Outcomes of Secondary Intraocular Lens Implantation in the Infant Aphakia Treatment Study

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Abstract

Purpose: To report outcomes of secondary intraocular lens (IOL) implantation in the Infant Aphakia Treatment Study (IATS)

Setting: Multicenter clinical practice

Design: Secondary analysis of patients enrolled in a randomized clinical trial

Methods: Details regarding all secondary IOL surgeries conducted in children enrolled in the IATS were compiled. We evaluated visual outcomes, refractive outcomes, and adverse events at age 10½ years. Comparisons were made to eyes that remained aphakic and to eyes randomized to primary IOL placement.

Results: 55/57 patients randomized to aphakia with contact lens correction were seen for the 10½ year study visit; 24/55 eyes (44%) had secondary IOL surgery. Median age at IOL surgery was
5.4 years (range 1.7 to 10.3 years). Mean absolute prediction error was 1.0 ± 0.7D. At age 10 ½ years, the median log MAR VA was 0.9 (range 0.2 to 1.7), similar to VA in the 31 eyes still aphakic (0.8, range 0.1 to 2.9); the number of eyes with stable or improved VA scores between the 4 ½ and 10 ½ year study visits was also similar (78% secondary IOL eyes, 84% aphakic eyes). For eyes undergoing IOL implantation after the 4.5 year study visit (n=22), the mean refraction at age 10 ½ years was −3.2 ±2.7D (range −9.9D to 1.1D), compared to −5.5 ±6.6 D (n=53, range −26.5 to 3.0D) in eyes with primary IOL (p=0.03).

**Conclusions:** Delayed IOL implantation allows a more predictable refractive outcome at age 10 ½ years, though the range of refractive error is still large.

Visually significant cataracts in infants are typically surgically removed early in life to minimize deprivation amblyopia. Traditionally, infant eyes are left aphakic, with refractive correction provided by either contact lenses or spectacles. In unilateral cases, it is difficult to obtain good visual acuity because of the interocular competition with the phakic eye; poor visual results are generally attributed to deprivation amblyopia. The challenges in unilateral cataract management include the need for early detection and intervention, consistent compliance with refractive correction, and effective amblyopia therapy with occlusion of the sound fellow eye. Because of the high rate of subnormal visual outcomes in eyes of patients with unilateral infantile cataract, primary intraocular lens (IOL) placement was hypothesized to improve outcomes.

The Infant Aphakia Treatment Study (IATS) was a randomized multicenter clinical trial designed to compare outcomes between children who had cataract surgery with primary IOL insertion compared to those left aphakic, with a goal of maintaining the assigned treatment arm protocol until age 5 years. The results of the IATS revealed no difference in visual outcomes between the groups at age 1 year, 4 ½ years, or 10 ½ years, but there was a higher rate of adverse events (most commonly, secondary opacities and need for additional surgery) in eyes receiving primary IOL implantation. Prior to the age of 5 years, eyes randomized to aphakia only had IOL implantation if the IATS Executive Committee concluded that contact lens and spectacle correction could not be consistently maintained. After age 5 years, patients were treated at the discretion of their primary ophthalmologist, and children who were aphakic had the opportunity to have elective implantation of an IOL.

The purpose of this report is to describe outcomes for eyes that received secondary IOL implantation, including a comparison of outcomes to aphakic eyes that did not undergo secondary IOL implantation, and eyes that had primary IOL implantation in early infancy.

**Methods**

The protocol and primary outcomes of the IATS have been previously published. In brief, infants with a unilateral congenital cataract (≥3mm central opacity) undergoing surgery at an age of 28 to 209 days were eligible for randomization to primary IOL implantation or aphakia in the operative eye. The main exclusion criteria were persistent fetal vasculature with stretching of ciliary processes or involvement of the optic nerve or retina, corneal diameter <9mm, premature birth (<36 weeks gestational age), presence of a medical condition that might interfere with later visual acuity testing, acquired cataract, or inability...
to maintain follow-up for 5 years. The study was approved by the institutional review boards of all participating institutions and in compliance with the Health Insurance Portability and Accountability Act. The off-label research use of the Acrysof SN60AT and MA60AC IOLs (Alcon Laboratories, Fort Worth, Texas) was covered by US Food and Drug Administration investigational device exemption # G020021. The clinical trial is registered in clinicaltrials.gov by Identifier NCT00212134.

Prior to age 5 years, secondary IOL surgery only occurred if the IATS Executive Committee agreed that all other efforts to maintain refractive correction were exhausted. After age 5 years, refractive correction and the option for IOL insertion was left to the discretion of the family and the provider.

Refractive error was assessed by retinoscopy every 3 months until age 4 ½ years, then at age 5 years and 10 ½ years. The primary outcome of visual acuity (VA) was assessed at age 4 ½ years using HOTV optotypes, and at age 10 ½ years using the ETDRS research protocol. Adverse events and secondary operations were recorded at each study visit. Data forms and surgical records were used to collect information about details of secondary IOL surgery, biometry, IOL calculations, targeted post-operative and early post-operative refractions.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). Comparisons of visual outcomes were performed among eyes that had secondary IOL, eyes that remained aphakic, as well as those with primary IOL implementation. Chi-square tests were performed to compare proportions. Wilcoxon tests were used to compare medians. Two-sample t-tests assuming unequal variances were used to compare means.

Results

The IATS enrolled 114 infants, 57 in the aphakic group and 57 in the primary IOL group; 55/57 (96.5%) patients initially left aphakic were examined at the 10 ½ year study visit. Of these 55 patients, 24/55 (44%) were known to have had IOL implantation (2 prior to the 4 ½ year visit due to contact lens intolerance, at 20 and 38 months of age). The median age at secondary IOL surgery was 5.4 years (range, 1.7 to 10.3 years).

For secondary IOL surgery, biometry and surgical technique were by surgeon preference. Biometry technique included optical coherence (5), immersion ultrasound (16), non-specified ultrasound (1), or not specified (2). Keratometry (K) was recorded for 23 patients and axial length (AL) for 22 patients. Mean K was 43.7 ±1.6 D (range, 40.9 to 47.3 D) in the operative eye and 42.8 D ±1.7 D (range, 38.3 to 45.4 D) in the fellow eye. Mean AL was 21.4 ±1.0 mm (range, 19.6 to 23.9 mm) in the operative eye, and 22.6 ±0.9 mm (range, 20.9 to 25.1 mm) in the fellow eye, with a mean AL difference of 1.3 ±1.2 mm. In 16/22 (73%) cases the operative eye was >.5mm shorter than the fellow eye (7 cases by ≥1 to 2mm, and in 5 cases by ≥2mm). Only 3 operative eyes were longer than the fellow eye, and 2 of these had glaucoma. IOL calculation formulas used were the Holladay (14 cases), Sanders-Retzlaff-Kraff theoretic (SRK/T, 4 cases), the SRK-II (1 case), and not specified in 4 cases. The targeted post-operative refraction was typically low hyperopia (mean 1.1 ±1.3 D; range -1.8 to 3.9 D).
In 11 cases, the Soemmerring ring was opened, lens material aspirated, mechanical vitrectomy performed, and the IOL implanted within the capsular bag. In 12 cases, the IOL was placed in the ciliary sulcus; in all 11 cases for which operative reports were available anterior vitrectomy was performed, and the Soemmerring ring was debulked in 3 cases. A foldable IOL was implanted in all but one eye, which had a polymethylmethacrylate (PMMA) single piece IOL implanted in the ciliary sulcus due to limited capsular support. The mean IOL power implanted was 26.5 D (median 26 D; range 20 to 34 D; Figure 1).

The early post-operative refraction was recorded for 17/24 cases. Mean Prediction error (PE= Predicted Refraction - Actual Refraction) was 0.5 D ±1.1 D (range, −1.6 to 2.4 D). Mean absolute PE was 1.0 ±0.7 D (range, 0.1 to 2.3 D).

At age 10 ½ years, the mean refraction in eyes receiving a secondary IOL was −2.75 ±3.1 D (range, −11.0 to 1.0 D), and the median refraction was −2.6 D. After excluding the 2 children who had IOL implantation very early, the mean refraction was −3.2 ±2.7 D (range −9.9 to 1.1 D). Figure 2 shows the distribution of refractions based on age at secondary IOL surgery, with a trend for more variability in refraction for children who had earlier surgery. However, when we performed analyses using age at secondary IOL surgery, IOL power implanted, axial length at surgery, visual acuity, and refractive error in the fellow eye to look for associations with more myopia at age 10 ½ years (in the group of 22 eyes with secondary IOL after age 4 ½ years), no significant associations were found.

Figure 3 compares the early post-operative refraction after IOL implantation to the refraction at 10 ½ years for 16 patients that had data for both visits and at least 6 months between the IOL implantation and 10 ½ year visit. The mean myopic shift was −3.2 ±2.4 D (range −8.3 to 1.0 D), with a mean shift per year of −0.7 ±0.4 D (range, −1.4 to 0.2 D).

The mean refraction for eyes undergoing secondary IOL implantation was significantly less at age 10 ½ years than the mean refraction of eyes with primary IOL implantation (n=53, mean −5.5 ±6.6 D, range −26.5 to 3.0 D; p=0.04); the median refraction in the secondary IOL eyes was −2.6 D compared to −3.9 D in eyes with primary IOL (ns, p=0.3). High myopia (>6D) at the 10 ½ year visit was noted in 17/53 (32% of eyes undergoing primary IOL implantation, compared to 3/22 (13.6%) of eyes undergoing secondary IOL implantation; 17/20 (85%) pseudophakic eyes with high myopia had undergone primary IOL implantation.

There was no difference in the median log MAR VA in the secondary IOL group compared to the group remaining aphakic at 10 ½ years of age (Table). The percentage of eyes achieving 20/40 or better VA at age 10 ½ years was 22% in the secondary IOL group and 29% in the group that remained aphakic. There were similar proportions of patients in each group with ≥0.2 logMAR worsening in VA score between the 4 ½ year and the 10 ½ year study visits (25% in the secondary IOL group and 26% in the contact lens group), and the median change in these groups of eyes was not significantly different: median 0.6 logMAR (25th percentile 0.4, 75th percentile 0.9 logMAR) in the secondary IOL group, and median 0.4 logMAR (25th percentile 0.3, 75th percentile 0.5 log MAR) in the aphakic group.
Adverse events and other surgeries were compared between the secondary IOL group and the group of eyes that remained aphakic. No significant intraoperative complications were noted on review of secondary IOL operative reports; one patient required re-operation for removal of nylon sutures. Adverse events reported on 10 ½ year data forms (since the 5 year visit) included one corneal abrasion in the aphakic/contact lens group, one case of transient retained lens cortex and one case of lens re-proliferation requiring surgery in the secondary IOL group. The number of patients diagnosed with glaucoma before and after age 5 years was similar between the secondary IOL group (3 before, 0 after age 5 years) and the group that remained aphakic (7 before, 3 after age 5 years).

**Discussion**

Implantation of an IOL is an anticipated event for many patients with infantile cataracts, though the timing of implantation has been controversial. Primary IOL implantation does provide most of the refractive correction continuously, but infants require overcorrection with spectacles as there is axial elongation and a large myopic shift in the first few years of life. Most pediatric cataract surgeons prefer to leave infant eyes with residual hyperopia, anticipating the myopic shift, but as evidenced by the eyes in the IATS, this refractive change is variable and at times unpredictable. Since the IATS has shown there is no visual advantage to primary IOL implantation for children < 7 months of age, investigators recommended leaving these children aphakic if it is deemed likely that they could adhere with contact lens correction until secondary IOL surgery could be performed.

Secondary IOL surgery techniques have been previously described with good visual outcomes and low complication rates. With uncomplicated primary cataract surgery in infancy, a Soemmerring ring will develop in virtually all eyes, which can later be opened, reproliferated lens material aspirated, and then a foldable lens can be secured within the capsular bag. If the capsular leaflets cannot be opened, there is usually sufficient residual capsule for ciliary sulcus IOL placement (3-piece foldable or single piece PMMA). It is uncommon to have insufficient capsular support requiring special techniques; all the children in this study had capsular bag or ciliary sulcus IOL placement. No significant intraoperative complications were noted in this cohort. However, it should be noted that placement of an IOL within the capsular bag is preferred whenever possible, because placement in the ciliary sulcus carries a higher risk of long-term iris chafing, chronic inflammation, pigment dispersion, glaucoma, and late IOL dislocation.

Prediction error (PE) after pediatric cataract surgery is more variable than after adult cataract surgery. This is due to many factors, including inconsistencies and inaccuracy of ultrasound biometry (especially contact technique) on small soft eyes, formula errors (which can be exaggerated in small eyes), and variation in effective lens position. The mean absolute PE for eyes in the IATS that had primary IOL implantation (and did not have glaucoma) was 1.8D (± 1.3D), which is higher than the prediction errors reported for pediatric cohorts that include older children. In the IATS, the Holladay 1 IOL calculation formula was used for primary cataract surgery IOL power selection, which showed the lowest median absolute PE (1.2D), but clinically similar results were calculated using the SRK/T formula, which showed the lowest mean absolute PE (1.4 ±1.1D). Mean absolute
PE for secondary IOL surgery in older pediatric cohorts has been shown to be similar to that of primary IOL surgery, ranging from 0.9 to 2.1D.\textsuperscript{19–21} Even though most children were older than 5 years of age at the time of secondary IOL surgery, most eyes were still short (<22mm), and use of a newer theoretical IOL calculation formula appropriate for short eyes can help achieve the intended post-operative refraction. It should be noted that sulcus placement of an IOL, particularly over a Soemmering ring, changes the effective lens position, but formulas assume IOL placement within the capsular bag. Therefore, when selecting an IOL for sulcus implantation, in order to achieve the desired post-operative refraction, the IOL power selected should be .5 to 1.5D less than the power calculated by the formula.\textsuperscript{22} While surgical technique, biometry, IOL type, and formula choice were at the discretion of the surgeons for this cohort, we found the PE to be acceptable and similar to other studies of pediatric patients.

Performing secondary IOL surgery at an older age can mitigate the uncertainty of unpredictable axial elongation that may occur between infancy and age 5 years. Two important factors impacting axial elongation in very young children are development of early glaucoma or secondary visual axis opacities requiring surgery. In the IATS, 13% of eyes were diagnosed with glaucoma or glaucoma suspect by 1 year of age, and 16% of eyes with primary IOL implantation developed a glaucoma-related adverse event.\textsuperscript{23,24} AL growth in non-glaucomatous treated eyes was similar to that of the fellow eye (3.3 vs. 3.5 mm at 5 years, ns; 4.7 vs. 4.7 mm at 10½ years, ns), with no significant difference between the aphakic group and the primary IOL group.\textsuperscript{25,26} However, the mean AL elongation was significantly greater in eyes with glaucoma compared to those without glaucoma at 5 years (5.7 mm, \textit{P}<0.0001) and 10½ years (7.3 mm, \textit{P}<0.05). Additionally, eyes requiring additional surgery for secondary opacification grew more than those that did not (3.8 vs. 2.7 mm by 5 years, \textit{P}=0.013; 3.7 vs 5.2 mm by 10½ years, \textit{P}=0.05). Early surgery, glaucoma, and secondary opacities all contribute to increased rates of axial elongation and variability in myopic shift. Even when excluding eyes with glaucoma, by 5 years of age IATS eyes with primary IOL implantation before 6 months showed a mean refractive shift of 9D, with a mean refraction of −2.53 D (and high variability with refraction range of +5D to −15D).\textsuperscript{27} Most publications about refractive change after pediatric cataract surgery exclude eyes with glaucoma from analysis since glaucoma is a confounding variable, but this cannot be ignored in clinical practice.

No associations were found with group final VA or changes in VA among eyes with secondary IOL implantation compared to eyes remaining aphakic. The VA after IOL implantation is not expected to be significantly different than the VA obtained with contact lens or spectacle use; the main advantage of IOL implantation is improved uncorrected vision and continuous correction of refractive error. The decision to offer surgery should take this into consideration, particularly for eyes known to have significant periods of uncorrected aphakia when the contact lens is not being worn. This consideration applies even to eyes with subnormal vision. Sensorimotor function should also be considered since correction of refractive error by any method can improve ocular alignment. Although primary IOL implantation was not shown to improve rates of strabismus or sensory outcomes by 5 years in the IATS,\textsuperscript{28} secondary IOL implantation may benefit alignment compared to an uncorrected refractive error. Undergoing a second surgery for IOL
implantation introduces potential adverse events associated with anesthesia or surgery, though none were reported for this cohort.

Strengths of this study include well defined cohort with good long-term follow-up, management by surgeons with expertise in secondary IOL surgery, and strong adherence to protocol that required surgery to implant the secondary IOL be delayed until after age 4.5 years. A separate analysis of variables that may be predictive of the need for secondary IOL is planned.

One limitation of this study is that there is inherent bias in the timing of and the selection of eyes that had secondary IOL surgery. For example, we noted a higher rate of glaucoma in the eyes that remained aphakic, which likely impacted decisions about IOL surgery. Also, even though the distribution of eyes with good and poor vision was similar between this group and the group that remained aphakic, there is lack of specific information about other diagnoses or anatomic findings that may not allow them to be secondary surgical candidates. In practice, families often elect to proceed with surgery due to either intolerance to or the financial burden of contact lens wear.

There are other limitations to consider when applying these findings to clinical practice. First, the expertise and experience of the IATS surgeons may not fully represent the experience of patients in a community setting. Secondly, these study families received significant financial and emotional support with patching and contact lenses that may not be available in other settings, enhancing their ability to comply with aphakic care and delay secondary IOL surgery until after age 5 years. In other contexts, children may be much younger at the time of secondary IOL implantation, introducing the possibility that the adverse event rates of surgery could be higher, and the final residual refractive error greater than what was found for this cohort. Thirdly, a variety of other factors influence the decision whether to proceed with and the timing of secondary IOL surgery outside of a clinical trial, including surgeon and family preference, visual acuity, socioeconomic status, ability to pay or insurance coverage for contact lenses or surgery. Finally, some children with unilateral cataract would not have been eligible for enrollment into this study at all, either because of baseline ocular features, neurodevelopmental or systemic diagnoses, or ability to follow-up for 5 years. Eligibility for IOL implantation (whether primary or secondary) should be considered on an individual basis.

Despite the above-mentioned limitations, this report suggests that there are refractive advantages to delaying secondary IOL surgery until elementary school age, with a more predictable refractive outcome and less chance of high myopia. When elective surgery is done by an experienced surgeon after age 5 years, the complication rate is low, and there are far fewer adverse events than when IOL implantation is performed in infancy.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.
Acknowledgments

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Biography

References

Value Statement

What Was Known

Secondary intraocular lens (IOL) surgery is an often anticipated event after cataract surgery in infancy

Significant axial elongation occurs in early childhood, so large degrees of myopic shift can occur in pseudophakic eyes

Post-operative myopic shift is thought to be minimized when IOL implantation is performed after age 5 years

What This Paper Adds

In this multicenter study, half of the infants with unilateral cataract were randomized to surgery with contact lens correction of aphakia and delayed IOL implantation until age 5 years; less than half underwent IOL surgery by age 10 ½ years

IOL implantation was not correlated with differences in visual acuity outcome

Even with delayed IOL implantation, myopic shift was greater than anticipated in many eyes
Synopsis

After unilateral cataract surgery in infancy, delaying IOL implantation until age 5 years results in less myopic shift, but still some cases of high myopia at age 10½ years.
Figure 1.
Intraocular lens (IOL) power vs. age at secondary IOL surgery. Abbreviations: n=sample size; SD = standard deviation; r = Pearson correlation coefficient. P-value is for a t-test for the significance of the correlation.
Figure 2.
Refraction at age 10½ years vs. age at secondary IOL surgery. Abbreviations: n=sample size; SD = standard deviation; r = Pearson correlation coefficient. P-value is for a t-test for the significance of the correlation.
Figure 3.
Change in refraction after secondary IOL surgery to 10 ½ year visit for 16 patients that had data for both visits and at least 6 months between the IOL implantation and 10 ½ year visit. For each patient, a line is shown that connects the refraction after implantation and the refraction at the 10 ½ year visit.
Log MAR visual acuity at 10 ½ years of age.

<table>
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<th>Randomized group</th>
<th>Status</th>
<th>log MAR VA median (range)</th>
<th>VA 20/40 or better</th>
<th>VA &gt;20/40 to &lt;20/200</th>
<th>VA 20/200 or worse</th>
</tr>
</thead>
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<tr>
<td>Aphakic</td>
<td>Secondary IOL (n=23)*</td>
<td>0.9 (0.2–1.7)</td>
<td>5 (22%)</td>
<td>9 (39%)</td>
<td>9 (39%)</td>
</tr>
<tr>
<td>Aphakic</td>
<td>(n=31)</td>
<td>0.8 (0.1–2.9)</td>
<td>9 (29%)</td>
<td>8 (26%)</td>
<td>14 (45%)</td>
</tr>
<tr>
<td>Primary IOL (n=53)</td>
<td></td>
<td>0.9 (0.0–2.6)</td>
<td>11 (21%)</td>
<td>18 (34%)</td>
<td>24 (45%)</td>
</tr>
</tbody>
</table>

* One subject did not have ETDRS VA data, so was excluded from VA analyses.