed capsule irrigation device was introduced by Maloof et al[77] and other investigators.[78-81] This device consists of a foldable suction ring with 2 separate lines, one for vacuum application and the other for irrigation. The device allows the temporary seal of the capsulorrhexis after cataract removal and selective irrigation of the capsular bag with a pharmacological agent without damaging surrounding tissues. This device is minimally invasive and easy to use, fits through a small incision, is relatively inexpensive, and does not add significant time to cataract surgery and therefore shows great promise in

combating PCO. Hara et al[82] reported the advantages of a closed endocapsular ring to prevent PCO. This approach was shown to be promising in PCO prevention in the eyes of adults and children.[83,84] Recently, primary capsulorrhexis with anterior vitrectomy has been suggested to be a necessary and effective procedure to lower PCO rates in pediatric cataract surgery.[49]

IOL Materials and Designs

Since IOLs were first implanted, a wide range of improvements has been introduced specifically to prevent PCO. Among these, several advancements have been made in IOL materials and designs to improve biocompatibility assessed in terms of the eye's foreign body reaction against the IOL (uveal biocompatibility) and interaction of the IOL with residual LECs within the capsular bag, which influences LEC proliferation, migration, and EMT, resulting in anterior capsular opacification and PCO (capsular biocompatibility).[85]

There are 2 main types of materials used for IOL manufacturing: acrylic and silicone. Acrylic lenses are rigid (made from PMMA) or foldable (made from hydrophobic material such as AcrySof [Alcon Inc, Fort Worth, Texas] and Sensar [Staar Surgical Company, Monrovia, California] or hydrophilic material [also known as hydrogels] such as Hydroview [Bausch and Lomb Surgical, Rochester, New York] and Centriflex [Edge Biosystems, Gaithersburg, Maryland]). Silicone lenses were initially made from polydimethylsiloxane.[86,87]

Several clinical and experimental studies have been performed to demonstrate the role of the IOL materials and designs to reduce the incidence of PCO. Comparison of hydrophobic and hydrophilic materials showed that the type of material might influence PCO development.[88-90] Although it is well recognized that a hydrophilic acrylic material is more biocompatible,[91] IOLs made of this material have been shown to support LEC adhesion, migration, and proliferation and thus PCO development[92-94] compared with an IOL made of PMMA or hydrophobic acrylic materials.[95,96] Modification of the IOL surface, which can inhibit cell and protein adhesion, has been suggested as one of the most tolerable methods for preventing PCO because it does not require any manipulation within the eye or the use of any active or harmful agents during IOL implantation. Surface modifications of PMMA IOLs by carbon and titanium,[97] heparin,[98] and polytetrafluoroethylene (Teflon; Dupont de Nemours, Wilmington, Delaware)[99] and of silicon IOLs by oxygen and carbon dioxide plasma[100] or a sulfonate and carboxylate group containing polymer[101] have been reported to have higher biocompatibility and effectiveness in prevention of PCO. Recently, IOL surface modification by gas plasma[102] and polyethylene glycol[103] has been shown to influence LEC behavior and to prevent PCO.

Many advances have been made in IOL designs that have reduced PCO incidence. A higher PCO inhibitory effect has been observed with IOLs that provide a mechanical barrier effect on the posterior lens capsule.[2,4,19,104-106] Nishi et al[106-110] demonstrated that the sharp-edge optic IOL and the formation of a capsular bend are highly effective in reducing PCO. Adhesion of the IOL material with the lens capsule also plays a role in PCO prevention by creating a sharp capsular bend,[89,109-111] which inhibits LEC migration onto the posterior capsule. Nishi and other investigators[106,107,112,113] also demonstrated that contact inhibition of migrating LECs is induced at the capsular bend, which leads to PCO prevention. Recently, Zemaitiene et al[114] showed that there is no difference in PCO development between 3-piece and 1-piece acrylic hydrophobic IOLs.

Posterior capsular opacification is a multifactorial process. The 3 main factors for PCO development are patient related (eg, age and ocular disease), surgery related (eg, irrigation/aspiration of the capsule, hydrodissection-enhanced cortical cleanup, sealed capsule irrigation, capsulorrhexis size, and in-the-bag IOL fixation), and IOL related. It is well accepted that PCO incidence is greatly influenced by IOL material and design.[103,115] A recent meta-analysis of 23 randomized controlled trials concluded that the sharp-edge optic IOLs made of acrylic and silicone are superior in lowering the rates of PCO and laser capsulotomy.[116]

Therapeutic Agents

Improvements in surgical techniques and IOL materials and designs have lowered PCO rates but have not eradicated the problem. Therefore, despite several complications and the cost burden, Nd:YAG laser capsulotomy is still the most frequently used treatment of PCO. Consequently, the development of an alternative medical treatment of PCO is of critical importance. Alternatives include selectively destroying residual LECs while avoiding toxic effects on other intraocular tissues. Intraocular application of pharmacological agents to prevent PCO has been investigated by several laboratories, and the commonly used methods for this application are direct injection into the anterior chamber, addition to the irrigating solution, or impregnation of the IOL. Pharmacological agents such as thermosetting plastic prepared with phenol formaldehyde resins (Catalin), methotrexate, mitomycin, daunomycin, and fluorouracil have been shown to be effective in preventing PCO in vitro,[19,117,118] but in vivo studies have shown their toxicity to corneal endothelial cells, iris, ciliary body epithelial cells, and retina.[19] Studies tested cytotoxic and therapeutic agents, including diclofenac sodium,[119] saporin,[120] thapsigargin,[22] salmosin,[121] minoxidil,[122] a matrix metalloproteinase inhibitor (Ilomostat),[41] and cyclo-oxygenase 2 inhibitors.[123] These studies showed promise for finding medical treatment of PCO by targeting the survival, adhesion, proliferation, migration, and transdifferentiation of residual LECs, but the risk of their toxic effects on surrounding intraocular tissues has restricted their clinical use. Malecaze et al[124,125] provided a gene therapy approach to target LECs in the capsular bag by inducing therapeutic apoptosis by overexpression of proapoptotic genes. Walker et al[126] showed the blocking effect of an Src family kinase inhibitor on PCO development in a chick model of the lens capsular bag.

Posterior capsular opacification is a multifactorial disease and is influenced by the increased levels of several cytokines and growth factors, including TGF-β, FGF-2,

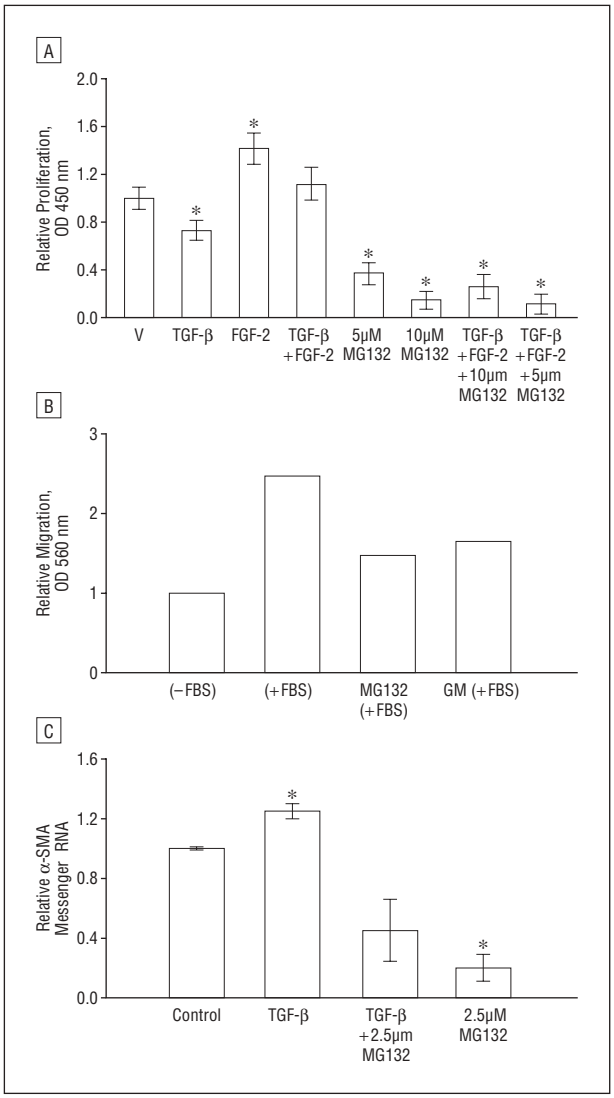

Figure 4. The proteasome inhibitor MG132 inhibits lens epithelial cell (LEC) proliferation, migration, and epithelial-to-mesenchymal transition (EMT) marker production in primary human LECs. A, Cell proliferation assay was performed by treating cells with transforming growth factor β (TGF-β) (1 ng/mL), fibroblast growth factor 2 (FGF-2) (20 ng/mL), or MG132 (5μM or 10μM), alone or in combination. After 12 hours of incubation, proliferation was evaluated with a colorimetric WST-1 assay. B, Cell migration assay was performed using a transwell chamber assay. Serum-starved cells were treated with MG132 (10μM) or matrix metalloproteinase inhibitor GM600 (GM, 10μM) and added in upper polycarbonate membrane inserts in 24-well plates. Lower wells contained Dulbecco Modified Eagle Medium with or without 20% fetal bovine serum (FBS), indicated in parentheses, as chemoattractant. After 6 hours of incubation, migratory cells were stained and quantitated by absorption at 560 nm. C, Expression of the EMT marker α-smooth muscle actin (α-SMA) was observed by means of reverse-transcriptase polymerase chain reaction analysis after 16 hours of treatment with TGF-β (1 ng/mL) and MG132 (2.5μM), alone or in combination. OD indicates optical density; V, vehicle control. Reprinted from Hosler et al[127] and Awasthi et al[128,129] with permission from the Association for Research in Vision and Ophthalmology.

hepatocyte growth factor, IL-6, and epithelial growth factor. These cytokines and growth factors differentially affect residual LEC behavior that leads to PCO development. We recently demonstrated that a reversible peptide aldehyde inhibitor of the proteasome MG132 can simultaneously block EMT markers[127] and proliferation[128] and migration[129] of LECs, suggesting that proteasome inhibition might be a good therapeutic strategy for PCO prevention (**Figure 4**[127-129]). Maloof et al[77] developed the PerfectCapsule device (Milvella Ltd, Sydney, Australia), which permits cytotoxic agents to be delivered selectively to the capsular bag, thus selectively targeting residual LECs. This device also allows cytotoxic agents to be removed after treatment during the cataract surgery procedure. Duncan et al[5] demonstrated that the applications of the PerfectCapsule device in conjunction with the cytotoxic drug thapsigargin is effective in the prevention of PCO. A recent study by Kim et al[130] showed that in rabbit eyes mitomycin is more effective than distilled water for reducing PCO and that the sealed capsule irrigation device protected the surrounding tissue from mitomycin toxicity.

CONCLUSIONS

In recent years, our understanding of mechanisms of PCO development has increased significantly; therefore, several advances have been made to improve cataract surgery techniques, IOL materials and designs, and the use of therapeutic agents. Because of these improvements, PCO occurrence has decreased, or at least PCO onset has been delayed. Nevertheless, PCO remains the most common complication of cataract surgery, especially in young adults and children. Therefore, research aimed at improving surgical techniques to eliminate almost all LECs from the capsular bag at the time of surgery, optimizing IOL biocompatibility, minimizing postoperative inflammation reaction, and targeting residual LECs by therapeutic agents that have minimal or no effect on other ocular tissues is highly desirable.

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