Visual axis opacity following IoL implantation in children aged under 2 years: Findings from the IoLunder2 cohort study

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This article contains additional online-only material. The following should appear online-only:

Tables A-G

Abstract

Objective/ Purpose: Appropriate correction of aphakia is key to good outcomes. There may be clinical settings and populations where accessing or managing aphakic contact lenses is challenging. Strategies to target the increased risk of visual axis opacity (VAO) following primary IoL implantation in infancy are necessary.

We describe the predictors of VAO following primary IoL implantation for unilateral or bilateral congenital or infantile cataract in children aged under 2 years.

Design: Population based (UK and Ireland) prospective inception cohort study undertaken through a national clinical network.

Participants: 105 children (57 bilateral cataract, 48 unilateral, total 162 eyes) undergoing primary IoL implantation in the first two years of life between January 2009 and December 2010.

Methods: Observational longitudinal study with multilevel, multivariable modelling to investigate associations between outcome of interest, and child and treatment specific factors including age, axial length, socioeconomic status, IoL model, and post operative steroid use.

Main outcome measures: Post operative proliferative and / or inflammatory visual axis opacity (VAO) requiring surgical correction.

Results: Visual axis opacity occurred in 67 eyes (45%), typically within the first post-operative year. Use of a three piece IoL model (odds ratio/OR 0.28, 95% confidence interval/CI 0.09 – 0.87, p=0.03), and increasing age at surgery (OR 0.97, 95% CI 0.95-0.99, p=0.02), were each independently protective against the development of proliferative VAO. Inflammatory VAO was independently associated with socioeconomic deprivation (OR 4.86, 95%CI .43 – 16.31, p=0.01).

Conclusions: Visual axis opacification is common following IoL implantation in early childhood. The findings of this prospective cohort study suggest that the use of three piece IoL models may reduce the risk of pseudophakic VAO in children aged under 2 years.

Introduction

Congenital and infantile cataract is an important cause of childhood blindness,[1] and a target for national and international public health policies.[2-4] Primary intraocular lens (IoL) implantation held the promise of improved visual outcomes for these children. However, the UK and Ireland prospective study of outcomes following cataract surgery in children under 2 years old (IoLunder2), and the Infant Aphakia Treatment Study (IATS) randomised controlled trial have both reported an absence of visual benefit with primary IoLs in early childhood.[5-7] Moreover, IoL implantation in children aged under 2 years old carries greatly increased risk of requiring secondary procedures for visual axis (re-)opacification (VAO).[7, 8] VAO following congenital or infantile cataract surgery typically occurs either due to proliferation of remnant lens cells (proliferative VAO), or organisation of inflammatory material (inflammatory or membranous VAO).[7, 8]

Whilst the currently available high level evidence from IATS and IoLunder2 suggest that IoL implantation is not recommended in infancy, there remain populations or health settings where other forms of refractive correction cannot be undertaken successfully for these children.[9] Aphakic glasses can be heavy for the infant face, and result in sub-optimal optical correction beyond the central field.[10] Aphakic contact lenses requires family members or carers to be able to manage insertion and removal.[11,12] More importantly, limited access to clean water and optometric support are obstacles to the use of aphakic contact lens in lower income countries.[9] In some of these settings, IoL implantation may be considered the only feasible option. This makes it necessary to develop strategies to reduce the risk of VAO in the setting of contemporary clinical practice. We sought to identify the predictors of visual axis opacity (VAO) following IoL implantation for unilateral or bilateral congenital or infantile cataract surgery for children within the IoLunder2 study.

Methods

IoLunder2 is a prospective longitudinal bi-national (UK and Ireland) inception cohort study investigating outcomes following cataract surgery in the first two years of life. The details of case ascertainment, recruitment and data collection have been reported previously.[5,13,14] In summary, active surveillance was undertaken through the British Isles Congenital Cataract Interest Group (BCCIG). Eligible children were those resident in UK or Ireland, and undergoing surgery for congenital or infantile cataract in the first two years of life, with or without primary IOL implantation, between January 2009 and December 2010. Definitions for outcomes of interest and potential predictors were harmonised prior to data collection. Following informed consent, pre, per and post-operative data collection was undertaken using forms developed and piloted by the BCCIG. Visual axis opacification (VAO) was defined as any postoperative re-opacification of the axis requiring surgical intervention, so as to ensure consistency in assessing severity. Non exclusionary dichotomous categories were also created for the presence of each of proliferative VAO, membranes across the pupillary axis, and anterior capsular contraction or phimosis. The incidence of fibrinous postoperative inflammation, as a precedent to later development of pupillary membranes, was also noted. Date of intervention for VAO was recorded, alongside the incidence of any complications related to reoperation. Potential predictors of VAO for children were identified *a priori* based on the existing literature and selected through group consensus. These comprised:

age at surgery, age at surgery corrected for gestation (as continuous variable and categorised using accepted infant milestones[5]), ethnicity of child, deprivation index of residence child at time of surgery, axial length in mm (as continuous variable and categorised using microphthalmia diagnostic thresholds[5]), horizontal corneal diameter in mm (as continuous variable and categorised using microcornea diagnostic thresholds[5]) surgeon experience level (dichotomised by volume of surgery with threshold of 20 cases/year), presence of persistent fetal vasculature, per-operative iris trauma, anterior / posterior capsulotomy technique, IoL power, IoL model, IoL fixation position, use of per operative heparin, postoperative topical steroid regimen, use of

postoperative systemic steroid, occurrence of postoperative fibrinous anterior chamber response, first eye status for bilateral cataract cases (ie, whether the eye had undergone surgery first or second).

Multivariable logistic regression analysis, with multilevel adjustment for the within-child correlation of data from eyes of children with bilateral cataract, was undertaken to describe associations between VAO and the potential predictors, for the subset of children who had undergone IoL implantation. Only eyes which had undergone primary posterior capsulotomy and primary anterior vitrectomy were included in analysis of VAO outcomes. Unilateral and bilateral cases were analysed both separately, and combined, using only the first operated eye for those with bilateral cataract. Correlations between factors were investigated using non-parametric tests ($\chi 2$, Mann Whitney U, Kruskal-Wallis and Spearman's), with p-value threshold of 0.05 selected as indicative of a significant correlation. Multivariable models were constructed using conventional forward and backward stepwise regression, included variables significant at a 10% level in initial univariable analysis. Factors were retained in the multivariable model if they altered the risk ratio estimate by more than 10% or were independently associated at a 5% significance level. The most clinically relevant or statistically significant factors of any highly correlated factors identified from the univariable analysis were included in multivariate models.

Analyses were undertaken using Stata (version 15.1, StataCorp, College Station, Texas).

The research followed the tenets of the Declaration of Helsinki. Institutional Review Board (IRB)/Ethics Committee approval was obtained. Participants were included only after individual informed parental consent.

Results

In total, 256 children were recruited to IoLunder2 (figure 1). The characteristics of the whole IoLunder2 cohort have been reported previously.[14] Of the 256 children, 110 underwent primary IoL implantation. Surgery was undertaken by 39 surgeons across 31 centers. Follow up data at

five years following surgery are available for 105 of the 110 children (total 162 eyes), and this group forms the subsample for analysis presented in this paper. The baseline pre-operative characteristics of the children who underwent implantation are described in table 1.

Table 1. Baseline sociodemographics and clinical features, and clinical management details

		Bilateral cataract	Unilateral cataract
		n=57 (114 eyes)	n=48
Sex (female)		25 (44%)	21 (44%)
Ethnicity			
	Missing	3	2
	White British / Irish	36 (63%)	37 (77%)
Socioeconomic status: index of multiple deprivation (IMD) rank of family residence			
	Missing	3	2
	Residence within most deprived IMD quintile	15 (28%)	4 (9%)
Age at diagnosis in weeks, median (range)		10 (0-97)	20 0-94
Age at surgery in months, median (range)		4 (0.7–23)	7 (0.5–23)
Ocular co-morbidity, eyes (%)			
	Microphthalmia or microcornea	68 (60%)	26 (54%)
	Persistent fetal vasculature	8 (7%)	14 (29%)
	Any significant ocular co-morbidity*	14 (12%)	9 (19%)
Systemic disorder or neurodevelopmental impairment		17 (30%)	7 (15%)
Perioperative management, eyes (%)			
	High volume surgeon	67 (59%)	35 (74%)
	Corneolimbal wound	114 (100%)	45 (94%)
	Anterior capsulotomy curvilinear capsulorhexis	92 (81%)	38 (79%)
	Primary posterior capsulotomy + anterior vitrectomy	103 (90%)	46 (96%)
	IoL power, median (range)	28 (18 – 36)	27 (13 – 37)
	Implantation of single piece hydrophobic acrylic implant	33 (29%)	20 (42%)
	IoL bag fixation	101 (90%)	42 (88%)
	Intraocular heparin used	25 (22%)	4 (8%)
	No periocular or intraocular perioperative steroids	9 (8%)	2 (4%) (96%)
	Intraocular and / or subconjunctival steroid	63 (55%)	25 (52%)
	Intraocular and orbital floor steroid	42 (37%)	21 (44%)
	Intensive regimen of topical steroids post op	53 (46%)	18 (38%)
	Systemic steroids post op	7 (12%)	4 (8%)
	Time between 1st and 2nd eye surgery in days, median (range)	7 (0 – 35)	-
Peri operative adverse events eyes (%)			
	Per operative iris trauma	15 (13%)	4 (8%)
	Post-operative fibrinous inflammation	21 (18%)	11 (23%)

*Significant ocular co-morbidity comprised severe microphthalmia, severe microcornea, complex persistent fetal vasculature or other structural ocular anomaly

Data are children(%) unless otherwise stated. All data available for full cohort unless otherwise stated.

Pre-operative diagnosis of ocular comorbidity was common in eyes which underwent IoL implantation, in particular microphthalmos (table 1). Per-operative iris trauma occurred in 19 eyes (12%). This included 8 cases of purposeful iris manipulation (hooks, stretch, iridectomy). All implanted IoLs had square edged optics and acrylic monofocal optics. The specific IoL models implanted at primary surgery were: Acrysof™ MA60 (hydrophobic acrylic 3 piece IoL, 6mm optic diameter, 13mm haptic diameter, n=52 bilateral cataract eyes, n=20 unilateral cataract eyes), Acrysof® MA30 (hydrophobic, 3 piece, 5mm, 12.5mm, n=26, n=6); AMO Sensar® (hydrophobic, 3 piece, 6mm, 13mm, n=2, n=0); Hoya AF™ (hydrophobic, 3 piece, 6mm, 12.5mm, n=0, n=1); Acrysof® SN60IQ (hydrophobic, single piece, 6mm, 13mm, n=15, n=12); Acrysof® SA60 (hydrophobic, single piece, 6mm, 13mm, n=15, n=9); AMO Technis® (hydrophobic, single piece, 6mm, 13mm, n=2, n=0); Rayner C-flex™ (hydrophilic acrylic single piece, 5.7mm, 12mm). Peroperative steroid at closure was used in all but 10 eyes. Post operatively, children were treated with either intensive (at least every 2 hours of parental waking daytime, n=71/162 eyes, 43.8%) topical corticosteroids, or were treated with less frequent drop regimens. Post-operative systemic corticosteroids were not used in children receiving intensive postoperative topical treatment, but were used in a third (11/34, 32%) of the eyes of children who were prescribed four times daily or less frequent drops. One child developed pneumonia whilst on systemic steroids following primary surgery.

Visual axis opacity (VAO)

Visual axis opacity occurred in 45% of eyes which underwent implantation with primary posterior capsulotomy and primary anterior vitrectomy (67/149 eyes). Surgery to address VAO occurred within a year of primary cataract surgery in all but 3 of the 67 eyes affected by VAO. Median time to surgery was 4.3 months for children with bilateral cataract (range 1 – 20.4months) and 4.1months in unilateral (range 0.5 – 30months),

All children received post operative topical steroids. A post-operative fibrinous response was noted postoperatively in 32 eyes (20%, (22 eyes of children with bilateral cataract, 10 eyes unilateral cataract). Although 11 of these 32 eyes had resolution of the inflammation using

additional topical steroids alone, 2 eyes required intraocular tissue plasminogen injection, and 19 eyes developed or presented with post-operative pupillary fibrinous membranes which required surgical correction (table 2).

Table 2. Occurrence of visual axis opacity (VAO) requiring surgery by five years following surgery*

	Bilateral cataract 103 eyes / 52 children	Unilateral cataract 46 eyes / children	Total 149 eyes / 105 children
Any VAO	47 (46%)	20 (43%)	67 (45%)
Pupillary membrane	13 (13%)	6 (13%)	19 (13%)
Proliferative	33 (32%)	17 (37%)	50 (34%)
Anterior capsular phimosis	3 (3%)	2 (4%)	5 (3%)
2 or more surgical corrections for VAO	7 (7%)	5 (11%)	12 (8%)

** The 13 eyes which did not undergo primary capsulotomy have been excluded from this analysis*

For the 13 eyes which had not undergone primary capsulotomy and anterior vitrectomy, surgical intervention for any opacification of the visual axis was needed in 9 of the 11 bilateral cataract eyes (82%, median time from primary surgery to reoperation 4 months, range 2m to 7m) and 2 of the 2 eyes with unilateral cataract (at 2 weeks and 3 months post-op).

Factors associated with the risk of VAO

Interrogation of potential factors associated with VAO risk was preceded by identification of associations between potential risk predictors (supplemental tables A,B). Increasing axial length and increasing horizontal corneal diameter were strongly positively associated with each other ($p<0.001$) and both were positively associated with increasing age at surgery ($p<0.001$, Mann Whitney U test). Decreasing ocular size and decreasing age was positively associated with increasing implant power. At the time of recruitment to the study (January 2009 to December 2010) there was limited availability of three piece IoL implants in powers above 30 dioptre.

Consequently, within this cohort smaller ocular size and younger age at surgery are associated with the use of a single piece IoL model type.

Factors independently associated with the risk of visual axis opacity requiring surgery are described in tables 3 and 4, whilst the results of the univariable analyses are presented in supplemental tables C-G. Factors independently associated with reduced risk of proliferative VAO were older age at surgery and the use of three piece intraocular lens models over single piece models. For children with unilateral cataract, the use of two hourly topical steroids in the week following primary surgery .also appeared to be protective against the development of proliferative VAO These associations were present following adjustment for age at surgery and ocular size.

Living in areas with indicators of increased deprivation (as measured through zipcode /postcode derived index of multiple deprivation score) was independently associated with the development of pseudophakic inflammatory membranes following unilateral or bilateral cataract surgery (tables 3 and 4). For children with bilateral cataract, first or second eye status was not associated with the development of proliferative or membranous visual axis opacity at univariable (supplementary tables or multivariable level.

Table 3: Factors independently associated with the risk of proliferative visual axis opacity

Bilateral cataract		
	Adjusted odds ratio (OR)* (95% CI)	p
Increasing age at surgery unadjusted (weeks)	0.98 (0.96 – 0.99)	0.03
Three piece IoL	0.27 (0.07 - 1.00)	<0.05
Unilateral cataract		
	Adjusted odds ratio (OR)* (95% CI)	p
Increasing age at surgery unadjusted (weeks)	0.96 (0.93 – 0.99)	0.01
Intensive post operative topical steroids	0.12 (0.01 – 0.82)	0.03
First eye bilateral and all unilateral cataract		
	Adjusted odds ratio (OR)* (95% CI)	p
Increasing age at surgery unadjusted (weeks)	0.97 (0.95 – 0.99)	0.02
Three piece IoL	0.28 (0.09 – 0.87)	0.03

**Including adjustment for IoL power (bilateral and unilateral cataract), intense post operative topical steroid use and first eye status (bilateral cataract) and use of three piece IoLs (unilateral cataract)*

Table 4: Factors independently associated with the risk of post operative pupillary membranes

Bilateral cataract		
	Adjusted odds ratio (OR)* (95% CI)	p
Increasing relative deprivation	2.45 (1.44 – 4.20)	0.001
First eye bilateral and all unilateral cataract		
	Adjusted odds ratio (OR)** (95% CI)	p
Increasing relative deprivation	4.86 (1.43 – 16.31)	0.01
Increasing axial length	0.50 (0.27 – 0.69)	0.03

**Adjusted for first eye status, axial length and ethnicity, age at surgery and per-operative iris trauma*

***Adjusted for age at surgery, ethnicity, and per-operative iris trauma*

Discussion

From a national cohort study, we report that visual axis opacity is common after IoL implantation in children aged under 2 years old. Proliferative forms are more common than pupillary membranes. Proliferative VAO is more common in those who undergo surgery at a younger age, and in eyes implanted with single piece IoL models. Intensive administration of topical post-operative steroids may be protective against the development of proliferative VAO but use of systemic steroids was not associated with reduced odds of developing any form of visual axis opacity. Within this high income country, children living in deprived areas are more likely to develop inflammatory pupillary membranes.

IoLunder2 is a population based observational study of young children undergoing surgery across several centres in the UK and Ireland. Surgical techniques were not standardised, and there was clinical heterogeneity amongst the cohort, bringing the risk of confounding. Confounding was addressed by comprehensive prospective data collection with standardised and harmonised clinical definitions that permitted thorough multi-variable analysis and reporting of adjusted independent associations of child- and treatment-specific factors with outcomes of interest. The possible protective effect of second eye surgery (either through the presence of post-operative steroid or the presence of significant inflammation in the first operated eye) was interrogated through adjustment for first eye status and exclusion of second eyes in the analysis of outcomes for all children. It is uncertain how ‘laterality’ (unilateral versus bilateral) of cataract impacts on the risk of re-operation for VAO, but our findings suggest that similar risk factors drive VAO development in all children with congenital and infantile cataract. A potential limitation within IoLunder2 is the failure to objectively capture the type of VAO (ie proliferative versus inflammatory). This reliance on clinical assessment may have resulted in misclassification of VAO type. However, clinical definitions were harmonised across the cohort prior to study start, limiting the potential for misclassification. Additionally, the close association between post-operative fibrinous inflammation and the development of inflammatory VAO within IoLunder2 suggests robust capture of VAO type. Another potential limitation is the failure to record parental

concordance with postoperative topical therapy. This precludes analysis of the association of treatment concordance by socioeconomic status to explore whether this accounts for the observed association with deprivation. Nevertheless, we are able to describe the association of prescribing intensive topical treatment with reduction in proliferative VAO risk. Finally, our findings do not support the view that variations in surgeon experience level impacted on rates of VAO within this multi-center study.[15]

Ours is the first prospective population based study to suggest that intensive topical treatment may lead to reduced rate of re-operation following congenital or infantile unilateral cataract surgery. With regards to the most effective post-operative regimen of topical steroids, our data suggests that at least two hourly drops should be used, in the first week following surgery, to reduce the risk of later VAO. The increased need for topical anti-inflammatory treatment following childhood cataract surgery, when compared to adult cataract surgery, is well recognised.[16] There is no evidence of increased risk of glaucoma with two hourly versus four times daily topical steroid for the first post-operative week following congenital cataract surgery.[5] Randomised controlled trials (RCTs) of peri- and postoperative corticosteroid delivery may be needed to further evaluate the effectiveness of different regimens for young children. These studies would require assessment of family concordance with topical therapy, as there is some evidence that families struggle to instil frequent topical medication in young children.[17] These trials would also require tools which permit objective assessment of the degree of post-operative intraocular inflammation, as biomicroscopic assessment of mild to moderate levels of inflammation by an ophthalmologist is open to significant intra-observer variability.[18,19] Until these tools are developed, and until the necessary RCTs are undertaken, data from IoLunder2 suggests that practitioners should consider counselling parents on the potential benefit of using frequent topical corticosteroids in the initial post-operative period.

IoLunder2 has found no evidence that the use of systemic steroids is associated with lower risk of inflammatory visual axis opacity. The reported complications of systemic steroids in infancy include hyperglycaemia and infection, as occurred in one child in this cohort. The use of systemic

steroids may also delay the timing of routine early life vaccinations for infants who undergo cataract surgery aged between two and six months. Given the risk of harm with systemic steroids, our finding of no apparent benefit suggests that systemic corticosteroids should be used with caution in these children.

IoLunder2 is also the first study to report an association between single piece IoLs and the occurrence of pediatric pseudophakic VAO.[15] Crude VAO rates within the Infant Aphakia Treatment Study (IATS), the randomised controlled trial comparing IoL implantation with aphakic contact lens in children aged under 7 months at surgery, were higher than those reported here. In particular, proliferative VAO rates of 23/57, 40.3% of pseudophakic eyes within IATS by 5 years after surgery, are higher than those within IoLunder2.[8] However, the association between age at surgery and VAO risk is well known.[20] The children in IATS were younger at surgery (all aged under 7 months) and the IATS protocol involved use of the Acrysof™ SA60 single piece IoL. This may account for the higher rate of proliferative visual axis opacity. Other studies have examined outcomes in older populations, or have not differentiated between different forms of VAO (inflammatory versus proliferative) or on VAO rates following implantation of different models of IOLs.[20-23] The risk of increased rates of VAO in adults with single piece IoLs was first theorized in reports from the 2003 European Society of Cataract and Refractive Surgery meeting, and related to the 'step' between the optic / haptic junction acting as a potential focus for lens epithelial cell proliferation.[24, 25] Later work suggested that the converse was true.[26] The adult lens capsule (average diameter 9-10mm) and intraocular environment differs from that of an infant (average capsule diameter 7-8mm).[27, 28] A randomised controlled trial of different IoL models in early childhood may be useful. However, as findings from both IoLunder2 and the Infant Aphakia Treatment study have led to the conclusion that IoL implantation is not recommended in infancy,[15] it may be difficult to undertake such a trial.

The association between lower socioeconomic status (estimated using the conventional measure of area-based deprivation score at time of surgery) and the risk of inflammation sequelae is novel. This maybe a chance finding, but it is independent of ethnicity, which is closely associated

with socioeconomic status in the UK,[29] and itself may be associated with the ocular inflammatory response.[30,31] The drivers of a relationship between deprivation and inflammation may include diet, microbiomic profile, or gestational exposure to maternal stress.[30] There may also be socio-economic factors affecting the family's ability to concord with prescribed topical steroid regimen. Practitioners should be aware of the extra support which may be required by families living in areas of relative deprivation.

Bag-in-lens (BIL) IoL implantation, comprising insertion of the anterior and posterior capsulotomy edges into the ridged diaphragm of a haptic-less implant, has been advocated as a way of avoiding VAO.[32] However the reproducibility of the technique is unclear as it has not yet been widely adopted.[15] Optic capture, in which the IoL haptics sit within the bag whilst the optic is positioned through a posterior capsulotomy into the anterior hyaloid space, has also been mooted to reduce the risk of VAO,[33] but high level evidence of the effectiveness of this procedure in early childhood is not available.

Pseudophakic VAO typically occurs within the first post-operative year in children aged under 2 years at primary surgery. Preclinical animal studies report that repeated exposure to general anaesthetic causes significant pathohistological damage to the developing mammalian brain,[34] and several large studies have suggested an association between general anaesthetic in the first years of life and later life cognitive deficits.[35,36] Unidentified confounding factors may partly contribute to these associations, but whilst there is the possibility of an association, it is increasingly advocated by pediatricians that multiple occurrences of general anaesthetic should be avoided for young children where possible.[37] The American Academy of Ophthalmology has recently called for further research to develop improved techniques, lens designs, and adjuvant therapies to reduce the incidence of visual axis opacities after IOL implantation during early childhood.[15] Findings from IoLunder2 on the modifiable risk factors for the development of VAO should help to reduce the risk of re-operation for these vulnerable children.

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