Glaucoma-Related Adverse Events in the Infant Aphakia Treatment Study

1-Year Results

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Objectives: To report the incidence of glaucoma and glaucoma suspects in the IATS, and to evaluate risk factors for the development of a glaucoma-related adverse event in patients in the IATS in the first year of follow-up.

Methods: A total of 114 infants between 1 and 6 months of age with a unilateral congenital cataract were assigned to undergo cataract surgery either with or without an intraocular lens implant. Standardized definitions of glaucoma and glaucoma suspect were created and used in the IATS.

Results: Of these 114 patients, 10 (9%) developed glaucoma and 4 (4%) had glaucoma suspect, for a total of 14 patients (12%) with a glaucoma-related adverse event in the treated eye through the first year of follow-up. Of the 57 patients who underwent lensectomy and anterior vitrectomy, 5 (9%) developed a glaucoma-related adverse event; of the 57 patients who underwent an intraocular lens implant, 9 (16%) developed a glaucoma-related adverse event. The odds of developing a glaucoma-related adverse event were 3.1 times higher for a child with persistent fetal vasculature and 1.6 times higher for each month of age younger at cataract surgery.

Conclusions: Modern surgical techniques do not eliminate the early development of glaucoma following congenital cataract surgery with or without an intraocular lens implant. Younger patients with or without persistent fetal vasculature seem more likely to develop a glaucoma-related adverse event in the first year of follow-up. Vigilance for the early development of glaucoma is needed following congenital cataract surgery, especially when surgery is performed during early infancy or for a child with persistent fetal vasculature. Five-year follow-up data for the IATS will likely reveal more glaucoma-related adverse events.

Trial Registration: clinicaltrials.gov Identifier: NCT00212134


Glaucoma is an important complication of pediatric cataract surgery, with a wide range of reported frequencies of occurrence, depending on the definition used and the length of follow-up. Two large, retrospective series reported a 15% to 21% frequency of glaucoma being diagnosed 5 years after cataract surgery. Numerous risk factors for the development of glaucoma have been noted, including cataract surgery in the first year of life, postoperative complications such as secondary membrane surgery, small corneal diameters, type of cataract, a family history of aphakic glaucoma, and primary posterior capsulotomy/anterior vitrectomy performed at the time of cataract surgery.

Cataract surgery in the first year of life and a small corneal diameter have been the most consistent risk factors for glaucoma development in reported studies. The effect of the placement of an intraocular lens (IOL) at the time of cataract surgery on the risk of developing glaucoma is unknown, although one retrospective review suggested a decreased incidence of glaucoma in patients who received an IOL. However, the eyes that received an IOL in that report were older at the time of surgery (mean age, 5.1 years for pseudophakia vs 2.7 years for aphakia), and children with corneal diameters less than or equal to 10 mm were excluded from analysis. Other studies have noted similar rates of glaucoma in aphakic and pseudophakic children who had cataract surgery performed in the first year of life.

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The Infant Aphakia Treatment Study (IATS) is a multicenter, randomized, controlled clinical trial sponsored by the National Eye Institute. The objective of the study is to compare the use of primary IOL implantation to surgery without IOL implantation in infants with a unilateral congenital cataract removed between 1 and 6 months of age. The results of the IATS during the first year after cataract surgery (including visual acuities, number of adverse events, and number of additional surgery) have been previously reported. In our study, we report the development of glaucoma-related adverse events in IATS patients through 1 year of follow-up.

METHODS

The study design, surgical technique, follow-up schedule, patching and optical correction regimens, evaluation methods, and patient characteristics at baseline have been previously reported in detail and are therefore only briefly summarized in this report. Our study was approved by the institutional review boards of all the participating institutions and was 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.

STUDY DESIGN

The main inclusion criteria were a visually significant congenital cataract (≥3 mm central opacity) in 1 eye and an age range of 28 days to less than 210 days at the time of cataract surgery. Patients with a unilateral cataract due to persistent fetal vasculature (PFV) were allowed in our study as long as the PFV was not associated with visible stretching of the ciliary processes or with involvement of the retina or optic nerve as determined by the treating IATS investigator. The other main exclusion criteria were an acquired cataract, a corneal diameter of less than 9 mm, and prematurity (<36 gestational weeks). Patients were randomly assigned to have either an IOL placed at the time of the initial surgery (with spectacle correction) or to be left aphakic (with contact lens correction). Patients were examined at 1 day, 1 week, and 1, 3, 6, 9, and 12 months after surgery. Grating visual acuity was measured at 1 year of age (±2 months) by a traveling examiner using Teller Acuity Cards (Stereo Optical, Chicago, Illinois).

SURGICAL TECHNIQUE

Patients randomly assigned to the contact lens group underwent a lensectomy and anterior vitrectomy. Patients randomly assigned to the IOL group had the lens contents aspirated followed by the implantation of an AcrySof SN60AT IOL into the capsular bag. In the event that both haptics could not be implanted into the capsular bag, an AcrySof MA60AC IOL was implanted into the ciliary sulcus. Following IOL placement, a posterior capsulotomy and an anterior vitrectomy were performed through the pars plana/plicata.

DEFINITIONS FOR ADVERSE EVENTS

Glaucoma was defined as intraocular pressure (IOP) greater than 21 mm Hg with one or more of the following anatomical changes: (1) corneal enlargement, (2) asymmetrical progressive myopic shift coupled with enlargement of the corneal diameter and/or axial length, (3) increased optic nerve cupping defined as an increase of 0.2 or more in the cup-to-disc ratio, or (4) the use of a surgical procedure for IOP control. A patient was designated as a glaucoma suspect if he or she had 2 consecutive IOP readings above 21 mm Hg on different dates after topical corticosteroids had been discontinued without any of the anatomical changes listed above or if he or she had received glaucoma medication to control IOP without any of the anatomical changes listed above.

ASSESSMENT OF IOP, OCULAR DIMENSIONS, AND OPTIC NERVE

The investigator could perform tonometry with a Tono-Pen (Reichert, Depew, New York), a handheld Goldmann applanation tonometer, or a pneumatonometer. A protocol assessment of IOP was performed at the initial examination of the patient under anesthesia (ie, immediately after the induction of anesthesia prior to randomization and surgery) and at an examination of the patient under anesthesia at 1 year of age. All other IOP measurements were performed at the discretion of the principal investigator. Corneal diameters (measured using calipers), axial length assessment (A-scan biometry using immersion or applanation techniques), and indirect ophthalmoscopy of the optic nerve were also part of the protocol assessment during examination of the patient under anesthesia prior to randomization and at 1 year of age.

STATISTICAL CONSIDERATIONS

Statistical comparisons were made between patients with and patients without a glaucoma-related adverse event by using the Fisher exact test for percentages, the independent groups t test for means, and the Wilcoxon rank sum test for medians. The non-parametric test was used for factors that were highly skewed (age at surgery and visual acuity at 1 year of age). The exact binomial method was used to compute the 95% CI for a proportion, and the normal approximation was used to compute the 95% CI for the difference between 2 proportions. Stepwise logistic regression was used to assess the relationship between the development of glaucoma and a selected set of patient characteristics: age at surgery, diagnosis of PFV, and corneal diameter. A significance level of .10 was set for the Wald χ² statistic for including and retaining independent variables in the logistic regression model, and 90% CIs were calculated for the odds ratios. For all other analyses, a P < .05 was considered statistically significant, and 95% CIs were computed. No adjustment was made for multiple testing. Given that relatively few of the patients in our study developed glaucoma or were suspected of having glaucoma, the statistical power of our study is limited.

RESULTS

DEVELOPMENT OF GLAUCOMA

There were 114 patients enrolled in our study. During the first year after cataract surgery, 10 patients (9%) developed glaucoma, and 4 patients (4%) had glaucoma suspect, for a total of 14 patients (12%) with a glaucoma-related adverse event in the treated eye (Table 1). There were 57 patients randomly assigned to each treatment group (57 to the contact lens group and 57 to the IOL group). Glaucoma developed in 3 patients (5%) in the contact lens group and in 7 patients (12%) in the IOL group (P = .02, with a 95% CI for the difference between
the groups of −3% to 17%). Two patients (4%) in the contact lens group and 2 patients (4%) in the IOL group were in the glaucoma suspect category. Combining glaucoma and glaucoma suspect, 5 patients (9%) in the contact lens group and 9 patients (16%) in the IOL group developed a glaucoma-related adverse event (P = .08, with a 95% CI for the difference between the groups of −5% to 19%).

**INFLUENCE OF PATIENT CHARACTERISTICS**

We investigated the effect of age at surgery, corneal diameter, a diagnosis of PFV, preoperative IOP, and additional surgery performed after cataract surgery on the development of a glaucoma-related adverse event. The median age at surgery among patients in our study was 1.8 months (interquartile range, 1.2-3.2 months). The mean (SD) corneal diameter of the treated eyes was 10.5 (0.7) mm. A diagnosis of PFV was made by the treating IATS investigator for 25 patients (22%). Patients who developed a glaucoma-related adverse event tended to be younger at surgery than those who did not (median age, 1.2 vs 2.2 months; P = .02; Table 2). There was a trend toward a smaller corneal diameter among patients developing glaucoma or glaucoma suspect compared with the other patients (mean diameter, 10.1 vs 10.5 mm; P = .08; Table 2). There was also a trend toward a higher percentage of patients with PFV among those who developed glaucoma or glaucoma suspect compared with those without this diagnosis (43% vs 19%; P = .08; Table 2). Preoperative IOP, intraoperative complications, and additional surgery after cataract extraction failed to demonstrate any relationship with a glaucoma-related adverse event (analyses not shown). As expected, we found some associations among these 3 patient characteristics. Age and corneal diameter were moderately correlated (r = 0.56, P < .001). Corneal diameter tended to be slightly smaller for patients diagnosed with PFV than for other patients (mean diameter, 10.5 vs 10.3 mm; P = .17), although this difference was not statistically significant. However, age at surgery did not appear to be associated with PFV because the median age was 2.5 months for patients with PFV compared with 2.3 months for those not having this diagnosis (P = .61).

A multivariable analysis using stepwise logistic regression was performed to relate age, corneal diameter, and PFV to the development of glaucoma or glaucoma suspect status. An alpha level of .10 was set for a patient characteristic to be included in the model. Persistent fetal vasculature was the first patient characteristic entered, followed by age. With PFV and age in the model, corneal diameter did not meet the entry criteria for inclusion in the model, which was not unexpected given the correlation between age and corneal diameter. As estimated from the model and after adjusting for age, we found that the odds of developing a glaucoma-related adverse event were 3.1 (90% CI, 1.2-8.6) times higher for a patient with PFV than for a patient without this diagnosis (P = .06). Also, after adjusting for PFV, we found that the odds of developing a glaucoma-related adverse event were 1.6 (90% CI, 1.0-2.6) times higher for a patient 1 month younger than another patient (P = .08). The Hosmer-Lemeshow test did not suggest a significant lack of fit for the model (P = .31). The relationship between age, PFV, and the development of a glaucoma-related adverse event is demonstrated in Table 3.

**INFLUENCE OF IOL PLACEMENT**

The rate of glaucoma or suspect status was 13% (7 of 52 eyes) in patients who had the IOL placed in the capsular bag and 50% (2 of 4 eyes) in patients who had the IOL placed in the ciliary sulcus. This difference was not statistically significant (P = .12). Both of the eyes with a sulcus IOL and a glaucoma-related adverse event had PFV, and one of these patients was enrolled in our study despite having met the exclusion criteria for PFV (stretching of the ciliary processes). The exclusion of this case with the protocol violation would leave 1 of 3 eyes (33%) with sulcus IOL placement and a glaucoma-related adverse event (P = .38).

**TYPE OF GLAUCOMA AND TREATMENT**

Although detailed gonioscopic information was not collected as part of the IATS, 9 of 10 eyes with glaucoma (90%) were assumed to be open angle, whereas only 1 eye (10%) was noted to have iris bombe and angle closure.

Glaucoma surgical procedures were required to control the glaucoma in 6 of 10 eyes (60%): 4 of 7 eyes (57%) in the IOL group and 2 of 3 eyes (67%) in the contact lens group. Three of the eyes with open-angle glaucoma underwent a trabeculotomy (1 eye underwent a standard trabeculotomy, and 2 eyes underwent a 360° trabeculotomy), and 2 eyes underwent a Baerveldt glaucoma drainage implant. The eye with angle closure had a pupillary membrane removed and underwent a peripheral iridectomy. In 3 of 6 eyes (50%) with glaucoma that required surgical intervention, the patients were treated with glaucoma medication 1 year after cataract surgery. The remaining 4 of the 10 eyes with glaucoma (40%) were treated with glaucoma medication alone. All 4 patients who received a diagnosis of glaucoma suspect were treated with glaucoma medication.

**GLAUCOMA AND VISUAL ACUITY**

The median visual acuity at 1 year of age was 0.3 logMAR units (3 Snellen lines) worse for patients who de-
developed glaucoma or suspected glaucoma during the first year after surgery (1.1 logMAR) vs those without this adverse event (0.80 logMAR). This difference was not statistically significant (P=.15).

**Table 2. Patient Characteristics vs Development of Glaucoma and Glaucoma Suspect Status During the First Year After Cataract Surgery**

<table>
<thead>
<tr>
<th>Patient Characteristica</th>
<th>No (n=100)</th>
<th>Yes (n=14)</th>
<th>P Value</th>
<th>Difference Between the Groups, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR), mo</td>
<td>2.2 (1.2-3.2)</td>
<td>1.2 (1.0-1.7)</td>
<td>.02</td>
<td>0.1 to 1.5</td>
</tr>
<tr>
<td>Corneal diameter, mean (SD), mm</td>
<td>10.5 (0.7)</td>
<td>10.1 (0.8)</td>
<td>.08</td>
<td>−0.1 to 0.9</td>
</tr>
<tr>
<td>Persistent fetal vasculature, No. (%)</td>
<td>19 (19)</td>
<td>6 (43)</td>
<td>.08</td>
<td>−33% to 3%</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

*Refers to characteristics at initial cataract surgery.

**Table 3. Development of Glaucoma and Glaucoma Suspect Status According to Persistent Fetal Vasculature and Age**

<table>
<thead>
<tr>
<th>PFV Status, Age, d</th>
<th>No. of Patients</th>
<th>Development of Glaucoma and Glaucoma Suspect, No. (% [95% CI])</th>
</tr>
</thead>
<tbody>
<tr>
<td>No PFV ≤48</td>
<td>37</td>
<td>5 (14 [5-29])</td>
</tr>
<tr>
<td>&gt;49</td>
<td>52</td>
<td>3 (6 [1-16])</td>
</tr>
<tr>
<td>PFV ≤48</td>
<td>13</td>
<td>4 (31 [9-61])</td>
</tr>
<tr>
<td>&gt;49</td>
<td>12</td>
<td>2 (17 [2-48])</td>
</tr>
</tbody>
</table>

Abbreviation: PFV, persistent fetal vasculature.

Glaucoma developed in the operated eyes of 10 of 114 infants (9%) with unilateral cataract who were enrolled in the IATS through the first year of follow-up. More eyes developed glaucoma after primary IOL implantation (7 of 57 eyes [12%]) than after cataract removal without IOL (3 of 57 [5%]). This difference was not statistically significant, although the power of this calculation is low. Multivariate regression analysis showed that, after we adjusted for age, the odds of developing a glaucoma-related adverse event were 3.1 times higher for a patient with PFV than for a patient without this diagnosis and that, after we adjusted for PFV, the odds of developing a glaucoma-related adverse event were 1.6 times higher for a patient 1 month younger than another patient. Corneal diameter was not statistically significant in multivariate analysis, possibly owing to the correlation of corneal diameter with age and the small range of corneal diameters in the IATS.

Modern lensectomy/vitrectomy surgical techniques for pediatric cataract surgery have reduced the number of early postoperative complications, such as pupillary block, that can cause angle-closure glaucoma. However, a significant percentage of children who have undergone congenital cataract surgery go on to develop glaucoma, usually with predominantly open angles, and the onset of glaucoma frequently occurs years after the cataract surgery. Numerous potential mechanisms for the development of glaucoma have been postulated, including congenital angle anomalies, postoperative inflammation leading to angle dysfunction or progressive synchial closure, corticosteroid-induced mechanisms, and some unknown effect of the aphakic state or the vitreous interaction with the developing angle structures leading to reduced outflow facility. An ultrasound biomicroscopy study of the anterior segment after congenital cataract surgery has demonstrated a more anterior iris insertion with a smaller angle opening distance and a flatter pars plicata, compared with normal controls. Because the IATS was not designed as a study of the development of glaucoma following congenital cataract surgery, limited information on the mechanisms of glaucoma can be ascertained from the 1-year follow-up outcome data. It is clear, however, that modern surgical techniques do not eliminate the early development of glaucoma, with 10 of 114 eyes (9%) from the total group developing glaucoma by the 1-year follow-up visit. Most cases were assumed to be open angle, with a single case (1 of 10 eyes [10%]) of angle closure reported.

A retrospective study of older children has suggested that the placement of an IOL reduces the incidence of glaucoma following congenital cataract surgery. Two other studies of congenital cataract surgery with and without an IOL failed to demonstrate a difference in the incidence of glaucoma. Although the number of eyes developing glaucoma by the 1-year follow-up in the IATS suggested a higher incidence in the pseudophakic eyes than in the aphakic eyes (12% vs 5%), this difference was not statistically significant. Continuing follow-up in the IATS for the development of glaucoma and glaucoma suspect status is critical, given that the mean interval between cataract surgery and diagnosis of glaucoma has been reported to range from 4.0 to 5.2 years.

Many previous studies of glaucoma in aphakic and pseudophakic children have lacked a consistent definition of glaucoma and a standard protocol for surveillance of at-risk eyes. Glaucoma has frequently been defined by elevated IOP alone, without structural change to the eye as part of the diagnostic criteria. The definition for glaucoma in the IATS included criteria for structural change (enlarged ocular dimensions or an increased cup-to-disc ratio). A standardized definition of a glaucoma suspect was also created for the IATS.

Persistent fetal vasculature is believed to be a risk factor for the development of glaucoma following congenital cataract surgery because of the associated microph-
thalamos and the possibility of anterior segment anomalies, but previous studies have failed to confirm this opinion. The IATS provides evidence that PFV is likely a risk factor for the development of glaucoma. Younger age at surgery was also noted in the IATS to be a risk factor for the development of a glaucoma-related adverse event, despite the fact that cataract surgery was deferred until at least 4 weeks of age based on previous studies.4,6 Furthermore, eyes that developed glaucoma (based on optic nerve changes) had a thicker CCT than those that did not, which argues against the concept that a thicker CCT in children leads to a lower risk of glaucoma, as in adult patients with ocular hypertension, with thinner central corneal measurements noted to be a powerful predictor for the development of open-angle glaucoma.19 Various correction factors for applanation IOP measurements based on CCT measurements have been proposed20,21 but statistical analyses of these formulas have demonstrated that the effect of CCT on IOP was less than predicted, suggesting an increased risk of glaucoma if surgery is performed in the first 4 weeks of life. Cataract surgery in the IATS was performed between 1 and 6.9 months of age, providing 2 nearly equal-sized cohorts aged 48 days or younger and 49 days or older (Table 3). Further evaluation of the visual outcomes in the IATS cohort may provide information as to the optimum timing of cataract surgery in the setting of unilateral cataract.

Central corneal thickness (CCT) is a recently recognized risk factor for the development of glaucoma in adult patients with ocular hypertension, with thinner central corneal measurements noted to be a powerful predictor for the development of open-angle glaucoma.19 Various correction factors for applanation IOP measurements based on CCT measurements have been proposed but statistical analyses of these formulas have demonstrated that the effect of CCT on IOP was less than predicted, potentially leading to erroneous conclusions about "corrected" IOP.22 Aphakic and pseudophakic children have significantly thicker corneas than age-matched controls, and CCT has been noted to increase following cataract surgery.23 Furthermore, eyes that developed glaucoma (based on optic nerve changes) had a thicker CCT and higher IOP than those that did not, which argues against the concept that a thicker CCT in children leads to a lower risk of glaucoma, as in adult patients with ocular hypertension. The measurement of CCT was not part of the study protocol in the IATS. Children noted to have
elevated IOP without structural change were placed in the glaucoma suspect category. Treatment of children who develop glaucoma following congenital cataract surgery frequently requires surgical intervention. Chen et al noted that surgical treatment was performed in 57.1% of 170 eyes with aphakic glaucoma, with medical therapy recommended for 92% of eyes. However, in another study24 of pediatric aphakic glaucoma, surgical interventions were performed in only 15 of 55 eyes (27%) that were likely representative of less severe glaucoma. The 60% rate of glaucoma surgery (among eyes with glaucoma) in the IATS is comparable to the rates in these studies.7,24 Of note, 3 of the patients with glaucoma in the IATS who underwent a trabeculotomy were controlled for 1 year after cataract surgery. Angle surgery in children who develop open-angle glaucoma following congenital cataract surgery was noted to be successful in 57% of 14 eyes with a mean follow-up of 4.7 years (some patients required more than 1 angle surgery) and may decrease the need for filtering or shunt procedures.25 Visual acuity in children who develop glaucoma following congenital cataract surgery may be limited by glaucomatous optic nerve damage, amblyopia, pupillary membranes, corneal decompensation, or complications from glaucoma surgical intervention.7,24,25 In the IATS, eyes that developed a glaucoma-related adverse event had a median visual acuity that was 3 Snellen lines worse than those that did not. Although this difference did not reach statistical significance, likely owing to the small sample size of the glaucoma group, it is reasonable to expect that a statistically significant difference in visual acuity will develop in the glaucoma group with longer follow-up.

The limitations of our study are the small sample size of the group of patients with glaucoma-related adverse events, only 1 year of follow-up data, and the inclusion of the glaucoma suspect group with the glaucoma group for statistical evaluation. The strengths of our study are the prospective data collected and the standardized definitions of glaucoma, glaucoma suspect, and glaucoma-related adverse events. Planned 5-year IATS follow-up data should provide long-term incidence data and should identify the risk factors for the development of glaucoma and the effect of glaucoma on visual outcomes in patients with unilateral cataract.

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