

Posterior Capsule Opacity Rate Superiority Claims for IOL Studies Study Controls

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1. What factors should be considered in choosing an appropriate control IOL?

For the best comparative study, the control IOL should optimally be equal to the study IOL in all important variables (those which are known or suspected to affect PCO incidence) *except the variable to be studied*. Consequently, a study which showed a statistically significant PCO reduction in the experimental lens could be attributed to the specific design change put forward by the manufacturer.

Alternatively, a "gold standard" control IOL could be an IOL presently on the market that has been used for years such as the PMMA lens with optimalization of other variables such as lens shape -perhaps biconvex with sharp edge -but lacking the newer innovations e.g. more adhesive material found in silicone or acrylic lenses.

The variables in lens design which have been shown to impact PCO incidence are:

1. Intraocular lens shape (Schaumberg 1997, Nishi 1999) Biconvex shape demonstrates less PCO than plano convex possibly because of increased contact area between the lens and the capsule inhibiting lens epithelial growth.
2. Intraocular lens optic edge-In a retrospective study by Nagata and Watanabe 1996, eyes with sharp edged PMMA IOLs had significantly lower degree of PCO than eyes with round edged PMMA IOLs. They postulated that the sharp posterior optic edge created a capsular bend which induced contact inhibition of migrating lens epithelial cells. Peng et al 2000 confirmed this in postmortem studies.
3. Intraocular lens loop angle-Increased posterior capsule angulation (eg 10 degrees compared to 6 degrees) could result in more contact with the posterior capsule and less ingrowth of lens epithelial cells (Wang 1999)
4. Intraocular lens material- It is suggested that lens materials that are more adhesive to the capsule decrease PCO. Hayashi (1999) found more PCO with PMMA lenses than with silicone or soft acrylic lenses. Olson et al 1998 reported more PCO in PMMA IOL than the silicone IOL. Hollick et al (1997) reported less PCO in acrylic lenses as compared to silicone or PMMA.
5. Surface modification of intraocular lens-In vitro fewer lens epithelial cells adhere to heparin surface modified and poly-HEMA lenses than on PMMA lenses (Power et al 1994) In a clinical studied by Winther-Nielsen et al 1998, HSM convex plano laser ridge IOL had higher PCO rate than unmodified convex-plano lens. The authors admitted their study was weakened by inclusion of 7 surgeons which could lead to different amounts of posterior capsular cleaning and capsulorhexis techniques.

Variations in surgical technique can impact on PCO rate.

1. Capsulorhexis size-Ravalico et al 1996, reported that capsulorhexis with slightly smaller diameter than the IOL optic decreased PCO incidence when compared to large size capsulorhexis.

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2. Cortical Cleanup-More thorough cortical clean up will remove more lens epithelial cells and presumably decrease risk of PCO (Nishi et al 1999, Peng et al 2000). Posterior capsule vacuuming should also decrease number of lens epithelial cells.

3. IOL Placement-Placement of IOL in the capsular bag rather than the ciliary sulcus should decrease PCO incidence (Schaumberg et al 1998)

Is there a "gold standard" control lens that could be designated by FDA?

No. There does not appear to be a lens on the market presently which is agreed upon as the gold standard. In Hollick et al's 1999 paper demonstrating less PCO at 3 years in the Alcon Acrysoft acrylic lens, the other lenses studied were the Alcon MC60BM PMMA lens and the IOLAB L141U silicone lens. All lenses were biconvex with 6 mm optics although the silicone lens had 5 degree haptic flexions and the other two lenses had 10 degree flexions. Hayashi et al in 1998 compared the Alcon Acrysoft acrylic lens, the Alcon MZ60BD PMMA lens and the AMO silicone SI 30-NB. All had 6.0 mm optics. Olsen et al in 1991 compared the silicone AMO SI 30 with an unnamed PMMA lens.

The most informative study would be similar to those performed by Hollick's group who compared similar shaped (biconvex) and similar sized optic (6.0 mm) IOLs made of acrylic, silicone and PMMA to determine the impact of lens material on PCO rate. It would be optimal to have the control lens similar to the experimental lens in all variables except the one to be studied. Presently, it appears that PMMA lenses have a higher rate of PCO than either silicone or acrylic. Consequently, a PMMA lens such as the Alcon MC60BM *could* be chosen as the minimal standard of control although it seems scientifically restrictive to recommend a specific "gold standard" IOL.

Is there a "gold standard" PCO rate that could be designated by the FDA?

Schlote et al reported in 1895 that 30% of eyes developed secondary cataract. Schaumberg et al in 1997 reviewed the 22 published studies on the incidence of posterior capsule opacification and used a weighted linear regression model to estimate an incidence of PCO at 1 year of 11.8%, and 3 years of 20.7% and at 5 years of 28.4%. Remarkably, the 5 year PCO incidence of 28.4% reported by Schaumberg is approximately the same as the 5 year PCO incidence of 30% reported by Schlote in 1895! This 5 year incidence of 28.4% would likely be fairly accurate but few studies will have this duration.

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PCO incidence in individual studies vary from a 1 year incidence of 3% (Barrett 1986) to 30% (Martin 1992) ; a 2 year incidence of 10% to 50% (Kappelhof 1992), and a 5 year incidence of 11% (Leisgang 1989) to 50% (Aron-Rosa 1992).

Consequently, case controlled comparative studies or similar investigative efforts will likely remain the preferred way to determine whether PCO incidence can be lowered by alteration in IOL or surgical technique although Schaumberg's data could be used as a guide.

What factors are important to be matched in the trial and control populations?

Age should be be matched and most studies performed have addressed the age of the patient and type of cataract (e.g. exclusion of traumatic cataracts). Speed of PCO development in a 10 year old was reported by Tetz et al 1999 to be more than triple that of a 70 year old. The importance or lack thereof of sex on incidence of PCO does not appear to have been examined.

Because of the potential influence of various ocular and medical diseases on PCO incidence some researchers exclude patients with these potentially confounding conditions from the study population. Hollick et al 1999 excluded patients with history of any ocular disease, intraocular surgery, laser treatment, diabetes requiring medical control, glaucoma, previous uveitis and any posterior segment pathology precluding a postop vision of 20/40 or better. Patient using topical medications (not including artificial tears) or systemic steroids were excluded.

There may be more PCO in eyes with severe proliferative retinopathy (Dureau et al 1997) but there is no conclusive evidence that there is accelerated PCO in other diabetics. Retinitis pigmentosa, pseudoexfoliation, glaucoma, uveitis and possibly high myopia (Tetz 1999) may be associated with increased incidence of PCO.

It would be helpful to match age in the trial and control populations. It would be beneficial to exclude patients with glaucoma, retinitis pigmentosa, uveitis, high myopia, pseudoexfoliation, use of immunosuppressive or cytotoxic agents, or previous use of cytotoxic drugs, total body irradiation or previous ocular trauma.

Optimally, surgical procedure should use a standard capsulorhexis size, standard degree of cortical cleanup and capsular polishing and use of intra-op and post-op meds. Use of a limited number of surgeons or just one surgeon would also limit variation in technique. Ideally, surgical technique and IOL variables should be matched between the experimental and control populations *except for the variable being altered in the trial population* e.g. IOL material, size of capsulorhexis, size of IOL optic.....