Posterior capsular opacification after cataract surgery

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ARTICLE

Abstract

This is a review of the current status of clinical research on the prevention of posterior capsular opacification (PCO), which is now the commonest complication of cataract surgery occurring in up to 50% of patients by 2 to 3 years after the operation. PCO is caused by lens epithelial cells retained in the capsular bag following surgery which then proliferate, migrate and transform to myofibroblasts. Interest in the prevention of PCO has centred around surgical technique, pharmacological methods to remove or destroy lens epithelial cells and changes in intraocular lens material and design. Changes in surgical technique have little effect in prevention of PCO although a capsulorhexis size which lies on the optic diameter appears to be beneficial. Many different cytotoxic drugs and pharmacological agents have been used experimentally to prevent PCO but the problem has limited damage only to lens epithelial cells. So far, no method has been shown to be safe for clinical use. Current interest is centred once again on the intraocular lens itself, particularly the material that it is made from and changes in its edge profile.

Key words Cataract surgery, Intraocular lens, Posterior capsular opacification.

The change from extracapsular cataract surgery to phacoemulsification has removed many of the wound-related problems from cataract surgery but we are still left with significant problems related to the implant itself such as decentration and posterior capsule opacification (PCO). PCO is now, in effect, the commonest complication of cataract surgery, requiring treatment in up to 50% of patients by 3 years post-operatively,[1] and the rate of PCO seems to have remained unchanged in recent years.[2] PCO can be easily treated with YAG laser capsulotomy but this carries a small risk of medical complications such as raised intraocular pressure, cystoid macular oedema or retinal detachment. PCO usually takes about two years to develop after surgery and there are considerable problems in screening elderly patients for PCO when many will now have been discharged within a few weeks of surgery. They and their family doctors frequently have little insight into their failing vision, believing that as they have already had cataract surgery any further deterioration is due to 'old age' and that nothing further can be done. Once PCO has been suspected this is compounded by the logistics of getting elderly people back to hospital for treatment. Another extremely important factor that is often overlooked is that in the developing world PCO is a major bar to implant surgery as there is often not the finance, equipment or expertise readily available for its treatment. In view of these problems there is now considerable interest in strategies to reduce PCO. These fall into changes in surgical technique, drugs or toxins to destroy lens epithelial cells, and changes in implant design or material.

Pathology of PCO

At surgery it is physically impossible to remove all lens epithelial cells from the capsular bag; those that remain proliferate and undergo metaplasia. In an aphakic eye they cover the posterior capsule after surgery and can be thought of conceptually as the normal wound-healing response. A major advance in PCO research has been the development of *in vitro* 'organ culture' systems in which the isolated human capsular bag can be maintained in culture medium for over a year, allowing the cellular changes to be studied.[3] Tissue culture studies have shown that within days of surgery the residual cells have proliferated to cover the posterior capsule surface completely. They have a tendency to spread along folds in the posterior capsule and considerable remodelling and fibrous metaplasia takes place as they grow. PCO has two basic forms: Elschnig's pearls and fibrotic changes. Traditionally it is thought that the cells in the equatorial region are the most mitotically active and are the most important in contributing to PCO, particularly pearl formation, but the anterior capsular epithelium has the same embryological origin and the role of these cells is still not fully understood. After surgery the lens epithelial cells around the rhexis express alpha smooth muscle actin,[4] a

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marker for myofibroblast differentiation, and may contribute more to the fibrotic appearances seen after surgery. Organ culture allows the cellular events to be studied in isolation. The lens epithelial cells can survive and grow in protein-free medium containing only amino acids, but proliferate more rapidly with increasing concentration of protein in the culture medium. This is an interesting analogy to the increased PCO which is seen in diabetics and uveitis patients. Clinical studies suggest these patients are more likely to develop fibrotic changes than pearls.[5]

Such experiments will be be invaluable in dissecting out the role of cytokines and growth factors in the promotion of lens epithelial cell growth after surgery.

Quantification of PCO

To study the influence of various parameters on PCO we need to be able to measure the amount of PCO. Until recently this has been done by YAG rates. Although this is a clinically relevant parameter it is in fact a surrogate marker of PCO, depending on such factors as when the patient complains of symptoms, when the surgeon offers treatment, the accessibility of a YAG laser and financial factors. YAG laser capsulotomy is the second highest call on Medicare in the USA after cataract surgery, costing $250 million in 1993.[6] At St Thomas' Hospital we have developed a system to quantify PCO by analysing high-resolution retroillumination images obtained through a purpose-built system with dedicated software.[7] The digitised images have a resolution of 25 000 pixels per square millimetre, allowing exceptional detail of lens epithelial cells to be seen. Computerised image analysis of these images offers the possibility of an objective and more sensitive method of assessing PCO thereby shortening the length of follow-up required for clinical studies of a process which takes 2 to 3 years to reach a clinical outcome. Previous systems have used analysis programs based on intensity thresholding where dark pixels in the image equate to opacity.[8] This approach creates difficulties in being unable to compensate for changes in the image of background illumination from uneven fundus reflection and changes in illumination between follow-up visits or from varying contrast and highlights in areas of PCO. To avoid these problems we have developed purpose-designed software, derived from military software, where the image is analysed by texture, opacity being defined as areas of high texture in comparison with clear areas where the texture is low. Experience shows this has major advantages. It measures percentage area of PCO in each image to an accuracy of ±10% but has the disadvantage that the area does not necessarily correlate with 'severity' or visual function. The reason for this is that we see PCO as backward-scattered light from the opaque capsule whereas the patient's symptoms are due to the forward-scattering of light by the opacity casting a veiling luminance over the retina. At present we are working to correlate mathematical measures of severity with psychophysical tests of light scattering in the eye.

Clinical studies on PCO

Clinical studies on PCO need to be planned meticulously to avoid confounding variables, and the prospective randomised trial must be the gold standard. Inclusion criteria have to reflect a homogeneous group of patients excluding, for example, younger patients, diabetics or traumatic cataracts together with patients who have ocular structural abnormalities, previous surgery or laser treatment as these might predispose to PCO. Surgery should be performed by a single surgeon using a standardised technique with a standarised therapeutic regime post-operatively.

The effect of surgical technique on PCO

Many studies have tried to manipulate surgical technique to reduce PCO but these have shown little clinical benefit. Phacoemulsification, with reduced damage to the blood–aqueous barrier, good cortical clean-up and capsulorhexis, might be expected to be associated with less PCO, but this has yet to be proven. Routinely polishing the posterior capsule at operation is of no benefit.[9] The lens epithelial cells cannot be removed from the equator by polishing but those from the anterior capsule can. The benefit of removing these cells remains unproven, probably because it is difficult to ensure their complete removal unless meticulous bimanual techniques with specially designed currettes are used; these add to the length and complexity of the operation.

Some surgeons have expressed the belief that if the capsulorhexis is larger than the implant it will allow fusion of the anterior and posterior capsules post-operatively, confining lens epithelial cells to the equator and restricting their proliferation onto the posterior capsule. We tested this hypothesis by randomising two groups of patients to insertion of a 5.5 mm diameter PMMA intraocular lens (IOL) with a rhexis either totally on or off the anterior implant surface. To our surprise we found a totally different pattern of PCO between the two groups, with those patients who had a rhexis larger than the implant developing extensive wrinkling of the capsule within weeks of operation. This fibrotic wrinkling failed to provide a barrier to lens epithelial cell migration and these patients went on to develop more PCO and decreased vision over the first year after surgery in comparison with the patients in whom the rhexis lay completely on the IOL surface.[10] Patients with the rhexis totally off the IOL surface had much less capsular wrinkling and developed slower migration of cells onto the posterior capsule. We believe that the explanation is that a large rhexis allows the anterior capsular epithelium to come into contact with the posterior capsule and migrate forwards. These cells manifest alpha smooth muscle actin and differentiate into myofibroblasts producing the wrinkling; if the capsular flaps are separated by the implant their access to the posterior capsule is restricted. Many factors influence the choice of rhexis size but our conclusion was that in terms of reducing PCO it is better to have the

anterior capsule completely in contact with the IOL surface. The worst results are seen in those patients where the rhexis lies asymmetrically on and off the IOL allowing uneven forces on it. In this situation there is excessive wrinkling and lens epithelial cell migration producing early and severe PCO.

Pharmacological destruction of lens epithelial cells

Osmotic hydration, cytotoxic drugs, immunotoxins, antiprostaglandins and calcium blockers[11–13] have all been used to destroy residual lens epithelial cells. The problem lies not in destroying the cells but in limiting the damage to the lens epithelium and protecting the rest of the eye. For this reason, and the enormous cost of developing and proving the ocular safety of these systems, few have ever made the transition from the laboratory to human trials.

Perhaps the most clinical work has been done on a human monoclonal anti-lens epithelial cell antibody produced in a mouse hybridoma and linked to ricin A.[14] Ricin, derived from the castor oil plant, is one of the most toxic substances known to man. It destroys cells by blocking intracellular protein synthesis. The molecule consists of two chains: the B chain, which is responsible for attachment and binding to the cell, and the A chain, which destroys the cell. Without the B chain the A chain does not attach and is non-toxic. To produce the antibody the molecule is cleaved at a disulphide bond and the binding chain replaced by a monoclonal antibody targeting the toxin to lens epithelial cells, the so-called magic bullet concept. This toxin has been developed and refined over a number of years and has been used in a number of FDA-approved studies. We have recently completed a double-masked prospective ocular safety study at St Thomas' Hospital.[15] Following the injection of toxin into the anterior chamber at the end of surgery our patients showed increased uveitis post-operatively which was usually subclinical and had settled by 4 weeks after surgery. We found no overt evidence of corneal or trabecular toxicity and by 6 months the toxin appeared to reduce PCO although the response was variable and sometimes partial. The immunotoxin offers an interesting way of controlling PCO at the expense of some increased post-operative inflammation. Large-scale clinical trials are needed to establish whether the risks of this outweigh the benefit.

Intraocular lens design and materials

The influence of IOL lens design on PCO has been recognised for many years. Virtually all IOLs are manufactured now in a biconvex format so that the posterior capsule and optic surface are apposed – the no space, no cells concept.[16–18] PCO research took a major step forward when Alcon introduced their AcrySof lens in 1994. This lens was a novel matrix of two crosslinked polymers – phenylethyl acrylate and phenylmethyl methacrylate – developed as a high refractive index foldable IOL alternative to silicone. Serendipitously in early clinical trials the lens was found to have unique characteristics, totally different from other IOL materials.

Work in our department and now elsewhere has established that this lens has exceptionally low PCO rates in comparison with PMMA and silicone disc lenses.[19,20] Three years after surgery we found areas of PCO to be 57% for PMMA, 39% for silicone and 9% for AcrySof – a highly significant result that was reflected in YAG rates of 26% for PMMA, 14% for silicone and 0 for AcrySof.[21] AcrySof has other characteristics such as reduced anterior capsule fibrosis and stability of the anterior capsule on the IOL surface.[22] These are features that are clinically important in preventing tilting and decentration of the lens post-operatively, and this lens is very stable even when the rhexis has torn out. With our high-resolution imaging system we have also observed that in some eyes lens epithelial cells grow onto the posterior capsule in the first few weeks after operation but then regress, a unique phenomenon not seen with other IOL materials.[23] Pathologically, eyes with Acrysof IOLs have reduced Soemmering's ring formation (presented by David Apple, ESCRS 1998).

The question arises of why AcrySof behaves so differently in the eye. Studies for FDA approval showed no evidence that the polymer was toxic to lens epithelial cells or contained leachable monomer. Recent Japanese work has drawn attention to the IOL edge profile and the fact that AcrySof has a squared edge in comparison with the rounded edge of other IOL materials.[24] Nishi has shown both *in vitro* and in animal studies (presented at ESCRS 1998) that lens epithelial cell migration is inhibited at a square edge and our own clinical studies support this. However, the edge profile will not explain the anterior capsule stability or lens epithelial cell changes. AcrySof is also unique in that the IOL has a tacky surface and Japanese work shows the capsule adheres to the implant.[25] We feel that a tight seal between the capsule and the IOL is likely to be an important additional factor in restricting access of aqueous and nutrients to the lens epithelial cells leading to cell atrophy and apoptosis.

Conclusion

The advent of AcrySof IOLs has focused commercial attention on the problems of PCO and the benefits of its prevention, and for the first time has provided a clinically effective technique that does not have side effects. It is interesting that as the mechanism of action of the lens becomes better understood research is becoming focused once again on the importance of IOL materials and design. It is highly likely that the next generation of IOLs will have inherent advantages in protecting the eye from PCO, and it is remarkable that this can be achieved without the problems of drug toxicity. The impact on cataract surgery and blindness in developing countries will be enormous.

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