Outcomes of bilateral cataracts removed in infants 1 to 7 months of age using the TAPS registry

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Abbreviations: TAPS (Toddler Aphakia and Pseudophakia Treatment study), IATS (Infant Aphakia Treatment Study), IOL (Intraocular lens), IRB (Institutional Review Board), AE (Adverse Event), BCVA (Best corrected visual acuity.

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Purpose: This study evaluates outcomes of bilateral cataract surgery in infants ages 1 to 7 months performed by Infant Aphakia Treatment Study (IATS) investigators during IATS recruitment and compares them to IATS outcomes of unilateral cases.

Design: Retrospective case series review at 10 IATS sites.

Participants: The Toddler Aphakia and Pseudophakia Study (TAPS) is a registry of children treated by surgeons who participated in the IATS.

Intervention: Children underwent bilateral cataract surgery with or without intraocular lens (IOL) placement during IATS enrollment years of 2004 through 2010.

Main Outcome Measures: Visual acuity, strabismus, adverse events (AE), reoperations.

Results: 178 eyes (96 children) were identified with a median age of 2.5 months (range 1-7) at cataract surgery. 42 (24%) eyes received primary intraocular lens (IOL) implantation. Median visual acuity of the better-seeing eye at final study visit closest to age 5 years with optotype visual acuity (VA) testing was 0.35 logMAR (20/45) (range, 0.00 – 1.18) in both aphakic and pseudophakic children. Corrected visual acuity was excellent (<20/40) in 29% of better-seeing eyes and 15% of worse-seeing eyes. One percent had poor acuity (≥20/200) in the better-seeing eye and 12% in the worse-seeing eye. Younger age at surgery and smaller (<9.5 mm) corneal diameter at surgery conferred an increased risk for glaucoma or a designation of glaucoma suspect (OR 1.44; *P* = 0.037 for younger age and OR 3.95; *P* = 0.045 for smaller cornea). AEs were also associated with these two variables on multivariate analysis (OR 1.36; *P* = 0.023

for younger age and OR 4.78; *P* = 0.057 for smaller cornea). Visual axis opacification was more common in pseudophakic (32%) than aphakic (8%) eyes (p=0.009). Unplanned intraocular reoperation occurred in 28% of first enrolled eyes (including glaucoma surgery in 10%).

Conclusions: Visual acuity after bilateral cataract surgery in infants younger than 7 months is good despite frequent systemic and ocular co-morbidities. Although aphakia management did not affect visual acuity outcome or AE, IOL placement increased the risk of visual axis opacification. AE and glaucoma correlated with a younger age at surgery and glaucoma with the presence of microcornea.

The optimal age for the primary insertion of an intraocular lens (IOL) at the time of pediatric cataract surgery is uncertain.[1-10] The Infant Aphakia Treatment Study (IATS), along with other series involving unilateral IOL implantation, documented the adverse events (AEs) and complications associated with unilateral cataract surgery with either aphakia and the use of a contact lens, or pseudophakia and glasses to manage the post-surgical optical needs in children within the first 6 months of life.[11-14] As a consequence of the findings of these studies, infants in the first six months of life operated for a unilateral cataract are more commonly left aphakic.[15-16] The effects of age and aphakia management on bilateral cataract surgery outcomes are less well understood.

The Toddler Aphakia and Pseudophakia Study (TAPS) examines in a retrospective fashion the data in a registry of children with bilateral and unilateral cataracts operated on by IATS surgeons during the IATS enrollment period (2004 through 2010). Unilateral cataract outcomes from this registry of children who were slightly older than those in IATS at surgery have recently been published.[17] As the care of TAPS children was provided by the same surgeons who simultaneously enrolled in IATS, the outcomes for infants age 1 – 7 months with bilateral cataracts in the TAPS registry may be compared to those reported with unilateral cataracts in IATS.

Patients and Methods

This study was approved by the Institutional Review Board (IRB)/Ethics Review Board at all participating institutions and complied with the Health Insurance Portability and Accountability Act. Data sharing agreements were established between IATS investigator sites and the Mayo Clinic.

Eligibility criteria

Eligible criteria for the TAPS series mirrored the IATS in that it included those with a history of bilateral cataract surgery with at least one eye operated between 28 days and 7 months (210 days) of age and during the enrollment period of IATS (January 1, 2004 and December 31, 2010). Exclusion criteria included prior or concurrent intraocular surgery (corneal transplant, iris coloboma repair, etc.), pre-existing ocular disease (retina, uveitis, optic nerve / glaucoma, trauma), and follow up to an age less than 4 years.

Study Design

The TAPS is a retrospective consecutive case registry of cataract surgery of children whose care was provided by surgeons who were simultaneously enrolling infants into IATS.(e-supplement) The IATS standardized best-practice surgical and postoperative care protocol was modeled by surgeons for other children in their practices.[11] Thus, during the years of IATS recruitment (2004 through 2010), the surgical and clinical management of infants with bilateral cataracts in TAPS likely mirrored that of the infants

with unilateral cataracts in IATS. However, as a retrospective study, TAPS children were not supported by the benefits of a prospective, funded study including financial support for optical and patching equipment or a standardized protocol and case report forms. Also, since the optical treatment of bilateral infantile cataracts was not randomized, the decision to implant an IOL at the time of surgery or leave the eye aphakic was made at the time of each surgery at the discretion of the surgeon and the infant's family.

Patient clinical and surgical records were reviewed and entered into the TAPS registry. Documentation included gender, age at surgery, cataract description (including if more than one layer of the lens was involved), surgical detail, including IOL power and intraoperative complications. Visual acuity, refractive status, ocular motility, anterior segment and fundus findings were summarized from the latest study visit between ages 4 and 6 years. If more than one visit qualified, preference was given for the examination closest to 5 years of age. Intraoperative complications and AEs were recorded separately using the criteria in the IATS study.[11-14] Although vision outcomes were evaluated for both eyes, risk analysis of complication and AE was performed on the first eligible surgical eye. Definitions for both glaucoma and glaucoma suspect were developed for the IATS. It was assumed these enrolling clinicians for TAPS utilized those same definitions in their diagnoses, which were gleaned from record review and reported by the investigators based upon these records. Diagnoses of glaucoma and glaucoma suspect status were based on the year 5 examination and any prior surgical management of glaucoma. Microcornea (< 9.5 mm) and microphthalmia (axial length <

17.5 mm for infants between 1 – 4 months at surgery, and < 18.5 mm between 4 – 7 months) were defined as such for consistency with a previous cataract registry study.[18-20]

Statistical Analysis

Continuous variables were summarized with the sample median and range. Categorical variables were summarized with numbers and percentages. Comparisons between infants who had surgery at age 28-49 days (younger group) vs. those with surgery 50–210 days (older group) were performed using a Wilcoxon rank-sum test for continuous variables and a Fisher's Exact test for categorical variables. Adverse event and additional surgery data were calculated using only the first eye enrolled to avoid correlation effect in statistical analysis. The overall AE endpoint as well as the risk of developing glaucoma or glaucoma suspect diagnosis was estimated using Logistic Regression. All statistical tests were two-sided, and p-values of 0.05 or lower were considered as statistically significant. All statistical analysis was performed using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina)

Results

A total of 164 children (311 eyes) with a history of bilateral cataract surgery before age 2 years and with a surgical date between 2004 and 2010 (the years of the IATS recruitment) were registered into the TAPS by 10 IATS sites. Two of the original 12

IATS clinical sites did not participate due to IRB limitations. Both eyes were enrolled in 147 patients. In 17 patients, only one eye was enrolled as the fellow eye's cataract surgery was performed outside of the age eligibility window. Nine children (14 eyes) were excluded due to disqualifying baseline history or findings, and 23 (41 eyes) were not included because their follow-up examinations were not documented between ages 4 and 6. Forty-three infants (78 eyes) had surgery after 7 months of age and will be included in a separate study. Seven infants that were enrolled as bilateral had one eye excluded from the risk analyses for one of the above reasons. Ninety-six children (178 eyes) were eligible for inclusion and review.

The median age of surgery was 2.5 months (range 1-7) and median follow-up in the study window (age 4 – 6 years) was 4.9 years (range 4.0 – 5.8 years). Fifty-four (56%) children were female; 69 (72%) were Caucasian, 14 (15%) African-American, and 13 (14%) other or unknown. A family history of pediatric cataract was identified in 45/96 (47%) children. A chromosomal or neurodevelopmental anomaly was identified in 23/96 (24%) (Table 1). Systemic abnormalities not felt to be associated with neurodevelopmental abnormality included cleft palate (n=2), acute myelogenous leukemia (n=1), and Immune Deficiency Syndrome (n=1).

The cataract morphology was classified as nuclear (n=102), cortical and lamellar (n=76), total white / mature (n=10), posterior capsular / subcapsular (n=9), posterior lenticonus (n=8), anterior capsular / subcapsular (n=3), ectopia lentis et pupillae (n=2)

and unknown (n=25). Microphthalmia was detected in 117 (66%) eyes. Microcornea was present in 19 eyes (11%) and other anterior segment abnormalities in 12 (7%). Surgery was initially performed on the right eye in 81 (84%) children and on the left eye in 15 (16%). The median time interval between first and second eye surgeries was 4 days (range 0 – 33 days). A primary IOL was inserted in 42/178 eyes (24%) with a median power of 29 diopters (range 22 – 40). IOLs were implanted in 6 of 86 (7%) children 28 – 49 days of age and in 36 of 92 (39%) children at age 50 - 210 days. A single-piece or three-piece foldable AcrySof® (Alcon, Fort Worth, Texas) IOL was implanted in all 42 eyes in which IOLs were chosen and 36 of these (86%) were placed within the capsular bag. Primary posterior capsulotomy and anterior vitrectomy were performed in 98% of implanted eyes (69% via limbal and 29% via pars plana approach). Anterior vitrectomy was performed in 100% of eyes. No other additional surgical procedures were concurrently performed. Intraoperative complications included inadvertent anterior (n=1) or posterior (n=5) capsular disruption in 6/178 (3.4%) eyes during lens removal or IOL insertion. IOL insertion was aborted in one case due to shallowing of the anterior chamber.

At the final visit, the median visual acuity was 0.35 logMAR (20/45) (range, 0.00 – 1.18) in the better-seeing eye and 0.48 (20/60) (range, 0 – 1.30) in the worse-seeing eye.(Table 2) The median interocular difference was 0.10 logMar (range 0 to 1.20). Twenty-nine percent of patients saw better than 20/40, and 1% had VA equal to or worse than 20/200 in the better-seeing eye. Fifteen percent of patients saw better than 20/40 in the worse-seeing eye, while 12% had a VA equal to or worse than 20/200.

Figure 1 displays the visual acuity of the better-seeing eye at the final exam plotted against the age of the first lensectomy. The correlation coefficient between the better-seeing eye's visual acuity at final exam and age at first cataract surgery was not significant for either the entire group (r=-0.13 p=0.29) or the 21 children with 20/40 or better (r=0.17, p=0.46). The presence of microcornea was associated with poorer vision. Median visual acuity was 0.59 (20/80), (range 0.10 – 1.18) with corneal diameter < 9.5 mm versus 0.30 (20/40), range 0.00 – 0.80 (*P* = 0.004) when $\geq$ 9.5 mm. Nystagmus (infantile nystagmus or latent /fusional maldevelopment nystagmus) was present in 47/90 children (52%); this included 31/60 (52%) children operated prior to 90 days of age and 16/30 (53%) after 90 days (nystagmus data was not recorded in 6 children). Median age at the time of surgery for children with nystagmus (1.5 months) was the same as those without nystagmus (1.5 months) (*P*=0.64). Visual acuity in the better-seeing eye was worse in patients with nystagmus {0.40 (20/50), range 0-0.80} than in those without it {0.24 (20/35), range, 0 – 0.80}, (*P*=<0.001).

Twenty four children were unable to complete optotype acuity testing at their final study visit. Of these, 23 (96%) had a diagnosis of a chromosomal or neurodevelopmental abnormality. These infants were more likely to have nystagmus 16/21 (76%) vs. 31/69 (45%) without such disease (P=0.014) but were not more likely to have AEs (11/23 (49%) vs. 34/73 (47%) respectively (*P* = 1.00)) or additional intraocular surgery (7/23 (30%) vs. 20/73 (27%) (*P* = 1.00)).

Table 3 shows the AEs in 45 of 96 (47%) of first operated eyes. The most common AEs were glaucoma or a designation of glaucoma suspect, identified in 29 (30.2%) cases. Visual axis opacification, including pupillary membranes, occurred in 13 (13.5%) cases (6/74 (8%) aphakic eyes and 7/22 (32%) pseudophakic eyes (p=0.009)), requiring surgical intervention in 15 (16%) of first surgical eyes). Corectopia was noted in 10 (10%) of children. AE and outcomes of eyes with and without microcornea are summarized in Table 4. No AEs were identified in the 6 patients with a ciliary sulcus-placed IOL. Table 5 details the additional unplanned surgeries performed in 27 eyes.

With univariate analysis, AE and glaucoma or glaucoma suspect were each associated with age at surgery and microcornea (< 9.5 mm).(Table 6) On multivariate analysis, younger age at surgery and smaller (<9.5 mm) corneal diameter at surgery conferred an increased risk for glaucoma or a designation of glaucoma suspect (OR 1.44; *P* = 0.037 for age and OR 3.95; *P* = 0.045 for smaller cornea). AEs were also associated with these two variables on multivariate analysis (OR 1.36; *P* = 0.023 for younger age and OR 4.78; *P* = 0.057 for smaller cornea). Although primary IOL insertion appeared negatively associated with risk of glaucoma or glaucoma suspect in univariate analysis, this association did not hold up with multivariate analysis that included age at surgery and the use of an IOL; hence the presence of an IOL was not associated with glaucoma or glaucoma suspect (OR 0.29; 95% CI, 0.06 – 1.47; *P*=0.14 for IOL) or AE (OR 0.82; 95% CI, 0.26 – 2.64; *P*=0.74 for IOL). The same result was found when the use of an IOL was modeled with both younger age and microcornea (OR 0.98; 95% CI, 0.30 – 3.20; p=0.97). Axial length was not associated with AE, glaucoma or glaucoma suspect

status. Younger age at surgery was the only variable associated with the need for additional surgeries (OR 1.47; 95% CI, 1.04 – 2.04; *P*=0.028).

Eyes without AEs were more likely to have a better visual acuity than those with AE (median acuity 0.30 (range, 0 – 0.80) vs. 0.40 (range, 0 – 1.18), P=0.034). No statistically significant association was found between visual acuity outcome and primary IOL implantation vs. primary aphakia (median acuity 0.35 with IOL vs. 0.35, respectively, *P*=0.42) or an additional unplanned intraocular surgery (acuity 0.40 with vs. 0.40 without, *P*=0.095). No association was found between visual acuity and optical correction with glasses only vs. the use of contacts and/or IOL (median acuity 0.35 if "glasses only" and 0.35 with use of contacts or IOL, *P* = 0.59).

At the exam used as a final encounter for this study, 52 (29% of entire cohort, 52% of aphakic cohort) eyes used aphakic contact lenses (power median +20, range 14 – 32 diopters), 42 (25% of entire cohort, 32% of aphakic cohort) wore spectacles (median +13.5, range -4.1 to + 20.00), 40/136 (29%) had received a secondary IOL (mean age 5.1 years, range 4.2 – 5.9), and 42/178 (24%) utilized their primary IOL and glasses for any residual refractive error. Children who had received primary IOL implantation had a median refraction (spherical equivalent) of -0.8 diopters in their first operated eyes (range -8.80 to +3.00). Forty of 72 (56%) patients with strabismus measurements were orthophoric at distance without prior strabismus surgery (61% for cataract surgery performed between 28 – 49 days of age and 50% for surgery when 50 – 210 days, irrespective of IOL use, *P*=0.37). Exotropia was the most common deviation, occurring

in 50% (range 8 – 40 PD) followed by esotropia 39% (range 4 – 35 PD) and hypertropia in 4% (2 PD). Strabismus surgery was performed in 12 patients prior to 5 years of age.

Discussion

The Toddler Aphakia and Pseudophakia Study (TAPS) is a large registry of unilateral and bilateral cataracts in children operated at age 1 – 24 months.[17] Despite the limitations of retrospective data analysis, TAPS cataract surgery outcome data are informative and important because these procedures were performed by IATS surgeons during the same time period as the IATS and provide comparisons that can guide clinical practice. This case series is the first TAPS study on bilateral cataracts outcomes and involves children 1 – 7 months of age at surgery. The significant rates of AEs and reoperations after bilateral cataract surgery in these infants, with or without IOL implantation, are comparable to the results for infants of the same age whose unilateral cataracts were treated in IATS.[13,14]

In the early 2000s, the IATS was designed to prospectively study the visual acuity outcomes and risks of IOL implantation in infants with unilateral cataract.[1,2,4,21-27] The IATS randomized infants age 1 to 7 months at 12 sites across the United States to cataract surgery with and without primary IOL implantation. The aphakic and pseudophakic cohorts of the study had statistically similar visual acuity, strabismus, stereopsis, and glaucoma outcomes at age 5 years. However, infants undergoing IOL implantation proved to have a more complex course including high rates of lens

proliferation into the visual axis, pupillary membrane, corectopia, and reoperations.[13,14,18-28] As a result of the study, many surgeons leave children aphakic after cataract surgery in the first few months of life.[15,16] Using the TAPS registry, we recently reported significantly lower rates of AE, glaucoma, and reoperation in children whose monocular cataract surgery occurred between 7 – 24 months of age as compared to the IATS cohort, despite that fact that the majority were implanted with an IOL primarily. These results are consistent with other smaller series and suggest that the period of heightened risk for AE, glaucoma, and reoperation for unilateral lensectomy involves the first 6 months of life.[9,10]

The outcome and complications of IOLs in infants with bilateral cataracts compared to unilateral cases studied in IATS (including mild Persistent Fetal Vasculature phenotype) need to be explored further.[18-28,29] A recent study using the Delphi approach showed a lack of consensus amongst pediatric ophthalmologists surrounding the minimum age for primary IOL implantation in children with bilateral cataracts.[6] Two recent series including bilateral cataracts have been reported in children less than age 2 years of age; one by a single surgeon in India and a second from a consortium of surgeons in the United Kingdom and Ireland.[18-20,29] Limitations of these studies in determining the effect of age on complications and AEs include the empirical grouping of children from birth to age 24 months and more importantly, the non-standardized surgical techniques in the group of 63 surgeons in the UK group.

The participating surgeons in the TAPS were consistent in their documentation, clinical care, and surgical practice with IATS surgeons. Each surgeon was certified to perform both arms of the IATS via submission and review of unedited surgical videos. This TAPS retrospective review of children with bilateral cataracts performed during the same period as the IATS cohort under the care of the same surgeons during the same study time frame (2004 through 2010) is uniquely able to compare the outcomes of children with bilateral cataracts to the unilateral cases studied in the IATS. Despite limitations of retrospective data collection including the use of non-randomized patients and non-standardized documentation, this TAPS series is the largest cohort of bilateral cataract outcomes in infants operated at 1 – 7 months of age.

Limitations exist when comparing the visual acuity and binocularity of TAPS children after bilateral lensectomy to the IATS cohort. As is the case in other studies, greater symmetry of refractive correction and ocular health appears to lessen the risk of and depth of amblyopia. In this group of infants with bilateral cataracts, we evaluated the visual acuity of the better- and worse-seeing eye for each child at the encounter closest to age 5 years.(Table 2) The median of better eye visual acuity of infants undergoing bilateral cataract surgery at 1 – 7 months of age 0.35 (20/45) was better than the median acuity of the unilaterally involved IATS eyes (0.90(20/159). In this bilateral TAPS cohort, the visual acuity of the better-seeing eye was better than 20/40 in 29% of children compared to 17% in the IATS. Ipsilateral poor visual outcome ($\leq$20/200) occurred in 49% children in the IATS and correlated with poor amblyopia treatment compliance.[30] For this bilateral TAPS cohort, only one better-seeing eye (1.4%) and 9

worse-seeing eyes (13%) had VA ≤20/200. Traditionally, and in order to maximize visual acuity outcomes, bilateral cataract extraction is typically performed in the first months of life.[31-33] In the present TAPS registry cohort, we did not detect a significant correlation between age at surgery in months and either final visual acuity or the development of nystagmus.

Twenty-four (25%) children in this series had bilateral cataracts associated with chromosomal and neurodevelopmental anomalies. The IoLunder2 study reported a systemic disorder or neurodevelopmental impairment in 55% of children with bilateral cataracts.[18-20] It is not surprising that 23/24 (96%) of TAPS children with chromosomal or neurodevelopmental anomalies were unable to complete quantitative visual acuity testing at age 5 and we decided to exclude them from the visual acuity summaries. This certainly is a limitation to the present study.

Projecting a myopic refraction shift with axial growth, surgeons typically target moderate hyperopia immediately after IOL implantation in infants.[1,3,9,10] Despite targeting 6 - 8 diopters of residual hyperopia for IOL implantation, the 5 year mean refractive error in IATS was -2.25 diopters. The postoperative hyperopic target refraction for the children with bilateral cataracts in this retrospective TAPS review was often not recorded but presumed to be comparable to IATS planning. The refraction of bilateral TAPS children at 5 years of age was similar to affected eyes in IATS.

Consistent with existing pediatric cataract literature, strabismus and strabismus surgery were less common in the present study after bilateral lens extraction than in unilateral cataract surgery in the IATS.[21,26,27,34-36] In the present series, 56% of patients maintained orthophoria without strabismus surgery compared to 19% in the IATS.[34-36] Exotropia was the most commonly described strabismus in these bilateral cataract surgery TAPS infants (54% exotropia, 42% esotropia). Conversely esotropia was more frequently seen in IATS (50% esotropia, 27% exotropia).[34-36]

After a median age of 5.1 years, AEs had occurred in 47% of the first eyes of bilateral cataracts in the TAPS registry compared to 81% of pseudophakic eyes and 56% of aphakic eyes in the IATS.[14] The most common AE was glaucoma or glaucoma suspect status in 31% (and the most common additional intraocular surgery was for glaucoma (trabeculotomy (n=5)/ glaucoma drainage device n=(8)). These results are consistent with the 5 year IATS (31% pseudophakic and 17% aphakic eyes).[14] Vasavada et. al reported glaucoma in 16% of aphakic eyes and 14% of pseudophakic eyes at age 5 years.[29] IoLunder2 study described glaucoma or persistent ocular hypertension in 23% of aphakic eyes and 10% of pseudophakic eyes.[18-20] However, since glaucoma risk has been inversely correlated with age at surgery, it is important to recognize that both the Vasavada et al report and the IoLunder2 study included children up to 24 months.[18-20, 29]

Visual axis opacification (VAO) is a common AE after cataract surgery in infants and children. [5,8,12,13,19,28,29] Because the implanted IOL's presence and volume in the capsular bag limits the formation of a closed Soemmerring ring, VAO occurs more

commonly in pseudophakic eyes. In the present cohort for which IOL insertion was at surgeon discretion, VAO was more common in first operated eyes that received primary IOLs (32%) vs. those that did not (8%). This is notably similar to the randomized IATS findings of retained cortex or lens reproliferation (45% of primary IOL eyes and 8% of aphakic eyes). As also identified in IATS, corectopia (10%) and pupillary membranes (4%) sometimes occur after infant cataract surgery.[13,14]

The morphology and ocular co-morbidities of cataracts documented in the physician notes of this TAPS registry may be different from those in the IATS, and the unilateral cohort of TAPS.[17] Unilateral cataract surgery may carry an increased risk when the eye has PFV.[37,38] Bilateral congenital cataracts are commonly associated with microcornea, microphthalmia and anterior segment anomalies. The common association of microcornea (11%) and/or microphthalmia (66%) in the present study parallels that identified in the bilateral cases in IoLunder2.[18-20]

The inverse correlation between patient age at infant cataract surgery and risk of glaucoma and glaucoma suspect designation has been previously documented.[17,20,28,39-42] The IATS and unilateral TAPS study also documented this relationship, suggesting that the heightened risk of glaucoma during infancy diminishes for surgery after 6 months of life.[17,42] Multivariate analysis in this bilateral cohort also revealed that younger age at surgery conferred an increased risk for AEs and an increased risk of glaucoma or glaucoma suspect designation. The odds ratio analysis suggests that each month of

reduced age increased the risk of any AE and the risk of glaucoma or glaucoma suspect designation by approximately 40% (44% for glaucoma and 36% for AE).

Less is known about the additional risks conferred by the association of cataracts with microcornea or microphthalmia. In this TAPS study, microcornea < 9.5 mm was associated with a poorer visual acuity outcome. Wallace and Plager suggested that children with a small corneal diameter were at increased risk for aphakic glaucoma.[44] In the IATS, the unilateral cataracts associated with smaller corneal diameter showed increased risk for glaucoma and glaucoma suspect designation.[42] In this study, microcornea strongly correlated with risk of glaucoma or glaucoma suspect designation and showed a trend with any AE. Univariate modeling showed no relationship between axial length and AE or glaucoma or glaucoma suspect. This would suggest that the anterior segment diameter is more important predictor of glaucoma risk than other measures of eye size.

Some have used retrospective data to suggest primary IOL implantation in children is protective against the development of glaucoma.[6,43] However, as identified elsewhere, retrospective data on IOL implantation is unavoidably affected by confounding bias. IOLs are less commonly implanted in the youngest infants and eyes with significant co-morbidities. Neither the prior IATS, IoLunder2, nor the Vasavada, et al studies found IOL implantation protective against glaucoma in children undergoing cataract surgery.[18-20,29,42] In this study, when IOL use was modeled alongside age and microcornea, there was no positive nor negative relationship to the use of an IOL with AE, glaucoma or

glaucoma suspect designation. The TAPS registry reveals that during the same period that surgeons were participating in the IATS, they implanted an IOL in 6/86 (7%) of bilateral cases between 28-49 days of age and in 36/92 (39%) of bilateral cases 50 – 210 days of age. Since the IATS results regarding AEs were published after this bilateral cataract surgery series was performed, it is likely that even a lower percentage of bilateral cases in the first 6 months of life receive IOLs today.[15,16]

Conclusion

Bilateral cataract surgery in infants less than 7 months of age performed by IATS surgeons led to good visual outcomes despite frequent associations of systemic and ocular co-morbidities. Although neither preoperative axial length nor primary IOL implantation affected visual or total AE outcomes, VAO was associated with IOL use. Younger age at surgery and microcornea correlated with increased risk of glaucoma and glaucoma suspect designation.

REFERENCES

1. Wilson ME, Bartholomew LR, Trivedi RH. Pediatric cataract surgery and intraocular lens implantation: practice styles and preferences of the 2001 ASCRS and AAPOS memberships. *J Cataract Refract Surg.* 2003;29(9):1811-1820.
2. Lambert SR, Lynn M, Drews-Botsch C, et al. Intraocular lens implantation during infancy: perceptions of parents and the American Association for Pediatric Ophthalmology and Strabismus members. *J AAPOS.* 2003;7(6):400-405.
3. Repka, MA. Visual rehabilitation in pediatric aphakia. *Dev Ophthalmol* 2016;57:49-68.
4. Raina UK, Mehta DK, Monga S, Arora R. Functional outcomes of acrylic intraocular lenses in pediatric cataract surgery. *J Cataract Refract Surg.* 2004;30:1082-1091.
5. Magli A, Raimondo F, Carelli R, Rombetto L, Magli G. Long-term outcomes of primary intraocular lens implantation for unilateral congenital cataract. *Semin Ophthalmol.* 2015:1-6.
6. Serafino M, Trivedi RH, Levin AV, Wilson ME, Nucci P, Lambert SR, Nischal KK, Plager DA, Bremond-Gignac D, Kekunnaya R, Nishina S, Tehrani NN, Ventura MC. Use of the Delphi process in paediatric cataract management. *Br J Ophthalmol.* 2016;100(5):611-615.
7. Lu Y, Ji YH, Luo Y, Jiang YX, Wang M, Chen X. Visual results and complications of primary intraocular implantation in infants aged 6 to 12 months. *Graefes Arch Clin Exp Ophthalmol* 2010;248:681-686.

8. Kumar P, Lambert SR. Evaluating the evidence for and against the use of IOLs in infants and young children. *Expert Rev Med Devices* 2016;13(4):381-389.
9. Yeh AG, Kong L, Yen KG. Long term Outcomes of Primary Intraocular Lens Implantation in Patients Age 7 to 24 months. *J Pediatr Ophthalmol Strabismus*. 2017;54(3):149-155.
10. Struck MC. Long-term results of pediatric cataract surgery and primary intraocular lens implantation from 7 to 22 months of life. *JAMA Ophthalmol*. 2015;133(10):1180-1183.
11. Infant Aphakia Treatment Study Group. The Infant Aphakia Treatment Study: design and clinical measures at enrollment. *Arch Ophthalmol.* 2010;128(1):21-27.
12. Infant Aphakia Treatment Study Group. A randomized clinical trial comparing contact lens with intraocular lens correction of monocular infancy: HOTV optotype acuity at age 4.5 years and clinical findings at age 5 years. *JAMA Ophthamol.* 2014;132(6):676-682.
13. Plager DA, Lynn MJ, Buckley EG, Wilson ME, Lambert SR; Infant Aphakia Treatment Study Group. Complications, adverse events, and additional intraocular surgery 1 year after cataract surgery in the Infant Aphakia Treatment Study. *Ophthalmology*. 2011;118(12):2330-2334.
14. Plager DA, Lynn MJ, Buckley EG, Wilson ME, Lambert SR. Complications in the first 5 years following cataract surgery in infants with and without intraocular lens implantation in the Infant Aphakia Treatment Study. *Am J Ophthalmol* 2014;158(5)892-898.

15. McAnena L, McCreery K, Brosnahan D. Migration to aphakia and contact lens treatment is the trend in management of unilateral congenital cataract in Britian and Ireland. *Ir J Med Sci*. 2019; 188(3):1021-1024
16. Poole ZB, Trivedi RH, Wilson ME. Primary IOL implantation in children: the effect of the Infant Aphakia Treatment Study on practice patterns. *J AAPOS*. 2019 May 14. https://doi.org/10.1016/j.jaapos.2018.12.013. [in production].
17. Bothun ED, Wilson ME, Traboulsi EIMD, Diehl NN, Plager DA, Vanderveen, Freedman SF, Yen KG, Weil NC, Loh AR, Morrison D, Anderson JS, Lambert SR (Toddler Aphakia and Pseudophakia Study). Outcomes of Unilateral Cataracts in Infants and Toddlers age 7 to 24 Months: Toddler Aphakia and Pseudophakia Study (TAPS). *Ophthalmology*. 2019;126(8):1189 - 1195
18. Solebo AL, Russell-Eggit I, Nischal KK, Moore AT, Cumberland P, Rahi JS; British Isles Congenital Cataract Interest Group. Cataract surgery and primary intraocular lens implantation in children ≤2 years old in the UK and Ireland: finding of national surveys. *Br J Ophthalmol* 2009;93(11):1495-1498.
19. Solebo AL, Cumberland P, Rahi JS; British Isles Congenital Cataract Interest Group. 5-year outcomes after primary intraocular lens implantation in children aged 2 years or younger with congenital or infantile cataract: findings from the IoLunder2 prospective inception cohort study. *Lancet Child Adolesc Health*. 2018 ;2(12):863-871.
20. Solebo AL, Russell-Eggitt I, Cumberland PM, Rahi JS on behalf of the British Isles Congenital Cataract Interest Group. Risks and outcomes associated with primary intraocular lens implantation in children under age 2: the IOLunder2

cohort study. *Br J Ophthalmol.* 2015;99:1471-1476.

21. Greenwald MJ, Glaser SR. Visual outcomes after surgery for unilateral cataract in children more than two years old: posterior chamber intraocular lens implantation versus contact lens correction of aphakia. *J AAPOS* 1998;2(3):168-176.
22. Zwaan J, Mullaney PB, Awad A, Al-Mesfer S, Wheeler DT. Pediatric intraocular lens implantation: surgical results and complications in more than 300 patients. *Ophthalmology.* 1998:105(1):112-119.
23. Eibschitz-Tsimhoni M, Archer SM, Del Monte MA. Intraocular lens poswer calculation in children. *Surv Ophthalmol*. 2007;52(5):474-482.
24. McClatchey SK, Dahan E, Maselli E, et al. A comparison of the rate of refractive growth in pediatric aphakic and pseudophakic eyes. *Ophthalmology* 2000;107(1):118-122.
25. Plager DA, Kipfer H, Sprunger DT, Sondhi N, Neely DE. Refractive change in pediatric pseudophakia: 6-year follow-up. *J Cataract Refract Surg* 2002;28(5):810-815.
26. Spanou N, Alexopoulos L, Manta G, et al. Strabismus in pediatric lens disorders. *J Pediatr Ophthalmol Strabismus* 2011;48:163-166.
27. Weisberg OL, Sprunger DT, Plager DA, Neely DE, Sondhi N. Strabismus in pediatric pseudophakia. *Ophthalmology*. 2005;112(9):1625-1628.
28. Writing Committee for the Pediatric Eye Disease Investigator Group (PEDIG), Repka MX, Dean TW, Kraker RT, Bothun ED, Morrison DG, Lambert SR, Stahl ED, Wallace DK. Visual acuity and ophthalmic outcomes in the year after

cataract surgery among children younger than 13 years. *JAMA Ophthalmol*. 2019 Jul 1;137(7):817-824.

29. Vasavada AR, Vasavada V, Shah SK, Praveen MR, Vasavada VA, Trivedi RH, Rawat FR, Koul AA. Five-year postoperative outcomes of bilateral Aphakia and pseudophakia in children up to 2 years of age: A randomized clinical trial. *Am J Ophthalmol* 2018;193:33-44.

30. Drews-Botsch CD, Celano M, Kruger S, Hartmann EE; Infant Aphakia Treatment Study Group. Adherence to occlusion therapy in the first six months of follow-up and visual acuity among participants in the Infant Aphakia Treatment Study (IATS). *Invest Ophthalmol Vis Sci* 2012;53(7):3368-3375.
31. Eileen EE, Cheng C, Stager DR Jr., Weakley DR Jr., Stager DR Sr. The critical period for surgical treatment of dense congenital bilateral cataracts. *J AAPOS* 2009 (13):67-71.
32. Young MP, Heidary G, VanderVeen DK.Relationship between the timing of cataract surgery and development of nystagmus in patients with bilateral infantile cataracts. *J AAPOS.* 2012 Dec;16(6):554-7.
33. Lambert SR, Lynn MJ, Reeves R, Plager DA, Buckley EG, Wilson ME. Is there a latent period for the surgical treatment of children with dense bilateral congenital cataracts? *J AAPOS.* 2006 Feb;10(1):30-6.
34. Bothun ED, Cleveland J, Lynn MJ, Christiansen SP, Vanderveen DK, Neely DE, Kruger SJ, Lambert SR; Infant Aphakia Treatment Study. One-Year Strabismus Outcomes in the Infant Aphakia Treatment Study. *Ophthalmology*. 2013

;120(6):1227-1231.

35. Bothun ED, Lynn MJ, Christiansen SP, Kruger SJ, Vanderveen DK, Neely DE, Lambert SR; Infant Aphakic Treatment Study. Strabismus surgery outcomes in the Infant Aphakia Treatment Study (IATS) at age 5 years. *J AAPOS*. 2016 ;20(6):501-505.
36. Bothun ED, Lynn MJ, Christiansen SP, Neely DE, Vanderveen DK, Kruger SJ, Lambert SR; Infant Aphakia Treatment Study. Sensorimotor outcomes by age 5 years after monocular cataract surgery in the Infant Aphakia Treatment Study (IATS). *J AAPOS*. 2016;20(1):49-53.
37. Wilson ME, Trivedi RH, Morrison DG, Lambert SR, Buckley EG, Plager DA, Lynn MJ; Infant Aphakia Treatment Study Group. The Infant Aphakia Treatment Study: evaluation of cataract morphology in eyes with monocular cataracts. *J AAPOS*. 2011;15(5):421-426.
38. Morrison DG, Wilson ME, Trivedi RH, Lambert SR, Lynn MJ; Infant Aphakia Treatment Study Group. Infant Aphakia Treatment Study: effects of persistent fetal vasculature on outcome at 1 year of age. *J AAPOS*. 2011;15(5):427-431.
39. Lambert SR, Purohit A, Superak HM , Lynn MJ, Beck AD. Long-term risk of glaucoma after congenital cataract surgery. *Am J Ophthalmol*. 2013;156(2):355-361.e2.
40. Egbert JE, Christiansen SP, Wright MM, Young TL, Summers CG. The natural history of glaucoma and ocular hypertension after pediatric cataract surgery. *J AAPOS*. 2006;10(1):54-57.
41. Mataftsi A, Haidich AB, Kokkali S, Rabiah PK, Birch E, Stager DR Jr, Cheong-

Leen R, Singh V, Egbert JE, Astle WF, Lambert SR, Amitabh P, Khan AO, Grigg J, Arvanitidou M, Dimitrakos SA, Nischal KK. Postoperative glaucoma following infantile cataract surgery: an individual patient data meta-analysis. *JAMA Ophthalmol.* 2014;132(9):1059-67.

42. Freedman SF, Lynn MJ, Beck AD, Bothun ED, Orge F, Lambert SR. Glaucoma-Related Adverse Events in the First Five Years After Unilateral Cataract Removal in the Infant Aphakia Treatment Study. The Infant Aphakia Treatment Study Group. *JAMA Ophthalmol* 2015; 133(8):907-914.
43. Zhang S, Wang J, Li Y, Liu Y, He L, Xia X. The role of primary intraocular lens implantation in the risk of glaucoma following congenital cataract surgery: A systemic review and meta-analysis. *PLOS ONE.* 2019 April 1; 14(4): e0214684. doi: 10.1371/journal.pone.0214684. eCollection 2019.
44. Wallace DK, Plager DA. Corneal Diameter in Childhood Aphakic Glaucoma. *J Pediatr Ophthalmol Strab*. 1996;33(5):230-234.

Legend

eSupplement: IATS Sites and Eligible Surgeons

Table 1. Chromosomal and neurodevelopmental anomaly

Table 2. Better-seeing and worse-seeing eye distance visual acuity at final exam

Table 3. Adverse events before age 5.

Table 4. Outcomes for eyes with and without microcornea (< 9.5 mm).

Table 5. Additional intraocular surgeries prior to age 5.

Table 6. Association with any adverse event or glaucoma or glaucoma suspect adverse event (Based on first surgical eye N = 96)

Figure 1. Better-seeing eye visual acuity at age 5 verses age (in months) at the time of first cataract surgery.