Incidence and Risk Factors of Glaucoma Following Pediatric Cataract Surgery With Primary Implantation

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• PURPOSE: To determine the incidence and risk factors for glaucoma after pediatric cataract surgery with intraocular lens (IOL) implantation.
• DESIGN: Retrospective, consecutive case series.
• METHODS: In this single-center study, we reviewed 136 children (199 eyes) who underwent pediatric cataract surgery before 1 year of age with a minimum of 1 year of follow-up. The intervention used was pediatric cataract surgery with IOL implantation, and the primary outcome measure was the presence or absence of secondary glaucoma.
• RESULTS: The mean age at surgery was 148 ± 93 days (range 30-359 days) with a mean follow-up of 6.3 ± 3.6 years (range 1.1-12.8 years). Glaucoma developed in 31 eyes (16%) with 5- and 10-year incidence rates of 12% and 28%, respectively. The incidence of glaucoma seemed to be bimodal, with a first peak occurring after a mean delay of 2.5 months (range 1.6-4.1 months) and a second peak occurring after a mean delay of 5.7 years (range 2.6-11.7 years). Younger age at surgery, shorter axial length, longer follow-up, use of trypan blue, reintervention, and bilateral surgery were associatied with a higher incidence of glaucoma. Multivariate analysis including the aforementioned variables indentified longer follow-up (odds ratio [OR] = 1.3 [95% confidence interval {CI} 1.1-1.6], $P = .001$), reintervention (OR = 4.1 [95% CI 1.2-13.4], $P = 0.02$), and the use of trypan blue (OR = 4.1 [95% CI 1.3-13.1], $P = .02$) as predictors for the development of glaucoma.
• CONCLUSION: Glaucoma is a common complication after pediatric cataract surgery. It seemed to have a bimodal incidence. Risk factors for glaucoma development were reintervention, the use of trypan blue, and a long follow-up. (Am J Ophthalmol 2021;224:1–6. © 2020 Published by Elsevier Inc.)

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CONGENITAL CATARACT IS ONE OF THE LEADING causes of visual impairement and blindness in children. It represents a serious threat to the development of the visual system and results in severe amblyopia.[1,2] Early surgery is essential to clear the visual axis and achieve a good visual outcome.[3–5] After lens removal, several methods have been proposed to correct aphakia, such as glasses, aphakic contact lenses, and intraocular lenses (IOLs). Primary implantation of a posterior chamber IOL is now increasingly performed, even in younger childrenn and for both uni- and bilateral cataracts.[6–8]

Despite advances in congenital cataract management, secondary glaucoma (SG) remains a major postoperative sight-threatening complication,[2] with open-angle glaucoma being the predominant type in both aphakic and pseudophakic children.[9] Although the pathogenesis of glaucoma after cataract surgery remains unclear, several risk factors have been identified. They include early surgery,[4] chronic postoperative inflammation,[10] primary posterior capsulotomy,[11] persistence of fetal vasculature,[12] and microphthalmia.[13] Recent prospective studies have rejected the protective role of IOL implantation in the development of glaucoma after cataract surgery.[8,14] The incidence of SG is not yet precisely identified. It ranges from 3%-41% depending on the follow-up period and the criteria chosen to define glaucoma.[15,16]

The purpose of the present retrospective study was to estimate the incidence of and to determine the risk factors for glaucoma after cataract removal with primary IOL implantation performed in children during the first year of life.

METHODS

THIS RETROSPECTIVE OBSERVATIONAL CONSECUTIVE CASE series included all children who underwent unilateral or bilateral cataract surgery with primary IOL implantation in the first year of their life at the Fondation Ophtalmologique Adolphe de Rothschild, a tertiary referral center, between January 2003 and December 2012. Retrospective analysis of data was approved by the institutional review board and the study adhered to the tenets of the Declaration of Helsinki.

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All eyes presenting with an isolated cataract or an anterior form of persistence of fetal vasculature not requiring posterior vitrectomy or a moderate microphthalmia allowing primary IOL implantation and with a follow-up of ≥1 year were included in the study. Children that developed SG without reaching the 1-year follow-up were also included. Exclusion criteria were children with associated ocular malformations, including anterior segment dysgenesis, pre-existing intraocular pressure (IOP) elevation, congenital glaucoma, syndromic cataract (ie, Lowe syndrome, congenital rubella), history of trauma or uveitis, and premature children born before 32 weeks' gestation.

Baseline parameters included age at surgery, gender, laterality, axial length (AL), and preoperative IOP. IOP was obtained by Goldmann applanation tonometry (GAT) using the Perkins tonometer (Clement Clarke, Haag-Streit, Harlow, United Kingdom) or the iCare rebound tonometer (Icare; Tiolat Oy, Helsinki, Finland) when GAT was not possible. The use of trypan blue during surgery, the location of IOL implantation, and peroperative complications were also noted.

All infants had an examination under general anaesthesia (GA) 1 month after surgery to measure refraction, AL, cornea, anterior chamber, IOP, and fundus. In the follow-up, regular examinations under general anesthesia were performed until the child was able to sit for a full and reliable slit-lamp examination (SLE). At each visit the following variables were recorded: IOP, corrected distance visual acuity when measurable, complications, additional surgical interventions, the need for antiglaucoma drops, and the need for glaucoma sugery.

• **SURGICAL TECHNIQUE AND POSTOPERATIVE CARE:** All patients were under GA during the procedure, using a standardized surgical protocol consisting of clear corneal incision, anterior capsulorhexis, lensectomy using a vitrectome, posterior capsulorhexis, anterior vitrectomy, and posterior chamber IOL implantation. The IOL was implanted in the capsular bag when possible or in the sulcus in the remaining cases.

A topical postoperative treatment was prescribed for a period of 1 month, including atropine 0.3% (Alcon Laboratories, Fort Worth, Texas, USA) twice daily and a steroid/antibiotic combination (dexamethasone-neomycin-polymixin B [Maxidrol]; Alcon Laboratories) 4 times daily with a weekly tapering. An oral steroid treatment (Celestene; Merck and Co, Inc, Whitehouse Station, New Jersey, USA) at a dose of 0.5 mg/kg was added for 1 week.

Postoperative visual rehabilitation was started 1-2 weeks after cataract surgery and included refraction correction with glasses and patching when indicated.

• **GLAUCOMA DIAGNOSIS AND FOLLOW-UP:** Ocular hypertension was defined as an IOP ≥21 mm Hg during SLE or ≥14 mm Hg under GA. The diagnosis of SG was based on the presence of ocular hypertension with any of the following: asymmetric optic nerve cupping (>0.2), large cup-to-disc ratio (>0.4), corneal edema, enlargement of corneal diameter, myopic shift, or abnormal and asymmetric increase in AL. AL was considered abnormal when it was 30% higher than the normal established for the age, defined as 17 mm at birth, 18.5 mm at 6 months of age, 20 mm at 1 year of age, and 21 mm at 4 years of age.[17] Topical antiglaucoma medications were started once the diagnosis of glaucoma was established. In case of insufficient IOP control with medication a surgical treatment was performed.

TABLE 1. Baseline, Intraoperative, and Postoperative Characteristics

Initial Characteristics	Children (N = 136)
Female, n (%)	73 (54)
Bilateral cataract, n (%)	63 (47)
Age at surgery (days) (SD [range])	148.3 (92.7 [30-359])
Axial length (mm) (SD [range])	18.3 (1.6 [15.2-23.4])
Follow-up (years) (SD [range])	5.8 (3.1 [1.0-12.4])
Age at follow-up (years) (SD [range])	6.3 (3.6 [1.1-12.8])
Intra- and postoperative characteristics	Eyes (N = 199)
IOL implantation, n (%)	
Capsular bag	98 (49)
Sulcus	75 (38)
Undetermined	26 (13)
Trypan blue use, n (%)	
Yes	100 (50)
No	72 (36)
Undertermined	27 (17)
Additional interventions	93 (47)

IOL = intraocular lens; SD = standard deviation.

• **STATISTICAL ANALYSIS:** Statistical analysis was done using the SPSS software (version 22.0; IBM Corp, Chicago, Illinois, USA). Categorical variables were tested for association with the incidence of SG using the χ^2 test for the univariate analysis. Continuous variables were compared between the 2 groups using the Student *t* test. Mann–Whitney and Fisher exact tests were used to compare nonparametric variables. Multivariate analysis was then used to control for confounding factors and to calculate the odds ratio for SG development. Time-related occurrence of glaucoma after surgery was analysed using the Kaplan–Meier estimator.

RESULTS

• **STUDY POPULATION:** Of the initial 196 children, 60 were excluded, among which 31 did not reach the 1-year follow-up, 10 had posterior persistence of fetal vasculature, 8 had missing data, 5 had anterior segment dysgenesis, 2

TABLE 2. Effects of Different Variables on the Development of Secondary Glaucoma

Variables	No Glaucoma	SG (31 Eyes)	*P* Value
Follow-up time (y)	5.5	8.0	<.001[a]
Age at surgery (months)	5.0	3.9	.047[a]
Age at surgery <3 months, n (%)	53 (32)	16 (52)	.03[a]
Axial length (mm)	18.4	17.8	.09
AL <16.5 mm, n (%)	19 (11)	8 (26)	.03[a]
Preoperative IOP (mm Hg)	5.2	5.7	.29
Bilateral cataract, n (%)	99 (59)	27 (87)	.003[a]
Use of trypan blue, n (%)	78 (54)	22 (81)	.008[a]
Bag implantation, n (%)	90 (59)	8 (40)	.1
Reintervention, n (%)	68 (41)	25 (81)	<.001[a]

AL = axial length; IOP = intraocular pressure; SG = secondary glaucoma.
[a]Statistically significant ($P < .05$).

had pre-existing ocular hypertension, 2 had Lowe syndrome, 1 had congenital rubella, and 1 was premature.

One hundred thirty-six children (199 eyes) were included in the study, of which 63 (46%) had bilateral cataract, 73 were female (54%), and 63 were male (46%). Baseline, intraoperative, and postoperative charateristics of included cases are reported in Table 1. Children with bilateral cataracts were operated on earlier than children with unilateral cataracts (mean 124.7 vs 176.6 days, $P < .001$) but both groups had comparable follow-up (mean 6.2 vs 5.5 years, $P = .16$).

• **SG:** SG occured in 31 eyes (16%) of 21 children (16%). Elevated IOP was identified under GA in 14 children (21 eyes) and with SLE in 7 children (10 eyes). Mean IOP was 18.8 ± 4.5 mm Hg (range 14-28 mm Hg) under GA and 27.9 ± 5.5 (range 20-35 mm Hg) with SLE. SG was more frequent in children with bilateral cataract (17 vs 4 children, $P < .001$) with 10 children (47.6%) developing bilateral glaucoma.

The mean time to glaucoma diagnosis was 3.6 years (median 3.0; range 1.6 months to 11.7 years). In 12 eyes (39%), SG appeared in the first postoperative year (mean delay of 2.5 months; range 1.6-4.1 months). In the remaining 19 eyes, SG developed after a mean delay of 5.7 years (range 2.6-11.7 years).

Comparing the SG group to the group that did not develop glaucoma, follow-up time was longer (mean 8.0 vs 5.5 years, $P < .001$), age at surgery was lower (mean 3.9 vs 5.0 years; $P = .047$), reintervention was more frequent ($P < .001$), and trypan blue was used more frequently ($P = .008$). Table 2 compares the characteristics of eyes that did not develop SG to the eyes that developed SG.

• **KAPLAN–MEIER SURVIVAL CURVE:** A Kaplan-Meier survival curve of eyes remaining glaucoma-free over time is presented in Figure. In our cohort, the cumulative risk of developing a SG after cataract removal increased from 12% at 5 years (95% CI 6-16%) to 28% at 10 years (95% CI 15-36%). The estimated linear incidence of SG was 2.8 new cases per 100 eyes per year.

• **PREDICTIVE FACTORS FOR SG:** In univariate analysis, the following factors were significantly associated with an increased risk of SG: axial length <16.5 mm, bilateral cataract, perioperative use of trypan blue, additional surgical procedures, and younger age at surgery. Multivariate analysis for the development of SG is shown in Table 3.

DISCUSSION

IN THIS RETROSPECTIVE STUDY, WE REVIEWED ALL CHILdren with congenital cataract who were operated on before 1 year of age and had an IOL implanted in the bag or in the sulcus during the same intervention. Those children were evaluated for the development of postoperative glaucoma. The cumulative risk of SG increased from 12% at 5 years to 28% at 10 years, with an estimated linear incidence rate of 2.8 per 100 eyes per year.

The risk of developing SG after a mean follow-up of 5.8 years was 16% in our studies, a result comparable to the Infant Aphakia Treatment Study (IATS). The IATS prospectively included 114 infants with unilteral congenital cataract who were operated on before 6 months of age and found that 17% of eyes developed SG after 4.8 years of follow-up (16% in the aphakia group and 19% in the pseudophakia group).[14] A recent meta-analysis reported 17% of SG after an early congenital cataract surgery, with a median follow-up of 4.3 years. In this analysis, there were large discrepancies between included infants and different glaucoma definitions, and 77.4% of infants were

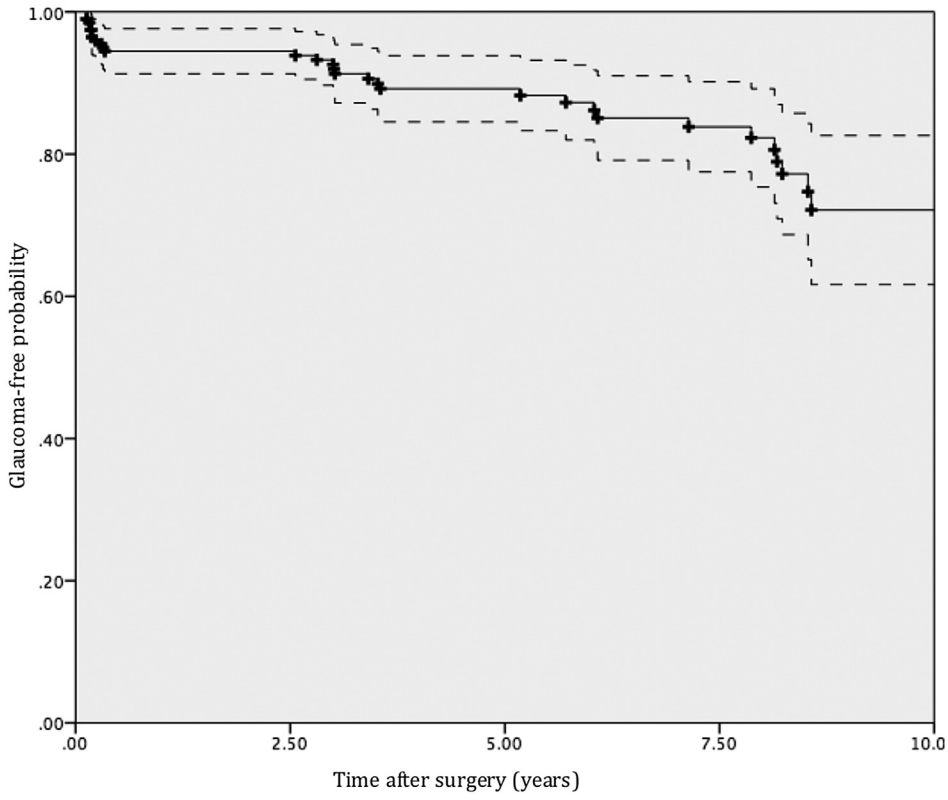

FIGURE. Kaplan–Meier curve (±95% confidence intervals) showing eyes remaining without secondary glaucoma over time (years). The graph is truncated at a follow-up of 10 years.

TABLE 3. Multivariate Analysis in All Secondary Glaucoma Cases (31 Eyes)

Variables	*P* Value	OR (95% CI)
Years of follow-up	.001[a]	1.3 (1.1-1.6)
Use of trypan blue	.02[a]	4.1 (1.3-13.1)
Reintervention	.02[a]	4.1 (1.2-13.4)
Bilateral cataract	.09	3.1 (0.8-11.4)
Age at surgery <3 months	.2	1.9 (0.7-5.7)
AL<16.5 mm	.6	1.4 (0.4-4.2)

AL = axial length; CI = confidence interval; OR = odds ratio; SG = secondary glaucoma.
[a]Statistically significant ($P < .05$).

left aphakic.[15] IOL implantation does not seem to decrease the risk of developing SG.[8,14]

Multiple risk factors for the development of SG have been identified in previous studies and include early age at surgery, additional procedures, and bilateral cataract surgery.[12,15,18] In our cohort, we found in the univariate analysis that the risk factors were bilateral cataract, age at surgery, axial length <16.5 mm, additional procedures, and the use of trypan blue. Multivariate analysis of potential risk factors showed that only longer follow-up, additional interventions, and the use of trypan blue increased the risk of developing SG with respective odds ratios of 1.3, 4.1, and 4.1.

To our knowledge, this is the first description of the influence of the use of trypan blue on the development of SG. We believe that the relationship is not causal, but that trypan blue was used for more complex surgeries, in severe cataracts or in smaller, more immature eyes. These are also the eyes that were at a higher risk of developing postoperative inflammation and on having an immature trabecular meshwork, thus resulting in a higher rate of SG. However, a direct effect of the trypan blue on the trabecular meshwork collagen, which could result in a stiffening of the collagen matrix via photochemical mechanisms, is also possible. Similar stiffening effects were reported in the use of trypan blue to dye the lens capsule and the Descemet membrane.[19,20]

Several studies have discussed the effect of follow-up period on the development of SG, noting that the onset of glaucoma occurs at a mean 4-5 years after cataract removal.[12,15,18] This was also observed with an increased incidence noted between the 1- and 5-year follow-ups of the IATS.[14,21] Similarly, the effect of additional interventions has been described, with Mataftsi and associates[15] reporting on the effect of additional surgeries on the development of SG with a hazard ratio of 2.52. The location of IOL implantation (sulcus vs bag) did not seem to affect the development of SG as previously described in litterature.[21]

However, in our cohort we could not demonstrate in multivariate analysis the effect of young age at surgery on the risk of developing SG. It must be noted that in our practice we did not perform surgery before 1 month of age because this was suggested to be a significant risk factor for the development of glaucoma.[3,4,22–24] The lack of a significant difference could be related to the fact that the age at surgery in our study was higher than other studies (4.1 months vs 1.8 months in the IATS) and that different variables were taken into consideration while performing the multivariate analysis including peri- and postoperative variables.

Futhermore, the effect of age at surgery could progressively disappear with longer follow-up, since in our cohort we have a longer follow-up than in the IATS (5.8 vs 4.8 years).[14] In fact, when analyzing the data of SG in our cohort, we found that there seems to be a bimodal incidence of SG with early onset of SG before 1 year (range 1.6-4.1 months) and a late onset of SG occurring after a mean delay of 5.7 years (range 2.6-11.7 years). This would suggest that early age at surgery could possibly increase the risk of developing early onset SG.

The mechanism of SG is not clearly understood and can be multifactorial.[25] The role of age at surgery as a risk factor could be explained by the stress and the inflammation secondary to surgery interfering with the maturation of trabecular meshwork, partly explaining the first peak of SG incidence. The use of corticosteroid in the postoperative period could also play a role in the development of the first peak SG in steroid responder eyes. In addition, a chronic trabeculitis with increased outflow resistance caused by lens remnants in pediatric cataracts or toxic substances from the vitreous or even chronic inflammation could also be involved.[24,26] This could explain the association between additional interventions after cataract surgery and the development of SG. Lastly, the loss of accommodation after surgery could have an effect on the Schlemm canal permeabilty mediated by the ciliary muscle and could partly explain the second peak of SG incidence.[27]

One limitation of the present study is that it is retrospective with many children lost to follow-up. Some of the children were refered to our center for surgery and after surgery they continued the rest of the follow-up with their referring physician. We tried to limit this follow-up bias by excluding infants with a follow-up <1 year and we used the statistical model of Kaplan–Meier to estimate the incidence of SG.

In conclusion, SG is a sight-threatening complication occurring in 16% of eyes following congenital cataract surgery. This real-life study focuses on a homogeneous pediatric population of early cataract removal with primary IOL implantation in the first year of life. Our data suggest that the risk of SG accumulates over time, with an estimated linear incidence rate of 3% per year. There seems to be a bimodal incidence of SG. Follow-up should be started early and continued for an extended duration after surgery, and physicians should be particularly cautious in patients with one or several factors increasing the risk of SG (cataract surgery before 3 months of age, additional interventions, and the use of trypan blue during surgery).

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