

## Issues related to the appropriate trial design for evaluation of Clear Lens Extraction for the correction of Presbyopia

Clear-lens extraction (CLE) is a surgical procedure in which the non-cataractous crystalline lens is removed and replaced with an intraocular lens for refractive purposes. This paper is written in an attempt to delineate issues specific to the correction of presbyopia with multifocal intraocular lenses (MIOLs) in a cohort of subjects whose crystalline lens is clear.

Our literature review revealed very limited published information specific to clear lens extraction for the correction of presbyopia.

Dick et al.<sup>1</sup> report on a prospective study of 25 patients undergoing bilateral CLE followed by posterior chamber multifocal intraocular lens (MIOL) implantation. These patients ranged from 44 to 62 years of age with the average age of 51 years. Their preoperative refractive spherical equivalent (SE) error ranged from -15.50 to +5.75 diopters (D). The follow-up period of this study was limited to 6 months. During this time there were no eyes with any potential sight threatening complication or posterior capsular opacification (PCO). However, 48% (12/25) of patients reported starbursts and 36% (9/25) had halos. Efficacy appeared acceptable in all patients with binocular uncorrected visual acuity (UCVA) of 20/30 and J4 or better in all patients

Packer et al.<sup>2</sup> report on a retrospective study of 68 eyes in 36 patients with CLE followed by posterior chamber MIOL implantation. Thirty four percent (23/68) of the eyes had an additional refractive procedure to correct preoperative astigmatism. Only short term follow-up (3 and 6 months) is available for this study. Efficacy outcomes were acceptable with 94% (64/68) having UCVA of 20/40 and J5 or better. YAG capsulotomies were performed in 5.9% (4/68) of the patients who had symptomatic PCO. This article did not provide complication rates or assessment of visual symptoms.

Due to the lack of good long term studies in the literature on safety and efficacy of clear lens extraction for the correction of presbyopia, we analyzed what is known about clear lens extraction with insertion of monofocal intraocular lenses for correction of refractive errors.

Vicary et al.<sup>3</sup> present analyses of 138 cases of clear lens extraction performed by a single surgeon for correction of ametropia. The pre-operative SE refraction ranged from -23.75 to +11.62 D. The mean age in this retrospective study was 48.9 years (range from 22 to 69). Mean follow-up was 5 months (range 2 to 26 months). Efficacy outcomes at 3 months showed 90% of eyes with UCVA of 20/40 or better; and 49.3% with 20/20 or better. Complications included one eye (0.7%) with a retinal detachment (RD) at 5 months after surgery; 1 eye (0.7%) with uveitis; 11 eyes (8.0%) with significant PCO requiring YAG capsulotomy. Seven cases (4.9%) were in need of additional refractive surgery (3 eyes for piggyback IOL and 4 eyes for IOL exchange).

Several studies of CLE for hyperopia<sup>4-8</sup> in United States, England, Belgium, India and Greece have reported positive results for efficacy. These studies tended to be rather small (18 to 50 eyes), with the aggregate total number of eyes for these 6 studies being 181. The overall age ranged between 19 and 86 years and the range of pre-operative SE refractive error was +2.75 to +13 D. The follow-up for these studies tended to be rather short (1 month to 60 months). PCO was the most common complication observed in these studies. Rates of PCO requiring YAG capsulotomy ranged from 5.6%<sup>6</sup> to 54%<sup>7</sup>. Posterior capsular tears were reported<sup>5,7</sup> at rates of 2.9% to 5.3%. De Smets and Vrijghem<sup>5</sup> reported single cases (1/38) of iris prolapse, iridodialysis, and corneal burn. There were reports of 2 IOL exchanges; one for power miscalculation<sup>5</sup> and another one due to nanophthalmos<sup>6</sup>. One case of malignant glaucoma<sup>6</sup> was reported 2 years after surgery. Endothelial cell loss of 7.38% (range 3% -15%) at 12 months was reported by Signanos and Pallikaris<sup>7</sup>.

Several studies of CLE for high myopia<sup>9,10,11,12</sup> in Spain, Italy and France have reported high efficacy rates and low RD and other complication rates. However, problems with these studies are short follow-up times and exclusion of those lost to follow-up.

Colin et al.<sup>14</sup> present an extended 7 year follow-up of 52 eyes in 30 patients having CLE with IOL for high myopia (> -12 D). The mean preoperative SE was -16.9D (+/- 3.2) and 64% had an axial length of >29mm. The mean age for these patients was 36.2 years with a range of 22 to 51 years. Thirty eyes (61.2%) developed significant PCO and had YAG capsulotomies. During the first 4 years post-CLE 18 eyes (36.7%) had capsulotomies. The mean time to capsulotomy after CLE was 48.4 months with a range of 9 to 75 months. Forty percent of the PCOs occurred between 4 and 7 years after CLE. Patients with lattice degeneration, retinal tears or holes were treated with argon laser photocoagulation prior to CLE. However, the 7 year retinal detachment rate in this cohort was 8.1% (4/49). At 4 years, the retinal detachment rate in this cohort was 2.0%. Three of the 4 eyes had YAG capsulotomies, one eye 1 year prior and two eyes 2 years prior to the RD. One eye had a subfoveal choroidal neovascularization at 9 months after CLE with a decrease in BCVA from 20/50 to 20/200. After 7 years, the predictability analyses revealed SEs of 59.1% of eyes were within +/- 1.0 D of emmetropia and 85.7% of eyes within +/- 2.0 D.

Ripandelli et al.<sup>13</sup> report on 53 eyes seen by vitreoretinal surgeons due to retinal detachments secondary to CLE for high myopia. The average age was 37.5 years with a range of 25 to 58 years. The average pre-CLE operative SE was -19.5 D with a range of -14 to -29 D. Thirty of the eyes had received prophylactic treatment before CLE. All of the 41 eyes in 39 patients (12 patients lost to follow-up) had macular involvement. The average time from CLE to RD was 2.25 years with a range of 1 month to 4 years. Fourteen eyes had YAG capsulotomies. The authors comment on the difficulties with the surgical management of these cases due to proliferative vitreoretinopathy (17 eyes) and posterior retinal breaks (14 eyes). Thirty six had the retina reattached. Only 9 eyes ended up with a final visual acuity of 20/60 or better. One patient, with visual acuity prior to CLE of 20/20 and 20/25, ended up with hand motion (HM) in one eye and 20/100 in the other after bilateral surgery.

In a recent review of CLE for myopia, O'Brien et al.<sup>15</sup> point out that even though the efficacy in refractive results are encouraging, based on the available literature, the potential complications still outweigh these benefits.

### **Retinal Detachment after Cataract Surgery**

Review of the literature on clear lens extraction for various refractive indications, revealed that only CLE for high myopia studies have significant length of follow-up (7 years). These studies clearly indicate that rates of RDs continue to increase post-operatively (2% at 4 years, 8.1% at 7 years). Since cataract removal increases the risk of RD irrespective of the subject's refractive error and approximately 40% of all RDs occur in those having had cataract extraction<sup>18</sup>, we conducted a literature search to estimate the rates of RDs in the overall population after cataract extraction with IOL implantation.

The annual incidence of RD in phakic eyes over all ages is approximately 0.0071%<sup>18</sup> The Eye Disease Case-Control Study Group<sup>19</sup> (n=253 cases) found the annual incidence of idiopathic RD in persons over 50 to be approximately 0.03% after elimination of patients with previous intraocular surgery, myopia greater than -8.0 D, congenital vitreoretinal abnormalities, vasoproliferative disease, or intraocular inflammatory disease.

Review of the literature demonstrates that several variables have a significant effect on the rate of RD after cataract surgery. Patient-dependent variables include age, gender, refractive state, status of fellow eye and condition of the posterior vitreous. Surgeon-dependent variables include surgical technique and intraoperative complications. Postoperative factors include trauma and YAG capsulotomy<sup>17</sup>.

A large Danish study<sup>20</sup> of more than 19,000 cataract surgery patients followed for more than 4 years revealed several important findings. The authors showed the highest cumulative 4 year rate of RD was experienced by subjects with ECCE without an IOL at 3.2%; followed by ICCE without IOL at 2.8%; and ECCE with IOL at 0.93%. The cumulative 4 year risk for RD after cataract surgery was significantly greater than the cumulative 4 year risk for RD in an age controlled sample (n=7636) with no previous ocular surgery(0.12%). The first year after ECCE with IOL the RD rate was 0.42% (44/10,493). Younger age was found to be associated with a greater risk of RD with cumulative 4 year risk of RD after ECCE with IOL at 2.43% (95% CI 0.97-3.87) for 50-59 y/o; 1.51% (95% CI 0.87-2.15) for 60-69 y/o; 0.82% (95% CI 0.48-1.15) for 70-79 y/o; and 0.47% (95% CI 0.20-0.73) for 80+ y/o (Fig. 1).

Javitt et al.<sup>16</sup> had similar findings in their study of Medicare beneficiaries with over 300,000 patients. Subjects older than 65 years of age at the time of surgery had RD rates over a 4 year period of 1.55% after ICCE; 0.9% after ECCE; and 1.17% after PE. From the graph of this article, it appears that the first year RD rate after ECCE was 0.3% and after phacoemulsification was 0.4%. There was a significant increase in risk of RD in subjects who were younger at the time of cataract surgery. The percent with RD after 4

years was 2.2% for 65 to 69 years; 1.3% for 70 to 79 years; 0.6% for 80 to 89 years; and 0.2% for 90 years and older (Fig 2).

In a later publication, Javitt et al.<sup>21</sup> showed a significant increase in risk of RD in patients of younger age at the time of ECCE. The 3 year risk increased with each decreasing decade of age (n=57,103): 0.08% for 90 years or older; 0.24% for 80 to 89 years; 0.51% for 70 to 79 years; and 0.95% for 66 to 69 years (Fig 3). The overall 3 year risk of RD after ECCE in this study was 0.46% (261/57103). Our interpretation of the graph in this article points to a first year RD rate of 0.35% (ECCE and PE patients combined).

A retrospective study of a single surgeon's postcataract surgical outcomes<sup>22</sup> reported cumulative rates of RD after phacoemulsification at 0.4% (follow-up 1 to 8 years), after ICCE at 5.4% (follow-up 18 to 22 years), and after ECCE at 1.6% (follow-up 8 to 18 years). Even though this was a large study (n=2739), the outcomes are difficult to interpret due to a significant variation in follow-up time and accountability.

In a Medicare nested case-control study (n=291 cases / 870 controls)<sup>23</sup>, YAG capsulotomy after ECCE was a significant risk factor for RD with an odds ratio of 3.8. A retrospective study comparing RD rates in those having YAG capsulotomies<sup>24</sup> (n=198) with an equal number of matched postoperative controls not having YAG, reported RD rates of 1.0% and 0.5% respectively. Alldredge et al.<sup>25</sup> reported no cases of RDs in their retrospective review of charts of 80 eyes in 61 patients who had preoperative myopia of 7 D or more and underwent phacoemulsification with PC IOL between February 1989 and June 1992. The mean follow-up in this study was 43 months with a range of 9 to 77 months. Six eyes were excluded from the study because they had less than 9 months follow-up and could not be contacted. Twenty four eyes had a YAG capsulotomy for PCO. The mean follow-up after capsulotomy was 20 months with a range of 1 to 49 months.

Rowe et al.<sup>26</sup> reported cumulative probabilities of RD at 2, 5, and 10 years after ECCE and phacoemulsification of 0.36%, 0.77%, and 1.29%, respectively. The estimated cumulative probabilities of RD at the same intervals for a reference group not having cataract surgery were 0.034%, 0.13%, and 0.25%, respectively (Fig. 4).

In summary, it appears that RD rates are significantly higher for younger subjects and higher after phacoemulsification as compared to ECCE. The overall rates of RD during the first postoperative year range from 0.35%<sup>21</sup> to 0.42%<sup>20</sup> (we are assuming that CLE will be performed by phacoemulsification). The RD rate increases to 0.46% at 3 years. The four year cumulative RD rates range between 0.93%<sup>20</sup> to 1.17%<sup>16</sup>. The ten year cumulative RD rate is 1.29%<sup>26</sup>.

Increased rates of RD are clearly of great concern for subjects undergoing clear lens extraction. The next natural question to ask is how large does the study need to be to detect significantly different rates of RD than those seen in subjects who have not undergone any ocular surgery. In order to help Panel members to determine the appropriate sample size and study design, we have calculated appropriate sample sizes for detection of various retinal detachment rates for studies from 1 to 3 years (Table 1).

With the non-treatment historical control rate of 0.01%, the sample size associated with the maximum allowable retinal detachment rate of 0.3% per year is 1014 subjects for a one year study and 321 subjects for a 3 year study.

**Table 1**  
**Sample Size for Retinal Detachment Rate vs Non-Treatment Historical Control**

	Maximum Allowable RD Rate Per Year				
	0.3%	0.5%	1.0%	1.5%	2.0%
1 year study	1014	575	290	195	150
2 year study	482	290	150	100	75
3 year study	321	195	100	65	50

Ho: Experimental RD Rate = Maximum Allowable Rate \* Yrs

Ha: Experimental RD Rate < Maximum Allowable Rate \* Yrs

$\alpha=0.05$ ;  $\beta=0.20$  assuming that the experimental RD rate is  $\sim 0.0001$  per year

## Endothelial Cell Loss

Subjects that undergo CLE with multifocal lens implantation for correction of presbyopia might experience visual symptoms that may require exchange of the IOL. Therefore, their endothelial cell densities need to be adequate to withstand several potential surgeries.

Endothelial cell loss of 7.38% with a range from 3% to 15% at 12 months after CLE was reported by Signanos and Pallikaris<sup>7</sup>.

As part of the development of a joint ANSI and ISO standard for ophthalmic viscosurgical devices, Don Calogero and Malvina Eydeman, MD from FDA in collaboration with Dr. Arsenoff's group from Toronto's Eye Foundation performed a comprehensive review of the ophthalmic literature to determine the endothelial cell loss experienced in the post-operative time (2-6 months) after cataract surgery. Meta-analysis of all of the qualifying literature revealed 8.9% cell loss associated with ECCE and 7.4% associated with phacoemulsification. (see Fig 5). Thus, it appears that endothelial cell loss reported by Signanos and Pallikaris<sup>7</sup> is consistent with the operative endothelial cell loss expected secondary to phacoemulsification.

There is no data in the literature on long term endothelial cell loss after clear lens extraction. Furthermore, there is very little known on long term effects of cataract surgery on the endothelium.

Bourne et al.<sup>27</sup> found a mean loss of 2.5% loss per year over 10 years in eyes implanted with lenses (49 eyes) or remaining aphakic (15 eyes). These were intracapsular and extracapsular surgeries from 1976 to 1982.

While we do not know the true rate of chronic endothelial cell loss after modern cataract surgery, it is perhaps an important variable to be established for clear lens extraction surgeries. Since the alternative to this surgery is glasses for presbyopia, the widely accepted 0.6% annual cell rate loss is probably the appropriate control.

What is the appropriate sample for study / substudy in order to address this issue? Tables 2a and 2b summarize our statistical estimates of the required sample sizes with different scenarios. In order to generate these tables, we assumed the annual cell loss of 0.6% beginning at 3 months (to exclude the surgical loss).

We have performed calculations assuming 4 possible acceptable cell densities in a 75 year old subject who has undergone clear lens extraction when they became presbyopic (41-50 years): 1500, 1400 and 1200 and 1000 cells/mm<sup>2</sup>. Please keep in mind that the normal cell density for subjects 71-80 is 2400 cells/mm<sup>2</sup> (SD=500)<sup>24</sup>. Tables 2a and 2b include separate rows for 1 year, 2 year and 3 year studies. A more thorough explanation of the calculation is provided below.

The ECD for 41-50 year old people is 2880 cells/mm<sup>2</sup> (SD=270)<sup>24</sup>. Therefore, the average person in this age range has 2880 cells/mm<sup>2</sup> and a person with 2 SD less has 2340 cells/mm<sup>2</sup>. The reduction from 2340 cells/mm<sup>2</sup> to 1500 cells/mm<sup>2</sup> over 35 years corresponds to a rate of 1.2% per year. Therefore, the study should have a precision of 0.6% per year (1.2 % - 0.6 % = 0.6%).

With a 3 year study, we would evaluate the cumulate ECD loss from 3M to 36M. Therefore, the precision that we need is 1.65 %. Assuming a SD of 7% (achieved in current studies), a 3 year study with the acceptable cell density of 1500 cells/mm<sup>2</sup> at age 75 requires a sample size of 113 subjects (see bottom right cell in Table 2a).

**Table 2a: Sample Size for Endothelial Cell Loss**

Experimental Group vs. Fixed Historical Rate of 0.6%/yr

	<b>1000 cells/mm<sup>2</sup> at age 75 (2.4%/yr Loss)</b>	<b>1200 cells/mm<sup>2</sup> at age 75 (1.9%/yr)</b>	<b>1400 cells/mm<sup>2</sup> at age 75 (1.45%/yr)</b>	<b>1500 cells/mm<sup>2</sup> at age 75 (1.2%/yr)</b>
<b>1 year study</b>	162	319	745	1497
<b>2 year study</b>	32	60	139	275
<b>3 year study</b>	14	26	57	113

Ho: Experimental Mean Loss = (Given Rate of Loss per Year)\*Yrs

Ha: Experimental Mean Loss < (Given Rate of Loss per Year)\*Yrs

a=0.05; β=.20 assuming that the experimental group has a loss of 0.6%/yr

Table 2b summarizes sample sizes for endothelial cell density evaluation with an active concurrent control having an annual rate of endothelial cell loss of 0.6%. A 3 year study with the acceptable cell density of 1500 cells/mm<sup>2</sup> at age 75 requires a sample size of 223 subjects in this case (see bottom right cell in Table 2b).

**Table 2b: Sample Size for Endothelial Cell Loss**

Experimental Group vs. Active Control

	<b>1000 cells/mm<sup>2</sup> at age 75 (2.4%/yr Loss)</b>	<b>1200 cells/mm<sup>2</sup> at age 75 (1.9%/yr)</b>	<b>1400 cells/mm<sup>2</sup> at age 75 (1.45%/yr)</b>	<b>1500 cells/mm<sup>2</sup> at age 75 (1.2%/yr)</b>
<b>1 year study</b>	333	638	1490	2993
<b>2 year study</b>	62	118	274	550
<b>3 year study</b>	25	48	111	223

Ho: Experimental Mean – Control Mean = (Given Rate of Loss per Year – 0.6%/yr)\*Yrs

Ha: Experimental Mean – Control Mean < (Given Rate of Loss per Year – 0.6%/yr)\*Yrs

$\alpha=0.05$ ;  $\beta=.20$  for assumed equality of the two groups

As one can see, the number of subjects needed for endothelial cell evaluation ranges from 14 to 2,993 depending on the study design and the assumptions made. Panel members will be asked to take these numbers into consideration during their deliberations.