A thesis submitted for the degree of Master of Philosophy (Surgery) of the Australian National University

The effect of Xylocaine Hydrodissection on posterior capsule opacification after cataract surgery

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SIGNED ____________________________________________________________

THOMAS DAVID WALKER

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ABBREVIATIONS

5FU – 5-FLUOROURACIL
AMD – AGE-RELATED MACULAR DEGENERATION
BAB – BLOOD AQUEOUS BARRIER
BCVA- BEST CORRECTED VISUAL ACUITY
DALY- DISABILITY ADJUSTED LIFE YEAR
DNA – DEOXYRIBONUCLEIC ACID
ECCE – EXTRA CAPSULAR CATARACT EXTRACTION
EDTA – ETHYLENEDIAMINE TETRAACETIC ACID
FGF– FIBROBLAST GROWTH FACTOR
ICCE – INTRA CAPSULAR CATARACT EXTRACTION
IOL – INTRAOCULAR LENS
MMC – MITOMYCIN-C
ND:YAG- NEODIMIUM:YTTRIUM-ALUMINIUM-GARNET LASER
OCT – OPTICAL COHERENCE TOMOGRAPHY
PCO – POSTERIOR CAPSULE OPACIFICATION
PXF– PSEUDOEXFOLIATION OF THE LENS CAPSULE
QALY – QUALITY ADJUSTED LIFE YEAR
RNA – RIBONUCLEIC ACID.
RR – RELATIVE RISK
TASS – TOXIC ANTERIOR SEGMENT SYNDROME
TGF – TRANSFORMING GROWTH FACTOR
UVA – ULTRAVIOLET LIGHT BAND A
VEGF – VASCULAR ENDOTHELIAL GROWTH FACTOR
Abstract

BACKGROUND

The purpose of this study is to assess the efficacy in reduction in posterior capsule opacification following cataract surgery by the use of Xylocaine brand of lidocaine 1% unpreserved 1 mL as hydrodissection fluid replacing balanced salt solution.

METHOD

The author performed all surgeries without any change in lens design or operative technique except for the change in hydrodissection fluid. There was no increase in complication rate of surgeries performed with Xylocaine as compared to those with balanced salt. The efficacy of the change in technique was assessed by the change in incidence of neodymium:yttrium alluminium garnet (Nd:YAG) laser requirement which was separately assessed by an independent ophthalmologist. Minimum follow up exceeds two years with a maximum of eight years.

RESULTS

Xylocaine hydrodissection in this series did not reduce the already decreasing incidence of posterior capsule opacification at the 2 year review. The ‘p’ value was 0.855 representing no significant difference. The result must be seen against the general improvement worldwide and also by the author in the reduction of posterior capsule opacification to less than 5% over the years by improving operative techniques, lens materials and lens designs.
CONCLUSION

Hydrodissection with unpreserved Xylocaine 1% mL is safe, and cheap and requires no change in surgical technique.

Xylocaine is known to be toxic to some bacterial cells and in a dose dependent relationship with corneal endothelial cells. A further larger double masked prospective trial would cover a shorter time span and eliminate the comparison with an overall trend line. There are very few safe pharmacological methods currently available clinically for PCO reduction and none in common use.

KEYWORDS

Cataract surgery, posterior capsule opacification, Xylocaine unpreserved brand of lidocaine local anaesthetic.
CHAPTER 1

Introduction

The hypothesis involved is that the opacity that occurs in the posterior capsule following some lens surgeries can be reduced by using Xylocaine brand of unpreserved lidocaine 1% 1 mL during the hydrodissection technique. The preparation is the product of Astra-Zeneca (Sydney Australia) and is used throughout this surgical series. It is strongly recommended that the findings herein be not transferred to any other product branded as “equivalent” or “generic” because there are issues with pH, osmolality and buffers in other preparations which may be toxic to the corneal endothelium as will be discussed later. (Spalton, 1999) In quoting references, the original words of the author whether lidocaine, lignocaine or Xylocaine are used and no transposition is assumed.

The word “cataract” describes the opacification of the crystalline lens of the eye. The word owes its origin to the erroneous belief that a sort of curtain fell down like a waterfall from the “humour” of the brain. (May and Worth, 1954) In fact, the lens protein becomes denatured and disrupted destroying the optical clarity.

The importance of a good long term surgical result is emphasised by taking a global view of the problem. Cataract is the most common cause of treatable blindness in Australasia and most of the world and posterior capsule opacification post operatively is the most common unwanted result. The essential success of any lens surgery lies in maintaining a perfectly clear posterior capsule permanently. (Findl et al., 2007) (Pandey et al., 2004, Apple et al., 2001, Apple et al., 2000) Any technique that improves the permanent clarity of the capsule, even by a small percentage, benefits the individual and the community both socially and economically.
Although often overlooked, vision loss must be one of the archetypal chronic diseases of adults. (Taylor et al., 2007)

Cataract surgery “is now extraordinarily successful”. (Taylor and Keefe, 2002) “Cataract removal and intraocular lens (IOL) implantation is by far the most common and one of the most successful of all operations in all of medicine” (Survey of Ophthalmology Editors, 2000) and probably the most common surgery performed around the world each day because there is no effective medical treatment for cataract. (Toh et al., 2007). Surgeons in India perform more than 4 million operations each year. (Nirmalan et al., 2006)

Cataract is usually due to ageing but may also follow trauma, intraocular or systemic inflammation, systemic metabolic diseases (especially diabetes mellitus), corticosteroid therapy (local or systemic), congenital and hereditary factors, irradiation (including Ultraviolet), and smoking. Multiple risk factors may be operative in any one individual. Some causes are still unknown (West, 2007). A survey among older Australians estimates that at least 444,400 persons aged over 55 years are visually impaired to some extent, representing 9.4% of that group. Senile cataract is the largest subgroup. (Bennett and Australian Institute of Health and Welfare, 2005)

The incidence of clinically significant cataract reaches almost 50% of persons over 75 years because of reduced visual acuity and contrast sensitivity and glare interfering with function. (Bennett and Australian Institute of Health and Welfare, 2005)

The definition of ‘legally blind’ (that is entitlement to a disability pension on the basis of vision loss) is central vision of less than 6/60 (Snellen) corrected in the better eye. (allowance can also be made for visual field defects). Centrelink Australia records indicate that 0.8% of all pension recipients are in this category. But this underestimates the true number as many were receiving a pension before
they became legally blind and the reclassification is not done, as it may make no
difference to their pension payment. (Bennet and Australian Institute of Health and Welfare, 2005)

In USA, over the years 1991-1999, “the clinical diagnosis of major chronic eye
diseases associated with ageing increased dramatically in a longitudinal sample. At
the end of nine years, nearly half of the sample of surviving US Medicare
beneficiaries had at least one of these diseases. (Lee et al., 2003)

Cataract is the main treatable cause of visual loss but others are age related macular
degeneration (AMD), glaucoma and diabetic retinopathy and these may all occur
coincidentally. This means that even after a technically successful cataract surgery
the vision may still be impaired to some degree if there is comorbidity. Long term
cigarette smoking and Ultraviolet-B exposure bring on cataract earlier and
probably are summative in effect. (Bennet and Australian Institute of Health and Welfare, 2005)

The impact of the visual loss on the individual can be severe, causing not only
depression because of isolation, loss of quality of life, loss of independence, social
relationships and sensory stimulation, but also increasing the risk of falls and
injury with subsequent hospitalisation and costs to the community. (Bennet and Australian
Institute of Health and Welfare, 2005), (Klein et al., 2006, Owsley and McGwin, 2007) The health system cost
of cataract surgery per person in Australia in 2005 was $178. (Access Economics, 2008)

The importance of keeping the ageing population independent of government and
volunteer services has been emphasised recently by the Australian Government’s
programmes to assist in keeping older Australians at home for as long as possible
rather than admission to hospital or hostel. The burden of dependence of this group
of persons on external care is not only in the cost of services provided by
government agencies but in the immeasurable cost of volunteer help and the
restriction of employment on family members acting as volunteers or carers who
would otherwise be in the workforce. This restriction on the life of carers has a cumulative effect on their future lives by limiting their work experience and therefore job opportunities when their care role ends.
CHAPTER TWO

History and Perspectives

The identification of cataracts goes back at least to the code of Hammurabi in Babylon around 2000 BC. The Egyptians around 1600 BC wrote of the problem and their techniques appear to be variations on couching (that is pushing the complete lens into the vitreous by rupturing the zonule after inserting a broad knife through the corneoscleral junction of the eye). This technique may have been brought from Greece at the time of Alexander when he invaded Egypt in 336 BC. This technique was also mentioned by the Roman, Celsus around 25AD probably with little change.\(^{(Porter, 1996, Oguz et al., 2004, Chua, 2000)}\)

The Turkish surgeon Serefeddin Sabuncouğlu (1385-1468) performed cataract surgery using sharp pointed straight flat forceps instead of a knife for the incision then couching the cataract into the vitreous with the same instrument slightly opened.\(^{(Oguz et al., 2004)}\)

Extraction of the opaque lens was probably practised in the 17\(^{th}\) and 18\(^{th}\) centuries in Europe but the practitioners guarded their knowledge against competitors and documentation is poor.

About this time a more scientific approach to medicine was emerging and it was widely accepted that the cause of the cataract was not washing down of the cerebral fluid into the eye from the brain but that the opacity was in the lens itself. Removal of the opaque material was performed in France in 1722 by Mery and later Daviel in 1748, the latter being commonly credited with the honour. By making a large incision in the eye at the limbus and then, after opening the anterior capsule with serrated forceps, the opaque material was expressed. Sutures were not possible and the patient’s head needed to be kept immobile (and bowels confined) for 2 weeks.\(^{(Chua, 2000)}\) This left the patient aphakic and with a need of thick
spectacles of at least +10 dioptres for distance and separate stronger reading glasses. This was the beginning of extracapsular lens extraction without implant and without sutures. Fine sutures were not then available so human hair was later used. Despite the large incision many patients benefited though complications were common. The technique reached its peak with the work of Von Graefe and his famous cataract knife. The impressionist painter Monet had one successful cataract removal and subsequently revised his famous paintings of the bridge in his garden in Giverny because the brown cataract had filtered the blue end of the colour spectrum from his vision. (Ravin, 1985) This retouching confused analysts of his work who were unaware of the changes. (Hale, 1975)

Posterior capsule opacification certainly occurred after many of these operations and attempts were made to incise (needling) the opacity post operatively to clear the visual axis. The Ziegler knife has a small crescent tip on a thin tapering shaft which could be inserted at the limbus without the loss of aqueous and cut the posterior capsule on two sides of a triangle folding it backwards then into the vitreous on the third side.

Older 20th century text books in English such as Torok E 1913, Parsons JH 1918, Stallard HB 1946, May and Worth 1954, (Torok and Grout, 1913, Parsons, 1918, Stallard, 1946, May and Worth, 1954) all mention posterior capsule opacification as a complication of the surgery but the incidence is not well documented and may be as high as 50%. The problem may still be as high as 80% in surgery for congenital cataracts even with current techniques.

All of these early operations were performed without anaesthetic until the use of cocaine topically by Koller in 1884 on the suggestion of Sigmund Freud. (Chua, 2000)
Lidocaine and other currently used local anaesthetics are chemical modifications of naturally occurring narcotics. (Ruetch et al., 2001)

Sir Harold Ridley implanted the first intraocular lens after extracapsular cataract extraction (ECCE) at St Thomas’ Hospital London England in 1949 (Apple, 2000, Survey of Ophthalmology Editors, 2000) publishing his results in 1951, (Ridley, 1951) recording the problem of posterior capsule opacification. His peers did not receive his technique enthusiastically at that time.

Intracapsular cataract extraction (ICCE) that is, removing the whole of the cataract and its capsule in one piece was an attempt in the middle of the 20th century to avoid the problem of posterior capsule opacification and is attributed anecdotally to Col. Smith (RANZCO/RVEEH Museum, 2005), a British surgeon working in the Indian medical service. This brought it’s own complications and is rarely used now.

Current cataract surgery technique is a modification of the techniques proposed by Charles Kelman in about 1967. It now consists of a self sealing incision of less than 3mm and introduction of a viscoelastic fluid into the anterior chamber. This is followed by the removal of a 5-6mm circle of anterior capsule by continuous tear, hydrodissection of the capsule away from the cataract. Removal of the cataract is by various techniques based on phacoemulsification (ultrasound), irrigation and aspiration of any remaining material and a foldable intraocular lens is inserted into the capsular bag. Sutures are not routinely used. In situations where phacoemulsification is not available, manual techniques with small incisions can give comparable results but recovery times may be longer.
Figure 1 – Cataract and intraocular lens

Figure 1. Showing the position of the natural lens behind the iris and of the implanted lens prosthesis in the capsular bag remaining after the irrigation and aspiration of the cataract through an anterior capsular opening (capsulorhexis). The natural lens zonules (suspensory ligaments) support both structures. The posterior part of the lens capsule remains preventing displacement of the implanted lens into the vitreous.
Permanent increase in visual acuity after surgery depends on the posterior capsular bag remaining clear and intact. (Findl et al., 2007) Medical treatment of cataract is not possible at this time.

Demand for cataract surgery will continue to increase with time because of the ageing population and increasing life expectancy in all countries. Maldistribution of the availability of cataract surgery across any country, and sadly, lack of money aggravate the waiting times. The ageing ophthalmic surgeon population in Australia and financial restriction on the number of surgeries performed in public hospitals add to increasing backlogs.

The Australian Department of Health and Ageing, from various sources, estimates that the number of cataract operations in the general population increased threefold from 1989 to 1997 and the need will double over the subsequent 20 years. (Taylor and Keefe, 2002) The estimated cost of cataract operations in the 2003 fiscal year was AU$378 million of which Medicare Australia rebated AU$47,718,000. With the inclusion of outpatient visits, drugs and ancillary expenses this reaches AU$1.9 billion annually. Estimated figures vary from Medicare Australia statistics because some surgeries are not claimed and/or rebated under Medicare. The operation rate was 6.2 per 1000 population compared with 7.26 in Sweden and 4.75 in England and increasing in all three countries. (Taylor, 2007)

In Australia, the incidence of Medicare funded cataract surgery is increasing (but not fast enough to cope with need), whereas the incidence of Nd:YAG laser capsulotomy is not increasing reflecting better surgical results as shown in Figure 2. The costs are in Figure 3 and the trend in Figure 4.
Cataract surgery may cost as little as US$15 per disability adjusted life year (DALY) in developing countries and is still cost effective at US$2020 in developed countries. \(^{(Taylor \ et \ al., \ 2007)}\)

One million Nd:YAG capsulotomies cost USA Medicare US$250 million in 2001. \(^{(Schmidbauer \ et \ al., \ 2001)}\) Value based cost-utility analysis over the years 1992–2003 in USA concluded that “the majority of ophthalmic interventions are especially cost effective by conventional standards” and the median cost utility was US$5,219/quality adjusted life year (QALY). \(^{(Brown \ et \ al., \ 2004)}\) Unfortunately differing bases for assessment of benefit make strict comparisons difficult and costs vary from lower in Europe and Canada to higher in USA. In both relative and absolute terms, cataract surgery is cost effective compared with other common operations such as hip and knee surgery and defibrillator implantation. \(^{(Landsingh \ et \ al., \ 2007)}\) Cataract also increases mortality and systemic morbidity. \(^{(Cugati \ et \ al., \ 2007)}\) Cataracts “are associated with some measures of frailty (that are) independent of visual acuity and systemic comorbidities.” \(^{(Klein \ et \ al., \ 2003, \ Klein \ et \ al., \ 2006, \ Bennet \ and \ Australian \ Institute \ of \ Health \ and \ Welfare, \ 2005, \ Walker \ et \ al., \ 2006)}\)

Bulletin of the World Health Organisation in 2004 concluded that “extracapsular surgery (ECCE) for cataracts at a high level of coverage is the most effective way of restoring sight in all epidemiological subregions considered”. \(^{(Baltussen \ et \ al., \ 2004)}\) This is supported by a Cochrane Collaboration review. \(^{(Riaz \ et \ al., \ 2006)}\) This same review found that “ECCE with a posterior chamber lens implant provides better visual outcome than intracapsular extraction with aphakic glasses or anterior chamber intraocular lens”. Unfortunately, costs put cataract surgery beyond reach for many millions in the world. This is still true whether paid by the individual or the state or shared or subsidised by volunteer surgeons and support workers and organizations. The Cochrane Collaboration drew up a protocol in 2006 for a
systemic review assessing interventions for preventing posterior capsule opacification and reported in 2007. (Findl et al., 2002, Findl et al., 2007).

The results of cataract surgery with IOL implant has been improving particularly over the last 10 years. This applies to both the intraoperative and long term performance (Figures 2,3 and 4) and is a world wide trend. Reliable statistics for countries without access to phacoemulsification are hard to find but verbal reports from surgeons who visit confirm improvement there also.

As the incidence of posterior capsule opacification after elective phacoemulsification surgery is now often below 5% and reducing, we must look towards ways other than surgical technique, IOL design and IOL materials to approach the ideal of a permanently clear posterior capsule after every operation.

Medical methods for the prevention and treatment of cataract are currently in their infancy and are reviewed below. Considering the above costs, any improvement in surgical technique, however small, resulting in reduced need for posterior capsulotomy has large global and individual socio-economic benefit.
Figure 2. Medicare Australia Figures showing the increasing number of cataract surgeries performed in Australia over the years 1997-2007 compared with the steady rate of posterior capsulotomy for the same years. This confirms the overall reduction in percentage of operations requiring capsulotomy.
Figure 3 – Medicare Australia - Benefits paid from January 1997 to December 2007 for cataract surgery (42702) and Nd:YAG laser (42788)

Figure 3. The same years as Figure 2 reflecting the reduced cost of capsulotomies as a percentage of the cost of surgeries.

In both Figures the dip in December quarter each year is due to hospital closures for maintenance and to staff holidays.
Figure 4 – Clinical incidence trend of posterior capsule opacification (PCO) 1980 to 2000 (various sources) (Pandey et al., 2006)

Figure 4. Reducing incidence of capsulotomy over a range of sources covering the years 1980-2000. This trend continues but possibly more slowly.
Figure 5. Photograph from the front of the eye after both cataract extraction with intraocular lens implantation followed by laser posterior capsulotomy. The IOL is not seen as it is transparent but the difference in transparency between the opaque capsule (labelled PCO) and the opened capsule (labelled edge of the capsulotomy) is obvious. The patient would have experienced a marked increase in central and peripheral best corrected visual acuity (BCVA) after capsulotomy.
CHAPTER THREE

The scope of the posterior capsule opacification problem

The enduring success of any lens surgery depends on the permanent clarity of the posterior capsule no matter which surgical technique is used otherwise the vision becomes blurred again and sensitivity of the macula of the retina is reduced. (Varga et al., 2007)

In developed countries, the next most common surgical procedure after IOL is laser to clear any opacity that may occur in the posterior capsule. (Taylor and Keefe, 2002)
This improves both best corrected visual acuity (BCVA) and sensitivity of the macula. (Varga et al., 2007)

Sourdille (a French ophthalmologist) is quoted on the importance of the subject; “isn’t it intriguing to read reports on the remarkably low incidence of posterior capsule opacification (PCO) after cataract surgery and to learn simultaneously that Neodymium:yttrium-aluminium-garnet (Nd:YAG) laser capsulotomy is the second most frequently performed surgery in some industrialised countries”. (Emery, 1999)
This is partly explained by the lag time of years between IOL implantation and need for Nd:YAG laser. There is a marked and continuing decrease in Nd:YAG laser capsulotomy rates since that quote in 2001 due to better surgical technique, better lens designs and improved materials. (Apple et al., 2001, Schmidbauer et al., 2001) “PCO has impeded the spread of successful cataract surgery and IOL implantation to the 25 million persons (and 110 million persons with visual disability) worldwide with cataract, by far the most common cause of visual impairment”. (Schmidbauer et al., 2001)
Figure 6: sections through the developing eyes of e10-14 rat embryos stained with haematoxylin and phloxine. At e10 (a) bilateral outgrowths from the developing brain form the optic vesicles (ov). In early e11 embryos (b) the optic vesicle is closely associated with a region of head ectoderm that is destined to form lens. In the late e11 embryo (c) both the ectoderm and the neuroectoderm are thickened along the region of close proximity, forming the lens placode (lp) and retinal disc (rd), respectively. Invagination of lens placode and optic vesicle at day 12 (d) leads to the formation of the lens pit (lp) and optic cup (oc), respectively. By e13 (e) the lens vesicle (lv) has formed and detached from the optic cup (oc). The posterior lens vesicle cells elongate to form primary lens fibre cells leading to narrowing of the vesicle lumen. By e14 (f) the lens vesicle lumen has disappeared and the primary lens fibres (lf) are in contact with the anterior lens vesicle cells which form the epithelium (e). Vitreous humour (vit) and hyaloid vasculature forms between the developing lens and retina. The inner layer of the optic cup will form the neural retina (nr). Adapted from de Longh and McAvoy. 8 scale bars: (a) 50 μm; (b,c) 75 μm; (d–f) 100 μm.
To understand how lens epithelial cell proliferation occurs inside a cavity lined by endothelial cells requires a review of the embryology. Very early in embryonic development a plaque of ectoderm becomes intimately associated with the cranial end of the developing neural tube. This invaginates maintaining the intimate contact so that the plaque is surrounded by a doughnut of ectoderm rising up to enclose the lens epithelial plaque to form the anterior segment of the eye. This ectodermal cell plaque forms the lens of the eye which continues to grow throughout life, albeit very slowly, in both axial and equatorial meridia. The lens cells align themselves in an antero-posterior direction under the influence of growth factors and become so thin they are called fibres and the nuclei are all under the anterior capsule resulting in best optical clarity.

This ectodermal-neural integration means that the optic nerve (cranial nerve II) is in fact brain being third order neuron. The cell bodies are in the ganglion cell layer in the inner aspect of the retina. The eye is fully developed at 34 weeks gestation. The whole of the capsule of the lens is a basement membrane structure laid down by the lens epithelial cells and is transparent during life. After cataract surgery the equatorial cells (‘e’-cells), which provide normal slow growth of the lens, may proliferate and spread across the posterior capsule causing opacity and visual impairment requiring a further procedure.
Figure 7. Lens fibres are originally ectodermal cells which have become elongated under the influence of natural growth factors. The nuclei align under the anterior capsule where they obstruct light less than if they were posterior. All the fibres are of the same diameter and spacing thus reducing light scatter improving acuity.

The lens grows slightly through life by mitosis of the ‘e’ cells at the equator. Not all of these cells can be removed at operation and they may continue to proliferate in a random fashion causing opacity on the remaining posterior capsule. This will reduce the post operative best corrected visual acuity and require further surgery to improve vision again.

As with cataract, there is no effective medical treatment for reducing or preventing posterior capsule opacification although many have been tried.

In industrialised countries, Nd:YAG laser is available to clear this opacity, but many millions of persons throughout the world have no access to this cure and the visual benefit of surgery may be indeed temporary. This means that cataract surgery in less developed countries earns an unwarranted bad name for long term effectiveness and may discourage other poor persons from seeking a cure. Taking Nd:YAG lasers to remote sites is not currently feasible because of electro-
mechanical problems, especially variable electricity supplies and heavy, short charge batteries. (Gillies, 1998)

Although surgical correction by incision of the posterior capsule is available to these persons, the numbers become overwhelming and the effort would be better directed towards new cataract surgeries for the (perhaps 25+) millions in poor circumstances, who currently require but have no access to treatment. For example, it is estimated that for the hundreds of millions of persons who live in Bangladesh there are only about twenty-eight ophthalmic surgeons active full time. If they did not have to deal with PCO they would, like everybody else, be vastly more effective.

Currently the cost of cataract surgery in underdeveloped and remote areas is borne partly by governments with restricted budgets. Significant contribution comes from individual volunteer surgeons who initiate the surgical trips in coordination with the local surgeons, by charities, by equipment companies, by drug companies and by private organizations that provide manpower and money and equipment aided by local volunteers and patients’ family. Those locals who can contribute to the cost are helping to subsidise the poor. For example, in the city of Lumbini in Nepal (the birthplace of Buddha) the cost is US$35 maximum if it is affordable but no one is turned away according to the Royal Australian and New Zealand College of Ophthalmologists’ Newsletter June 2007.

Since the world health organisation has assessed that cataract surgery is the cost effective way of dealing with cataract problems, perfecting it would increase its cost effectiveness even more. (Baltussen et al., 2004, Riaz et al., 2006)

Even in sophisticated countries the cost of treatment of PCO is significant. Nd:YAG laser treatment of posterior capsule opacification is the next most
common claim to cataract surgery on Medicare in the USA. (Apple et al., 1992, Emery, 1999)

Australian Medicare figures for 2006 are AU$1 million (approx) compared with AU$8.8 million (approx) for cataract surgery. The trends are in Figures 2&3.

Nd:YAG laser does have a very small but well documented incidence of complications (see later) and should not be a routine procedure. Analyses of the effectiveness of measures to reduce PCO are delayed because the opacity usually takes years to become visually significant. It is much more common in paediatric surgery and less so in the very aged. It is very important to identify PCO early in children to prevent irreversible amblyopia in that eye. (Survey of Ophthalmology Editors, 2000)

For the purposes of this thesis, symptomatic visual impairment was taken as the end point indication for capsulotomy. This can be criticised because it is subjective but it is the current practice.

Many objective assessments of PCO are under trial but there is no agreement on uniformity. Computer analysis of digital retro illumination photographs is valid and reliable (Aslam, 2005, Aslam, 2006) but the most promising is the use of optical coherence tomography (OCT-1) which can measure thickness of the opacity and capsule thickness down to 10 microns. (Moreno-Montanes et al., 2005) This could standardise accurately assessment of PCO rates if widely available when used in conjunction with visual acuity, contrast sensitivity and spatial discrimination. It will allow standardised measurement of area, density and site so that prevention measures can be accurately evaluated against a background of changes in lens design and surgical technique. Unfortunately this examination is expensive and not readily accessible outside large centres.
CONCLUSION

Of the many millions of IOL implants performed around the world every day, a PCO incidence of even 5% still represents considerable cost and functional impairment (see causes and prevention below) so that any incremental improvement in surgical performance is worthwhile. It would permit successful expansion of IOL surgery in underdeveloped communities since Nd:YAG laser is not widely available and takes up valuable time and resources when it is.

The cost of posterior capsulotomy is considerable in any country when gauged against the local currency. When the time and resources needed is added to the time and opportunity lost in performing primary cataract surgery the problem is much greater than it first appears. This is not to say that capsulotomy should be abandoned for it returns the patient to independence and production. The aim should be to improve primary prevention.

Even a mild degree of PCO can reduce visual efficiency especially of multifocal and accommodating IOLs, reducing sensitivity of the macula and limiting the patient’s performance in their environment.
CHAPTER FOUR

Causes and prevention of posterior capsule opacification

Posterior capsule opacification (PCO) is becoming less common after lens surgery and is effectively treated by laser.

MECHANISMS

Extracapsular cataract extraction (ECCE) with posterior chamber intraocular lens (IOL) implantation is the preferred surgical technique for the treatment of cataract whether in developed or developing countries. The Hollows Foundation is famous for its work in this latter area but many other organizations also work to provide low cost intraocular lenses, training of local surgeons and develop an effective technique not requiring sophisticated technology.

Leaving the posterior capsule intact improves safety of cataract operation but may result in its opacification requiring further surgery and therefore any technique that can reduce this incidence and allow surgeons to perform more primary surgeries is worthwhile. The Cochrane Collaboration has published a protocol and analysis for “interventions for preventing posterior capsule opacification”. (Findl et al., 2007, Riaz et al., 2006)

That the capsular bag can survive long term without functioning lens epithelial cells was shown in a well constructed study of 100 cadaver pseudophakic eyes. The reason was unable to be explained. Thus the possibility of long term stability of the IOL and capsular integrity is assured. (Kleinmann et al., 2006)
At the completion of the current surgical technique of phacoemulsification and intraocular lens implant (IOL), there is very little inflammatory response and inflammatory cells are not a feature of the postoperative course or of PCO. If the eye had been the subject of previous trauma or inflammation resulting in intraocular fibrosis, then inflammatory cells may be important in the initiation of PCO. This can be interpreted as a wound healing response. (Bertelmann and Kojetinsky, 2001)

This means that the posterior capsule, a basement membrane structure which remains clear throughout life, does not itself go opaque. The cells spreading onto its anterior surface behind the intraocular lens may cause visually significant opacity. This ingrowth may also be seen as a membrane between twin implanted (“piggy back”) IOLs. Despite the nicety of the distinction of the site of the opacity, the term posterior capsule opacification is universally used for this condition and is continued here.

Clinically, PCO (also called secondary cataract) is subdivided into regeneratory or fibrotic with the former being the more common. Both cause opacity that can interfere significantly with vision if there is progress over time. Fibrotic PCO is randomly arranged and scatters the light causing symptoms as opposed to the orderly arrangement of fibres in the natural lens (Figure 7). “Posterior capsule thickness was a factor in reduction in best corrected visual acuity” as judged by optical coherence tomography (OCT-1). (Moreno-Montanes et al., 2008)

Regeneratory PCO is a result of lens epithelial equatorial (‘e’ cells) migrating onto the posterior capsule behind the intraocular lens. These are either remnants of cortical cells left on the capsule during surgery or proliferation of equatorial cells which have not been able to be removed. They may be transitory clearing within 8 weeks. They are sometimes referred to as “bladder” or “Wedl” cells and were

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described originally more than a hundred years ago when they were referred to by eponymous name of Elschnig’s pearls. (Parsons, 1964)

Fibrotic PCO occurs when anterior capsule cells (‘a’ cells) undergo transformation into myofibroblasts and cause fibrosis and contraction of the capsular bag or of the capsulorhexis. ‘E’ and ‘a’ cells both come from one continuous cell line but ‘a’ cells tend to stay anterior and ‘e’ cells tend to migrate across the posterior capsule (Marcantonio and Vrensen, 1999) unless prevented by lens design (see below). (Schmidbauer et al., 2001, Apple et al., 2001)

It would seem logical that any attempt to remove as many epithelial cells as possible from the capsule during surgery would reduce posterior capsule opacification and aggressive polishing of the anterior and posterior capsule has been recommended by many authors over many years. The problem is that the removal of equatorial cells is technically the most difficult and dangerous part of the procedure. In a study of 194 uneventful cataract surgeries of various densities the authors concluded that “the results indicate that aggressive polishing of peripheral or adherent residual capsular opacity is not advisable as only five eyes with central residual opacity developed significant visible PCO”. (Mootha et al., 2004)

Similarly, after polishing the posterior capsule of 200 consecutive patients, the incidence of PCO still rose to 50% at three years. (Wilhelmus and Emery, 1980)

Conflicting results of the benefit of anterior capsule polishing in 130 silicon IOL implants in a randomised masked trial led to the conclusion that “this trend did not reach statistical significance”. (Bolz et al., 2006)

Opacity and slight contraction of the anterior capsule (like a purse string) may in fact have some beneficial effect by increasing the posterior capsular bend at the posterior peripheral edge of the intraocular lens, tightening the posterior capsule
against the posterior surface of the lens and thus mechanically preventing in
growth of any sort of cell between the lens and the capsule (the “shrink wrap
effect”). (Dewey, 2006)

Sommering’s ring is an almost universal finding in post mortem eyes with
intraocular lenses and consists of cells trapped between the anterior and posterior
capsules peripheral to the intraocular lens in a doughnut fashion. It is not
particularly important visually while it remains contained and peripheral which is
the majority of the time. (Apple et al., 1992, Schmidbauer et al., 2001)

Even if the posterior capsule remains clear, asymmetrical fibrosis peripheral to the
intraocular lens may result in wrinkling of the capsule which may slightly reduce
the visual acuity but does not always require intervention. (Marcantonio et al., 2000)
Figure 8. Miyake–Apple images are obtained by sectioning a post mortem fixed eye through the equator. The anterior half is then set on an optically correct glass plate and photographed/videoed from behind.

This image shows the doughnut of residual proliferated lens cells outside the IOL and behind the iris with a clear visual axis. Visual acuity probably was not affected in this patient.
Technical features that are proven to reduce posterior capsule opacity have been identified as: (Apple et al., 2001, Pandey et al., 2004, Pandey et al., 2006)

1. Cortical cleaving hydrodissection;
2. Careful cortical clean-up;
3. In-the-bag placement and fixation of the intraocular lens;
4. Central anterior capsulorhexis of slightly smaller diameter than the intraocular lens;
5. A lens material that is biocompatible;
6. Maximum contact between the posterior capsule and intraocular lens;
7. A square posterior truncated edge on the intraocular lens where it contacts the capsule. (Apple et al., 2000, Apple et al., 2001, Pandey et al., 2006, Pandey et al., 2004, Nishi et al., 2004a)
8. Maximum capsular bend at the posterior edge of the IOL with 360 degree barrier. (Dewey, 2006, Nishi et al., 2007) This is called the “shrink wrap effect”.
9. Rotation of the hydrodissected nucleus of the lens three times before removal. (Vasavada et al., 2005)
10. A second hydrodissection before irrigation/aspiration of the cortex. (Dewey, 2006)

Items 7 and 8 appear to be the most important. (Nishi et al., 2004b)

Ultraviolet-A irradiation of the capsule at the time of surgery to remove lens epithelial cells (dose not specified) is an innovative approach recently reported (p=0.17) in a comparative study of 30 eyes. (Rajeev, 2007) This concept needs larger series to consolidate efficacy and safety.

Routine posterior optic buttonholing in a primary posterior capsulorhexis for eradication of PCO in adults was reported in 500 intraocular lens implants with a low complication rate of 1% associated with the technique and no increase in
cystoid macular oedema post operatively. This technique has been used for a long time in paediatric IOL implants where PCO may still exceed 50%. (Mammalis, 2006, Menapeace, 2006)

Systemic diseases appear to have little effect on posterior capsule opacification even though diabetes mellitus and steroid treatment, both local and systemic, are associated with posterior subcapsular opacities prior to surgery. These opacities usually come free of the capsule during surgery and do not often contribute to PCO. Diabetes was found not to be a factor in PCO in a study of 434 human eyes undergoing routine cataract surgery and intraocular lens implant. (Mian et al., 2005)

Pseudoexfoliation (PXF) of the lens capsule has been anecdotally noted to increase the fragility of the capsule but also increase the fibrosis post operatively. But a study comparing 800 eyes with PXF against 1600 patients without showed that, using phacoemulsification, results can be obtained similar to routine surgeries. (Aldinci et al., 2008)

Biochemical studies have shown that the lens epithelial cells involved in the PCO may change their protein matrix to smooth muscle in the form of actin thus representing a mesenchymal transition (see above). Cytokines, especially transforming growth factor-beta (TGF-beta), are thought to be involved in this metamorphosis from studies of donor human eyes. (Marcantonio and Vrensen, 1999, Marcantonio et al., 2000, McAvoy et al., 2000) Normally occurring fibroblast growth factor (FGF) and transforming growth factor-beta (TGF-beta) play important roles influencing the lens epithelial cell behaviour and persist in the capsular bag after surgery. (Marcantonio et al., 2000)
Figure 9. Diagram illustrating the proposed roles played by fibroblast growth factor (fgf) and transforming growth factor (tgf-β) in modulating the lens cell phenotype. Fibroblast growth factor initiates and promotes fibre differentiation but tgf-β is also required for fibre maturation and/or survival. In contrast to its normal role in fibre differentiation, tgf-β induces lens epithelial cells to form fibrotic plaques and disrupts normal cellular architecture.
An interesting experiment confirming the importance of growth factors on lens epithelial cells was performed by culturing human epithelial cells in vitro from post mortem eyes. The mitotic activity returned at a rate comparable to that of intact cultured non-cataractous lenses showing that the potential for proliferation persists for a very long time after surgery. (Rakic et al., 2000)

FGF has 3 receptor genes in lens epithelial cells and is important for ensuring that normal lens cell polarity is maintained as the new fibres continue to differentiate throughout life and maintain the ordered cellular architecture responsible for transparency of the normal human lens. FGF has a higher concentration in vitreous than aqueous. Explanted lens cells exposed to vitreous lose organelles and assume the characteristics of lens fibres but not when exposed to aqueous. It is logical to imply that FGF in persisting lens cells continues to enable them to differentiate and proliferate.

TGF-beta is a family of factors present in the eye that can induce apoptotic cell death and localised capsule wrinkling. These have been identified in subcapsular cataracts and posterior capsule opacification. Transgenic studies have shown that TGF-beta can induce cataract and the epithelial-mesenchymal transition that is seen in fibrotic PCO. Thus, in general, FGF is good and TGF-beta is bad for normal lens clarity. (McAvoy et al., 2000)

The mechanism of regulation of these families of factors in vivo, their bioavailability and mediation is not known but “will be fundamental to understanding the molecular basis of cataract”. (McAvoy et al., 2000)

Detailed analysis of these factors is beyond the scope of this paper. An extensive review of the research into these factors can be found in the Peter Bishop Lecture of 2000. (McAvoy et al., 2000) and good reviews of the pathophysiology of posterior...

The incidence of clinically significant PCO was conservatively quoted as 25% in 1998 and 7.5% in 2005 at twenty-four months over a variety of IOL materials. (Figure 4) some materials and lens designs performed better over time than others especially those with “sharp” posterior edges to the optic. (Schmidbauer et al., 2001, Schaumberg et al., 1998, McLeod, 2005, Nishi et al., 2007) This improvement is reported in many other papers and is attributed to the factors listed above being improved and implemented worldwide. (Pandey et al., 2006)

With new techniques and lens design including accommodating and multi focal intraocular lenses, refractive surgery involving the lens and presbyopia surgery, the permanent clarity of the posterior capsule becomes paramount and integral for the success of the operation and PCO must be eliminated. (Dewey, 2006)

TREATMENT OF POSTERIOR CAPSULE OPACIFICATION

MEDICAL

There is no universally accepted medical treatment for the prevention of cataract or PCO. It is appropriate to review briefly published measures that have been tried in vivo, in vitro and ex vivo. (see chapter 5)

N-acetylcarnosine drops have been claimed to be effective particularly by investigators in Europe using mainly animal in vivo trials. The drug is on sale in Europe and apparently extensively used by the public. (Personal Communication Milverton)

N-acetylcarnosine 1% was studied in a clinical trial of 26 cataract patients
compared to 13 placebo and 10 untreated. The treated group had two drops twice a day for six months without surgery. Stereocinematographic image and retroilllummation photography were used to assess the results as well as corrected visual acuity. Ninety percent showed a gradual improvement in acuity, glare sensitivity and less density in the patients who had posterior subcapsular cataracts. An extension of the study to 24 months claimed that the effect is sustainable. The mechanism of action is unknown but is thought to be an antioxidant. (Babizhayev, 2001)

L-carnosine is a related natural peptide containing histidine and similar results are claimed but not well documented.

Gene therapy is in its infancy and the appropriate target genes are being researched using proapoptotic molecule manipulation. (Malecase, 2006)

Lens regeneration is a concept which is unlikely to be feasible in the foreseeable future. (Gwon, 2006, Gwon et al., 1993)

Immunotoxin MDX-RA is in extended human trials (see below).

**SURGICAL**

Despite the eight proven items and two new techniques listed above reducing the incidence of PCO, it has not been eliminated. Creating an opening in the opacity of the capsule requires either surgical needling or laser. The former is another penetration of the globe with the small risk of infection but requires no sophisticated equipment; the latter is elegant, safe and expensive but not suitable for remote locations.

Nd:YAG laser ablation (393 nm) of the posterior capsule is accepted as the best form of treatment of PCO. It acts by photo disruption using acoustic shock waves generated by ionisation and plasma formation to cut the opacity without the need
for pigment absorption and producing carbon dioxide and water. The physics of these reactions is discussed in detail by Puliafito and Steinert. (Puliafito and Steinert, 1984)

This treatment is indicated when the opacity affects the best corrected visual acuity and is symptomatic. It may take five years (rarely more) to be clinically significant but more commonly this occurs at around two to three years. “Patients with PCO seemed to have more disturbed visual function than cataract patients with the same visual acuity” and request treatment sooner. (Sundelin et al., 2006, Sundelin and Sjostrand, 1999)

In 1996, when the incidence of PCO was around 43% (Figure 4), it was estimated that 9% of the surgically treated population still had clinically significant untreated PCO 5 years post operation. (Sundelin and Sjostrand, 1999) this delay skewed incidence Figures based on Nd:YAG treatments but other objective criteria were not available. The incidence of Nd:YAG capsulotomy post operatively is falling worldwide but it is higher in children and lower in old age. (Maltzman, 1989) these Figures are confirmed by Medicare Australia statistics 2006. (Figures 1 and 2)

**COMPLICATIONS OF ND:YAG LASER**

Nd:YAG laser is a very effective and successful technique and a second treatment is rarely necessary. It may damage the IOL or let it displace, raise intraocular pressure, precipitate cystoid macular oedema or retinal detachment, or exacerbate localised endophthalmitis. Fortunately, in experienced hands, these are very rare.

The costs are still considerable; “1 million patients per year costs the USA health care system up to us$250 million annually” (Schmidbauer et al., 2001) and Medicare Australia rebated AU$8,888,000 in 2006.

A statistically significant increase (p=0.02) in the incidence of retinal detachment or retinal break was found in young white males by reviewing 57,103 randomly
selected USA Medicare beneficiaries covering the years 1986-1987; 337 retinal detachments and 194 retinal breaks were found. This is a small incidence but possibly a lifelong problem.\textsuperscript{(Javitt et al., 1992)} Similar results were found for both diabetic and non-diabetic patients (n = 806) confirming that diabetes mellitus is not a factor in retinal detachment after Nd:YAG laser.\textsuperscript{(Elgohary and Dowler, 2006)}

**CONCLUSION.**

The incidence of PCO after cataract surgery is still falling worldwide to less than 5%. Improved surgical techniques, better IOL designs and more biocompatible lens materials have all combined synergistically to reduce the incidence over time. Pharmacological attempts to reduce PCO are still rudimentary.

Nd:YAG laser obliteration of PCO is very effective and safe when reserved for patients with symptomatic loss of best corrected postoperative visual acuity. Polishing of the capsule prior to implantation is not worth the risk and time. Surgical treatments such as needling of the capsule or primary buttonholing may have a place in specific cases.
CHAPTER FIVE

Pharmacological attempts to reduce posterior capsule opacification

Experiments using Xylocaine (lidocaine) will be detailed in a separate chapter.

Experiments to find a substance which would reduce PCO go back to the early 1970s when many substances were rejected because they were too toxic to the corneal endothelium. Table 1 lists most of the substances which have been used experimentally. Carbachol (Birnbaum et al., 1987) and acetylcholine (Hull, 1979), which have been used intraocularly for many years to constrict the pupil, were cleared of toxic effect to the corneal endothelium and do not increase PCO rates as judged by Nd:YAG laser rates. (West, 2007) Xylocaine 1% 1 mL unpreserved is the drug most commonly injected into the anterior chamber without toxic effect on the corneal endothelium (see later). Adrenalin is often used in the infusion fluid and occasionally in small dose into the anterior chamber to help keep the pupil dilated and has no measured effect on the corneal endothelium in the concentrations used clinically. (Hull, 1979)
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**Note**
Some substances have more than one action and could be reclassified in this Table.
ANIMAL EXPERIMENTS

IN VITRO

The validity of using rabbit eyes as a model for studies to elucidate human PCO was assessed in a series of experiments analysing postoperative slit lamp examination and aqueous humour analysis. “The study showed that the same components that are reported in human PCO are also components of PCO in the rabbit” but that they develop much more rapidly e.g. 2 months as opposed to 2 years. (Wallentin, 2002)

The pH tolerance of both rabbit and human corneal endothelial cells was tested using a dual chambered specular microscope over the range of pH 3.5 to 10.0. It was concluded that outside the range of 6.5 to 8.5 structural and perhaps functional changes start to occur in the cells after three hours perfusion compared with balanced salt as control. As few cataract surgeries last three hours (less than thirty minutes is more likely) a slight extension of the pH range over a shorter time was thought to be possibly acceptable. (Gonnering, 1979)

The osmotic tolerance of both rabbit and human corneal endothelium was tested on excised corneae mounted in a specular microscope. They were perfused with balanced salt solutions of varying osmolality from 192 to 498 milliosmoles per litre (mOsm/L) at 37°C and 15 mmHg for 15 minutes then fixed and studied by transmission electron microscopy; 300 mOsm/L was taken as “normal” for the purposes of the experiment. The conclusion was that “the corneal endothelium can tolerate a wide range of solution osmolalities (200 to 400) without marked endothelial cell breakdown if the essential ions are present”. (Edelhauser, 1981)
The effect of commercially available eye drops which may be washed into the eye during surgery was assessed using rabbit corneae perfused for five minutes.

Epinephrine (adrenalin) 1/1000 was toxic to corneal endothelium but a five fold dilution showed no change in the cells. This is important because epinephrine may be combined with other drugs in fixed ratios in commercial preparations of eye drops. Preservatives such as benzalkonium chloride 0.01% (a cationic surfactant), and Chlorhexidine are toxic to corneal endothelial cells in rabbits in the bacteriostatic concentrations currently in use and therefore should never be used in intraocular surgery. (Eleftheriadis et al., 2002) Special care must be taken in the operating theatre to keep antiseptic preparations separate from solutions used for intraocular use.

Carbachol (carbamyl choline) 0.01% which may be used to contract the pupil at the end of the surgery causes transient corneal swelling and this may be due to the relatively low pH of 5.2 of older preparations. (Hull, 1979) newer preparations have a pH of 6.95. (Birnbaum et al., 1987) Acetylcholine 1% is used for the same purpose. It is reconstituted with 5% mannitol giving a pH of 7.1. Although the osmolality is high at 430 mOsm/l there is little change in the corneal endothelium in rabbits as assessed by scanning and transmission electron microscopy. (Hull, 1979)

Calcimycin (a calcium ion antibiotic ionophore) was tested against human and rabbit endothelial cells suspended in foetal calf serum. The drug produced apoptosis and it was found that it was toxic to the cells after thirty minutes exposure. The author of the study concluded that induction of apoptosis was a possible treatment mechanism for preventing posterior capsule opacification but required further experimentation. (Geissler, 2001) There have been no further reports found.

Salmosin, a disintegrin, was tested ex vivo on the excised anterior capsule lens epithelial cells of both rabbit and human eyes. Adhesion and migration and
proliferation were all inhibited but not as much as it was in an in vivo experiment with rabbit eyes. (Kim, 2002)

Local anaesthetic eye drops of bupivacaine 0.75%, unpreserved, lidocaine HCl 0.5% and tetracaine HCl 0.5% are commercially available. Tested in 72 rabbits by anterior chamber infusion, all showed corneal thickening and opacification, the least so with tetracaine. (Judge et al., 1998) They must not be used intraocularly.

The effect of intraocular lens materials (as opposed to design) was tested against bovine lens epithelial cells cultured for one month. Polymethylmethacrylate (PMMA), silicone and hydrophobic acrylic lenses were treated with a gas plasma to modify the surface characteristics of the material. This increased the surface hydrophilicity and prevented the lens epithelial cells from converting to the characteristic fibroblast phenotype of the cells found in posterior capsule opacification. It was suggested that this relatively simple method would reduce PCO in human lens surgery. (Yuen et al., 2006) To date there is no report of this being available commercially.

Heparin was used as a coating for intraocular lenses about 12 years ago by the Pharmacia Company but is not currently available.

5-fluorouracil (5FU) is an antimetabolite with antifibrotic properties used in glaucoma surgery to prevent closure of the filter created. In the cell it is converted into active metabolites that interfere with the metabolism of DNA and RNA. Forty-six sheep corneae were exposed to 5FU concentrations varying from 0.01 mg/mL to 10.0 mg/mL for four hours at room temperature and compared with saline as a positive control and chlorhexidine gluconate as a negative (toxic) control. Up to a concentration of 1.0 mg/mL, 5FU showed no difference from the corneal buttons
exposed to normal saline. (Mannis et al., 1988) There is a dearth of documentation in the literature of toxicity to the cornea of 5FU 50 mg/mL used during glaucoma surgery suggesting that it is safe in the concentrations used. Corneal micro ulcers from 5FU spilled during subconjunctival injection after glaucoma surgery are well known and are transient.

In summary, many chemicals are toxic to lens epithelial cells and may mediate their effect by apoptosis, disintegration or change in adherence or combinations of these. Many are also toxic to the corneal endothelium and a compromise concentration is not always possible making them unsuitable for clinical use.

**IN VIVO**

5-fluorouracil (5FU) in a concentration of 50 mg/mL was compared against both distilled and deionised water and commercial balanced salt solution in a group of 34 week old rabbits having clear lens extractions in both eyes. Randomly chosen one eye had the substances instilled using the “perfect capsule” (Milvella, Sydney, Australia) sealed capsular irrigation device. The post mortem histology showed significant reduction in posterior capsule opacification in the 5FU group (p=0.0039). (Abdelwahab et al., 2006)

5FU in a sustained release (0.2 microgram/hr) intracapsular ring was studied in six rabbit eyes undergoing phacoemulsification. Transmission electron microscopy eight weeks after surgery showed that the potential effects anticipated were not demonstrated but there was no toxicity to intraocular structures. (Pandey et al., 2002) No reference to other concentrations was found.

Mitomycin-c (MMC) inhibits DNA synthesis. 0.2 mg/mL dissolved in sodium hyaluronate was compared with the same concentration in balanced salt solution
using 36 rabbit eyes. Three months after cataract surgery, visible light obstruction by PCO was halved in the first group. \textsuperscript{(Chung et al., 2000)}

5FU 12.5 mg/mL and MMC were compared in 12 rabbits having bilateral phacoemulsification. After four weeks these doses did not show significant inhibitory effect on after cataract (PCO) formation. \textsuperscript{(Chew et al., 2006)}

Colchicine, an anti inflammatory, inhibits cell division by interfering with the mitotic spindle. In a sustained drug delivery system from an intraocular lens studied after phacoemulsification in 34 rabbit eyes it was effective in reducing the mean PCO compared to control. The side effects were of an inflammatory anterior chamber reaction and corneal and retinal toxicity. The author suggested that an acceptable biocompatible dose may be determined by further investigation. \textsuperscript{(Legler et al., 1993)}

Daunorubicin, an early antimetabolic antibiotic used in some leukaemias, was encapsulated in liposomes in varying concentrations from 0.2 mg/mL to 20 microg/mL. Rabbit eyes were studied after extracapsular extraction of the lens. Only a few lens epithelial cells remained in the bag eight weeks post operatively but corneal oedema and eosinophilic infiltration and loss of corneal endothelial cells resulted. \textsuperscript{(Wu, 2000)}

Daunorubicin 33 microg was compared with indomethacin 715 microg in a sustained drug delivery system in 89 rabbit eyes after intraocular lens implant. Indomethacin is not an ideal drug because of its relative insolubility in the carrier. The daunorubicin reduced posterior capsular fibrosis by approximately 50% but produced a mild inflammation and some endothelial cell loss. The indomethacin group showed inflammation of the ciliary body. \textsuperscript{(Tetz et al., 1996, Tetz and Nimsgern, 1999)} Neither drug has progressed to clinical use.
Cyclooxygenase-2 inhibition was tested using rofecoxib and celecoxib in canine cataracts *ex vivo*. This is the only positive result found for these substances and the authors suggested that “*in vivo* may be an effective technique in preventing PCO”. (Chandler et al., 2007)

RGD peptide (arginine-glycine-aspartate acid sequence) was compared with ethylene diaminetetraacetic acid (EDTA) in an attempt to prevent cell migration and adhesion in five rabbit eyes after intraocular lens implant. This produced a “significant inhibition”. (Nishi et al., 1997b) No further follow up of this substance can be found.

Retinoic acid 250 μg/mL and mitomycin-C 0.04 mg/mL were injected into the capsular bag of 27 rabbit eyes after phacoemulsification. Both reduced the incidence of PCO as compared to controls. Two eyes in the mitomycin group had corneal oedema with the author concluding “the optimum biocompatible dose must be carefully determined by further investigation”. (Inan et al., 2001a)

Mitomycin-C and distilled water were compared in sealed capsule irrigation in 24 rabbit eyes assessed at three months. MMC had statistically less PCO. (Kim et al., 2007)

The same group of authors then explored different substances using the same techniques in rabbit eyes. Dexamethasone 4 mg/mL had a very weak effect on preventing posterior capsule opacification and diclofenac had some effect. EDTA, EDTA+ RGD peptide and mitomycin-C “significantly prevented the development of posterior capsule opacification in the rabbit eye”. (Inan et al., 2001b)

Mitomycin-C 0.2 mg/mL in the viscoelastic sodium hyaluronate in 6 rabbit eyes reduced PCO compared with placebos without toxic effects to the eye. (Chung et al., 2000)
Comparison of a number of substances in rabbit eyes in a small study showed that distilled water and EDTA 10 mg/mL were the most efficient in retarding the appearance of PCO. It was noted that 5FU 33 mg/mL still prevented anterior capsular opacification. This concentration is less than the 50 mg/mL used in other experiments. The study also found that distilled water reduced the appearance of PCO but not as much as 5FU. (Fernandez et al., 2004)

Demineralised water was compared with Triton X-100 (a detergent) in the sealed capsule irrigation device in four rabbit eyes compared with the same substances without the sealed capsular irrigation. Histological examination of the enucleated eyes immediately after surgery showed that there was no collateral damage in the sealed capsular group. In the triton-x group there was significant damage to the eye, even though there was complete destruction of lens epithelial cells, when the sealed capsular device was not used. (Maloof et al., 2005)

The antimitotics 5FU (12.5 mg/mL) and MMC 0.1 mg/mL were compared in twelve rabbits having bilateral phacoemulsification. After four weeks it was found that these low doses did not show a significant inhibitory effect on after cataract formation. (Chew et al., 2006)

Saporin, a cytotoxic, was conjugated with polylysine because that substance binds to lens capsule membranes but not surrounding tissues. Of nine rabbit eyes followed for forty weeks, six showed a delay of cortical regrowth approximately two to three times that of control eyes. The proposition was that a conjugate of substances may be more effective than saporin alone. (Bretton et al., 1999)

Inflating an endocapsular balloon following cataract extraction was a novel approach trying to avoid drug toxicity in fifteen rabbits and thirteen primates followed
four to thirty two months after surgery. “filling of the capsule tautly and removing the lens epithelial cells effectively reduced capsular opacification but did not completely inhibit lens epithelial cell migration” (Nishi et al., 1997a)

Gene therapy to induce apoptosis in aspirated rabbit and human lens epithelial cells was explored using several proapoptotic molecules. Some were effective and further research on this novel approach was suggested. (Malecase, 2006)

Heparin is a mucopolysaccharide that occurs in mammalian tissues. It inhibits the formation of a stable fibrin clot. Heparin in an intraocular drug delivery system was compared with 5% drops in 50 rabbits and achieved a higher aqueous humour level for longer. “The findings indicate potential prevention of PCO with minimum toxic and side effects”. (Xie et al., 2003)

Tranilast, n-(3,4-dimethoxycinnamoyl)-anthranillic acid, was introduced as an antiallergic drug acting as a mast cell stabiliser and antihistamine. Subsequently it was found to have antifibrotic effect both by inhibition of fibroblast proliferation and also transformation into myofibroblasts thus reducing collagen formation. It also inhibits, prostaglandin e2, vascular endothelial growth factor VEGF and transforming growth factor TGF-beta. Tranilast has low bioavailability as eye drops (5%) and short life so a comparison of 0.15mg free $t_{free}$ and bound in microspheres ($t_{micro}$) was injected into the capsule after phacoemulsification without IOL in 37 rabbits. A severe anterior chamber exudation was noted in all animals but not histological evidence of tissue damage was seen. In the animals with the sustained release preparation, reduced PCO was noted for up to 3 months. The mode of action may be by inhibiting TGF-beta. Because the eye drop form has been available commercially in Japan without toxic effects, the authors felt “further studies are needed to determine the lowest effective concentration and the long-term safety profile”. (Wang et al., 2007)
Immunotoxin 4197x-ricin a “inhibits protein synthesis and human epithelial cell proliferation on the inner surface of the posterior capsule” (Tarsio, Kelleher et al. 1997). Human lens epithelial cells cultured in vitro on their original lens capsules were almost completely inhibited at relatively low concentrations and the effect lasted up to 3 weeks after withdrawal of the immunotoxin and several media exchanges. (Tarsio et al., 1997)

In summary, in vivo animal experiments suggest that currently the most effective and least toxic chemical appears to be 5FU used with a sealed capsular irrigation device. The safe effective dose without sealed capsule is not yet determined but appears to lie between 12.5 and 50 mg/mL.

**HUMAN EXPERIMENTS**

The most interesting and specific approach to reducing PCO is by immunotoxins. Immunotoxin (MDX-RA) specific for lens epithelial cells, assessed in a trial of 42 patients against 21 controls, the incidence of PCO was reduced (p=0.004) over a twenty four month follow up. Need for Nd:YAG laser was taken as the endpoint. This is now in larger clinical trials. (Spalton, 1999, Clark, 2000, Clark, 1998)

Heparin eye drops post operatively was used in a case controlled study lasting four years. One hundred patients and 100 controls were followed for at least twenty four months with no complications in the control group. The incidence of fibrotic PCO requiring Nd:YAG was halved in the control group (p=0.15). (Mastropasqua, 1997)

Demineralised water in conjunction with a sealed capsule device used for two minutes after phacoemulsification and implantation of one hydrophilic acrylic IOL was assessed in 17 patients. No side effects were noted compared with controls but “it is not possible to reduce PCO development significantly, thus alternative substances
should be evaluated”. (Rabsilber and I-J., 2006) This is in contrast to the in vitro experiment using excised human anterior capsule specimens. (Crowston et al., 2004)

MMC as used in glaucoma surgery is promptly toxic to the corneal endothelium if it inadvertently enters the eye in a concentration of 200-500 μg/mL but 20 μg/mL “appears non toxic” but perhaps not effective. (McDermott et al., 1994)

Antioxidant vitamins orally have been used to try to reduce the incidence of cataract with conflicting conclusions. (Kuzniarz and al., 2001, Gritz et al., 2006) NO reliable report of their use to reduce PCO could be found.

5FU is being trialed clinically using 50 mg/mL in the sealed capsule device. Short term results are optimistic but long term follow up is awaited. (Milverton, Personal Communication 2006).

In conclusion, there is no pharmacologic preparation currently available clinically for the prevention of PCO in routine cataract surgery.
CHAPTER SIX

Xylocaine - properties and actions

Xylocaine was chosen for this investigation because of its well known safety profile and its lesser known slight cytotoxicity.

Xylocaine is lidocaine hydrochloride, formerly known in some markets as lignocaine. Marketed by the Astra-Zeneca (Sydney, Australia) company, it is the most commonly used drug injected into the eye. Chemically it is 2-diethylaminoaceto-2, 6-xylidide. It is classified as a membrane stabilising agent and is a local anaesthetic of the amide type. It is extremely stable and can be sterilised by autoclaving. The safety of this compound for intraocular use in the form of Xylocaine unpreserved 1% 1mL has been confirmed both short and long term.

Unpreserved Xylocaine solutions are sterile, isotonic and contain also sodium chloride, sodium hydroxide for pH adjustment (between 5 and 7) and water for injection. There is no specific antimicrobial agent. Therefore to prevent cross infection multiple dose containers must not be used. (Spalton, 2000)

PHARMACOLOGY

Lidocaine, like other local anaesthetics, causes a reversible blockade of nerve impulse propagation and is thought to act on the sodium channels of the nerve membrane. They all have effects on the peripheral sensory and motor nerves, brain and myocardium and have been used as therapy for these latter organs.

PHARMACOKINETICS

Lidocaine has rapid onset and medium duration of action compared to other local anaesthetics. Onset of less than five minutes after peripheral infiltration or injection in
the orbit is routine. The 1% concentration has less effect on motor than on sensory nerves.

Plasma binding is dependent on drug concentration and decreases with increasing drug dose so that 60-80% is protein bound in whole blood. Lidocaine passes across the blood-brain and placental barriers by passive diffusion and therefore can diffuse into the brain and brain stem from the orbit in rare circumstances with potentially serious cerebral depression if not promptly recognised.

Approximately 90% of a parenteral dose is rapidly metabolised by the liver by deethylation and less than 10% is excreted unchanged in urine. Metabolic products are active. *(Product Information, eMIMS 2007)*

Injected into the anterior chamber, it is rapidly taken up by the ciliary body and iris, dilating the pupil. It is washed out unmetabolised with a half life of about nine minutes. *(Anders, 1999)* Traces of Xylocaine can be detected in the aqueous after retro and parabulbar block but no ocular or systemic toxicity has been recorded from these injections. *(Salomon, 1990)*

**ADVERSE REACTIONS**

Systemic toxicity has been recorded and begins with central nervous system depression followed, in high concentrations by bradycardia, hypotension and systemic collapse. This is more extensive if systemic absorption follows vascular penetration and in epidural administration where there may be concomitant sympathetic nerve block. Systemic reactions are rare and are generally dose-related to high plasma levels and rarely to hypersensitivity, idiosyncrasy or cardiac intolerance. Xylocaine is sometimes used intravenously in cardiac arrhythmias for its myocardial depressant effect.
Persistent extraocular muscle dysfunction may be due to direct trauma of the injection rather than chemical effect and is rare.

Xylocaine 1% with adrenaline 1:100,000 (or less) may perhaps be safe for the corneal endothelium but studies are lacking. Its main disadvantage would be the low pH of 4.5 approximately which exceeds the pH tolerance of the endothelium (Gonnering, 1979).

**CELL TOXICITY IN VITRO**

In common with other local anaesthetics in this group, lidocaine has some antibacterial and cell toxicity. (Mullin and Rubinfeld, 1997)

Bacterial growth of common nosocomial organisms is also suppressed by various concentrations of lidocaine in a dose dependent fashion in *vivo*. Gram negative organisms were more sensitive than *Staphylococcus aureus*. The authors suggested that local anaesthesia “may have a role in the prophylaxis and, in the case of methicillin resistant and vancomycin resistant bacteria, the treatment of surgical wound infection”. (Parr et al., 1999)

Concentrations of 1% and 2% lidocaine caused a significant decline in colony counts of *E coli* but not *P aeruginosa* and *S epidermidis* and slightly of *S aureus* but when in propofol, “did not exhibit adequate antibacterial activity to prevent infective complications”. (Labetouille et al., 2002) In contrast, the opposite is claimed in another in *vitro* study! (Garaj et al., 1999)
Sodium bicarbonate (NaHCO₃) when added to lidocaine to reduce the uncomfortable sensation of injection by raising the pH, enhanced the killing effect. (Thompson et al., 1993)

(Peck et al., 1985) with reduced cell respiration and dehydrogenase activity. (Fazly and Salt, 1983)

Chinese hamster lung fibroblast cultures exposed up to 48 hours to varying concentrations of bupivacaine, procaine and lidocaine showed “local anaesthetic drugs produce major toxic effects on several cell functions, including cell division and survival”. (Sturrock and Nunn, 1979) Granulocyte phagocytosis activity was depressed by both lidocaine and bupivacaine in vitro. This does not help to explain their antibacterial activity. (Kiefer et al., 2003)

Murine macrophage cell production of nitric oxide was suppressed by lidocaine, suggesting a protective effect against this inflammatory mediator. (Shiga et al., 2001)

Whether these antibacterial actions translate also to lower postoperative endophthalmitis rates is unknown and will take time to evaluate because of the inherent difficulty of assessing the already very low incidence of this complication.

**CELL TOXICITY IN ANIMALS**

Xylocaine 1% and 2% 0.1 mL preservative free anterior chamber injections were compared in 16 healthy dogs. “no adverse ocular effects were observed after intracameral injection.” (Gerding, 2004)

Lidocaine 10 mg or bupivacaine 5 mg was injected into the vitreous of 32 rabbits to determine retinal toxicity. The electroretinogram b-wave (which assessed the outer retina) was depressed for about four hours. Oscillatory potentials (assessing the inner retina) and visually evoked potentials (assessing the ganglion cells and nerve fibre
layer) were not depressed. Histological examination by light microscopy showed no
damage. The authors concluded that these local anaesthetics were safe to the retina in
the doses used clinically. (Zemel et al., 1995) The same results were recorded using 34 rabbits
using intra-vitreal injections of lidocaine 2% 0.2 mL, and bupivacaine 0.75% and a
1:1 mixture of the two. (Liang et al., 1998)

Rabbit corneae were excised and the endothelium was exposed for 20 minutes to
three concentrations of lidocaine in sodium hyaluronate, sodium hyaluronate alone,
balanced salt, distilled water, mitomycin-c 0.02% or dextran 15%. Viscoanaesthetic
solutions of lidocaine were safe to a concentration of 1.65%. (Trivedi et al., 2003)

Porcine corneae (n=18) were exposed to lidocaine unpreserved concentrations of
1%, 5% and 10% for 60 minutes. The 1% did not cause significantly more corneal
endothelial cell toxicity than the controls, indicating that only the 1% should be used
clinically. (Eggeling et al., 2000)

Lidocaine 2% and bupivacaine 0.5% injected intra-camerally caused significant
corneal thickening and opacity in rabbits. These concentrations are available
commercially and “may be a potential risk factor for corneal endothelial injury”. (Guzey
et al., 2002)

Xylocaine 1% and 5% were applied to excised rabbit corneae for 20 minutes and
then stained with trypan blue and alizarin red (which stain collagen). There was no
staining but the “5% had more marked cell alterations”. (Werner et al., 1998)

Lidocaine 4%, bupivacaine 0.75%, proparacaine 0.5% and tetracaine 0.5% were
injected into the anterior chambers of rabbits at lens surgery. All produced corneal
thickening and opacification, tetracaine being the least toxic. These are the
concentrations available commercially as eye drops and therefore should not enter the eye. (Judge et al., 1998)

Electron microscopy of 8 rabbit corneae and irides after intracameral lidocaine 1% 0.2 mL and phacoemulsification were compared with a control of 8 eyes. Even a short exposure of intracameral lidocaine to the ocular tissues can induce histological changes that may result in functional defects”. (Atilla et al., 2003)

Lidocaine 1% was evaluated against balanced salt solution by exposing excised anterior capsule fragments for up to five minutes and then stained and analysed by photomicrographs. “Preservative free lidocaine 1% may help diminish the amount of live lens epithelial cells by facilitating cortical cleanup, by loosening the desmosomal area of cell adhesion with decreased cellular adherence or by direct toxic effect. The use of this agent may help prevent posterior capsule opacification”. (Vargas et al., 2003)

Lidocaine 1% preservative free plus carbachol 0.01% 0.02 mL compared with normal saline in rabbits “did not produce morphological changes in the corneal endothelium” on scanning electron microscopy of the excised buttons after intracameral injection. The evaluation was at one week and at one month. (Liou et al., 2004)

In conclusion, lidocaine in the form of Xylocaine unpreserved is not toxic to the cornea in the concentrations currently in clinical use, (1% or less) but has definite cytotoxic effects in higher concentrations. In many of the reports, the pharmaceutical name lidocaine was used and it is not clear whether Xylocaine was the agent. This may be important in view of the observations on pH and osmolality mentioned above.
ACTIONS OF XYLOCAINE (LIDOCAINE)

Xylocaine has a well known reputation as a safe local anaesthetic for injection and topical use. It has interesting effects on cell viability, reducing respiration and dehydrogenase activity and this effect is explored in the clinical series reported here.

IN VITRO

It has been noted for a long time that the positive culture rate from clinically diagnosed bacterial conjunctivitis is much lower than expected. This is because local anaesthetics are used in the conjunctival sac before taking the culture but they have an antibacterial effect. (Mullin and Rubinfeld, 1997)

Comparison of the inhibitory effects of topical proparacaine 0.5%, tetracaine 0.5% and cocaine 4% on Pseudomonas aeruginosa and Staphylococcus aureus was tested in culture over 24 hours. Cocaine had the weakest inhibition but the greatest anaesthesia. The authors’ suggestion that cocaine be used before taking a conjunctival culture is impractical in the clinic because of the need to maintain a dangerous drug register. Tetracaine may produce more positive cultures while giving satisfactory anaesthesia. (Mullin and Rubinfeld, 1997) Similarly, common pathogenic bacteria have a poor recovery rate in skin biopsy specimens when Xylocaine is used. (Thompson et al., 1993)

Lidocaine 1% was not as effective as oxybuprocaine 0.2% or tetracaine 0.4% against 48 bacterial strains using minimum inhibitory concentrations against standard bacterial concentrations. This is contrary to the above report but the author agreed that commercially available eye drops might lead to false negative bacterial cultures. (Labetoulle et al., 2002)

Lidocaine 1,846 micromole, bupivacaine 770 micromole and ropivacaine 801 micromole were tested against staphylococcus aureus suspended in human blood
cells. Monoclonal antibody staining was used as the test method showing that granulocyte capability to ingest bacteria was significantly reduced by the first two but not the third. No comment was made as to whether bacterial growth was inhibited or enhanced. (Kiefer et al., 2003) Natural killer cell inhibition by lidocaine occurs very rapidly at concentrations that are clinically relevant for infiltration anaesthesia. (Krog et al., 2002) This point becomes important in the clinical setting as local anaesthetics, usually Xylocaine, are sometimes mixed with solutions for intravenous use to reduce discomfort to the patient. A common combination of lidocaine (various concentrations) in the centrally acting intravenous anaesthetic propofol tested against \( E\ coli, S\ aureus, S\ epidermidis \) and \( P\ aeruginosa \) showed that lidocaine needed to be in a concentration of 2% to reduce the number of bacteria. (Oser et al., 2002), (Gajraj et al., 1999)

Lidocaine may also be infiltrated into incisions at the end of operations to reduce post operative pain. Would the above findings lead to increased wound infection? Tested against \( E\ faecalis, E\ coli, P\ aeruginosa \) and \( S\ aureus \) in lidocaine with and without epinephrine demonstrated a dose dependent (1 to 4%) inhibition of growth of all strains especially gram-negative but least \( S\ aureus \). The author recommended wider application of the method. (Parr et al., 1999) In contrast, lidocaine used in liposuction does not reach concentrations significant to inhibit the growth of commonly encountered bacteria. (Craig et al., 1999)

In summary, lidocaine has a dose related toxic effect on a wide variety of cells. It acts by reducing cell respiration and dehydrogenase release and reduces the desmosomal area, reducing cell adhesion. Its effects on the cells of the posterior capsule of the lens of the human eye are considered in the next chapter.

The study in this thesis attempts some improvement in PCO rates by a pharmacological method that has not been reported previously. It utilises the known
safety of Xylocaine unpreserved 1% 1mL commonly used intraocularly with its known toxicity against some bacteria in this concentration. Higher volumes and/or concentrations can be toxic to corneal endothelial cells.

By using the Xylocaine as hydrodissection fluid instead of balanced salt solution it was hoped that sufficient lens epithelial cells would be killed to reduce PCO rates. It is well documented that this dose does not damage the corneal endothelium and all should be removed from the eye during the lens removal that follows. Even if some remains, the half life of Xylocaine in the anterior chamber of the eye is approximately 9 minutes so that long term effects are unlikely.
Chapter Seven

Xylocaine - the Human Experience

Xylocaine unpreserved intraocularly is safe if infused in concentrations of 1% or less, a volume of 1 mL or less and especially if used underneath a viscoelastic device.

The pH tolerance of the human cornea is 6.5 to 8.5 (Gonnering, 1979) and osmotic tolerance 200 to 400 mOsm/L, (Edelhauser, 1981) as discussed above. The pH of unpreserved Xylocaine is 5.7 approximately according to the manufacturer.

“Preservative free lidocaine 1% may help diminish the amount of live lens epithelial cells by facilitating cortical cleanup, by loosening the desmosomal area of cell-cell adhesion with decreased cellular adherence, or by direct toxic effect”. (Vargas 2003)

The purpose of this study was to seek empiric evidence to support the utility of hydrodissection with Xylocaine 1%, mL preservative free in the prevention of posterior capsule opacification and not to study the mechanisms whereby this may occur. In this context, a detailed discussion of the interaction of Xylocaine with lens epithelial cells is not warranted.

Accidental injection of local anaesthetic into the eye has been recorded. A high standard report summarised three patients who had intravitreal injection of local anaesthetic inadvertently during ocular procedures. Even though these preparations contained epinephrine 1:100,000 there was no permanent damage to the retina. Retinal function was lost immediately but recovered starting in four and being complete within sixteen hours. One patient developed traumatic retinal damage at the perforation site. (Lincoff et al., 1985) Note that these good results in patients will be achieved
only if the perforation of the globe is recognised immediately by the surgeon or anaesthetist and the raised intraocular pressure which develops from the increased volume from the injection is treated without delay; otherwise ischaemic retinal damage will follow.

These authors followed these observations by intravitreal injection in four adult cats using saline as control, lidocaine 2%, lidocaine 2% with epinephrine 1:100,000 and hyaluronidase 15 units/cc. Electroretinogram (ERG) recordings showed rapid extension for about four hours but full recovery by eighteen hours. Histological examination of the retinae at twenty-four hours showed no significant retinal damage from any of the three preparations. (Lincoff et al., 1985)

Another instance of intra-cameral lidocaine injection was recorded in a patient who had a traumatic rupture of a penetrating corneal graft having undergone a planned vitrectomy previously. 0.5 cc of unpreserved lidocaine 1% was used as anaesthesia during the surgery and it diffused back to the retina causing temporary visual loss with complete recovery one day postoperatively. (Heuermann et al., 2002)

These results were supported as an incidental observation in a study that looked at levels of local anaesthetic in aqueous humour following retrobulbar injection of local anaesthetic. Small amounts of anaesthetic do reach the aqueous humour following peribulbar or retrobulbar injection. These techniques have been used for many years and there are no records of toxicity to the cornea from these injections. (Salomon, 1990) A study of 1,000 eyes having cataract and intraocular lens surgery was conducted to determine lidocaine efficacy as anaesthesia. This study found no toxic effects to the eye from lidocaine unpreserved 1%. (Koch, 1997)
Lidocaine unpreserved 1% 0.1 mL was used in a well designed prospective double masked study of 183 patients compared with balanced salt solution as control. Although the study was designed to assess efficacy as anaesthesia, the authors observed that in neither group was there significant endothelial cell loss or other adverse event. (Gills et al., 1997) These findings were confirmed by a series of 80 patients using 0.3 mL unpreserved lidocaine 1% against a control of normal saline. (Roux, 1998)

Safety was also confirmed by a number of studies using preservative free lidocaine 1% up to 0.5 mL volume showing that specular microscopy and/or computer assisted morphometry showed no increase in the corneal endothelial cell loss or mean cell size in the short term. There is always some endothelial cell loss in any intraocular surgery. (Garcia et al., 1998, Martin, 1998, Maskett and Gokomen, 1998, Elvira et al., 1999)

A study that looked at 200 consecutive cataract surgeries compared 0.15 mL of intracameral 1% unpreserved lidocaine with patients who had parabulbar anaesthesia. The flash electroretinogram (ERG) was also evaluated in this study. There was no statistically significant difference to the transient suppression of the erg between the groups and all recovered fully. (Anders, 1999)

A single centre, prospective, randomised, double masked study comparing 0.5 mL unpreserved lidocaine 1% with balanced salt in 190 patients undergoing cataract surgery set out to assess whether the additional intraocular anaesthesia was superior to drops of tetracaine only preoperatively. The authors concluded that there was little difference in pain but did note that although there was no evidence of corneal endothelial toxicity in the short term, the long term studies were not available at that time and urged caution in the use of the procedure. (Boulton et al., 2000)
As mentioned in previous chapters it is important to use an agent which has pH and osmolarity close to isotonic. A report of corneal endothelial haze immediately after injection of generic lidocaine product showed that it was hypotonic with an osmolarity of 129 mOsm/L and a pH of 5.06. This hypotonicity was potentially damaging to the corneal endothelium. The manufacturer’s data sheets did not record these parameters. (Spalton, 2000) These facts must be obtained prior to intraocular use of any generic product. Pharmacists may not check these parameters when searching for the cheapest supplier. This step is extremely important and neglect would possibly be culpable.

Blood-aqueous barrier (BAB) permeability was studied in 60 patients having uneventful cataract surgery comparing sub-tenon’s anaesthesia with 0.2 mL of 1% preservative free lidocaine. It was concluded that the BAB permeability one month after surgery had recovered. No additional inflammation was induced by the intraocular lidocaine. Endothelial cell morphology was also not compromised. (Iradier et al., 2000)

A further study of 67 patients having cataract surgery with intraocular unpreserved lidocaine 1% 0.3 mL compared to a placebo found no toxic effects from the lidocaine in the short term. (Roberts and Boytell, 2002)

Similar findings of no untoward events using 0.5 mL of preservative free 1% Xylocaine in the anterior chamber were found in a study that was designed to assess the pupil dilating effect without preoperative eye drops. (Cionni et al., 2003) This result was supported in the study of 30 patients without and 27 with intracameral lidocaine 1% 0.5 mL. (Nikeghbali et al., 2007)
Lidocaine mixed with mydriatics was injected intracamerally in 60 patients to try to avoid preoperative drops. “The corneal cell loss in our study is in accordance with that reported in modern phacoemulsification surgery”. This study also shows that there is no negative interaction between Xylocaine 1% and pupil dilating substances. (Lundberg and Behndig, 2003) Whether the combination was more effective than either alone was not noted.

The long term effect on corneal endothelial safety was addressed in a study of fifty-three patients using Xylocaine 0.2 mL 1% preservative free compared to controls and followed for twelve months. Using specular microscopy and ultrasound corneal pachymetry it was concluded that “intracameral preservative free 1% Xylocaine does not appear to effect the corneal endothelium during phacoemulsification”. (Shah, 2004) Similar results at twenty months after surgery using specular microscopy were found in 78 eyes comparing 0.15 mL of unpreserved lidocaine 1% with peribulbar anaesthesia. (Heuermann et al., 2002)

Systemic levels of lidocaine after intracameral injection of 0.5 mL 1% preservative free was studied in ten patients. It revealed no systemic therapeutic concentrations so that the technique would be safe for patients in whom the anti-arrhythmic effects of Xylocaine may be contra-indicated. (Wirbelauer et al., 1999)

An extensive report by the American Academy of Ophthalmology on the effectiveness of intracameral anaesthesia summarised the published literature in 2001. It noted “short term studies seem to indicate that preservative free lidocaine 1% up to a dose of 0.5 mL is well tolerated by the corneal endothelium in the short term”. There was no evidence at that time of the effects of higher concentrations. (Karp et al., 2001)
Pharmacodynamics of lidocaine in the eye was studied in both rabbits and humans. This showed rapid uptake of radioisotope labelled 1% Xylocaine into the ciliary body but also a rapid washout with half life of nine minutes with no metabolites detected.\(^{(\text{Anderson et al., 1999})}\)

Toxic anterior segment syndrome (TASS) was reported in three patients when 1% Xylocaine 1.5 mL was used for hydrodissection. It was recommended that the volume used should not exceed 1 mL\(^{(\text{Gills, 2004})}\). The cause of the TASS was attributed to the Xylocaine but they were a small number in a large series and being postoperative there was no opportunity to analyse the ampoules used, as they had already been disposed. The clinical safety of intracameral lidocaine was summarised by an evidence based medicine supporter. “the clinical toxicity is negligible, the cost is extremely low”\(^{(\text{Schuster, 2001})}\).

**SUMMARY**

The short term safety to the corneal endothelium of intracameral Xylocaine 1% unpreserved in humans during routine phacoemulsification is well established and two long term studies support this as well as extensive clinical experience. In the study reported herein, the volume of 1% preservative free Xylocaine was limited to 1 mL and it was used underneath a viscoelastic protecting the cornea. The lack of untoward events in this series also confirms its safety.

Xylocaine was used because of its extensive clinical experience and well established safety record and consistent pharmacological composition when compared to other preparations of lidocaine especially generic ones.
CHAPTER EIGHT

Materials and methods

**STUDY DESIGN.**

The concept is to assess the incidence of PCO after cataract surgery with IOL implantation comparing hydrodissection with conventional balanced salt solution against unpreserved Xylocaine 1% 1mL.

Generic preparations vary in their specifications and were not used in this reported series for safety reasons and for consistency. In some of the research papers quoted, it is not stated whether the lidocaine reported was generic or specific.

**PATIENT RECRUITMENT.**

All surgery was performed by the author at Calvary Hospital, Bruce, Australian Capital Territory and Calvary John James Hospital, Deakin, Australian Capital Territory. Ethics committee approval was obtained from each hospital authority prior to commencement (HREC ref 10-2004; and 03/11.2004). Surgical technique and IOL design was standardised throughout. All patients with uncomplicated cataract on the surgical list at each hospital were included in the prospective cohort of the series starting 01.01.03. A retrospective balanced cohort was used for comparison extending back up to 8 years.

**SURGICAL TECHNIQUE.**

After a full ophthalmological examination, the need for cataract surgery including risks was discussed with the patient. Cataracts other than of senile cause were not included in this series. All patients had an anaesthetic block of the anaesthetist’s and patient’s choice. At surgery, a sclerocorneal incision using a 2.65mm keratome was
made. Viscoelastic was introduced into the anterior chamber using the two components of ‘Duovisc’ (Alcon, Sydney, Australia) in a soft shell technique. Anterior capsulorhexis of 5-6 mm was performed with either a needle or with the author’s design of multi function capsulorhexis forceps. Hydrodissection was performed in at least two sites using either the standard balanced salt solution or Xylocaine unpreserved 1% 1 mL. If a further volume of fluid was needed for complete rotation of the lens nucleus in the Xylocaine group, balanced salt was used. Phacoemulsification was performed with two side ports using either the Millenium machine (Bausch and Lomb) or the Sovereign (AMO) and a Kelman style angled microflow-plus needle in both. Irrigation-aspiration of the remaining material was done with automated bimanual technique. In all cases, foldable lens (AMO ar40e) was inserted in the bag and all viscoelastic was aspirated leaving the eye at a normal pressure. Sutures were not used routinely. No attempt to assess pain relief was made in this series.

The patients were assessed at a minimum of one day, one week and three weeks post operatively and then as clinically necessary and were routinely re-assessed at one year unless they requested earlier review.

The need for posterior capsulotomy by Nd:YAG laser was assessed after ruling out other reasons for reduced vision although capsulotomy was done in some patients with multiple causations of loss of best corrected visual acuity post operation.

Another surgeon who had not been involved with the patient previously then independently reassessed the need for capsulotomy and performed all the laser treatments as indicated. Capsulotomy was not done unless the vision was reduced by at least 1 Logmar line beyond their best corrected post operative acuity and the patient was symptomatic. Subsequent follow up depended on clinical need.
There were 842 eyes in the control group and 692 in the Xylocaine group totalling 1534. Age and sex distribution are in Tables 3 and 4 and are comparable.

There was no change in postoperative progress between the two groups.

**STATISTICAL ANALYSIS.**

This was conducted independently by Dr K Dear, Australian Centre for Epidemiology and Health, Australian National University. The methodological details are in Chapter 9 to avoid replication and to enhance readability.
CHAPTER NINE

Results of the current study

The author used identical surgical technique and the same IOL and performed all surgeries. The single variable was the substitution of Xylocaine 1% 1 mL unpreserved for hydrodissection for the routine balanced salt solution. Time from IOL to Nd:YAG varied from 33 days to over 8 years.

STATISTICAL METHOD

The data was analysed using Cox regression, with date of IOL as a covariate. A nonparametric smooth curve was fitted (natural spline with 4df) plus a two-level factor distinguishing IOL operations done before and after 1/1/2003. The last Nd:YAG laser operation on a patient in the study took place on 21/8/2007 (that patient’s IOL was dated 9/12/2004). Patients who had not required Nd:YAG treatment by then were ‘censored’ at that date for purposes of time-to-failure analysis (“survival analysis”). Analysis was done using stata 9.2.

(http://www.ststa.com/support)

RESULTS

Of 842 IOL operations prior to the change over date of 1/1/2003, 155 have required Nd:YAG (18%). Of 692 subsequently, 26 have required Nd:YAG (4%). However, as Figure 11 shows, this percentage was already declining steeply before 2003, and rose slightly in 2004 (data for 2005 are incomplete). Figure 10 shows the percentage of patients requiring Nd:YAG within two years of the operation (data for 2005 are incomplete).
### TABLE 2 – ND:YAG REQUIRED IN THE SERIES

<table>
<thead>
<tr>
<th>YEAR</th>
<th>NO</th>
<th>YES</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>55</td>
<td>27</td>
<td>82</td>
</tr>
<tr>
<td>%</td>
<td>67.07</td>
<td>32.93</td>
<td>100.00</td>
</tr>
<tr>
<td>1999</td>
<td>97</td>
<td>32</td>
<td>129</td>
</tr>
<tr>
<td>%</td>
<td>75.19</td>
<td>24.81</td>
<td>100.00</td>
</tr>
<tr>
<td>2000</td>
<td>95</td>
<td>36</td>
<td>131</td>
</tr>
<tr>
<td>%</td>
<td>72.52</td>
<td>27.48</td>
<td>100.00</td>
</tr>
<tr>
<td>2001</td>
<td>211</td>
<td>38</td>
<td>249</td>
</tr>
<tr>
<td>%</td>
<td>84.74</td>
<td>15.26</td>
<td>100.00</td>
</tr>
<tr>
<td>2002</td>
<td>233</td>
<td>22</td>
<td>255</td>
</tr>
<tr>
<td>%</td>
<td>91.37</td>
<td>8.63</td>
<td>100.00</td>
</tr>
<tr>
<td>2003</td>
<td>264</td>
<td>8</td>
<td>272</td>
</tr>
<tr>
<td>%</td>
<td>97.06</td>
<td>2.94</td>
<td>100.00</td>
</tr>
<tr>
<td>2004</td>
<td>251</td>
<td>14</td>
<td>265</td>
</tr>
<tr>
<td>%</td>
<td>94.72</td>
<td>5.28</td>
<td>100.00</td>
</tr>
<tr>
<td>2005</td>
<td>151</td>
<td>4</td>
<td>155</td>
</tr>
<tr>
<td>%</td>
<td>97.42</td>
<td>2.58</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### TABLE 3 – AGE DISTRIBUTION (YEARS)

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>MEAN</th>
<th>MEDIAN</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SALINE (PRE 1/1/2003)</td>
<td>75</td>
<td>77</td>
<td>40-96</td>
</tr>
<tr>
<td>XYLOCAINE (POST 1/1/2003)</td>
<td>76</td>
<td>77</td>
<td>41-97</td>
</tr>
<tr>
<td>TREATMENT</td>
<td>FEMALES</td>
<td>MALES</td>
<td>TOTAL</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Saline (pre 1/1/2003)</td>
<td>546</td>
<td>296</td>
<td>842</td>
</tr>
<tr>
<td>PERCENTAGE</td>
<td>64.85</td>
<td>35.15</td>
<td>100.00</td>
</tr>
<tr>
<td>XYLOCAINE (POST 1/1/2003)</td>
<td>428</td>
<td>264</td>
<td>692</td>
</tr>
<tr>
<td>PERCENTAGE</td>
<td>61.85</td>
<td>38.15</td>
<td>100.00</td>
</tr>
<tr>
<td>TOTAL</td>
<td>974</td>
<td>560</td>
<td>1,534</td>
</tr>
<tr>
<td>PERCENTAGE</td>
<td>63.49</td>
<td>36.51</td>
<td>100.00</td>
</tr>
</tbody>
</table>
Figure 10. Percentage of patients requiring posterior capsulotomy by laser at 2 years post op. The data for year 2005 are incomplete.
Figure 11 shows the relative risk of requiring Nd:YAG relative to the minimum (optimum) time in early 2004. The model permitted a step change at 1/1/2003, coinciding with the introduction of Xylocaine. The estimated change at this date is not statistically significant (p=0.855). Figure 12 shows the (very similar) result of fitting the same model, but ignoring the change at 1/1/2003.

Figure 12 – Relative risk of requiring Nd:YAG by date of IOL. Grey bands are 95% ci. Coloured tickmarks show dates of IOL (below) and of Nd:YAG (above). Yellow=saline; green=Xylocaine. P=0.855 for the step at 1/1/2003: not statistically significant. Patients with IOL operations performed after august 2005 are not included.
CONCLUSION

There was a strong trend of reducing risk from 1999 to 2004, with a seven-fold risk difference between the highest and lowest points on the curve. There is no evidence of any effect from the 1/1/2003 introduction of Xylocaine 1% unpreserved 1 mL during IOL operations.

The slight rise in 2004, noted in Figure 10 and already identified in the results, did not achieve significance in the modelling. The modelling is accepted, as the basis for the conclusion that improved operator effect is the most likely explanation for what at first sight appears to be a positive effect of Xylocaine. The 2004 results do not distort the overall model and the conclusions drawn from it.

The original concept by the author of using a known safe drug in a novel way did not result in any statistical improvement in PCO occurrence in this series and had no untoward effects.
POSTERIOR CAPSULE OPAQUE AFTER CATARACT EXTRACTION AND INTRAOCULAR LENS EXTRACTION IS A CONTINUING PROBLEM FOR PATIENT AND SURGEON EVEN THOUGH RATES ARE REDUCING WORLD WIDE WITH IMPROVEMENTS IN SURGICAL TECHNIQUE AND IOL DESIGN AND MATERIALS.

PHARMACOLOGICAL METHODS OF REDUCING PCO WILL BECOME MORE IMPORTANT IN THE FUTURE WITH THE INTRODUCTION OF NEW STYLES OF IOLs (SUCH AS ACCOMMODATING) THAT DO NOT APPOSE THE POSTERIOR CAPSULE AND IN REFRACTIVE LENS EXCHANGE. THESE OPERATIONS DEPEND ON A PERMANENTLY CLEAR CAPSULE IN EVERY CASE AND CAPSULOTOMY MAY PERHAPS THREATEN THE STABILITY OF THE IOL.

THE AUTHOR CHOSE TO UTILISE THE KNOWN SAFETY TO THE CORNEAL ENDOTHELIAL CELLS OF XYLOCAINE UNPRESERVED 1% 1mL AND ITS LESSER KNOWN CELLULAR TOXICITY IN A WAY PREVIOUSLY UNREPORTED. A PROSPECTIVE GROUP OF 842 PATIENTS WITH UNCOMPILCATED CATARACTS WAS TAKEN IN ORDER OFF THE HOSPITAL SURGERY WAITING LISTS AND WAS MATCHED WITH AN AGE AND SEX BALANCED GROUP OF 692 RETROSPECTIVELY. A SMALL NUMBER OF PATIENTS REQUIRED EXTRA FLUID IN THE FORM OF BSS FOR ADEQUATE HYDRODISSECTION. IT WAS FELT THAT THIS DID NOT INVALIDATE THE HYPOTHESIS BECAUSE OF THE SHORT HALF LIFE OF XYLOCAINE IN THE EYE.

THE END POINT FOR YAG LASER POSTERIOR CAPSULOTOMY WAS TAKEN AS THE SYMPTOMATIC LOSS OF BEST CORRECTED POST OPERATIVE VISUAL ACUITY OF AT LEAST ONE LOGMAR LINE. AN INDEPENDENT OPHTHALMOLOGIST WHO HAD NOT PREVIOUSLY BEEN INVOLVED WITH THESE PATIENTS AND WHO PERFORMED ALL THE TREATMENTS REASSESSED THE NEED FOR YAG. NO TOXIC EFFECTS FROM THE XYLOCAINE WERE NOTED.
An expert statistician then assessed statistical analysis again independently. His conclusion was that the trial of Xylocaine hydrodissection showed no improvement as compared with the author’s trend line (which was also consistent with world wide trends).

In the continuing search for a substance that will kill lens epithelial cells and not corneal endothelial cells, Xylocaine unpreserved 1% 1 mL is shown to be the safest. Higher concentrations are not proven to be safe and in some cases are toxic in a dose related fashion. Larger volumes may not be toxic because of the short half life but are not proven safe. Xylocaine kills cells by reducing respiration and dehydrogenase levels and reducing desmosomal area thus reducing adhesion.

Incorporating Xylocaine into a hydrophilic IOL as a sustained release delivery mechanism as described above for 5FU has not been explored in humans but should be safe at a release dose to be determined.

5FU is cheap and is effective at a dose perhaps 33 mg/mL which may be toxic to the corneal endothelium. Use in a sealed capsule irrigation device should be safe and the technique should be able to establish a minimum inhibitory dose and concentration for this and for other substances including some of the above substances (chapter 5). These can be tested in vitro and later in vivo.

In the future, elegant methods of preventing lens epithelial cell proliferation such as immunotoxins and gene therapy may prove to be safe and effective in clinical practice. More evidence is needed particularly which toxins and which genes even though some are currently under investigation. A suggestion that growing the patient’s own lens epithelial cells and reinjecting them into the capsular bag is probably impractical in view of a time lag that would be unacceptable to the patient.
Disclaimers

Conflict of interest – none.

External funding – none.

Ethics committee approvals obtained before starting the series, see Appendix.

APPENDIX

John James
Memorial Hospital

03/11/2004
Dr Thomas D. Walker
PO Box 3171 MANUKA
ACT 2603

Dear Dr Walker

Re: Potential Paper for Publication

The John James Memorial Hospital Ethics Committee, at its meeting on 28th of October 2004, noted your letter and feel that there is no ethical problem given that you already had the data outside the usual requirements of confidentiality. There are no further questions at this time.

Yours sincerely

[Signature]
10 October 2006

Dr Tom Walker
c/- Post Office
Yarralumla
ACT 2600

Dear Dr Walker

Re: The effect of hydro dissection in cataract surgery with Lignocaine 1 % plain (HREC ref: 10-2004)

I am writing on behalf of the Calvary Health Care ACT Human Research and Ethics Committee to request a brief progress report on the above-named study. Please note that the NH&MRC’s guidelines on Ethical Conduct in Research Involving Humans require that reports be provided at least annually. It would be appreciated if you could ensure that we receive your report by 20 October to enable it to be tabled at the next meeting of the HREC.

Annual reports should include the following information:

- Progress to date (or outcome in the case of completed research)
- Maintenance and security of records
- Compliance with the approved protocol
- Compliance with any conditions of approval

The HREC also requires an immediate report in any of the following events:

- Any serious or unexpected adverse effect on participants
- Any proposed changes to the protocol
- Any unforeseen events that might affect continued ethical acceptability of the project
- Discontinuation of the project before the expected date of completion

I look forward to receiving your report in due course.

Yours sincerely

Tricia Ewing
Manager, Human Research & Ethics Committee
Services of the Sisters of the Little Company of Mary
with values of hospitality, healing, stewardship and respect
Calvary Public Hospital | Calvary Private Hospital | ACT Hospice | Calvary Clinic | Calvary Foundation
Two fully accredited hospitals - Public and Private
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Pharmacological attempts to reduce PCO after cataract surgery: A review

Thomas D Walker FRANZCO.
Calvary Hospital, Bruce and Calvary John James Hospital, Deakin
Australian Capital Territory.

ABSTRACT
Reduction of Posterior Capsule Opacification (PCO) after cataract surgery has been achieved since the general acceptance of posterior chamber intraocular lens implantation thirty years ago. Attention to surgical technique on one hand and changes in lens design and materials on the other, have synergistically reduced the incidence of PCO to less than 5% at 5 years. But lens epithelial cells still proliferate and pharmacological prevention has so far been largely unsuccessful. Any agent must be toxic to these lens epithelial cells without being toxic to the corneal endothelium. This review looks at many substances that have been tried and a few that have been partly successful without yet entering clinical practice. Possibilities for future clinical research are canvassed.

For reasons of copyright, the full text of article can be seen in Clinical and Experimental Ophthalmology 2008; 36: 883-890.