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MECHANISM, PREVENTION & MANAGEMENT OF *POSTERIOR CAPSULAR OPACIFICATION*- A REVIEW ARTICLE

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ABSTRACT
Expectation of patients receiving modern day cataract surgery has become similar to refractive surgery. Over the last few decades, PCO has been the most common visually disabling sequel of cataract surgery and has important medical, social and economic implications. Posterior capsule opacification (PCO) refers to the opacity that develops in the posterior capsule after cataract surgery. In recent years, with better understanding of the mechanism of PCO formation, advancement in technique of surgery, introduction of 360 degrees sharp optic edge IOLs, recognition of the importance of thorough cortical clean-up, there has been a reduction in the incidence of PCO (to < 10%). However, PCO has not yet been eradicated as it has not been possible to totally get rid of regenerative cells in the equatorial lens bow at cellular level, by any interventional method currently known. The present article reviews literature related to the mechanism, prevention and management of PCO, highlighting current concepts and developments in last few years and future endeavours to manage, prevent and eradicate PCO.

KEYWORDS: posterior capsule, Soemmering's ring, Elschnig's pearls, lens epithelial cells, Nd:YAG.

Posterior capsular opacity (PCO) is the most common late onset complication after cataract surgery.[1] After cataract & secondary cataract are synonyms for PCO. Incidence of PCO ranges from 5 – 50% in eyes after cataract surgery for senile cataract.[2,3] Ignjatovic[4] reported a higher incidence in myopes while Vasavada et al[5] reported no significant difference between myopic & normal population. Hayashi et al[6] reported higher incidence in diabetic cataract as compared to non-diabetic cataract. Incidence of PCO is decreased over past few decades with advancement in surgical techniques, IOL material & design. Visual axis opacification (VAO) due to PCO is common after cataract surgery & IOL implantation in children & reported to occur in upto 40% of patients even with primary posterior capsulotomy.[7] Incidence of VAO has been reported to be much higher in patients without primary posterior capsulotomy. Low recurrence was found in patients with Nd:YAG laser capsulotomy.

MECHANISM

PCO is of 2 types as described by Apple et al.,[10]- fibrous (Figure 1) & proliferative/pearl (Figure 2). PCO develops mainly by 3 processes- migration, proliferation & differentiation of lens epithelial cells (LECs).

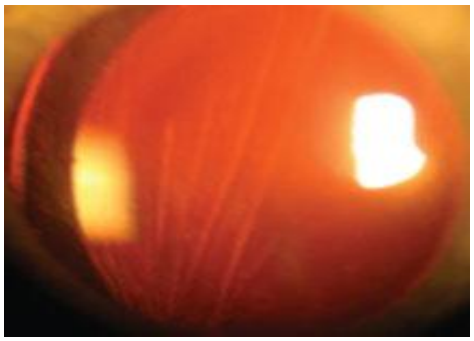


Figure 1- Fibrous PCO with posterior capsular wrinkling

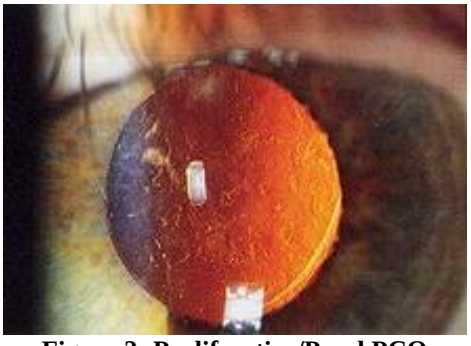
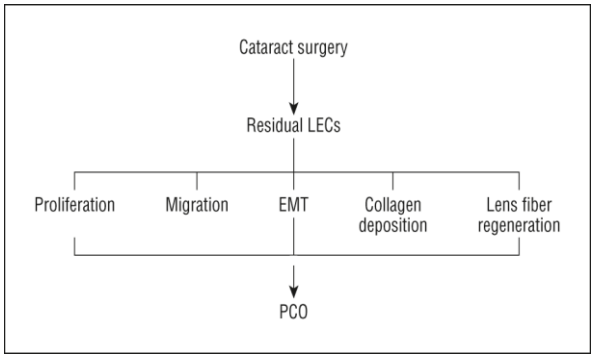


Figure 2- Proliferative/Pearl PCO



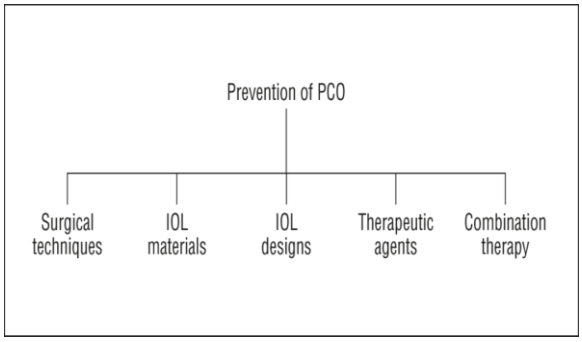
LECs are located on the inner surface of lens capsule at anterior, pre-equatorial & equatorial region. They proliferate at equatorial region throughout life to form lens fibres which are laid down in concentric manner. Fibrosis-type PCO is caused by the proliferation and migration of LECs, which undergo EMT, resulting in fibrous metaplasia and leading to significant visual loss by producing folds and wrinkles in the posterior capsule.[9] Pearl type PCO is caused by the LECs located at the equatorial lens region (bladder/Wedl cells)[8] causing regeneration of crystalin - expressing lenticular fibers and forming Elschnig pearls and Soemmering ring, responsible for most cases of PCO-related visual loss.[10,11] Proliferation occurs most frequently in the first week following surgery. Risk factors that promote proliferation are retained cortical matter, iris pigments & cells from blood due to breakdown of aqueous barrier.[9]

Studies show that levels of several cytokines and growth factors increase in aqueous humour influence the behaviour of the remaining LECs after cataract surgery. These factors include transforming growth factor β (TGF-β), fibroblast growth factor 2 (FGF-2), hepatocyte growth factor, interleukins 1 and 6 (IL-1 and IL-6) and epithelial growth factor.[12]

Wormstone et al[13] & Duncan et al[14] 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. Migration of human LECs plays an important role in the remodeling of the lens capsule[15,16] & is associated with matrix metalloproteinase activity in the lens.[17] Changes in lens capsule structure during PCO development may include remodeling of the extracellular matrix by matrix metalloproteinases. Abnormal differentiation of LECs forms bladder cells & myofibroblasts and lays down cellular material to form opacification.

PREVENTION

The modifications which could help in prevention of PCO are related to the surgical technique, IOL & use of therapeutic agents.



a) Surgical technique related

PCO is predominantly caused by residual LECs in the capsular bag after cataract surgery.[10,18,19] Several surgical techniques have been attempted for the removal of these LECs at the time of lens extraction.

1. *Continuous curvilinear capsulorhexis (CCC)*- adequately sized[20], circular CCC[21] is associated with lesser incidence of PCO.
2. *Cortical cleaving hydrodissection with rotation*- creates gap between lens capsule & cortical matter & hence helps in complete removal of cortical matter. Hydraulic force generated during hydrodissection with rotation helps remove the LECs. Multi quadrant cortical cleaving hydrodissection helps in early & complete removal of epinucleus & cortical matter.[22]
3. *Cortical cleanup*- by bimanual irrigation and aspiration in the presence of PCIOL, helps in complete removal of cortical matter especially in areas like sub-incisional part & deep capsular fornices, without disrupting the posterior capsule.[23]
4. *Polishing of anterior capsule*- has a role in decreasing fibrotic type of PCO while is less effective for proliferative type.[24]
5. *In the bag fixation of IOL*- reduces incidence of central PCO. IOL provides barrier for migration of LECs.[22] Incidence of PCO was found to be more in sulcus fixated IOLs as compared to in the bag fixation.[25]
6. *Buttonholing of posterior capsule*- posterior CCC with posterior buttonholing of IOL haptic through it can be done to prevent development of PCO. IOL optic prevents migration of LECs into retrolental space and posterior capsule over anterior edges of optic prevents formation of anterior capsular fibrosis.[26]
7. *Anterior capsule overlap of IOL optic*- difference in size of CCC causes variable anterior capsular overlap of IOL optic. The size of this CCC has not got any significant effect on severity of PCO.[27] The anterior capsular overlap leads to variable incidence of PCO formation with different IOL materials. It remains an important factor for eyes with PMMA IOLs and Silicone IOLs.[28] However, it is not a crucial factor in eyes with Acrylic IOL implantation.[29]

b) IOL related

1. *IOL design & material*- IOL optic size, edge, angular ion of haptics and material play an important role in preventing PCO. Meacock WR et al reported less PCO with 6mm optic size as compared to 5.5mm optic.[30] Sharp-edge optic IOLs made of acrylic and silicone are superior in lowering the rates of PCO and laser capsulotomy.[31] Square edge IOL optic was found to be more effective than round edge IOL optic to exert pressure on posterior capsule and reduce PCO formation.[32] Angulated IOL haptics also decrease PCO formation by inducing more pressure on posterior capsule.

Surface modifications of PMMA IOLs by carbon and titanium[33], heparin[34] & polytetrafluoroethylene[35] and of silicon IOLs by oxygen and carbon dioxide plasma[36], a sulfonate and carboxylate group containing polymer[37] have been reported to have higher biocompatibility and effectiveness in prevention of PCO. Recently, IOL surface modification by gas plasma[38] & polyethylene glycol[39] has been shown to influence LEC behavior and to prevent PCO.

Hydrogel IOLs are associated with maximum occurrence of PCO followed by PMMA & silicone. Acrylic IOL is comparatively associated with lesser amount of PCO formation.[40]

2. *Single piece versus multiple piece IOL*- there is no difference in PCO development between 3-piece and 1-piece acrylic hydrophobic IOLs.[41]

c) Therapeutic agents

Many drugs like anti-proliferative, anti-coagulant, anti-inflammatory, anti-adherence & anti-migratory, have been tried to decrease incidence of PCO.

I) *Anti-proliferative drugs*- 5-fluorouracil, doxorubicin, daunorubicin, mitomycin-c, octreotide & colchicines were tried in vitro but no outcome was significant.[42]

II) *Anti-coagulant drugs*- Irrigation of eyes with heparin solution (25 IU/ml) before implantation of IOL was significantly associated with less PCO as compared to the non-irritant group.[43] Heparin-surface-modified PMMA IOLs were associated with less incidence of PCO formation.[34]

III) *Anti-inflammatory drugs*- reduce release of cytokines and prevent proliferation of LECs.[44] Topical diclofenac[45] drops were tried in post-operative period without any significant results.

IV) *Anti-adherence & anti-migratory compounds*- prevent migration & adherence of LECs to posterior capsule. These agents include ilomastat (a matrix metalloproteinase inhibitor)[46], RGD peptide[47], mibefradil (Ca-channel inhibitor), EDTA and coating an acrylic IOL surface with MPC polymer.

Maloof et al developed the Perfect Capsule device (Milvella Ltd, Sydney, Australia) (Figure 3), which permits cytotoxic agents to be delivered selectively to the capsular bag, thus selectively targeting residual LECs.[48]

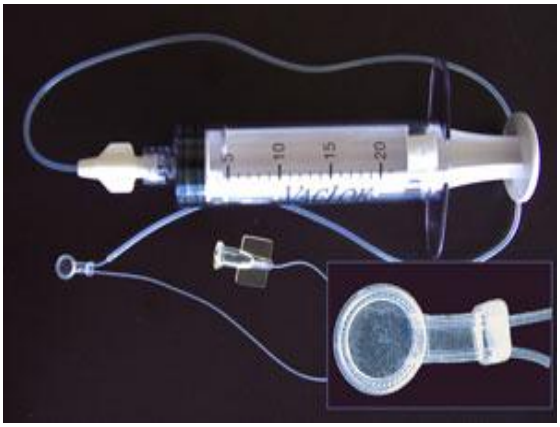


Figure 3- PerfectCapsule device, (Milvella)

MANAGEMENT

PCO involving the visual axis can cause blurring of vision, glare and decrease in visual acuity and contrast sensitivity. Management of PCO has undergone a paradigm shift in strategy and technique. It can be managed by invasive & non-invasive methods.

1. *Non-Invasive methods*

Now, Nd: YAG (Neodymium:yttrium-aluminium-garnet) laser capsulotomy[49,50,51] has replaced invasive surgery as the most common treatment modality for PCO management. It was first proposed by Aron-Rosa and Frankhauser in 1980s as an effective treatment for PCO.

CONTRAINDICATIONS OF Nd:YAG LASER CAPSULOTOMY[49,50]

I) ***Absolute***

a) Corneal scarring/edema- inadequate visualisation of target aiming beam
b) Glass IOL- chances of fracture of glass IOL
c) Inability to maintain stability of eye- risk of inadvertent damage to adjacent intraocular structures.

II) ***Relative***

a) Active intraocular inflammation- gets aggravated by the procedure
b) Cystoid macular edema- due to laser induced breakdown of barrier functions of posterior capsule
c) High risk of retinal detachment

TECHNIQUE[52,53]

I) *Pre-operative Assessment*- complete ophthalmology all history & examination should be carried out before proceeding
a) Direct ophthalmoscopic visualisation of PCO- most reliable method for assessment
b) Slit lamp biomicroscopy & retro illumination
c) Laser interferometry to assess potential vision

d) Optical coherence tomography & fundus fluorescein angiography in suspected cases of cystoid macular edema.

II) Preparation of patient

a) Informed consent explaining the nature & consequences of the procedure is taken
b) Pupillary dilatation is not required unless the pupil is miotic or surgeon is inexperienced. The visual axis is marked with a single laser spot in the centre before dilatation
c) Topical anaesthesia is generally not required unless contact lens is used. Peribulbar anaesthesia is used rarely in cases of nystagmus.

III) Procedure

a) Abraham central contact lens / Peyman lens can be used to stabilise the eye, improve laser beam optics & for accurate focussing
b) Minimum amount of laser energy is used to create capsular opening (1-2mJ/pulse)
c) Stress lines are seen as wrinkles in the posterior capsule & shots are placed at these stress lines for maximum effect per shot
d) Laser shots are given at posterior 150um from a datum point to avoid IOL damage
e) Types of opening
i) *Cruciate opening*- extends from 12 o'clock to 6 o'clock position. Post procedure glare and increase in vitreous floaters can occur
ii) *Can opener method*- laser capsulotomy is done along the circumference of the optic. It prevents potential damage to IOL in the visual axis, but the cut capsular fragment might obscure the visual axis
iii) *Inverted-U method*- capsular fragment remains attached to inferior part of opening. But it is associated with the problem of early visual recovery as time is needed for flap to sink in intravitreal space due to gravity and to get contracted
iv) *Circular pattern with vitreous strand cutting*- includes the conventional procedure along with cutting of vitreous strands attached to capsular fragment by laser
f) *Size of opening*- capsulotomy size should be large enough to cover the pupil under mesopic conditions and avoid glare from edges that occurs during night driving. Small opening is better in eyes with dense membrane that gives excellent optics as well as in eyes at risk of retinal detachment.

IV) Postoperative care

Immediately after the procedure, topical anti-glaucoma agents should be administered in the eye to minimise post procedure IOP spike (which is transient in most cases). In cases of advanced glaucoma, oral hyper osmotic agents can be used during and after the procedure.

Topical antibiotics are instilled after the procedure if contact lens is used. Topical steroids and cycloplegics can be given on an individual basis.

COMPLICATIONS[51]

I) Rise in IOP- due. To trabecular meshwork block (by debris, inflammatory cells, liquid vitreous) or pupillary block. Peak elevation occurs within 6hours of capsulotomy which usually returns to baseline within a week.
II) Cystoid macular edema(CME) (0.5-2.5%) – due to shockwave damage to vitreous & release of inflammatory mediators.
III) IOL pitting/damage (9.4-33%)- degree of damage depends on nature of IOL material, highest damage occurs to silicone IOLs and lowest to acrylic IOLs. Glass IOL might fracture after Nd:YAG capsulotomy. IOL pitting in visual axis can cause degradation of image quality and glare
IV) Retinal Detachment(RD) (1.6-1.9% cases over 3 years)- It might be due to increased rate of post procedure posterior vitreous detachment. Increased risk of retinal detachment was found in patients with previous history of retinal detachment, axial length > 24mm & lattice degeneration.
V) Iritis
VI) Malignant glaucoma
VII) Endophthalmitis
VIII) IOL displacement
IX) Macular hole

RESULTS

Improvement in visual acuity was reported in most of the eyes with PCO, after Nd:YAG capsulotomy.

Stager et al. evaluated the effectiveness of Nd: YAG laser capsulotomy for the treatment of PCO in children with acrylic IOLs. A total of 51 eyes (70%) maintained a clear visual axis after a single Nd: YAG procedure, 10 eyes (84% cumulative) after two procedures and another 3 eyes (88% cumulative) after three procedures (follow-up period range: 3–92 months; median: 25 months). They concluded that Nd: YAG laser capsulotomy is an acceptable option for the management of PCO a er acrylic IOL implantation in children.[54]

In a prospective study on 474 patients with PCO who had Nd: YAG laser capsulotomy, Bhargava et al. found a significant relation between mean total laser energy and complications like IOL pitting, IOP rise, CME and retinal detachment. They concluded that subtype of PCO and IOL fixation significantly influences laser energy required for capsulotomy, whereas IOL biomaterials did not. Rate complications like IOL pitting, uveitis, IOP elevation, RD and CME was significantly more when total laser energy delivered to treatment site was higher.[55]

2. *Invasive methods*- surgical removal of capsular opacity is done in selected cases.

INDICATIONS

I) Visual axis opacification in young children.
II) Thick PCO.
III) Cases where Nd:YAG laser capsulotomy is ineffective in clearing visual axis.

TECHNIQUE

Posterior capsule can be approached by 2 routes- limbal & pars plana routes.

Surgical removal of PCO using 25guage transconjunctival sutureless vitrectomy in children was evaluated by Lam et al. All cases showed significant visual improvement.[56]

Pars plana capsulotomy in cases with PCO in which Nd:YAG laser was not successful in clearing the visual axis was performed by Mitra et al and they found success in penetrating the thick pupillary membranes.[57]

COMPLICATIONS[58]

I) Vitreous loss.
II) Endophthalmitis.

CONCLUSION

PCO is a physiological complication of uneventful cataract surgery. Main culprits are LECs that proliferate & form PCO. Despite advances in our understanding of the mechanism of PCO formation, it remains a significant problem, although there has been a reduction in its incidence. 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. Biological mechanisms leading to PCO formation have now been revealed and agents to inhibit these signalling systems are currently under evaluation. Nd:YAG laser remains the treatment of choice for managing PCO, though correct technique should be used to prevent complications.

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